DOSE-RESPONSE ANALYSIS FOR TIME-DEPENDENT EFFICACY

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ABSTRACT

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In dose-response studies, a critical research issue is to estimate the minimum effective dose (MED) and the Maximum Tolerated dose (MTD) of a drug. The problems of identifying the minimum effective dose and the maximum tolerated dose of a drug have been studied by many researchers when the endpoints are continuous and binary, and are measured at a particular time point. However, in recent dose-response related research, the responses are measured over a sequence of time points. In this situation, the previously developed procedures for the continuous and binary outcomes at a single time point are not applicable for the estimations of MED and the MTD of a drug when the longitudinal effect of the drug is taken into consideration.

In this dissertation, we developed statistical procedures to find the MED and the MTD of a drug when the responses are observed over a period of time at different dose levels. Since finding the time-dependent MED and MTD of a drug is a multiple comparison problem, we need to control the family-wise error rate, the probability of incorrectly declaring any ineffective doses of a drug as effective for MED (or any unsafe doses as safe for MTD) at a pre-specified level $\alpha$ for the adjustment of multiplicity.

Two types of statistical procedures are developed to address the problem of time dependent MED (and MTD) in this dissertation. One type is with multiplicity adjustment such as the Bonferroni Correction method for MED (and for MTD, respectively). And another is without multiplicity adjustment such as the partitioning method for MTD (and for MTD, respectively).

In our study, we assumed that both the efficacy and the toxicity of a drug increase with the dose level over time. The consequence of this assumption is that if a dose is not declared as efficacious, then we stop checking the lower doses when evaluating efficacy (or if a dose is not declared as safe, we do not need to test the higher doses for toxicity investigation). In this dissertation, we used the partitioning principle to propose confidence-set based procedures for estimating the minimum effective dose (MED) and the maximum tolerated dose (MTD) of a drug when the responses
are measured over time at different dose levels. The proposed procedures are compared by simulation studies, which cast new lights on the power performance of different innovative procedures proposed in this dissertation. We proved that the simultaneous confidence regions have the correct coverage probability $1 - \alpha$, and applied these procedures to analyze two real data sets. One is for the beetle killing effect on a plant based insecticide (Pyrethrum); and another is for the hind-limb grip strength of rats under different levels of toxicity over time. The new confidence procedures proposed in this dissertation reveal new insights on the efficacy for insecticide over time, and neurotoxic effects on nervous system of rats over time. They also enhance the literature on statistical methodologies for time dependent dose-response research.
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CHAPTER 1 INTRODUCTION

1.1 Introduction

Finding the correct dose of a drug is an important objective of drug development. In order to identify the right dose of a drug, a dose-response study is conducted in phase II and phase III clinical trials. The selection of too high dose of a drug can result in harmful even fatal consequences to the patients; too low dose of a drug, on the other hand, may have low chance of showing its efficacy in Phase III trials, and consequently, it has very low possibility to be approved by the regulatory authority. Therefore, a dose-response study in clinical trials evaluates the efficacy and toxicity of a drug to determine the effective and safe doses of a drug. Moreover, the efficacy and toxicity generally change as the dose level increases. But for some drugs, the efficacy declines or be a plateau at higher doses. So, the efficacy and toxicity considerations are taken into account (Tamhane and Logan, 2002) while determining the correct dose of a drug.

Since the efficacy and adverse effect of a drug increase with the increasing dose levels, in order to avoid too much side effects of a drug, a minimum effective dose is of interest in a dose-response study. The Minimum effective dose (MED) of a drug is defined as the minimum dose that provides clinically and statistically better mean response than that of the baseline dose. When the safety of a drug is of interest, on the other hand, the focus is on maximum tolerated dose. The maximum tolerated dose (MTD) of a drug is defined as the maximum dose of a drug whose mean adverse effect does not exceed the mean toxicity of the active control dose by a specified threshold.

The range of doses between minimum and maximum dose is called a therapeutic window, within the range all doses are considered as safe. The MED and the MTD are determined individually or simultaneously in a single study. The problem of finding minimum effective dose (MED, maximum tolerated dose (MTD), as well as therapeutic window when the endpoints are continuous, and discrete and are measured at single-time point have been studied by Tamhane and Dunnett (1999); Hsu and Berger (1999); Chen (2008); Neuhäuser and Hothorn (1997); Tamhane and Logan (2002).
and Dunnett (1999), just to name a few. However, there is no study concentrating on the feature of dose-response curve as time varies.

In this dissertation, we will focus on the development of statistical tools to identify the MED and the MTD of a drug when the responses are recorded over time at various dose levels.

1.2 Motivating Examples

In this section, we will give two different real examples that motivate us to develop the statistical procedures for the MED and the MTD of a drug when the responses are continuous, and binary and are measured over a period of time at different increasing doses. The first example is for the beetle killing effect (Binary response) on a plant based insecticide (Pyrethrum); and the second one is for the hind-limb grip strength of rats (continuous response) under different levels of toxicity over time.

1.2.1 Example 1

In toxicological and pharmaceutical studies where the response is binary, the parameter of interest is the probability of success at a particular time point (Chen, 2008; Neuhausen and Hothorn, 1997; Tamhane and Dunnett, 1999). However, when the subjects are monitored over a sequence of time points at different dose levels, especially when the longitudinal drug effect is taken into consideration to allow the human body (such as the immune system) to take care of the disease, it is necessary to estimate the MED with longitudinal effects. When the response is dichotomous and the subjects are monitored over time points at different dose levels, the existing MED methods (such as the one proposed by Chen (2008)) are not appropriate due to the lack of consideration on longitudinal effect. In this section, we will present a motivating example that gives rise to estimate MED of a drug with longitudinal effect.

Consider a toxicity study where a control group and $K$ treatment groups are used and the binary responses (such as mortality) in a group of subjects are measured over a sequence of time points across the doses. In Table 1.1 for example, Hewlett (1974), and Laurence and Morgan (1989), provided the cumulative mortality counts of adult flour beetles (Tribolium Castaneum) exposed to
pyrethrum, a well-known plant based insecticide over 13 days under four dose levels.

Table 1.1: Number of cumulative mortality of adult flour beetles

<table>
<thead>
<tr>
<th>Time(Day)</th>
<th>Dose (mg/cm²)</th>
<th>0.20(Control)</th>
<th>0.32</th>
<th>0.50</th>
<th>0.80</th>
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<td>50</td>
<td>47</td>
<td>48</td>
</tr>
</tbody>
</table>

| Group Size | 144 | 69 | 54 | 50 |

Let the control and the treatment groups be indexed as \( j = 0 \) and \( j = 1, 2, 3, \ldots, K \) respectively. Assume the dose levels are in increasing order. Let \( i = 1, 2, 3, \ldots, T \) be the time in increasing order at which the response of the dose is measured. Let \( X_{ijl} \) be the dichotomous response of the \( l \)th subject in the \( i \)th time and \( j \)th dose with \( \Pr(X_{ijl} = 1) = p_{ij} \), where \( l = 1, 2, 3, \ldots, n_{ij} \). Further, let \( \theta_{ij} = \{p_{ij} - p_{i0}\} \), \( i = 1, 2, \ldots, T, j = 1, \ldots, K \) be the vector of the differences of treatment effects. For a clinically given threshold \( \delta > 0 \), define \( \Theta_{ij}^C = \{p_{ij} - p_{i0} > \delta\}, i = 1, 2, 3, \ldots, T, j = 1, 2, 3, \ldots, K \).

Suppose a drug is effective at dose \( j \) and time \( i \) if \( p_{ij} - p_{i0} > \delta \) for all \( i \geq L \) and \( j \geq M \). It means that all doses higher than \( M - 1 \) at all time points longer than \( L - 1 \) have statistically significant potency by a pre-specified threshold level \( \delta \). The minimum effective dose (MED) is
defined as MED = \( \min\{i, j : p_{ij} - p_{io} > \delta\} \).

As the cumulative mortality increases over the time, and the efficacy with the increasing dose, it is desirable to give inference on the drug effect in a specific order, and failure to claim significance at any dose stops the inference on subsequent doses. The possible inference results of interest at time point \( i, i = 1, 2, \ldots, T \) are as follows:

\begin{align*}
\text{Step 1 : } & p_{iK} \leq p_{i0} + \delta \\
\text{Step 2 : } & p_{i(K-1)} \leq p_{i0} + \delta < p_{iK} \\
& \quad \vdots \\
\text{Step 1 : } & p_{il} \leq p_{i0} + \delta < p_{ij} \quad \text{for all } j, l < j \leq K \\
& \quad \vdots \\
\text{Step K : } & p_{i1} \leq p_{i0} + \delta < p_{ij} \quad \text{for all } j, 1 < j \leq K
\end{align*}

(1.1)

In other words, the possible inference results of interest in (1.1) can be written as follows:

\begin{itemize}
    \item Step 1 : Dose \( K \) at time \( i \) is not efficacious
    \item Step 2 : Dose \( K \) is efficacious at time \( i \) but dose \( K - 1 \) is not efficacious
    \item \quad \vdots
    \item Step 1 : Dose \( l + 1, \ldots, K \) are efficacious at time \( i \) but dose \( l \) is not efficacious
    \item \quad \vdots
    \item Step K : Doses \( 2, \ldots, K \) are efficacious at time \( i \) but dose 1 is not efficacious.
\end{itemize}

(1.2)

So, we are interested in finding the smallest \( L \) and \( M \) such that \( p_{ij} - p_{io} > \delta \) for all \( i \geq L \) and \( j \geq M \) simultaneously to infer on the MED of a drug.
1.2.2 Example 2

The prevalence of chemical substances in the environments is increasing over time and it is estimated that about 3% to 28% of all chemical substances are neurotoxicants (OTA, 1990). The increasing number of people, especially workers, are exposed to these chemical, resulting in severe adverse effect on the nerve systems. Neurotoxic effects are, therefore, an important endpoint in environmental regulations (USEPA, 1998). There are an increasing scientific and regulatory interest in testing and quantifying neurotoxic impact on human health. In order to see the effect of these neurotoxic substances in the environment, neurobehavioral screenings are conducted by using a functional observational battery (FOB) test. This functional observational battery test generates the longitudinal dose response data.

Consider the longitudinal dose response data from Zhu (2005) in Table 1.2. This dataset is about the hindlimb grip strengths of rats. Hindlimb grip strength is a continuous variable that is assumed to follow normal distribution with constant variance across time and dose. This data was collected through an experiment called FOB (Functional Observational Battery) test. In FOB test, TET (Triethyl Tin), a highly neurotoxic agent in human and animals producing severe brain edema, was administered on ten Long-Evans rats. The dose levels of TEF are as follows: 0, 0.75, 1.5, 3, and 6 mg/kg.

Table 1.2: Mean(S.E) of the variable-hindlimp grip strength of rats exposed to the dose of triethyl tin (TET)

<table>
<thead>
<tr>
<th>Time(h)</th>
<th>0(control)</th>
<th>0.75</th>
<th>1.5</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.9140(0.1596)</td>
<td>0.9660(0.1314)</td>
<td>0.8645(0.1330)</td>
<td>0.7680(0.1772)</td>
<td>0.8580(0.1791)</td>
</tr>
<tr>
<td>2</td>
<td>1.0030(0.2383)</td>
<td>0.8030(0.2067)</td>
<td>0.6283(0.1700)</td>
<td>0.4930(0.1090)</td>
<td>0.4580(0.1105)</td>
</tr>
<tr>
<td>24</td>
<td>0.8495(0.1743)</td>
<td>0.8015(0.1310)</td>
<td>0.6185(0.1672)</td>
<td>0.5285(0.0907)</td>
<td>0.4360(0.0829)</td>
</tr>
<tr>
<td>168</td>
<td>0.8950(0.2114)</td>
<td>0.8605(0.1083)</td>
<td>0.7515(0.1572)</td>
<td>0.7960(0.2204)</td>
<td>0.4689(0.1855)*</td>
</tr>
</tbody>
</table>

Note 1: Ten rats per dose group, each measured at four time points.
Note 2: * One rat died, resulting in loss of one observation.
Due to the longitudinal aspect of the data, the statistical procedures developed by Tamhane and Dunnett (1999); Hsu and Berger (1999) are not appropriate to find the maximum safe dose of these neurotoxic substances in the environment. This problem motivates us to develop statistical procedures to identify the maximum safe dose of a drug when the responses are observed over a sequence of time at increasing dose levels.

1.3 Multiple Comparison Problems

In this dissertation, our objective is to determine the minimum effective dose (MED) and the maximum tolerated dose (MTD) of a drug along with the time effect on the response variable. We need to use an appropriate simultaneous inference on the difference of the treatment effects in time-wise and treatment-wise. In the process of identifying the MED and the MTD, a zero dose of a drug is included as a control against higher doses, this leads to the multiple comparisons. For the notations used in Section 1.1, consider a simple hypothesis:

\[ H_{ij}^0 : p_{ij} - p_{i0} \leq \delta \quad \text{versus} \quad H_{ij}^1 : p_{ij} - p_{i0} > \delta, \ i = 1, 2, \ldots, T, j = 1, 2, \ldots, K. \]

For each hypothesis test, let the Type I error rate be \( \alpha \), which is the probability of any ineffective dose being declared effective. Then, the probability of making one or more than one Type I error among any set of true null hypotheses, which is called family wise error rate (FWER), must be less than \( \alpha \). Therefore, we need to address this problem in order to control FWER within prespecified significance level \( \alpha \). Corresponding to each of the above hypothesis tests, there is a \((1 - \alpha)\) level one-sided confidence interval for each of the treatment effect difference consisting of the set of \( \delta \)-values for which \( H_{ij}^0 \) is not rejected by the given test. Thus, for the above test we have a lower one-sided \((1 - \alpha)\) level confidence interval for the treatment effect difference \( p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K. \)

Since there are \( K \) treatment effect differences at a time point in which for each one, a one-sided confidence interval \( C_i(X), i = 1, 2, \ldots, K \) has coverage probability \((1-\alpha)\)%. Then the probability that they all cover their respective parameters is less than \((1 - \alpha)\)%. If the effect differences are of
primary interest, and the objective is to infer on all effect differences simultaneously, controlling
the pre-specified confidence level $1 - \alpha$ is an important issue in simultaneous confidence interval
estimation procedure.

In order to make sure that all simultaneous inferences on the treatment effect differences are
correct with a probability of $1 - \alpha$, we need to adjust for multiplicity. It means that for each
confidence interval with a probability $1 - \alpha$, all inferences that are simultaneously correct have the
probability of at least $1 - \alpha$. The simultaneous inference of the interest in Section 1.2 need not
multiplicity adjustment to control family wise error rate (FWER) because possible inferences are
disjoint. In other words, only one inference can be true.

In this dissertation, in order to find the MED and the MTD of a drug when the responses are are
recorded over a sequence of time at different dose levels, we propose three simultaneous confidence
interval based procedures by using a fundamental approach called partitioning principle. Two of
them need not multiplicity adjustment to control the family wise error rate, but the remaining one
uses Bonferroni adjustment to control the family-wise error rate. Bonferroni method for confidence
interval is introduced in the next section.

1.4 Bonferroni Correction Method

Let $C_{ij}$ be a $100(1 - \alpha)\%$ one-sided lower confidence interval for the parameters- treatment
effect difference $\theta_{ij} = \{ p_{ij} - p_{i0} \}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. Then we want $\Pr(\theta_{ij} \in C_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K) \geq 1 - \alpha$. In order to maintain the overall confidence level $1 - \alpha$ in
simultaneous confidence inference on the parameters of $\theta_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$, we
apply the Bonferroni adjustment. The idea of Bonferroni adjustment is as follows:

Let $P$ be the probability function and $A_{i1}, A_{i2}, \ldots, A_{iK}$ be a sequence of events at time $i, i = 1, 2, \ldots, T$. Then we have by using the De-Morgan’s law

$$P(A_{i1} \cup A_{i2} \cup \cdots \cup A_{iK}) = 1 - P(A'_{i1} \cap A'_{i2} \cap \cdots \cap A'_{iK}).$$  \hspace{1cm} (1.3)
Using Bonferroni inequality, it follows from (1.1) that

\[ P(A_{i1} \cup A_{i2} \cup \cdots \cup A_{iK}) \geq 1 - \sum_{l=1}^{K} P(A'_{il}). \]  

(1.4)

Suppose that \( P(\theta_{ij} \in C_{ij}) = 1 - \alpha \). Let \( A_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K \) be the event that \( \theta_{ij} \in C_{ij} \). Then from Bonferroni inequality (1.2), we have at time \( i \)

\[ P(\theta_{i1} \in C_{i1}, \theta_{i2} \in C_{i2}, \ldots, \theta_{iK} \in C_{iK}) \geq 1 - \sum_{l=1}^{K} P(\theta_{il} \notin C_{il}) \geq 1 - \sum_{l=1}^{K} \alpha = 1 - K\alpha. \]

Note that the simultaneous confidence level is \( \geq 1 - K\alpha \), which is smaller than \( 1 - \alpha \) because \( m \geq 1 \). In order to have a simultaneous confidence level \( 1 - \alpha \), we need to adjust the confidence level for each of lower confidence interval for the parameter \( \theta_{ij} \). Therefore, the confidence level for each confidence interval for parameter \( \theta_{ij} \) is \( 1 - \frac{\alpha}{K} \).

1.5 Stepwise Inference

In some dose-response studies, it is believed that the higher dose has the higher efficacy than the lower dose. So, one might start with the high dose and proceed to infer on the low dose if the high dose shows efficacy. Similarly, in toxicity studies, it is generally assumed that the adverse effect (toxicity) increases with the doses. Therefore, the low amount of safety endpoint is expected at the higher concentration of toxic compound. This leads to make inference on the doses by testing the lowest one and proceeds to infer on the higher dose if the lower doses are safe. These situations motivate to develop the stepwise procedure. The stepwise procedure tests the hypothesis in a specific order. The decision on any hypothesis in the order affect the remaining hypotheses in the order. There are two types of procedures in stepwise inference: Step-down and step-up procedure. In step-down approach, the hypotheses are tested starting with the most significant one and testing continues until a hypothesis is not rejected(accepted), at which the remaining hypotheses are not needed to be tested and accepted by implication. On the other hand, a step-up procedure starts
with the least significant one and continues testing until a hypothesis is rejected at which point the remaining hypotheses are rejected without actually testing them. It is desirable for a method to not declare a lower dose to be efficacious if it does not declare a higher dose to be efficacious. For this purpose, Hsu and Berger (1999) and Tao et al. (2002) proposed a stepwise confidence interval procedure. In the following section, we discuss the partitioning principle.

1.5.1 Partitioning Principle

The idea of Partitioning principle is to divide the entire parameter space into non-empty disjoint sets such that the union of the all disjoint sets equals to the entire parameter space. More specifically, consider, for example, \( \Theta \) is a parameter space and \( C = \{C_1, C_2, \ldots, C_n\} \) is a partition of \( \Theta \), where \( C_i \cap C_j = \emptyset, i, j = 1, 2, \ldots, n \), and \( \bigcup_{i=1}^{n} C_i = \Theta \).

Finner and Strassburger (2002) formally introduced the partitioning principle in the hypothesis testing problems. In the partitioning principle, the parameter space is partitioned into several disjoint subsets and only one disjoint subset contains the true parameter of interest. If each partition is tested with a suitable test at level \( \alpha \), then the multiple test procedure strongly controls the family wise error rate at level \( \alpha \).

Hsu and Berger (1999), on the other hand, used partitioning principle to derive powerful simultaneous confidence intervals for estimating the minimum effective dose (MED). In addition, another important terminology, which is important in multiple comparisons, is the directed toward a set of parameter space introduced by Hsu and Berger (1999).

Suppose that the data \( X \) have a distribution with the parameter \( \theta \), where \( \theta \in \Theta \), and \( \Theta \) is the parameter space. A confidence set, \( C(X) \) for \( \theta \) is called the directed toward \( \Theta^* \), where \( \Theta^* \) is a subset of the parameter space \( \Theta \), if \( \Theta^* \subset C(X) \) or \( C(X) \subset \Theta^* \) for every sample point \( X \).

Now consider a dose-response study with longitudinal effect, where the control and the treatment groups are indexed as \( j = 0 \) and \( j = 1, 2, 3, \ldots, K \) respectively. Assume the dose levels are in increasing order. Let \( i = 1, 2, 3, \ldots, T \) be the time in increasing order at which the response of the dose is measured.

Let \( X_{ijl} \) be the dichotomous response of the \( l \)th subject in the \( i \)th time and \( j \)th dose with
Pr\((X_{ijl} = 1) = p_{ijl}\), where \(l = 1, 2, 3, \ldots, n_{ijl}\). Further, let \(\theta_{ij} = \{p_{ij} - p_{i0}\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\) be the vector of the difference of treatment effects. Since we are interested in \(\Theta_{ij}^c = \{\theta_{ij} > \delta\} = \{p_{ij} - p_{i0} > \delta\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\), where \(\delta > 0\), a clinically given threshold, the confidence interval \(C_{ij}(X)\) for \(\theta_{ij} = \{p_{ij} - p_{i0}\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\), which is directed toward \(\Theta_{ij}^c\), has the form \((L_{ij}(X), 1)\), where \(L_{ij}(X)\) is the lower limit of the confidence interval. If \(D_{ij}(X)\) is a 100\((1 - \alpha)\)% confidence set for \(\theta_{ij}\), then a 100\((1 - \alpha)\)% confidence set, which is directed toward \(\Theta_{ij}^c\), for \(\theta_{ij}\) is

\[
C_{ij}(X) = \begin{cases} 
D_{ij}(X), & \text{if } D_{ij}(X) \in \Theta_{ij}^c \\
D_{ij}(X) \cup \Theta_{ij}^c, & \text{otherwise} 
\end{cases}
\]

We derive a sequence of lower confidence intervals directed toward \(\Theta_{ij}^c\) for the parameter of \(\theta_{ij} = \{p_{ij} - p_{i0}\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\) and use the partitioning principle to develop three stepwise confidence interval procedures to find the MED of a drug when there is a longitudinal effect present. The lower confidence interval for the parameter of \(\theta_{ij} = \{p_{ij} - p_{i0}\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\) is constructed by using the idea given by Peskun (1993). The reason for choosing the Peskun’s idea of constructing lower confidence interval is that a good agreement of their coverage probability with nominal confidence level values, the shortest width of the confidence interval and the smallness of their sample sizes compared to other normal approximate confidence intervals for the parameter of effect differences. In addition, this confidence interval avoids the problem of aberrations. In other words, the confidence interval constructed by Peskun (1993) for the parameter \(\theta_{ij} = \{p_{ij} - p_{i0}\}, i = 1, 2, \ldots, T, j = 1, \ldots, K\) is within the range of \((-1, 1)\).

1.6 Confidence Interval for Effect Difference

With the notations given in Section 1.2, the total number of responses at time \(i\) and at dose \(0\) is \(X_{i0} = \sum_{l=1}^{n_{i0}} X_{i0l}\) and for dose \(j\) at time \(i\) \(X_{ij} = \sum_{l=1}^{n_{ij}} X_{ijl}\). Let \(X_{i0}\) and \(X_{ij}\), \(i = 1, 2, \ldots, T, j = 1, 2 \ldots, K\) be two statistically independent binomial random variables with parameters \(n_{i0}, p_{i0}\)
and $n_{ij}, p_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. Let $T_{ij} = t(X_{ij}, X_{i0}) = \frac{X_{ij}}{n_{ij}} - \frac{X_{i0}}{n_{i0}}$ be the unbiased maximum likelihood estimator for the unknown effect difference $p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. If $t_{ij}$ is an observed value of $T_{ij}$, a one-sided exact lower $100(1 - \alpha)$% confidence interval for $p_{ij} - p_{i0}$ is given by

$$L_{ij} = \inf_{0 \leq p_{i0}, p_{ij} \leq 1} \{ p_{ij} - p_{i0} \mid \Pr[T_{ij} \geq t_{ij}, n_{i0}, p_{i0}, n_{ij}, p_{ij}] \geq 1 - \alpha \}. \quad (1.5)$$

For sufficiently large $n_{i0}$ and $n_{ij}, j = 1, 2, \ldots, K$, $T_{ij} = \frac{X_{ij}}{n_{ij}} - \frac{X_{i0}}{n_{i0}}$ is approximately normally distributed with mean $p_{ij} - p_{i0}$ and variance $\frac{p_{ij}(1-p_{ij})}{n_{ij}} + \frac{p_{i0}(1-p_{i0})}{n_{i0}}$. The probability $\Pr(T_{ij} \geq t_{ij})$ in (1.5) can be calculated approximately as follows:

$$\Pr(T_{ij} \geq t_{ij}) = \Pr \left[ Z \geq \frac{t_{ij} - (p_{ij} - p_{i0})}{\sqrt{\frac{p_{i0}(1-p_{i0})}{n_{i0}} + \frac{p_{ij}(1-p_{ij})}{n_{ij}}} \geq \frac{t_{ij} - (p_{ij} - p_{i0})}{\sqrt{\frac{p_{i0}(1-p_{i0})}{n_{i0}} + \frac{p_{ij}(1-p_{ij})}{n_{ij}}}} \right] \approx \Pr \left[ Z \geq \frac{t_{ij} - a_{ij} - (p_{ij} - p_{i0})}{\sqrt{\frac{p_{i0}(1-p_{i0})}{n_{i0}} + \frac{p_{ij}(1-p_{ij})}{n_{ij}}}} \right]. \quad (1.6)$$

Here $Z$ is the standard normal variable and $a_{ij} = a_{ij}(x_{ij}, n_{ij}, x_{i0}, n_{i0})$ is a continuity correction equal to half the absolute difference between the sample value $t_{ij} = \frac{x_{ij}}{n_{ij}} - \frac{x_{i0}}{n_{i0}}$ and the next smaller possible of $T_{ij}$.

It follows from (1.5) and (1.6) that

$$L_{ij} = \min_{0 \leq p_{i0}, p_{ij} \leq 1} \left\{ p_{ij} - p_{i0} \left[ t_{ij} - a_{ij} - (p_{ij} - p_{i0}) \right] \div \left[ \frac{p_{i0}(1-p_{i0})}{n_{i0}} + \frac{p_{ij}(1-p_{ij})}{n_{ij}} \right]^{\frac{1}{2}} = z_{1-\alpha} \right\}. \quad (1.7)$$

By minimizing $p_{ij} - p_{i0}$ under the restriction that

$$\left[ t_{ij} - a_{ij} - (p_{ij} - p_{i0}) \right] \div \left[ \frac{p_{i0}(1-p_{i0})}{n_{i0}} + \frac{p_{ij}(1-p_{ij})}{n_{ij}} \right]^{\frac{1}{2}} = z_{1-\alpha}, \quad (1.8)$$
we have \( p_{ij} \) and \( p_{i0} \) with the condition

\[
n_{ij}p_{ij} + n_{i0}p_{i0} = \left( n_{ij} + n_{i0} \right)/2 = n/2. \tag{1.9}
\]

Now letting \( p_{ij} - p_{i0} = d \), it follows from the equation (1.8) and (1.9) that

\[
(t_{ij} - a_{ij} - d) \div (n/4n_{ij}n_{i0} - d^2/n)^{1/2} = z_{1-\alpha}.
\tag{1.10}
\]

A 100(1 - \( \alpha \))% lower confidence limit for the unknown effect difference \( p_{ij} - p_{i0} \) is the smaller solution of the quadratic equation (1.10) is

\[
L_{ij} = \frac{t_{ij} - a_{ij} - z\alpha \sqrt{n_{ij} + n_{i0} + z^2}}{4n_{ij}n_{i0}} - \frac{(t_{ij} - a_{ij})^2}{n_{ij} + n_{i0}} \left(1 + \frac{z^2}{n_{ij} + n_{i0}}\right),
\tag{1.11}
\]

where \( t_{ij} = \frac{x_{ij}}{n_{ij}} - \frac{x_{i0}}{n_{i0}} = \hat{p}_{ij} - \hat{p}_{i0}, \ i = 1, 2, \ldots, T, \ j = 1, 2, \ldots, K, \) and \( z_\alpha \) is the upper percentage point of the standard normal distribution with \( z_\alpha = -z_{1-\alpha}. \)

In what follows in this dissertation, Chapter 2 describes three new procedures to find the MED along with three theorems related to these procedures that show the correct coverage probability for the simultaneous confidence intervals for the parameters of interest. In Chapter 3, we propose procedures for determining the maximum tolerated dose with the longitudinal effect. Chapter 4 investigates the power properties of the proposed procedures through stimulation studies. In Chapter 5, we use our procedures to find the MED and the MTD by using the real datasets. Chapter 6 concludes with some final remarks, including a discussion of the assumptions. In the appendix, some selected R-codes are presented.
CHAPTER 2  STEPWISE PROCEDURES FOR MINIMUM EFFECTIVE DOSE

2.1 Introduction

The problem of identifying the minimum effective dose of a drug in the dose-response study designed in Chapter 1 induces multiple comparison procedures. In such a problem, we want to guarantee that the family wise error rate which is the probability of declaring a dose as efficacious when it is in fact not statistically significant from the control, is no more than a pre-specified level $\alpha$.

In order to determine the minimum effective dose (MED) of a drug when the responses are binary and are observed in a sequence of time across at increasing dose levels, we extend the procedures given by Hsu and Berger (1999) in the next section. In their methods, MED is identified by generating confidence sets for the parameter of interest in a step-down fashion, stopping when the treatment effect is statistically insignificant by using the partitioning principle when the responses are continuous and are measured at a single time point. With the partitioning principle, the parameter space is partitioned into several disjoint sets based on the hypothesis and only one partition contains the true parameter. This approach controls the family wise error rate.

In addition to the stepwise confidence interval procedures for finding the MED, we propose a method that integrates Bonferroni correction to find the MED. The Bonferroni correction method adjusts the confidence level for each confidence interval for parameter which is the effect difference of a dose and control. But Bonferroni correction method is usually too conservation.

In the following section, we present our proposed procedures for determining the MED using the step-down confidence interval procedures proposed by Hsu and Berger (1999) and integrating Bonferroni Correction when the responses are binary outcomes and are observed over time. For individual confidence intervals, consider an approximate $(1 - \alpha)$ one-sided lower bound given by Peskun (1993) and discussed in Section 1.6 for the effect difference of treatment $p_{ij} - p_{i0}$ at time $i, i = 1, 2, \ldots, T$. 
2.2 Partition of Vectorized Space

Since we want to examine the maximal possible effect over time before increasing the dose, let the effect difference of $K \times T$ treatments be $\theta_1, \ldots, \theta_{1T}, \theta_{2T}, \ldots, \theta_{KT}$ denoted as $\theta = \{\theta_1, \theta_2, \ldots, \theta_{KT}\}$. Let $C_l(X)$ be an individual 100 * (1 – $\alpha$)% confidence set for $\theta_l$, $l = 1, 2, \ldots, K \times T$.

We construct the simultaneous confidence sets for $\theta$ in a stepwise way as follows. First, we screen from $K \times T$ to 1 and stop at the first time $M$ when $C_M(X) \not\subset \Theta_M^c$ for a set of data $X$. Since $C_M(X)$ is a lower confidence interval, and $\Theta_M^c$ is a one-sided set, $p_{ij} - p_{i0} \in C_M(X)$ if $C_M(X) \not\subset \Theta_M^c$, then $\Theta_M^c \subset C_M(X)$.

Now, the individual lower confidence interval for $p_{ij} - p_{i0}$ at time $i$, $i = 1, 2, \ldots, T$, is

$$C_{ij} = \left(\frac{\hat{p}_{ij} - \hat{p}_{i0} - a_{ij} - z_\alpha \sqrt{\frac{n_{ij} + n_{i0} + z^2_\alpha}{4n_{ij}n_{i0}}}}{\left(1 + \frac{z^2_\alpha}{n_{ij} + n_{i0}}\right)}^2, 1\right),$$

where $Z_\alpha$ is the value satisfying $P(Z \geq z_\alpha) = \alpha$, and $a_{ij} = a_{ij}(x_{ij}, n_{ij}, x_{i0}, n_{i0})$ is a continuity correction equal to half the absolute difference between the sample value $\hat{p}_{ij} - \hat{p}_{i0}$ and the next smaller possible value of $p_{ij} - p_{i0}$.

The simultaneous confidence procedures for $p_{ij} - p_{i0}$, $i = 1, 2, \ldots, T$, $j = 1, 2, \ldots, K$ are constructed with the following steps:

1. Compute the individual lower confidence bounds $C_j(X)$, $j = 1, 2, \ldots, T \times K$.

2. Start at $T \times K$ to search for the largest integer $M$ (if such a $M$ exists) such that $C_j(X) \not\subset \Theta_j^c$, $j = 1, 2, \ldots, T \times K$.

   For two extreme cases, if $(\delta, 1) \subset C_{TK}(X)$, then no dose is effective, that is, no MED can be identified; if $C_1(X) \subset (\delta, 1)$, then all doses are effective.

3. Continue the process described in Step 2 to find the MED. Once $M$ is determined, the time $i$th and dose $j$th position are determined correspondingly.
The above procedure can be illustrated as follows:

Step 1  If \( C_{T*K}(X) \subset \Theta^c_{T*K} \), then assert \( \theta_{T*K} \in \Theta^c_{T*K} \) and go to Step 2; else assert \( \theta_{T*K} \in C_{T*K}(X) \), claim that no dose is efficacious and stop.

Step 2  If \( C_{T*K-1}(X) \subset \Theta^c_{T*K-1} \), then assert \( \theta_{T*K-1} \in \Theta^c_{T*K-1} \) and go to Step 3; else assert \( \theta_{T*K-1} \in C_{T*K-1}(X) \), claim that MED=\( T^*K \) and stop.

\vdots

Step k  If \( C_{1}(X) \subset \Theta^c_{1} \), then assert \( \theta_{1} \in \Theta^c_{1} \) and go to Step \( K+1 \); else assert \( \theta_{1} \in C_{1}(X) \), claim that MED=2 and stop.

Step \( K+1 \)  assert all doses are efficacious, claim MED=1.

The following theorem shows that the above procedure to find the MED has the correct coverage probability \( 1 - \alpha \) for the simultaneous confidence set:

**Theorem 2.1.** Let \( X \) be the observed data, and let \( \Theta \) be the parameter space for the parameter vector \( \theta = (\theta_{11}, \theta_{12}, \ldots, \theta_{1K}, \ldots, \theta_{T1}, \theta_{T2}, \ldots, \theta_{T*K})' \). Further, let the vector of effect difference of \( T^*K \) treatments \( (\theta_{11}, \theta_{12}, \ldots, \theta_{1K}, \ldots, \theta_{T1}, \theta_{T2}, \ldots, \theta_{T*K})' \) be denoted as \( (\theta_{1}, \theta_{2}, \ldots, \theta_{T*K}) \).

Suppose the stepwise procedure stops at step \( M(1 \leq M \leq T^*K + 1) \), that is, \( M \) is the largest integer \( j \) such that \( C_{j}(X) \not\subset \Theta^c_{j} \), and \( C_{j}(X) \) is a \( 100(1 - \alpha)\% \) lower confidence interval for \( \theta_{j}, j = 1, 2, \ldots, T^*K \). Then, for all \( \theta \in \Theta \), we have

\[
\Pr(\theta \in \Theta^c_{T*K} \ldots \Theta^c_{M-1}C_{M}(X)) \geq 1 - \alpha.
\]

**Proof.** Denote \( \Theta^c_{i} = \{ \theta_{i} > \delta \} \) and \( \Theta_{i} = \{ \theta_{i} \leq \delta \}, i = 0, 1, 2, \ldots, T^*K \).

Now partition the parameter space as follows:
It is clear that \( \Theta = \bigcup_{l=0}^{T*K} \Theta_l \). Let \( C(X) = \bigcup_{l=0}^{T*K} C_l(X) \Theta_l^* \).

Note that \( \bigcup_{l=0}^{T*K} \Theta_l^* C_l(X) \) is a 100(1 - \( \alpha \))% confidence set for \( \theta \). This is because if \( \theta \in \Theta_l^* \), then
\[
\Pr(\theta \in \bigcup_{l=0}^{T*K} \Theta_l^* C_l(X)) = \Pr(\theta \in \Theta_l^* C_l(X)) = \Pr(\theta \in C_l(X)) \geq 1 - \alpha.
\]

Now, since \( M \) is the largest integer \( l \) such that \( C_l(X) \not\subseteq \Theta_l^* \), \( l = 1, 2, \ldots, T*K \), for \( M + 1 < l < T*K \),
\[
\bigcup_{l=M+1}^{T*K} \Theta_l^{c*} \Theta_l^{c*} \Theta_{l+1}^{c*} \cdots \Theta_{T*K}^{c*} C_l(X) = \emptyset \text{ because } C_l(X) \Theta_l = \emptyset.
\]

So, we have
\[
C(X) = \bigcup_{l=0}^{T+K} C_l(X) \Theta^*_l
\]

\[
= \bigcup_{l=0}^{M-1} \bigcup_{l=M}^{M+1} C_l(X) \Theta^*_l
\]

\[
= \bigcup_{l=0}^{M-1} C_l(X) \Theta^*_l
\]

\[
= (C_M(X) \Theta^*_M)^{M-1}_{l=0} \bigcup_{l=0}^{M-1} C_l(X) \Theta^*_l
\]

\[
= (\Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M+1} C_M(X)) \bigcup_{l=0}^{M-1} (\bigcup_{l=0}^{M-1} C_l(X) \Theta^*_l)
\]

\[
\subset (\Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M+1} C_M(X)) \bigcup (\Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M})
\]

\[
= \Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M-1}
\]

This is because \( \bigcup_{l=0}^{M-1} (\Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{l+1} \Theta_l C_l(X)) \subset \Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_M \)

and \((C_M(X) \Theta^*_M) \bigcup (C_M(X) \Theta^c_M) = (C_M(X) \Theta^*_M) \bigcup \Theta^c_M = C_M(X) \) since \( \Theta^*_M \subset C_M(X) \).

Thus

\[
C(X) = \bigcup_{l=0}^{T+K} C_l(X) \Theta^*_l
\]

\[
\subset \Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M-1} C_M(X)
\]

Now for all \( \theta \in \Theta \) we have

\[
\Pr(\theta \in \Theta^c_{T+K} \Theta^c_{T+K-1} \ldots \Theta^c_{M-1} C_M(X)) \geq 1 - \alpha.
\]
2.3 Double Partition Method

In previous sets, the arrangement of $p_{ij} - p_{0j}$ into $\theta$ treats the time effect as the primary endpoint for the investigation of drug effect. In this section, instead of vectorizing the parameters of interest, we partition the parameter space based on time, followed by a partition of the dosages to find the MED. We consider the following procedure: (I) At each time point, we find 95% confidence set using partition method. (II) Then we screen from time $T$ to time 1 using the confidence set constructed and stop at the first time $L$ such that $C_{ij}(X) \not\subset \Theta_{ij}$ for all $j, j = 1, 2, \ldots, K$, with the same notations used in [1.2]. The lower confidence interval for $p_{ij} - p_{i0}$ at time $i, i = 1, 2, \ldots, T$ is calculated by using the equation given in [1.11].

The Double Partition Method to find the MED is as follows:

- **Step 1:** Find the lower confidence interval for $p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$.

- **Step 2:** Start with the highest dose $K$ at the highest time point $T$ to search for the largest integer $M$ such that $C_{TM}(X) \not\subset \Theta_{TM}$ in the following way:

  - If at the highest time point $T, C_{TK}(X) \not\subset (\delta, 1)$, then no dose is effective. No MED can be identified.

  - On the other hand, if there exists a dose $M$ so that $C_{Tj}(X) \subset (\delta, 1), j = M + 1, M + 2, \ldots, K$ and $C_{TM} \not\subset (\delta, 1), \text{then } (T, M + 1), (T, M + 2), \ldots (T, K)$ are effective, and $\theta_{TM} - \theta_{T0} \in C_{TM}(X)$.

  - If $C_{Tj}(X) \subset (\delta, 1), j = 1, 2, \ldots, K$, move to examine the time point $T - 1$.

- **Step 3:** Continue the process described in Step 2 in order to find the MED. If at the lowest time 1, $C_{1j}(X) \not\subset (\delta, 1)$ for all $j = 1, 2, \ldots, K$, then MED is at time 2 and Dose 1. By Applying the above procedure, if the largest time $L$ and the largest treatment $M$ are found such that $C_{ij}(X) \not\subset \Theta_{ij}^c$ for all $i = 1, 2, \ldots, L, j = 1, 2, \ldots, M$, then MED = $(L+1, M+1)$. It renders the lower time and doses are unnecessary to be computed.
The following theorem guarantees the correct confidence level for the above simultaneous confidence procedures being at least $1 - \alpha$ for $p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$ using partition principle in time-wise and treatment-wise.

**Theorem 2.2.** Let $X$ be the observed data, and $\Theta$ be the parameter space for the parameter vector $\theta$. Suppose that $C_{ij}(X)$ is a $100(1 - \alpha)\%$ lower confidence interval for $\theta_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. Let $(L, M)$ be the dose-time combination that satisfies the following condition: $M$ is the largest integer $j$ such that $C_{ij}(X) \not\subset \Theta_{ij}^c$ and $L$ is the largest integer $i$ such that $C_{iM}(X) \not\subset \Theta_{iM}^c$, where $\{\Theta_{ij}^c = \theta_{ij} > \delta\}$, and $\{\Theta_{ij} = \theta_{ij} \leq \delta\}$. Further, let $\Delta_i$ be defined as $\Theta_{ij} \in \bigcup_{j=1}^{K} \Theta_{ij}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. That is, $\Delta_i$ means at least one treatment effect is insignificant at time $i, i = 1, 2, \ldots, T$. All effects with time longer than $L$ are significant, at time $L$, all doses longer than $M$ are significant. At $(L, M)$ the treatment effect is bounded by $C_{LM}(X)$. Then, for all $\theta \in \Theta$,

$$\Pr(\theta \in \Delta_T^c \theta_{L+1}^c \Theta_{LM}^c) \geq 1 - \alpha.$$  

**Proof.** Consider the following partition of the parameter space $\Theta$ in time-wise:

$$\Delta_T^* = \Delta_T$$

$$\Delta_{T-1}^* = \Delta_T^c \Delta_{T-1}$$

$$\vdots$$

$$\Delta_1^* = \Delta_T^c \Delta_{T-1}^c \cdots \Delta_2^c \Delta_1$$

$$\Delta_0^* = \Delta_T^c \Delta_{T-1}^c \cdots \Delta_1^c \Delta_0.$$
Now consider the following partition of the parameter space $\Theta$ in dose-wise for a given time $i$, 

$$
\tau_{i*K}^s = \Theta_{i*K}
$$

$$
\tau_{i*K-1}^s = \Theta_{i*K}^c \Theta_{i*K-1}^c
$$

$$
\vdots
$$

$$
\tau_{i*1}^s = \Theta_{i*K}^c \Theta_{i*K-1}^c \cdots \Theta_{i*2}^c \Theta_{i*1}.
$$

Then, $\bigcup_{i=0}^T \bigcup_{j=1}^K \Delta_i^* \tau_{ij}^* C_{ij}(X)$ is a $100(1 - \alpha)$% confidence set for $\theta$ because

$$
\Pr(\theta \in \bigcup_{i=0}^T \bigcup_{j=1}^K \Delta_i^* \tau_{ij}^* C_{ij}(X)) = \Pr(\theta \in \Delta_i^* \tau_{ij}^* C_{ij}) = \Pr(\theta \in C_{ij}(X)) \geq 1 - \alpha.
$$

Let $C_i^*(X) = \Theta_{iK}^c \Theta_{iK-1}^c \cdots \Theta_{iM+1}^c C_{iM}(X)$, where $M$ is the largest $j$ integer such that $C_{ij}(X) \not\subset \Theta_{ij}^c$ at time $i$.

Now

$$
\bigcup_{j=1}^K \Delta_i^* \tau_{ij}^* C_{ij}(X)
$$

$$
= \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^K \tau_{ij}^* C_{ij}(X) \right)
$$

$$
= \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^K \bigcup_{j=M+1}^K \tau_{ij}^* C_{ij}(X) \right)
$$

Here,

$$
\bigcup_{j=M+1}^K \tau_{ij}^* C_{ij}(X)
$$

$$
= \bigcup_{j=M+1}^K \Theta_{iK}^c \Theta_{iK-1}^c \cdots \Theta_{iM+1}^c \Theta_{ij} C_{ij}(X)
$$

$$
= \emptyset.
$$
This is because \( M \) is the largest \( j \) integer such that \( C_{ij}(X) \not\subset \Theta_{ij}^c \) and for \( M + 1 \leq j \leq K \), \( C_{ij}(X) \subset \Theta_{ij}^c \) for fixed \( i \), thus \( C_{ij}(X) \cap \Theta_{ij}^c = \emptyset \).

We have now

\[
\bigcup_{j=1}^{K} \Delta_i^* \tau_{ij}^* C_{ij}(X)
\]

\[
= \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{K} \tau_{ij}^* C_{ij}(X) \right)
\]

\[
= \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{K} \bigcup_{j=M+1}^{M-1} \tau_{ij}^* C_{ij}(X) \right)
\]

\[
= \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{M+1} \tau_{ij}^* C_{ij}(X) \right)
\]

\[
\subseteq \Delta_i^* \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{M+1} \bigcup_{j=M+1}^{M} \tau_{ij}^* C_{ij}(X) \right)
\]

\[
\subseteq \Delta_i^* \left( \bigcup_{j=1}^{M} \bigcup_{j=M}^{M+1} \bigcup_{j=M+1}^{M} \tau_{ij}^* C_{ij}(X) \right)
\]

\[
= \Delta_i^* \left( \bigcup_{j=1}^{M} \bigcup_{j=M}^{M+1} \bigcup_{j=M+1}^{M} \tau_{ij}^* C_{ij}(X) \right)
\]

This is because \( \Theta_{iM}^c \subset C_{iM}(X) \) and \( \Theta_{iM}^c C_{iM}(X) = \Theta_{iM}^c \). So \( \Theta_{iM}^c \cup (C_{iM}(X) \Theta_{iM}^c) = (\Theta_{iM}^c C_{iM}(X) \cup C_{iM}(X) \Theta_{iM}) = C_{iM}(X) \).

Now

\[
\bigcup_{i=1}^{T} \bigcup_{j=1}^{K} \Delta_i^* \tau_{ij}^* C_{ij}(X) \subseteq \bigcup_{i=1}^{T} \Delta_i^* \tau_{ij}^* C_{ij}(X)
\]

\[
= \bigcup_{i=1}^{T} \bigcup_{j=L}^{L+1} \bigcup_{i=L}^{T} \Delta_i^* \tau_{ij}^* C_{ij}(X)
\]
Here

\[
\bigcup_{i=L+1}^{T} \Delta_i^c C_i^*(X) = \bigcup_{i=L+1}^{T} \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{i+1}^c \Delta_i^c C_i^*(X) \\
= \emptyset,
\]

since for \( i = L + 1, L + 2, \ldots, T \), \( C_i^*(X) \subset \Delta_i^c \) and \( C_i^*(X) \cap \Delta_i = \emptyset \). It means that \( C_i^*(X) \) has no common point with \( \Delta_i \). Also,

\[
\bigcup_{i=1}^{L-1} \bigcup_{i=L}^{L} \Delta_i^c C_i^*(X) = (\Delta_L^c C_L^*) \cup \bigcup_{i=1}^{L-1} (C_i^*(X) \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{i+1}^c \Delta_i^c) \\
= (C_L^*(X) \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{L+1}^c \Delta_L^c) \cup \bigcup_{i=1}^{L-1} (C_i^*(X) \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{i+1}^c \Delta_i^c) \\
\subseteq ((C_L^*(X) \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{L+1}^c \Delta_L^c) \cup \Delta_T^c \Delta_{T-1}^c \cdots \Delta_{L+1}^c \Delta_L^c) \\
= C_L^*(X) \Delta_T^c \cdots \Delta_{L+1}^c.
\]

This is because \( \Delta_T^L \subset C_L^*(X) \) and \( \Delta_T^L C_L^*(X) = \Delta_L^c \). So \( \Delta_L^c \cup (C_L^*(X) \Delta_L) = (\Delta_L^c C_L^*(X) \cup C_L^* \Delta_L) = C_L^*(X) \).

Finally,

\[
\bigcup_{i=1}^{T} \bigcup_{j=1}^{K} \Delta_i^c \tau_{ij}^c C_{i,j}^*(X) \subseteq \bigcup_{i=1}^{T} \Delta_i^c C_i^*(X) \subseteq C_L^*(X) \Delta_T^c \cdots \Delta_{L+1}^c \\
= C_{LM}(X) \Theta_L^c \Theta_{LK\cdots}^c \Theta_{LM+1}^c \Delta_T^c \cdots \Delta_{L+1}^c.
\]

Therefore, \( \Pr(\theta \in C_{LM}(X) \Theta_L^c \Theta_{LK\cdots}^c \Theta_{LM+1}^c \Delta_T^c \cdots \Delta_{L+1}^c) \geq 1 - \alpha \).
The Double Partition procedure to find the MED can be presented as follows:

**Time T**

- **Step 1** If $C_{TK}(X) \subset \Theta_{TK}^{c}$, then assert $\theta_{TK} \in \Theta_{TK}^{c}$, and go to Step 2; else assert $\theta_{TK} \in C_{TK}$, claim no dose is efficacious and stop.

- **Step 2** If $C_{T(K-1)}(X) \subset \Theta_{T(K-1)}^{c}$, then assert $\theta_{T(K-1)} \in \Theta_{T(K-1)}^{c}$ and go to Step 3; else assert $\theta_{T(K-1)} \in C_{T(K-1)}$, claim MED= $K$ at time $T$ and stop.

- **Step K** If $C_{T1}(X) \subset \Theta_{T1}^{c}$, then assert $\theta_{T1} \in \Theta_{T1}^{c}$ and go to Time $T - 1$; else assert $\theta_{T1} \in C_{T1}$, claim MED= 2 at time $T$ and stop.

- (If all doses at time $T$ are efficacious, move to time $T - 1$)

**Time i**

- **Step 1** If $C_{iK}(X) \subset \Theta_{iK}^{c}$, then assert $\theta_{iK} \in \Theta_{iK}^{c}$ and go to Step 2; else assert $\theta_{iK} \in C_{iK}$, claim MED= 1 at time $i$ and stop.

- **Step 2** If $C_{i(K-1)}(X) \subset \Theta_{i(K-1)}^{c}$, then assert $\theta_{i(K-1)} \in \Theta_{i(K-1)}^{c}$ and go to Step 3; else assert $\theta_{i(K-1)} \in C_{i(K-1)}$, claim MED= $K$ at time $i$-1 and stop.

- **Step K** If $C_{i1}(X) \subset \Theta_{i1}^{c}$, then claim $\theta_{i1} \in \Theta_{i1}^{c}$ and go to Time $i - 1$; else assert $\theta_{i1} \in C_{i1}$, claim MED= 2 at time $i$ and stop.

- (...)

**Time 1**

- **Step 1** If $C_{1K}(X) \subset \Theta_{1K}^{c}$, then assert $\theta_{1K} \in \Theta_{1K}^{c}$ and go to Step 2; else assert $\theta_{1K} \in C_{1K}$, claim MED= 1 at time 2 and stop.

- **Step 2** If $C_{1(K-1)}(X) \subset \Theta_{1(K-1)}^{c}$, then assert $\theta_{1(K-1)} \in \Theta_{1(K-1)}^{c}$ and go to Step 3; else assert $\theta_{1(K-1)} \in C_{1(K-1)}$, claim MED= $K$ at time 1 and stop.

- **Step K** If $C_{11}(X) \subset \Theta_{11}^{c}$, then assert $\theta_{11} \in \Theta_{11}^{c}$, claim all doses are efficacious, MED= 1 at time 1, and stop.

2.4 Partition with Bonferroni Correction

The previous two procedures make inference for MED at individual dose taking into the time effect as the primary endpoint. However, it fails to address all dosages at a time point in one statement. For instance, at time $T$, if $\theta_{T(K-1)}$ is not significant, the procedure stops without claiming any conclusion on $\theta_{T(K-2)}$. In what follows, we propose a method that is able to draw a statement for all dosages at a given time point. Consider a partition method with Bonferroni correction procedure as follows: First, we find $100(1 - \frac{\alpha}{K})\%$ confidence set for all treatment effects at each time $i, i = 1, 2, \ldots, T$, where $K$ is the total number of treatment comparisons at time $i$. Then we screen from time $T$ to time 1 using the confidence set found before and stop at the first time $L$ such that
$C_{ij} \not\subset \Theta_{ij}$, for some $j \in \{1, 2, \ldots, K\}$ and $C_{ij} \in \Theta_{ij}^c, i = L + 1, \ldots, T, j = 1, 2, \ldots, K$. The lower confidence interval for $\theta_{ij} = p_{ij} - p_{i0}$ at time $i, i = 1, 2, \ldots, T$, is

$$C_{ij} = \left( \frac{\hat{p}_{ij} - \hat{p}_{i0} - a_{ij} - z_\alpha \sqrt{\frac{n_{ij} + n_{i0} + z^2/\sqrt{K}}{4n_{ij}n_{i0}} - \frac{(\hat{p}_{ij} - \hat{p}_{i0} - a_{ij})^2}{n_{ij} + n_{i0}}}}{1 + \frac{z^2}{n_{ij} + n_{i0}}}, 1 \right),$$

where $Z$ is the standard normal random variable with $p(Z \geq z_\alpha) = \frac{\alpha}{K}$, and $a_{ij}$ is the continuity correction as usual.

Now the simultaneous confidence procedures for $\theta_{ij} = p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$ are constructed in the following way:

1. Find the $1 - \frac{\alpha}{K}$ lower confidence interval for $\theta_{ij} = p_{ij} - p_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$ as stated above.

2. Start with the highest time point $T$ to find the smallest time point $L$ such that $C_{ij}(X) \subset \Theta_{ij}^c, i = L + 1, L + 2, \ldots, T$, and there exists $j \in \{1, 2, \ldots, K\}$ so that $C_{Lj}(X) \not\subset \Theta_{Lj}^c$.

If $C_{Tj}(X) \not\subset (\delta, 1), j = 1, 2, \ldots, K$ at the highest time point $T$, then no dose is effective. It means that no MED can be identified regardless of time effect. On the other hand, if $C_{Tj}(Y) \subset (\delta, 1)$, for all $j, j = 1, 2, \ldots, K$, then all doses at time $T$ are effective. Then go to the time point $T - 1$ and find the largest integer $M$ as before.

3. Continue the process described in Step 2 to find the MED. For example, if $C_{1j}(Y) \not\subset (\delta, 1)$ for all $j = 1, 2, \ldots, K$ at the lowest time 1, then MED is located at the time when $T = 2$.

The following theorem shows that the coverage probability of the stepwise simultaneous confidence procedure presented above is at least $1 - \alpha$.

**Theorem 2.3.** Let $X$ be the observed data, and $\Theta$ be the parameter space for the parameter vector $\theta$. Suppose that $C_{ij}(X)$ is a $(1 - \frac{\alpha}{K})100\%$ confidence interval for $\theta_{ij}$ toward $\Theta_{ij}^c$, where $i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$, and $T$ is the treatment time and $K$ is the number of dosages. Then Bonferroni method ensures that the following overall statement is at least $1 - \alpha$ for each time point $i, i = 1, 2, \ldots, T, \Pr(\theta_{ij} \in C_{ij}, j = 1, 2, \ldots, K) \geq 1 - \alpha.$
Now, let $C_i(X)$ be the vector of $(1 - \frac{\alpha}{K})100\%$ confidence interval for the difference of treatment effect at time $i$, $i = 1, 2, \ldots, T$, where $K$ is the number of dosages. That is, $C_i(X) = \{\theta_{ij} \in C_{ij}(X), j = 1, 2, \ldots K\}$ for each $i$.

Let $\Delta^c_i = \otimes_{j=1}^{K}(\delta, 1), i = 1, 2, \ldots T$. Let $L$ be the largest integer $i$ such that $C_{ij} \not\subset \Theta^c_{ij}, i = 1, 2, \ldots, T$, and for all $j, j = 1, 2, \ldots, K$.

Then, for all $\theta \in \Theta$,
\[ \Pr(\theta \in \Delta^c_T \Delta^c_{T-1} \ldots \Delta^c_{L+1}C_L(X)) \geq 1 - \alpha. \]

**Proof.** Now consider the partition of the parameter space for time effect:

\[
\begin{align*}
\Delta^*_{T} &= \Delta_{T} \\
\Delta^*_{T-1} &= \Delta^c_{T} \Delta_{T-1} \\
& \vdots \\
\Delta^*_{1} &= \Delta^c_{T} \Delta^c_{T-1} \ldots \Delta^c_{2} \Delta_{1} \\
\Delta^*_{0} &= \Delta^c_{T} \Delta^c_{T-1} \ldots \Delta^c_{2} \Delta^c_{1}
\end{align*}
\]

Note that $\bigcup_{i=0}^{T} \Delta^i_{i}C_i(X)$ is a $100(1 - \alpha)%$ confidence set for $\theta$. This is because if $\theta \in \Delta^*_i$, then
\[
\Pr(\theta \in \bigcup_{i=0}^{T} \Delta^i_{i}C_i(X)) = \Pr(\theta \in \Delta^i_{i}C_i(X)) = \Pr(\theta \in C_i(X)) \geq 1 - \alpha
\]

by Bonferroni adjustment.

Now,
\[
\bigcup_{i=0}^{T} \Delta^i_{i}C_i(X) = \bigcup_{i=0}^{L-1} \bigcup_{i=L}^{L} \bigcup_{i=L+1}^{T} \Delta^i_{i}C_i(X)
\]
Here

\[ \bigcup_{i=L+1}^{T} \Delta_i^c C_i(X) = \bigcup_{i=L+1}^{T} (\Delta_{T-1}^c \Delta_{T-2}^c \ldots \Delta_i^c \Delta_i) C_i(X) \]

\[ = \emptyset, \]

Since for \( i = L + 1, L + 2 \ldots T \), \( C_i(X) \subset \Delta_i^c \) and \( C_i(X) \cup \Delta_i = \emptyset \). It means that \( C_i(X) \) has no common point with \( \Delta_i \).

Now

\[ \bigcup_{i=0}^{L-1} \bigcup_{i=L}^{L} \Delta_i^c C_i(X) \]

\[ = (\Delta^*_L C_L) \bigcup \bigcup_{i=0}^{L-1} (\Delta_i^c C_i(X)) \]

\[ = (\Delta^*_T \Delta^*_T \ldots \Delta_{L+1}^c \Delta_L C_L(X)) \bigcup \bigcup_{i=0}^{L-1} (\Delta^*_T \Delta^*_T \ldots \Delta^*_T \Delta_i^c C_i(X)) \]

\[ \subseteq (\Delta_{T-1}^c \Delta_{T-2}^c \ldots \Delta_{L+1}^c \Delta_L C_L(X)) \bigcup \bigcup_{i=0}^{L-1} \bigcup (\Delta_{T-1}^c \Delta_{T-2}^c \ldots \Delta_{T-1}^c \Delta_L^c) \]

\[ = (\Delta_T^c \Delta_{T-1}^c \ldots \Delta_{L+1}^c C_L(X)), \]

This is because \( \Delta^*_L \subset C_L^c(X) \) and \( \Delta^*_L C_L(X) = \Delta^*_L \). So \( \Delta^*_L \cup (C_L(X) \Delta_L) = (\Delta^*_L C_L(X) \cup C_L(X) \Delta_L) = C_L(X) \).

Therefore, \( \Pr(\theta \in \Delta_T^c \Delta_{T-1}^c \ldots \Delta_{L+1}^c C_L(X)) \geq 1 - \alpha. \)

\( \square \)
The procedure corresponding to the above theorem is presented below:

Step 1: If \( C_{T_j}(X) \subset \Theta_{c_{T_j}} \) for all \( j \), then claim \( \theta_{T_j} \in \Theta_{c_{T_j}} \) for all \( j \) and go to Step 2;
else claim \( \theta_{T_j} \in C_{T_j} \) for some \( j \in \{1, 2, \cdots, K\} \), and stop.

Step 2: If \( C_{(T-1)j}(X) \subset \Theta_{c_{(T-1)j}} \) for all \( j \), then claim \( \theta_{(T-1)j} \in \Theta_{c_{(T-1)j}} \) for all \( j \) and go to Step 3;
else claim \( \theta_{(T-1)j} \in C_{(T-1)j} \) for some \( j \in \{1, 2, \cdots, K\} \), and stop.

\vdots

Step T: If \( C_{1j}(X) \subset \Theta_{c_{1j}} \) for all \( j \), then claim \( \theta_{1j} \in \Theta_{c_{1j}} \) for all \( j \) and all doses ar efficacious,
claim MED =1 at time 1, stop ;
else claim \( \theta_{1j} \in C_{1j} \) for some \( j \in \{1, 2, \cdots, K\} \), and stop.

2.5 Partition of Vectorized Space vs Double Partition Method

Among the three procedures, the Bonferroni method provides drug intervention of all dosages at time \( i \), but the first two obvious are more powerful than Bonferroni procedure. Now, we prove a proposition that shows that the first two procedures : "Partitioning Vectorized Space" and "Double Partition method" are equivalent, though the algorithms to find the MED are different in both methods.

**Proposition 2.4.** The MED detected by the method of Partitioning Vectorized Space is the same as the MED detected by the method of Double Partition . In this sense, the two procedures are equivalent, although they stop at the step without providing inference for following dosages.

**Proof.** If procedure 1 stops at time \( i_0 \), and dose \( j_0 \), then for time \( i > i_0 \), p-value \((i, j) < \alpha\) for all \( j = 1, 2, \ldots, K\); and for time \( i = i_0 \) \( p_{ij} < \alpha\) for dose \( j > j_0 \).

Now, putting the sample information in the Double Partition method, since we use time-wise before dose-wise partition, the procedure will stop at time \( i_0 \) in the first partition, and at dose \( j_0 \) in the second partition.

If the Double Partition method stops at \((i_0, j_0)\), then in the first partition on time, we have p-value \((i) < \alpha\) for all \( i > i_0 \).

For the second partition on dose, p-value \((i, j) < \alpha\) for all \( j > j_0 \).

Putting such information into procedure 1, we have p-value \((i, j) < \alpha\) for \( i > i_0, j = 1, 2, \ldots, K\) and p-value \((i_0, j) < \alpha\) for \( j > j_0 \).
Thus, the Partitioning Vectorized Space procedure stops at $(i_0, j_0)$. 
CHAPTER 3  STEPWISE PROCEDURES FOR MAXIMUM TOLERATED DOSE

3.1 Identifying the Maximum Tolerated Dose

In Chapter 2, we proposed three procedures for MED of a drug when the responses are dichotomous and are measured over a sequence of time at increasing dose levels. Although in many clinical trials, the data arising from the safety and efficacy study have binary form like each experimental subject is classified as death or alive, or patient is classified as cured or uncured, the experimental subjects are observed over a sequence of times at each dose level and continuous endpoints (responses) are measured. The procedures developed in Chapter 2 are concerned with finding the minimum effective dose of a drug in a dose-time-response study with the binary data.

However, drug safety is one of the important concerns in drug development process. The safety of a drug or a toxic substance is needed to be evaluated by conducting an extensive battery of tests. In order to assess the safety of a drug or a toxic chemical, a functional observational battery test over a period of time is conducted in a dose-response study. The results found through the functional observational study are longitudinal dose response data. In Section 1.2, the second motivating example is a typical longitudinal dose response data with continuous response variable. Tamhane et al. (2011) used multiple test procedures in order to identify the maximum tolerated dose (MTD) of a drug when the response is a continuous variable and is measured at a particular time point. In Chapter 3, we develop procedures to find the Maximum Tolerated Dose (MTD) of a drug or a toxic substance when the responses are continuous variables and are measured over a sequence of times at increasing dose levels.

Let us consider a set of increasing dose levels $0, 1, \ldots, K$. The dose level 0 is the control dose. At each dose level $j, j = 1, 2, \ldots, K$, the subjects are assessed over a sequence of time period $i = 1, 2, \ldots, T$. Suppose that the response variable is continuous. The model that generates the longitudinal dose-response data is assumed to be

$$y_{ijl} = \mu_{ij} + \varepsilon_{ijl},$$
where \( y_{ijl} \) is the observed data at time point \( i, i = 1, 2, \ldots, T \) and at dose \( j, j = 0, 1, 2, \ldots, K \); \( n_j \) are the experimental units tested at the \( j \)th dose with \( l = 1, 2, \ldots, n_j \), and are observed at all time points. The \( \mu_{ij} \) is the mean adverse effect at the \( i \)th time and \( j \)th dose, and \( \varepsilon_{ijl} \) are i.i.d. normal with mean 0 and variance \( \sigma_i^2 \).

Assume that toxicity increases as the doses and time increase. Further, suppose that a low amount of a safety endpoint \( \mu_{ij} \) implies more toxicity. Therefore, the adverse effect of the drug \( \mu_{ij} \) is decreasing when dosage and time increase. Thus, a drug is safe at dose \( j \) and time \( i \) if \( \mu_{ij} - \mu_{0j} > -\delta \) for all \( i \leq L \) and \( j \leq M \), where \( \delta \) is a clinically given positive threshold. The threshold \( \delta \) can be determined by the experts or the knowledge of the previous studies. From the definition of safe dose, it is clear that all doses less than \( M - 1 \) at all time points less than \( L - 1 \) have statistically insignificant adverse effect by a pre-specified threshold level \( \delta \). Then, the Maximum Tolerated Dose (MED) is defined as \( \text{MTD} = \max\{i, j : \mu_{ij} - \mu_{i0} > -\delta, \text{ordering first} \ i, \text{then} \ j\} \).

The possible inference results of interest at time point \( i = 1, 2, \ldots, T \) are as follows:

**Step 1**: \( \mu_{i1} \leq \mu_{i0} - \delta \)

**Step 2**: \( \mu_{i2} \leq \mu_{i0} - \delta < \mu_{i1} \)

\[ \vdots \]

**Step \( l \)**: \( \mu_{il} \leq \mu_{i0} - \delta < \mu_{ij} \) for all \( j, j < l \leq K \)

\[ \vdots \]

**Step \( K \)**: \( \mu_{ik} \leq \mu_{i0} - \delta < \mu_{ij} \) for all \( j, 1 < j \leq K \)
In other words, the above possible inference results can be written as follows:

Step 1: Dose 1 at time $i$ is not safe

Step 2: Dose 1 is safe at time $i$ but dose 2 is not safe

\[ \vdots \]

Step $l$: Dose 1, 2, \ldots, $l - 1$ are safe at time $i$ but dose $l$, $l + 1$, \ldots, $K$ is not safe

\[ \vdots \]

Step $K$: Doses 1, 2, \ldots, $K - 1$ are safe at time $i$ but dose $K$ is not safe

Therefore, our objective is to find the smallest $L$ and $M$ for MTD such that $\mu_{ij} - \mu_{i0} > -\delta$ for all $i \leq L$ and $j \leq M$ simultaneously to find the MTD of a drug.

Define $T$ to be the t-statistic for $\mu_{ij} - \mu_{i0}$

\[
T_{ij} = \frac{\bar{y}_{ij} - \bar{y}_{i0} - (\mu_{ij} - \mu_{i0})}{\hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}} \sim t_v,
\]

where $\bar{y}_{ij} = \frac{\sum_{j=1}^{n_j} y_{ijl}}{n_j}$, and $\hat{\sigma}_i = \sqrt{\frac{\sum_{j=0}^{K} \sum_{l=1}^{n_j} (y_{ijl} - \bar{y}_{ij})}{\sum_{j=0}^{K} (n_j - 1)}}$ are the sample mean adverse effect at dose level $j = 1, 2, \cdots, K$ and at time point $i = 1, 2, \cdots, T$ and the pooled sample standard deviation at time $i$ respectively. The test statistic $T$ follows a $t$ distribution with degrees of freedom $v = \sum_{j=0}^{K} n_j - (K + 1)$. Then a $100(1 - \alpha)$% lower confidence interval for the unknown effect difference $\mu_{ij} - \mu_{i0}$ is

\[
U_{ij} = (\bar{y}_{ij} - \bar{y}_{i0} - t_{\alpha, v} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}, \infty),
\]

where $t_{\alpha, v}$ is the upper $100\alpha$ percentile of a student’s $t$ distribution with $v$ degrees of freedom.

Since we assume that the adverse effect of a drug increases with the time and dose, it is desirable to give inference on the drug adverse effect in a specific order, and failure to claim significance at any dose stops the inference on subsequent doses. Therefore, in order to identify the
MTD of a drug in a dose-response study described above, we use stepwise confidence intervals based procedures using partitioning principle. In the construction of lower confidence interval for the treatment adverse effect difference, we assume that the data follow a normal distribution and the equal variance across the dose levels at each time point for the simplicity of the calculation. In the next section, we present the step-up confidence interval based procedures for determining the MTD when the responses are continuous and are observed over time.

3.2 Method of Partitioning the Vectorized Space

Since the responses are observed over a sequence of time across the increasing dose levels, in order to see the maximal time effect on the subjects, we organize the adverse effect difference $\theta_{ij} = \{\mu_{ij} - \mu_{i0}\}, i = 1, 2 \ldots, T, j = 1, 2, \ldots, K$ in a vector denoted as $\theta = \{\theta_1, \theta_2, \ldots, \theta_{K*T}\}$.

Then we partition the parameter space so that only one partition contains the true parameter of interest. This stepwise confidence interval procedures works as follows:

- **Step 1**: If $\bar{y}_1 - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_1} + \frac{1}{n_0}} \geq -\delta$, then assert $\mu_1 - \mu_0 > -\delta$, and go to step 2; else claim $\mu_1 - \mu_0 > \bar{y}_1 - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_1} + \frac{1}{n_0}}$, and no dose is safe and stop.

- **Step 2**: If $\bar{y}_2 - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_2 \sqrt{\frac{1}{n_2} + \frac{1}{n_0}} \geq -\delta$, then assert $\mu_2 - \mu_0 > -\delta$, then claim $\mu_2 - \mu_0 > \bar{y}_2 - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_2 \sqrt{\frac{1}{n_2} + \frac{1}{n_0}}$, and go to step 3; else claim $\mu_2 - \mu_0 > \bar{y}_2 - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_2 \sqrt{\frac{1}{n_2} + \frac{1}{n_0}}$, and dose 1 is MTD and stop.

- **Step $T*K - 1$**: If $\bar{y}_{T*K-1} - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_{T*K-1} \sqrt{\frac{1}{n_{T*K-1}} + \frac{1}{n_0}} \geq -\delta$, then assert $\mu_1 - \mu_0 > -\delta$, and go to step 2; else claim $\mu_{K-1} - \mu_0 > \bar{y}_{T*K-1} - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_{T*K-1} \sqrt{\frac{1}{n_{T*K-1}} + \frac{1}{n_0}}$, and dose $T*K - 2$ is MTD and stop.

- **Step $T*K$**: If $\bar{y}_{T*K} - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_{T*K} \sqrt{\frac{1}{n_{T*K}} + \frac{1}{n_0}} \geq -\delta$, then assert $\mu_{T*K} - \mu_0 > -\delta$, so all doses are safe and MTD=K; else claim MTD=K-1 and stop.

The following theorem shows that the above procedure controls simultaneous confidence level at $1 - \alpha$. 
Theorem 3.1. Let $Y$ be the observed data, and $\Theta$ be the parameter space for the parameter vector $\theta$. Let $\bar{y}_l - \bar{y}_0 - t_{v,\alpha} \hat{\sigma}_l \sqrt{\frac{1}{n_l} + \frac{1}{n_0}}$ be a $100(1 - \alpha)$% confidence lower bound for $\mu_l - \mu_0$ with confidence level $1 - \alpha$, where $l = 1, 2, \ldots, T \ast K$. Suppose that the stepwise procedure stops at step $M(1 \leq M \leq T \ast M + 1)$, that is, $M$ is the smallest integer $l$ such that $\mu_l - \mu_0 > \bar{y}_l - \bar{y}_0 - t_{v,\alpha} \hat{\sigma}_l \sqrt{\frac{1}{n_l} + \frac{1}{n_0}}$ for $1 \leq l \leq T \ast K$. Then for all $\theta \in \Theta$, we have

$$\Pr\left(\bigcap_{l=1}^{M-1} \{\mu_l - \mu_0 > -\delta\} \cap \{\mu_M - \mu_0 > \bar{y}_M - \bar{y}_0 - t_{v,\alpha} \hat{\sigma}_M \sqrt{\frac{1}{n_M} + \frac{1}{n_0}}\} \right) \geq 1 - \alpha.$$

Proof. Denote $\Theta^c_l = \{\mu_l - \mu_0 > -\delta\}$ and $\Theta_l = \{\mu_l - \mu_0 \leq -\delta\}, l = 1, 2, \ldots, T \ast K + 1$. Also, denote $U_l(Y) = \{\mu_l - \mu_0 > \bar{y}_l - \bar{y}_0 - t_{v,\alpha} \hat{\sigma}_l \sqrt{\frac{1}{n_l} + \frac{1}{n_0}}\}, for l = 1, 2, \cdots, T \ast K + 1$. Now consider the partition of the parameter space as follows:

$$\Theta_1^* = \Theta_1$$
$$\Theta_2^* = \Theta_1^* \Theta_2$$
$$\Theta_3^* = \Theta_1^* \Theta_2^* \Theta_3$$
$$\vdots$$
$$\Theta_{T \ast K + 1}^* = \Theta_1^* \Theta_2^* \Theta_3^* \cdots \Theta_{T \ast K}^* \Theta_{T \ast K + 1}.$$ 

Note that $\Theta = \bigcup_{l=1}^{T \ast K + 1} \Theta_l = \bigcup_{l=1}^{T \ast K + 1} \Theta_l^*$. 

If $\theta \in \Theta_l^*$, then

$$\Pr(\theta \in \bigcup_{l=1}^{T \ast K + 1} \Theta_l^* U_l(Y)) = \Pr(\theta \in \Theta_l^* U_l(Y)) = \Pr(\theta \in U_l(Y)) \geq 1 - \alpha.$$ 

In order to prove the theorem, we use the following properties of $M$:

1. $U_l(Y) \cap \Theta_l^* = \emptyset$ for all $l < M$, because $\Theta_l^* \subset \Theta_l$;
2. $\Theta^c_1 \Theta^c_2 \Theta^c_3 \ldots \Theta^c_M \ldots \Theta^c_{l-1} \Theta_l \subset \Theta^c_1 \Theta^c_2 \ldots \Theta^c_M$ for all $l > M$.

3. $\Theta^c_M \subset U_M(Y)$.

Now

$$
\bigcup_{l=1}^{T*+1} U_i(Y) \Theta^*_l
= \bigcup_{l=1}^{M-1} \bigcup_{l=M}^{T*+1} U_i(Y) \Theta^*_l
= \bigcup_{l=M}^{T*+1} U_i(Y) \Theta^*_l \quad \text{(by property 1)}
$$

$$
= (U_M(Y) \Theta^*_M) \bigcup_{l=M+1}^{T*+1} U_i(Y) \Theta^*_l
= (\Theta^c_1 \Theta^c_2 \ldots \Theta^c_{M-1} \Theta_M U_M(Y)) \bigcup_{l=M+1}^{T*+1} U_i(Y) \Theta^*_l
\subset (\Theta^c_1 \Theta^c_2 \ldots \Theta^c_{M-1} \Theta_M U_M(Y)) \bigcup \Theta^c_1 \Theta^c_2 \ldots \Theta^c_M \quad \text{(by property 2)}
= \Theta^c_1 \Theta^c_2 \Theta^c_3 \ldots \Theta^c_M U_M(Y) \quad \text{(by property 3)}.
$$

We also use this property to have the above result

$$(U_M(Y) \Theta_M) \bigcup (U_M(Y) \Theta^c_M) = (U_M(Y) \Theta_M) \bigcup \Theta^c_M = U_M(Y) \text{ since } \Theta^c_M \subset U_M(Y).$$

Hence, we have for all $\theta \in \Theta$,

$$
\Pr \left( \theta \in \bigcap_{l=1}^{M-1} \{ \mu_l - \mu_0 > -\delta \} \cap \{ \mu_M - \mu_0 > \bar{y}_M - \bar{y}_0 - t_{v, \alpha} \hat{\sigma}_M \sqrt{\frac{1}{n_M} + \frac{1}{n_0}} \} \right)
\geq \Pr \left( \theta \in \bigcup_{l=1}^{T*+1} \Theta^*_l U_i(Y) \right) \geq 1 - \alpha.
$$
3.3 Method of Double Partition

We now partition the parameter space based on time, followed by a partition of the dosages instead of vectorizing the parameters of interest to find the MTD. The Double Partition procedure for MTD can be described as follows:

- **Step 1:** Construct a 95% lower confidence interval set for $\mu_{ij} - \mu_{i0}$ at time $i, i = 1, 2, \ldots, T$ by using the formula given in Section 3.1.

- **Step 2:** Then screen from time 1 to time $T$ using the confidence set constructed and stop at the first time $L$ such that $\bar{y}_{ij} - \bar{y}_{i0} - t_{v,\alpha}\hat{\sigma}_1\sqrt{\frac{1}{n_j} + \frac{1}{n_0}} \leq -\delta$ for all $j, j = 1, 2, \ldots, K, i = L, L + 1, \ldots, T$.

Specifically, start with the lowest dose 1 at the lowest time point 1 to search for the largest integer $M$ such that $U_{1M}(X) \not\subseteq \Theta_{1M}$ in the following way:

If at the lowest time point 1, $\bar{y}_{11} - \bar{y}_{10} - t_{v,\alpha}\hat{\sigma}_1\sqrt{\frac{1}{n_1} + \frac{1}{n_0}} \leq -\delta$, then no dose is safe. No MTD can be identified.

On the other hand, if there exists a dose $M$ so that $\bar{y}_{1j} - \bar{y}_{10} - t_{v,\alpha}\hat{\sigma}_1\sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta, j = 1, 2, \ldots, M - 1$ and $\bar{y}_{1M} - \bar{y}_{10} - t_{v,\alpha}\hat{\sigma}_1\sqrt{\frac{1}{n_M} + \frac{1}{n_0}} \leq -\delta$, then $(1, 1), (1, 2), \ldots, (1, M - 1)$ are safe.

If $\bar{y}_{lj} - \bar{y}_{l0} - t_{v,\alpha}\hat{\sigma}_1\sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta, j = 1, 2, \ldots, K$, then move to examine the time point 2.

- **Step 3:** Continue the process described in Step 2 in order to find the MTD. If at the highest time $T$, $\bar{y}_{Tj} - \bar{y}_{T0} - t_{v,\alpha}\hat{\sigma}_T\sqrt{\frac{1}{n_j} + \frac{1}{n_0}} \leq -\delta$ for all $j = 1, 2, \ldots, K$, then MTD is at time $T - 1$ and Dose $K$.

By Applying the above procedure if the smallest time $L$ and the smallest treatment $M$ are found such that $\bar{y}_{LM} - \bar{y}_{L0} - t_{v,\alpha}\hat{\sigma}_L\sqrt{\frac{1}{n_M} + \frac{1}{n_0}} \leq -\delta$, then MTD is at time $= L - 1$, and dose $= M - 1$. It renders the higher time and doses are unnecessary to be computed.
The following theorem shows that the method of Double Partition controls simultaneous confidence level at $1 - \alpha$.

**Theorem 3.2.** Let $Y$ be the observed data, and $\Theta$ be the parameter space for the parameter vector $\theta$. Suppose that $U_{ij}(Y) = \{\mu_{ij} - \mu_{i0} > \bar{y}_{ij} - \bar{y}_{i0} - t_{v,\alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}\}$ is a $100(1 - \alpha)$% lower confidence interval for $\mu_{ij} - \mu_{i0}$, $i = 1, 2, \ldots, T$, $j = 1, 2, \ldots, K$ with confidence level $1 - \alpha$. Let $M$ be the smallest $j$ integer such that $U_{ij}(Y) \not\subset \Theta_{ij}^c$ at time $i$ and let $L$ be the smallest $i$ integer such that $U_{ij}(Y) \not\subset \Theta_{ij}^c$ where $\Theta_{ij}^c = \{\mu_{ij} - \mu_{i0} > -\delta\}$ for all $j, j = 1, 2, \ldots, K$. Let $\Delta_i$ be defined as $\theta \in \bigcup_{j=1}^{K} \Theta_{ij}$, $i = 1, 2, \ldots, T$, $j = 1, 2, \ldots, K$. That is, $\Delta_i$ means at least one dose is not safe at time $i$, $1 \leq i \leq T$. Then for all $\theta \in \Theta$, we have

$$\Pr(\theta \in \Delta_1^c \cdots \Delta_{L-1}^c \Theta_{L,1}^c \Theta_{L,2}^c \cdots \Theta_{L,(M-1)}^c U_{LM}(Y)) \geq 1 - \alpha.$$ 

**Proof.** Consider the following partition of the parameter space $\Theta$ in time-wise:

$$\Delta_1^* = \Delta_1$$
$$\Delta_2^* = \Delta_1^c \Delta_2$$
$$\vdots$$
$$\Delta_T^* = \Delta_1^c \Delta_2^c \cdots \Delta_{T-1}^c \Delta_T$$
$$\Delta_{T+1}^* = \Delta_1^c \Delta_2^c \cdots \Delta_T^c \Delta_{T+1}.$$ 

Now consider the following partition of the parameter space $\Theta$ for a given time $i$,

$$\tau_{i+1}^* = \Theta_{i+1}$$
$$\tau_{i+2}^* = \Theta_{i+1}^c \Theta_{i+2}$$
$$\vdots$$
$$\tau_{i+(K+1)}^* = \Theta_{i+1}^c \Theta_{i+2}^c \cdots \Theta_{i+K}^c \Theta_{i+(K+1)}.$$
If $\theta \in \Delta^*_i \tau_{ij}^*$, then

$$\Pr(\theta \in \bigcup_{i=1}^{T+1} \bigcup_{j=1}^{K+1} \Delta^*_i \tau_{ij}^* U_{ij}(Y)) = \Pr(\theta \in \Delta^*_i \tau_{ij}^* U_{ij}) = \Pr(\theta \in U_{ij}(Y)) \geq 1 - \alpha.$$ 

Note

$$\bigcup_{j=1}^{K+1} \Delta^*_i \tau_{ij}^* U_{ij}(Y)$$

$$= \Delta^*_i \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{K} \tau_{ij}^* U_{ij}(Y) \right)$$

$$= \Delta^*_i \left( \bigcup_{j=1}^{M-1} \bigcup_{j=M}^{K+1} \bigcup_{j=M+1}^{K+1} \tau_{ij}^* U_{ij}(Y) \right)$$

$$= \Delta^*_i \left( \bigcup_{j=M+1}^{K+1} \bigcup_{j=1}^{K+1} \tau_{ij}^* U_{ij}(Y) \right) \quad \text{(because } U_{ij}(Y) \cap \tau_{ij}^* = \emptyset, \text{ for } 1 \leq j \leq M - 1, \text{ at fixed } i)$$

$$= \Delta^*_i \left( \bigcup_{j=M+1}^{K+1} U_{ij}(Y) \tau_{ij}^* \right) \cup \left( \tau_{iM}^* U_{IM}(Y) \right)$$

$$= \Delta^*_i \left( \bigcup_{j=M+1}^{K+1} U_{ij}(Y) \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c \Theta_{iM} \right) \cup \left( U_{IM}(Y) \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c \Theta_{iM} \right)$$

$$\subseteq \Delta^*_i \left( \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{iM}^c \right) \cup \left( U_{IM}(Y) \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c \Theta_{iM} \right)$$

$$= \Delta^*_i \left( U_{IM}(Y) \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c \right)$$

$$= \Delta^*_i U^*_i(Y).$$

This is because $\Theta_{iM}^c \subset U_{IM}(Y)$ and $\Theta_{iM}^c U_{IM}(Y) = \Theta_{iM}^c$. So, $\Theta_{iM}^c U_{IM}(Y) \cap U_{IM}(Y) \Theta_{iM} = U_{IM}(Y)$.

Let $U^*_i(Y) = \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c U_{IM}(Y)$. 

Let $U^*_i(Y) = \Theta_{i1}^c \Theta_{i2}^c \ldots \Theta_{i(M-1)}^c U_{IM}(Y)$.
Now

\[ \bigcup_{i=1}^{T+1} \bigcup_{j=1}^{K+1} \Delta_i^* \tau_{ij} U_{ij}(Y) \]
\[ \subseteq \bigcup_{i=1}^{T+1} \Delta_i^* U_i^*(Y) \]
\[ = \bigcup_{i=1}^{T+1} \bigcup_{L=L+1}^{L-1} \bigcup_{i=1}^{T} \Delta_i^* U_i^*(Y) \]
\[ = \bigcup_{i=L+1}^{T+1} \Delta_i^* U_i^*(Y) \quad \text{(because } U_i^*(Y) \cap \Delta_i^* = \emptyset, \text{ for } i = 1, 2, \ldots, L-1) \]
\[ = (\Delta_L^* U_L^*(Y)) \cup \bigcup_{i=L+1}^{T+1} (U_i^*(Y) \Delta_i^* U_i^*(Y) \cup \bigcup_{i=L+1}^{T+1} \Delta_i^* U_i^*(Y) \Delta_i^* \Delta_L) \]
\[ \subseteq (U_L^*(Y) \Delta_L^* \Delta_L) \cup \bigcup_{i=L+1}^{T+1} (U_i^*(Y) \Delta_i^* \Delta_L) \]
\[ = U_L^*(Y) \Delta_T \ldots \Delta_L \]

The above result is found by using the fact that \( \Delta_L^* \subset U_L^*(Y) \) and \( \Delta_L^* U_L^*(Y) = \Delta_L^* \) and \( \Delta_L^* \cup (U_L^*(Y) \Delta_L) = (\Delta_L^* U_L^*(Y) \cup U_L^* \Delta_L) = U_L^*(Y) \). Finally,

\[ \bigcup_{i=1}^{T+1} \bigcup_{j=1}^{K+1} \Delta_i^* \tau_{ij} U_{ij}(Y) \subseteq \bigcup_{i=1}^{T+1} \Delta_i^* U_i^*(Y) \subseteq U_L^*(Y) \Delta_L \ldots \Delta_L \]
\[ = U_{LM}(Y) \Theta_{L1} \Theta_{L2} \ldots \Theta_{L(M-1)} \Delta_L^* \ldots \Delta_L^* \]

Therefore, \( \Pr(\theta \in U_{LM}(Y) \Theta_{L1} \Theta_{L2} \ldots \Theta_{L(M-1)} \Delta_L^* \ldots \Delta_L^*) \geq \Pr(\theta \in \bigcup_{i=1}^{T+1} \Delta_i^* U_i^*(Y)) \)
\[ \geq \Pr(\theta \in \bigcup_{i=1}^{T+1} \bigcup_{j=1}^{K+1} \Delta_i^* \tau_{ij} U_{ij}(Y)) \geq 1 - \alpha. \]

The double Partition procedure for finding the MTD can be illustrated as follows:
Time 1
Step 1: If $\overline{y}_{11} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_1} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{11} - \mu_{10} > -\delta$, and go to Step 2;
else assert $\mu_{11} - \mu_{10} > \overline{y}_{11} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_1} + \frac{1}{n_0}}$, claim no dose is safe and stop.

Step 2: If $\overline{y}_{12} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_2} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{12} - \mu_{10} > -\delta$ and go to Step 3;
else assert $\mu_{12} - \mu_{10} > \overline{y}_{12} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_2} + \frac{1}{n_0}}$, claim MTD = 1 at time 1 and stop.

Step K: If $\overline{y}_{1K} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_K} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{1K} - \mu_{10} > -\delta$,
(all doses at time 1 are safe) and go to Time 2;
else assert $\mu_{1K} - \mu_{10} > \overline{y}_{1K} - \overline{y}_{10} - t_{v, \alpha} \hat{\sigma}_1 \sqrt{\frac{1}{n_K} + \frac{1}{n_0}}$, claim MTD = $K - 1$ at time 1 and stop.

Time $i$
Step 1: If $\overline{y}_{i1} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_1} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{i1} - \mu_{i0} > -\delta$ and go to Step 2;
else assert $\mu_{i1} - \mu_{i0} > \overline{y}_{i1} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_1} + \frac{1}{n_0}}$, claim MTD = $K$ at time $i - 1$ and stop.

Step 2: If $\overline{y}_{i2} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_2} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{i2} - \mu_{i0} > -\delta$ and go to Step 3;
else assert $\mu_{i2} - \mu_{i0} > \overline{y}_{i2} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_2} + \frac{1}{n_0}}$, claim MTD = 1 at time $i$ and stop.

Step K: If $\overline{y}_{iK} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_K} + \frac{1}{n_0}} > -\delta$, then claim $\mu_{iK} - \mu_{i0} > -\delta$
all doses at time $i$ are safe) and go to Time $i + 1$;
else assert $\mu_{iK} - \mu_{i0} > \overline{y}_{iK} - \overline{y}_{i0} - t_{v, \alpha} \hat{\sigma}_i \sqrt{\frac{1}{n_K} + \frac{1}{n_0}}$, claim MED = $K - 1$
at time $i$ and stop.

Time $T$
Step 1: If $\overline{y}_{T1} - \overline{y}_{T0} - t_{v, \alpha} \hat{\sigma}_T \sqrt{\frac{1}{n_1} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{T1} - \mu_{T0} > -\delta$ and go to Step 2;
else assert $\mu_{T1} - \mu_{T0} > \overline{y}_{T1} - \overline{y}_{T0} - t_{v, \alpha} \hat{\sigma}_T \sqrt{\frac{1}{n_1} + \frac{1}{n_0}}$, claim MTD = $K$
at time $T - 1$ and stop.

Step 2: If $\overline{y}_{T2} - \overline{y}_{T0} - t_{v, \alpha} \hat{\sigma}_T \sqrt{\frac{1}{n_2} + \frac{1}{n_0}} > -\delta$, then assert $\mu_{T2} - \mu_{T0} > -\delta$ and go to Step 3;
else assert $\mu_{T2} - \mu_{T0} > \overline{y}_{T2} - \overline{y}_{T0} - t_{v, \alpha} \hat{\sigma}_T \sqrt{\frac{1}{n_2} + \frac{1}{n_0}}$, claim MTD = 1
at time $T$ and stop.

Step K: If $\overline{y}_{TK} - \overline{y}_{T0} - t_{v, \alpha} \hat{\sigma}_T \sqrt{\frac{1}{n_K} + \frac{1}{n_0}}$, then assert $\mu_{T2} - \mu_{T0} > -\delta$,
claim all doses are safe, MTD = $K$ at time $T$, and stop.
3.4 Method of Partition with Bonferroni Correction

In the previous two procedures (1) Method of Partitioning Vectorized Space, and (2) Method of Double Partition, we make inference for identifying the MTD at individual dose taking into the time effect as the primary endpoint. However, they fail to address all dosages at a time point in one statement. For example, at time $T_i$, if $\mu_{T(K-1)}$ is not safe, the procedure stops without claiming any conclusion on $\mu_{T_K}$. In this section, we introduce a method that is able to draw a statement for all dosages at a given time point, the method of Partition with Bonferroni Correction. It is described as follows:

**Step 1:** We find a $100(1 - \frac{\alpha}{K})\%$ confidence set for all treatment effects at each time $i, i = 1, 2, \ldots, T$, where $K$ is the total number of treatment comparisons at time $i$. The $100(1 - \frac{\alpha}{K})\%$ lower confidence interval for $\theta_{ij} = \mu_{ij} - \mu_{i0}$ is

$$U_{ij} = (\bar{y}_{ij} - \bar{y}_{i0} - t_{v, \frac{\alpha}{K}} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}, \infty), i = 1, 2, \ldots, T, j = 1, 2, \ldots, K,$$

where $t$ is the Student $t$ distribution with $P(t \geq t_{v, \frac{\alpha}{K}}) = \frac{\alpha}{K}$, and $v = \sum_{j=0}^{K} n_i - (K + 1)$.

**Step 2:** We screen from time 1 to time $T$ using the confidence set calculated in Step 1 and stop at the first time $L$ such that $\bar{y}_{Lj} - \bar{y}_{L0} - t_{v, \frac{\alpha}{K}} \hat{\sigma}_L \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} \leq -\delta$ for some $j \in \{1, 2, \ldots, K\}$, and $\bar{y}_{ij} - \bar{y}_{i0} - t_{v, \frac{\alpha}{K}} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta, i = 1, 2, \ldots, L - 1, j = 1, 2, \ldots, K$.

**Theorem 3.3.** Let $Y$ be the observed data, and $\Theta$ be the parameter space for the parameter vector $\theta$. Suppose that $\{\mu_{ij} - \mu_{i0} > \bar{y}_{ij} - \bar{y}_{i0} - t_{v, \frac{\alpha}{K}} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}\}$ is a $(1 - \frac{\alpha}{K})100\%$ lower confidence interval for $\mu_{ij} - \mu_{i0}, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. Let $L$ be the smallest integer $i$ such that $\mu_{ij} - \mu_{i0} \leq -\delta, i = L, L + 1, \ldots, T$, and for some $j \in \{1, 2, \ldots, K\}$.

Denote $U_i(Y)$ to be a vector of $(1 - \frac{\alpha}{K})100\%$ lower confidence interval for $\mu_{ij} - \mu_{i0}$ at time $i, i = 1, 2, \ldots, T, j = 1, 2, \ldots, K$. That is, $U_i(Y) = \{\mu_{ij} - \mu_{i0} > \bar{y}_{ij} - \bar{y}_{i0} - t_{v, \frac{\alpha}{K}} \hat{\sigma}_i \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}, j = 1, 2, \ldots K\}$. $\Delta_i^c$ is such that $\{\mu_{ij} - \mu_{i0} > -\delta\}$ for all $j = 1, 2, \ldots K$ at time $i, i = 1, 2, \ldots T$. 

Then, for all \( \theta \in \Theta \),

\[
\Pr \left( \theta \in \Delta_1 \Delta_2 \ldots \Delta_{L-1} U_L(Y) \right) \geq 1 - \alpha.
\]

Proof. Now consider the partition of the parameter space for time effect:

\[
\begin{align*}
\Delta_1^* &= \Delta_1 \\
\Delta_2^* &= \Delta_1^2 \Delta_2 \\
&\vdots \\
\Delta_K^* &= \Delta_1^c \Delta_2^c \ldots \Delta_{K-1}^c \Delta_K \\
\Delta_{K+1}^* &= \Delta_1^c \Delta_2^c \ldots \Delta_{K-1}^c \Delta_K^c \Delta_{K+1}.
\end{align*}
\]

Clearly, \( \Theta = \bigcup_{i=1}^{T+1} \Theta_i^* \). If \( \theta \in \Delta_i^* \), then

\[
\Pr(\theta \in \bigcup_{i=1}^{T+1} \Delta_i^* U_i(Y)) = \Pr(\theta \in \Delta_i^* U_i(Y)) = \Pr(\theta \in U_i(Y)) \geq 1 - \alpha. \quad (3.4.1)
\]
Since

\[
\bigcup_{i=1}^{T+1} \Delta_i^* U_i(Y) \\
= \bigcup_{i=L}^L \bigcup_{i=L+1}^{T+1} \Delta_i^* U_i(Y) \\
= \bigcup_{i=L}^L \bigcup_{i=L+1}^{T+1} \Delta_i^* U_i(Y) ( \text{because } U_i(Y) \cup \Delta_i^* = \emptyset, \text{for } i = 1, 2 \ldots L - 1 ) \\
= (\Delta_L^* U_L(Y)) \bigcup_{i=L+1}^{T+1} (\Delta_i^* U_i(Y)) \\
= (\Delta_1^* \Delta_2^* \ldots \Delta_{L-1}^* \Delta_L U_L(Y)) \bigcup_{i=L+1}^{T+1} (\Delta_i^* \Delta_2^* \ldots \Delta_{i-1}^* \Delta_i U_i(Y)) \\
\subseteq (\Delta_1^c \Delta_2^c \ldots \Delta_{L-1}^c \Delta_L U_L(Y)) \bigcup_{i=L+1}^{T+1} (\Delta_i^* \Delta_2^* \ldots \Delta_i^c) \\
= (\Delta_1^c \Delta_2^c \ldots \Delta_{L-1}^c U_L(Y)),
\]

This is because \(\Delta_L^c \subset U_L^c(Y)\) and \(\Delta_L^c U_L(Y) = \Delta_L^c\). So \(\Delta_L^c \cup (U_L(Y) \Delta_L) = (\Delta_L^c U_L(Y) \cup U_L(Y) \Delta_L) = U_L(Y)\).

Therefore, \(\Pr\left(\theta \in \Delta_1^c \Delta_2^c \ldots \Delta_{L-1}^c U_L(Y)\right) \geq \Pr\left(\theta \in \bigcup_{i=1}^{T+1} \Delta_i^* U_i(Y)\right) \geq 1 - \alpha. \quad (\text{by equation 3.4.1})\)

The procedure corresponding to the above theorem is presented below:

- **Step 1:** If \(\bar{y}_{1j} - \bar{y}_{10} - t_R \sigma_1 \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta\), for all \(j\), then claim \(\mu_{1j} - \mu_{10} > -\delta\) for all \(j\) and go to Step 2; else claim \(\mu_{1j} - \mu_{10} \in \left\{\mu_{1j} - \mu_{10} > \bar{y}_{1j} - \bar{y}_{10} - t_R \sigma_1 \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}\right\}\) for some \(j \in \{1, 2, \ldots, K\}\), and stop.

- **Step 2:** If \(\bar{y}_{2j} - \bar{y}_{20} - t_R \sigma_2 \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta\), for all \(j\), then claim \(\mu_{2j} - \mu_{20} > -\delta\) for all \(j\) and go to Step 3; else claim \(\mu_{2j} - \mu_{20} \in \left\{\mu_{2j} - \mu_{20} > \bar{y}_{2j} - \bar{y}_{20} - t_R \sigma_2 \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}\right\}\) for some \(j \in \{1, 2, \ldots, K\}\), and stop.

...
• Step T: If \( \bar{y}_{Tj} - \bar{y}_{T0} - t_{\frac{\alpha}{2}, v} \hat{\sigma}_T \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} > -\delta \), for all \( j \), then claim \( \mu_{Tj} - \mu_{T0} > -\delta \) for all \( j \) and all doses are safe, claim MTD = \( K \) at time \( T - 1 \), and stop;

else claim \( \mu_{Tj} - \mu_{T0} \in \{ \mu_{Tj} - \mu_{T0} > \bar{y}_{Tj} - \bar{y}_{T0} - t_{\frac{\alpha}{2}, v} \hat{\sigma}_T \sqrt{\frac{1}{n_j} + \frac{1}{n_0}} \} \) for some \( j \in \{1, 2, \ldots, K\} \), and stop.
CHAPTER 4 SIMULATION STUDIES

In this chapter, we investigate the performance of our proposed stepwise confidence intervals based procedures through a Monte Carlo simulation study. Section 4.1 presents simulation results for MED, and Section 4.2 for MTD.

4.1 Simulation Study for MED

Table 4.1 shows two different mean response configurations for treatment effect including control over time. The mean response are monotonically increasing with the doses over time. Since the control group does not have any significant effect over time, the mean response of control over time are considered as equal. In the mean response configuration in case 1, for example, if an increase of 0.45 mortality rate is clinically pre-specified as effective, the effect of dose 1 at time 6 is not effective but dose 2 and dose 3 at time 6 are effective. Therefore, the MED in the configuration case 1 is 2 at time 6. Configuration case 2 and other notations are self-evident.

For sample size selection in this simulation study, we consider two different sample sets such as (i) small sample size with (15, 20, 25), and (ii) large sample size with (50, 75, 100). Since our confidence interval based procedures are based on the normal approximate, we want to see how the power of the procedures in identifying the true MED is affected by the different sample sizes.

We simulate the power of three procedures under different conditions. Sample sizes, pre-specified thresholds and the corresponding MED are given in Table 4.2. With a specific sample, we generate a set of binomial random numbers that is considered as the number of successes (mortality) using each of the mean response given in Table 4.1.

Once we generate a set of binomial random numbers for each of the sample sizes, we calculate confidence intervals for $p_{ij} - p_{i0}$, $i = 1, 2, \ldots, T$, $j = 1, 2, \ldots, K$ and apply our stepwise procedures given in Chapter 2 to find the MED. The above process is repeated 10,000 times. Then we
Table 4.1: Parameter Configurations

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Responses(Case 1)</th>
<th>Mean Responses(Case 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( p_0 ) (control)</td>
<td>( p_1 )</td>
</tr>
<tr>
<td>1</td>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>0.26</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>0.28</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>0.29</td>
</tr>
<tr>
<td>6</td>
<td>0.10</td>
<td>0.50</td>
</tr>
</tbody>
</table>

calculate the power of each of the procedures as

\[
\text{Power} = P(\text{MED} = \hat{\text{MED}}),
\]

where \( \hat{\text{MED}} \) is the estimated minimum effective dose. Thresholds, MED and sample sizes along with simulated powers and simulated standard deviations for the two methods are given in Table 4.2.

Table 4.2: Simulated Powers

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Configuration</th>
<th>Threshold</th>
<th>MED</th>
<th>Bonferroni</th>
<th>Double Partition</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.1076(0.0031)</td>
<td>0.1314(0.0034)</td>
</tr>
<tr>
<td>20</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.1548(0.0041)</td>
<td>0.3140(0.0046)</td>
</tr>
<tr>
<td>25</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.2513(0.0036)</td>
<td>0.3561(0.0044)</td>
</tr>
</tbody>
</table>

**Note 1:** The values in the parenthesis under Bonferroni, and Double Partition are the standard errors of the simulated powers.

**Note 2:** The first value in the parenthesis under MED is Time and the second one Dose. For example, (6,2) means that MED locates on the time 6 and dose 2.

As is seen in Table 4.2 for the small sample size less than 30, both procedures are less accurate in identifying the true MED. This is because the procedures, as mentioned before, are based on the normal approximation but due to small sample sizes, the test statistic may not follow normal
distribution. Hence, the lower confidence intervals for the effect difference \( p_{ij} - p_{i0} \) constructed based on the test statistic is inaccurate. However, the Double Partition is more powerful in detecting the true MED than the method of partition with Bonferroni Correction. For example, when sample size \( n = 25 \), the method of Double Partition correctly identifies the MED about 36% of the time with standard error of 0.44%. On the other hand, for the same sample size, the power of the method of Partition with Bonferroni Correction is about 25% with 0.36%, which is less than 11% compared to that of the procedure of Double Partition.

Table 4.3: Simulated Powers

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Configuration</th>
<th>Threshold</th>
<th>MED</th>
<th>Bonferroni</th>
<th>Double Partition</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.6666(0.0047)</td>
<td>0.8421(0.0036)</td>
</tr>
<tr>
<td>75</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.7125(0.0034)</td>
<td>0.9013(0.0020)</td>
</tr>
<tr>
<td>100</td>
<td>Case 2</td>
<td>0.50</td>
<td>(6,2)</td>
<td>0.8321(0.0021)</td>
<td>0.9597(0.0011)</td>
</tr>
</tbody>
</table>

**Note 1:** The values in the parenthesis under Bonferroni, and Double Partition are the standard errors of the simulated powers.

**Note 2:** The first value in the parenthesis under MED is Time and the second one Dose. For example, (6,2) means that MED locates on the time 6 and dose 2.

With the large sample sizes, a significant increase in power of both procedures in detecting the true MED is observed, as Table 4.3 shows. This improvement in power is due to the correctness of the distribution of test statistic. The large sample sizes ensure the normal approximation of the test statistic. With compared to the method of Partition with Bonferroni Correction, the Double Partition is more accurate in determining the true MED. Improvement of the method of Double Partition over the method of Partition with Bonferroni Correction is about 20% when the sample size increases from 50 to 75. When sample size \( n = 100 \), the power of identifying the correct MED improves in both the procedures but not too much compared to the sample sizes of 50, and 75.

In both small and large sample sizes, the method of Double Partition has more power compared to the method of Partition with Bonferroni Correction because the method of Double Partition starts with the highest dose, then sequentially screens the next dose without adjusting the confidence level.
for each lower confidence interval $1 - \alpha$, but the method of partition with Bonferroni correction adjusts the confidence level $1 - \alpha$ level at each of the three steps where the confidence level at each step is $1 - \frac{\alpha}{3}$ to control the overall confidence level at each time point. In addition, partition with Bonferroni adjustment does not follow any specified order in treatment wise at a particular time point.

Table 4.4: Simulated Powers

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Configuration</th>
<th>Threshold</th>
<th>MED</th>
<th>Bonferroni</th>
<th>Double Partition</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Case 1</td>
<td>0.25</td>
<td>(5,2)</td>
<td>0.4692(0.00499)</td>
<td>0.7201(0.00449)</td>
</tr>
<tr>
<td>100</td>
<td>Case 1</td>
<td>0.45</td>
<td>(6,2)</td>
<td>0.8883(0.00315)</td>
<td>0.9586(0.00199)</td>
</tr>
<tr>
<td>100</td>
<td>Case 1</td>
<td>0.65</td>
<td>(6,3)</td>
<td>0.7821(0.00423)</td>
<td>0.8623(0.00345)</td>
</tr>
</tbody>
</table>

**Note 1:** The values in the parenthesis under Bonferroni, and Double Partition are the standard errors of the simulated powers.

**Note 2:** The first value in the parenthesis under MED is Time and the second one Dose. For example, (5,2) means that MED locates on the time 5 and dose 2.

Table 4.4 shows how the power of the procedures depends on the pre-specified threshold. With the same sample size of 100, and different thresholds, the power of correctly identifying the MED is affected. For example, when the threshold changes from 0.25 to 0.45 for fixed sample size of 100, improvement of power in both the method of Double Partition and the method of Partition with Bonferroni Correction is evident.

4.2 Simulation Study for MTD

In this section, we conduct a simulation study to investigate the performance of our proposed stepwise confidence interval based procedures in Chapter 3 to determine the MTD under different mean vectors and variances. Different mean vectors are considered in this simulation study to compare the power of detecting the true MTD under different scenarios. Similarly, variance vectors, on the other hand, are set to be different to see the effect of sample variability on the procedures’ power in detecting the true MTD of a drug.

Consider the equal variance vector and the increasing mean response vector over time and doses. Table 4.3 shows the increasing mean response vector and equal variance vector. We
simulate adverse effect of a dose at a specific time by using normal distribution with mean, 
\( \mu_j, j = 0, 1, 2, 3, 4 \) and standard deviation, \( \sigma \) for different sample size \( n = 50, 100, 150 \).

Table 4.5: Parameter Configurations- Equal variance and Decreasing mean response vector

<table>
<thead>
<tr>
<th>Time</th>
<th>( \mu_0 ) (control)</th>
<th>( \mu_1 )</th>
<th>( \mu_2 )</th>
<th>( \mu_3 )</th>
<th>( \mu_4 )</th>
<th>Standard Deviation (( \sigma ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.90</td>
<td>0.85</td>
<td>0.80</td>
<td>0.75</td>
<td>0.70</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>0.80</td>
<td>0.75</td>
<td>0.70</td>
<td>0.65</td>
<td>0.15</td>
</tr>
<tr>
<td>24</td>
<td>0.90</td>
<td>0.75</td>
<td>0.70</td>
<td>0.65</td>
<td>0.60</td>
<td>0.15</td>
</tr>
<tr>
<td>169</td>
<td>0.90</td>
<td>0.70</td>
<td>0.65</td>
<td>0.60</td>
<td>0.55</td>
<td>0.15</td>
</tr>
</tbody>
</table>

For the simulated responses of a dose at a particular time point, we calculate the sample mean response and standard deviation. With the sample mean response and standard deviation, we construct the lower confidence bound for the effect difference of a dose and control effect at a time point using the stepwise procedures proposed in Chapter 3 for MTD. The 95% lower confidence limits for the parameters of interest \( \mu_{ij} - \mu_{i0}, i = 1, 2, 3, 4; j = 1, 2, 3, 4 \) are calculated by using the method of Double Partition and the method of Partitioning Vectorized Space to identify the MTD. On the other hand, the 98.50% lower confidence bounds for the same parameters are constructed by using the method of Partition with Bonferroni Correction.

Table 4.6: Power of the procedures correctly identifying the MTD under the different sample sizes when \( \delta = 0.20 \) with true MTD = dose 3 at time 1 and linearly decreasing mean and equal variance vector.

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Bonferroni</th>
<th>Double Partition</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.2660(0.0044)</td>
<td>0.4480(0.0050)</td>
</tr>
<tr>
<td>100</td>
<td>0.5330(0.0050)</td>
<td>0.7140(0.0045)</td>
</tr>
<tr>
<td>150</td>
<td>0.7250(0.0045)</td>
<td>0.8350(0.0036)</td>
</tr>
</tbody>
</table>

In order to calculate the simulated power, we replicate the process 10000 times. The simulated power of a procedure is calculated as as

\[
\text{Power} = P(MTD = \hat{MTD}),
\]
where \( \hat{M_{TD}} \) is the estimated maximum safe dose. In toxicological studies, the adverse effect from 5% to 25% is generally considered to be a biologically significant effect (Tamhane et al., 2011). Therefore, we take an increase of 20% in the mean response of doses as a clinically significant, threshold denoted by \( \delta = 0.20 \). Hence the true MTD is at dose 2 at time 1. The simulated power of the procedures as a percentage along with standard error are provided in Table 4.4 for different sample size. As the sample size increases, the power of detecting the true MTD in both the procedures increases. But the Double Partition method performs better than the method of Partition with Bonferroni Correction. In addition, in all sample sizes the method of Double Partition has more power in detecting the correct MTD of a drug.

Now consider the unequal variance vector and the decreasing mean response vector. Table 4.5 shows the parameter configuration for the simulation study. If the threshold \( \delta = 0.20 \), according to Table 4.7: Parameter Configurations-Unequal variance and Decreasing mean response vector

<table>
<thead>
<tr>
<th>Time</th>
<th>( \mu_0 ) (control)</th>
<th>( \mu_1 )</th>
<th>( \mu_2 )</th>
<th>( \mu_3 )</th>
<th>( \mu_4 )</th>
<th>Standard Deviation (( \sigma ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.90</td>
<td>0.85</td>
<td>0.80</td>
<td>0.75</td>
<td>0.70</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>0.80</td>
<td>0.75</td>
<td>0.70</td>
<td>0.65</td>
<td>0.20</td>
</tr>
<tr>
<td>24</td>
<td>0.90</td>
<td>0.75</td>
<td>0.70</td>
<td>0.65</td>
<td>0.60</td>
<td>0.17</td>
</tr>
<tr>
<td>169</td>
<td>0.90</td>
<td>0.70</td>
<td>0.65</td>
<td>0.60</td>
<td>0.55</td>
<td>0.25</td>
</tr>
</tbody>
</table>

the Theorem 3.2 and 3.3, the MTD is dose 2 at time 0 because the mean effect difference of dose 1, 2, and 3 from the control effect is greater than -0.20. Table 4.5 shows the parameter configuration for the simulation study. It is similar in content to Table 4.7 except that the variance is unequal. This parameter configuration is the same as the first parameter configuration except the variance.

Under the same simulation setting as discussed above, the power of the procedures (Method of Double Partition, and Partition with Bonferroni Correction) in detecting the correct MTD along with their standard error are presented in Table 4.8.

Table 4.8 shows that the Double Partition procedure outperforms the method of Partition with Bonferroni Correction in terms of identifying the true MTD. Note that the powers of both procedures-
Table 4.8: Power of the procedures correctly identifying the MTD under the different sample size when $\delta = 0.20$ with true MTD = dose 3 at time 1 and linearly decreasing mean and unequal variance vector.

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Bonferroni</th>
<th>Double Partition</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.2654(0.0044)</td>
<td>0.4582(0.0050)</td>
</tr>
<tr>
<td>100</td>
<td>0.5344(0.0050)</td>
<td>0.7193(0.0045)</td>
</tr>
<tr>
<td>150</td>
<td>0.7322(0.0044)</td>
<td>0.8456(0.0036)</td>
</tr>
</tbody>
</table>

The method of Double Partition and the Partition with Bonferroni Correction remains the same as when the variance vector is unequal. The power of both procedures increases as the sample size increases in case of unequal variance vector. Also, the power of the procedures depends on the pre-specified threshold.

The method of Partition with Bonferroni Correction is not so powerful in detecting the true MTD as the method of Double Partition because the Partition with Bonferroni Correction adjusts the confidence level $1 - \alpha$ level at each of the four steps at a particular time point where the confidence level at each step is $1 - \frac{\alpha}{4}$ to control the overall confidence level $1 - \alpha$. Moreover, the method of Partition with Bonferroni Correction does not follow any specified order in treatment wise at a particular time point. The method of Double Partition, on the other hand, proceeds with the lowest dose level, then sequentially screens the next dose without adjusting the confidence level for each lower confidence interval $1 - \alpha$. 
CHAPTER 5 APPLICATIONS

In this chapter, we will illustrate how to apply the statistical procedures developed in Chapter 2 and Chapter 3 for MED and MTD by using two different real datasets introduced in Section 1.2. In section 5.1, we will estimate the MED of a drug when the responses are binary and are measured over time at different increasing doses. Section 5.2 will present the results of data analysis for identifying the MTD of a drug when the endpoints are continuous.

5.1 Applications for MED

In this section, the method of Partitioning Vectorized Space, the Double Partition method and the method of Partition with Bonferroni Correction discussed in Chapter 2 can be used to construct the lower confidence bound to identify the MED of a drug when the responses are recorded over times and binary outcomes. Consider the data in Table 5.1 taken from Hewlett (1974), and Laurence and Morgan (1989).

Table 5.1 provides the cumulative mortality counts of adult flour beetles (Tribolium Castaneum). In order to assess the toxicity of pyrethrum, a well-known plant based insecticide, the adult Tribolium Castaneum flour beetles are bred and are prepared for test at 25°C. The beetles were dosed when 3-5 weeks old.

Beetles were sprayed with the solutions of the pyrethrum mixed with oil in groups. Then beetles were kept at 25°C and were confined within glass rings with diameter of 6 cm standing on filter papers. Beetles were allowed to move freely and food was given in an attempt to prevent natural mortality within the observation period. Numbers of dead beetles were determined at intervals of 24 hr through a low-power microscope. The mortality was counted over 13 days under four concentration levels of the pyrethrum such as 0.20, 0.32, 0.50 and 0.80 mg/cm². 144, 69, 54 and 50 beetles are exposed to the concentration levels of the pyrethrum 0.20, 0.30, 0.50 and 0.80 mg/cm² respectively. Over the time period of 13 days, the mortality of beetles are recorded. As time increases, the cumulative mortality increases.
Table 5.1: Number of cumulative mortality of adult flour beetles

<table>
<thead>
<tr>
<th>Time(Day)</th>
<th>Dose (mg/cm²)</th>
<th>0.20(control)</th>
<th>0.32</th>
<th>0.50</th>
<th>0.80</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>14</td>
<td>17</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>24</td>
<td>28</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>31</td>
<td>44</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>35</td>
<td>47</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>38</td>
<td>49</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>40</td>
<td>50</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>41</td>
<td>50</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>41</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>41</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>41</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>41</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>42</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>43</td>
<td>50</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Group Size</td>
<td>144</td>
<td>69</td>
<td>54</td>
<td>50</td>
</tr>
</tbody>
</table>

Hewlett (1974) and Laurence and Morgan (1989) used this mortality data to describe dose-response curve by estimating the parameters of the distribution of tolerances. In dose-response study, the dose-response relationship is estimated and then to estimate the tolerance level of the individuals in the population. The tolerance levels are generally referred to as the median effective dose to produce a response in 50% of individuals on average in the population. In toxicity study, on the other hand, the parameters of interest are called median lethal dose or median lethal concentration. Since the modeling approaches to investigate the dose-response relationship are not appropriate to fit the small dataset, we use multiple comparisons procedures developed in Chapter 2 to find the minimum effective dose defined in Chapter 1 by using the above does-time response mortality data.

Consider the dose of 0.20 as the control dose. Assume $\delta = 0.20$ as a threshold. A dose
level, for example, is effective if it increases the chance of killing beetles by 20%. The 95% lower confidence intervals for the difference effect between treatment and control, given by the Double Partition method, and the method of Partitioning Vectorized Space are shown in Table 5.2.

Table 5.2: Simultaneous Lower Confidence Limits with Confidence Level 95% on $p_{ij} - p_{i0}$

<table>
<thead>
<tr>
<th>Time(Day)</th>
<th>$p_{11} - p_{i0}$</th>
<th>$p_{12} - p_{i0}$</th>
<th>$p_{i3} - p_{i0}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.0399</td>
<td>-0.0604</td>
<td>-0.0758</td>
</tr>
<tr>
<td>2</td>
<td>0.0286</td>
<td>0.0111</td>
<td>0.0476</td>
</tr>
<tr>
<td>3</td>
<td>0.1193</td>
<td>0.1465</td>
<td>0.1391</td>
</tr>
<tr>
<td>4</td>
<td>0.3069</td>
<td>0.3824</td>
<td>0.3770</td>
</tr>
<tr>
<td>5</td>
<td>0.3232</td>
<td>0.4309</td>
<td>0.5162</td>
</tr>
<tr>
<td>6</td>
<td>0.3316</td>
<td>0.4480</td>
<td>0.5366</td>
</tr>
<tr>
<td>7</td>
<td>0.3323</td>
<td>0.4528</td>
<td>0.5432</td>
</tr>
<tr>
<td>8</td>
<td>0.3251</td>
<td>0.4650</td>
<td>0.5357</td>
</tr>
<tr>
<td>9</td>
<td>0.3251</td>
<td>0.4650</td>
<td>0.5357</td>
</tr>
<tr>
<td>10</td>
<td>0.3251</td>
<td>0.4650</td>
<td>0.5571</td>
</tr>
<tr>
<td>11</td>
<td>0.3251</td>
<td>0.4650</td>
<td>0.5571</td>
</tr>
<tr>
<td>12</td>
<td>0.3179</td>
<td>0.4577</td>
<td>0.5497</td>
</tr>
<tr>
<td>13</td>
<td>0.3107</td>
<td>0.4504</td>
<td>0.5423</td>
</tr>
</tbody>
</table>

A 95% lower confidence intervals for the effect differences given in Table 5.2 for example, at time $T = 13$ and for all doses are (0.3107, 1), (0.4504, 1), and (0.5423, 1) respectively. With the threshold 20%, all lower confidence intervals are subset of (0.20, 1). Similarly, the 95% lower confidence intervals up to time day 4 and for all doses are the subset of (0.20, 1). Thus, by Theorems 1, and 2, we claim that the minimum effective dose level is 0.32 (mg/cm$^2$) at time day 4. It means that after day 3 all treatment effects are statistically significant from the effect of control 0.20 (mg/cm$^2$) when the threshold is set to $\delta = 0.20$.

In order to apply Theorem 3 to find the MED (The method of Partition with Bonferroni Correction), for illustration purpose, we calculate a 98.33% lower confidence intervals for the difference
effect between treatment and control. The 98.33% lower confidence intervals for the difference effect between treatment and control are shown in Table 5.3.

Table 5.3: Simultaneous Lower Confidence Limits with Confidence Level 98.33% on $p_{ij} - p_{i0}$

<table>
<thead>
<tr>
<th>Time(Day)</th>
<th>$p_{i1} - p_{i0}$</th>
<th>$p_{i2} - p_{i0}$</th>
<th>$p_{i3} - p_{i0}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.0749</td>
<td>-0.0985</td>
<td>-0.1149</td>
</tr>
<tr>
<td>2</td>
<td>-0.0068</td>
<td>-0.0274</td>
<td>0.0078</td>
</tr>
<tr>
<td>3</td>
<td>0.0837</td>
<td>0.1076</td>
<td>0.0990</td>
</tr>
<tr>
<td>4</td>
<td>0.2716</td>
<td>0.3442</td>
<td>0.3376</td>
</tr>
<tr>
<td>5</td>
<td>0.2879</td>
<td>0.3930</td>
<td>0.4780</td>
</tr>
<tr>
<td>6</td>
<td>0.2964</td>
<td>0.4102</td>
<td>0.4987</td>
</tr>
<tr>
<td>7</td>
<td>0.2970</td>
<td>0.4152</td>
<td>0.5053</td>
</tr>
<tr>
<td>8</td>
<td>0.2898</td>
<td>0.4275</td>
<td>0.4977</td>
</tr>
<tr>
<td>9</td>
<td>0.2898</td>
<td>0.4275</td>
<td>0.4978</td>
</tr>
<tr>
<td>10</td>
<td>0.2898</td>
<td>0.4275</td>
<td>0.5194</td>
</tr>
<tr>
<td>11</td>
<td>0.2898</td>
<td>0.4275</td>
<td>0.5194</td>
</tr>
<tr>
<td>12</td>
<td>0.2826</td>
<td>0.4201</td>
<td>0.5119</td>
</tr>
<tr>
<td>13</td>
<td>0.2753</td>
<td>0.4127</td>
<td>0.5044</td>
</tr>
</tbody>
</table>

The 98.33% lower confidence intervals for the effect difference $p_{ij} - p_{0j}$, $j = 1, 2, 3$ are (0.2753, 1), (0.4127, 1), and (0.5044, 1) for time 13 and for all doses are the subset of (0.20, 1). With the same threshold 0.20, the method of Partition with Bonferroni Correction find the MED to be 0.32 (mg/cm$^2$) at time day 4. With these procedures, we find the same MED. But the width of confidence interval for the effect differences by the Partition with Bonferroni Correction procedure is wider than that of the others two procedures.

Now for illustration, let the threshold be $\delta = 0.40$. In order to find the MED, we apply the method of Double Partition. At the highest time point 13, the lower confidence intervals for the effect differences $p_{ij} - p_{i0}$ for $j = 1, 2, 3$ are (0.3107, 1), (0.4504, 1), and (0.5423, 1) respectively. Three lower confidence intervals at time 13 are subset of (0.40, 1). Similarly, the 95% lower
confidence intervals up to time day 6 for all doses are the subset of \((0.20, 1)\). On the other hand, at
time point 5, the lower confidence intervals \((0.4309, 1), (0.5162, 1)\) for \(p_{ij} - p_{i0}, j = 2, 3\) are
the subset of \((0.40, 1)\), but the lower confidence interval \((0.3232, 1)\) for \(p_{ij} - p_{i0}\) for \(j = 1\) is not subset
of \((0.40, 1)\). Therefore, the estimated MED is the dose 1 at time point 5. Similarly, with the same
threshold \(\delta = 0.40\), the estimated MED by the method of Partition with Bonferroni Correction is
dose 3 at the time point 5.

5.2 Applications for MTD

In this section, we use the procedures presented in Chapter 3 to find the MTD using a dataset
from Zhu (2005). This dataset is about the hindlimb grip strength of rat. Grip strength is the force
applied to pull on or suspend from objects. The effects of drugs, toxins, muscle relaxants, disease,
ageing or neural damage on muscle strength result in deficits in muscular strength. Therefore,
muscle strength of forelimbs, one of few continuous measures of FOB(Functional Observational
Battery), is used to assess the adverse effect of neurotoxic compounds on nervous system. The
primary role of nervous system is to control the psychological functions of human and animal
as well as other bodily processes (Zhu, 2005). Neurotoxic effects on nervous system result in
the transient or persistent adverse effect on behavior, neurochemistry, neurophysiology and neu-
ropathology of human and animal. In FOB test, TET(Triethyl Tin), a highly neurotoxic agent in
human and animals producing severe brain edema, was administered on ten Long-Evans rats. The
dose concentration levels of TET are as follows: 0, 0.75, 1.5, 3, and 6 mg/kg. At the beginning
of the experiment, \(n_j = 10\) rats are exposed to each of dose concentration where \(j = 0, 1, 2, 3, 4\)
and hindlimb grip strength of rats are measured over a sequence of time such as 0, 2, 24, and 168
hours intervals. One rat died at the time point 168 hour when dose level is 6 mg/kg. Table 5.4
shows the summary statistics of the control group and other four dose groups.

The summary statistics show that hindlimb grip strength decreased with dose concentration
levels and time. Analysis of Variance(ANOVA) with repeated measurements is a recommended
statistical tool to analyze the neurobiological experimental data for finding the reference dose- the
highest dose level at which the responses are not different from those of the control(Moser et al.
Table 5.4: Mean(S.E) of the variable-hindlimp grip strength of rats exposed to the dose of triethyl tin (TET)

<table>
<thead>
<tr>
<th>Time(h)</th>
<th>0(control )</th>
<th>0.75</th>
<th>1.5</th>
<th>3</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.9140(0.1596)</td>
<td>0.9660(0.1314)</td>
<td>0.8645(0.1330)</td>
<td>0.7680(0.1772)</td>
<td>0.8580(0.1791)</td>
</tr>
<tr>
<td>2</td>
<td>1.0030(0.2383)</td>
<td>0.8030(0.2067)</td>
<td>0.6283(0.1700)</td>
<td>0.4930(0.1090)</td>
<td>0.4580(0.1105)</td>
</tr>
<tr>
<td>24</td>
<td>0.8495(0.1743)</td>
<td>0.8015(0.1310)</td>
<td>0.6185(0.1672)</td>
<td>0.5285(0.0907)</td>
<td>0.4360(0.0829)</td>
</tr>
<tr>
<td>168</td>
<td>0.8950(0.2114)</td>
<td>0.8605(0.1083)</td>
<td>0.7515(0.1572)</td>
<td>0.7960(0.2204)</td>
<td>0.4689(0.1855)*</td>
</tr>
</tbody>
</table>

Note 1: Ten rats per dose group, each measured at four time points.
Note 2: * One rat died, resulting in loss of one observation.

[1996], [Zhu (2005)], on the other hand, used modeling approach to quantify the benchmark dose. However, in the study, we use the procedures proposed in Chapter 3 to identify the maximum tolerated dose (MTD) of the neurotoxic agent, Triethyl Tin.

Table 5.5 shows the 95% lower confidence intervals for the adverse effect difference between treatment and control, given by the method of Double Partition.

Table 5.5: Simultaneous lower Confidence Limits with Confidence Level 95% on $\mu_{ij} - \mu_{i0}$

<table>
<thead>
<tr>
<th>Time(h)</th>
<th>$\mu_{i1} - \mu_{i0}$</th>
<th>$\mu_{i2} - \mu_{i0}$</th>
<th>$\mu_{i3} - \mu_{i0}$</th>
<th>$\mu_{i4} - \mu_{i0}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.0662</td>
<td>-0.1677</td>
<td>-0.2642</td>
<td>-0.1742</td>
</tr>
<tr>
<td>2</td>
<td>-0.3312</td>
<td>-0.5057</td>
<td>-0.6412</td>
<td>-0.6762</td>
</tr>
<tr>
<td>24</td>
<td>-0.1491</td>
<td>-0.3321</td>
<td>-0.4221</td>
<td>-0.5146</td>
</tr>
<tr>
<td>168</td>
<td>-0.1706</td>
<td>-0.2796</td>
<td>-0.2351</td>
<td>-0.5659</td>
</tr>
</tbody>
</table>

For illustration purpose, we assume $\delta = 0.25$. Take $\alpha = 0.05$. Then $t_{45,0.05} = 1.679427$. The estimate of pooled sample standard deviation $\hat{\sigma}_0$ at time 0 hour is 0.0248. The 95% lower confidence bound, $\bar{y}_{0j} - \bar{y}_{00} + \hat{\sigma}_0 \sqrt{\frac{1}{n_j} + \frac{1}{n_0}}$ for the adverse effect difference $\mu_{0j} - \mu_{00}$ for $j = 1, 2$ are $(-0.0662, \infty), (-0.1677, \infty)$ respectively at time point 0 hour. They are all subset of $(-0.25, \infty)$. But the 95% lower confidence interval for $\mu_{02} - \mu_{00}$ is $(-0.2642, \infty)$, which is not the subset of $(-0.25, \infty)$. Therefore, according to the Theorem 3.2, we declare that the maximum tolerated
dose (MTD) is the dose level 1.5 mg/kg at time 0 hour at 95% confidence level.

Let us take a different threshold $\delta = 0.65$. The 95% lower confidence intervals at time 0 hour for the mean difference $\mu_{0j} - \mu_{00}$ for $j = 1, 2, 3, 4$ are $(-0.0662, \infty), (-0.1677, \infty), (-0.2642, \infty)$ and $(-0.1742, \infty)$ respectively. They are all subsets of $(-0.65, \infty)$. According to the Theorem [3.2] we need to move to the next time point 2 hour. At the time point 2 hour, the 95% confidence intervals for $\mu_{2j} - \mu_{20}$ for $j = 1, 2, 3$ are $(-0.3312, \infty), (-0.5057, \infty), (-0.6412, \infty)$ which are the subset of $(-0.65, \infty)$. But the 95% confidence interval for mean difference at time point 2 hour $\mu_{24} - \mu_{20}$ is $(-0.6762, \infty)$ which is not a subset of $(-0.65, \infty)$. According to the definition of safe dose given in Chapter 3, all doses at time point 0 hour are safe and the first three doses at time point 2 hour are also safe. Therefore, by the Theorem [3.2] the MTD is dose 3 mg/kg at time point 2 hour.

The method of Partition with Bonferroni Correction proceeds by comparing a lower confidence bound for $\mu_{ij} - \mu_{i0}, j = 1, 2, 3, 4, i = 1, 2, 3, 4$ with the threshold, starting at the lowest dose and the lowest time point. In order to identify the MTD, we calculate a $100(1 - \frac{\alpha}{4})\%$ lower confidence interval for the mean difference $\mu_{ij} - \mu_{i0}, j = 1, 2, 3, 4, i = 1, 2, 3, 4$. For this procedure, the level of significance is $\frac{\alpha}{4}$ because there are comparisons within each time point. Therefore, the confidence level is $100(1 - \frac{\alpha}{4})\% = 98.75\%$.

The 98.75% lower confidence intervals for the adverse effect difference between treatment and control, given by the method of partition with Bonferroni Correction are shown in Table 5.6.

Table 5.6: Simultaneous lower Confidence Limits with Confidence Level 98.75% on $\mu_{ij} - \mu_{i0}$

<table>
<thead>
<tr>
<th>Time(h)</th>
<th>$\mu_{i1} - \mu_{i0}$</th>
<th>$\mu_{i2} - \mu_{i0}$</th>
<th>$\mu_{i3} - \mu_{i0}$</th>
<th>$\mu_{i4} - \mu_{i0}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.1112</td>
<td>-0.2127</td>
<td>-0.3092</td>
<td>-0.2192</td>
</tr>
<tr>
<td>2</td>
<td>-0.3811</td>
<td>-0.5556</td>
<td>-0.6911</td>
<td>-0.7261</td>
</tr>
<tr>
<td>24</td>
<td>-0.1876</td>
<td>-0.3706</td>
<td>-0.4606</td>
<td>-0.5531</td>
</tr>
<tr>
<td>168</td>
<td>-0.2224</td>
<td>-0.3314</td>
<td>-0.2869</td>
<td>-0.6192</td>
</tr>
</tbody>
</table>

If $\delta = 0.25$, then at time 0 hour, the 98.75% lower confidence bound for the adverse mean
effect difference $\mu_{ij} - \mu_{i0}$ for $j = 1, 2$ are -0.0662 and -0.2127 respectively. They are all greater than -0.25. But the 98.75% lower confidence bound for the $\mu_{ij} - \mu_{i0}$ when $j = 3$ is -0.3092, which is smaller than -0.25.

With the same threshold ($\delta = 0.25$) used in the method of Double Partition, the Theorem 3.3 finds dose 1.5 mg/kg at time 0 hour at 0.9825% confidence level. This finding is the same as that found in the method of Double Partition.

Next, for illustration, if $\delta = 0.65$, then the 98.75% lower confidence bound for the mean difference $\mu_{ij} - \mu_{i0}$ for $j = 1, 2, 3, 4$ are -0.1112, -0.2127, -0.3092 and -0.2192 respectively at time $i = 0$ hour. They are all greater than -0.65. According to the definition of safe dose, they are safe. Then we move to the next time line and start with the lowest dose level. Within time period 2 hour, the 98.75% lower confidence bound for $\mu_{ij} - \mu_{i0}$ for $i = 1, j = 1, 2$ are -0.3811 and -0.5556 respectively which are greater than -0.65. So they are safe. But the dose 3 mg/kg is not safe because the 98.75% lower confidence bound for $\mu_{ij} - \mu_{i0}$ when $i = 1, j = 3$ is -0.6911, which is smaller than -0.65. Thus, by the Theorem 3.3, the recommended MTD is the dose of 3 mg/kg at time point 2 hour. This result is different from that found in the Theorem 3.3.
CHAPTER 6  CONCLUDING REMARKS

In this dissertation, we propose three stepwise confidence interval based procedures to identify the minimum effective dose (MED) and the maximum tolerated dose (MTD) of a drug when the responses are observed over a sequence of time at increasing dose levels. The three procedures are the method of Double Partition, the method of Partitioning Vectorized Space and the method of Partition with Bonferroni Correction. The method of Double Partition and the Partition of Vectorized Space are found to be superior compared to the method of Partition with Bonferroni Correction in detecting the true MED and MTD of a drug. These new confidence procedures show new insights on the efficacy for insecticide over time, and neurotoxic effects on nervous system of rats over time. They also enhance the literature on statistical methodologies for time dependent dose-response research.

In this study, we assume that both the efficacy and toxicity of a drug increase with the dose level over time. The consequence of this assumption is that if a dose is not declared as efficacious, then we stop checking the lower doses when evaluating efficacy (or if a dose is not declared as safe, we do not need to test the higher doses for toxicity investigation). This pre-determined ordering of the doses leads to the partitioning of parameter space into the disjoint possible null hypotheses where only one contains the true parameter, consequently making inference for MED and MTD automatically forms the step-down and step-up procedures respectively and controls the proper error rate at a pre-specified level. The two stepwise confidence interval procedures (the method of Double Partition and the method of Partitioning Vectorized Space) developed in this dissertation based on the monotonicity assumptions on the dose-response do not need for multiplicity adjustment. However, the method of Partition with Bonferroni Correction needs multiplicity adjustment.

In the development of three stepwise procedures, we treat the data as from independent populations in which the conditions of the theorems are plausibly assumed for illustration purpose and convenience by ignoring the correlation among the measurements in time-wise. But how to deal with correlations among the test statistics induced by correlations among the measurements
in time-wise will be a hard but more realistic problem. We will extend the procedures developed in this study to capture the correlation structure among the measurements in time-wise in our future research.

In addition, the procedures developed in this dissertation are applicable when the monotonicity assumption on dose-response is hold. If that assumption is violated, lower dose than the true maximum tolerated dose (higher dose than the true minimum effective dose) is unsafe (ineffective). Therefore, we will address this problem in our future study.

We use Peskun’s (1993) lower bound for the inference on MED, which is an asymptotic confidence lower bound. However, for the small sample sizes, as indicated in simulation study, the performance of the proposed procedures for MED are not satisfactory. Therefore, for small sample, we need to develop the exact confidence method that will incorporate the correlation among the measurements. On the other hand, in making inference on MTD, we assume that the variance across all doses in a single time point are equal. In practice, this assumption is rarely hold. How to deal with this unequal variance across dosages in detecting the MTD of a drug will be a good research area. We will extend our stepwise confidence interval procedures to the case of heteroscedasticity.
BIBLIOGRAPHY


APPENDIX: SELECTED R PROGRAMS

# Finding the MED by using the Partition of Vectorized Space Method

beetle.data = read.table("C:/Users/Najib/OneDrive/Deleted File/Users/rprev_000/Documents/Dose_Response/beetle_data.txt", header=T)

# Calculation of mortality rate

dd <- subset(beetle.data, Sex=="M", select=c(Sex, Time, n))
new.data <- NULL
for ( i in c(0.20, .32, 0.5, 0.8))
{
  new.data <- cbind(new.data, subset(dd, Dose==i))
}

# end of mortality rate

con.fn <- NULL
for ( k in 1:13)
{
  beetle.Time <- subset(beetle.data, Sex=="M" & Time==k, select=c(Sex, Time, n))
  n <- beetle.Time$Total
  x <- beetle.Time$CMort
  x <- c(5, 7, 11, 6)
  n <- c(50, 20, 18, 10)
  alpha <- -0.05
  c.fun <- function(n)
  {
    c <- NULL
    n0 <- n[1]...
n1<-n[2:4]

for ( i in 1:length(n1))
{
  c.f<-function (r,s)
  {
    n1[i]*(r+s)-n0*s
  }
  r=seq(1,20)
  s=seq(1,20)
  tt.1<-outer(r,s,FUN=c.f)
  tt.2<-as.vector(tt.1)
  tt.v<-min(tt.2[tt.2>0])
  c[i]<-tt.v/(n0*n1[i]*2)
}
return(c)

# Calculation of Ci and Peskun confidence lower bound

ff<-function(n, x)
{
  n0<-n[1]
  n1<-n[2:4]
  x0<-x[1]
  x1<-x[2:4]
  t=x1/n1-x0/n0
  z=qnorm(1-alpha)
  c<-c.fun(n)
  L=(t-c-z*sqrt(((n1+n0+z^2)/(4*n1*n0)-(t-c)^2/(n1+n0)))/(1+z^2/(n1+n0))
  # delta =0.20
  #L=(t-c-delta)/sqrt(((x0/n0*(1-x0/n0))/n0+(x1/n1*(1-x1/n1)))/n1)
# \( L = (t - z \cdot \sqrt{((x_0/n_0 \cdot (1 - x_0/n_0)) / n_0) + ((x_1/n_1 \cdot (1 - x_1/n_1)) / n_1))} \)

return(L)

con.fn <- rbind(con.fn, ff(n, x))

con.fn
effect.diff <- NULL

for (i in 1:13)
{
  for (j in 1:3)
  {
    effect.diff <- c(effect.diff, con.fn[i, j])
  }
}
effect.diff
delta <- 0.20

i <- 39

while (effect.diff[i] >= delta)
{
  i <- i - 1
}
effect.diff[i + 1]
k <- i + 1
effect.diff

i <- (k) %% 3
j

if (j == 0) j <- 3 else
\{ j \leftarrow j \\
i \leftarrow i + 1 \}

\text{con.fn}[i, j] \\
\text{c}(\text{Time}=i, \text{Dose}=j) \\

# Finding the MED using Partition with Bonferroni Correction

\text{beetle.data} = \text{read.table}("C:/Users/Najib/OneDrive/Deleted File/Users/rperv_000/Documents/Dose_Response/beetle_data.txt", \text{header=TRUE})

\text{con.fn} \leftarrow \text{NULL}

\text{for} (\text{k in 1:13}) \\
\{ \\
\text{beetle.Time} \leftarrow \text{subset(beetle.data, Sex="M" & Time=k, select=c(Sex, Time, n))} \\
\text{n} \leftarrow \text{beetle.Time}$\text{Total} \\
\text{x} \leftarrow \text{beetle.Time}$\text{CMort} \\
\text{alpha} \leftarrow -0.05 \\
\text{c.fun} \leftarrow \text{function(n)} \\
\{ \\
\text{c} \leftarrow \text{NULL} \\
\text{n0} \leftarrow \text{n[1]} \\
\text{n1} \leftarrow \text{n[2:4]} \\
\text{for} (\text{i in 1:length(n1)}) \\
\{ \\
\text{c.f} \leftarrow \text{function(r, s)} \\
\{ \\
\text{n1[i]*(r+s)-n0*s} \\
\} \\
\text{r} = \text{seq}(1,20) \}
s = seq(1, 20)
tt.1 <- outer(r, s, FUN = c.f)
tt.2 <- as.vector(tt.1)
tt.v <- min(tt.2[tt.2 > 0])
c[i] <- tt.v / (n0 * n1[i] * 2)
}
return(c)
}

# calculation of Ci and Peskun confidence lower bound

ff <- function(n, x)
{
  n0 <- n[1]
n1 <- n[2:4]
x0 <- x[1]
x1 <- x[2:4]
t = x1 / n1 - x0 / n0
z = qnorm(1 - alpha / 3)
c <- c.fun(n)
L = (t - c - z * sqrt((n1 + n0 + z^2) / (4 * n1 * n0) - (t - c)^2 / (n1 + n0))) / (1 + z^2 / (n1 + n0))
return(L)
}
con.fn <- rbind(con.fn, ff(n, x))
}
con.fn
delta <- 0.20
for (k in 13:1)
{
  if (any(con.fn[k] < delta)) break
}
if (k < 13 & all(con.fn[k,] < delta)) k <- k + 1 else
k <- k
if (con.fn[k,3] < delta) {MED.D <- 4} else
if (con.fn[k,2] < delta) {MED.D <- 3} else
if (con.fn[k,1] < delta) {MED.D <- 2} else
MED.D <- 1
(c(k,MED.D))

# Finding the MED using Double Partition Method

beetle.data = read.table("C:/Users/Najib/OneDrive/Deleted File/Users/rperv.000/Documents/Dose_Response/beetle.data.txt", header=T)
con.fn<-NULL
for(k in 1:13)
{
beetle.Time<-subset(beetle.data, Sex="M" & Time==k, select=c(Sex, Time, n))
n<-beetle.Time$Total
x<-beetle.Time$CMort
alpha <- 0.05
c.fun<-function(n)
{
c<-NULL
n0<-n[1]
n1<-n[2:4]
for (i in 1:length(n1))
{
c.f<-function(r,s)
{


n1[i]*(r+s)-n0*s
}
r=seq(1,20)
s=seq(1,20)
tt.1<-outer(r,s,FUN=c.f)
tt.2<-as.vector(tt.1)
tt.v<-min(tt.2[tt.2>0])
c[i]<-tt.v/(n0*n1[i]*2)
}
return(c)

# Calculation of Ci and Peskun confidence lower bound
ff<-function(n, x)
{
  n0<-n[1]
n1<-n[2:4]
x0<-x[1]
x1<-x[2:4]
t=x1/n1-x0/n0
z=qnorm(1-alpha)
c<-c.fun(n)
L=(t-c-z*sqrt((n1+n0+z^2)/(4*n1*n0)-(t-c)^2/(n1+n0)))/(1+z^2/(n1+n0))
return(L)
}
con.fn<-rbind(con.fn,ff(n,x))
}
con.fn
delta <- 0.20
for ( k in 13: 1)
```r
if (any(con.fn[,]<delta)) break

if (k< 13 & all(con.fn[,]<delta)) k=k+1 else
k=k

if (con.fn[k,3]<delta) { MED.D<-4 } else
if (con.fn[k,2]<delta) {MED.D<-3} else
if (con.fn[k,1]<delta) {MED.D<-2} else
MED.D<-1
(c(k,MED.D))

#Simulation Study for MED with Partition with Bonferroni Correction

#prob
```
x.data<-NULL
for ( k in 1: nrow(prob) )
{
  # generate the response
  x.data<-rbind(x.data, rbinom(4, size=sample.size[s], prob=prob[k,]))
}
for ( k in 1: nrow(prob) )
{
  x<-x.data[k,]
  n<-rep(sample.size[s], 4)
  alpha <-0.05
  c.fun<-function(n){
    c<-NULL
    n0<-n[1]
    n1<-n[2:4]
    for ( i in 1:length(n1) )
    {
      c.f<-function(r,s)
      {
        n1[i]*(r+s)-n0*s
      }
      r=seq(1,n0)
      s=seq(1,n0)
      tt.1<-outer(r,s,FUN=c.f)
      tt.2<-as.vector(tt.1)
      tt.v<-min(tt.2[tt.2>0])
      c[i]<-tt.v/(n0*n1[i]*2)
    }
  return(c)
# Calculation of Ci and Peskun confidence lower bound

```R
ff <- function(n, x) {
  n0 <- n[1]
n1 <- n[2:4]
x0 <- x[1]
x1 <- x[2:4]
t <- x1/n1 - x0/n0
z <- qnorm(1 - alpha / 3)
c <- c.fun(n)
L <- (t - c - z * sqrt((n1 + n0 + z^2) / (4 * n1 * n0) - (t - c)^2 / (n1 + n0))) / (1 + z^2 / (n1 + n0))
return(L)
}
con.fn <- rbind(con.fn, ff(n, x))
}
con.fn
for (k in 6:1) {
  if (any(con.fn[k,] < delta)) break
}
if (k < 6 & all(con.fn[k,] < delta)) k <- k + 1 else
k <- k
if (con.fn[k,3] < delta) { MED.D <- 4 } else
if (con.fn[k,2] < delta) {MED.D <- 3} else
if (con.fn[k,1] < delta) {MED.D <- 2} else
MED.D <- 1
return(c(k, MED.D))
```

r <- 10000
result <- replicate(r, expr=sim.fun())

power <- mean(I(result[,1]==6)*I(result[,2]==3))
se.power <- sqrt(power * (1 - power) / r)
c(power=power, SE=se.power)

#########################################################################
# Simulation Study for MED with the method of partitioning the Vectorized Space
#########################################################################
rm(list=ls())
sample.size <- c(20, 50, 100)
prob <- as.matrix(data.frame(p0=rep(0.1, 6),
    p1=c(0.2, 0.25, 0.26, 0.28, 0.29, 0.50),
    p2=c(0.6, 0.63, 0.66, 0.69, 0.72, 0.75),
    p3=c(0.8, 0.82, 0.84, 0.86, 0.88, 0.9)))
prob

sim.fun <- function()
{
    s <- 3
delta <- 0.25
con.fn <- NULL
x.data <- NULL
for (k in 1: nrow(prob))
{
    # Generating the response
    x.data <- rbind(x.data, rbinom(4, size=sample.size[s], prob=prob[k,]))
}
for (k in 1: nrow(prob))
\[
\{ \\
    x<-x.data[k,] \\
    n<-rep(sample.size[s], 4) \\
    alpha<-0.05 \\
    c.fun<-function(n){ \\
        c<-NULL \\
        n0<-n[1] \\
        n1<-n[2:4] \\
        for ( i in 1:length(n1)) 
        { \\
            c.f<-function(r, s) 
            { \\
                n1[i]*(r+s)-n0*s \\
            } \\
            r=seq(1,n0) \\
            s=seq(1,n0) \\
            tt.1<-outer(r, s, FUN=c.f) \\
            tt.2<-as.vector(tt.1) \\
            tt.v<-min(tt.2[tt.2>0]) \\
            c[i]<-tt.v/(n0*n1[i]*2) \\
        } \\
        return(c) \\
    } \\
# Calculation of Ci and Peskun confidence lower bound \\
ff<-function(n, x) 
    { \\
        n0<-n[1] \\
        n1<-n[2:4] \\
        x0<-x[1] 
\}
x1 <- x[2:4]
t = x1 / n1 - x0 / n0
z = qnorm(1 - alpha)
c <- c.fun(n)
L = (t - c - z * sqrt((n1 + n0 + z^2) / (4 * n1 * n0) - (t - c)^2 / (n1 + n0))) / (1 + z^2 / (n1 + n0))
return(L)
}
con.fn <- rbind(con.fn, ff(n, x))
}
con.fn

effect.dif <- NULL
for (i in 1:6) {
for (j in 1:3) {
effect.dif <- c(effect.dif, con.fn[i, j])
}
}
effect.dif
i <- 18
while (effect.dif[i] >= delta) {
i <- i - 1
}
effect.dif[i + 1]
k <- i + 1

effect.dif
i <- (k) %% 3
i
j <- (k) %% 3
j
if (j == 0) j <- 3 else
\[
\{ \begin{array}{l}
  j < j \\
i < i + 1
\end{array} \}
\]

\[
\text{return}(c(i, j))
\]

\[
r < - 10000
\]

\[
\text{result} <- \text{replicate}(r, \text{expr=sim.fun()})
\]

\[
\text{power} <- \text{mean}(I(\text{result}[1,]==5)*I(\text{result}[2,]==2))
\]

\[
\text{se.power} <- \text{sqrt}(\text{power}*(1-\text{power})/r)
\]

\[
\text{round}(c(\text{power}=\text{power}, \text{SE} = \text{se.power}), 6)
\]

#Simulation Study for MED with Double Partition Method

```
rm(list=ls())
sample.size <- c(20, 50, 100)

prob <- as.matrix(data.frame(p0=c(0.1, 0.1, 0.1, 0.1, 0.1, 0.1),
                              p1=c(0.2, 0.25, 0.26, 0.28, 0.29, 0.50),
                              p2=c(0.6, 0.63, 0.66, 0.69, 0.72, 0.75),
                              p3=c(0.8, 0.82, 0.84, 0.86, 0.88, 0.9)))

prob

sim.fun <- function(m.type=TRUE){
  s <- 3
  delta <- -0.25
  con.fn <- NULL
  x.data <- NULL
  for (k in 1:nrow(prob)) {
    # generate the response
    x.data <- rbind(x.data, rbinom(4, size=sample.size[s], prob=prob[k,]))
  }
  return(c(i, j))
}
result <- replicate(r, expr=sim.fun())
```
for (k in 1: nrow(prob)) {
    x <- x.data[k,]
    n <- rep(sample.size[s], 4)
    alpha <- 0.05
    c.fun <- function(n) {
        c <- NULL
        n0 <- n[1]
        n1 <- n[2:4]
        for (i in 1:length(n1)) {
            c.f <- function(r, s) {
                n1[i]*(r+s) - n0*s
            }
            r = seq(1, n0)
            s = seq(1, n0)
            tt.1 <- outer(r, s, FUN = c.f)
            tt.2 <- as.vector(tt.1)
            tt.v <- min(tt.2[tt.2 > 0])
            c[i] <- tt.v / (n0 * n1[i] * 2)
        }
        return(c)
    }
    # Calculation of Ci and Peskun confidence lower bound
    ff <- function(n, x) {
        n0 <- n[1]
        n1 <- n[2:4]
\[ x_0 \leftarrow x[1] \]
\[ x_1 \leftarrow x[2:4] \]
\[ t = x_1 / n_1 - x_0 / n_0 \]
\[ z = qnorm(1 - \alpha) \]
\[ c \leftarrow c.\text{fun}(n) \]
\[ L = \frac{(t - c) - z \cdot \sqrt{((n_1 + n_0 + z^2) / (4 \cdot n_1 \cdot n_0)) - (t - c) \cdot 2 / (n_1 + n_0)) / (1 + z \cdot 2 / (n_1 + n_0))}}{1 + z^2 / (n_1 + n_0)} \]
\[ \text{return}(L) \]

```
c.\text{fn} \leftarrow \text{bind}(c.\text{fn}, \text{ff}(n, x))
```

```for (k in 6:1)
{
  if (any(c.\text{fn}[k] < \text{delta})) break
}
```

```
if (k < 6 & all(c.\text{fn}[k] < \text{delta})) k <- k + 1 else
k <- k
```

```if (c.\text{fn}[k, 3] < \text{delta}) \{ \text{MED.D} <- 4 \} else
if (c.\text{fn}[k, 2] < \text{delta}) \{ \text{MED.D} <- 3 \} else
if (c.\text{fn}[k, 1] < \text{delta}) \{ \text{MED.D} <- 2 \} else
\text{MED.D} <- 1
```

```
\text{return}(c(k, \text{MED.D}))
```

```
}\}
```

```r <- 10000
\text{result} \leftarrow \text{replicate}(r, \text{expr=sim.fun()})
```

```
power \leftarrow \text{mean}(\text{I(result[1,] == 5)} \times \text{I(result[2,] == 2)})
```

```
\text{se.power} \leftarrow \sqrt{\text{power} \times (1 - \text{power}) / r}
```

```
c(\text{power} = \text{power}, \text{SE} = \text{se.power})
```
In the following section, R programs for finding maximum tolerated dose (MTD) and program for simulation studies are presented.

Finding lower confidence interval for MTD by the method of Partition with Bonferroni Correction.


Toxicity.data

conf.u<-NULL

for ( k in c(0,24,168)){
  Data.T<-subset(Toxicity.data, Time==k, select=c( Time, Dose))

  Mean<-Data.T$Mean

  n<-Data.T$n
  STD<-Data.T$STD
  ff<-function(n, Mean, STD){
    K=4
    alpha <- 0.05
    n0<-n[1]
    n1<-n[2:5]
    Mean0<-Mean[1]
    Mean1<-Mean[2:5]
    t=Mean1-Mean0
\[
\sigma^2 = (\text{STD}_1^2 \cdot (n_1 - 1) + \text{STD}_2^2 \cdot (n_2 - 1) + \text{STD}_3^2 \cdot (n_3 - 1) \\
+ \text{STD}_4^2 \cdot (n_4 - 1) + \text{STD}_5^2 \cdot (n_5 - 1)) / (n_1 + n_2 + n_3 + n_4 + n_5 - 5)
\]

cu <- \text{t-cal} \cdot \sqrt{\sigma^2} \cdot \sqrt{1/n0+1/n1}
return(cu)
}

conf.u <- rbind(conf.u, ff(n, Mean, STD))
}

conf.u
delta <- 0
for (k in 1:4){
  if (any(conf.u[k,] <= delta)) break
}
if (k==1 & all(conf.u[k,] > delta)) k<-k+1 else k<-k

if(k==1 & conf.u[1] <= delta) {k<-k-1; MTD<-0} else
if (conf.u[k,1] <= delta) {k<-k-1; MTD<-4 } else
if (conf.u[k,2] <= delta) {k<-k; MTD<-1} else
if (conf.u[k,3] <= delta) {k<-k; MTD<-2} else
if (conf.u[k,4] <= delta){k<-k; MTD<-3} else
{k<-k; MTD<-4}
(c(k,MID))

#####################################################

#####################################################

# Finding the MTD by Double Partition method

Toxicity.data
conf.u<-NULL
for ( k in c(0,2,24,168)){
  Data.T<-subset(Toxicity.data, Time==k, select=c( Time, Dose))
  Mean<-Data.T$Mean
  n<-Data.T$n
  STD<-Data.T$STD

  ff<-function(n, Mean, STD){
    alpha <- -0.05
    n0<-n[1]
    n1<-n[2:5]
    Mean0<-Mean[1]
    Mean1<-Mean[2:5]
    t=Mean1-Mean0
    sigma2 <- (STD[1]*2*(n[1]-1)+STD[2]*2*(n[2]-1)+STD[3]*2*(n[3]-1)
    cu<-t-t.cal*sqrt(sigma2)*sqrt(1/n0+1/n1)
    return(cu)
  }
  conf.u<-rbind(conf.u, ff(n, Mean, STD))
}
conf.u
delta<- -0.50
for ( k in 1:4){
  if (any(conf.u[,]==delta)) break
}
if (k==1 & all(conf.u[,]> delta )) k<-k+1 else
k<-k
if (k==1 & conf.u[1]<= delta) {k<-k-1; MTD<0} else
if (conf.u[k,1]<=delta) {K<-k-1; MTD<-4} else
if (conf.u[k,2]<=delta) {K<-k; MTD<-1} else
if (conf.u[k,3]<=delta) {k<-k; MTD<-2} else
if (conf.u[k,4]<=delta) {k<-k; MTD<-3} else
{k<-k;MTD<-4}
result <-c(k, MTD)
result

#########################################################
# Simulation Study for MTD with the method of Partition
# with Bonferroni Correction
#########################################################
rm(lis=ls())
sample.size <-c(50,100, 150)
mean<-as.matrix(data.frame(mean0=c(0.90,0.90,0.90,0.90),
                           mean1=c(0.85,0.80,0.75,0.70),
                           mean2=c(0.80,0.75,0.70,0.75),
                           mean3=c(0.75, 0.70,0.65,0.60),
                           mean4=c(0.70, 0.65,0.60,0.55)))
mean
sigma<-c(0.15, 0.15, 0.15, 0.15)
sim.fun<-function(m.type=TRUE){
s<-3
con.fn<-NULL
x.data<-NULL
mean.x<-matrix(0, nrow(mean), ncol(mean))
sigma.2<-matrix(0, nrow(mean), ncol(mean))
for ( k in 1:nrow(mean)) {
for (j in 1: ncol(mean)) {
    x.data <- cbind(x.data, rnorm(n=sample.size[s], mean=mean[k, j], sd=sigma[k]))
}
mean.x[k,] <- apply(x.data, 2, mean)
sigma.2[k,] <- apply(x.data, 2, sd)
x.data <- NULL
}

# Calculation of confidence lower bound

conf.u <- NULL
for (k in 1: 4) {
    Mean <- mean.x[k,]
    n <- rep(sample.size[s], 5)
    STD <- sigma.2[k,]
    ff <- function(n, Mean, STD) {
        alpha <- 0.05
        n0 <- n[1]
        n1 <- n[2:5]
        Mean0 <- Mean[1]
        Mean1 <- Mean[2:5]
        t = Mean1 - Mean0
        sigma2 <- (STD[1]*2*(n[1]-1)+STD[2]*2*(n[2]-1)+STD[3]*2*(n[3]-1)
        cu <- t - t.cal * sqrt(sigma2) * sqrt(1/n0 + 1/n1)
        return(cu)
    }
    conf.u <- rbind(conf.u, ff(n, Mean, STD))
}
conf.u

delta <- -0.20

for ( k in 1:4 ){
  if ( any ( conf.u[k,] <= delta ) ) break
}

if ( ( k == 1 & all ( conf.u[k,] > delta ) ) ) k <- k + 1 else
  k <- k - 1

if ( k == 1 & conf.u[1,] <= delta ) { k <- k - 1; MTD <- 0 } else
if ( conf.u[1,1] <= delta ) { k <- k - 1; MTD <- 4 } else
if ( conf.u[1,2] <= delta ) { k <- k; MTD <- 1 } else
if ( conf.u[1,3] <= delta ) { k <- k; MTD <- 2 } else
if ( conf.u[1,4] <= delta ) { k <- k; MTD <- 3 } else

  return ( c ( k, MTD ) )
}

r <- 10000

result <- replicate ( r , expr = sim.fun () )

power <- mean ( I ( result [1,] == 1 ) * I ( result [2,] == 3 ) )

se.power <- sqrt ( power * ( 1 - power ) / r )

c ( power = power , SE = se.power )

# Simulation Study for MTD with the method of Double Partition

# rm ( list = ls () )

sample.size <- c ( 50, 100, 150 )

mean <- as.matrix ( data.frame ( mean0 = c ( 0.90, 0.90, 0.90, 0.90 ),
                                 mean1 = c ( 0.85, 0.80, 0.75, 0.70 ),
                                 mean2 = c ( 0.80, 0.75, 0.70, 0.65 ),
                                 mean3 = c ( 0.75, 0.70, 0.65, 0.60 ) ) )
mean4=c(0.70, 0.65, 0.60, 0.55))

mean
sigma<-c(0.15, 0.15, 0.15, 0.15)
sim.fun<-function(m.type=TRUE){
  s<-3
  con.fn<-NULL
  x.data<-NULL
  mean.x<-matrix(0, nrow(mean), ncol(mean))
  sigma.2<-matrix(0, nrow(mean), ncol(mean))
  for (k in 1:nrow(mean)) {
    for (j in 1:ncol(mean)) {
      x.data<-cbind(x.data, rnorm(n=sample.size[s], mean=mean[k,j], sd=sigma[k]))
    }
    mean.x[k,]<- apply(x.data, 2, mean)
    sigma.2[k,]<- apply(x.data, 2, sd)
    x.data<-NULL
  }
  # calculation of confidence lower bound

  conf.u<-NULL
  for (k in 1:4){
    Mean<-mean.x[k,]
    n<-rep(sample.size[s], 5)
    STD<-sigma.2[k,]
    ff<-function(n, Mean, STD){
      alpha <- 0.05
      n0<-n[1]
      n1<-n[2:5]
      Mean0<-Mean[1]
Mean1<-Mean[2:5]
t=Mean1-Mean0
cu<-t.cal*sqrt(sigma2)*sqrt(1/n0+1/n1)
return(cu)
}
conf.u<-rbind(conf.u, ff(n, Mean, STD))
}
conf.u
delta<-−0.20
for ( k in 1:4){
if (any(conf.u[k,]<=delta)) break
}
if (k==1 & all(conf.u[k,]>delta)) k<-k+1 else k<-k
if(k==1 & conf.u[1,]<=delta) {k<-k-1; MTD<-0} else
if (conf.u[k,1]<=delta) {K<-k-1; MTD<-4} else
if (conf.u[k,2]<=delta) {K<-k; MTD<-1} else
if (conf.u[k,3]<=delta) {K<-k; MTD<-2} else
if (conf.u[k,4]<=delta) {K<-k; MTD<-3} else
{k<-k; MTD<-4}
return(c(k, MTD))
}
r<-10000
result<-replicate(r, expr=sim.fun())
power<-mean(I(result[1,]==1)*I(result[2,]==3))
se.power<-sqrt(power*(1-power)/r)
c(power=power, SE=se.power)