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Titrating and Evaluating Multiple Drug Regimens within Subjects

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

TITRATING AND EVALUATING MULTIPLE DRUG REGIMENS WITHIN SUBJECTS

By Margaret Shih, Bachelor of Science at the University of California at Berkeley

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2001

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The dosing of combination therapies is commonly undertaken empirically by practicing physicians, and there is a lack of a coherent algorithm to approach the problem of combination dosing. Current methods of evaluating multiple drug combinations in clinical trials generally do not provide information regarding the location of more effective dosages when the combination is not found to differ from the standard, even though the absence of a difference does not necessarily mean the new combination is ineffective. Additionally, if a new combination is found to be more effective, often a large proportion of the subjects has not benefited from the trial. This may lead to problems with patient enrollment and adherence to the study protocol, and even with early stopping rules, the time patients spend on inferior treatments may have lasting detrimental effects. This

paper describes an evolutionary operation (EVOP) direct-search procedure to titrate combination doses within individual patients. The Nelder-Mead simplex direct-search method is used to titrate a combination of drugs within individual subjects. Desirability functions are incorporated to define the main response of interest and additional responses or constraints. Statistical methodology for determining whether the titrated treatment combination has resulted in an improvement in patient response and for evaluating whether a therapeutic synergism exists is developed. Inferences can be made about the efficacy of the combination or about the individual drugs that comprise the combination. This approach allows every patient the potential to benefit from the combination under study and permits the consideration of multiple endpoints simultaneously.

Chapter 1

Introduction

1.1 Motivation

1.1.1 Combination Therapies and Clinical Practice

The use of multiple medications in the treatment of individual patients is an increasingly commonplace occurrence. The elderly population, who consume the most drugs and in whom relative drug consumption continues to increase, is rapidly growing in the United States and other developed nations. The pace of new drug development, from drug discovery to drug production, has accelerated greatly, and single diseases are now treated with multiple drugs targeting different biochemical pathways or different aspects in the pathophysiology of a disease. This increase in drug consumption brings with it a dramatic increase in the potential for drug interactions and adverse drug reactions. New approaches to treatment and prescribing are needed to address these increasingly complicated dosing regimens.

Dose titration with single compounds is a relatively straightforward process employed by physicians to identify appropriate dose levels which produce improved

responses in patients while simultaneously minimizing the adverse side effects a patient may experience. After taking into account a patient's age, weight, and other factors specific to the patient, the physician will prescribe an initial dose which may be increased or decreased as needed, depending on how the patient responds. This titration continues until a favorable balance between the desired response and undesirable side effects is achieved.

The difficulty arrives in attempting to translate this approach to determining dosages in the case where multiple drugs are being prescribed in the treatment of a single disease, or where the consideration of multiple endpoints is needed in the case where a single treatment is prescribed. There is currently no systematic or efficient method for determining dosages in multi-drug regimens. The physician generally either chooses to address the problem empirically, or will employ an ad-hoc approach, varying the levels of one drug while keeping the doses of all the other drugs in the combination fixed. Unfortunately, this approach does not account for potential interactions among the drugs, which may be crucial when searching for the most desirable therapy.

1.1.2 Combination Therapies and Clinical Trials

Not only is combination dosing difficult for practicing physicians in the day-to-day care of their patients, but it also presents a problem in both clinical trials research and drug evaluation research. Suppose we are evaluating a novel two-drug combination, which is composed of a new therapy plus the standard therapy. A typical approach which may be used

is to randomize half of the subjects to the standard drug group and the other half to the two-drug combination. There are several problems with this approach. The first problem is that if no difference in response is found between the groups, this does not necessarily mean that the new combination is ineffective. The lack of effect may lie in the dose chosen for use in the study. Secondly, this approach does not provide any information regarding the location of more effective doses if the combination is not found to differ from the standard. On the other hand, if the new combination is found to be more effective, approximately half the subjects enrolled in the study, those randomized to the standard treatment, have not benefited from the trial. Finally, even with early stopping rules, the time a patient spends on the inferior treatment can have lasting detrimental effects. These problems can lead to difficulties with patient recruitment and adherence to the study protocol.

1.1.3 Combination Therapies and Response Surface Methods

Outside of the clinical trials arena, a common approach which has been used to evaluate combination therapies is the use of response surface methodology (RSM). With this approach, an experiment is carried out using a grid of fixed dose combinations. The fixed combinations are administered to subjects, often using a factorial design, and the response is observed over the range of dose combinations. The resulting response surface can then be used to identify areas of improved response. This is an effective approach, but one limited in its application by several aspects. Firstly, this approach requires the use of prede-

terminated, fixed combinations, none of which may actually correspond to the best treatment. Also, the ideal treatment may lie entirely outside of the range of doses used in the study. Furthermore, these studies quickly become expensive due to the numerous dose combinations required. Finally, RSM requires the pre-specification of the dose-response relationship, which is usually unknown. This requires an additional assumption that the dose-response relationship is well approximated by the equation specified.

1.1.4 Research Objectives

The goal of our research has been to develop a more systematic and efficient, yet practical and flexible, method for titrating combination therapies within individual patients and for evaluating the efficacy of multiple drug therapies. We have addressed the problem using an evolutionary operation (EVOP) approach and by incorporating desirability functions, both of which have been successfully applied in industrial settings but which until now have not seen much application in the field of medicine. The methodology described allows each subject to benefit by receiving a personalized ‘best’ therapy. The titration is carried out using practical therapeutic units (e.g. whole pills) and permits the consideration of multiple endpoints simultaneously. Finally, inferences can be made regarding therapeutic synergism and the efficacy of combination therapies without requiring the specification of either the dose-response relationship or distributional assumptions.

1.2 Prospectus

Chapter 2 is a literature review of EVOP, EVOP direct-search methods, and desirability functions. Chapter 3 is written in the format of a paper submitted for journal publication and contains an overview of the mechanics of the titration process as well as a more detailed discussion of statistical inference and methodological issues. The figures and tables are provided at the end of the chapter. Chapter 4 contains a discussion of possible clinical applications of EVOP direct-search methods and an example of a proposed study protocol employing this methodology in the titration of a two-drug combination therapy for the treatment of type 2 diabetes. Chapter 5 is a summary of the simulation studies which were conducted to examine the effectiveness of the multi-drug titration algorithm in combination dosing and the effects of the sample size, the number of steps, the shape of the desirability function, and the initial step size. Chapter 6 is a research summary.

References for the sample study protocol are listed at the end of Chapter 4. All other references are listed in the main Reference section after Chapter 6.

Chapter 2

Literature Review

2.1 Evolutionary Operation (EVOP)

The optimization of functions of multiple variables has always been of interest to statisticians (Hotelling, 1941). Friedman and Savage (1947) proposed a sequential one-factor-at-a-time optimization procedure, and Box and Wilson (1951) discussed the simultaneous optimization of multiple factors, which was the groundwork for the evolutionary operation procedure (EVOP) eventually introduced by Box in 1957. The EVOP technique has since been widely and successfully applied in the industrial setting, particularly in manufacturing processes, where it is used as a method of increasing plant efficiency by increasing the rate at which improvements to production can be made.

The evolutionary operation technique allows one to search for improved conditions while a process is in production by observing the effects of small, deliberate changes in the operating conditions which result in a type of forced or artificial evolutionary process. Traditional applications of EVOP have involved the use of factorial designs (Fisher, 1935; Yates, 1935; D.R. Cox, 1958; and Snedecor and Cochran, 1980) to introduce variations in the operating conditions. EVOP utilizes information from the process itself to

make improvements to the resulting product and has proven useful in optimizing multidimensional relationships without requiring specification of either a model or distribution (Box, 1957; Box and Draper, 1969; Spendley, Hext, and Himsworth, 1962).

Whereas response surface methods are a static research technique, evolutionary operation can be applied as a continuous and automatic production-line method. Hunter and Kittrell (1966) present an extensive review of various industrial applications of EVOP, most of which take place in the chemical industry, although applications in the automotive and food industries are also discussed. For a more detailed, in-depth discussion of EVOP techniques, one is referred to the text by Box and Draper (1969).

As an example of how EVOP would work in practice, suppose we are trying to optimize the response of an ongoing industrial manufacturing process, and suppose the response to be optimized is the yield of chemical product. The yield of the product would be continuously monitored, as would the operating conditions, which might consist of the temperature, pressure, and amount of starting material. Minor variants in the operating conditions are then introduced in a factorial pattern. When a significant change in the yield is found in either a positive or negative direction, the operating conditions which produced the change in yield can be identified and subsequently adjusted in the direction of optimizing the yield. The monitoring process would then resume and could be continued indefinitely.

Two of the most appealing aspects of EVOP are the simplicity with which it can be carried out and the fact that it is conducted as an inherent part of a normal process, not as an artificially conducted experiment. The everyday application of EVOP techniques does

not require the input of professional mathematicians or statisticians, and after the initial setup, the EVOP process can continue indefinitely, with new variables being added or old variables being removed at any time.

There are several issues which arise in adapting EVOP, in its original form, to the problem of finding therapeutic treatment combinations which result in an improved outcome status in individual patients. The first problem is that traditionally, EVOP requires the use of many design points. Use of a factorial design would require the introduction of multiple small variations in treatment dosages which would be applied continuously to each patient. This presents obvious ethical problems regarding patient treatment, which overshadow other relatively minor issues of patient compliance and inefficiency in the design.

A second problem arises from the traditional application of a statistical test of significance to determine whether movement should be made to a new experimental region. Movement to a new dose region would not be made until there was statistical evidence that this would result in an improved patient response. In this case, the patient would be given multiple but varying doses of the drug combination within a limited dose range. The same set of doses would be repeatedly administered until there was evidence that changing the dose levels would benefit the patient. While it is appropriate that changes to the dose levels should not be made until there is some apparent benefit to be gained, this is again inefficient and results in a slower optimization process.

An automatic EVOP procedure, which is more easily adapted to the clinical arena, was introduced by Spendley, Hext, and Himsworth (1962). Their sequential simplex

method, a modification of Box's original approach, is automatic, does not utilize a factorial design, and does not require hypothesis testing before each movement. Instead, they use a direct search method approach to optimizing multiple factors. Direct search methods are a group of procedures also referred to as hill-climbing or steepest ascent procedures, which are often used for minimizing or maximizing functions. Pre-specification of the dose-response relationship is not necessary, one is not limited to predetermined combinations, and compounds can be added or removed from the combination under study at any time.

This initial simplex EVOP method was later modified by Nelder and Mead (1965), who developed a more flexible method termed the Nelder-Mead Simplex procedure. Their method has the advantage of allowing the simplex to accelerate and adapt to the contour to the response surface. Segreti (1977) has discussed the use of the Spendley, Hext, and Himsworth EVOP method in combination chemotherapy studies, and more recently, Berenbaum (1990) has discussed another modified approach, the partition method, in relation to the problem of optimizing cancer chemotherapy regimens in animal studies. Box also modified the procedure, creating complexes and incorporating constraints (1965). However, all of these applications refer to patients or animals randomized to a single treatment group and do not discuss dose optimization within individual patients.

In our simulation studies, described in more detail in Chapter 5, we use the Nelder-Mead Simplex algorithm to carry out the titration of combination therapies within each patient. While numerous other optimization methods, such as those listed in the previous

paragraphs could be applied, we elected to use the Nelder-Mead method because of its simplicity in application and the rapidity and efficiency with which it optimizes processes.

2.2 Titration with the Nelder-Mead Simplex Procedure

The Nelder-Mead procedure has been widely applied to a broad range of problems. In our simulations, the Nelder-Mead simplex algorithm was used to carry out the within-patient titration. The first step of the procedure is to establish an initial simplex, a geometric figure with a fixed number of vertices. In the p -dimensional case, where p is the number of variables being evaluated, the number of vertices required for the simplex is $p+1$. At each step, the simplex adapts its form, moving away from the vertex with the lowest response toward the direction of maximum response.

This is most easily illustrated in the two-dimensional case where the simplex is a triangle. More specifically, if we are evaluating a two-drug combination, each vertex A, B, and C, of the triangle (Figure 2.1) would represent different dose levels of the combination. At the initial step, the subject's response is measured at each of these three dose combinations, and the composite desirability resulting from the administration of each combination is compared, with the simplex reflecting away from the least desirable response, through the centroid of the face created by the remaining vertices to a new point, E. In addition to reflection, the simplex can also extend, contract, or perform a shrinkage

contraction, depending on the contour of the response surface. The possible cases are

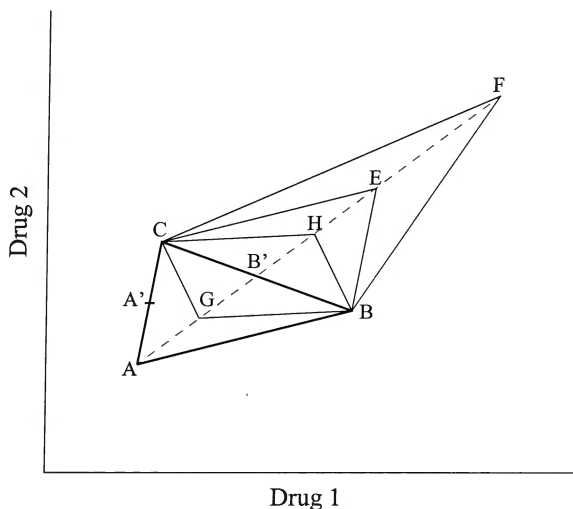


Figure 2.1: Nelder-Mead simplex ABC with possible subsequent points (Table 2.1)

listed in Table 2.1 and correspond to the diagram in Figure 2.1.

The initial simplex step size, which specifies how far apart the initial vertices are, and the reflection and expansion coefficients used by the Nelder-Mead procedure, which

Table 2.1: Conditions governing the formation of subsequent simplex. (Adapted from Olsson and Nelson, 1975)

Condition	Action	New Simplex
$f(C) \leq f(E) \leq f(B)$	Reflect	BCE
$f(E) < f(C)$	Extend	BCF
$f(A) < f(E)$	Contract	BCG
$f(B) < f(E) \leq f(A)$	Contract	BCH
$f(A) \leq f(G)$ or $f(E) \leq f(H)$	Shrink	A'B'C

determine how far the simplex can move or expand in one step, must be carefully specified by working with experts knowledgeable about the response and process variables being evaluated. Our application of the Nelder-Mead algorithm to within-patient titration is described in more detail in Chapter 3.

2.3 Desirability Functions

Desirability functions also address the problem of optimizing multiple responses simultaneously. However, while EVOP techniques focus on monitoring and optimizing the different operating conditions to optimize a single response, desirability functions are used to optimize multiple endpoints. The desirability function approach was first introduced by Harrington (1965) and later modified by Derringer and Suich (1980). Gibb (1998) further extended the methodology to desirability functions which are continuous and differentiable.

Desirability functions have been successfully applied in the industrial setting. Each endpoint of interest is transformed to a continuous desirability function, d_i , with values ranging from 0 to 1, where a value of 0 designates the response as not at all desirable, while a value of 1 is assigned to the most desirable response. The basic shape of the function is determined by whether one is trying to maximize or minimize the response, or aim for a range of target values. The exact shape of each desirability function is determined in collaboration with physicians or other experts knowledgeable about the disease under study and the therapeutic effects of the treatments being administered.

Gibb (1998) describes the use of both the normal cumulative distribution function and logistic cumulative distribution function in defining continuous desirability functions, but any function which maps the response to the (0,1) interval and which is continuous and differentiable could be used. In this study, a logistic cumulative distribution function was used. With the logistic function, the form of the ‘bigger-is-better’ or maximizing desirability function is

$$d_{i(max)} = \left[1 + \exp\left(-\frac{Y_i - a_i}{b_i}\right) \right]^{-1},$$

where

$$a_i = \frac{(Y_i^* + Y_{i*})}{2}, b_i = \frac{Y_i^* - Y_{i*}}{2 \ln\left(\frac{1 - \gamma_i}{\gamma_i}\right)}, Y_{i*} < Y_i^*, \text{ and } \gamma_i \in (0, 1).$$

The parameter a_i is an average of the upper (Y_i^*) and lower (Y_{i*}) bounds of the response level being targeted, b_i controls the function spread, and γ_i is such that $d_i(Y_{i*}) = \gamma_i$ and $d_i(Y_i^*) = 1 - \gamma_i$. An example of a maximizing desirability function is given in Figure 2.2.

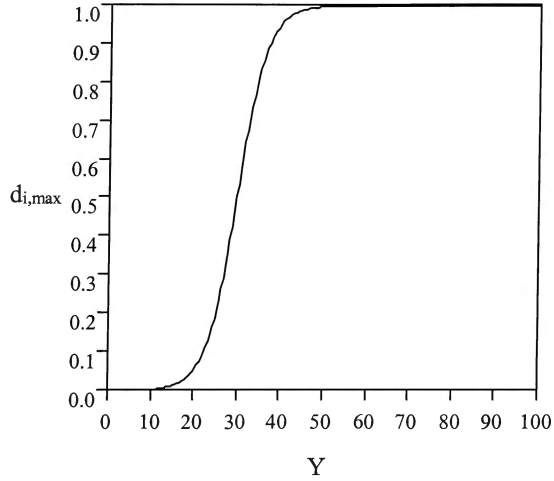


Figure 2.2: Example of a maximizing desirability function. $Y_{i*} = 20$, $Y_i^* = 40$, $\gamma_i = 0.05$.

The ‘smaller-is-better’ or minimizing desirability, shown in Figure 2.3, is obtained

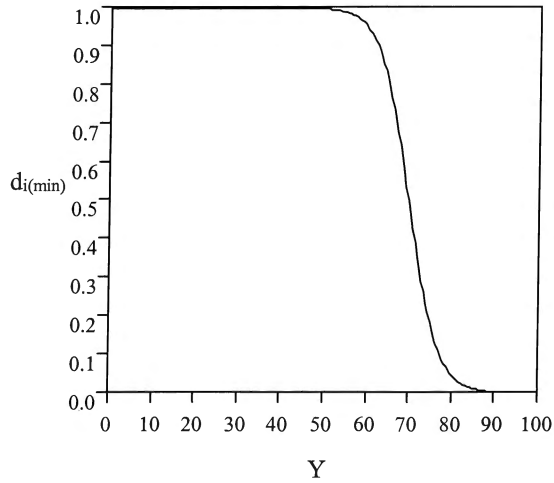


Figure 2.3: Example of a minimizing desirability function. $Y_{i*} = 60$, $Y_i^* = 80$, $\gamma_i = 0.05$.

simply by reversing the sign of the exponential argument, having the resulting form,

$$d_{i(\min)} = \left[1 + \exp\left(\frac{(Y_i - a_i)}{b_i}\right) \right]^{-1}.$$

A target desirability function, shown in Figure 2.4, can then be constructed by multiplying a minimizing and a maximizing desirability such that $d_{i(\text{tar})} = d_{i(\text{max})} \times d_{i(\text{min})}$. This allows the researcher to incorporate asymmetry into the desirability function. The parameters a_i , b_i , and γ_i , allow the researcher flexibility in defining the desirability function and the degree of conservativeness to incorporate. These individual desirability functions can

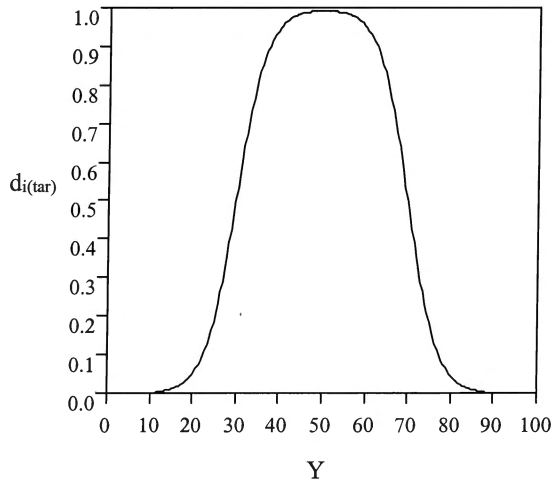


Figure 2.4: Example of a target desirability function. This function is the product of the maximizing desirability function, $d_{i(\text{max})}$, shown in Figure 2.1, and the minimizing desirability function, $d_{i(\text{min})}$, shown in Figure 2.2.

then be combined using the geometric mean to arrive at a single continuous measure of the overall composite desirability, D , such that $D = (d_1 * d_2 * \dots * d_k)^{1/k}$.

Derringer (1994) has also described the use of weights, in the specification of the desirability function, so that different responses can be assigned different levels of importance. Each response is weighted by an exponent, w_i , so that the composite desirability with weights has the form

$$D = (d_1^{w_1} d_2^{w_2} \dots d_k^{w_k})^{1/\sum w_i}, i = 1, \dots, k.$$

In our simulation studies, unweighted desirability functions are used. Specific examples of the application of desirability functions are detailed in Chapter 3.

Chapter 3

Titration and Evaluating Multi-Drug Regimens within Subjects

3.1 Introduction

The use of multiple medications in the treatment of a single disease in an individual patient is an increasingly common occurrence. With single compounds, dose titration is relatively straightforward. Dose titration of single compounds is commonly employed by practicing physicians to find appropriate dose levels which produce improved responses in patients, or to maintain response levels as a disease progresses, while limiting the side effects a patient experiences. The physician, depending on a number of patient factors, chooses a starting dose which he or she may later increase or decrease incrementally depending on how the patient responds. Treatment changes continue to occur until a favorable balance between response and undesirable factors is achieved. However, this has never been extended for use in determining dosages in a multi-drug regimen and there is currently no accepted algorithm in use for combination titration. The physician generally approaches the problem empirically, or undertakes an ad hoc approach, where levels

of one drug are varied while the other drugs in the combination are kept fixed at a constant dose. Such an approach does not account for potential interactions among the drugs, which may be crucial when one is searching for the most desirable therapy.

In this paper, we address the problem of titrating and evaluating multi-drug regimens using an evolutionary operation (EVOP) approach to climb through the dose space to a location of improved patient response. EVOP techniques have been successfully applied in the industrial setting (Hunter and Kittrell, 1966), where they have proven useful in optimizing multidimensional relationships and do not require specification of either a model or distribution (Box, 1957; Box and Hunter, 1959; Box and Draper, 1969; Spendley, Hext, and Himsworth, 1962). With EVOP, one searches for improved conditions while a process is in production by observing the effect of small changes in the environment or operating conditions. No movement is made toward a new experimental region until there is evidence the changes will result in an improved response.

EVOP can be effectively adapted to the clinical setting where a combination of drugs is being used for treatment or being evaluated for efficacy. While the multidimensional dose-response relationship is unknown, it can be observed at specific treatment combinations, and a predetermined algorithm can be followed to adjust the therapeutic doses toward improving patient outcome. For example, a patient may make periodic visits to a physician who monitors the patient for improvements in outcome in response to the multiple drugs being prescribed. The physician or researcher can use an EVOP direct search procedure to adjust the doses comprising the treatment combination in response to the patient's continuously evolving condition. The titration is carried out within each

patient, allowing every patient to benefit from the therapy if there is any benefit obtainable.

Direct search methods are a group of procedures also referred to as hill-climbing or steepest ascent procedures, which are often used for minimizing or maximizing functions. Using direct search methods allows compounds to be easily added or removed from the combination under study and does not require specification of distributional assumptions. There are several direct search algorithms that can be applied to the titration process. The first automatic simplex EVOP algorithm was introduced by Spendley, Hext, and Himsworth in 1962. Nelder and Mead modified the procedure, adding the adaptive feature, which allows the simplex to conform to the characteristics of the response surface (Nelder and Mead, 1965). M.J. Box (1965) also modified the procedure, creating complexes and incorporating constraints. Segreti (1977) has discussed the use of the Spendley, Hext, and Himsworth EVOP method in combination chemotherapy studies, and more recently, Berenbaum (1990) has discussed another modified approach, the partition method, in relation to the problem of optimizing cancer chemotherapy regimens in animal studies. However, both of their approaches refer to patients or animals randomized to a single treatment group and do not discuss dose optimization within individual patients.

In the current paper, the within-patient titration is described using the Nelder-Mead algorithm, which is more flexible than the Spendley, Hext, and Himsworth method, permitting acceleration and adaptation to the response surface. In order to extend the flexibility of this approach, we utilize a continuous desirability function (Gibb, 1998), which incorporates both the main response of interest and additional responses or constraints, as

the overall measure of response. In this way, the main response or responses may be improved while simultaneously satisfying multiple additional constraints.

This paper describes an EVOP direct-search procedure to titrate doses within individual patients. It also discusses statistical methodology useful for determining whether there has been an improvement in response and whether a therapeutic synergism exists among the drugs comprising a multi-drug regimen.

3.2 Methods

3.2.1 Desirability Functions

The desirability function approach was developed by Harrington (1965) and later modified by Derringer and Suich (1980). Gibb (1998) extended the methodology to desirability functions which are continuous and differentiable. Desirability functions have been successfully used in the industrial setting. Each response of interest is transformed to a continuous desirability function, d_i , with values ranging from 0 to 1, where a value of 0 designates the response as not at all desirable, while a value of 1 is assigned to the most desirable response. The index i represents the i^{th} desirability function or the i^{th} response of interest. The basic shape of the function is determined by whether one is trying to maximize or minimize the response, or aim for a range of target values. The exact shape of each desirability function is determined in collaboration with physicians or other experts knowledgeable about the disease under study and the therapeutic effects of the treatments being administered.

In this study, a logistic cumulative distribution function was used for the desirability, but any function which maps the response to the (0,1) interval and which is continuous and differentiable could be used. With the logistic function, the form of the ‘bigger-is-better’ or maximizing desirability function (Gibb, 1998) is

$$d_{i(\max)} = \left[1 + \exp\left(-\frac{Y_i - a_i}{b_i}\right) \right]^{-1},$$

where

$$a_i = \frac{(Y_i^* + Y_{i*})}{2}, b_i = \frac{Y_i^* - Y_{i*}}{2 \ln\left(\frac{1 - \gamma_i}{\gamma_i}\right)}, Y_{i*} < Y_i^*, \text{ and } \gamma_i \in (0, 1).$$

The parameter a_i is an average of the upper (Y_i^*) and lower (Y_{i*}) bounds of the response level being targeted, b_i controls the function spread, and γ_i is such that $d_i(Y_{i*}) = \gamma_i$ and $d_i(Y_i^*) = 1 - \gamma_i$. The ‘smaller-is-better’ or minimizing desirability is obtained simply by reversing the sign of the exponential argument, having the resulting form,

$$d_{i(\min)} = \left[1 + \exp\left(\frac{(Y_i - a_i)}{b_i}\right) \right]^{-1}.$$

A ‘target’ desirability function can then be constructed by multiplying a set of desirability functions, such as a minimizing desirability and a maximizing desirability to give $d_{i(\text{target})} = d_{i(\max)} \times d_{i(\min)}$. This allows the researcher to incorporate asymmetry into the desirability function. The parameters a_i , b_i , and γ_i allow the researcher flexibility

in defining the desirability function and the degree of conservativeness to incorporate.

These individual desirability functions can then be combined using the geometric mean to arrive at a single continuous measure of the overall composite desirability, D , such that

$D=(d_1*d_2*...*d_k)^{1/k}$. Derringer (1994) has also described the use of weights, in the specification of the desirability function, so that different responses can be assigned different levels of importance. Each response is weighted by an exponent, w_i , so that the composite desirability with weights has the form

$$D = (d_1^{w_1} d_2^{w_2} \dots d_k^{w_k})^{1/\sum w_i}, i = 1, \dots, k .$$

In our simulation studies, we use unweighted desirability functions.

As an example, consider the case where a physician is treating a type 2 diabetes patient with a combination of a sulfonylurea and metformin. There are numerous clinical endpoints the physician may monitor, including fasting plasma glucose (FPG), glycosylated hemoglobin levels (HbA_{1c}), the patient's lipid profile, weight, and blood pressure, and the number of adverse gastrointestinal and hypoglycemic events the patient experiences. For any or all of these endpoints, a specific target, maximizing, or minimizing desirability function can be assigned and incorporated into the composite desirability function. Note that this method tends to weight small desirability values heavily so that if any of the individual desirabilities are small, the overall desirability remains small.

As a simple case, suppose we only wish to monitor two endpoints, the patient's fasting plasma glucose (FPG) and the patient's body weight. Suppose we would like to

target the patient's FPG to be within the 80-140mg/dL range. Additionally, we want to minimize the increase in weight the patient may experience due to the treatment. Example desirability functions for each response are specified in Figure 3.1.

Table 3.1 describes three cases which could occur. In Case 1, the patient has reasonable fasting plasma glucose values and has experienced minimal weight gain. Referring to the desirability functions specified in Figure 3.1, the glucose value of 140 corresponds to a desirability (d_1) of 0.95, and the weight gain of 10 corresponds to a desirability (d_2) of 1. This gives an overall desirability (D) of 0.98. This high desirability suggests that the patient is doing well with the current treatment. In the second case, the patient has a less desirable glucose value of 155, which corresponds to a desirability of 0.19, and a weight gain of 30 lbs, which corresponds to a desirability of 0.5. This patient has an overall desirability of 0.31, which indicates that changes to the patient's current therapeutic regimen may be needed to improve the treatment of this patient. The last example is of a patient with a high serum glucose value which is further outside the desirable limits, corresponding to a desirability of 0.05, but one who has experienced no weight gain and so has a weight gain desirability of 1. Although this patient is doing well in terms of preventing weight gain, the glucose level is objectionably high, so the overall desirability decreases to 0.22.

The application of desirability functions to within-patient titration can be useful for both the multiple drug case and the single agent case where multiple endpoints are being monitored. In the single agent case, desirability functions can provide the physician or researcher with a more objective way of evaluating the overall effect of a therapy and

can provide information about individual clinical endpoints and side effects. In the multiple drug case, by combining desirability functions with EVOP direct-search methods, we can titrate combination therapies within individual subjects and make inferences about the efficacy of the combination.

3.2.2 Titration Procedure

Once the individual desirability functions are defined, they are incorporated into the overall composite desirability function, which becomes the response undergoing optimization during the titration process. In our simulations, the Nelder-Mead simplex algorithm was used to carry out the within-patient titration. The first step of the procedure is to establish an initial simplex, a geometric figure with a fixed number of vertices. In the p -dimensional case, where p is the number of drugs comprising the combination under evaluation, the number of vertices required for the simplex is $p+1$. This is most easily illustrated in the two-dimensional case where the simplex is a triangle. Each vertex of the triangle represents different dose levels of the two-drug combination. At the initial step, the subject's response is measured at each of these three dose combinations, and the composite desirability resulting from the administration of each combination is compared, with the simplex reflecting away from the least desirable response, through the centroid of the face created by the remaining vertices to a new point. In addition to reflection, the simplex can also extend, contract, or perform a shrinkage contraction, depending on the contour of the response surface.

The Nelder-Mead algorithm is run on a continuous scale, and therefore the new

dose combination determined by the algorithm is not given in units of whole pills or whole dose units. To enhance the practicability of the EVOP titration approach, the dose combinations are adjusted to whole units (e.g. whole pills). The new dose combination to be administered is determined by either rounding to the nearest whole dose unit, or more conservatively, by rounding down to the dose unit.

The initial simplex step size, which specifies how far apart the initial dose combinations are, and the reflection and expansion coefficients used by the Nelder-Mead procedure, which determine how far the simplex can move or expand in one step, are decided in collaboration with the physician expert, and can be modified to be more or less conservative depending on factors such as the therapeutic index of the drug involved. The step size of the initial simplex will depend on the potency and toxicity of the drugs under study, with smaller initial step sizes prudent for compounds of higher potency and/or toxicity. In the case where the drugs are already being used in combination in practice, a reasonable starting combination would be the number of pills or dose units with which the practicing physician generally initiates therapy. With a new and yet untested combination of drugs, where one cannot draw from previous experience, a more conservative approach is advisable.

Each subject begins the process by being evaluated at each of the $p+1$ combinations of p drugs in the regimen. The subject receives the initial combination and the response is recorded. The subject then receives the second combination, which is determined by the initial step size, and the response is measured after a time interval sufficient to preclude carryover effects. This continues for each of the $p+1$ drug combinations. It

should be noted that in the situation where there is a lengthy time to response, EVOP may not be practical due to the time required in setting up the initial simplex. After the initial simplex is established, the new simplex is formed, determining the next dose combination to be administered. This process repeats until the subject has passed through a fixed number of steps or until other specific stopping criteria are reached and further titration is deemed unnecessary. The simplex movement can be continuously monitored by the physician, and the reflection, expansion, and contraction coefficients can be modified if the simplex expands to a dose with which physician is uncomfortable. Otherwise, a dose constraint can be put in as a boundary to prevent the simplex from moving above a certain dose in one or more dimensions. At the final step, the last simplex is evaluated and the combination producing the most desirable response is determined to be the 'best' treatment combination. Possible stopping criteria include running the process until convergence to a 'best' treatment or until an 'acceptable' response is reached. Since disease processes are dynamic and often chronic, the physician may continue to periodically monitor subjects after the initial optimized dose level is reached, and may restart the titration process if changes in the patient's status are observed.

After a group of subjects has passed through the titration process, the initial and final dose locations and corresponding initial and final responses are used to determine whether there has been an improvement in response and whether a therapeutic synergism exists among the drugs comprising the combination.

3.3 Inference about the Patient Population

The set of final treatment dose combinations observed from the n subjects enrolled in the study can be considered a sample from a multivariate distribution. We would like both to test for an improvement in response after all subjects have passed through the titration process and to test the efficacy of the combination or individual components of the combination. The first goal can be accomplished by identifying it as a one-sample location problem on paired responses which can easily be addressed using existing tests, which are described in section 3.3.1. The second goal can be accomplished by construction of a p -dimensional confidence ellipsoid about the central location of the 'cloud' of final dose combinations in the p -dimensional dose space. Both a parametric approach and nonparametric approach are described in section 3.3.2. Based on the estimated confidence ellipsoid, we can evaluate whether a therapeutic synergism (Mantel, 1974) exists between all treatments comprising the combination, and we can also estimate a region of improved therapy (Carter, 1982).

3.3.1 The One-Sample Location Problem

To test for an improvement in response, it is possible to apply the Wilcoxon Signed Rank Test (Wilcoxon, 1945) or Fisher Sign Test (Fisher, 1925). We define $\text{diff}_i = y_{(k)i} - y_{(0)i}$, $i = 1, \dots, n$, where $y_{(k)i}$ is the response of the i th subject after undergoing k steps of the titration process and $y_{(0)i}$ is the response of the i th subject at baseline. For the signed rank statistic, we assume the diff_i are independent and each comes from a common distribution symmetric about δ . We wish to test the hypothesis:

$$H_0: (\delta \leq 0) \text{ vs. } H_1: (\delta > 0) ,$$

where without loss of generality, an increase in response indicates improvement. Forming the absolute differences $|\text{diff}_1|, \dots, |\text{diff}_n|$ and letting R_i denote the rank of the absolute differences in the joint ranking from least to greatest of $|\text{diff}_1|, \dots, |\text{diff}_n|$, we define

$$\psi_i = \begin{cases} 1 & \text{if } (\text{diff}_i > 0) \\ 0 & \text{if } (\text{diff}_i < 0) \end{cases}, i = 1, \dots, n$$

and

$$T^+ = \sum_{i=1}^n R_i \psi_i .$$

A large sample approximation is:

$$T^* = \frac{T^+ - \left[n \frac{(n+1)}{4} \right]}{\sqrt{\left[n(n+1) \frac{(2n+1)}{24} \right]}} \sim N(0, 1) .$$

Thus, we reject H_0 if $T^* \geq Z_{\alpha}$.

For the Sign Test, we assume the diff_i are independent and each comes from a distribution with median δ . We wish to test the hypothesis: $H_0: (\delta \leq 0)$ vs. $H_1: (\delta > 0)$.

We define

$$B = \sum_{i=1}^n \psi_i ,$$

where ψ_i is defined as above, so that B is the number of positive diff_i 's. We reject H_0 if

$$B \geq \text{Bin}\left(\alpha, n, \frac{1}{2}\right),$$

where $\text{Bin}(\alpha, n, 1/2)$ satisfies

$$P_0\left[B \geq \text{Bin}\left(\alpha, n, \frac{1}{2}\right)\right] = \alpha.$$

Rejection of the hypothesis of 'no improvement' indicates that the titration process has been successful in finding a dose combination which improves the patient's response from a baseline response. The responses used in these tests are from the desirability functions discussed in section 3.2.1. Therefore an improved response indicates not only an improvement in the primary endpoint of interest but improvement in the overall health status of the patient, as defined by the physician through the desirability function. Determination of sample size and power requirements for the Wilcoxon signed-rank and Fisher sign tests are detailed in Lehmann (1975).

3.3.2 Construction of the Confidence Ellipsoid About a Multivariate Location

We would like to estimate a region of improved therapy based on the estimated confidence ellipsoid about the location of the multivariate distribution of each individual's final treatment combination. If the combination treatment includes p elements, the multivariate sampling model involves n independent, identically distributed p -component random vectors $\mathbf{x}_1, \dots, \mathbf{x}_n$, each with the p -variate distribution function $F(t_1 - \theta_1, \dots, t_p - \theta_p)$, where F is absolutely continuous with continuous marginal distribution functions

$F_1(t_1 - \theta_1), \dots, F_p(t_p - \theta_p)$. The vector of location parameters $\theta = [\theta_1 \ \theta_2 \ \dots \ \theta_p]$ con-

tains the marginal medians, and if each F_j is symmetric, θ is also the vector of marginal means.

A parametric inferential approach would be to assume a form for F and to construct the confidence ellipsoid for θ . One obvious choice of distribution is the multivariate normal. Let $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_n$ be a p -variate sample which is i.i.d.

$N_p(\theta = [\theta_1 \ \theta_2 \ \dots \ \theta_p]', \Sigma)$. The maximum likelihood estimate for θ is

$$\bar{\mathbf{x}} = \frac{1}{n} \sum_{i=1}^n \mathbf{x}_i,$$

and an unbiased estimate (Morrison, 1976) for Σ is

$$\mathbf{S} = \frac{1}{n-1} \mathbf{A},$$

where $\mathbf{A} = \sum_{i=1}^n (\mathbf{x}_i - \bar{\mathbf{x}})(\mathbf{x}_i - \bar{\mathbf{x}})'$. Since $\sqrt{n}(\bar{\mathbf{x}} - \theta) \sim N_p(\mathbf{0}, \Sigma)$, replacing Σ with its con-

sistent and unbiased estimate and recalling the relationship between Hotelling's T^2 and the F distribution, an exact $100(1-\alpha)\%$ confidence ellipsoid for θ is

$$\left\{ \theta: n(\bar{\mathbf{x}} - \theta)' \mathbf{S}^{-1} (\bar{\mathbf{x}} - \theta) \leq \frac{(n-1)p}{n-p} F_{1-\alpha; p, n-p} \right\}.$$

For small or medium-sized samples, a more robust approach, which does not require distributional assumptions, would be to construct a confidence ellipsoid about the multivariate median. An efficient estimator of θ associated with Wilcoxon's Signed Rank statistic is the Hodges-Lehmann estimator based on ranks (Hodges and Lehmann, 1963).

Let $\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_n$ be a p -variate sample which is i.i.d. F such that the p -vector of marginal medians for F is $\boldsymbol{\theta} = [\theta_1 \ \theta_2 \ \dots \ \theta_p]'$ and F is diagonally symmetric about $\boldsymbol{\theta}$. We can estimate $\boldsymbol{\theta}$ using signed rank statistics (Hettmansperger, 1984). Let $\hat{\boldsymbol{\theta}}_j$ be the p -vector of the sample medians of Walsh averages (Tukey, 1949) with components

$$\hat{\theta}_j = \text{median} \left\{ \frac{(x_{ij} + x_{i'j})}{2}, 1 \leq i \leq i' \leq n \right\}, j = 1, \dots, p.$$

If $W_{(1)j} \leq W_{(2)j} \leq \dots \leq W_{(N)j}$, are the ordered Walsh averages, where $N = n(n+1)/2$, the $100(1-\alpha)\%$ confidence interval for θ_j is $[W_{(a_j+1)j}, W_{(N-a_j)j}]$, where a_j can be approximated by

$$a_j \approx \frac{n(n+1)}{4} - 0.5 - z_{1-\frac{\alpha}{2}} \sqrt{\frac{n(n+1)(2n+1)}{24}}.$$

Finding $\hat{\boldsymbol{\theta}}_j$ is equivalent to finding θ_j such that the signed rank statistic

$$T_j(\theta_j) = \sum_{i=1}^n \frac{R_{ij} \theta_j}{n+1} \text{sign}(x_{ij} - \theta_j)$$

is approximately equal to zero, where $R_{ij} \theta_j$ is the rank of $|x_{ij} - \theta_j|$ among

$|x_{1j} - \theta_j|, |x_{2j} - \theta_j|, \dots, |x_{nj} - \theta_j|$. Then $\sqrt{n}(\hat{\boldsymbol{\theta}}_w - \boldsymbol{\theta}) \rightarrow^D N_p(0, \Gamma_w^{-1} \boldsymbol{\gamma}_w \Gamma_w^{-1})$, where

$\Gamma_w = \text{Diag}(\gamma_{w,1}, \dots, \gamma_{w,p})$ such that

$$\gamma_{w,j} = 2 \int_{-\infty}^{\infty} f_j^2(x) dx, j = 1, \dots, p,$$

and v_w is a $p \times p$ matrix such that

$$v_{w, jj'} = 4 \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} F_j(x_j) F_{j'}(x_{j'}) dF_{jj'}(x_j - x_{j'}) - 1, \quad 1 \leq j \neq j' \leq p$$

and $v_{w, jj} = 1/3$ (Hettmansperger, 1998). A consistent estimate of $\gamma_{w, j}, j = 1, \dots, p$ is found from the asymptotic length of a confidence interval for θ_j based on the Walsh averages (Lehmann, 1975)

$$\hat{\gamma}_{w, j} = \left(\frac{\left(4z_{1-\frac{\alpha}{2}} \right)}{\sqrt{12n}(W_{(N-a_j)j}, W_{(a_j+1)j})} \right).$$

When the variability is such that a large proportion of subjects arrives at the same, or similar, final dose locations, an inordinate number of ties results due to the effect of rounding to whole units. As a consequence, $W_{(a_j+1)j}$ and $W_{(N-a_j)j}$ become identical, and the confidence interval for θ_j , $[W_{(a_j+1)j}, W_{(N-a_j)j}]$, goes to zero. To correct for this, we use the smallest viable interval of $2\varepsilon=0.5$ as the lower limit for $W_{(N-a_j)j}$ - $W_{(a_j+1)j}$, such that

$$\hat{\gamma}_{w, j} = \left(\frac{\left(4z_{1-\frac{\alpha}{2}} \right)}{\sqrt{12n}(0.5)} \right).$$

A consistent estimate of $v_{w, jj}, j, j' = 1, \dots, p$ (Hettmansperger, 1998), is

$$\hat{v}_{w,jj'} = \frac{1}{n} \sum_{i=1}^n \left\{ \frac{R_{ij}(\hat{\theta}_{w,j})}{n+1} \right\} \left\{ \frac{R_{ij'}(\hat{\theta}_{w,j'})}{n+1} \right\} \text{sign}(x_{ij} - \hat{\theta}_{w,j}) \text{sign}(x_{ij'} - \hat{\theta}_{w,j'}) .$$

Replacing v_w and Γ_w with consistent estimates, an approximate $100(1-\alpha)\%$ confidence ellipsoid for θ is

$$\left\{ \theta: n(\hat{\theta}_w - \theta)' [\hat{\Gamma}_w^{-1} \hat{v}_w \hat{\Gamma}_w^{-1}]^{-1} (\hat{\theta}_w - \theta) \leq \chi_{1-\alpha;p}^2 \right\} .$$

After the confidence ellipsoid is established, the ellipsoids can be evaluated using the approach described by Carter, et al. (1982). The confidence ellipsoid is evaluated along a grid of points on each single axis. As an illustration, in the 2-dimensional case, it is determined whether the ellipsoid a) contains the origin, implying the combination is not different from no treatment at all; b) contains both axes but not the origin, implying that treatment with the combination is better than having no treatment, but that the same response could be obtained by using either drug by itself; c) contains only one axis, implying that treatment with the combination is no better than treatment with the single drug, or d) does not contain either axis, implying the presence of a therapeutic synergism, that the combination of drugs produces a greater response than either drug alone (Figure 3.2).

3.4 Simulation Study

3.4.1 The Response Surface

A simulation study was performed to examine the effectiveness of the multi-drug titration algorithm in combination dosing and the effects of the number of steps, the shape of the

desirability function, and the initial step size. The estimated dose response surface was obtained from a published multicenter, factorial design clinical trial studying the efficacy of the combination therapy of the diuretic hydrochlorothiazide (HCTZ) and a slow-release formulation of diltiazem hydrochloride (DLTZ), a calcium channel blocker, in the treatment of mild to moderate hypertension (Burris, et.al., 1990).

The trial was conducted over a period of six weeks, following a 4- to 6-week placebo 'run-in' period. A 4 by 5 factorial grid of treatment doses was used, with 4 twice-a-day doses of hydrochlorothiazide ranging from 0 to 25 mg, and 5 twice-a-day doses of diltiazem hydrochloride ranging from 0 to 180 mg. Mild-to-moderate essential hypertension was defined as supine diastolic blood pressure in the range of 95 to 110 mmHg. The goal of treatment was to achieve a supine diastolic blood pressure of less than 90 mmHg, with no limiting adverse experience. 261 patients completed the six-week treatment protocol, with 13 to 17 patients randomized to each treatment group.

Using Proc RSREG in SAS, Version 6.12 (SAS Institute, Cary, NC), data from the plots published in the study were used to generate the response surfaces for the three main variables of interest: diastolic blood pressure (DBP), $4.16+1.60x_{\text{HCTZ}}+0.39x_{\text{DLTZ}}-0.12x_{\text{HCTZ}}^2+0.020x_{\text{DLTZ}}^2-0.033x_{\text{HCTZ}}*x_{\text{DLTZ}}$; serum cholesterol (CHO), $0.12+0.092x_{\text{HCTZ}}+0.033x_{\text{DLTZ}}-0.0073x_{\text{HCTZ}}^2-0.0032x_{\text{DLTZ}}^2-0.0013x_{\text{HCTZ}}*x_{\text{DLTZ}}$; and serum glucose (GLU), $-0.12+0.076x_{\text{HCTZ}}-0.011x_{\text{DLTZ}}-0.00011x_{\text{HCTZ}}^2+0.0030x_{\text{DLTZ}}^2-0.0011x_{\text{HCTZ}}*x_{\text{DLTZ}}$. The dose units were converted from milligrams to whole pill counts. One pill was equivalent to 3.125mg of HCTZ or 15mg of DLTZ.

A desirability function was defined for each of these three variables, d_1 - d_3 (Figure 3.3) and combined into an overall desirability function, $D=(d_1*d_2*d_3)^{1/3}$. The Nelder-Mead simplex procedure was then used to carry out the titration using the composite desirability. The Nelder-Mead algorithm is run on a continuous scale to maintain the flexibility allowed by simplexes of differing shapes. Therefore at each step, to determine the next dose combination, the doses output by the algorithm are rounded to the nearest whole dose unit. As discussed previously, it is also possible to round down to the nearest integer value.

3.4.2 Simulation Example

For each subject, the starting dose for the initial simplex was chosen to be the same as the smallest combination dose used in the original study: 6.25mg (2 pills) of HCTZ and 60mg (4 pills) of DLTZ. The initial step size was chosen to be the initial dose combination increased by four pill counts.

In order to simulate subject responses more realistically, a mixed effects model with a first order autoregressive covariance structure was used. Let $y_{ij}=\mathbf{x}_{ij}'\beta+\varepsilon_{ij}$, where y_{ij} represents the j th response from the i th subject, $\mathbf{x}_{ij}=[1 \ x_{i1} \ x_{i2} \ x_{i1}^2 \ x_{i2}^2 \ x_{i1}x_{i2}]$ represents the 6×1 vector of doses and dose functions for the i th subject at the j th time point, β represents the 6×1 vector of parameters taken from the study, and ε_{ij} represents the random error. The covariance between two observations w time intervals apart on the same subject is $\sigma_\varepsilon^2\rho^w$, where ρ is the correlation between adjacent observations within the same subject,

and w is the number of time intervals between the observations. For this study, the root MSE for DBP, σ_{DBP} , was 6.2mmHg (pers. comm.), and 0.35mmol/L was used for both CHO, σ_{CHO} , and GLU, σ_{GLU} .

The simulated response at each vertex of the simplex was obtained in triplicate and the responses were averaged. The desirability for each averaged response was compared, and the location of the next dose combination to be given was determined by the Nelder-Mead algorithm, rounding to the nearest whole pill. The titration continued through the specified fixed number of steps (either 16 or 32). At the last step, the final simplex was evaluated and the dose combination associated with the most desirable response was taken as the final treatment combination. Figure 3.4 demonstrates the final dose locations for a simulated group of 175 subjects who have completed the titration process. The mean final dose combination was 4.6 pills HCTZ and 16.2 pills DLTZ with a simulated mean decrease in DBP of 17.7mmHg. Figure 3.5 shows the asymptotic confidence ellipsoid about the central location estimate for the Wilcoxon Signed Rank statistic. A correlation between successive blood pressure observations of $\rho=0.7$ was used and the process continued for 16 steps.

3.4.3 Simulation Results

Five groups of 100 simulations were run using sample sizes of $N=175$ with 16 and 32 steps. The simulations were run first using the desirability function for DBP alone, d_1 (Fig. 3a), and then repeated using the composite desirability function, $D=(d_1*d_2*d_3)^{1/3}$, which took into account serum cholesterol and serum glucose measurements in addition to

the DBP. Additionally, to examine the effect of the correlation between successive observations, ρ , the correlation was varied from 0.1 to 0.8. In the simulations with the composite desirability function, the correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7.

Using the desirability function for DBP, d_1 , we see in Table 3.2 that the proportion of subjects showing improvement over the baseline was 1 (i.e. 100%) for all cases, using either the Fisher Sign test or the Wilcoxon Signed Rank test. All subjects also showed improvement when the final response was compared to the simulated response to single drug treatment with 25mg of HCTZ, the highest dose used in the study. A similar result was seen in comparing the response to treatment with a 180mg dose of DLTZ. The mean decrease in DBP, shown in the far right column, did not appear to change as the number of steps was increased from 16 to 32. However, the size of the reduction in DBP did appear to increase as the correlation increased. Table 3.3 shows the percentage of confidence ellipsoids which included the origin, included the hydrochlorothiazide axis only, included the diltiazem axis only, or included both axes, also using the desirability for DBP alone. The final central dose locations for hydrochlorothiazide and diltiazem are also given in the far right columns, using both the mean and the Wilcoxon Signed Rank statistics as measures of central location. Using Mardia's test (1974), in many instances the multivariate distribution of the final dose locations for each simulation showed some departure from normality, suggesting the nonparametric approach to be most appropriate. As the correlation was increased from 0.1 to 0.8, the simplex appeared to move further up the DLTZ axis, resulting in a higher final dose of DLTZ and a tighter confidence ellipsoid. Increas-

ing the number of steps from 16 to 32 did not appear to have much effect, suggesting that the simplex had already arrived at a final dose after 16 steps.

From our simulations, it appears that the evolutionary simplex approach is effective in arriving at dose combinations producing improved responses in patients being treated with multiple drug regimens, although inferences on the location do not appear to be as sharp as inferences on the response. In comparing the simulation results with the original response data, the final dose locations were found to correspond well with the area of higher response seen in the Burris, et.al. study.

The simulations were then repeated using the composite desirability function, D , which combined the main outcome of interest, DBP, with two other endpoints which the study authors reported, serum glucose and serum cholesterol. The correlation for successive DBP measurements within a patient was increased from 0.1 to 0.8, while the correlation for both CHO and GLU were fixed at 0.7. In Tables 3.4 and 3.5, we see that the simplex does not move as far along the DLTZ axis or HCTZ axis when these other endpoints are taken into consideration. However, from Table 3.4, we see that even at these doses, there is still a significant improvement in the response for all subjects in all cases.

We were also interested in determining how sensitive the titration method was to variability in the chosen desirability function. To determine whether small modifications in the desirability function had any effect on the resulting dose locations and responses, we ran simulations using three modified desirability functions in addition to d_1 , the desirability function for DBP, with 16 steps, a correlation of 0.7, and a sample size of 175.

Tables 3.6 and 3.7 show that sharpening the peak desirability as with d_a , increasing the

width of the desirability function as with d_b , or decreasing the width and sharpening the peak simultaneously as with d_c , did not result in any appreciable change in the outcome with respect to either response or dose location. There was little or no change in the decrease in DBP or final dose combinations, indicating that the process is robust, or relatively insensitive, to small changes in the definition of the desirability function. So while desirability functions should be defined carefully, there is some room for variation when deciding on the parameters.

To examine the effect of changing the initial step size, the step size was changed from an increase of 6 pills in the HCTZ axis and 8 pills in the DLTZ axis, to an increase of only 5 pills/7 pills, or 4 pills/6 pills over the initial dose combination. After 16 steps, using the desirability function for DBP, a correlation of 0.7, and a sample size of 175, there was a slightly smaller decrease in the DBP response. In addition, the final dose combinations also decreased as the initial step size became smaller. This would suggest that either the simplex has not had enough time to reach the same improved dose as with the larger step size, or perhaps the simplex has reached a plateau and the variability is too large for it to move further along the dose response surface. However, increasing the number of steps from 16 steps to 32 steps did not noticeably change the results, suggesting that the latter situation might be the cause of the differences in the outcome measures. This underscores the need to be prudent in choosing the parameters for the Nelder-Mead algorithm.

3.5 Discussion

In this paper, we have demonstrated the application of a method for titrating and evaluating multiple drug combinations within individual patients. This approach is well suited to the treatment of chronic diseases with long courses, where the condition of the patient is constantly evolving, and it lends itself especially well to conditions with a readily measured response, where there are regular treatment intervals, and where dose escalation within a patient is reasonable. After the patient completes an initial titration, the patient can continue to be monitored with periodic measurements of the response or marker of interest, and the simplex can be restarted if the treatment appears to need later adjustment. Some care must be used when determining parameters to use for the initial step size, for the reflection, expansion, and contraction coefficients, and for the stopping criteria. This requires a close collaboration between the statistician and physician investigator. The choice of these parameters will be affected by the variability in the response and the therapeutic index of the drugs involved. However, there is flexibility built into the procedure which allows one to start with a more cautious approach and to modify the conservativeness as the titration progresses.

This method of patient titration can be used in a modified clinical trials setting to evaluate the efficacy of a therapy composed of a combination of therapeutic agents. The first step would be for the physician researcher and statistician to define the desirability function for each response of interest, develop a composite desirability, and specify the parameters for the direct-search algorithm. A regular treatment or visit schedule should be set up so the physician can regularly monitor the patient response. The patient will be treated with each of the dose combinations comprising the initial simplex, with a change

in the treatment dose occurring at pre-specified intervals. After the initial simplex is established, the physician can run the direct search procedure himself, using specially designed software to determine the next combination of doses to administer; or, he can report the results to a central statistician or agency who can then advise the physician on the next dose combination to prescribe. This titration is then continued for the duration of the study. Inference on the sample of patients can then be made using the methods described in this paper.

This method has several advantages over the approach often used in clinical trials. One key advantage is that each patient has the potential to benefit from the treatment being administered. In contrast, in the typical clinical trials setting, a large percentage of patients, specifically, those randomized to the placebo group, often receive no benefit from the trial, leading to problems with patient recruitment and compliance with the study protocol. Another important advantage is the flexibility inherent in this approach. While this method is easily automated, it allows the investigator to incorporate his own experience and knowledge about the response and to include multiple outcomes of interest as well as multiple constraints, mirroring the way physicians approach dose titration in practice.

This approach also has advantages over the response surface methods sometimes used to evaluate multiple drug combinations. Response surface methods usually require the inclusion of many dose levels and dose combinations. This results in studies that are expensive and where there is no guarantee that any of the study subjects receives the optimum dose. Furthermore, the response surface approach requires an assumption that the

dose-response relationship is well approximated by the equation specified.

The method discussed in this paper does not require specifying the form of the dose-response relationship and automatically takes into account interactions between therapeutic components. It allows investigators to easily evaluate for the presence or absence of therapeutic synergism and to determine whether subjects have experienced an improvement in outcome.

In our simulation studies, we simulated how this method would work in titrating two blood pressure medications within patients with mild to moderate hypertension, using the response surface data provided in the study by Burris, et.al. Our studies demonstrated that with proper choice of the initial simplex and step size, all simulated subjects experienced an improvement in response over the baseline, with a significant decrease in the diastolic blood pressure. Minor changes to the desirability function did not appear to modify the results significantly, demonstrating some resilience in the specification of the desirability function. Modifying, or more specifically, decreasing, the size of the initial step in the Nelder-Mead algorithm, did appear to have some effect on the final dose locations, emphasizing that the careful choice of the initial step size, reflection, expansion, and contraction coefficients, is critical in the application of this methodology. Use of Mardia's multivariate test for normality showed that the final dose locations did not generally follow a multivariate normal distribution, suggesting that the use of the nonparametric approach when constructing confidence ellipsoids would be more appropriate. The confidence ellipsoid then provides a way to evaluate therapeutic synergism and to make inferences about the treatment efficacy of individual therapeutic components.

There are several limitations to this approach that should be addressed. One possible criticism is that there is no control group in the titration process to provide internal validation. As a result, it could be argued that the improvement in response displayed by the group of n patients may be due simply to physician attention or the possibility that the disease has gone into remission. This should be considered when interpreting the results of the statistical tests discussed in section 3.3.1. One possible solution is for researchers to provide some form of external validity. For example, the investigator may find published reports on a similar patient population showing a lack of patient improvement in untreated patients or patients undergoing monotherapy.

This method is also likely to be sensitive to the number of drugs comprising the combination under evaluation. As the number of therapies in a combination increases above a certain level, this method may become cumbersome due to time constraints and compliance problems in establishing the initial simplex. The subject would be required to rotate through numerous sets of different dose combinations to establish the initial simplex before information useful for treatment could be collected and applied. On the other hand, the alternative, using response surface methodology, would also be impractical because of the extremely large number of subjects which would be required. In addition, it is unlikely that the number of drugs in a combination would reach the level where this might become problematic.

Another limitation is that this method may be less efficient in specific cases, e.g., when the variability in the response value is large relative to the effect, resulting in too much noise in the system, or when the time required to observe a response is overly long,

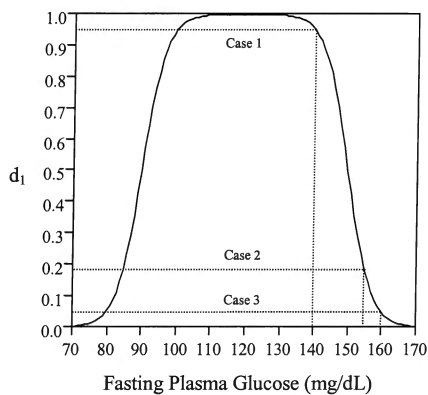
making the establishment of the initial simplex impractical. Additionally, the simplex movement may move too slowly to be of benefit in treating the patient.

In conclusion, we have described an evolutionary operation approach to evaluating multiple drug therapies while simultaneously titrating therapies within individual patients, where every patient has the potential to benefit from the combination being studied. This flexible approach is useful not only in titrating multiple agents, but also can similarly be applied to the titration of single agents with multiple endpoints. The utilization of desirability functions allows us to emulate how physicians approach dose titration in the single drug case, allowing the consideration of multiple endpoints and constraints. Practicing physicians may find this approach useful for improving the way both single therapies and combination therapies are prescribed for individual patients. Clinical researchers may find this methodology useful for evaluating whether therapeutic synergism exists within specific drug combinations and for evaluating individual therapeutic components.

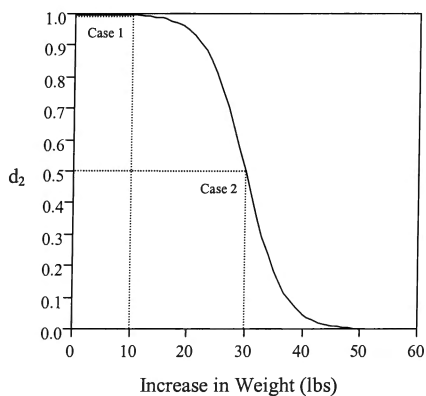
The current procedure is not far from the one described by Box in 1958. He envisioned using evolutionary methods which “might in fact be used to get maximum information from the normal treatment of patients by practicing practitioners. It would be necessary for a central agency to obtain agreement that doctors, in using a particular therapy in normal practice (as contrasted with special research studies), would vary the therapy slightly in accordance with a prescribed plan. With a suitable statistical plan, differences arising from small deliberate changes in the therapy can be detected when the information is collected. In this way a steady evolution in medical practice might be set in motion to augment more specialized research studies.” This ‘evolution in medical prac-

tice' was anticipated by Box over 40 years ago, where practicing physicians would apply evolutionary principles in the treatment of their patients, with a parallel evolution in the conduct of clinical research studies. Certainly there is technology currently available which would allow the physician to enter the patient data directly into a handheld computer or personal digital assistant, to calculate the desirabilities, and to run the evolutionary direct search procedure at the bedside to obtain an immediate prescription. With drug consumption continuing to rise, and along with that the dramatic increase in the potential for drug interactions, new approaches to prescribing and treatment are needed. Our methodology may be useful for both treating the individual patient and for characterizing new drug combinations.

3.6 Figures

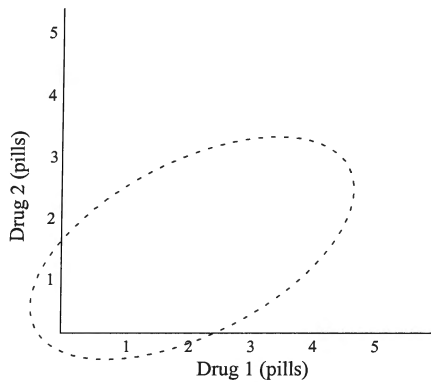


a) $(Y_1^*, Y_1^{**}) = (80, 100)$, $(Y_1^{***}, Y_1^{****}) = (140, 160)$,
 $\gamma_1 = 0.05$, $d_1 = d_1^* * d_1^{**}$

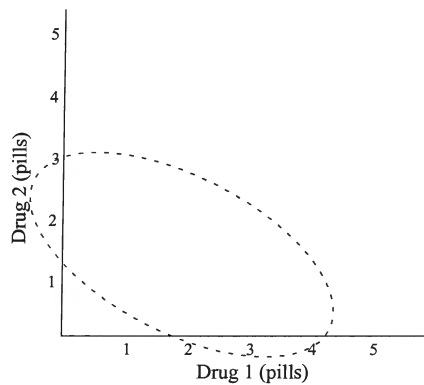


b) $Y_2^* = 20$, $Y_2^{**} = 40$, $\gamma_2 = 0.05$

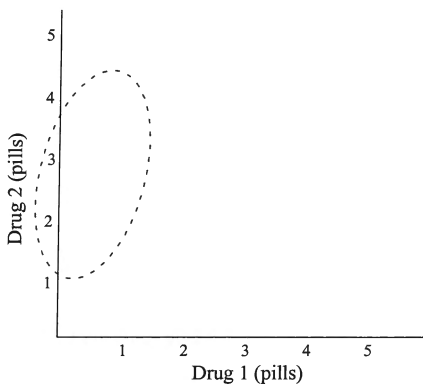
Figure 3.1: Examples of desirability functions: (a) target desirability function for fasting plasma glucose; (b) minimizing desirability function for increase in body weight. Cases are from Table 3.1.



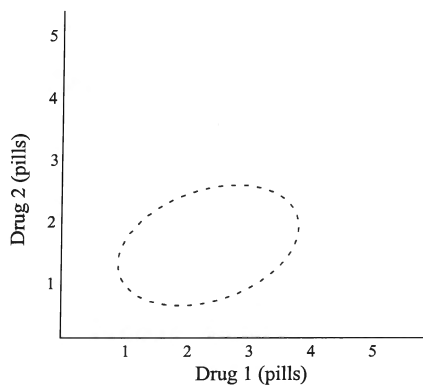
a) Confidence ellipsoid contains the origin



b) Confidence ellipsoid contains both axes but not the origin

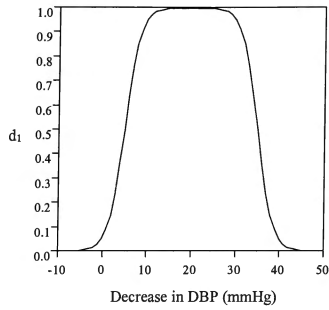


c) Confidence ellipsoid contains only one axis

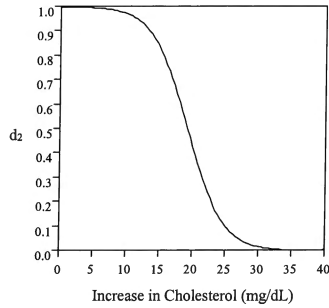


d) Confidence ellipsoid does not contain either axis or the origin

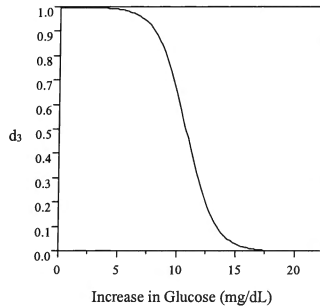
Figure 3.2: Evaluating confidence ellipsoids



$$\text{a) } (Y_1^*, Y_1^{**}) = (0, 10), (Y_1^*, Y_1^{**}) = (30, 40), \\ \gamma_1 = 0.05, d_1 = d_1' * d_1''$$



$$\text{b) } Y_2^* = 11.6, Y_2^* = 27.1, \gamma_2 = 0.05$$



$$\text{c) } Y_3^* = 11.6, Y_3^* = 27.1, \gamma_3 = 0.05$$

Figure 3.3: Desirability functions: (a) decrease in diastolic blood pressure; (b) increase in cholesterol; (c) increase in glucose.

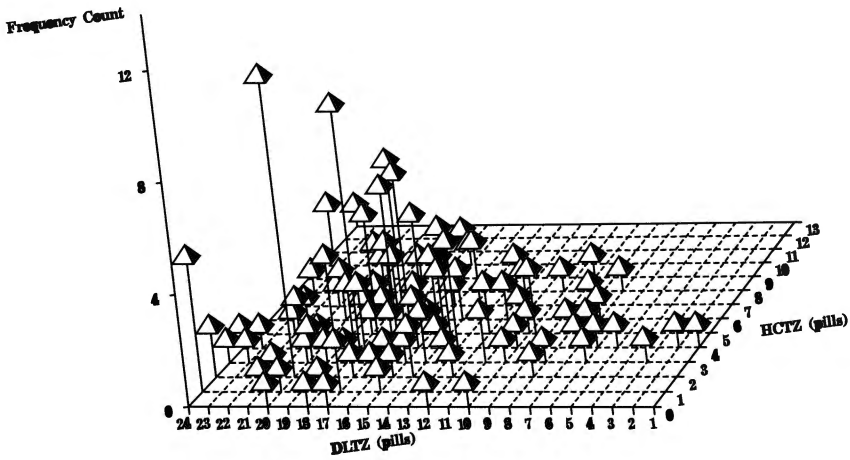


Figure 3.4: Pyramid plot of final dose locations for a simulated group of 175 subjects who have completed the 16 steps of titration, using a correlation of 0.7. In this simulation, the desirability function shown in Figure 3.3a was used to target a reduction in diastolic blood pressure (DBP). The mean decrease in DBP was 17.7mmHg. The mean final dose combination was 4.6 pills HCTZ and 16.2 pills DLTZ.

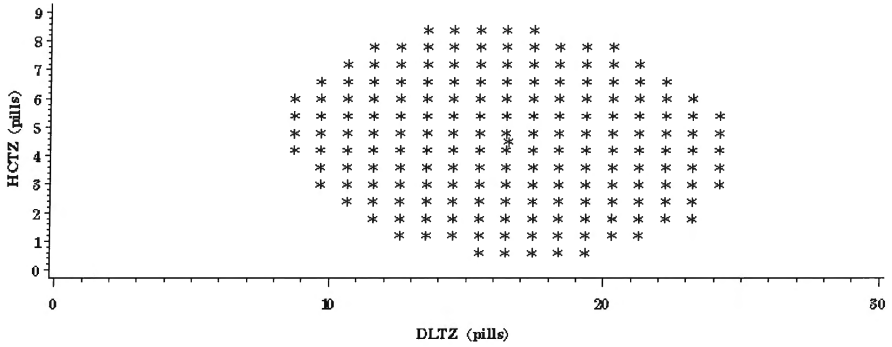


Figure 3.5: Asymptotic confidence ellipsoid based on the Wilcoxon signed rank statistic for a group of 175 subjects using the desirability function in Figure 3.3a.

3.7 Tables

Table 3.1: Desirability example for differing fasting plasma glucose and weight gain levels. $D=(d_1*d_2)^{1/2}$.

	FPG (mg/dL)	d_1	Weight Gain (lbs)	d_2	D
Case 1	140	0.95	10	1.0	0.98
Case 2	155	0.19	30	0.5	0.31
Case 3	160	0.05	0	1.0	0.22

Table 3.2: Proportion of improved responses using the Fisher sign test or Wilcoxon signed-rank test. Simulations were done using the desirability function for diastolic blood pressure alone (d_1). The mean decrease in DBP is shown in the far right column.

N	Steps	ρ		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)
175	16	0.1	Fisher(SE)	1	1	1	16.4
			Wilc(SE)	1	1	1	
	0.3	Fisher(SE)	1	1	1	16.8	
		Wilc(SE)	1	1	1		
	0.5	Fisher(SE)	1	1	1	16.9	
		Wilc(SE)	1	1	1		
	0.7	Fisher(SE)	1	1	1	17.7	
		Wilc(SE)	1	1	1		
	0.8	Fisher(SE)	1	1	1	18.6	
		Wilc(SE)	1	1	1		
	32	0.1	Fisher(SE)	1	1	1	16.3
			Wilc(SE)	1	1	1	
		0.3	Fisher(SE)	1	1	1	16.9
			Wilc(SE)	1	1	1	
0.5		Fisher(SE)	1	1	1	17.1	
		Wilc(SE)	1	1	1		
0.7		Fisher(SE)	1	1	1	18.2	
		Wilc(SE)	1	1	1		
0.8		Fisher(SE)	1	1	1	18.6	
		Wilc(SE)	1	1	1		

Table 3.3: Evaluation of the confidence ellipsoids using a parametric and nonparametric approach. Simulations were done using the desirability function for diastolic blood pressure alone (d_1). The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the DLTZ axis only, containing the HCTZ axis only, or containing both axes. The rightmost columns show the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

N	Steps	ρ		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
175	16	0.1	Mean(SE)	0	0	97.2(1.30)	2.8(1.30)	4.5(0.03)	14.0(0.02)
			Wilc(SE)	1.6(1.52)	13.4(2.92)	39.0(2.92)	23.2(4.97)	4.4(0.03)	14.2(0.03)
	0.3	Mean(SE)	0	0	99.6(0.89)	0.4(0.89)	4.5(0.02)	14.5(0.01)	
		Wilc(SE)	0.8(0.45)	9.6(2.70)	43.4(4.22)	16.2(3.27)	4.4(0.03)	14.7(0.01)	
	0.5	Mean(SE)	0	0	100	0	4.5(0.02)	15.2(0.02)	
		Wilc(SE)	0	4.8(1.92)	51.2(5.12)	8.2(2.17)	4.4(0.02)	15.5(0.03)	
	0.7	Mean(SE)	0	0	100	0	4.6(0.02)	16.2(0.02)	
		Wilc(SE)	0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)	
	0.8	Mean(SE)	0	0	100	0	4.6(0.02)	17.1(0.02)	
		Wilc(SE)	0	0	68.0(3.94)	0	4.5(0.03)	17.3(0.03)	
32	0.1	Mean(SE)	0	0	99.4(0.55)	0.6(0.55)	4.4(0.01)	14.2(0.05)	
		Wilc(SE)	0.6(0.55)	10.8(4.87)	49.4(4.10)	21.8(4.44)	4.2(0.02)	14.4(0.05)	
	0.3	Mean(SE)	0	0	100	0	4.4(0.01)	14.7(0.06)	
		Wilc(SE)	0.2(0.45)	8.2(0.84)	54.0(3.87)	17.6(2.30)	4.3(0.02)	15.0(0.07)	
	0.5	Mean(SE)	0	0	100	0	4.4(0.02)	15.3(0.03)	
		Wilc(SE)	0	2.6(1.14)	61.4(8.88)	5.6(1.95)	4.3(0.02)	15.7(0.02)	
	0.7	Mean(SE)	0	0	100	0	4.5(0.02)	16.4(0.01)	
		Wilc(SE)	0	0	71.0(3.87)	0	4.4(0.02)	16.7(0.02)	
	0.8	Mean(SE)	0	0	100	0	4.5(0.004)	17.1(0.04)	
		Wilc(SE)	0	0	75.4(2.30)	0	4.4(0.01)	17.4(0.05)	

Table 3.4: Proportion of improved responses using the Fisher sign test or Wilcoxon signed-rank test. Simulations were done using the composite desirability function (D). The correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7. The rightmost columns show the mean decrease in diastolic blood pressure, the mean change in cholesterol and the mean change in serum glucose.

N	Steps	ρ		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)	Change in Chol (mmol/L)	Change in Glu (mmol/L)	
175	16	0.1	Fisher (SE)	1	1	1	11.9	0.24	0.29	
			Wilc (SE)	1	1	1				
		0.3	Fisher (SE)	1	1	1	11.9	0.25	0.29	
			Wilc (SE)	1	1	1				
		0.5	Fisher (SE)	1	1	1	11.9	0.25	0.31	
			Wilc (SE)	1	1	1				
	0.7	Fisher (SE)	1	1	1	12.0	0.24	0.29		
		Wilc (SE)	1	1	1					
	0.8	Fisher (SE)	1	1	1	12.1	0.24	0.27		
		Wilc (SE)	1	1	1					
	32	0.1	0.1	Fisher (SE)	1	1	1	11.3	0.25	0.27
				Wilc (SE)	1	1	1			
0.3			Fisher (SE)	1	1	1	11.3	0.27	0.26	
			Wilc (SE)	1	1	1				
0.5			Fisher (SE)	1	1	1	11.6	0.25	0.31	
			Wilc (SE)	1	1	1				
0.7		Fisher (SE)	1	1	1	11.9	0.24	0.27		
		Wilc (SE)	1	1	1					
0.8		Fisher (SE)	1	1	1	11.8	0.23	0.27		
		Wilc (SE)	1	1	1					

Table 3.5: Evaluation of the confidence ellipsoids using a parametric and nonparametric approach. Simulations were done using the composite desirability function (D). The correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the DLTZ axis only, containing the HCTZ axis only, or containing both axes. The rightmost columns show the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

N	Steps	ρ		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
175	16	0.1	Mean (SE)	0	0	34.0(5.70)	66.0(5.70)	3.1(0.02)	9.2(0.02)
			Wilc (SE)	9.0(1.41)	0	61.4(2.07)	38.6(2.07)	3.0(0.02)	9.2(0.02)
		0.3	Mean (SE)	0	0	35.6(3.05)	64.4(3.05)	3.1(0.02)	9.2(0.02)
			Wilc (SE)	8.8(4.92)	0	60.8(4.32)	39.2(4.32)	3.0(0.02)	9.3(0.03)
		0.5	Mean (SE)	0	0	38.2(4.44)	61.8(4.44)	3.1(0.02)	9.3(0.02)
			Wilc (SE)	9.8(2.28)	0	61.4(2.70)	38.6(2.70)	3.0(0.02)	9.4(0.02)
		0.7	Mean (SE)	0	0	44.0(5.24)	56.0(5.24)	3.1(0.02)	9.4(0.02)
			Wilc (SE)	8.8(3.27)	0	61.4(5.77)	38.6(5.77)	3.0(0.01)	9.5(0.02)
		0.8	Mean (SE)	0	0	51.4(3.58)	48.6(3.58)	3.1(0.02)	9.5(0.02)
			Wilc (SE)	9.2(2.17)	0	59.8(4.21)	40.2(4.21)	3.0(0.02)	9.6(0.03)
	32	0.1	Mean (SE)	0	0	36.4(3.71)	63.6(3.71)	3.0(0.02)	9.2(0.03)
			Wilc (SE)	9.2(1.64)	0	59.2(5.26)	40.8(5.26)	2.8(0.03)	9.3(0.03)
		0.3	Mean (SE)	0	0	38.6(3.78)	61.4(3.78)	3.0(0.02)	9.2(0.04)
			Wilc (SE)	6.4(1.67)	0	56.4(3.13)	43.6(3.13)	2.8(0.02)	9.3(0.04)
		0.5	Mean (SE)	0	0	40.8(3.56)	59.2(3.96)	3.0(0.01)	9.3(0.05)
			Wilc (SE)	5.2(2.05)	0	55.0(3.39)	45.0(3.39)	2.8(0.01)	9.4(0.05)
		0.7	Mean (SE)	0	0	48.6(4.16)	51.4(4.16)	2.9(0.01)	9.4(0.03)
			Wilc (SE)	7.0(2.55)	0	59.4(2.07)	40.6(2.07)	2.8(0.02)	9.5(0.03)
		0.8	Mean (SE)	0	0	54.2(1.92)	45.8(1.92)	2.9(0.01)	9.5(0.04)
			Wilc (SE)	6.8(2.17)	0	53.0(3.54)	47.0(3.54)	2.8(0.02)	9.6(0.04)

Table 3.6: A comparison of desirability functions. The table shows the proportion of improved responses using the Fisher sign test or the Wilcoxon signed-rank test. The parameters for the modified desirability functions are shown, with the mean decrease in diastolic blood pressure given in the rightmost column.

Dsbl	N=175 Steps=16 $\rho=0.7$	(Y_i^*, Y_i^{**})	(Y_i^{***}, Y_i^{****})	Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)
d_1	Fisher (SE)	(0,10)	(30,40)	1	1	1	17.7
	Wilc (SE)			1	1	1	
d_a	Fisher (SE)	(0,20)	(20,40)	1	1	1	17.5
	Wilc (SE)			1	1	1	
d_b	Fisher (SE)	(-5,10)	(30,45)	1	1	1	17.5
	Wilc (SE)			1	1	1	
d_c	Fisher (SE)	(10,20)	(20,30)	1	1	1	17.5
	Wilc (SE)			1	1	1	

Table 3.7: A comparison of desirability functions. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the DLTZ axis only, containing the HCTZ axis only, or containing both axes. The parameters for the modified desirability functions are shown, with the rightmost columns giving the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

Dsbl	N=175 Steps=16 $\rho=0.7$	(Y_{1*}, Y_{1*}^*)	(Y_{1*}, Y_{1*}^*)	Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
d_1	Mean (SE)	(0,10)	(30,40)	0	0	100	0	4.6(0.02)	16.2(0.02)
	Wilc (SE)			0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)
d_a	Mean (SE)	(0,20)	(20,40)	0	0	100	0	4.6(0.01)	16.3(0.03)
	Wilc (SE)			0	0.2(0.45)	64.0(3.81)	0.2(0.45)	4.5(0.02)	16.6(0.04)
d_b	Mean (SE)	(-5,10)	(30,45)	0	0	100	0	4.6(0.02)	16.3(0.02)
	Wilc (SE)			0	0.4(0.55)	66.8(3.90)	0.4(0.89)	4.4(0.03)	16.6(0.04)
d_c	Mean (SE)	(10,20)	(20,30)	0	0	100	0	4.6(0.01)	16.3(0.02)
	Wilc (SE)			0	0.2(0.45)	63.6(3.44)	0.2(0.45)	4.5(0.02)	16.6(0.04)

Chapter 4

Applications of EVOP Titration

4.1 Discussion of Clinical Applications

There are many diseases or clinical syndromes to which the evolutionary operation direct-search titration methodology could be applied. The characteristics of a condition which would favor its use include an easily and rapidly measured response, a lengthy time course, and a condition where dose escalation within a patient is reasonable. Examples of diseases or syndromes which may benefit from this treatment approach are hypertension, diabetes, rheumatoid arthritis, asthma, AIDS, and some cancers.

It is important that the responses being monitored are easily measureable and reproducible. In the ideal case, they might consist of laboratory tests or measurements that are already performed periodically as part of the regular standard of care so as to minimize additional discomfort or inconvenience to the patient. Accuracy and reproducibility of measurement are also important to ensure that the simplex is moving purposefully according to the clinical endpoint (or signal) rather than moving haphazardly in response to a large variability in the measurement (or noise). Some examples of suitable clinical

endpoints are blood pressure, fasting plasma glucose, forced expiratory volume, and the reported number of side effects a patient is experiencing each week.

In the situation where a lengthy time to response is required, the use of EVOP may not be appropriate. A sufficient time interval between measurements must be allowed to preclude any carryover effects from the previous treatment. In this case, the time required to set up the initial simplex may become impractical, and the subsequent simplex movement may be too slow to be of benefit in treating the patient. EVOP titration may also be problematic when the number of therapies in a combination is extremely large. Establishing the initial simplex may become cumbersome due to time constraints, and problems with patient compliance are more likely. EVOP would also be of limited application when the course of a disease is too brief to provide substantial information.

On the other hand, the application of EVOP is very well suited to the treatment of chronic conditions with long time courses. This allows sufficient time for the establishment of the initial simplex and for titration to a maintenance therapy. Since disease processes are dynamic, EVOP can be continued indefinitely to track the patient's progress. After an initial maintenance dose is identified, the physician can continue to periodically monitor the patient, and the titration process can be restarted when changes to the patient's status are observed.

The following section is an example of a study protocol applying the evolutionary operation direct-search methodology to the treatment of type 2 diabetes patients.

4.2 Study Protocol using EVOP Direct-Search Methodology

A comparison of multi-drug titration with glyburide and metformin to treatment with Glucovance

4.2.1 Hypothesis

Drug titration within individual patients using the two drug combination of glyburide and metformin results in a higher proportion of patients achieving target HbA_{1c} when compared to fixed dosing with Glucovance.

4.2.2 Specific Aims

Preliminary

To conduct a twenty week pilot study to determine the proportion of subjects achieving a target HbA_{1c} < 7% after treatment with a 2-drug titration approach using glyburide and metformin in combination, and to adjust, if necessary, the titration parameters to be used in the primary study.

Primary

To determine whether a 2-drug titration approach using glyburide and metformin in combination is superior to fixed dosing with Glucovance in achieving acceptable serum glucose levels, using a test of proportions to determine whether the proportion of subjects achieving a target HbA_{1c} < 7% using the titration approach is as large as that for Gluco-

vance after 24 weeks.

Secondary

To determine whether a 2-drug titration approach using glyburide and metformin in combination results in a more desirable outcome status after 24 weeks than treatment with Glucovance, using a test of mean final desirability scores.

4.2.3 Background and Significance

It is estimated that approximately 16 million people in the U.S. have diabetes, only one-third of which are diagnosed. Type 2 diabetes accounts for 90-95% of all patients diagnosed with diabetes. An additional 15 million people have impaired glucose tolerance, putting them at a high risk for developing type 2 diabetes. Diabetes is currently the 4th leading cause of death by disease in the U.S., the leading cause of blindness in adults 20-74 years old, and the leading cause of end-stage renal disease. Sixty to seventy percent of diabetics have some form of mild to severe neuropathy, and diabetes is associated with a 2 to 4 fold increase in risk for both heart disease and stroke. The considerable morbidity and mortality associated with this disease is estimated to cost \$98 billion each year in direct medical costs and indirect costs to industry (1).

Recent reports (2,3) have added to the evidence that tighter glycemic control may delay or prevent both macrovascular disease and microvascular and neuropathic complications. Therefore it is of significant interest, both from the point of view of reducing mor-

bidity and mortality and of controlling health care costs, to find the most efficient strategy for applying our current arsenal of diabetes therapies to achieve the tightest glycemetic control.

In recent years, several new oral therapeutic agents have been introduced to treat diabetes, which has opened up new options for managing this disease. Diabetes treatment is typically first approached by recommending changes to both diet and activity levels. If treatment with lifestyle changes alone is unsuccessful, the physician has a choice of several oral agents that may be added alone or in combination to the treatment plan, including sulfonylureas, biguanides (metformin), alpha-glucosidase inhibitors and the thiazolidinediones.

The current therapeutic approach to treating type 2 diabetes is often first to find an effective dose with a single drug and then to incrementally increase levels of the drug to maintain the effect as time progresses. Currently, all type 2 diabetes treatments show secondary failure over time (4,5), with HbA_{1c} levels increasing by 0.2 to 0.3 percent per year (4). Therefore, all treatments must be subject to continuous adjustment and periodic increases. When the maximum dose of the single drug is reached or the single drug is no longer sufficient to maintain acceptable glucose levels, a new compound is often added to keep serum glucose measurements within the allowable range while keeping the first compound at its maximum dose. Such an approach, however, does not account for potential interactions among the drugs, and it is possible that the patient is not receiving the best available treatment. In addition, several studies have examined the use and benefits of

combination therapies, including the combination of sulfonylureas with metformin (6,7,8), and there is some evidence that these drugs, used in combination, provide better glucose control than either drug by itself (6,7). One company, Bristol-Myers Squibb, has combined the sulfonylurea, glyburide, with the biguanide, metformin, into a single tablet, recently approved and currently sold in the U.S. under the name Glucovance.

A preliminary study of ten type 2 diabetes patients will be conducted over a period of twenty weeks using an evolutionary operation (EVOP) approach to titrating the 2-drug combination of glyburide and metformin within each subject. The preliminary study will allow the fine tuning of the parameters used in the titration procedure before beginning the primary study. An estimate will also be obtained of the proportion of subjects attaining a $HbA_{1c} < 7\%$, which will be used to calculate the required sample size for the primary study.

The purpose of the primary study is to determine whether titration with the 2-drug combination of glyburide and metformin in type 2 diabetes reduces HbA_{1c} levels more effectively than treatment with fixed doses of Glucovance over a period of 24 weeks.

4.2.4 Review of Therapeutic Agents

Sulfonylureas (tolbutamide, chlorpropamide, tolazamide acetohexamide, glyburide, glipizide, glimepiride)

The sulfonylureas are a group of agents that increase insulin secretion by stimulating pancreatic beta cells (9). They are effective in lowering glycemia in about 50 percent of

patients who are unable to control their glycemia with diet and exercise alone (10). The effectiveness declines as the failure of the beta cells progresses, resulting in a secondary failure rate of 3 to 10 percent per year (10). The average decrease in HbA_{1c} is 1 to 2 percent (11). There is a small risk of hypoglycemia with use of the sulfonylureas and a modest associated weight gain. The effects on the lipid profile are minimal, with minor decreases in triglyceride levels. Treatment should be initiated at the lowest recommended dose and increased every four to seven days until the desired effect or maximum dose is reached.

Glyburide is a second generation sulfonylurea, administered twice a day in doses ranging from 1.25mg to 5mg, with a maximum daily dose of 20mg.

Biguanides (metformin)

Metformin is the only biguanide currently approved for use in the U.S. by the FDA. It acts on the liver to decrease hepatic glucose production and also promotes insulin sensitivity in both the liver and peripheral tissues (12). Treatment with metformin has been shown to decrease fasting and postprandial glycemia by 60-70mg/dL (13), with an average decrease in HbA_{1c} of 1.5 to 2 percent (13). Metformin shows initial effectiveness in approximately 75 to 80 percent of type 2 diabetes patients (9) and does not cause hypoglycemia. It is associated with less weight gain than the sulfonylureas (12) and is often used in combination with the sulfonylureas or with other agents. It also appears to have favorable effects on the lipid profile and is associated with small decreases in total cholesterol, LDL and

triglyceride levels (14). There are some gastrointestinal side effects, most notably nausea or diarrhea, which can be minimized by taking metformin with meals, and by initiating treatment at a low dosage and increasing the dose slowly over a period of several weeks. The most serious side effect is lactic acidosis (15), particularly in patients with impaired renal function. Therefore, metformin cannot be used when the creatinine clearance is greater than 1.4mg/dL in women, and greater than 1.5mg/dL in men. Metformin is also contraindicated in cardiac failure and pulmonary disease patients or anybody with a disease condition which interferes with lactate removal. Treatment with metformin is usually initiated at a dose of 500 mg, which may be increased in 500 mg increments every one to two weeks, with the maximum effect seen at a dose of 2000mg per day.

Glucovance

Glucovance is a combination of the sulfonylurea, glyburide, and the biguanide, metformin. It has been approved for use both as an initial adjunct therapy to diet and exercise and a second-line therapy in patients who have not successfully controlled their hyperglycemia with diet, exercise, or treatment with a sulfonylurea or metformin alone. Glucovance is available in fixed combination doses of 1.25mg glyburide/250mg metformin, 2.5mg/500mg, and 5mg/500mg, with a maximum daily dose of 20mg/2000mg. An unpublished study of 806 previously untreated type 2 diabetes patients, summarized on the package insert (16), found a mean change from baseline HbA_{1c} of 1.48% at 20 weeks treatment with Glucovance 1.25mg/250mg compared to a mean change from baseline of

1.24% for glyburide, and 1.03% for metformin. Information from another unpublished study, also summarized on the Glucovance package insert, involved 639 type 2 diabetes patients whose blood sugar was inadequately controlled with sulfonylureas alone. These patients were either given glyburide 20mg, metformin 500mg, Glucovance 2.5/500mg, or Glucovance 5/500mg. At the end of 16 weeks, the mean HbA_{1c} value of patients given either dose of Glucovance was reported as 1.7% lower than those treated with glyburide alone, and 1.9% lower than those treated with metformin alone (16,17).

Current ADA Guidelines for Glycemic Control (18)

Preprandial Glucose	80-120 mg/dL
Bedtime Glucose	100-140 mg/dL
HbA _{1c}	< 7%

4.2.5 Preliminary Progress/Data Report

A logistic regression analysis was performed using data from the study of 806 drug-naive type 2 diabetes patients printed in the package insert (16) to determine whether there was an interaction effect between the 2.5mg of glyburide and 500mg of metformin. The likelihood ratio χ^2 statistic associated with the test of additivity (i.e. no interaction) was 5.975, with a p-value of 0.0145, indicating the presence of a significant interaction between the two drugs. In addition, the coefficient of the interaction term was negative (-0.887), indicating that the interaction was antagonistic between the two drugs at the given doses. It should be noted that these were the starting doses given to the patients for a period of 4 weeks, after which the dose could be increased up to a maximum of four tablets daily.

This initial analysis emphasizes the need for a more systematic yet flexible approach to combination dosing. Presumably these two drugs, glyburide and metformin, are used in combination with the goal that they interact synergistically, or at least in an additive fashion. This analysis indicates that with the doses used in the study, the two drugs appear to be antagonistic to each other, rather than synergistic or additive. However, it should be emphasized that the combination of glyburide and metformin may be additive or synergistic at dose combinations other than those used in the study. Unfortunately the design of the study reported does not allow the identification of other possibly more favorable doses. An advantage of the titration approach proposed in this study is that it will be helpful in identifying the dose area producing the most favorable interaction response and in avoiding doses where the interaction is antagonistic.

4.2.6 Research Method and Design

Pilot Study

A 20 week pilot study will be conducted. Ten newly diagnosed type 2 diabetes patients, men and women, will be enrolled using the following eligibility criteria:

Inclusion Criteria

- Men and women newly diagnosed with type 2 diabetes and receiving no current or previous pharmacological treatment
- HbA_{1c} < 10%
- Informed Consent

Exclusion Criteria

- Women who are pregnant or nursing
- Subjects who have previously been treated with other diabetes therapies
- Subjects with hepatic or renal impairment
(creatinine > 1.4mg/dL in women, > 1.5mg/dL in men)
- Subjects with concomitant CHF or pulmonary disease

Each subject will begin the study by rotating through each of three starting combinations. Before beginning treatment, baseline values of fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), fingerstick HbA_{1c}, and HbA_{1c} will be recorded. The patient will be randomized to one of six sequences of initial dose combinations: ABC, ACB, BAC, BCA, CAB, or CBA where A=one 2.5mg tablet glyburide, one 500mg tablet metformin, B=two 2.5mg tablets of glyburide, one 500mg tablet metformin, or C=one 2.5mg tablet glyburide, two 500mg tablets metformin. Each dose combination will be administered for a period of 2 weeks. The patient will be instructed to keep a daily journal of his or her fasting glucose measurements and 2-hour postprandial glucose measurements. At the end of the first treatment period and each subsequent two week period, the fasting glucose measurements and 2-hour postprandial glucose measurements, recorded by the patient over the previous one week, will be reported to and averaged by the physician, along with a fingerstick HbA_{1c} measurement. In addition, the number of reported hypoglycemic episodes and the number of reported negative GI effects over the previous one week will also be recorded. Unless an office visit is requested by the patient at the end of each treatment period, the averaged fasting and 2-hour postprandial glucose measurements, the fingerstick HbA_{1c}, the number of hypoglycemic episodes, and the number of

GI complaints will be reported to the physician over the telephone at the end of the second week. The measurements will be combined into a single desirability measure (Appendix 4.A) and the Nelder-Mead algorithm (Appendix 4.B) will be used to determine the next dose combination to be administered to the patient. If the physician is uncomfortable with the algorithm determined dose, the physician will be permitted to adjust the dose, and the actual dose prescribed by the physician will be recorded, together with the algorithm determined dose. The following treatment dose will again be determined by the Nelder-Mead algorithm, using the adjusted dose information.

The study will continue for a period of 20 weeks. The dose combination for each patient will be titrated until an average fasting glucose of < 150 or an average 2-hour postprandial glucose of < 180 is achieved or until the end of the study period. After a maintenance dose is established, bi-monthly reports with data collection and monitoring will continue for the duration of the study period.

Laboratory Studies

BP, ALT, serum creatinine, cholesterol, HbA_{1c} (initial and final visit), fingerstick HbA_{1c}

Data Collection and Monitoring

The patient will keep a diary of daily fasting glucose and 2-hour postprandial glucose measurements. The measurements recorded by the patient over the previous one week will be averaged and recorded at each visit. Fingerstick HbA_{1c} will also be measured at

each visit. Serum HbA_{1c} will be measured at the initial visit and final visit.

Primary Study

Men and women with newly diagnosed type 2 diabetes will be enrolled into the study and randomized to either the 2-drug titration group or the Glucovance group. The number of subjects to be enrolled will be determined by the estimate of the proportion of subjects achieving a HbA_{1c} < 7% after twenty weeks in the preliminary study, together with Table 1 in the Statistical Analysis section. An estimate of the proportion of subjects achieving a HbA_{1c} < 7% with Glucovance after twenty weeks has already been reported (16). Subjects will be blinded as to which treatment approach they are receiving.

Glyburide+Metformin titration group

This group will follow the same study protocol as in the pilot study, with the exception that the study will continue for a period of 24 weeks.

Glucovance Group

Subjects will be treated using regular standard of care. The patient will be instructed to keep a daily journal of his or her fasting glucose measurements and 2-hour postprandial glucose measurements. The fasting glucose measurements and 2-hour postprandial glucose measurements will be reported to the physician, along with a fingerstick HbA_{1c} measurement every two weeks. The number of reported hypoglycemic episodes and the

number of reported negative GI effects over the previous one week will also be recorded. Unless an office visit is requested by the patient at the end of each treatment period, the averaged fasting and 2-hour postprandial glucose measurements, the fingerstick HbA_{1c}, the number of hypoglycemic episodes, and the number of GI complaints will be reported to the physician over the telephone at the end of every other week.

Laboratory Studies

BP, ALT, serum creatinine, cholesterol, HbA_{1c} (initial and final visit), fingerstick HbA_{1c}

Data Collection and Monitoring

The patient will keep a diary of daily fasting glucose and 2-hour postprandial glucose measurements. The measurements recorded by the patient over the previous one week will be averaged and recorded at each visit. Fingerstick HbA_{1c} will also be measured at each visit. Serum HbA_{1c} will be measured at the initial visit and final visit.

4.2.7 Statistical Analysis

To test the primary hypothesis of equal proportions HbA_{1c} < 7% between treatment groups, a continuity corrected χ^2 test will be used.

To test the secondary hypothesis of no difference in mean desirability score between treatment groups, a 2-sided t-test of means will be used.

The following table shows the sample size estimates for testing the primary

4.2.8 References

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4.2.9 Appendices

Appendix 4.A

Overview of Desirability Functions^{19, 20, 21, 22}

Each response of interest is transformed to a continuous desirability function, d_i , with values ranging from 0 to 1, where a value of 0 designates the response as not at all desirable, while a value of 1 is assigned to the most desirable response. The basic shape of the function is determined by whether one is trying to maximize or minimize the response, or aim for a range of target values. The exact shape of each desirability function is determined in collaboration with the physician or other experts knowledgeable about the disease under study and the therapeutic effects of the treatments being administered. The following is the mathematical form of a maximizing desirability function

$$d_{i(\max)} = \left[1 + \exp\left(-\frac{Y_i - a_i}{b_i}\right) \right]^{-1}, \text{ where}$$

$$a_i = \frac{Y_{i^*} + Y_i^*}{2}, b_i = \frac{Y_i^* - Y_{i^*}}{2 \ln\left(\frac{1 - \gamma_i}{\gamma_i}\right)}, Y_{i^*} < Y_i^*$$

The parameter a_i is an average of the upper (Y_i^*) and lower (Y_{i^*}) bounds of the response level being targeted, b_i controls the function spread, and γ_i is defined so that the desirability at Y_{i^*} equals γ_i , and the desirability at Y_i^* equals $1 - \gamma_i$. A minimizing desirability is obtained by reversing the sign of the exponential argument. A target desirability function

can then be constructed by multiplying a minimizing ($d_{i(\min)}$) and a maximizing ($d_{i(\max)}$) desirability function such that $d_i = d_{i(\max)} * d_{i(\min)}$. The parameters a_i , b_i , and γ_i , allow the researcher flexibility in defining the desirability function and the degree of conservativeness to incorporate. These individual desirability functions can then be combined using the geometric mean to arrive at a composite measure of the overall desirability, D , such that $D = (d_1 * d_2 * \dots * d_k)^{1/k}$. It is also possible to assign different weights to the individual desirabilities.

The following desirability functions will be used in the study and incorporated into a composite desirability measure $D = (d_1 * d_2 * d_3 * d_4 * d_5)^{1/5}$.

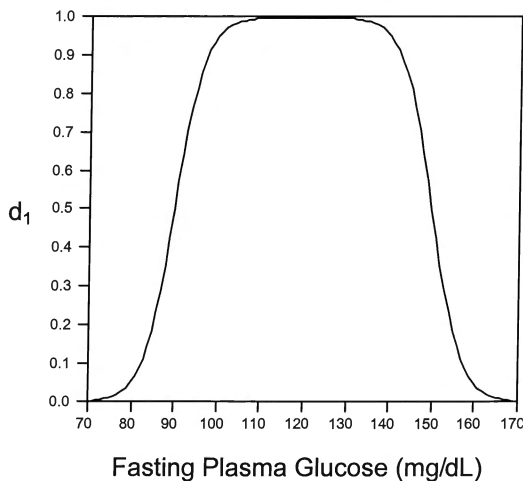


Figure 4.1. Target desirability function for fasting plasma glucose. The function is specified using the following parameters: $d_{1(\max)}$: $Y_1^* = 80$, $Y_1^{**} = 100$, $\gamma_1 = 0.05$,

$$d_{1(\min)}: Y_1^{**} = 140, Y_1^{***} = 160, \gamma_1^{**} = 0.05$$

$$d_1 = d_{1(\max)} * d_{1(\min)}$$

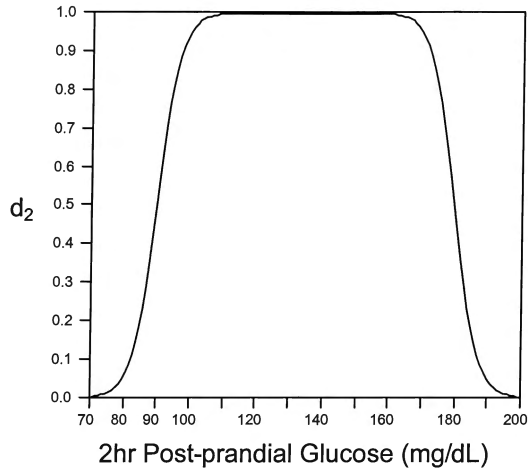


Figure 4.2. Target desirability function for 2-hour post-prandial plasma glucose. The function is specified using the parameters: $d_{2(\max)}$: $Y_{2*}' = 80$, $Y_{2*}'' = 100$, $\gamma_2' = 0.05$, $d_{2(\min)}$:

$$Y_{2*}''' = 170, Y_{2*}^{*''} = 190, \gamma_2'' = 0.05$$

$$d_2 = d_{2(\max)} * d_{2(\min)}$$

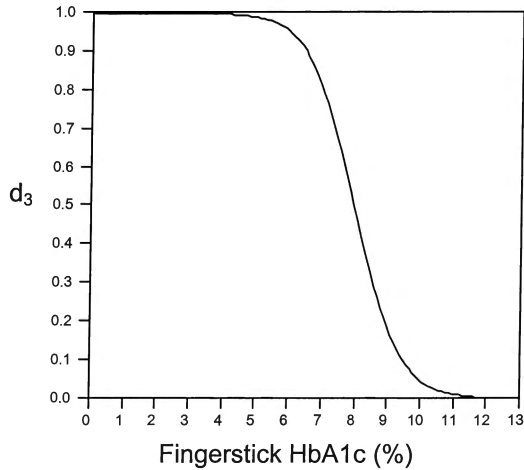


Figure 4.3. Minimizing desirability function for fingerstick HbA_{1c}. The function is specified using the parameters: $d_{3(\min)}$: $Y_{3*}' = 6$, $Y_{3*}'' = 10$, $\gamma_3 = 0.05$

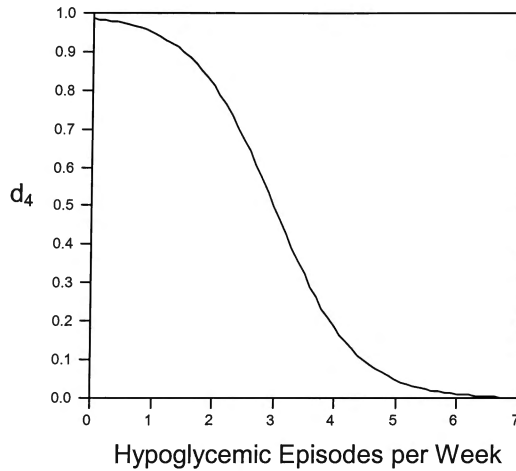


Figure 4.4. Minimizing desirability function for number of hypoglycemic episodes per week. The function is specified using the parameters: $d_{4(\min)}$; $Y_{4^*} = 1$, $Y_4^* = 5$, $\gamma_4 = 0.05$

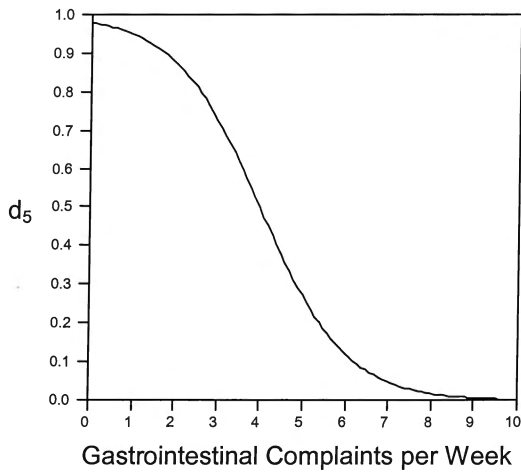


Figure 4.5. Minimizing desirability function for number of gastrointestinal complaints per week. The function is specified using the parameters: $d_{5(\min)}$; $Y_{5^*} = 1$, $Y_5^* = 7$, $\gamma_5 = 0.05$

Appendix 4.B

Description of the evolutionary titration procedure using the Nelder-Mead Simplex procedure²³

Once the individual desirability functions are defined, they are incorporated into a composite desirability function, D , which is the response undergoing optimization during the titration process. An evolutionary operation (EVOP)^{24, 25} approach is used to titrate the combination of drugs within each subject. The first step of the procedure is to establish an initial simplex, a geometric figure with a fixed number of vertices. In the two drug case, the simplex is a triangle. Each vertex A , B , and C , of the triangle (Figure 4.6) represents different dose levels of the two drug combination. At the initial step, the subject's response is measured at each of these three dose combinations, and the composite desirability resulting from the administration of each combination is compared, with the simplex reflecting away from the least desirable response, through the centroid of the face created by the remaining vertices to a new point, E . In addition to reflection, the simplex can also extend (point F), contract (points H or G), or perform a shrinkage contraction (points A' , B' , and C), depending on the contour of the response surface. The conditions for subsequent movement are listed in Table 4.2 and correspond to Figure 4.6.

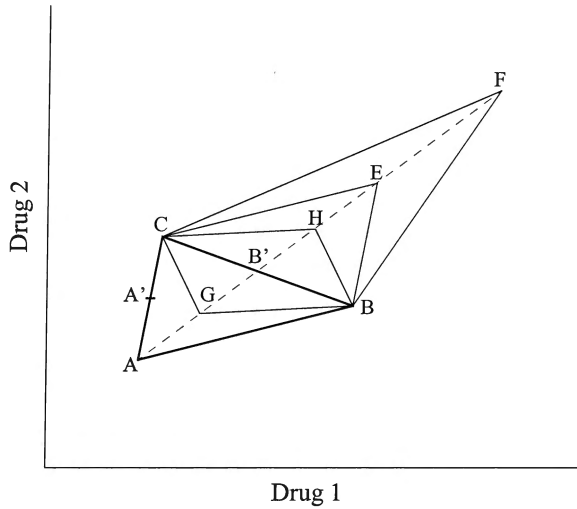


Figure 4.6: Nelder-Mead simplex ABC with possible subsequent points.

Table 4.2. Conditions governing the formation of subsequent simplex. $f(x)$ denotes the response evaluated at point x . Here a lower value represents a more favorable response.

Adapted from Olsson and Nelson²⁶.

Condition	Action	New Simplex
$f(C) \leq f(E) \leq f(B)$	Reflect	BCE
$f(E) < f(C)$	Extend	BCF
$f(A) < f(E)$	Contract	BCG
$f(B) < f(E) \leq f(A)$	Contract	BCH
$f(A) \leq f(G)$ or $f(E) \leq f(H)$	Shrink	A'B'C

The new dose combination determined by the algorithm is not given in units of whole pills or whole dose units, so the dose combinations are adjusted to whole units. The new dose combination to be administered is determined by either rounding to the nearest whole pill, or more conservatively, by rounding down to the dose unit. The initial simplex step size, which specifies how far apart the initial dose combinations are, and the reflection and expansion coefficients used by the Nelder-Mead procedure, which determine how far the simplex can move or expand in one step, are decided in collaboration with the physician, and can be modified to be more or less conservative depending on factors such as the therapeutic index of the drug involved

Each subject begins the process by being evaluated at each of the $p+1$ combinations of p drugs in the regimen. The subject receives the initial combination and the response is recorded. The subject then receives the second combination, which is determined by the initial step size, and the response is measured after a time interval sufficient to preclude carryover effects. This continues for each of the $p+1$ drug combinations. After the initial simplex is established, the new simplex is formed using the rules in Table 4.2, determining the next dose combination to be administered. This process repeats until the subject has passed through a fixed number of steps or until other specific stopping criteria are reached and further titration is deemed unnecessary. The simplex movement can be continuously monitored by the physician, and the reflection, expansion, and contraction coefficients can be modified if the simplex expands to a dose the physician is uncomfortable with. A dose constraint can also be put in as a boundary to prevent the simplex from moving above a certain dose in one or more dimensions. At the final step, the last simplex

is evaluated and the combination producing the most desirable response is determined to be the 'best' treatment combination.

Chapter 5

Simulation Study

5.1 Overview of Simulation Study

A series of simulation studies was performed to examine the effectiveness of the EVOP multi-drug titration algorithm in dosing a combination of therapeutic agents and to determine the effect of modifying the number of steps, the sample size, the shape of the desirability function, and the initial step size. The estimated dose response surface used in the simulations was obtained from a published multicenter, factorial design clinical trial conducted by Burris, et.al.²⁴, which studied the efficacy of the combination therapy of the diuretic hydrochlorothiazide (HCTZ) and a slow-release formulation of diltiazem hydrochloride (DLTZ), a calcium channel blocker, in the treatment of mild to moderate hypertension.

The trial was conducted over a period of six weeks, following a 4- to 6-week placebo 'run-in' period. A 4 by 5 factorial grid of treatment doses was used, with 4 twice-a-day doses of hydrochlorothiazide ranging from 0 to 25 mg, and 5 twice-a-day doses of diltiazem hydrochloride ranging from 0 to 180 mg. Mild-to-moderate essential hypertension was defined as supine diastolic blood pressure in the range of 95 to 110 mmHg. The goal

of treatment was to achieve a supine diastolic blood pressure of less than 90 mmHg, with no limiting adverse experience. 261 patients completed the six-week treatment protocol, with 13 to 17 patients randomized to each treatment group.

Using Proc RSREG in SAS, Version 6.12 (SAS Institute, Cary, NC)²⁵, data from the plots published in the study were used to generate the response surfaces for the three main variables of interest: diastolic blood pressure (DBP), $4.16+1.60x_{\text{HCTZ}}+0.39x_{\text{DLTZ}}-0.12x_{\text{HCTZ}}^2+0.020x_{\text{DLTZ}}^2-0.033x_{\text{HCTZ}}*x_{\text{DLTZ}}$; serum cholesterol (CHO), $0.12+0.092x_{\text{HCTZ}}+0.033x_{\text{DLTZ}}-0.0073x_{\text{HCTZ}}^2-0.0032x_{\text{DLTZ}}^2-0.0013x_{\text{HCTZ}}*x_{\text{DLTZ}}$; and serum glucose (GLU), $-0.12+0.076x_{\text{HCTZ}}-0.011x_{\text{DLTZ}}-0.00011x_{\text{HCTZ}}^2+0.0030x_{\text{DLTZ}}^2-0.0011x_{\text{HCTZ}}*x_{\text{DLTZ}}$. The dose units were converted from milligrams to whole pill counts. One pill was equivalent to 3.125mg of HCTZ or 15mg of DLTZ.

A desirability function was defined for each of the three responses, DBP, CHO, and GLU. The three functions, d_1 - d_3 (Figs 5.1-5.3), were combined into an overall unweighted composite desirability function, $D = (d_1*d_2*d_3)^{1/3}$. The Nelder-Mead simplex procedure was used to carry out the within-patient titration using the composite desirability.

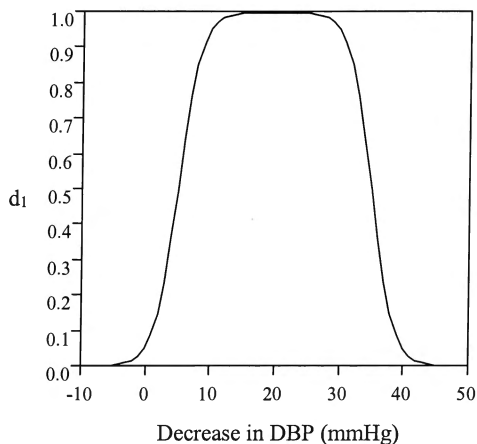


Figure 5.1: Target desirability function for diastolic blood pressure (d_1). This function is a product of a minimizing desirability function (d_1') with parameters $Y_{1*}' = 0$, $Y_{1*}'' = 10$, $\gamma_1' = 0.05$, and a maximizing desirability function (d_1'') with parameters $Y_{1*}'' = 30$, $Y_{1*}''' = 40$, $\gamma_1'' = 0.05$.

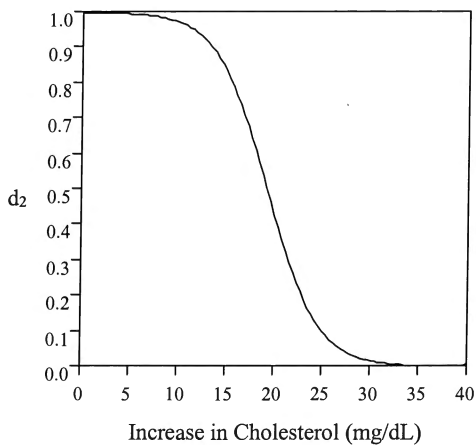


Figure 5.2: Minimizing desirability function for increase in cholesterol (d_2) with parameters $Y_{2*} = 11.6$, $Y_{2*}' = 27.1$, $\gamma_2 = 0.05$.

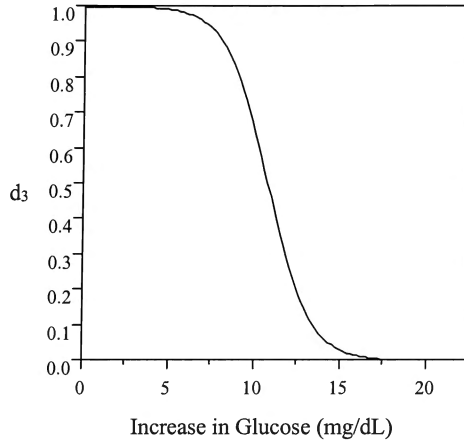


Figure 5.3: Minimizing desirability function for increase in serum glucose (d_3) with parameters $Y_{3*} = 7.2$, $Y_3^* = 14.4$ mmol/L, $\gamma_3 = 0.05$.

5.2 Simulation Example

For each subject, the starting dose for the initial simplex was chosen to be the same as the smallest combination dose used in the original study: 6.25mg (2 pills) of HCTZ and 60mg (4 pills) of DLTZ. The initial step size was chosen to be this initial dose combination increased by 6 pills in the HCTZ axis and by 8 pills in the DLTZ axis.

In order to simulate subject responses more realistically, a mixed effects model with a first order autoregressive covariance structure was used. Let $y_{ij} = \mathbf{x}_{ij}'\beta + \varepsilon_{ij}$, where y_{ij} represents the j th response from the i th subject, $\mathbf{x}_{ij} = [1 \ x_{i1} \ x_{i2} \ x_{i1}^2 \ x_{i2}^2 \ x_{i1}x_{i2}]$ represents the 6×1 vector of doses and dose functions for the i th subject at the j th time point, β represents

the 6×1 vector of parameters taken from the study, and ε_{ij} represents the random error.

The covariance between two observations w time intervals apart on the same subject is $\sigma_\varepsilon^2 \rho^w$, where ρ is the correlation between adjacent observations within the same subject, and w is the number of time intervals between the observations. For this study, the root MSE for DBP, σ_{DBP} , was 6.2mmHg (pers. comm.), and 0.35mmol/L was used for both CHO, σ_{CHO} , and GLU, σ_{GLU} .

The simulated response at each vertex of the simplex was obtained in triplicate and the responses were averaged. The desirability for each averaged response was compared, and the location of the next dose combination to be given was determined by the Nelder-Mead algorithm, rounding to the nearest whole pill. Figure 5.4 is an example showing the

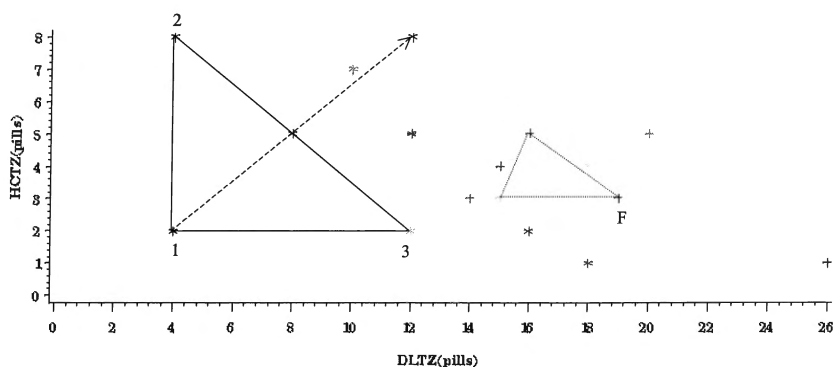


Figure 5.4: Simplex movement for one subject in a two-dimensional dose space. The subject is evaluated at each of three initial dose combinations (1,2,3) [2 pills HCTZ/4 pills DLTZ; 8 pills/4 pills; and 2 pills/12 pills]. The simplex reflects away from the combination producing the least desirable response (in this example, point 1). The final optimized dose combination (F) after 20 steps is 3 pills HCTZ and 19 pills DLTZ, corresponding to a simulated decrease in diastolic blood pressure of 18.4mmHg

simplex movement for a single subject. The titration was continued for 20 steps. At the last step, the final simplex was evaluated and the dose combination associated with the most desirable response was taken as the final treatment combination. This subject arrived at a final dose combination of 3 pills HCTZ and 19 pills DLTZ, with a simulated decrease in DBP of 18.4mmHg. Figure 5.5 demonstrates the simplex movement for the same subject starting with a smaller initial step size increase of 4 pills in the HCTZ axis and 6 pills in the DLTZ axis, with titration continuing for 20 steps. The final dose combi-

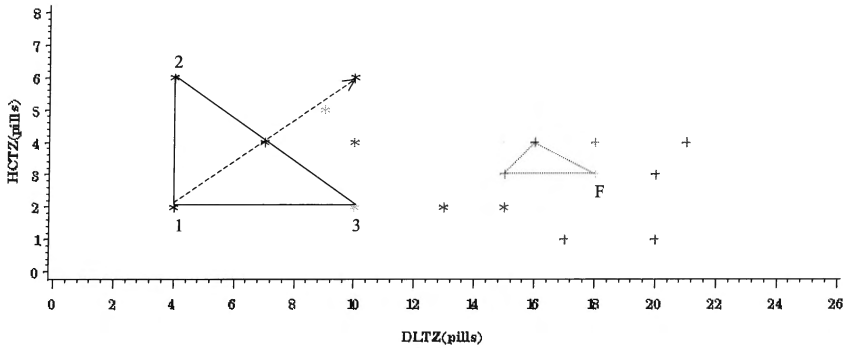


Figure 5.5: Simplex movement for one subject in a two-dimensional dose space with smaller initial steps. The subject is evaluated at each of three initial dose combinations (1,2,3) similarly to above, but the initial simplex is smaller [2 pills HCTZ/4 pills DLTZ; 6 pills/4 pills; and 2 pills/10 pills]. Note that the process ends with a combination similar to that reached above, 3 pills HCTZ and 18 pills DLTZ, corresponding to a simulated decrease in diastolic blood pressure of 15.7mmHg.

nation reached was 3 pills of HCTZ and 18 pills of DLTZ, similar to that obtained with the larger step size. The corresponding decrease in DBP was 15.7mmHg.

Figure 5.6 demonstrates the final dose locations for a simulated group of 175 subjects who have completed the titration process, and Figure 5.7 shows the asymptotic confidence ellipsoid about the central location estimate for the Wilcoxon Signed Rank statistic and Figure 5.8 shows the confidence ellipsoid about the mean. A correlation between successive blood pressure observations of $\rho=0.7$ was used and the process continued for 16 steps.

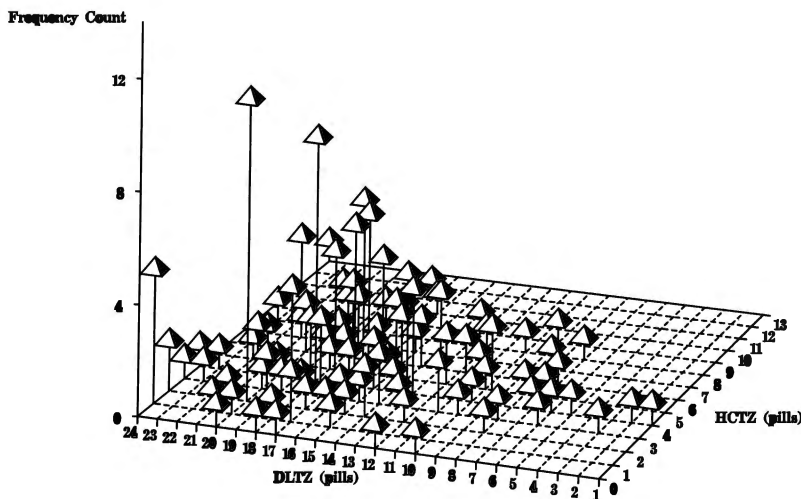


Figure 5.6: Pyramid plot of final dose locations for a simulated group of 175 subjects who have completed the 16 steps of titration, using a correlation of 0.7. In this simulation, the desirability function for DBP shown in Figure 5.1 was used to target a reduction in diastolic blood pressure (DBP). The mean decrease in DBP was 17.7mmHg. The mean final dose combination was 4.6 pills HCTZ and 16.2 pills DLTZ.

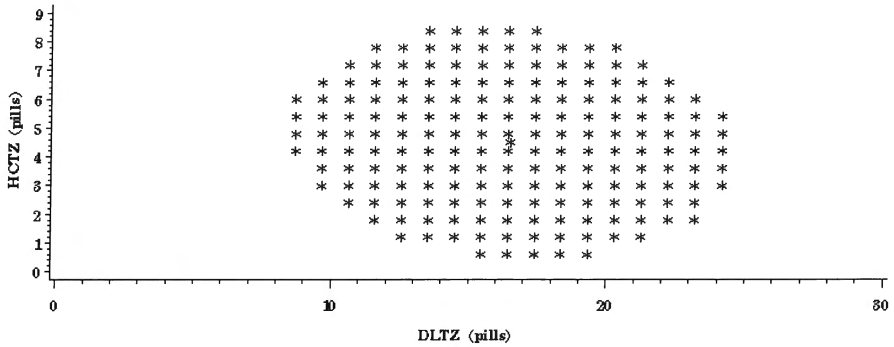


Figure 5.7: Asymptotic confidence ellipsoid based on the Wilcoxon signed rank statistic. A group of 175 subjects was simulated using the desirability function for DBP in Figure 5.1.

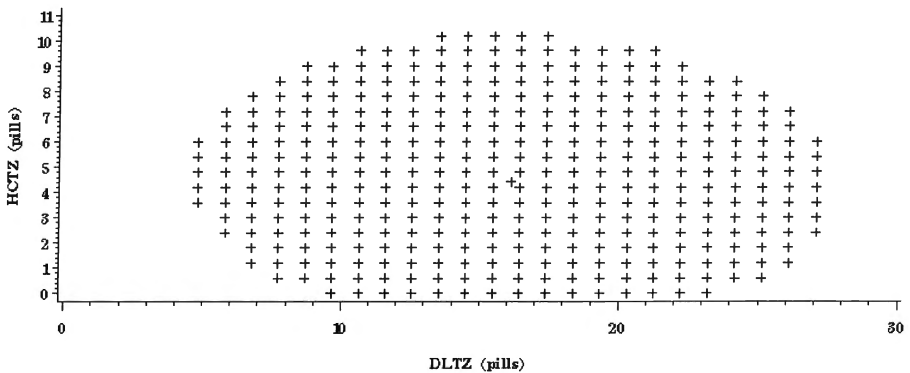


Figure 5.8: Asymptotic confidence ellipsoid based on the mean. A group of 175 subjects

was simulated using the desirability function for DBP in Figure 5.1.

5.3 Simulation Results

For the main simulation study, five groups of 100 simulations were run using sample sizes of $N=175$ with 16 and 32 steps. The simulations were run first using the desirability function for DBP alone, d_1 (Fig. 5.1), and then repeated using the composite desirability function, $D=(d_1*d_2*d_3)^{1/3}$, which took into account serum cholesterol and serum glucose measurements in addition to the DBP. Additionally, to examine the effect of the correlation between successive observations, ρ , the correlation was varied from 0.1 to 0.8. In the simulations with the composite desirability function, the correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7.

5.3.1 Number of Steps and Correlation Between Successive Observations within a Patient

Desirability function for diastolic blood pressure, d_1

Using the desirability function for DBP, d_1 , we see in Table 5.1 that the proportion of subjects showing improvement over the baseline was 1 (i.e. 100%) for all cases, using either the Fisher Sign test or the Wilcoxon Signed Rank test. All subjects also showed improvement when the final response was compared to the simulated response to single drug treatment with 25mg of HCTZ, the highest dose used in the study. A similar result was seen in comparing the response to treatment with a 180mg dose of DLTZ. The mean

decrease in DBP, shown in the far right column, did not appear to change as the number of steps was increased from 16 to 32. However, the size of the reduction in DBP did appear to increase as the correlation increased. Table 5.2 shows the percentage of confidence ellipsoids which included the origin, included the hydrochlorothiazide axis only, included the diltiazem axis only, or included both axes, also using the desirability for DBP alone. The final central dose locations for diltiazem and hydrochlorothiazide are also given in the far right columns, using both the mean and the Wilcoxon Signed Rank statistics as measures of central location. Using Mardia's test, in many instances the multivariate distribution of the final dose locations for each simulation showed some departure from normality, suggesting the nonparametric approach to be most appropriate. As the correlation was increased from 0.1 to 0.8, the simplex appeared to move further up the DLTZ axis, resulting in a higher final dose of DLTZ and a tighter confidence ellipsoid. Increasing the number of steps from 16 to 32 did not appear to have much effect, suggesting that the simplex had already arrived at a final dose after 16 steps.

Table 5.1: Proportion of improved responses using the Fisher sign test or Wilcoxon signed-rank test. Simulations were done using the desirability function for diastolic blood pressure alone (d_1). The mean decrease in DBP is shown in the far right column.

N	Steps	ρ		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)	
175	16	0.1	Fisher(SE)	1(0)	1(0)	1(0)	16.4	
			Wilc(SE)	1(0)	1(0)	1(0)		
		0.3	Fisher(SE)	1(0)	1(0)	1(0)	16.8	
			Wilc(SE)	1(0)	1(0)	1(0)		
		0.5	Fisher(SE)	1(0)	1(0)	1(0)	16.9	
			Wilc(SE)	1(0)	1(0)	1(0)		
	0.7	Fisher(SE)	1(0)	1(0)	1(0)	17.7		
		Wilc(SE)	1(0)	1(0)	1(0)			
	0.8	Fisher(SE)	1(0)	1(0)	1(0)	18.6		
		Wilc(SE)	1(0)	1(0)	1(0)			
	32	16	0.1	Fisher(SE)	1(0)	1(0)	1(0)	16.3
				Wilc(SE)	1(0)	1(0)	1(0)	
0.3			Fisher(SE)	1(0)	1(0)	1(0)	16.9	
			Wilc(SE)	1(0)	1(0)	1(0)		
0.5			Fisher(SE)	1(0)	1(0)	1(0)	17.1	
			Wilc(SE)	1(0)	1(0)	1(0)		
0.7		Fisher(SE)	1(0)	1(0)	1(0)	18.2		
		Wilc(SE)	1(0)	1(0)	1(0)			
0.8		Fisher(SE)	1(0)	1(0)	1(0)	18.6		
		Wilc(SE)	1(0)	1(0)	1(0)			

Table 5.2: Evaluation of the confidence ellipsoids using a parametric and nonparametric approach. Simulations were done using the desirability function for diastolic blood pressure alone (d_1). The columns show the percentage of confidence ellipsoids containing the origin, containing the HCTZ axis only, containing the DLTZ axis only, or containing both axes. The rightmost columns show the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

N	Steps	ρ		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ	
175	16	0.1	Mean(SE)	0	0	97.2(1.30)	2.8(1.30)	4.5(0.03)	14.0(0.02)	
			Wilc(SE)	1.6(1.52)	13.4(2.92)	39.0(2.92)	23.2(4.97)	4.4(0.03)	14.2(0.03)	
		0.3	Mean(SE)	0	0	99.6(0.89)	0.4(0.89)	4.5(0.02)	14.5(0.01)	
			Wilc(SE)	0.8(0.45)	9.6(2.70)	43.4(4.22)	16.2(3.27)	4.4(0.03)	14.7(0.01)	
		0.5	Mean(SE)	0	0	100	0	4.5(0.02)	15.2(0.02)	
			Wilc(SE)	0	4.8(1.92)	51.2(5.12)	8.2(2.17)	4.4(0.02)	15.5(0.03)	
	0.7	Mean(SE)	0	0	100	0	4.6(0.02)	16.2(0.02)		
		Wilc(SE)	0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)		
	0.8	Mean(SE)	0	0	100	0	4.6(0.02)	17.1(0.02)		
		Wilc(SE)	0	0	68.0(3.94)	0	4.5(0.03)	17.3(0.03)		
	32	0.1	0.1	Mean(SE)	0	0	99.4(0.55)	0.6(0.55)	4.4(0.01)	14.2(0.05)
				Wilc(SE)	0.6(0.55)	10.8(4.87)	49.4(4.10)	21.8(4.44)	4.2(0.02)	14.4(0.05)
0.3			Mean(SE)	0	0	100	0	4.4(0.01)	14.7(0.06)	
			Wilc(SE)	0.2(0.45)	8.2(0.84)	54.0(3.87)	17.6(2.30)	4.3(0.02)	15.0(0.07)	
0.5			Mean(SE)	0	0	100	0	4.4(0.02)	15.3(0.03)	
			Wilc (SE)	0	2.6(1.14)	61.4(8.88)	5.6(1.95)	4.3(0.02)	15.7(0.02)	
0.7		Mean (SE)	0	0	100	0	4.5(0.02)	16.4(0.01)		
		Wilc (SE)	0	0	71.0(3.87)	0	4.4(0.02)	16.7(0.02)		
0.8		Mean (SE)	0	0	100	0	4.5(0.004)	17.1(0.04)		
		Wilc (SE)	0	0	75.4(2.30)	0	4.4(0.01)	17.4(0.05)		

Composite desirability function, D

The simulations were then repeated using the composite desirability function, D, which combined the main outcome of interest, diastolic blood pressure, with two other endpoints which the study authors reported on, serum glucose and serum cholesterol. In these simulations, the correlation between successive DBP measurements within a patient was increased from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7. Tables 5.3 and 5.4, show that the simplex does not move as far along the HCTZ axis or DLTZ axis when these other endpoints are taken into consideration, indicating that one or both of these endpoints are acting as constraints. However, from Table 5.3, we see that even at these doses, there is still a significant improvement in the response for all subjects in all cases.

Table 5.3: Proportion of improved responses using the Fisher sign test or Wilcoxon signed-rank test. Simulations were done using the composite desirability function (D). The correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7. The rightmost columns show the mean decrease in diastolic blood pressure, the mean change in cholesterol and the mean change in serum glucose.

N	Steps	ρ		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)	Change in Chol (mmol/L)	Change in Glu (mmol/L)	
175	16	0.1	Fisher (SE)	1(0)	1(0)	1(0)	11.9	0.24	0.29	
			Wilc (SE)	1(0)	1(0)	1(0)				
		0.3	Fisher (SE)	1(0)	1(0)	1(0)	11.9	0.25	0.29	
			Wilc (SE)	1(0)	1(0)	1(0)				
		0.5	Fisher (SE)	1(0)	1(0)	1(0)	11.9	0.25	0.31	
			Wilc (SE)	1(0)	1(0)	1(0)				
	0.7	Fisher (SE)	1(0)	1(0)	1(0)	12.0	0.24	0.29		
		Wilc (SE)	1(0)	1(0)	1(0)					
	0.8	Fisher (SE)	1(0)	1(0)	1(0)	12.1	0.24	0.27		
		Wilc (SE)	1(0)	1(0)	1(0)					
	32	16	0.1	Fisher (SE)	1(0)	1(0)	1(0)	11.3	0.25	0.27
				Wilc (SE)	1(0)	1(0)	1(0)			
0.3			Fisher (SE)	1(0)	1(0)	1(0)	11.3	0.27	0.26	
			Wilc (SE)	1(0)	1(0)	1(0)				
0.5			Fisher (SE)	1(0)	1(0)	1(0)	11.6	0.25	0.31	
			Wilc (SE)	1(0)	1(0)	1(0)				
0.7		Fisher (SE)	1(0)	1(0)	1(0)	11.9	0.24	0.27		
		Wilc (SE)	1(0)	1(0)	1(0)					
0.8		Fisher (SE)	1(0)	1(0)	1(0)	11.8	0.23	0.27		
		Wilc (SE)	1(0)	1(0)	1(0)					

Table 5.4: Evaluation of the confidence ellipsoids using a parametric and nonparametric approach. Simulations were done using the composite desirability function (D). The correlation between successive DBP measurements was varied from 0.1 to 0.8, while the correlations for both CHO and GLU were fixed at 0.7. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the HCTZ axis only, containing the DLTZ axis only, or containing both axes. The rightmost columns show the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

N	Steps	ρ		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ	
175	16	0.1	Mean (SE)	0	0	34.0(5.70)	66.0(5.70)	3.1(0.02)	9.2(0.02)	
			Wilc (SE)	9.0(1.41)	0	61.4(2.07)	38.6(2.07)	3.0(0.02)	9.2(0.02)	
		0.3	Mean (SE)	0	0	35.6(3.05)	64.4(3.05)	3.1(0.02)	9.2(0.02)	
			Wilc (SE)	8.8(4.92)	0	60.8(4.32)	39.2(4.32)	3.0(0.02)	9.3(0.03)	
		0.5	Mean (SE)	0	0	38.2(4.44)	61.8(4.44)	3.1(0.02)	9.3(0.02)	
			Wilc (SE)	9.8(2.28)	0	61.4(2.70)	38.6(2.70)	3.0(0.02)	9.4(0.02)	
		0.7	Mean (SE)	0	0	44.0(5.24)	56.0(5.24)	3.1(0.02)	9.4(0.02)	
	Wilc (SE)		8.8(3.27)	0	61.4(5.77)	38.6(5.77)	3.0(0.01)	9.5(0.02)		
	0.8	Mean (SE)	0	0	51.4(3.58)	48.6(3.58)	3.1(0.02)	9.5(0.02)		
		Wilc (SE)	9.2(2.17)	0	59.8(4.21)	40.2(4.21)	3.0(0.02)	9.6(0.03)		
	32	0.1	0.1	Mean (SE)	0	0	36.4(3.71)	63.6(3.71)	3.0(0.02)	9.2(0.03)
				Wilc (SE)	9.2(1.64)	0	59.2(5.26)	40.8(5.26)	2.8(0.03)	9.3(0.03)
			0.3	Mean (SE)	0	0	38.6(3.78)	61.4(3.78)	3.0(0.02)	9.2(0.04)
				Wilc (SE)	6.4(1.67)	0	56.4(3.13)	43.6(3.13)	2.8(0.02)	9.3(0.04)
0.5			Mean (SE)	0	0	40.8(3.56)	59.2(3.96)	3.0(0.01)	9.3(0.05)	
			Wilc (SE)	5.2(2.05)	0	55.0(3.39)	45.0(3.39)	2.8(0.01)	9.4(0.05)	
0.7			Mean (SE)	0	0	48.6(4.16)	51.4(4.16)	2.9(0.01)	9.4(0.03)	
		Wilc (SE)	7.0(2.55)	0	59.4(2.07)	40.6(2.07)	2.8(0.02)	9.5(0.03)		
0.8		Mean (SE)	0	0	54.2(1.92)	45.8(1.92)	2.9(0.01)	9.5(0.04)		
		Wilc (SE)	6.8(2.17)	0	53.0(3.54)	47.0(3.54)	2.8(0.02)	9.6(0.04)		

5.3.2 Initial Step Size

Tables 5.5 and 5.6 show the results of changing the initial step size from an increase of 6 pills in the HCTZ axis and 8 pills in the DLTZ axis, to an increase of only 5 pills/7 pills, or 4 pills/6 pills over the initial dose combination. After 16 steps, using the desirability function for DBP, a correlation of 0.7, and a sample size of 175, there was a slightly smaller decrease in the DBP response. In addition, the final dose combinations also decreased as the initial step size became smaller. This would suggest that either the simplex has not had enough time to reach the same improved dose as with the larger step size, or perhaps the simplex has reached a plateau and the variability is too large for it to move further along the dose response surface.

Table 5.5: A comparison of initial step sizes. Simulations were done using the desirability function for diastolic blood pressure alone (d_1), with 16 steps, $\rho=0.7$. The table shows the proportion of improved responses using the Fisher sign test or the Wilcoxon signed-rank test. The effect of decreasing the initial step size is shown, with the mean decrease in diastolic blood pressure given in the rightmost column.

Step Size (pills HCTZ/ pills DLTZ)		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)
+6/+8	Fisher (SE)	1(0)	1(0)	1(0)	17.7
	Wilc (SE)	1(0)	1(0)	1(0)	
+5/+7	Fisher (SE)	1(0)	1(0)	1(0)	16.7
	Wilc (SE)	1(0)	1(0)	1(0)	
+4/+6	Fisher (SE)	1(0)	1(0)	1(0)	16.5
	Wilc (SE)	1(0)	1(0)	1(0)	

Table 5.6: A comparison of initial step sizes. Simulations were done using the desirability function for diastolic blood pressure alone (d_1), with 16 steps, $\rho=0.7$. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the HCTZ axis only, containing the DLTZ axis only, or containing both axes. The effect of decreasing the initial step size is shown, with the rightmost columns giving the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

Step Size (pills HCTZ/ pills DLTZ)		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
+6/+8	Mean (SE)	0	0	100	0	4.6(0.02)	16.2(0.02)
	Wilc (SE)	0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)
+5/+7	Mean (SE)	0	0	100	0	4.5(0.01)	15.2(0.05)
	Wilc (SE)	0	6.8(2.59)	55.4(5.18)	16.0(4.18)	4.4(0.02)	15.5(0.06)
+4/+6	Mean (SE)	0	0	90.4(1.95)	9.6(1.95)	4.2(0.02)	13.7(0.04)
	Wilc (SE)	4.2(2.77)	7.4(2.61)	49.2(2.59)	30.4(4.62)	4.1(0.02)	13.9(0.04)

5.3.3 Sample Size

Tables 5.7 and 5.8 display the results of changes to the sample size. Simulations were run with sample sizes of 25, 50, 175, and 300 subjects, using the desirability function for DBP alone. The between-observations correlation was fixed at 0.7, and the titration was continued for 16 steps. In general, changes to the sample size did not appear to significantly affect the outcomes.

In Table 5.7, the decrease in the DBP remains similar across cases and there is a significant improvement in the response for all cases. In Table 5.8, the final dose combinations also remain similar across the cases.

Table 5.7: Sample size comparison. Simulations were done using the desirability function for diastolic blood pressure alone (d_1), with 16 steps, $\rho=0.7$. The table shows the proportion of improved responses using the Fisher sign test or the Wilcoxon signed-rank test. The effect of increasing the sample size is shown, with the mean decrease in diastolic blood pressure given in the rightmost column.

Sample Size		Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)
25	Fisher (SE)	1(0)	1(0)	1(0)	18.2
	Wilc (SE)	1(0)	1(0)	1(0)	
50	Fisher (SE)	1(0)	1(0)	1(0)	16.6
	Wilc (SE)	1(0)	1(0)	1(0)	
175	Fisher (SE)	1(0)	1(0)	1(0)	17.7
	Wilc (SE)	1(0)	1(0)	1(0)	
300	Fisher (SE)	1(0)	1(0)	1(0)	17.7
	Wilc (SE)	1(0)	1(0)	1(0)	

Table 5.8: Sample size comparison. Simulations were done using the desirability function for diastolic blood pressure alone (d_1), with 16 steps, $\rho=0.7$. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the HCTZ axis only, containing the DLTZ axis only, or containing both axes. The effect of decreasing the initial step size is shown, with the rightmost columns giving the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

Sample Size		Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
25	Mean (SE)	0.6(0.89)	0	95.0(1.87)	3.6(1.52)	4.6(0.04)	16.3(0.08)
	Wilc (SE)	0.6(0.89)	0.4(0.54)	91.8(1.64)	3.4(0.89)	4.5(0.04)	16.6(0.09)
50	Mean (SE)	0	0	99.6(0.55)	0.4(0.55)	4.6(0.06)	16.3(0.06)
	Wilc (SE)	0	0.2(0.45)	84.0(2.24)	1.0(1.22)	4.4(0.06)	16.6(0.06)
175	Mean (SE)	0	0	100	0	4.6(0.02)	16.2(0.02)
	Wilc (SE)	0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)
300	Mean (SE)	0	0	100	0	4.6(0.06)	16.3(0.06)
	Wilc (SE)	0	0	97.2(1.10)	2.8(1.10)	4.5(0.01)	16.6(0.01)

5.3.4 Variation in the Desirability Function

We were also interested in determining how sensitive the titration method was to variability in the chosen desirability function. To determine whether small modifications in the desirability function had any effect on the resulting dose locations and responses, we ran simulations using three modified desirability functions in addition to d_1 , the desirability function for DBP, with 16 steps, a correlation of 0.7, and a sample size of 175. Tables 5.9 and 5.10 show that sharpening the peak desirability as with d_a , increasing the width of the desirability function as with d_b , or decreasing the width and sharpening the peak simultaneously as with d_c , did not result in any appreciable change in the outcome with respect to either response or dose location. There was little or no change in the decrease in DBP or final dose combinations, indicating that the process is robust, or relatively insensitive, to small changes in the definition of the desirability function. So while the desirability function has to be defined carefully, there is some room for variation when deciding on the parameters.

Table 5.9: A comparison of desirability functions. The table shows the proportion of improved responses using the Fisher sign test or the Wilcoxon signed-rank test. The parameters for the modified desirability functions are shown, with the mean decrease in diastolic blood pressure given in the rightmost column.

Dsbl	N=175 Steps=16 $\rho=0.7$	(Y_i^*, Y_i^{**})	(Y_i^{**}, Y_i^{***})	Baseline	HCTZ Alone	DLTZ Alone	Decrease in DBP (mmHg)
d_1	Fisher (SE)	(0,10)	(30,40)	1(0)	1(0)	1(0)	17.7
	Wilc (SE)			1(0)	1(0)	1(0)	
d_a	Fisher (SE)	(0,20)	(20,40)	1(0)	1(0)	1(0)	17.5
	Wilc (SE)			1(0)	1(0)	1(0)	
d_b	Fisher (SE)	(-5,10)	(30,45)	1(0)	1(0)	1(0)	17.5
	Wilc (SE)			1(0)	1(0)	1(0)	
d_c	Fisher (SE)	(10,20)	(20,30)	1(0)	1(0)	1(0)	17.5
	Wilc (SE)			1(0)	1(0)	1(0)	

Table 5.10: A comparison of desirability functions. The columns show the percentage of confidence ellipsoids (SE) containing the origin, containing the HCTZ axis only, containing the DLTZ axis only, or containing both axes. The parameters for the modified desirability functions are shown, with the rightmost columns giving the final dose locations for HCTZ and DLTZ using either the mean or Wilcoxon signed-rank statistic as the measure of central location.

Dsbl	N=175 Steps=16 $\rho=0.7$	(Y_i^*, Y_i^{**})	(Y_i^{**}, Y_i^{***})	Origin	HCTZ Axis Only	DLTZ Axis Only	Both Axes	Final Dose HCTZ	Final Dose DLTZ
d_1	Mean (SE)	(0,10)	(30,40)	0	0	100	0	4.6(0.02)	16.2(0.02)
	Wilc (SE)			0	0.4(0.89)	64.6(5.50)	0.4(0.89)	4.5(0.02)	16.6(0.03)
d_a	Mean (SE)	(0,20)	(20,40)	0	0	100	0	4.6(0.01)	16.3(0.03)
	Wilc (SE)			0	0.2(0.45)	64.0(3.81)	0.2(0.45)	4.5(0.02)	16.6(0.04)
d_b	Mean (SE)	(-5,10)	(30,45)	0	0	100	0	4.6(0.02)	16.3(0.02)
	Wilc (SE)			0	0.4(0.55)	66.8(3.90)	0.4(0.89)	4.4(0.03)	16.6(0.04)
d_c	Mean (SE)	(10,20)	(20,30)	0	0	100	0	4.6(0.01)	16.3(0.02)
	Wilc (SE)			0	0.2(0.45)	63.6(3.44)	0.2(0.45)	4.5(0.02)	16.6(0.04)

From our simulations, it appears that the evolutionary simplex approach is effective in arriving at dose combinations which yield improved responses in patients who are being treated with a combination of multiple therapies, although inferences on the location do not appear to be as sharp as inferences on the response. In comparing the simulation results with the original response data, the final dose locations were found to correspond well with the area of higher response seen in the Burris study²⁴.

Chapter 6

Summary

The goal of our research has been to demonstrate a method for titrating multiple drug combinations within individual patients and to develop the corresponding statistical methodology for evaluating whether the titrated treatment combination has resulted in an improvement in patient response and whether a therapeutic synergism exists. An evolutionary operation direct-search procedure is used to titrate a combination of agents within individual subjects. Desirability functions are incorporated to define the main response of interest and additional responses or constraints.

This approach permits every patient the potential to benefit from the combination under study and allows the consideration of multiple endpoints and constraints. It is well suited to the treatment of chronic diseases with long courses where there is a rapidly and easily measured response, where regular treatment intervals exist, and where dose escalation within a patient is reasonable. Practicing physicians may find this approach useful for improving the way both mono-therapies and combination therapies are prescribed for individual patients. Clinical researchers may find this methodology useful for evaluating whether a therapeutic synergism exists within specific drug combinations and for evaluating individual therapeutic components.

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List of References

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Appendix A

Computer Programs

The main computer programs used to perform the evolutionary operation direct-search titration procedure in the simulation studies are provided in this appendix. All programs were written in SAS[®], version 6.12, for Windows. The programs are a compilation of code written by the author, Chris Gennings, and Vernon Chinchilli.

Program NEWSBSIM

```

*****
* THIS PROGRAM USES THE NELDER-MEAD ALGORITHM *
* AND DESIRABILITY FUNCTIONS TO MINIMIZE A *
* GIVEN FUNCTION. IT INVOKES THE PROGRAMS *
* SIMPLEX AND RANK_LOC *
*****;

goptions ftext=centb colors=(blue) ;
*GOPTIONS ftext=centb NODISPLAY NOPROMPT DEVICE=cgmmw6c GSFMODE=replace
        colors=(blue) GSFNAME=PICNm;
OPTIONS LINESIZE=80;

DATA ONE;
  * diastolic bp surface;
  X0 = 4.16; x1=1.60; x2 = 0.39; x1sq=-0.12; x2sq=.020; x1x2 = -0.033;
  * to adjust to units of pills (hctz 1 pill=3.125 mg, dlt 1 pill=15 mg);

  * change in serum chol surface;
  z0 = .12; z1=.092; z2=.033; z1sq=-.0073; z2sq=-.0032; z1z2=-.0013;

  *change in serum glucose surface;
  w0 = -0.12; w1=0.076; w2=-0.011; w1sq=-0.00011; w2sq=0.0030; w1w2=-
0.0011;

PROC IML;
  USE ONE; READ ALL VAR{X0 X1 X2 x1sq x2sq X1X2} INTO XX;
          READ ALL VAR{z0 z1 z2 z1sq z2sq z1z2} INTO z;
          READ ALL VAR{w0 w1 w2 w1sq w2sq w1w2} INTO w;
  PRINT 'Regressions Coefficients', 'for diastolic bp' XX,
        'for serum cholesterol' z,
        'for serum glucose' w;

  _NITER_=16;

  sig_tot = 6.2;
  sig_ch1 = .35;

```

```

sig_glu = .35;

print _NITER_, sig_tot sig_ch1 sig_glu;

%include simprank;

rho_bp=0.1; rho_ch1=0.7; rho_glu=0.7;
print rho_bp rho_ch1 rho_glu;
sigvec=sig_tot||sig_ch1||sig_glu;
rhovec=rho_bp||rho_ch1||rho_glu;
numvars=3;
numcol=_NITER_+2;
do c=1 to numvars;
  do row=1 to (numcol);
    do col=1 to (numcol);
      if abs(col-row)<=10 then;
        pwr=abs(col-row);
      else pwr=10;
      tempr=tempr||((rhovec[c]##pwr);
    end;
    temp2=temp2//tempr;
    free tempr;
  end;
  temp3=root(temp2);
  thalf_r=(sigvec[c])#temp3;
  half_r=half_r//thalf_r;
  free temp2 temp3 thalf_r;
end;
START FUNCTION;

*   parms = int(parms);   *rounding down to an integer;
    parms = round(parms); *rounding to the nearest integer;

*   title4 'Rounding down doses (in units of pills) to an integer';
    title4 'Rounding doses (in units of pills) to nearest integer';

BETA = 1 || PARMS[1,] || parms[2,] || PARMS[1,]##2 || PARMS[2,]##2
        || PARMS[1,]#PARMS[2,];

```

```

parms1 = beta[2];
parms2 = beta[3];

TEMP=0; TEMPC=0; TEMPG=0;

DO J = 1 TO 3;
    response = BETA*XX`+ part_a[j,i];
    temp = temp+response;
END;

BP_VALUE = TEMP/3;
CN_VALUE = BETA*Z` + part_b[i_b];
GN_VALUE = BETA*w` + part_g[i_g];

* setup desirability functions;
y1L1=0; y1U1=10; y1L2=30; y1U2=40; gamma1=0.05;
a11=(y1L1+y1U1)/2; b11=(y1U1-y1L1)/(2#log((1-gamma1)/gamma1));
a12=(y1L2+y1U2)/2; b12=(y1U2-y1L2)/(2#log((1-gamma1)/gamma1));
d11=(1+exp(-(bp_value-a11)/b11))##(-1);
d12=(1+exp((bp_value-a12)/b12))##(-1);
d1=d11#d12;

y2L=0.3; y2U=0.7; gamma2=0.05;
a2=(y2L+y2U)/2; b2=(y2U-y2L)/(2#log((1-gamma2)/gamma2));
d2=(1+exp((cn_value-a2)/b2))##(-1);

y3L=0.4; y3U=0.8; gamma3=0.05;
a3=(y3L+y3U)/2; b3=(y3U-y3L)/(2#log((1-gamma3)/gamma3));
d3=(1+exp((gn_value-a3)/b3))##(-1);

* overall desirability function;
D = (d1#d2#d3)##(1/3);
*d=d1;
*d=d2;
*d=d3;

CONSTRT = 0;
IF PARMS[1,] > 16 THEN CONSTRT=1;
IF PARMS[2,] > 24 THEN CONSTRT=1;

```

```

IF PARMS[1,] < 0 THEN CONSTRNT=1;
IF PARMS[2,] < 0 THEN CONSTRNT=1;
IF CONSTRNT = 1 THEN fn_value = 9999999;
    ELSE IF CONSTRNT = 0 THEN fn_value = -D;
i=i+1; i_b=i_b+1; i_g=i_g+1;

FINISH;

START SIMULATE;
DO SAMPLE = 1 TO 175;
    PARMS = 0 // 0;

z_a=normal(j(numcol,numvars,21435));
do rows_a=1 to 3;
    temp_a=z_a[,rows_a]*half_r[1:numcol,];
    part_a=part_a//temp_a;
end;

z_b=rannor(j(numcol,1,34323));
part_b=z_b`*half_r[(numcol+1):(2*numcol),];

z_g=rannor(j(numcol,1,32995));
part_g=z_g`*half_r[(2*numcol+1):(3*numcol),];

i=1; i_b=1; i_g=1;
run function; * print parms fn_value cn_value gn_value;
f00_valu=-fn_value;

i=1; i_b=1; i_g=1;
parms = 0//12;
run function; * print parms fn_value cn_value gn_value;
f_0_x2a = -fn_value;

i=1; i_b=1; i_g=1;
parms = 0//24;
run function; * print parms fn_value cn_value;
f_0_x2b = -fn_value;

i=1; i_b=1; i_g=1;
parms = 8//0;

```

```

run function;    * print parms fn_value cn_value gn_value;
f_x1a_0 = -fn_value;

i=1; i_b=1; i_g=1;
parms = 16//0;
run function;    * print parms fn_value cn_value;
f_x1b_0 = -fn_value;

i=1;  i_b=1; i_g=1;

in_parms = 2//4;  *in units of pills;
in_steps = in_parms+4;

RUN SIMPLEX;
FO_VALUE=-FO_VALUE;
FN_VALUE=-FN_VALUE;

RESULTS = RESULTS // (SAMPLE || PARMS` || f_x1a_0 || f_x1b_0 ||
f_0_x2a || f_0_x2b
                        || F00_VALU || FN_VALUE
||bp_value|cn_value|gn_value|COUNT);
FREE FO_VALUE FN_VALUE part_a fn_vec z_b z_g;
END;

reslab = {'SAMPLE' 'X1' 'X2' 'f_x1a_0' 'f_x1b_0' 'f_0_x2a' 'f_0_x2b'
'FUNCTN_0'
          'FUNCTION' 'DECR_BP (mmHg)' 'CHG_cho (mmol/L)' 'CHG_glu
(mmol/L)' 'COUNT' };
* CREATE RESULTS FROM RESULTS[COLNAME=RESLAB];
* APPEND FROM RESULTS;

FINISH;

START IMPROVE;
PLACE=NCOL(RERESULTS);
Y = RESULTS[,PLACE-4]-RESULTS[,PLACE-5];
DEN = NROW(Y);
TPLUS = SUM((Y>0)#RANKTIE(ABS(Y)));
TJ = DESIGN(RANKTIE(Y))[+,];

```

```

VAR_T = (DEN#(DEN+1)#(2#DEN+1) - .5#SUM(TJ#(TJ-1)#(TJ+1)))/24;
ties = (den#(den+1)#(2#den+1))/24;
if var_t ^= ties then print group simul 'ties occur' var_t ties; free
ties;
TSTAR = (TPLUS - (DEN#(DEN+1)/4))/SQRT(VAR_T);
PVALUE=1-PROBNORM(TSTAR);
IF PVALUE > .05 THEN TSTRTEST=0; ELSE TSTRTEST=1;
* PRINT 'WILCOXON SIGN RANK TEST:' TSTAR PVALUE;
BSTAR = NCOL(LOC(Y>0));
PVALUEB = 1-PROBBNML(.5,DEN,BSTAR);
IF PVALUEB > .05 THEN BSTRTEST=0; ELSE BSTRTEST=1;
* PRINT 'FISHERS SIGN TEST:' BSTAR DEN PVALUEB;
free y tplus tj var_t ;

Y = RESULTS[,PLACE-4]-RESULTS[,PLACE-6];
TPLUS = SUM((Y>0)#RANKTIE(ABS(Y)));
TJ = DESIGN(RANKTIE(Y))[+,];
VAR_T = (DEN#(DEN+1)#(2#DEN+1) - .5#SUM(TJ#(TJ-1)#(TJ+1)))/24;
ties = (den#(den+1)#(2#den+1))/24;
if var_t ^= ties then print group simul 'ties occur' var_t ties; free
ties;
TSTAR2b = (TPLUS - (DEN#(DEN+1)/4))/SQRT(VAR_T);
PVALUE=1-PROBNORM(TSTAR2b);
IF PVALUE > .05 THEN TSTRTS2b=0; ELSE TSTRTS2b=1;
BSTAR2b = NCOL(LOC(Y>0));
PVALUEB = 1-PROBBNML(.5,DEN,BSTAR2b);
IF PVALUEB > .05 THEN BSTRTS2b=0; ELSE BSTRTS2b=1;
free y tplus tj var_t;

Y = RESULTS[,PLACE-4]-RESULTS[,PLACE-7];
TPLUS = SUM((Y>0)#RANKTIE(ABS(Y)));
TJ = DESIGN(RANKTIE(Y))[+,];
VAR_T = (DEN#(DEN+1)#(2#DEN+1) - .5#SUM(TJ#(TJ-1)#(TJ+1)))/24;
ties = (den#(den+1)#(2#den+1))/24;
if var_t ^= ties then print group simul 'ties occur' var_t ties; free
ties;
TSTAR2a = (TPLUS - (DEN#(DEN+1)/4))/SQRT(VAR_T);
PVALUE=1-PROBNORM(TSTAR2a);

```



```

IF PVALUE > .05 THEN TSTRTS2a=0; ELSE TSTRTS2a=1;
BSTAR2a = NCOL(LOC(Y>0));
PVALUEB = 1-PROBBNML(.5,DEN,BSTAR2a);
IF PVALUEB > .05 THEN BSTRTS2a=0; ELSE BSTRTS2a=1;
free y tplus tj var_t;

Y = RESULTS[,PLACE-4]-RESULTS[,PLACE-8];
TPLUS = SUM((Y>0)#RANKTIE(ABS(Y)));
TJ = DESIGN(RANKTIE(Y))[+,];
VAR_T = (DEN#(DEN+1)#(2#DEN+1) -.5#SUM(TJ#(TJ-1)#(TJ+1)))/24;
ties = (den#(den+1)#(2#den+1))/24;
if var_t ^= ties then print group simul 'ties occur' var_t ties; free
ties;
TSTAR1b = (TPLUS-(DEN#(DEN+1)/4))/SQRT(VAR_T);
PVALUE=1-PROBNORM(TSTAR1b);
IF PVALUE > .05 THEN TSTRTS1b=0; ELSE TSTRTS1b=1;
BSTAR1b = NCOL(LOC(Y>0));
PVALUEB = 1-PROBBNML(.5,DEN,BSTAR1b);
IF PVALUEB > .05 THEN BSTRTS1b=0; ELSE BSTRTS1b=1;
free y tplus tj var_t;

Y = RESULTS[,PLACE-4]-RESULTS[,PLACE-9];
TPLUS = SUM((Y>0)#RANKTIE(ABS(Y)));
TJ = DESIGN(RANKTIE(Y))[+,];
VAR_T = (DEN#(DEN+1)#(2#DEN+1) -.5#SUM(TJ#(TJ-1)#(TJ+1)))/24;
ties = (den#(den+1)#(2#den+1))/24;
if var_t ^= ties then print group simul 'ties occur' var_t ties; free
ties;
TSTAR1a = (TPLUS-(DEN#(DEN+1)/4))/SQRT(VAR_T);
PVALUE=1-PROBNORM(TSTAR1a);
IF PVALUE > .05 THEN TSTRTS1a=0; ELSE TSTRTS1a=1;
BSTAR1a = NCOL(LOC(Y>0));
PVALUEB = 1-PROBBNML(.5,DEN,BSTAR1a);
IF PVALUEB > .05 THEN BSTRTS1a=0; ELSE BSTRTS1a=1;
free y tplus tj var_t;

FREE DEN Y TJ VAR_T TPLUS PLACE ties;
FINISH;

```

```

start thersyn;
* CRITICAL VALUE FROM CHI SQUARE DISTN WITH P DF, ALPHA=.05;
  _CHI_ = 5.99;
  ddf = nrow(x)-p;
  _F_ = finv(.95,p,ddf);
  _fcrit_ = (_num_-1)*p/(_num_-p)*_f_;
  MAXX1 = X[<>,1] + 5;
  MAXX2 = X[<>,2] + 5;
  RX1 = MAXX1/30;
  RX2 = MAXX2/30;

  if simul=1 then do;
    wconf0=0; wconf1=0; wconf2=0; wconf12=0; wconfts=0;
    mconf0=0; mconf1=0; mconf2=0; mconf12=0; mconfts=0;
  end;
  wflag1=0; wflag2=0;
  mflag1=0; mflag2=0;

* checking origin;
  z1 = 0;
  z2 = 0;
  _THETA_ = Z1 // Z2;
  _WIL_ = (WILCOXON-_THETA_)`*INV(TAU_W)*(WILCOXON-_THETA_);
  _MU_ = (XBAR-_THETA_)`*INV(SIGMA)*(XBAR-_THETA_);
  IF _WIL_ <= _CHI_ THEN WCONFO = WCONFO+1;
  IF _mu_ <= _fcrit_ THEN MCONFO = MCONFO+1;

* checking axis1;
DO Z1 = rx1 TO MAXX1 BY RX1;
  z2 = 0;
  _THETA_ = Z1 // Z2;
  _WIL_ = (WILCOXON-_THETA_)`*INV(TAU_W)*(WILCOXON-_THETA_);
  _MU_ = (XBAR-_THETA_)`*INV(SIGMA)*(XBAR-_THETA_);
  IF _WIL_ <= _CHI_ THEN wflag1=1;
  IF _mu_ <= _fcrit_ THEN mflag1=1;
END;

*checking axis2;
DO Z2 = rx2 TO MAXX2 BY RX2;

```

```

z1 = 0;
  _THETA_ = Z1 // Z2;
  _WIL_ = (WILCOXON-_THETA_)`*INV(TAU_W)*(WILCOXON-_THETA_);
  _MU_ = (XBAR-_THETA_)`*INV(SIGMA)*(XBAR-_THETA_);
  IF _WIL_ <= _CHI_ THEN wflag2=1;
  IF _mu_ <= _fcrit_ THEN mflag2=1;
END;

if (wflag1=1)*(wflag2=1)=1 then wconf12=wconf12+1;
if (wflag1=1)*(wflag2=0)=1 then wconf1=wconf1+1;
if (wflag1=0)*(wflag2=1)=1 then wconf2=wconf2+1;
if (wflag1=0)*(wflag2=0)=1 then wconfts=wconfts+1;

if (mflag1=1)*(mflag2=1)=1 then mconf12=mconf12+1;
if (mflag1=1)*(mflag2=0)=1 then mconf1=mconf1+1;
if (mflag1=0)*(mflag2=1)=1 then mconf2=mconf2+1;
if (mflag1=0)*(mflag2=0)=1 then mconfts=mconfts+1;

thersyn = thersyn // (GROUP || SIMUL || wconf0 || wconf1 || wconf2 ||
                    wconf12 || wconfts || mconf0 || mconf1 ||
                    mconf2 || mconf12 || mconfts);
LABELTS = {'GROUP' 'SIMUL' 'WCONFO' 'WCONF1' 'WCONF2' 'WCONF12'
'WCONFTS'
          'MCONFO' 'MCONF1' 'MCONF2' 'MCONF12' 'MCON-
FTS'};

finish;

START FORPLOT;
* CRITICAL VALUE FROM CHI SQUARE DISTN WITH P DF, ALPHA=.05;
  _CHI_ = 5.99;
  ddf = nrow(x)-p;
  _F_ = finv(.95,p,ddf);
  _fcrit_ = (_num_-1)*p/(_num_-p)*_f_;
  MAXX1 = X[<>,1] + 5;
  MAXX2 = X[<>,2] + 5;
  RX1 = MAXX1/30;
  RX2 = MAXX2/30;
  WILCONF = WILCOXON` || 0;

```

```

XBARCONF = XBAR`  || 0;
DO Z1 = 0 TO MAXX1 BY RX1;
  DO Z2 = 0 TO MAXX2 BY RX2;
    _THETA_ = Z1 // Z2;
    _WIL_ = (WILCOXON-_THETA_)`*INV(TAU_W)*(WILCOXON-_THETA_);
    _MU_ = (XBAR-_THETA_)`*INV(SIGMA)*(XBAR-_THETA_);
    IF _WIL_ <= _CHI_ THEN WILCONF = WILCONF // (_THETA_` || _WIL_);
    IF _MU_ <= _fcrit_ THEN XBARCONF= XBARCONF // (_THETA_` ||
_MU_);
  END;
END;
LABEL = {'X1' 'X2' 'VALUE'};
CREATE WILCONF FROM WILCONF[COLNAME=LABEL]; APPEND FROM WILCONF;
CREATE XBARCONF FROM XBARCONF[COLNAME=LABEL]; APPEND FROM XBARCONF;
FREE MEDCONF WILCONF WBARCONF;
FINISH;

START JOB;
DO GROUP =1 TO 5;
DO SIMUL = 1 TO 100;
  RUN SIMULATE;

  RUN IMPROVE;

  P=NROW(IN_PARMS);
  X = RESULTS[,2:P+1];
  F=RESULTS[,P+7];
  _num_=nrow(results);

  RUN RANK_LOC;
  RUN THERSYN;
  gvar_sig = det(var_xbar);
  gvar_w = det(var_wilc);
  LOC = LOC // (GROUP || SIMUL || TSTAR || TSTRTEST || PVALUE ||
                BSTAR || BSTRTEST || PVALUEB || tstar1a || tstrts1a ||
bstar1a ||
                bstrts1a || tstar1b || tstrts1b || bstar1b || bstrts1b ||
                tstar2a || tstrts2a || bstar2a || bstrts2a || tstar2b ||
                tstrts2b ||bstar2b || bstrts2b);

```

```

    FINLOC=FINLOC // (GROUP || SIMUL || WILCOXON` || GVAR_W || XBAR` ||
GVAR_SIG ||
                median` || respwlcx` || respxbar`);
IF GROUP=1 THEN IF SIMUL=1 THEN RUN FORPLOT;
IF GROUP=1 THEN IF SIMUL=1 THEN DO;
    CREATE RESULTS FROM RESULTS[COLNAME=RESLAB];
    APPEND FROM RESULTS;
    END;
    free results;
END;
END;
    LABEL = {'GROUP' 'SIMUL' 'TSTAR' 'TSTRTEST' 'PVALUEU'
            'BSTAR' 'BSTRTEST' 'PVALUEB' 'TSTAR1a' 'TSTRTS1a' 'BSTAR1a'
'BSRSTS1a'
            'TSTAR1b' 'TSTRTS1b' 'BSTAR1b' 'BSRSTS1b' 'TSTAR2a'
'TSTRTS2a' 'BSTAR2a'
            'BSRSTS2a' 'TSTAR2b' 'TSTRTS2b' 'BSTAR2b' 'BSRSTS2b'};
    FLABEL ={'GROUP' 'SIMUL' 'WIL1' 'WIL2' 'GVAR_W' 'MU1' 'MU2'
'GVAR_SIG' 'MED1'
            'MED2' 'WIL_RESP' 'MU_RESP'};

CREATE LOC FROM LOC[COLNAME=LABEL];
APPEND FROM LOC;
CREATE FINLOC FROM FINLOC[COLNAME=FLABEL];
APPEND FROM FINLOC;
CREATE THERSYN FROM THERSYN[COLNAME=LABELTS];
APPEND FROM THERSYN;

FINISH;

RUN JOB;

PROC SORT DATA=THERSYN;
    BY GROUP SIMUL;
data thersyn;
    set thersyn; by group;
    if last.group;
PROC PRINT DATA=THERSYN;
    title4 'Evaluation of Confidence Ellipsoid';

```

```

Proc Means data=thersyn mean n std;

PROC SORT DATA=LOC;
    BY GROUP SIMUL;

PROC MEANS SUM N data=loc;
    VAR TSTRTEST BSTRTEST tstrts1a bstrts1a tstrts1b bstrts1b
        tstrts2a bstrts2a tstrts2b bstrts2b;
    title4 'Number of Improved Responses';

proc summary data=finloc mean n var;
    var WIL1 WIL2 MU1 MU2 MED1 MED2 WIL_RESP MU_RESP;
    by group;
    output out=newfloc mean=;
proc means data=newfloc mean n std;
    title4 'Summary of Final Locations and Final Response';

PROC summary data=loc MEAN N var;
    var tstar tstrtest bstar bstrtest tstar1a tstrts1a bstar1a bstrts1a
        tstar1b tstrts1b bstar1b bstrts1b tstar2a tstrts2a bstar2a bstrts2a
        tstar2b tstrts2b bstar2b bstrts2b;
    BY GROUP;
    output out=newsumm mean=;
proc means data=newsumm mean n std;
    title4 'TSTAR=Wilcoxon Sign Rank, BSTAR=Fisher Sign Test';
RUN;

PROC GPLOT DATA=WILCONF;
    PLOT X1*X2 /HZERO VZERO;
    label x1='HCTZ (pills)' x2='DLTZ (pills)';
    TITLE4
    'ASYMPTOTIC CONFIDENCE REGION BASED ON THE WILCOXON SIGN-RANK STATIS-
TIC';

PROC GPLOT DATA=XBARCONF;
    PLOT X1*X2 /HZERO VZERO;
    label x1='HCTZ (pills)' x2='DLTZ (pills)';
    TITLE4

```

```
'ASYMPTOTIC CONFIDENCE REGION BASED ON THE ESTIMATED MEAN';

DATA RESULTS;
  SET RESULTS;
  IF FUNCTION=-9999999 THEN FUNCTION=.;
proc print data=results;
  title4 ' ';
proc means data=results;
  var FUNCTION DECR_BP CHG_cho CHG_glu;
  title4 'Summary of Final Responses';

proc freq data=results;
  tables x1*x2/noprint nocol norow nocum nopercnt out=scatfreq;

PROC GPLOT DATA=scatfreq;
* SYMBOL1 V=STAR;
  PLOT X1*X2=count/VZERO HZERO;
  label x1='HCTZ (pills)' x2='DLTZ (pills)';
  TITLE4 'Scatterplot of Final Locations';
run;

proc g3d data=scatfreq;
  scatter x2*x1=count / xtcknum=11 yticknum=20 zmin=0;
  label x1='HCTZ (pills)' x2='DLTZ (pills)';
  title4 'Pyramid Plot of Final Locations';
run;
```

Program SIMPLEX

```
START SIMPLEX;
```

```
*****
* This program in PROC IML of SAS conducts the Nelder-Mead simplex *
* program for function minimization. The program is adapted from *
* Olsson (1974), Journal of Quality Technology 6, 53-57. *
* *
* The user needs to provide the module FUNCTION which contains the *
* code for calculating the function given the set of parameters. For *
* this module PARMs is the column K-vector of parameters and FN_VALUE *
* is the function evaluated at PARMs. Also, the user needs to *
* provide the column K-vectors of starting values IN_PARMs and *
* initial step values IN_STEPS when calling this module. *
* *
* There is no printed output that results from running this module. *
* However, the column K-vector PARMs (the set of parameters which *
* minimize the function), FN_VALUE (the function evaluated at PARMs), *
* and COUNT (the number of iterations) are available to the user. *
* *
* As a cautionary note, the user should not construct matrices in *
* PROC IML with the naming convention _MATRIX_ because the modules *
* use this for all temporary matrices. *
*****;
_EPS_=1.0E-4;_K_=NROW(IN_PARMs);_KK_=_K_+1;
_P_=J(_K_,_KK_,0);_Y_=J(1,_KK_,0);
COUNT=0;_DABIT_=2.04607E-20;_BIGNUM_=1.0E38;_KONVGE_=5;
_PBAR_=J(_K_,1,0);_PSTAR_=_PBAR_;_P2STAR_=_PBAR_;
_RCOCOFF_=1.0;_ECOCOFF_=1.5;_CCOCOFF_=0.5;

**CONSTRUCT INITIAL SIMPLEX**;

_P_[,_KK_]=IN_PARMs;PARMs=IN_PARMs;RUN FUNCTION;_A_=FN_VALUE;
FO_VALUE=_A_;
_Y_[_KK_]=_A_;COUNT=COUNT+1; *print count parms fo_value ;
DO _I_=1 TO _K_;
```



```

    _P_[,_I_]=IN_PARMS;_P_[_I_,_I_]=_P_[_I_,_I_]+IN_STEPS[_I_];
    _TEMP_=_P_[,_I_];PARMS=_TEMP_;RUN FUNCTION;_A_=FN_VALUE;
    _Y_[,_I_]=_A_;COUNT=COUNT+1;
END;

**SIMPLEX IS NOW CONSTRUCTED**;

HILO:
_YLO_=MIN(_Y_);_YNEWLO_=MAX(_Y_);
DO _I_=1 TO _KK_;
    IF _Y_[,_I_]=_YLO_ THEN _ILO_=_I_;
    IF _Y_[,_I_]=_YNEWLO_ THEN _IHI_=_I_;
END;

**PERFORM CONVERGENCE CHECK ON FUNCTION**;
**THE RATIO OF THE LARGEST TO SMALLEST VERTEX FUNCTION TEST**;

_DCHK_=( _YNEWLO_+_DABIT_)/( _YLO_+_DABIT_)-1;
IF ABS(_DCHK_)<_EPS_ THEN GOTO BEST;
_KONVGE_=_KONVGE_-1;
IF _KONVGE_=0 THEN DO;_KONVGE_=5;
    DO _I_=1 TO _K_;
        _COORD1_=_P_[_I_,1];_COORD2_=_COORD1_;
        DO _J_=2 TO _KK_;
            IF _P_[_I_,_J_]<_COORD1_ THEN _COORD1_=_P_[_I_,_J_];
            IF _P_[_I_,_J_]>_COORD2_ THEN _COORD2_=_P_[_I_,_J_];
        END;
        _DCHK_=( _COORD2_+_DABIT_)/( _COORD1_+_DABIT_)-1;
        IF ABS(_DCHK_)<=_EPS_ THEN GOTO BEST;
    END;
END;
if count>_niter_ then goto best;

**CALCULATE _PBAR_, THE CENTROID OF THE**;
**SIMPLEX VERTICES EXCEPTING THAT WITH _Y_ VALUE _YNEWLO_**;

DO _I_=1 TO _K_;_Z_=0;

```

```

DO _J_=1 TO _KK_;_Z=_Z+_P_[_I_,_J_];END;
_Z=_Z-_P_[_I_,_IHI_];_PBAR_[_I_]=_Z/_K_;
END;
_PSTAR_=(1+_RCOEFF_)*_PBAR_-_RCOEFF_*_P_[,_IHI_];

**REFLECTION THROUGH THE CENTROID**;

PARMS=_PSTAR_;RUN FUNCTION;_YSTAR_=FN_VALUE;
COUNT=COUNT+1; *print 'reflection' count parms fn_value ;
IF COUNT >=_NITER_ THEN GOTO retain;
IF _YSTAR_ >=_YLO_ THEN GOTO NOEXT;

**SUCCESSFUL REFLECTION, SO EXTENSION**;

_P2STAR_=_ECOEFF_*_PSTAR_+(1-_ECOEFF_)*_PBAR_;
PARMS=_P2STAR_;RUN FUNCTION;_Y2STAR_=FN_VALUE;
COUNT=COUNT+1; * print 'extension' count parms fn_value ;

**RETAIN EXTENSION OR CONTRACTION**;

IF _Y2STAR_ >=_YSTAR_ THEN GOTO RETAIN;

EXTCON:
_P_[,_IHI_]=_P2STAR_;
_Y_[_IHI_]=_Y2STAR_;
GOTO HILO;

**NO EXTENSION**;

NOEXT:
_L_=0;
DO _I_=1 TO _KK_;
IF _Y_[_I_]>_YSTAR_ THEN _L_=_L_+1;
END;
IF _L_>1 THEN GOTO RETAIN;

**CONTRACTION ON THE REFLECTION SIDE OF THE CENTROID**;
```

```

IF _L_=1 THEN DO;
  _P_[,_IHI_]=_PSTAR_;
  _Y_[_IHI_]=_YSTAR_;
END;

**CONTRACTION ON THE _Y_[_IHI_] SIDE OF THE CENTROID**;

IF COUNT >= _NITER_ THEN GOTO BEST;
_P2STAR_=_CCOEFF*_P_[,_IHI_]+(-_CCOEFF+1)*_PBAR_;
PARMS=_P2STAR_;RUN FUNCTION;_Y2STAR_=FN_VALUE;
COUNT=COUNT+1; *print 'contraction' count parms fn_value;
IF COUNT>=_NITER_ THEN GOTO BEST;
IF _Y2STAR_<_Y_[_IHI_] THEN GOTO EXTCON;

**CONTRACT THE WHOLE SIMPLEX**;

DO _J_=1 TO _KK_;
  DO _I_=1 TO _K_;
    _P_[_I_,_J_]=0.5*( _P_[_I_,_J_]+_P_[_I_,_ILO_] );
    END;_XMIN_=_P_[,_J_];
    PARMS=_XMIN_;RUN FUNCTION;_A_=FN_VALUE;_Y_[,_J_]=_A_;
    *print 'whole contraction' count parms fn_value ;
  END;
COUNT=COUNT+_KK_;
IF COUNT>=_NITER_ THEN GOTO BEST; ELSE GOTO HILO;

RETAIN:
_P_[,_IHI_]=_PSTAR_;_Y_[_IHI_]=_YSTAR_;GOTO HILO;

BEST:

_YNEWLO_=_BIGNUM_;
DO _J_=1 TO _KK_;
  IF _Y_[_J_]<_YNEWLO_ THEN DO;
    _YNEWLO_=_Y_[_J_];_IBEST=_J_;
  END;
END;

```

```
_Y[_IBEST]=_BIGNUM;_YSEC=_BIGNUM;
DO _J=1 TO _KK;
  IF _Y[_J]<_YSEC THEN DO;
    _YSEC=_Y[_J];_ISEC=_J;
  END;
END;
_XMIN=_P[_IBEST];_XSEC=_P[_ISEC];
PARMS=round(_XMIN);
FN_VALUE=_YNEWLO;

FREE _EPS _K _KK _P _Y _DABIT _BIGNUM _KONVGE;
FREE _PBAR _PSTAR _P2STAR _RCOEFF _ECOEFF _CCOEFF;
FREE _A _I _TEMP _YLO _YNEWLO _ILO _IHI;
FREE _DCHK _COORD1 _COORD2 _Z _YSTAR _L _J;
FREE _XMIN _IBEST _YSEC _XSEC;
FINISH;
```

Program RANK_LOC

```

START RANK_LOC;

N=NROW(X);P=NCOL(X);
XBAR=X[+,]/N;XBAR=XBAR`; * print x;

resp_xbar=F[+,]/N; resp_xbar=resp_xbar`;
epsilon=0.25;

SIGMA=((X`*X)-(N*XBAR*XBAR`))/(N-1);
VAR_XBAR=SIGMA/N;
DO _I_=1 TO N BY 1;
  _I1=_I1_|J(1,N-_I_+1,_I_);
  _I2=_I2_|(|_I_:N);
END;FREE _I_;
WILCOXON=J(P,1,0);MEDIAN=J(P,1,0); resp_wlcx=J(1,1,0);
GAMMA_W=J(P,P,0);GAMMA_M=J(P,P,0);

DO; _FWALSH_=(F[_I1_]+F[_I2_])/2;
  _FWTEMP_=_FWALSH_;
  _FWALSH_[RANK(_FWALSH_)]=_FWTEMP_;
  FREE _FWTEMP_;
  _FMID_=N#(N+1)/4;
  resp_wlcx=(_FWALSH_[_FMID_]+_FWALSH_[_FMID_+1])/2;
  FREE _FMID_ _FWALSH_;
END;

DO _J_=1 TO P BY 1;
  _WALSH_=(X[_I1_,_J_]+X[_I2_,_J_])/2;
  _WTEMP_=_WALSH_;
  _WALSH_[RANK(_WALSH_),]=_WTEMP_;
  FREE _WTEMP_;
  _MID_=N#(N+1)/4;
  WILCOXON[_J_,]=(_WALSH_[_MID_,]+_WALSH_[_MID_+1,])/2;
  _A_=ROUND(_MID_-0.5-(1.96#SQRT(N#(N+1)#((2#N)+1)/24)));
  _LENGTH_=(_WALSH_[(N#(N+1)/2)-_A_,]-_WALSH_[_A_+1,]);

```

```

if _LENGTH_=0 then _LENGTH_=2*epsilon;

GAMMA_W[_J_,_J_]=(4#1.96)/(SQRT(12#N)#_LENGTH_);
FREE _MID_ _WALSH_ _A_ _LENGTH_;
_XTEMP1_=X[,_J_];_XTEMP2=_XTEMP1_;
_XTEMP1_[RANK(_XTEMP1_),]=_XTEMP2_;
FREE _XTEMP2_;
_MID_=N/2;
IF MOD(N,2)=1 THEN MEDIAN[_J_,]=_XTEMP1_[ (N+1)/2, ];
ELSE MEDIAN[_J_,]=(_XTEMP1_[_MID_,]+_XTEMP1_[_MID_+1,])/2;
_Q1_=ROUND((N+1)/4);_Q3_=ROUND(3#(N+1)/4);
_IQR_=_XTEMP1_[_Q3_,]-_XTEMP1_[_Q1_,];_HN_=_IQR_/SQRT(N);
GAMMA_M[_J_,_J_]=2#SUM(ABS(MEDIAN[_J_,]-_XTEMP1_)<=_HN_)/(N#_HN_);
FREE _MID_ _XTEMP1_ _Q1_ _Q3_ _IQR_ _HN_;
END;FREE _J_ _i1_ _i2_;
NU_W=J(P,P,0);NU_M=J(P,P,0);
DO _J1_=1 TO P BY 1;
  _RANK1_=RANKTIE(ABS(X[,_J1_]-WILCOXON[_J1_,]))/(N+1);
  _SIGN1W_=(X[,_J1_]<=WILCOXON[_J1_,])-(X[,_J1_]>WILCOXON[_J1_,]);
  _SIGN1M_=(X[,_J1_]<=MEDIAN[_J1_,])-(X[,_J1_]>MEDIAN[_J1_,]);
  DO _J2_=1 TO _J1_ BY 1;
    _RANK2_=RANKTIE(ABS(X[,_J2_]-WILCOXON[_J2_,]))/(N+1);
    _SIGN2W_=(X[,_J2_]<=WILCOXON[_J2_,])-(X[,_J2_]>WILCOXON[_J2_,]);
    _SIGN2M_=(X[,_J2_]<=MEDIAN[_J2_,])-(X[,_J2_]>MEDIAN[_J2_,]);
    _T_=_SIGN1W_#_SIGN2W_;
    NU_W[_J1_,_J2_]=SUM(_RANK1_#_RANK2_#_T_)/N;
    NU_W[_J2_,_J1_]=NU_W[_J1_,_J2_];

    _T_=_SIGN1M_#_SIGN2M_;
    NU_M[_J1_,_J2_]=SUM(_T_)/N;
    NU_M[_J2_,_J1_]=NU_M[_J1_,_J2_];
  END;
END;
FREE _J1_ _J2_ _RANK1_ _RANK2_ _SIGN1W_ _SIGN1M_ _SIGN2W_ _SIGN2M_ _T_;
TAU_W=INV(GAMMA_W)*NU_W*INV(GAMMA_W);
VAR_WILC=TAU_W/N;

FINISH;

```

Vita

Margaret Shih was born on July 24, 1970 in Arcadia, California and is an American citizen. She graduated from La Cañada High School, La Cañada, California in 1988. She received her Bachelor of Science in Electrical Engineering and Computer Science from the University of California at Berkeley, Berkeley, California in 1992.