Title
Contributions in Design of Experiments: Methods and Applications

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Publication Date
2013

Peer reviewed|Thesis/dissertation

University of California
Los Angeles

Contributions in Design of Experiments: Methods and Applications

A dissertation submitted in partial satisfaction
of the requirements for the degree
Doctor of Philosophy in Statistics

by

Jessica Lynn Jaynes

2013

Abstract of the Dissertation

Contributions in Design of Experiments: Methods and Applications

by

Jessica Lynn Jaynes

Doctor of Philosophy in Statistics

University of California, Los Angeles, 2013

Professor Hongquan Xu, Co-chair

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Progresses in science and technology continuously raise new challenges to experimenters and statisticians, calling for innovation in methodological and theoretical development of experimental design. Factorial designs are popular experimental plans for identifying important factors. Motivated by real world applications, we construct efficient and optimal factorial designs with applications in the fields of, but not limited to, biomedical sciences, for drug combination determination, and marketing survey research. First, we provide a novel application of fractional factorial designs to investigate a biological system with Herpes simplex virus type 1 and six antiviral drugs. We show how the sequential use of two- and three-level fractional factorial designs can screen for important drugs and drug interactions, as well as determine potential optimal drug dosages. Second, we construct a new class of composite designs based on a two-level factorial design and a three-level orthogonal array. These new composite designs have many desirable features and are effective for factor screening and response surface modeling. Finally, motivated by the need for smaller optimal discrete choice experiments, we propose a novel application of blocked factorial designs for designing discrete choice experiments for estimating main effects, and main effects plus some two-factor interactions,

with 100% efficiency. These observations have major implications in the understanding of factorial designs, ultimately leading to a better design practice and theory.

The dissertation of Jessica Lynn Jaynes is approved.

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2013

To my Dad . . .

a best friend, a parent, a father, a role model,

and my inspiration

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Acknowledgments

First and foremost, I would like to take the time to thank the various people who have played a role in the completion of my Ph.D. No matter the size of the contribution, without your continued support this would not be possible.

I would like to thank my advisors: Dr. Wong Kee Wong and Dr. Hongquan Xu for sharing their expertise in their respective fields of the design of experiments. In addition, for their time and dedication, as well as their continued encouragement and mentorship throughout my graduate career. I would also like to thank Dr. Jan de Leeuw and Dr. Rick Paik Schoenberg for their support in playing key roles in my committee. I would like to thank each one of you for your support in preparing me for my career in academia.

I would like to thank Dr. Hongquan Xu and Dr. Jan de Leeuw for generously supporting me a substantial amount of time throughout my graduate career. In particular, Dr. Jan de Leeuw for the opportunity as an Assistant Editor at the Journal of Statistical Software, an experience has given me great insight and formed the type of researcher I have become. To Dr. Nicolas Christou, I express my sincere gratitude for sharing your many teaching experiences and advice. For Ms. Glenda Jones, always being there with a smiling face and forever lending an ear to listen.

Ultimately, I would like to thank my parents for everything that they have provided me with, for without them I would not be the person that I am. To my Daddy: for forever tiptoeing around the house during my study time, as well as the many runs to Office Depot. Your sacrifices and hard work have truly lent themselves to give me the opportunity to be where I am at today. I will forever hold these near and dear to my heart. You will always be my inspiration. To my Mom and Chubs, for always being a phone call away when my days just did not seem to go right, and the encouragement to keep on pushing. To my entire sibling

clan: Judy, Josh, John, Jacquelyn, and Julia, for providing me with the strength, support, and happiness only siblings can offer. To my niece, baby Alison, for making your appearance into the world just at the right time. Finally, to my entire extended family for always showing your patience and support.

Last and definitely not least, to my wonderful Husband Anthony ... Bug. I cannot express enough gratitude for your unconditional love, endless amounts of patience, compassion, and faith in me. You are my source of strength and happiness, and I am so blessed to have found you.

Chapter two is a version of Jaynes, Ding, Xu, Wong, and Ho (2013) published in Statistics in Medicine. Chapter three is a version of Xu, Jaynes, and Ding (2013) in press.

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Xu, H., Jaynes, J., and Ding, X. (2013) Combining Two-Level and Three-Level Orthogonal Arrays for Factor Screening and Response Surface Exploration. *Statistica Sinica*, in press. doi:10.5705/ss.2012.210

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CHAPTER 1

Introduction

In an experiment, we deliberately change one or more factors in order to observe the effect of the change on the outcome. That is, we design the experiment to test a cause and effect relationship. Experimental design is an effective and commonly used tool in scientific investigations and industrial applications to study the relationship between two or more variables. The framework for experimental design can be traced back to the 1930's by R.A. Fisher in agriculture. Typically, agricultural and biological experiments require vast amounts of land and time, as well as variation among the plots. This lead to the development of the core concepts of experimental design: blocking, randomization, replication, and orthogonality. By using experimental design techniques, we can represent a real world complexity to determine if one variable depends on another. Additionally, an experiment should be designed such that maximum information can be obtained from fewer experiments; therefore, efficient in terms of time and cost. A well designed study is often more important than the actual analysis because no statistical analysis can rescue a poorly designed experiment.

The design of experiments has a variety of applications. Since the early development of experimental design in agriculture, experimental designs have become common practice, particularly in engineering. Experiments are often iterative and involve several stages. Factorial designs are cost-effective for studying the effects of two or more factors simultaneously and commonly used for identifying important factors from a large pool of factors in early stages. Full factorial de-

signs at two- and three- levels are most commonly used to determine the effect of one factor on another. These designs allow the independent estimation of all the main effects as well as all of the interaction effects. However, the size (in terms of the number of runs) of these designs increases rapidly as the number of factors and level increases. Rather, consider a fraction of the full factorial design, which requires fewer runs. These designs can be selected such that the fractions are optimal according to a particular criteria. As a tradeoff for the reduced run size, some effects are aliased (indistinguishable from one another). Details on the construction of factorial designs are given in Chapter 2.

The goal of this dissertation is to develop new methodologies in the field of experimental design based upon and motivated by real world applications. Efficient and optimal factorial designs are constructed with applications in the fields of, but not limited to, biomedical sciences, for drug combination determination, and marketing survey research. We will illustrate that the design, and construction, of experiments can strongly benefit researchers in a wide variety of areas. More specifically, we will show that the ideas that have been used in engineering for many years can be applied to medical research, as well as consumer preference modeling. While fractional factorial designs have successfully, and effectively, been used in a wide array of areas, they have yet to make an impact in the area of virology and drug combinations. With the emerging use of experimental design in new areas of research, this calls for innovative, and alternative, design construction techniques and methods. With the construction of new composite designs and applications in various fields, the findings are similar to many successful applications of factorial designs used in engineering experiments, and gives us confidence that factorial designs can be useful in other disciplines.

The remainder of the dissertation is organized as follows: (1) we will provide a novel application of factorial designs in the area of virology; (2) develop a new class of composite designs; and (3) construct smaller efficient choice sets for the area of

discrete choice experiments. In comparison to current methods and techniques, generally these designs provide higher efficiency, more in depth analyses, and require a shorter time to run.

Chapter 2 illustrates the usefulness of fractional factorial designs to medical researchers to find optimal drug combinations and to screen out inactive components. We develop an application of fractional factorial designs to investigate a biological system versus current techniques of random search algorithms. An alternative approach to the feedback system control is presented, replacing part of the feedback system control by a fractional factorial design. By using a fractional factorial design to search for optimal drug combinations we present the following advantages: (1) fractional factorial designs are efficient for studying two or more factors, (2) a statistical model can be built with fewer runs, (3) important drugs and their combinations can be successfully identified, and (4) ability to predict optimal drug combinations.

Chapter 3 is motivated by an antiviral drug experiment. We construct a new class of composite designs by combining a two-level factorial design and a three-level orthogonal array. The resulting design is called an orthogonal-array composite design (OACD). This new class of composite designs is constructed with careful consideration of experimental cost, time and statistical efficiency, and can perform the entire experiment in one iteration, reducing cost and variation. An OACD has several advantages: (1) the OACD can use a better initial design than other existing composite designs, enabling all linear effects to be estimated clearly from any bilinear effects and offers higher efficiencies, (2) an OACD can be used in a single experiment or in a sequential experiment; this feature is particularly appealing in many industrial and engineering experiments, and (3) more in depth analyses than traditional designs using either a two- or three-level design. It is shown that this new class of composite designs provides a good trade-off between estimation efficiency and run size economy, and can be used as an alternative to

the popular other existing composite designs.

Chapter 4 presents an application of factorial designs in the research area of discrete choice experiments (DCEs). A DCE is an attribute based method that gives further insight into how individuals develop preferences for particular attributes. A DCE presents respondents with several choice sets of hypothetical scenarios, where each choice set is made up of 2 or more options. Motivated by the need for smaller optimal DCEs, we proposed a unique method applying blocked factorial designs to construct smaller DCEs for estimating main effects, and main effect plus some two-factor interactions, with 100% efficiency. There are many recent studies on the optimal choices of blocking schemes for fractional factorial designs (Cheng and Wu, 2002); however, DCEs have yet to incorporate recent developments in blocked fractional factorial designs. It is shown that in general, all DCEs constructed using a blocked factorial design for the estimation of the clear effects are: (1) always D-optimal and 100% efficient, (2) present equal or smaller number of choice sets to the respondent, and (3) do not need to assume any two-factor interactions negligible.

CHAPTER 2

An Application of Fractional Factorial Designs to Study Drug Combinations

Herpes simplex virus type 1 (HSV-1) is known to cause diseases of various severities. There is increasing interest to find drug combinations to treat HSV-1 by reducing drug resistance and cytotoxicity. Drug combinations offer potentially higher efficacy and lower individual drug dosage. In this paper, we report a new application of fractional factorial designs to investigate a biological system with HSV-1 and six antiviral drugs, namely, Interferon-alpha, Interferon-beta, Interferon-gamma, Ribavirin, Acyclovir, and TNF-alpha. We show how the sequential use of two- and three-level fractional factorial designs can screen for important drugs and drug interactions, as well as determine potential optimal drug dosages through the use of contour plots. Our initial experiment using a two-level fractional factorial design suggests that there is model inadequacy and drug dosages should be reduced. A follow-up experiment using a blocked three-level fractional factorial design indicates that TNF-alpha has little effect and HSV-1 infection can be suppressed effectively by using a right combination of the other five antiviral drugs. These observations have practical implications in the understanding of antiviral drug mechanism that can result in better design of antiviral drug therapy.

2.1 Introduction

Herpes simplex virus (HSV) is known to cause diseases of various severities, including mucocutaneous diseases, neonatal herpes and herpes encephalitis (McGrath, Anderson, Croxson, Powell, 1997). Recent reports also suggest HSV infection could strongly increase risk for HIV infection (Zuckerman, Lucchetti, et al., 2007). HSV has become one of the most common sexual transmitted diseases in U.S.A., U.K., French and other western societies (Malkin, Morand, Malvy et al., 2008; Scoular, Norrie, Gillespie, et al., 2002; Xu, Sternber, et al., 2006). Furthermore, HSV encephalitis is the most common form of fatal encephalitis in the U.S., occurring about two per 100,000 persons yearly in the U.S. (Whitley, Lakeman, 1995). Many therapeutic agents both pharmaceutical and chemical have been developed and to treat HSV infections (Rong, Alexander, et al., 2003; Andersen, Jenssen, et al., 2003). While these agents are generally effective, drug resistance and toxicity concerns have been increasingly reported (Biswas, Sukla, Field, 2009; Gray, Wilson, 2010). To reduce possible drug resistant viral mutant and the cytotoxicity, combinations of different antiviral drugs have been widely used (De Clercq, 2004). For two drugs, effective drug combinations can be found using some nonlinear modeling approaches (Chou, 2010; Straetemans, et al., 2005). Drug combinations have often been reported to have higher efficacy and lower individual drug dosage.

Many challenges and complexities arise when trying to understand a system with multiple drugs (e.g., three or more drugs) because the underlying biological system is intrinsically complex and there are potential multiple drug interactions. For example, to study six antiviral drugs, each with seven dosage levels, there are $7^6 = 117,649$ different drug combinations to be tested. It is time and labor consuming to test all possible drug combinations. Researchers have developed a feedback system control to identify optimal drug combinations with five to 10 drugs at six or more dosage levels (Wong, et al., 2008; Tsutsui, et al., 2011,

Ding, et al., 2012). The feedback system control technique combines two parts, 1) biological experiment and 2) search algorithm, into a feedback loop. It is a rapid platform and usually identifies optimal drug combinations in less than 15 iterations by testing 1% or less of the total searching space. Yet, with such an approach it is challenging to quantify drug contributions and drug interactions (Al-Shyoukh, et al., 2011).

Here, we introduce an alternative approach by using fractional factorial designs to replace the part of search algorithm in the feedback system control. Fractional factorial designs are an effective and commonly used tool in scientific investigations and industrial applications. Many successful applications have been reported in physical and chemical sciences, and engineering. Many textbooks on experimental design, such as Box, Hunter, Hunter (2005); Box and Draper (2007); Myers, Montgomery, Anderson-Cook (2007); Wu and Hamada (2009); Montgomery (2011); and Mee (2009), provide various real applications. However, fractional factorial designs have yet to make an impact in bioscience, particularly in virology study. A main advantage of fractional factorial designs is that they enable us to build statistical models with a small number of runs. Using the models we can not only identify important drugs and drug interactions, but also predict optimal drug combinations.

In this paper, we present one of the first uses of fractional factorial designs in the area of virology by sequentially using two- and three-level fractional factorial designs to investigate a biological system with Herpes simplex virus type 1 (HSV-1) and six antiviral drugs: Interferon-alpha (A), Interferon-beta (B), Interferon-gamma (C), Ribavirin (D), Acyclovir (E), and TNF-alpha (F). The experiments were conducted at the UCLA Micro Systems Laboratories. We show that our approach successfully identifies that Ribavirin (D) has the largest effect on minimizing the virus load and TNF-alpha (F) has the smallest effect on minimizing the virus load.

The paper is organized as follows. In Section 2.2, we first provide a brief overview of two-level factorial and fractional factorial designs, which are widely used in early stages of experiments to screen important factors from a large number of potential factors. We then describe our initial antiviral drug experiment using a two-level fractional factorial design and perform data analysis. We demonstrate how this two-level experiment helps us understand the HSV-1 system and identify potential effective drug combinations. Section 2.3 describes the follow-up experiment using a three-level blocked fractional factorial design when there is evidence of model inadequacy in the two-level experiment. In addition, we report our analysis results and show how we determine the optimal drug levels using contour plots. Section 2.4 contains conclusions.

2.2 Initial two-level experiment

2.2.1 Full factorial design

Factorial designs are very efficient for studying two or more factors. The effect of a factor can be defined as the change in response produced by a change in the level of the factor. This is referred to as the main effect. In some experiments, it may be found that the difference in the response between levels of one factor is not the same at all levels of the other factors. This is referred to as an interaction effect between factors. Collectively, main effects and interaction effects are called the factorial effects (Wu and Hamada, 2009). A full factorial design can estimate all main effects and higher-order interactions.

Another way to define the concept of main effects and interaction effects for two-level designs is using a regression model. Suppose we have a full factorial design studying the six antiviral drugs: A, B, C, D, E, and F with two levels for each drug. There are $2^6 = 64$ treatments or level combinations. A common

regression model for studying main effects and interactions is

$$\begin{aligned} y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 \\ + \beta_{12} x_1 x_2 + \cdots + \beta_{123} x_1 x_2 x_3 + \cdots + \beta_{1234} x_1 x_2 x_3 x_4 + \ldots \\ + \beta_{12345} x_1 x_2 x_3 x_4 x_5 + \cdots + \beta_{123456} x_1 x_2 x_3 x_4 x_5 x_6 + \epsilon. \end{aligned} \tag{2.1}$$

Here y is the response, the β's are unknown parameters, $x_1, \ldots, x_6$ represent drugs A–F, and ϵ is a random error term. The variables $x_1, \ldots, x_6$ are coded as 1 and -1, for the high and low levels for their respective factors. The interaction between x_1 and x_2 is denoted as $x_1 x_2$, and the other interaction effects are similarly defined. It is well known that the least squares estimates of the β's in the model (2.1) are half of the corresponding factorial effects (Wu and Hamada, 2009).

Using a full factorial design with 64 runs for all six drugs, we can estimate 6 main effects, 15 two-factor interactions, 20 three-factor interactions, 15 four-factor interactions, 5 five-factor interactions, and 1 six-factor interaction. Note that out of the 63 $(2^6 - 1)$ degrees of freedom in the 64-run (2^6) design, 42 are used for estimating three-factor or higher interactions. However, in many experiments, we often find that three-factor and higher order interactions are usually not important (Wu and Hamada, 2009). This means that we are using over half of the degrees of freedom to estimate effects that are potentially not significant. Therefore, using a full factorial design to study six drugs in 64 runs is quite wasteful. A more practical and economical approach is to use a fractional factorial design that allows the estimation of lower-order effects.

2.2.2 Fractional factorial design

For economical reasons, we study six drugs in the antiviral drug experiment, introduced in Section 2.2, in $2^{6-1} = 32$ runs, a half fraction of the full 2^6 design. To construct such a design, we write down all possible 2^5 level combinations for

drugs A, B, C, D, and E, and then set the level of drug F as the product of the levels of drugs A, B, C, D, and E, that is, $F = ABCDE$. Note that the low and high levels are coded as -1 and 1. The price we pay for using a half-fraction design is that the main effect of F is aliased with the $ABCDE$ interaction because they are identical in the model. Additionally, there is also aliasing among other effects. Indeed, each main effect is aliased with a fifth-order interaction: $A = BCDEF$, $B = ACDEF$, $C = ABDEF$, $D = ABCEF$, and $E = ABCDF$. Each two-factor interaction is aliased with a fourth-order interaction, i.e., $AB = CDEF$, $AC = BDEF$, $\ldots$, $EF = ABCD$, and each three-factor interaction is aliased with a third-order interaction, i.e., $ABC = DEF, ABD = CEF, \ldots, AEF = BCD$. To disentangle these effects, a common and reasonable assumption is that higher-order interactions are assumed to be negligible because they are less likely to be important than lower-order interactions (Wu and Hamada, 2009). This means that for this fractional factorial design we can estimate all main effects and all two-factor interactions assuming that fourth-order and higher interactions are negligible, which is quite reasonable in practice. Furthermore, every three-factor interaction is aliased with another three-factor interaction and so we can only estimate their sum.

Effect aliasing is a consequence of using a fractional factorial design. A related concept is resolution, which captures the amount of aliasing. This half-fraction design has resolution VI, which allows the estimation of all main effects and two-factor interactions under the assumption that fourth-order and higher interactions are negligible. In general, the higher the resolution of a fractional factorial design, the less restrictive the assumption is regarding which interactions are negligible to obtain a unique interpretation of the data. See Wu and Hamada (Wu and Hamada, 2009) for more details on aliasing and resolution for fractional factorial designs.

Table 2.1 gives the design and data for the initial experiment, where the two

levels are coded as -1 and 1. Each run represents a combinatorial drug treatment and the outcome, called readout, is the percentage of virus infected cells after the treatment. The first 32 runs correspond to the half fraction design obtained by setting $F = ABCDE$. Following the typical practice for two-level designs, we add three replicated runs (the last three runs) at the center (0). The addition of replicated center points allows an independent estimate of error to be obtained without affecting the estimates of the factorial effects. Generally, three to five center runs are recommended (Montgomery, 2011). Using these center points, we can obtain an estimate of the variability and conduct a lack-of-fit test.

2.2.3 Antiviral drug experiments

We now provide technical details of the antiviral drug experiment, where NIH 3T3 cells were chosen as host cells. Cells were initially cultured on 15mm plates covered with 25mL culture medium. The culture medium was made from DMEM in presence of 10% Fetal Bovine Serum (FBS) and 1% Penicillin-Streptomycin (Pen-Strep). The 15mm plates were maintained in 37^oC incubator filled with 5% CO_2. Cultures were propagated at 10^7 cells/plate every 24 hours for two times before use in experiment.

Cell infection was carried out in 24-well plates. Each well contained 2×10^5 cells in 1mL culture medium. Cells were allowed to grow for four hours before viral infection and drug treatments occurred. Drug combinations were added simultaneously with HSV-1 to the host cells in 24-well plates. The plates were incubated at 37^oC incubator with 5% CO_2 for 16 hours. The virus was engineered to carry the green fluorescent protein (GFP) gene. Thus, cells infected with the virus would be GFP positive. GFP served as a biomarker to assess the percentage of infected cells. The readout was defined as the percentage of GFP positive cells after combinatorial drug treatments. The readout was measured through a flow cytometer (BD FACSCanto II, BD Biosciences).

Table 2.1: Design and data for the initial two-level experiment: A 2^{6-1} design

	Factor						
Run	A	B	C	D	E	F	readout
1	−1	−1	−1	−1	−1	−1	31.6
2	−1	−1	−1	−1	1	1	32.6
3	−1	−1	−1	1	−1	1	13.4
4	−1	−1	−1	1	1	−1	13.2
5	−1	−1	1	−1	−1	1	27.5
6	−1	−1	1	−1	1	−1	32.5
7	−1	−1	1	1	−1	−1	11.6
8	−1	−1	1	1	1	1	20.8
9	−1	1	−1	−1	−1	1	37.2
10	−1	1	−1	−1	1	−1	51.6
11	−1	1	−1	1	−1	−1	14.1
12	−1	1	−1	1	1	1	19.9
13	−1	1	1	−1	−1	−1	27.3
14	−1	1	1	−1	1	1	40.2
15	−1	1	1	1	−1	1	19.3
16	−1	1	1	1	1	−1	23.3
17	1	−1	−1	−1	−1	1	31.2
18	1	−1	−1	−1	1	−1	32.6
19	1	−1	−1	1	−1	−1	14.2
20	1	−1	−1	1	1	1	22.4
21	1	−1	1	−1	−1	−1	32.7
22	1	−1	1	−1	1	1	41.0
23	1	−1	1	1	−1	1	20.1
24	1	−1	1	1	1	−1	18.7
25	1	1	−1	−1	−1	−1	29.6
26	1	1	−1	−1	1	1	42.3
27	1	1	−1	1	−1	1	18.5
28	1	1	−1	1	1	−1	20.0
29	1	1	1	−1	−1	1	30.9
30	1	1	1	−1	1	−1	34.3
31	1	1	1	1	−1	−1	19.4
32	1	1	1	1	1	1	23.4
33	0	0	0	0	0	0	16.8
34	0	0	0	0	0	0	17.5
35	0	0	0	0	0	0	16.2

Table 2.2: Factors and levels for the initial two-level antiviral drug experiment

	Levels	
Factor	Low (-1)	High ($+1$)
A= Interferon-alpha	3.12 ng/mL	50 ng/mL
B= Interferon-beta	3.12 ng/mL	50 ng/mL
C= Interferon-gamma	3.12 ng/mL	50 ng/mL
D= Ribavirin	1560 ng/mL	2.5e4 ng/mL
E= Acyclovir	31 ng/mL	5e3 ng/mL
F= TNF-alpha	0.31 ng/mL	5 ng/mL

Table 2.2 shows the actual dosage levels for the six drugs. Before this study, we performed single drug pilot studies and tested a wide range of dosages for each drug in order to find the "minimum response dosage", at which the drug started to show some efficacy, and the "plateau dosage", at which the drug's efficacy did not increase when higher dosage was used. The pilot study suggested that the minimum response dosage was about 16 times diluted from the plateau dosage. In this study, we chose the plateau dosage as the high level (coded as 1) and the minimum response dosage as the low level (coded as -1). A center level (coded as 0) was added for the additional runs at the center of the factorial design. The center level is four times diluted from the high level and the low level is four time diluted from the center level.

2.2.4 Analysis and results

As explained in Section 2.2.2, our design can estimate all six main effects, all 15 two-factor interactions, and 10 pairs of aliased three-factor interactions, assuming that four-factor and higher interactions are negligible. In the analysis, we use $y = \log(readout)$, i.e., log base 10 of the viral infection load, as the response because the distribution of the viral infections are positively skewed. The log transformation is also confirmed with the Box-Cox method. Table 2.3 presents the least squares estimates, the sum of squares, and the percentage of total sum of squares. The sum of squares of an effect here is simply 32 times the square of

its estimate.

Table 2.3 suggests that the effects of drugs D and E are the largest. The linear effect of drug D is the most significant with an estimate of three times the estimate of the next most significant drug, E; showing that drug D is very significant and important relative to the other drugs. Together, drugs D and E account for 75.3% of the total sum of squares in the data. Overall, the six main effects contribute 81.5% of the sum of squares, the fifteen two-factor interactions contribute 6.8%, the ten pairs of three-factor interactions contribute 3.2%, and the residuals account for 8.3%. In this antiviral experiment the main effects dominate the system, and drug D alone accounts for 68.0% of the total sum of squares within the system. Such finding is similar to many engineering experiments where fractional factorial designs are successfully used. This observation gives us confidence that fractional factorial designs can be useful for studying cellular system under multiple drug stimulations.

We observe that all of the estimates for drugs A-F have positive coefficients except for drug D. The practical implication is that in our experiment the minimum viral infection can be achieved when we set the dugs A, B, C, E, and F at the low level and D at the high level. Accordingly we decrease the dosage for the drugs A, B, C, E, and F and increase the dosage for D. However, while drug D is an effective antiviral drug, it often induces an unacceptable levels of toxic side effects for the subjects. To screen for less toxic drug combinations we reduce all of the drug dosages in a follow-up experiment.

We use the data from the three independent center runs to test for lack-of-fit. The lack-of-fit test is also known as a check for curvature (Wu and Hamada, 2009; Montgomery, 2011) for a two-level factorial design. The residuals sum of squares in Table 2.3 can be decomposed into two parts: lack-of-fit and pure error, with one and two degrees of freedom, respectively. The lack-of-fit test presented in Table 2.4 shows that lack-of-fit is very significant with an F value of 272.46 and

Table 2.3: Estimates for the initial two-level experiment

Effect	Estimates	Sum Sq.	% Sum Sq.
A	0.017	0.009	1
B	0.03	0.029	3.1
C	0.008	0.002	0.2
D	-0.141	0.636	68
E	0.046	0.068	7.3
F	0.024	0.018	1.9
AB	-0.022	0.015	1.6
AC	0.005	0.001	0.1
AD	0.019	0.011	1.2
AE	-0.009	0.002	0.3
AF	0.005	0.001	0.1
BC	-0.009	0.003	0.3
BD	0.008	0.002	0.2
BE	0.008	0.002	0.2
BF	-0.008	0.002	0.2
CD	0.024	0.018	1.9
CE	0.002	0	0
CF	0.003	0	0
DE	0.001	0	0
DF	0.014	0.006	0.7
EF	-0.001	0	0
ABC+DEF	-0.002	0	0
ABD+CEF	0.002	0	0
ABE+CDF	-0.006	0.001	0.1
ABF+CDE	-0.001	0	0
ACD+BEF	-0.017	0.009	0.9
ACE+BDF	-0.015	0.007	0.8
ACF+BDE	-0.012	0.004	0.5
ADE+BCF	-0.004	0	0
ADF+BCE	-0.009	0.002	0.2
AEF+BCD	0.014	0.007	0.7
Residuals	-	0.077	8.3
Total	-	0.935	100

Table 2.4: Lack-of-fit Test

Source	DF	Sum Sq.	Mean Sq.	F-statistic	p-value
Lack-of-fit	1	0.07663	0.07663	272.46	0.0037
Pure error	2	0.00056	0.00028		
Residuals	3	0.07719			

a p-value of 0.0037. This implies that the relationship between the response and the drugs is nonlinear; therefore, we need additional levels and runs to model the nonlinear relationship.

Summarizing the results, lower drug dosages for all drugs are desirable in order to reduce potential drug toxicity and minimize viral infection. In addition, we need to add a third level for each drug to model the nonlinear relationship. This naturally leads to a three-level design.

2.3 Follow-up three-level experiment

2.3.1 Experimental design

Two-level designs are commonly used to screen factors in the initial stage given a small number of runs. Three-level designs are widely used in practice to study the nonlinear relationship for quantitative factors. In the follow-up experiment, we use three levels for each drug. Table 2.5 shows the drug dosage levels for the follow-up three-level experiment, where the three levels are denoted as low (0), intermediate (1), and high (2). The highest concentration level for the follow-up experiment is the middle concentration level for the initial two-level experiment. Similar to the two-level experiment, the intermediate level is 16 times diluted from the high level and the low level is to be no drug.

One possible design to consider for the follow-up experiment is a resolution VI, 3^{6-1} design, which has 243 runs and enables the estimation of all main effects and two-factor interactions. However, this design is not so feasible in practice because

Table 2.5: Factors and levels for the follow-up three-level antiviral drug experiment

	Levels		
Factor	Low (0)	Mid (1)	High (2)
A= Interferon-alpha	0	0.78 ng/mL	12.5 ng/mL
B= Interferon-beta	0	0.78 ng/mL	12.5 ng/mL
C= Interferon-gamma	0	0.78 ng/mL	12.5 ng/mL
D= Ribavirin	0	390 ng/mL	6250 ng/mL
E= Acyclovir	0	80 ng/mL	1250 ng/mL
F= TNF-alpha	0	0.08 ng/mL	1.25 ng/mL

of the large number of runs required. Instead, we employ a 81-run design, a one-ninth fraction of the 3^6 design, 3^{6-2} design. First, the design is constructed by choosing the column for factor E to be equal to column A + column B + column C + column D (mod 3); that is, every entry in column E is the sum of the first four levels of the factors modulus 3. Here modulus 3 means that any multiple of 3 equals zero. Second, we choose F to be equal to column A + 2(column B) + column C (mod 3). The conventional notation for such a design is $E = ABCD$ and $F = AB^2C$, which are called the generators of this particular three-level design. If $x_1, \ldots, x_6$ represents the six factors, then $E = ABCD$ is equivalent to $x_5 = x_1 + x_2 + x_3 + x_4 \pmod 3$, and $F = AB^2C$ is equivalent to $x_6 = x_1 + 2x_2 + x_3 \pmod 3$. This design has resolution IV; therefore, all main effects are not aliased with any two-factor interactions and some two-factor interactions are aliased with other two-factor interactions. Moreover, this 81-run design has the ability to estimate each of the main effects as well as some of the two-factor interactions.

However, there are practical issues with this design. The antiviral drug experiments require cell culture preparation and adding virus and drug combinations manually. It is also not practical to perform the 81-run design using a single batch of cell culture. Experiences show that there are substantial batch to batch variation from the nature of cells. These systematic sources of variation are intrinsic and are independent of the researcher or the equipment. If such an issue is not addressed carefully, the precision of the experiment can be reduced greatly

by these systematic sources of variation. Blocking is a useful way to reduce the influence of these systematic sources of variation by arranging homogeneous experimental runs into groups. There are many recent studies on the optimal choices of blocking schemes for fractional factorial designs; see, among others, Sun, Wu, and Chen (1997); Sitter, Chen, Feder (1997); Chen and Cheng (1999); Cheng and Wu (2002); Xu (2006); Xu and Lau (2006); and Xu and Mee (2010). However, real applications of blocked fractional factorial designs is limited in the biomedical science area. Considering the experimental capacity and time, we divide the 81 runs in three blocks, each of size 27. Each block uses one batch of cell culture and the runs within a block are randomized. In particular, we arrange the 3^{6-2} design into 3 blocks with the block generator, block $= AC^2D$, or equivalently block$= x_1 + 2x_3 + x_4 \pmod 3$, following Xu and Lau (2006). Because the block effect and the three-factor interaction have the same estimate, the block effect is said to be confounded with the three-factor interaction effect. With this arrangement the main effects and two-factor interactions are not confounded with the block effects and therefore they can be estimated efficiently. Table 2.6 gives the design and data of the experiment.

2.3.2 Analysis

To analyze the data, we fit a second-order model with the addition of the block effects:

$$\begin{aligned} y = \log(readout) = \beta_0 + \sum_{i=1}^{6} \beta_i x_i + \sum_{i=1}^{6} \beta_{ii} x_i^2 \\ + \sum_{1=i<j}^{6} \beta_{ij} x_i x_j + \gamma_1 block1 + \gamma_2 block2 + \epsilon, \end{aligned} \tag{2.2}$$

where β_i represents the linear effect of x_i, β_{ii} represents the quadratic effect of x_i, and β_{ij} represents the bilinear (i.e., linear-by-linear) interaction between x_i

and x_j. For convenience, in the analysis, the three dosage levels (0, 1, and 2) are encoded as -1, 0, 1, respectively. The variables, $block1$ and $block2$, are indicators of blocks 1 and 2, respectively, with block 0 as a reference. As explained earlier, the blocking variables are not correlated with other variables in model (3.1).

Table 2.7 column (a) gives the estimates of the model. The model fits the data well with an R^2 value of 91.4%. Table 2.7(a) shows that the linear effects D and E, the quadratic effect D^2, and the interaction AD are significant at the 0.1% level; the linear effect B is significant at the 5% level. As expected, both blocking variables are significant at the 1% level, indicating that the batch-to-batch variation is large. Residual analysis indicates that the usual assumptions on the error are reasonable. However, run 80 turns out to be an outlier. This is obvious from inspecting Table 2.6. When factor D is at the high level the readout is usually small, except run 80. We remove this outlier and refit the model. Column (b) of Table 2.7 gives the results after the removal of the outlier. The new model has a slightly higher R^2 value of 94.5% and the significant effects identified earlier remain significant. We note that the linear effect B becomes more significant and the linear effect C becomes significant at the 5% significance level. We further perform variable selection via stepwise regression and confirm that there are no other significant effects. The final model at the 1% significance level is

$$\begin{aligned}\log(readout) = 0.839 - 0.036A - 0.054B - 0.045C - 0.508D - 0.119E \\ +0.168D^2 - 0.327block1 - 0.174block2 + 0.079AD,\end{aligned} \tag{2.3}$$

with R^2 of 92%. The linear effect A is not significant, but we keep the term in the model because the interaction AD is significant.

Table 2.6: Design and data for the follow-up three-level experiment: A 3^{6-2} design in 3 blocks

Run	A	B	C	D	E	F	block	readout	Run	A	B	C	D	E	F	block	readout	Run	A	B	C	D	E	F	block	readout
1	0	0	0	0	0	0	0	49.1	28	1	0	0	0	1	1	1	11.8	55	2	0	0	0	2	2	2	14.5
2	0	1	0	0	1	2	0	37.2	29	1	1	0	0	2	0	1	14.5	56	2	1	0	0	0	1	2	24.5
3	0	2	0	0	2	1	0	39.9	30	1	2	0	0	0	2	1	14	57	2	2	0	0	1	0	2	30.2
4	1	0	1	0	2	2	0	28.7	31	2	0	1	0	0	0	1	19.3	58	0	0	1	0	1	1	2	50.5
5	1	1	1	0	0	1	0	41.8	32	2	1	1	0	1	2	1	8.6	59	0	1	1	0	2	0	2	34.1
6	1	2	1	0	1	0	0	50.6	33	2	2	1	0	2	1	1	10	60	0	2	1	0	0	2	2	39.4
7	2	0	2	0	1	1	0	24.4	34	0	0	2	0	2	2	1	8.6	61	1	0	2	0	0	0	2	31
8	2	1	2	0	2	0	0	18.2	35	0	1	2	0	0	1	1	29.9	62	1	1	2	0	1	2	2	17.2
9	2	2	2	0	0	2	0	24.3	36	0	2	2	0	1	0	1	10.9	63	1	2	2	0	2	1	2	11.8
10	2	0	0	1	0	2	0	23.7	37	0	0	0	1	1	0	1	4.7	64	1	0	0	1	2	1	2	4.8
11	2	1	0	1	1	1	0	6.2	38	0	1	0	1	2	2	1	3.4	65	1	1	0	1	0	0	2	4.6
12	2	2	0	1	2	0	0	6.2	39	0	2	0	1	0	1	1	6.6	66	1	2	0	1	1	2	2	4.5
13	0	0	1	1	2	1	0	6.8	40	1	0	1	1	0	2	1	4.8	67	2	0	1	1	1	0	2	3.3
14	0	1	1	1	0	0	0	8.9	41	1	1	1	1	1	1	1	2.9	68	2	1	1	1	2	2	2	3.7
15	0	2	1	1	1	2	0	7.6	42	1	2	1	1	2	0	1	2.3	69	2	2	1	1	0	1	2	2.5
16	1	0	2	1	1	0	0	5.2	43	2	0	2	1	2	1	1	1.4	70	0	0	2	1	0	2	2	14.2
17	1	1	2	1	2	2	0	6	44	2	1	2	1	0	0	1	4.1	71	0	1	2	1	1	1	2	2.7
18	1	2	2	1	0	1	0	7.6	45	2	2	2	1	1	2	1	2.5	72	0	2	2	1	2	0	2	2.5
19	1	0	0	2	0	1	0	4.2	46	2	0	0	2	1	2	1	2.3	73	0	0	0	2	2	0	2	1.6
20	1	1	0	2	1	0	0	2.4	47	2	1	0	2	2	1	1	1.3	74	0	1	0	2	0	2	2	3.2
21	1	2	0	2	2	2	0	1.8	48	2	2	0	2	0	0	1	2	75	0	2	0	2	1	1	2	1.4
22	2	0	1	2	2	0	0	4.4	49	0	0	1	2	0	1	1	3	76	1	0	1	2	1	2	2	1.9
23	2	1	1	2	0	2	0	3.7	50	0	1	1	2	1	0	1	1.6	77	1	1	1	2	2	1	2	1.6
24	2	2	1	2	1	1	0	2.7	51	0	2	1	2	2	2	1	0.9	78	1	2	1	2	0	0	2	2.3
25	0	0	2	2	1	2	0	3.5	52	1	0	2	2	2	0	1	1.6	79	2	0	2	2	0	1	2	2.6
26	0	1	2	2	2	1	0	1.4	53	1	1	2	2	0	2	1	3.9	80	2	1	2	2	1	0	2	18.2
27	0	2	2	2	0	0	0	2.5	54	1	2	2	2	1	1	1	0.8	81	2	2	2	2	2	2	2	2.6

2.3.3 Results

The data analysis identifies that four drugs, Interferon-beta (B), Interferon-gamma (C), Ribavirin (D), Acyclovir (E), have a significant linear effect on HSV-1. The nonlinear (quadratic) effect of Ribavirin also has a very significant effect on HSV-1. We also observe a significant interaction between Interferon-alpha (A) and Ribavirin (D). We do not see any significance for the drug TNF-alpha (F), and it is considered inert in the minimization of the viral infection. The negative coefficients associated with drugs B, C, and E imply that these particular drugs have the potential to lower the virus. Therefore, to achieve the minimum viral infection we set drugs B, C, and E at the high level.

Since the interaction effect between A and D is significant we use a contour plot to identify potential optimal drug dosage levels. Contour plots are used in full and fractional factorial experimental designs and analyses to determine settings that will maximize, or minimize, the response of interest. The x and y axes of the plot represent the values of the first and second factors. We examine the contour plot of A and D for the predicted percentage of viral infection from the final fitted model (2.3). Figure 2.1 shows the contour plot of the predicted readout in terms of A and D, while drugs B, C, and E are held at the high level and block1 = block2 = 0, see Table 2.5. This contour plot suggests the minimum viral infection is achieved when A is set at the low level, no drug, and D is set at the high level. If multiple two-factor interactions are considered important, then one can generate a series of contour plots, each of which is drawn for two of these factors. Therefore, the optimal drug combinations to minimize the viral infection for the final model (2.3) are: B, C, D, and E at the high level and A at the low level. The predicted response for these recommendations comes out to be 1.72%.

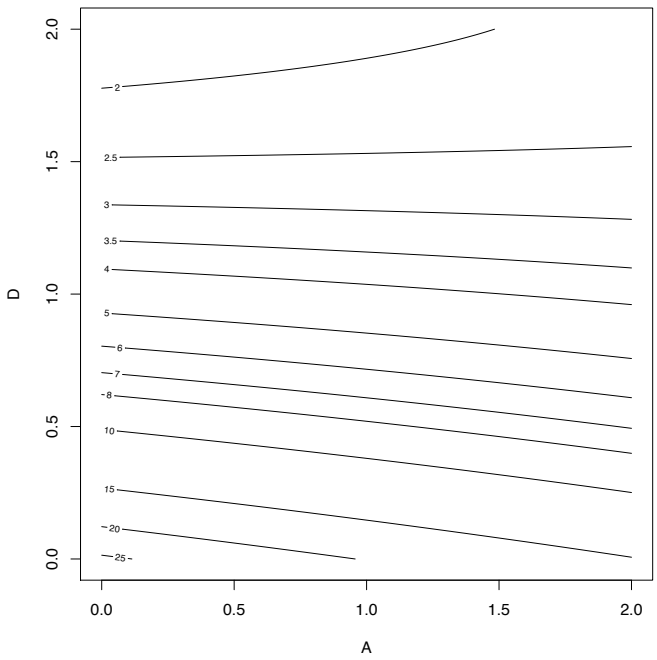
Ribavirin (D) is an effective antiviral drug; however, it can also induce toxic side effects. Hence, it is desirable to reduce the dosage level of Ribavirin to the

Table 2.7: Estimates for the follow-up three-level experiment

	(a)	(b)
(Intercept)	0.761***	0.761***
A	-0.018	-0.037
B	-0.054*	-0.054**
C	-0.027	-0.046*
D	-0.491***	-0.509***
E	-0.119***	-0.119***
F	-0.007	0.011
A^2	0.046	0.028
B^2	-0.026	0.011
C^2	-0.008	-0.026
D^2	0.185***	0.167***
E^2	0.018	0.054
F^2	0.069	0.051
AB	0.028	0.01
AC	0.047	0.005
AD	0.105***	0.078**
AE	0.036	0.036
AF	-0.05	-0.013
BC	0.012	-0.006
BD	-0.02	-0.02
BE	0.041	0.023
BF	-0.052	-0.025
CD	0.055	0.028
CE	-0.029	-0.029
CF	-0.019	0.018
DE	0.021	0.007
DF	0.000	0.036
EF	-0.038	-0.038
block1	-0.327***	-0.327***
block2	-0.139**	-0.176***
$\hat{\sigma}$	0.177	0.142
R^2	0.914	0.945

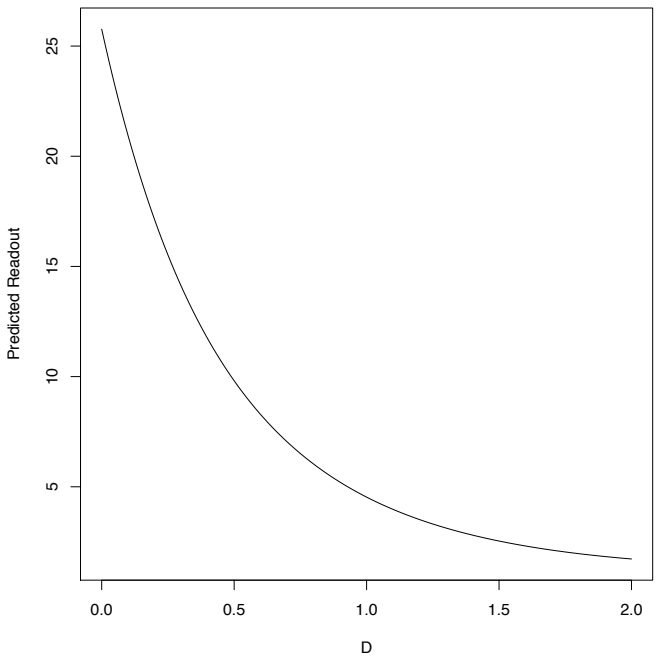
NOTE: (a) With all 81 runs (b) without run 80. Significance levels are coded as 0 (***) 0.001 (**) 0.01 (*) 0.05.

Figure 2.1: Contour plot of predicted readout for A and D



lowest possible setting in order to lower the toxicity. Figure 2.2 shows the predicted readout for Ribavirin using model (2.3), with the settings recommended for the other drugs above. Notice that the shape of the predicted response for Ribavirin is convex because the coefficient of D^2 is positive in model (2.3). The convexity has an important application, that is, reducing the Ribavirin dosage will not affect its efficacy substantially. For example, if we lower the drug dosage of Ribavirin from the high dosage level of 6,250 ng/mL to the middle dosage level, 390 ng/mL, the predicted response only changes from 1.72% to 3.84%, an absolute difference of approximately 2%. The relative change in the predicted response from the high dosage level to the middle dosage level, based on the percentage of viral infection with no drug treatment 49.1%, run 1 in Table 2.6, is approximately 4.3%. Therefore, we can potentially decrease the toxicity by reducing the dosage of Ribavirin by 16 times with only a relative change of 4% in the viral infection. This enables us to achieve the goal of finding drug combinations with higher efficacy and lower toxicity.

Figure 2.2: Plot of predicted readout for D



2.4 Concluding remarks

We provide a new sequential application of fractional factorial designs to investigate the complicated underlying biological system of HSV-1 and six antiviral drugs in virology. In the present study, we apply an initial two-level design to study six drugs at two dosage levels. The need for the quadratic model comes about upon testing the assumption of linearity in the two-level experiment. To investigate the possibility of insignificant drugs, and the need to change levels of the overall drug dosage levels, we use a three-level fractional factorial design with blocks in the follow-up experiment. We find that TNF-alpha has little effect and HSV-1 infection can be suppressed effectively by using a right combination of the other five antiviral drugs.

There is a growing demand for identifying drug combinations for a large number of drugs, say 10–50 drugs. We are currently working on a colon cancer project with 11 FDA approved drugs up to 10 dosage levels each. Our aim is to identify

effective and low-toxic combinations of these FDA approved drugs to treat colon cancer. To accommodate the large number of drugs and the large number of dosage levels, fractional factorial designs with large run sizes (128 runs or more) could be a viable alternative to high throughput methods. Efficient fractional factorial designs with 128–4,096 runs have been recently constructed, see: Xu (2005); Xu and Wong (2007); Xu (2009); and Ryan, Bulutoglu (2010), and could be potentially useful for our project. It is also possible that we need to construct new fractional factorial designs or develop new design strategies to meet our goal. A full exploration of the application of fractional factorial designs to study drug combinations for a large number of drugs is left as future research.

CHAPTER 3

Combining Two-Level and Three-Level Orthogonal Arrays for Factor Screening and Response Surface Exploration

Experimental design and analysis is an effective and commonly used tool in scientific investigations and industrial applications. Orthogonal arrays, such as factorial and fractional factorial designs, are popular experimental plans for identifying important factors. Motivated by an antiviral drug experiment, we introduce a new class of composite designs based on a two-level factorial design and a three-level orthogonal array. These designs have many desirable features and are effective for factor screening and response surface modeling. Some advantages are that they can use resolution IV designs in the screening stage, they can perform in-depth analyses, and they can be used in either a single or a sequential experiment. We study the construction method and compare the new composite designs with existing ones. We illustrate the methodology with data from an experiment that studies the effects of five antiviral drugs on the Herpes simplex virus type 1.

3.1 Introduction

In many experiments the researcher is faced with a number of factors that affect the response of interest. An appealing technique is the response surface methodology (Box and Wilson (1951)) that seeks to relate the response variable to several predictors through experimentation, modeling, data analysis, and optimization (Wu and Hamada (2009)). The initial stage of factor screening identifies important factors from a larger number of potential factors, typically using a two-level

factorial or fractional factorial design, possibly with some center points. The second stage of sequential experimentation determines the optimum region, and the final stage fits a polynomial model in this region. The last stage often uses some second-order designs that allow the estimation of a second-order model. Many second-order designs have been proposed in the literature, the most popular are the central composite designs (CCD) introduced by Box and Wilson (1951) and variations such as the small composite designs of Draper and Lin (1990). Other second-order designs include those of Box and Behnken (1960), augmented pairs designs (Morris (2000)), subset designs (Gilmour (2006)), and more. For a comprehensive account of response surface methodology, see Box and Draper (2007), Khuri and Cornell (1996), and Myers, Montgomery, and Anderson-Cook (2009).

Progress in science and technology often calls for innovation in methodological and theoretical development of experimental design. Since the successful demonstration of HIV treatment with drug combinations, combinatory drugs have been broadly applied to various aspects of disease treatment (De Clercq (2004)). The advantage of combinatory drugs is that they often have higher efficacy and lower drug dosages than individual drugs. However, it is challenging to identify potential drug combinations by trial and error because of the large number of possible combinations and the complexity of the underlying biological system. Researchers at UCLA Micro Systems Laboratories investigated a system with Herpes simplex virus type 1 (HSV-1) and six antiviral drugs: IFN-alpha (A), IFN-beta (B), IFN-gamma (C), Ribavirin (D), Acyclovir (E), and TNF-alpha (F). They chose seven dosage levels for each drug, which led to $7^6 = 117,649$ drug combinations. They used a feedback system control method to search for optimal drug combinations (Ding et al. (2012a)). The search was stochastic and performed in iterations. Each iteration tested 32 drug combinations and took up to 4 days due to the preparation of cell culture and viral infection. Each virus and drug combination was performed in a test tube, the experimental unit. They conducted 21 iterations

and found that the drug effects were nonlinear and non-additive and that there were complex drug interactions; however, they could not pinpoint drug interactions. One of the authors was consulted in order to understand the HSV-1 system and the interactions. Some standard designs such as fractional factorial designs and central composite designs were used for this purpose. After a few iterations, TNF-alpha (F) was found not effective in treating HSV-1 and dropped (Jaynes et al. (2013)). With consideration of experimental cost, time, and statistical efficiency, one of us constructed a composite design consisting of a 16-run factorial design with 2 levels and an 18-run orthogonal array with 3 levels. The resulting composite design had 3 levels and 34 runs so that the entire experiment could be conducted in one iteration. Two researchers conducted the experiment independently with different random orders, yielding two replicates. Table 3.1 shows the design and data of the experiment, where the run order was randomized. For each drug -1, 0, and 1 correspond to no drug, intermediate drug dosage, and high drug dosage, respectively. The observed data, readout, were the percentage of infected cells after the combination drug treatment. Ding et al. (2012a and 2012b) and Jaynes et al. (2013) give details of the experimental procedure and other technical issues.

Motivated by this, we introduce a new class of composite designs that combine a two-level factorial or fractional factorial design and a three-level orthogonal array, and refer to them as *orthogonal-array composite designs* (OACD). An orthogonal array of N runs, k columns, s levels, and strength t, denoted by $OA(N, s^k, t)$, is an $N \times k$ matrix in which all s^t level combinations appear equally often in every $N \times t$ submatrix. The strength t is often omitted when $t = 2$. Orthogonal arrays, including factorial or fractional factorial designs, are used in various applications. Hedayat, Sloane, and Stufken (1999) has a full account of the theory and application of orthogonal arrays. The current research is inspired by the recent developments in the study of nonregular fractional factorial designs; see Xu, Phoa,

Table 3.1: Design and data of the antiviral drug experiment

	Factor					Readout	
Run	A	B	C	D	E	Replicate 1	Replicate 2
1	1	−1	−1	−1	−1	69.8	72.0
2	−1	1	−1	−1	−1	66.4	67.4
3	−1	−1	1	−1	−1	83.0	68.6
4	−1	−1	−1	1	−1	16.2	23.4
5	−1	−1	−1	−1	1	46.1	33.6
6	1	1	1	−1	−1	68.6	65.5
7	1	1	−1	1	−1	6.8	7.2
8	1	1	−1	−1	1	15.6	19.1
9	1	−1	1	1	−1	11.1	7.0
10	1	−1	1	−1	1	19.8	20.3
11	1	−1	−1	1	1	3.7	4.7
12	−1	1	1	1	−1	5.8	3.9
13	−1	1	−1	1	1	2.6	4.0
14	−1	1	1	−1	1	42.2	23.2
15	−1	−1	1	1	1	1.8	5.2
16	1	1	1	1	1	3.1	3.4
17	−1	−1	−1	−1	−1	78.6	81.9
18	0	0	0	0	0	13.3	16.7
19	1	1	1	1	1	3.4	3.8
20	−1	−1	0	0	1	21.4	25.2
21	0	0	1	1	−1	8.6	4.4
22	1	1	−1	−1	0	18.0	27.3
23	−1	0	−1	1	0	7.3	2.4
24	0	1	0	−1	1	17.9	23.7
25	1	−1	1	0	−1	52.9	54.3
26	−1	1	1	0	0	13.2	8.8
27	0	−1	−1	1	1	2.1	4.5
28	1	0	0	−1	−1	73.4	73.9
29	−1	0	1	−1	1	19.6	14.6
30	0	1	−1	0	−1	59.1	41.7
31	1	−1	0	1	0	1.4	2.6
32	−1	1	0	1	−1	7.3	4.8
33	0	−1	1	−1	0	22.3	24.0
34	1	0	−1	0	1	14.1	18.3

and Wong (2009) for a comprehensive review.

There are numerous applications using either 2-level factorial designs or 3-level orthogonal arrays; see Box, Hunter and Hunter (2005), Dean and Voss (1999), Mee (2009), Montgomery (2009), and Wu and Hamada (2009) for examples. However, there are few published applications using both a 2-level factorial design and a 3-level orthogonal array in a single experiment. The goal here is to introduce the idea of combining two- and three-level designs and to provoke future research in the area. In Section 3.2 we formally introduce the concept of OACDs and explore their properties. Advantages include the ability of using resolution IV designs for factor screening, the ability of in-depth analyses, and the capability for sequential experimentation. In Section 3.3 we study the construction of OACDs and present a list of designs with 3 to 10 factors. In Section 3.4 we compare OACDs with other composite designs in terms of such statistical properties as estimation efficiency and projections. In Section 3.5 we consider blocking an OACD in a sequential experiment and give conditions when an OACD can be orthogonally blocked. In Section 3.6 we analyze the data from the antiviral drug experiments: fit three models using different parts of the data and compare the results. Section 3.7 gives a summary.

3.2 Orthogonal-array composite designs

We first give a general definition of composite designs. For k factors, denoted by x_1, ..., x_k, a composite design consists of: (i) n_c cube points $(x_1, \ldots, x_k)$ with all $x_i = -1$ or 1; (ii) n_a additional points with all $x_i = -\alpha, 0$ or α; (iii) n_0 center points with all $x_i = 0$. Note that the cube points have 2 levels and the additional points have 3 levels. A composite design has a total of $n_c + n_a + n_0$ points and has three or five different levels depending on whether $\alpha = 1$ or not. Two-level factorial or fractional factorial designs are often used as the cube points and referred to as the factorial portion. Box and Wilson (1951) and Box and

Hunter (1957) originally proposed to use a full factorial or a fractional factorial design of resolution V in a central composite design (CCD). This can lead to a large number of runs when $k > 5$. To reduce the run sizes, Draper and Lin (1990) proposed small composite designs (SCD) by using Plackett-Burman designs as the factorial portion. In both CCD and SCD, $n_a = 2k$ axial points (with one of $x_i = \alpha$ or $-\alpha$ and all other $x_i = 0$) are chosen as the additional points. Morris (2000) introduced the augmented pairs design (APD) by adding one point for each pair of the cube points. An APD has $n_a = n_c(n_c - 1)/2$ additional points.

We propose to use runs of a 3-level orthogonal array as the additional points and refer to the resulting design as an OACD: an OACD is a composite design such that its n_a additional points form a 3-level orthogonal array. The design in Table 3.1 is a 34-run OACD with $n_c = 16, n_a = 18, n_0 = 0$ and $\alpha = 1$. The factorial portion (the first 16 runs) is a 2-level fractional factorial design with resolution V defined by $I = ABCDE$; the 18 additional runs form a 3-level orthogonal array with a center point (run 18) and no extra center point. We can construct many OACDs with different run sizes by combining readily available 2-level factorial designs and 3-level orthogonal arrays.

Composite designs are often used to fit a second-order model. For k quantitative factors, the second-order model is

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i=1}^{k-1} \sum_{j=i+1}^{k} \beta_{ij} x_i x_j + \epsilon, \tag{3.1}$$

where $\beta_0, \beta_i, \beta_{ii}$ and β_{ij} are the intercept, linear, quadratic and bilinear (or interaction) terms, respectively, and $\epsilon \sim N(0, \sigma^2)$ is the error term. For the quadratic terms β_{ii} to be estimatable, all factors must have at least 3 levels. A design is called a *second-order design* if it allows all parameters in (3.1) to be estimated. The 34-run OACD given in Table 3.1 is a second-order design: we can use the 2-level factorial portion to estimate the linear effects and two-factor interactions among the factors, and use the 3-level orthogonal array to estimate linear and

quadratic effects.

The OACD differs from the CCD or SCD in the way they choose the additional points. The CCD or SCD employs a one-factor-at-a-time approach for the additional points because each axial point has only one nonzero component. As a consequence, the axial points provide no information on bilinear (or interaction) terms; resolution IV designs cannot be used as the two-level portion. For this reason, the SCD must use a resolution III design as the factorial portion even if a resolution IV design with the same size exists. In contrast, the additional points in the OACD study the effects in a factorial fashion and provide new information on bilinear terms as well as linear and quadratic terms. One immediate benefit is that the OACD can use resolution IV designs as the two-level portion, important in a sequential experiment because the OACD can use a better design than the SCD in the initial stage. Thus, to study 6 factors in 16 runs, the OACD approach can use a resolution IV design while the SCD approach has to start with an inferior resolution III design even though a resolution IV design with the same size exists. A resolution IV design enables all linear effects to be estimated apart from any bilinear effects, whereas in a resolution III design some linear effects are fully aliased with bilinear effects. Resolution IV designs are generally preferred to resolution III designs of the same size in the initial screening stage. In Section 3.4 we further demonstrate that using resolution IV designs instead of resolution III designs as the factorial portion leads to more efficient estimation, particularly the estimation of the linear effects.

Another reason for using an orthogonal array as the additional points is data analysis. The analysis of the initial screening stage can suggest some useful, but not conclusive, evidence on the significance of the effects. Even with the added runs the results may not be conclusive due to possible mistakes or errors in the experiment or variation of factors not used in the experiment. The OACD allows one to perform multiple analyses with different parts of the data for cross

validation. One can perform separate analyses for the two-level factorial portion and the three-level orthogonal array (if both have at least 8 runs). For the two-level portion, one can use standard analysis techniques and fit a model with linear and bilinear terms. For the three-level orthogonal array, one can fit a model with linear and quadratic effects. One can further use all of the data and fit a second-order or other model to estimate linear, bilinear and quadratic terms. Then each of the linear effects is estimated three times and each of the bilinear and quadratic effects is estimated twice, and one can check the consistency of the estimations from the three models. If the data are reliable and the models are appropriate, we expect the estimates to be consistent across different models; a discrepancy indicates possible problems with the models or potential outliers. The OACD thus has the build-in ability to perform some cross validation on the data quality and analysis results. We illustrate this in Section 3.6 with the antiviral drug experiment.

Like the CCD, the OACD can be used in a single experiment or in a sequential experiment. An OACD can be used in two ways in a sequential experiment. We can use the 2-level factorial portion in the first stage for factor screening and add the 3-level orthogonal array in the last stage for response surface modeling. Alternatively, we can use the 3-level orthogonal array for screening linear and quadratic effects in the initial stage and add the two-level portion for exploring the bilinear effects in the last stage. This feature is particularly appealing in practice as many industrial and engineering experiments use 3-level orthogonal arrays under the name of the Taguchi method. For example, we can use the popular $OA(18, 3^7)$ to study 5 or 6 factors in the screening experiment and use a 8 or 16-run two-level factorial in a follow-up experiment. Cheng and Wu (2001) and Xu, Cheng, and Wu (2004) previously studied methods of using a single 3-level design for both factor screening and response surface exploration. Their designs are not intended for sequential experiments.

3.3 Construction of the OACD

To construct an OACD, we need to select a 2-level design and a 3-level orthogonal array. In many cases, several 2-level and 3-level designs are available and the choice of individual designs is important. A general guideline is that we use good or optimal 2-level and 3-level designs, then properly align their columns so that the resulting OACD has good or optimal properties with respect to some criterion of interest.

For the 2-level design, we can choose a 2^k full factorial (if $k \leq 4$) or a regular 2^{k-p} fractional factorial design. When choosing a regular fraction, we recommend a minimum aberration design (which always has maximum resolution). Wu and Hamada (2009) gave many minimum aberration designs, up to 128 runs. To have a smaller design, we can use Plackett-Burman designs as the factorial portion, see Draper and Lin (1990). We recommend the generalized minimum aberration criterion (Tang and Deng (1999); Xu and Wu (2001)) to choose columns among Plackett-Burman designs. The generalized minimum aberration criterion is an extension of the minimum aberration criterion and can screen out poor designs effectively. Generalized minimum aberration designs minimize the overall contamination of nonnegligible interactions on the estimation of main effects (Tang and Deng (1999); Xu and Wu (2001)) and tend to be model-robust under traditional model-dependent efficiency criteria (Cheng, Deng and Tang (2002)).

For the 3-level portion, one can pick an orthogonal array that accommodates at least k 3-level factors and choose the minimum aberration or generalized minimum aberration subset. Once a 2-level and a 3-level design is chosen, they can be put together to form an OACD. For example, the 34-run OACD given in Table 3.1 is a simple combination of a minimum aberration 2_V^{5-1} design, $E = ABCD$, and a generalized minimum aberration five-column design that is a subdesign of the commonly used $OA(18, 3^7)$. The levels, $-1, 0$, and 1, in the 3-level orthogonal

array can be rescaled to $-\alpha, 0$ and α if necessary.

The properties of the resulting design may depend on which 2-level column is aligned with which 3-level column. A naive approach that puts two designs together works well and resulting designs often have good properties when we combine optimal 2-level and 3-level designs. In some situations, one can improve the properties of resulting designs by carefully aligning 2-level and 3-level columns. Each OACD has a total $k!$ different column alignments. One approach, when k is small, is to search all $k!$ alignments and find an optimal column alignment with respect to some criterion. This exhaustive search can be time consuming and often unnecessary for large k, say $k > 10$. A second more practical approach is to try a number of random alignments and choose the best column alignment with respect to some criterion.

A 3-level orthogonal array may contain a center point already and the number of extra center points (n_0) can be as small as 0. When $\alpha = 1$, the 2-level design and the 3-level orthogonal array may have some common runs so that the resulting OACD has repeat runs; for example, runs 16 and 19 in Table 3.1 are the same. If desirable one can avoid any repeat runs by permuting the levels in some columns of the 2-level or 3-level design, but repeat runs are useful in estimating the pure error and therefore we recommend keeping them. Furthermore, keeping them allows separate analyses for the two-level and three-level data. In cases where the run size is critical, one can delete the repeat runs.

For comparison purposes in Section 3.4, we list two OACDs for $k = 3$ and three OACDs for $k = 4, \ldots, 10$ in Table 3.2. The first column in Table 3.2 corresponds to the number of factors, k. The next three columns correspond to the two-level factorial portion: the specific design used, the number of cube points (n_c), and the design generators or columns. Here a 2^k design is a full factorial and no generators or columns are given. A 2_r^{k-p} design is a regular fractional factorial design with k factors, each at two levels, consisting of 2^{k-p} runs, and of resolution

r. The p generators are given in the fourth column. All the 2^{k-p} designs used in Table 3.2 have maximum resolution and minimum aberration. There are six cases where Plackett-Burman designs with 12 or 20 runs are used, and the fourth column shows the subset of the design. For convenience, the Plackett-Burman designs are given in the Appendix. The last two columns in Table 3.2 specify the 3-level orthogonal array: the specific design and the column choice. We use four commonly used orthogonal arrays of strength 2, namely $OA(9, 3^4)$, $OA(18, 3^7)$, $OA(27, 3^{13})$, and $OA(36, 3^{13})$; see the Appendix. The $OA(9, 3^4)$ and $OA(27, 3^{13})$ are regular fractional factorial designs. For convenience, we arrange $OA(27, 3^{13})$ according to Xu (2005) so that the first k columns form a minimum aberration design. All 3-level columns in Table 3.2, with the exception of $k = 6$, are chosen because they form a minimum aberration or generalized minimum aberration design. For $k = 6$, the generalized minimum aberration design from $OA(18, 3^7)$ consists of the column choice $(2-7)$; however, this choice does not lead to a second-order design when it is combined with the 12-run Plackett-Burman design. For this reason, we choose the first 6 columns.

Table 3.2: Some OACDs for $k = 3, \ldots, 10$

	2-level factorial portion			3-level OA	
k	Design	n_c	Columns and generators	Design(n_a)	Columns
3	2^3	8	-	OA(9)	(1-3)
3	2^{3-1}_{III}	4	$C = AB$	OA(9)	(1-3)
4	2^4	16	-	OA(9)	(1-4)
4	PB(12)	12	(1-4)	OA(9)	(1,3,4,2)
4	2^{4-1}_{IV}	8	$D = ABC$	OA(9)	(1-4)
5	2^{5-1}_{V}	16	$E = ABCD$	OA(18)	(2-6)
5	PB(12)	12	(1-5)	OA(18)	(2,5,3,4,6)
5	2^{5-2}_{III}	8	$D = ABC, E = AB$	OA(18)	(2-4,6,5)
6	2^{6-1}_{VI}	32	$F = ABCDE$	OA(18)	(1-6)
6	PB(20)	20	(1-5,13)	OA(18)	(1,4,6,3,2,5)
6	PB(12)	12	(1-5,7)	OA(18)	(2,5,3,4,6,1)
7	2^{7-1}_{VII}	64	$G = ABCDEF$	OA(18)	(1-7)
7	2^{7-2}_{IV}	32	$F = ABCD, G = ABE$	OA(18)	(1,2,5,3,4,7,6)
7	PB(20)	20	(1-5,13,16)	OA(18)	(3,1,5,7,4,2,6)
8	2^{8-2}_{V}	64	$G = ABCDE, H = ABCF$	OA(27)	(1-8)
8	2^{8-3}_{IV}	32	$F = ABCD, G = ABE, H = ACE$	OA(27)	(1,3,4,5,2,7,8,6)
8	PB(20)	20	(1-5,13,16,15)	OA(27)	(6,3,8,4,2,1,7,5)
9	2^{9-2}_{V}	128	$H = ABCDE, J = ABCFG$	OA(27)	(1-9)
9	2^{9-3}_{IV}	64	$G = ABCDE, H = ABCF, J = ADF$	OA(27)	(1,3,8,2,6,7,5,4,9)
9	2^{9-4}_{IV}	32	$F = ABCD, G = ABE, H = ACE, J = ADE$	OA(27)	(5,6,1,7,2,4,9,3,8)
10	2^{10-3}_{V}	128	$H = ABCDE, J = ABCFG, K = ABDF$	OA(27)	(1-10)
10	2^{10-4}_{IV}	64	$G = ABCDE, H = ABCF, J = ADF, K = ABEF$	OA(27)	(5,6,8,2,3,4,10,7,9,1)
10	2^{10-5}_{IV}	32	$F = ABCD, G = ABE, H = ACE, J = ADE,$ $K = BCDE$	OA(36)	(7,6,3,2,9,1,10,8,5,4)

We arrange the 3-level columns in Table 3.2 so that when the 2-level and 3-level designs are combined, the resulting OACD is optimal with respect to D-efficiency (defined in Section 3.4.2) under the second-order model. For example, consider the second design listed for $k = 5$ in Table 3.2. For the 2-level factorial portion we use a subset of a 12-run Plackett-Burman design with columns (1-5) and for the 3-level design we use an $OA(18, 3^7)$ with columns (2,5,3,4,6). The resulting OACD has maximum D-efficiency when columns (1,2,3,4,5) of the Plackett-Burman design are aligned with columns (2,5,3,4,6) of the $OA(18, 3^7)$, respectively.

We present two or three OACDs with different sizes in Table 3.2 for each k. We call them OACD X, OACD Y, and OACD Z, corresponding to the largest, the second largest, and the smallest run size, respectively. The three OACDs are chosen based on popular existing designs and run size consideration. In particular, for each k, the OACD X has a similar run size to the CCD and the OACD Z has a comparable run size to the SCD. It is possible to construct other OACDs with different sizes and properties, especially when $k \geq 6$, if we combine different 2-level or 3-level designs. In practice, one can choose or construct an OACD based on the consideration of the run size or design efficiency, which is to be discussed in the next session.

3.4 Comparisons with existing composite designs

We compare the OACDs given in Table 3.2 with three classes of composite designs: the CCD, APD, and SCD. The factorial portion of the CCD is a minimal fractional factorial design (or full factorial plan) of resolution V in all k factors. In all cases, the CCD and OACD X have the same factorial portion. The factorial portion used in the APD is the 8-run Plackett-Burman design for $k = 4, \ldots, 7$, and the 12-run Plackett-Burman design for $k = 8, \ldots, 10$; see Morris (2000). The factorial portion in the SCD is taken from a Plackett-Burman design according to Table 4 of Draper and Lin (1990). In the study performed by Morris (2000), the SCD

Table 3.3: Comparison of the number of runs and degrees of freedom, with $n_0 = 5$

	CCD		APD		SCD		OACD X		OACD Y		OACD Z	
k	N	df	N	df	N	df	N	df	N	df	N	df
3	19	4	15	4	15	4	22	7	18	4	-	-
4	29	4	41	8	21	4	30	6	26	7	22	5
5	31	4	41	6	27	4	39	6	35	6	31	6
6	49	4	41	4	33	4	55	5	43	5	35	5
7	83	4	41	4	43	4	87	4	55	4	43	5
8	85	4	83	4	57	4	96	4	64	4	52	5
9	151	4	83	4	63	4	160	5	96	4	64	4
10	153	4	83	4	73	4	160	4	96	4	73	4

for $k = 9$ was omitted due to singularity. We believe that the reason for the singularity is that Morris used a cyclical shift to the right when constructing Plackett-Burman designs, whereas Draper and Lin (1990) performed a cyclical shift to the left, which allows the SCD of 9 factors to be considered.

We need to specify the value of α and number of center points for comparison. Following Morris (2000), we choose $\alpha = 1$ so that all designs have 3 levels and are comparable, and five center points ($n_0 = 5$). Note that the number of center points is arbitrarily chosen, and can vary depending on the experimental requirements. As pointed out by Morris (2000), the choice of the number of center points can greatly influence the estimation efficiency of a design; however, the general relationship between designs remains roughly the same.

3.4.1 Number of runs and degrees of freedom

An important concern in the construction of experimental design is the trade-off between estimation efficiency and run size. Generally, a design with smaller number of runs is favorable due to cost; however, designs with a larger number of runs provide more efficiency. Table 3.3 compares the total number of runs, N, and the degrees of freedom, df, for replication for each design considered.

The CCD and OACD X have larger run sizes than other classes with the

exception of $k = 4$ and 5, when the APDs have the largest run sizes. The SCD and OACD Z have smaller run sizes than others with the exception of $k = 3$ and 7.

All designs have at least 4 degrees of freedom for pure error estimation, corresponding to the original 5 center point replicates taken. Generally, the OACD X, Y, and Z have more degrees of freedom for error estimation than the other designs, hence have a larger number of runs.

3.4.2 Model coefficient estimation

We compare design efficiencies in parameter estimation, D optimality the popular choice in this. For an N-point design, if X is the model matrix of the second-order model (3.1) with $p = (k + 1)(k + 2)/2$ parameters, the (overall) D-efficiency is $D = N^{-1}|X'X|^{1/p}$, describing the information per run for the design. For s, a subset of factors, the D_s-efficiency is

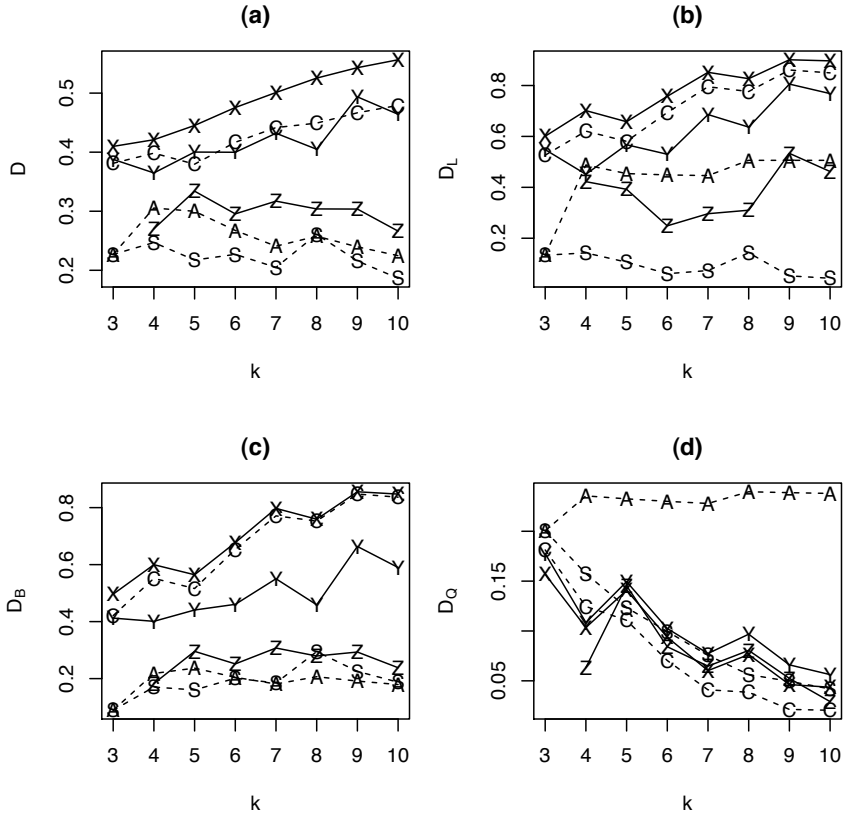
$$D_s = N^{-1}|X_s^T X_s - X_s^T X_{(s)}(X_{(s)}^T X_{(s)})^{-1} X_{(s)}^T X_s|^{1/q},$$

where X_s and $X_{(s)}$ are the submatrices of X corresponding to the parameters in s and not in s, respectively, and q is the number of parameters in s.

We divide the model parameters into three groups: the k linear parameters $(\beta_i, i = 1, \ldots, k)$, the $k(k-1)/2$ bilinear parameters $(\beta_{ij}, 1 \leq i < j \leq k)$, and the k pure quadratic parameters $(\beta_{ii}, i = 1, \ldots, k)$. For each subset of the model parameters we compute the D_s-efficiency, D_L, D_B, and D_Q, say.

Figure 3.1 shows a graphical representation of the D-efficiencies of the designs under consideration for $k = 3, \ldots, 10$. Figure 3.1(a) compares overall D-efficiency for all designs. Generally, OACD X has the highest D-efficiency, followed by CCD and OACD Y. The overall D-efficiency for OACD Z is higher than the APD and SCD, except for $k = 4$. Figure 3.1(b) shows D_L-efficiency. The general pattern is similar to the overall D-efficiency considered in Figure 3.1(a): the OACD X has

Figure 3.1: Efficiencies of composite designs with $n_0 = 5$: (a) D-efficiency; (b) D_L-efficiency; (c) D_B-efficiency; (d) D_Q-efficiency. Composite design (symbol): APD (A), CCD (C), SCD (S), OACD-X (X), OACD-Y (Y) and OACD-Z (Z).



the highest efficiency followed by the CCD and then the OACD Y. Figure 3.1(c) shows D_B-efficiency. The OACD X has slightly higher D_B-efficiency than the CCD, followed by the OACD Y; the OACD Z, APD, and SCD are similar in their efficiencies. Figure 3.1(d) shows D_Q-efficiency. For all k, the APD has the highest efficiency, with the exception of $k = 3$, where the SCD performs just as well. The other designs are all comparable.

For the OACDs in Table 3.2, the 2-level and 3-level columns are aligned to maximize overall D-efficiency. For OACD X, the D-efficiency is invariant under the column alignment since $X'X$ does not depend on the 2-level design when it is a full factorial or has resolution V. For OACD Y and Z, the D-efficiency could

be reduced, often slightly, with a random alignment; however, a few alignments could result in designs with D-efficiency of 0 for the OACD Y with $k \geq 8$ and the OACD Z with $k \geq 6$ due to small run sizes.

Among the three types of OACDs in Table 3.2, OACD X has the highest efficiency and largest run size, and OACD Z has the smallest run size and lowest efficiency. If the primary goal is precise estimations OACD X is recommended; if the runs are expensive and a small design is desirable, OACD Z is recommended. The OACD Y design compromises on run size and design efficiency and could be a better choice in other situations.

The original 34-run OACD used in the antiviral experiment was OACD X for $k = 5$. The comparison in Figure 3.1 confirms that the 34-run OACD is more effective than the CCD or other designs in estimating the parameters.

3.4.3 Projection properties

An OACD design has a simple and appealing structure when it is projected onto any two factors. The two-level portion produces four corner points $(\pm 1, \pm 1)$, each replicated $n_c/4$ times. When $\alpha = 1$, the three-level orthogonal array generates four corner points, four mid-side points $(0, \pm 1)$ or $(\pm 1, 0)$, and one center point $(0, 0)$, each replicated $n_a/9$ times.

Figure 3.2 gives a graphical representation of the projection properties for the six designs for $k = 4$, with $n_0 = 0$: CCD, APD, SCD, OACD X, OACD Y, and OACD Z. Each plot shows the number of design points in each corner, mid-side, and center, in a two-dimensional projection. Roughly speaking, more design points located at the corners leads to higher D, D_L and D_B efficiency, while more design points located at the mid-sides and center increases quadratic efficiency. The OACDs have relatively more corner points and less center point replicates than CCD, APD, and SCD. This is desirable for achieving high overall efficiency. The APD has more mid-side points than any of the other designs, which explains

why the estimates for the quadratic effects are more efficient.

3.5 Blocking the OACD

When OACDs are used in a sequential experiment, it is important to know how blocking affects the design properties and efficiency. A second-order design is said to *block orthogonally* if it is divided into blocks in such a manner that block effects do not affect the usual estimates of the parameters of the second-order model.

Box and Hunter (1957) showed that, in general, for a second order composite design to block orthogonally with N number of points assigned to b blocks with n_w points in the wth block, two conditions must hold.

1. Each block is a first-order orthogonal design, so,

$$\sum_{u=1}^{n_w} x_{iu}x_{ju} = 0, \qquad i \neq j = 0, 1, \ldots, k, \qquad \text{for all w,}$$

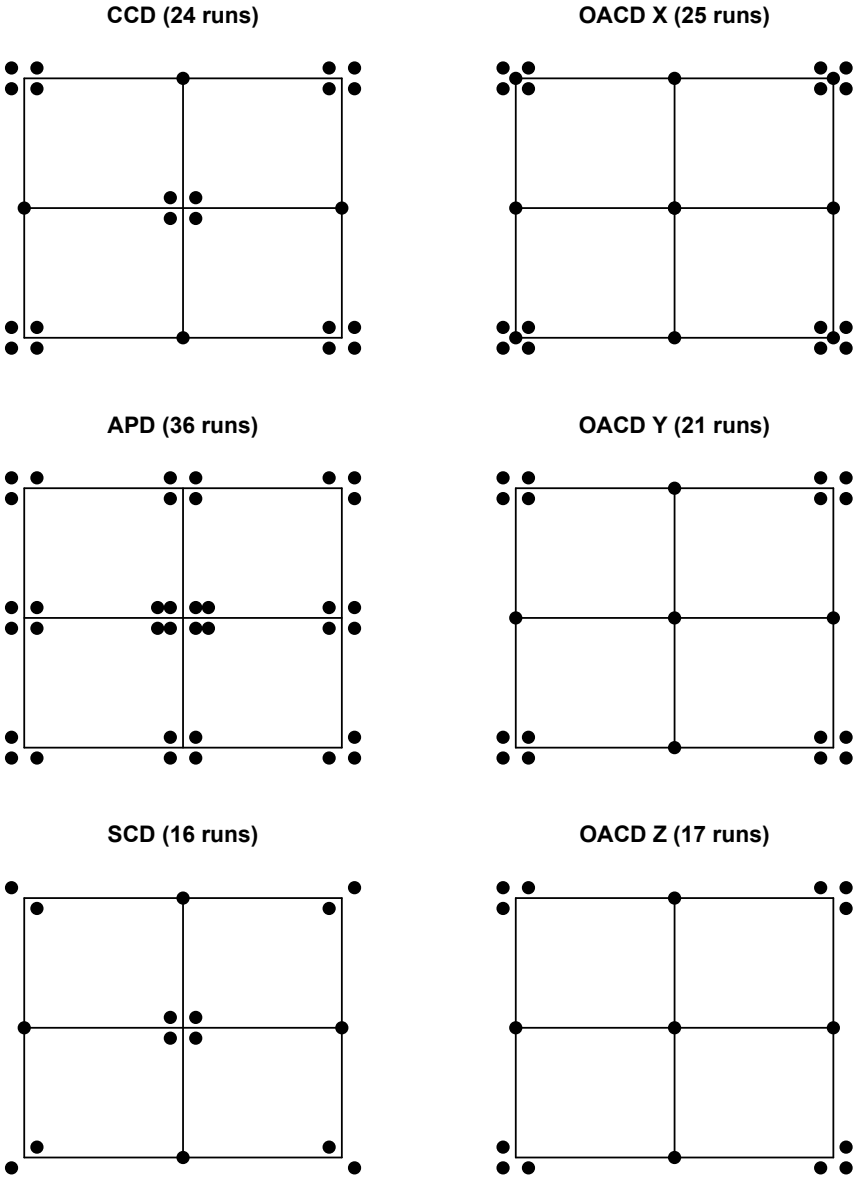
   where x_{iu} and x_{ju} are the levels of the ith and jth variables in the uth run of the wth block with $x_{0u} = 1$ for all u.

2. The fraction of the total sum of squares for each variable contributed by every block is equal to the fraction of the total observations that occur in the block, so,

$$\frac{\sum_{u=1}^{n_w} x_{iu}^2}{\sum_{u=1}^{N} x_{iu}^2} = \frac{n_w}{N} \qquad i = 1, 2, \ldots, k \qquad \text{for all w.}$$

These conditions can be used to orthogonally block an OACD. For simplicity, we consider arranging an OACD in two blocks. The first block consists of a two-level fractional factorial design (with n_c runs) plus n_{c0} center points, and the second block consists of a three-level orthogonal array (with n_a runs) plus n_{a0} center points. The first condition is always valid because the fractional factorial

Figure 3.2: Projection properties of composite designs in four factors, with n_0=0



and additional points are orthogonal. The second condition is equivalent to

$$\alpha = \sqrt{\frac{3n_c(n_a + n_{a0})}{2n_a(n_c + n_{c0})}}. \tag{3.2}$$

We obtain orthogonal blocking if we choose α according to (3.2) and, in particular, when $n_{a0} = n_{c0} = 0$, the choice of $\alpha = \sqrt{3/2}$ yields an orthogonal blocking.

3.6 Analysis of the antiviral drug experiment

Here we illustrate the analysis strategy for the OACD with the antiviral drug experiment in Table 3.1. Following Ding et al. (2012b), in the analysis we use the square root of the readout as the response so that the usual assumptions on the error are reasonable. We include a blocking variable (*replicate*) in the model to assess possible effects from the two researchers. It is coded as -1 for replicate 1 and 1 for replicate 2.

We began the analysis by fitting a standard second-order model plus the blocking variable using all of the data to estimate the linear, bilinear, and quadratic effects. The model fit the data very well with $R^2 = 0.96$. To verify that this is a reasonable model, we broke the data into: the first 16 and the last 18 runs. For the two-level 16-run design we fit a model containing all linear and bilinear effects. For the 18-run orthogonal array we fit a model with all linear and pure quadratic terms. To distinguish the three models, we use the run sizes and refer to them as 34-run, 16-run, 18-run models, respectively. Table 3.4 shows the estimates of the parameters for the three models. Each linear effect is estimated three times and each bilinear and quadratic effect is estimated twice. Among the three models, the 16-run model fits the 16-run data the best with $R^2 = 0.98$ while the 18-run model fits the worst with $R^2 = 0.92$. Figure 3.3 compares the absolute values of the t statistics for these three models, where the dashed and dotted lines correspond to a t value of 2 and 3, respectively.

Table 3.4: Estimates of parameters for the HSV-1 data

	34-Run	16-Run	18-Run
Intercept	3.99 ***	4.61***	3.62***
A	-0.13	-0.27**	0.18
B	-0.23**	-0.28 **	-0.42*
C	-0.20*	-0.14	-0.39*
D	-2.07***	-2.15***	-1.97***
E	-1.22***	-1.11***	-1.31***
AB	0.12	0.14	-
AC	0.26**	0.16	-
AD	0.08	0.18	-
AE	-0.13	-0.11	-
BC	0.14	0.27**	-
BD	-0.09	-0.07	-
BE	0.13	0.13	-
CD	-0.11	-0.13	-
CE	0.05	0.07	-
DE	0.54***	0.51***	-
A^2	0.26	-	0.38
B^2	0.09	-	0.22
C^2	-0.01	-	0.11
D^2	-1.17***	-	-1.07***
E^2	1.41***	-	1.47***
$replicate$	-0.03	-0.05	-0.01
$\hat{\sigma}$	0.55	0.48	0.78
R^2	0.96	0.98	0.92
df	46	15	24

NOTE: Significance levels are coded as 0 (***) 0.001 (**) 0.01 (*) 0.05.

Figure 3.3: Analysis of the antiviral drug experiment

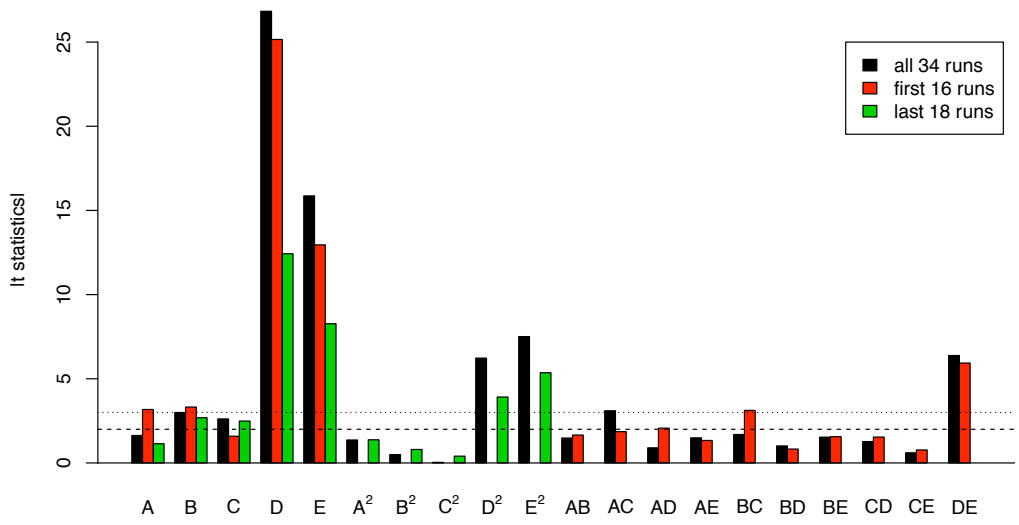


Figure 3.3 clearly shows that the linear effects D and E, the bilinear effect DE, and the quadratic terms D^2 and E^2 are consistently the most significant (p value < 0.001) terms. With, D, E, DE, D^2, and E^2 having estimates over the three models of approximately, -2, -1.2, 0.5, -1.1, and 1.4, respectively; see Table 3.4. The blocking variable (replicate) is not significant among all models, indicating that there was no significant difference between the two researchers.

We also observed some discrepancy among the estimates from different models. Among the bilinear effects, AC was significant (p value < 0.01) in the 34-run model only and BC was significant (p value < 0.01) in the 16-run model only. This is due to different data being used to fit different models with quite distinct aliasing or correlation structure. Here AC and BC were highly correlated with the five extremely significant effects (D, E, DE, D^2, and E^2) in the full second-order model, whereas all estimates in the 16-run model were uncorrelated. Among the linear effects, A, B and C were identified as significant at the 0.05 or 0.01 levels in one or more models. The estimates of A are negative in the 34-run and 16-run models but the estimate is positive in the 18-run model. This discrepancy is caused by the significant bilinear terms not included in the 18-run model. When we fit

a new model by adding the interaction DE in the 18-run model, the estimates of D and E remain unchanged and the estimates of A, B, and C were -0.01, -0.23 and -0.20, respectively, closer in value to the estimates in the 34-run and 16-run models. Further, the R^2 value in the 18-run design with DE included increased from 0.92 to 0.95 and the residual standard error ($\hat{\sigma}$) decreased from 0.78 to 0.60.

We performed residual analysis and found that replicate 1 of run 14 was an outlier. We refit the 34-run and 16-run models without it and found similar results with the addition that AB was significant in the 34-run model at the 0.05 level and AB and AC were significant in the 16-run model at the 0.05 level.

Overall, the data analysis identifies D and E as effective drugs, each having nonlinear (quadratic) effects on HSV-1. Drugs A, B, and C have some, but much smaller effects, than D and E. We further saw strong interaction between D and E, and some mild significant interactions among A, B and C. This can be explained by the fact that D and E are chemical drugs, while A, B, and C are Interferon protein drugs. The data suggest that the interactions within the Interferon and chemical drug groups are significant, which agrees with published reports from clinical trials (Sainz and Halford (2002); Terzano, Petroianni and (Ricci 2004)). The data further suggest that the interactions between the two groups are small, implying possible distinct antiviral pathways between these two drug categories.

3.7 Summary

We propose a class of new composite designs, OACDs, and study the construction and properties. The OACD designs provide a good trade-off between estimation efficiency and run size economy, and can be used as an alternative to the popular CCD and other existing composite designs.

We provide a general guideline in the construction of OACDs and present a

collection of OACDs based on popular 2-level and 3-level designs. Our use of regular designs can be done with suitable nonregular designs. Nonregular designs are flexible in terms of run sizes and have many appealing properties (Xu, Phoa, and Wong (2009)), so we can construct a wide range of OACDs based on available nonregular designs. We will further explore the properties and use of these OACDs in the future.

Appendix Tables

PB(12)

Run	1	2	3	4	5	6	7	8	9	10	11
1	+	+	−	+	+	+	−	−	−	+	−
2	−	+	+	−	+	+	+	−	−	−	+
3	+	−	+	+	−	+	+	+	−	−	−
4	−	+	−	+	+	−	+	+	+	−	−
5	−	−	+	−	+	+	−	+	+	+	−
6	−	−	−	+	−	+	+	−	+	+	+
7	+	−	−	−	+	−	+	+	−	+	+
8	+	+	−	−	−	+	−	+	+	−	+
9	+	+	+	−	−	−	+	−	+	+	−
10	−	+	+	+	−	−	−	+	−	+	+
11	+	−	+	+	+	−	−	−	+	−	+
12	−	−	−	−	−	−	−	−	−	−	−

PB(20)

Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−
2	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+
3	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+
4	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−
5	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−	−
6	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−	−
7	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+	−
8	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−	+
9	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+	−
10	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−	+
11	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+	−
12	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+	+
13	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+	+
14	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	+
15	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+
16	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−
17	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+	−
18	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+	+
19	+	−	−	+	+	+	+	−	+	−	+	−	−	−	−	+	+	−	+
20	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

OA(9)

Run	1	2	3	4
1	−	−	−	−
2	−	0	0	+
3	−	+	+	0
4	0	−	0	0
5	0	0	+	−
6	0	+	−	+
7	+	−	+	+
8	+	0	−	0
9	+	+	0	−

OA(18)

Run	1	2	3	4	5	6	7
1	−	−	−	−	−	−	−
2	−	0	0	0	0	0	0
3	−	+	+	+	+	+	+
4	0	−	−	0	0	+	+
5	0	0	0	+	+	−	−
6	0	+	+	−	−	0	0
7	+	−	0	−	+	0	+
8	+	0	+	0	−	+	−
9	+	+	−	+	0	−	0
10	−	−	+	+	0	0	−
11	−	0	−	−	+	+	0
12	−	+	0	0	−	−	+
13	0	−	0	+	−	+	0
14	0	0	+	−	0	−	+
15	0	+	−	0	+	0	−
16	+	−	+	0	+	−	0
17	+	0	−	+	−	0	+
18	+	+	0	−	0	+	−

OA(27)

Run	1	2	3	4	5	6	7	8	9	10	11	12	13
1	−	−	−	−	−	−	−	−	−	−	−	−	−
2	−	−	0	0	−	+	0	+	+	−	0	0	+
3	−	−	+	+	−	0	+	0	0	−	+	+	0
4	−	0	−	0	+	0	−	0	+	0	0	+	−
5	−	0	0	+	+	−	0	−	0	0	+	−	+
6	−	0	+	−	+	+	+	+	−	0	−	0	0
7	−	+	−	+	0	+	−	+	0	+	+	0	−
8	−	+	0	−	0	0	0	0	−	+	−	+	+
9	−	+	+	0	0	−	+	−	+	+	0	−	0
10	0	−	−	0	0	0	0	−	0	0	−	0	0
11	0	−	0	+	0	−	+	+	−	0	0	+	−
12	0	−	+	−	0	+	−	0	+	0	+	−	+
13	0	0	−	+	−	+	0	0	−	+	0	−	0
14	0	0	0	−	−	0	+	−	+	+	+	0	−
15	0	0	+	0	−	−	−	+	0	+	−	+	+
16	0	+	−	−	+	−	0	+	+	−	+	+	0
17	0	+	0	0	+	+	+	0	0	−	−	−	−
18	0	+	+	+	+	0	−	−	−	−	0	0	+
19	+	−	−	+	+	+	+	−	+	+	−	+	+
20	+	−	0	−	+	0	−	+	0	+	0	−	0
21	+	−	+	0	+	−	0	0	−	+	+	0	−
22	+	0	−	−	0	−	+	0	0	−	0	0	+
23	+	0	0	0	0	+	−	−	−	−	+	+	0
24	+	0	+	+	0	0	0	+	+	−	−	−	−
25	+	+	−	0	−	0	+	+	−	0	+	−	+
26	+	+	0	+	−	−	−	0	+	0	−	0	0
27	+	+	+	−	−	+	0	−	0	0	0	+	−

OA(36)

Run	1	2	3	4	5	6	7	8	9	10	11	12
1	−	−	−	0	0	−	−	0	−	+	+	−
2	−	−	−	−	+	−	+	−	+	−	−	0
3	−	−	0	−	−	+	0	+	−	−	0	−
4	−	−	+	+	−	0	−	−	0	0	−	−
5	−	0	+	+	−	−	0	0	+	−	+	+
6	−	0	+	0	+	0	+	+	+	+	0	−
7	−	0	−	−	+	+	−	+	0	0	+	+
8	−	0	0	+	0	+	+	−	−	+	−	+
9	−	+	0	+	0	−	−	+	+	0	0	0
10	−	+	0	−	−	0	+	0	0	+	+	0
11	−	+	+	0	+	+	0	0	−	0	−	0
12	−	+	−	0	0	0	0	−	0	−	0	+
13	0	0	0	+	+	0	0	+	0	−	−	0
14	0	0	0	0	−	0	−	0	−	0	0	+
15	0	0	+	0	0	−	+	−	0	0	+	0
16	0	0	−	−	0	+	0	0	+	+	0	0
17	0	+	−	−	0	0	+	+	−	0	−	−
18	0	+	−	+	−	+	−	−	−	−	+	0
19	0	+	0	0	−	−	0	−	+	+	−	−
20	0	+	+	−	+	−	−	0	0	−	0	−
21	0	−	+	−	+	0	0	−	−	+	+	+
22	0	−	+	0	0	+	−	+	+	−	−	+
23	0	−	−	+	−	−	+	+	0	+	0	+
24	0	−	0	+	+	+	+	0	+	0	+	−
25	+	+	+	−	−	+	+	−	+	0	0	+
26	+	+	+	+	0	+	0	+	0	+	+	−
27	+	+	−	+	+	0	−	0	+	+	−	+
28	+	+	0	0	+	−	+	+	−	−	+	+
29	+	−	0	0	+	+	−	−	0	+	0	0
30	+	−	0	−	0	−	0	0	0	0	−	+
31	+	−	+	+	0	0	+	0	−	−	0	0
32	+	−	−	0	−	0	0	+	+	0	+	0
33	+	0	−	0	−	+	+	0	0	−	−	−
34	+	0	−	+	+	−	0	−	−	0	0	−
35	+	0	0	−	0	0	−	−	+	−	+	−
36	+	0	+	−	−	−	−	+	−	+	−	0

CHAPTER 4

Application of Blocked Fractional Factorial Designs for Discrete Choice Experiments

A discrete choice experiment is an attribute based method that gives further insight into how individuals develop preferences for particular attributes. They are used in the traditional areas in health economics, transportation, marketing, and increasingly beyond these areas. However, there is limited work on designs for such studies to date. Motivated by the need for smaller optimal discrete choice experiments, we propose a novel application of blocked factorial designs for designing discrete choice experiments. Our method provides smaller choice experiments for estimating main effects with 100% efficiency at lower costs and require a shorter time to run. In addition, we propose the use of less commonly used resolution IV designs for constructing discrete choice experiments. With these designs all main effects are clear and thus unbiased and in many cases we have the added advantage of some clear two-factor interactions that can be estimated as well. An illustrative application involving consumer preference for trans-Atlantic flight travel for estimating main effects and some two-factor interactions for binary attributes is provided. We then demonstrate how these techniques can be extended for three-level attributes as well as asymmetric attributes.

4.1 Introduction

The process of making decisions is a daily activity. Decision making starts early in the morning and continues throughout the day. Decisions can range from what to eat for breakfast (based on nutrition, quality, price, or even quantity) to the modes of transportation (personal vehicle, bus, taxi, subway - based on price, time, or location). Hensher (1989) considered the valuation of travel timesavings from various modes of transportation and Van der Waerden et al. (2006) studied the transportation mode choice decisions. These are just a few examples of decisions that we encounter on a daily basis. Decisions must also be made on important and long-term issues, such as which healthcare provider to use or which medical treatment to receive. Bryan et al. (2002) studied patient preference for particular health care programs. Other researchers have studied patience preference for certain medical treatments, such as McKenzie et al. (2001) studied methods to assess patient preferences for Asthma medications and Ryan M et al. (2005) considered patient preference for prenatal diagnostic testing for Down syndrome. A Discrete choice experiment (DCE) can be used to give further insight into these choices. It is an attribute based method for measuring a respondent's preference and is quickly on the rise in numerous fields of research. From academic researchers to professional marketers in areas such as health economics, transportation, and many others. A DCE presents respondents with several choice sets of hypothetical scenarios, where each choice set is made up of 2 or more options.

Various techniques for constructing and analyzing discrete choice experiments have been proposed in the literature. For example, Street and Burgess focus on the construction of optimal DCEs and their research varies from experiments with two-level attributes to mixed level designs, see among others, Street et al. (2001),

Burgess and Street (2003), Street et al. (2005), and Burgess and Street (2005). Grossmann et al. (2012) construct DCEs for paired designs, i.e., choice sets with two options, for the estimation of first-order interactions for two-level attributes. Grasshoff et al. (2012) derive locally optimal designs for DCEs to improve those in the literature under the multinomial logit model. Recently, Li et al. (2012) studied the voice of the customer by designing robust DCEs. A comprehensive review on DCEs can be found in Louviere et al. (2003) and some unresolved issues in designing and analyzing DCEs can be found in Louviere (2006). A more focused review on DCEs in health economics can be found in Bekker-Grob et al. (2010). In our paper, we focus on comparing our proposed construction technique with the well established and widely accepted Street and Burgess (2007) method. We call DCEs constructed by the Street and Burgess (2007) method, Street and Burgess designs.

Published literature on DCEs primarily focuses on the parameter estimation and there is limited publications on the construction techniques. Louviere (2006) points out the importance of the design and states that "researchers should recognize that the designs chosen for DCEs are at least as, if not more important than, the models that one uses to analyze the resulting data." Therefore, the design itself should be provided within the publication for others to verify and replicate.

Current techniques for constructing DCEs predominately estimate main effects only, or main effects plus all two-factor interactions. Designs that estimate main effects only are good because they present a small number of choice sets, but assume that all two-factor interactions and higher are negligible. While this assumption is commonly accepted for the construction of DCEs estimating main effects, it is a strong assumption to make that may not always be correct to assume. Designs that estimate main effects plus all two-factor interactions assume

that all three-factor interactions and higher are negligible, a weaker and more generally accepted assumption. However, these designs often present too many choice sets for the respondents cognitive ability.

Motivated by the need for smaller optimal designs we propose the use of blocked fractional factorial designs for constructing DCEs. The concept of blocking naturally extends itself to the area of DCEs. Each choice set, is an inherent block. There are many recent studies on the optimal choices of blocking schemes for fractional factorial designs; see, among others: Sun et al. (1997); Sitter et al. (1997); Chen and Cheng (1999); Cheng and Wu (2002); Xu (2006); Xu and Lau (2006); Xu and Mee (2010). However, the practitioners in DCEs do not seem to be aware of the recent developments of blocked fractional factorial designs. We demonstrate that by using blocked fractional factorial designs we have ability to substantially decrease the number of choice sets posed to the respondent, while estimating the same number of effects as previous construction techniques.

The goal of this paper is to introduce blocked factorial designs to the area of DCEs providing smaller choice experiments for estimating main effects and main effect plus some two-factor interactions with 100% efficiency. Paired DCEs have been extensively studied and shown to be optimal or near-optimal for binary attributes. However, there is less research on choice experiments with choice sets of size 4 or larger, partially because the situation is more complicated than paired designs. In this paper we focus on DCEs with choice sets of size 4. Burgess and Street (2006) establish the D-optimal choice set size under the MNL model and find that generally choice sets of size 2 are rarely the most efficient size to use. Therefore, the size of the choice set should be as large as the respondent can handle. The larger the choice set, the larger the value of the determinant of the optimal design, and thus the more efficient the design (Burgess and Street 2006).

The paper is organized as follows. Section 4.2 starts with a trans-Atlantic airline example, which is used to illustrate various techniques, and then gives background on DCEs and factorial designs. In Section 4.3, we describe in detail how blocked factorial designs can be used for DCEs to estimate main effects, as well as some two-factor interactions. We focus on DCEs with choice sets of size 4 and give examples to show that blocked fractional factorial designs produce smaller numbers of choice sets, for estimating all main effects, than the Street and Burgess designs. We also give examples to show that how blocked fractional factorial designs can be used to estimate all main effects and some two-factor interactions, under the weak assumption that all three-factor interactions and higher are negligible. We give a table of blocked factorial designs for DCEs with binary attributes and choice sets of size 4.4. The run sizes of these designs are in general a half or one quarter of the size of the corresponding Street and Burgess designs so that the number of choice sets posed to the respondent is reduced by a half or three quarters. In Section 4.4, we explain how the methodology can be extended to multi-level or mixed-level DCEs.

4.2 Background

4.2.1 The trans-Atlantic airline example

Consider the following scenario from Green (1974). In this example, we are concerned with the consumer preference for trans-Atlantic travel and the effect of various attributes. Green considers the effects of nine attributes with varying levels. For the purpose of this paper, rather than using Green's full example, we consider a modified version and select 7 two-level attributes: departure time of the airplane relative to the consumers most preferred time (within 4 hours and

within 1 hour), the anticipated plan load (90% full and 50% full), the number of stops enroute to the destination (one stop and non-stop), the price of the airline ticket (full economy fare and 15% discount off full fare), the punctuality of arrival time at the destination (within 2 hours of scheduled time and within 1/2 of scheduled time), the quality of service offered to customers on the flight (average and superior), and the meal variety (one entree and choice of two entrees). These attributes and their levels are presented in Table 4.1. In this example, $k = 7$, $l_j = 2$, and $j = 1, \ldots, 7$. These attributes are then combined to create choice sets, which are then shown to the respondents who are asked to choose which option they prefer. A sample choice set with $m = 4$ options is presented in Table 4.2. Here the respondent must select one of the four options. In other words, the respondent is forced to choose one of the options presented; this is known as a forced choice experiment. This choice set can be represented by the four options coded as (0011111, 0110000, 1000010, 1101101). This design is considered a symmetric design since all 7 attributes have the same number of levels. The responses from these choice sets can then be used to estimate the effect each attribute has on trans-Atlantic flight choice and possibly estimate the effect of the interaction between any two of the attributes on trans-Atlantic flight choice.

4.2.2 Discrete choice experiments

The first step in the construction of a DCE is to define the problem of interest. Once the problem of interest has been defined we then determine the relevant attributes and their respective levels. Next, an appropriate experimental design and model choice are chosen (Ryan et al. 2008). In this paper, we focus on the construction of discrete choice experiments and the selection of the appropriate experimental design, a critical part in the construction of a discrete choice exper-

Table 4.1: Attributes and levels for trans-Atlantic travel

Attributes	**Attribute levels**	**Coded levels**
x_1: Departure time	Within 4 hours	0
	Within 1 hour	1
x_2: Anticipated plane load	90% full	0
	50% full	1
x_3: Number of stops enroute	One stop	0
	Non-stop	1
x_4: Price	Full economy fare	0
	15% discount off full fare	1
x_5: Arrival time punctuality	Within 2 hours of scheduled time	0
	Within 1/2 of scheduled time	1
x_6: In-flight service	Average	0
	Superior	1
x_7: Meal variety	One entree	0
	Choice of two entrees	1

Table 4.2: Which of the following 4 options do you prefer? Please only select one.

Attribute	Option 1	Option 2	Option 3	Option 4
Departure time	within 4 hrs	within 4 hrs	within 1 hr	within 1 hr
Anticipated plan load	90% full	50% full	90% full	50% full
Number of stops	non-stop	non-stop	one stop	one stop
Price	15% discount	full fare	full fare	15% discount
Arrival time	within 0.5 hr	within 2 hrs	within 2 hrs	within 0.5 hr
In-flight service	superior	average	superior	average
Meal variety	two	one	one	two

iment. We use techniques from traditional factorial designs to combine the given attributes and their levels into treatment combinations, forming individual choice sets. Each choice set is made up of m options (or alternatives). Each option is then described by k attributes, denoted here as: $x_1, x_2, \ldots, x_k$. The j^{th} attribute has l_j levels, $j = 1, \ldots, k$ (coded $0, 1, \ldots, l_j - 1$). Respondents are then shown these choice sets and asked which option they prefer.

Once the choice sets have been constructed, we then derive the information matrix to determine the properties of the corresponding design. The information matrix, C, is defined to be $C = X'\Lambda X$ (Street and Burgess, 2007), where X is the the matrix of contrasts for the effects to be estimated, i.e., the main effects or main effects plus some two-factor interactions, and Λ is the matrix of second derivatives of the likelihood function. Under the null hypothesis of no difference between the effects of the levels of each attribute, the matrix of second derivatives Λ can be evaluated by counting the occurrences of pairs of profiles (each profile is a treatment combination) and dividing by $m^2 n$ where n is the number of choice sets. The diagonal entries are chosen so that the row and column sums of Λ are 0.

The DCE estimates and designs can be compared by using the form of the information matrix. If the information matrix is diagonal, then all effects are independently estimated. The generalized variance, or the determinant of the variance-covariance matrix, $\det(C^{-1})$, can be used to compare different designs. The determinant of the variance-covariance matrix needs to be as small as possible, or equivalently to maximize the determinant of the information matrix, i.e., we want $\det(C)$ to be as large as possible (Atkinson and Donev 1992). Therefore, the design with the largest determinant of the information matrix, is said to be the D-optimal design. The information matrix of the D-optimal design is defined

as C_{opt}. The D-efficiency for any design d with information matrix C_d can be calculated as,

$$\text{D-efficiency} = [\frac{det(C_d)}{det(C_{opt})}]^{1/p}, \tag{4.1}$$

where p is the number of parameters to be estimated, i.e., number of columns in X. When estimating main effects only $p = k$, and when estimating main effects plus all two factor interactions $p = k+k(k-1)/2$. The D-efficiency of the optimal design is 100%.

There are various ways to analyze the results from a DCE and in this paper we assume that the multinomial logit (MNL) model is used. The MNL model is used to describe the attractiveness of each attribute on the product of interest. This model has the benefit of simplicity of estimation and interpretation, but comes at the cost of some restrictive assumptions. The MNL model assumes that the random error is independently and identically distributed as an extreme value type I random variable with a mean of zero. That is, we assume that the unobserved attributes have the same variance for all options in each choice set and that these attributes are uncorrelated over all options in each choice set (Train 2003). Given the strict assumptions for the MNL model researchers in the area of DCEs are currently working on other approaches with less restrictive assumptions. However, the purpose of this paper is to demonstrate a new application of blocked fractional factorial design to construct optimal DCEs with fewer choice sets.

4.2.3 Factorial designs

The idea of combining attributes and their levels into treatment combinations to form a DCE corresponds directly to the use of factorial designs from the area

of experimental design. Factorial designs are very efficient for studying two or more factors, or attributes. In the area of experimental design the term factor is used, while in the area of DCEs the term attribute is used, the two can be used interchangeably. Consider a DCE described by k attributes each at two levels. This class of designs then requires 2^k combinations or runs of the k factors at the two levels. This is referred to as a 2^k full or complete factorial design. A full factorial design has the advantage of being able to estimate all main effects plus all interaction effects. However, in many experiments, we often find that higher order interactions, such as three-factor and higher, are usually not important. In addition, full factorial designs are often too large and costly to perform. Therefore, using a full factorial design is quite wasteful.

A more practical and economical approach is to use a fractional factorial design that allows the estimation of lower-order effects (Wu and Hamada 2009). Here, the researcher selects a subset, or fraction, of the full factorial design. A (regular) fractional factorial design with k factors in 2^{k-p} runs is said to be a $2^{-p}th$ fraction of the full 2^k design, with p defining words. A word is the numbers or letters used to denote the attributes: traditionally denoted as $A, B, \ldots$; however, in this paper we use $x_1, x_2, \ldots, x_k$ or $1, 2, \ldots, k$. The group formed by these words is called the treatment defining contrast subgroup (Wu and Hamda 2009). The length of the shortest word is the resolution of the design. In order to obtain a smaller number of runs by using a fractional factorial design, one willingly trades off the measurement of possible interaction effects (Green 1974). That is, some attributes may be aliased with other attributes, i.e, their estimates are not distinguishable from another. The resolution of a design identifies which effects are estimable (Ryan, Gerard, Amaya-Amaya 2008). Throughout the paper we consider regular 2^{k-p} designs, where any two effects are either orthogonal or fully aliased.

A main effect or two-factor interaction is said to be *clear* if none of its aliases are main effects or two-factor interactions (Wu and Hamada 2009). We can estimate clear main effects or two-factor interactions under the weak assumption that all three-factor interactions and higher are negligible, without having to assume negligibility on other two-factor interactions.

Current construction techniques for the estimation of main effects begin with a starting design of at least resolution III. Resolution III designs are good because of their smaller size; however, a resolution III design for the estimation of main effects could be misleading because some main effects are correlated with the unobserved interaction effects, leading to biased estimates of the main effects. On the other hand, construction techniques for the estimation of main effects plus all two-factor interactions begin with at least a resolution V design; however, these designs expand rapidly with the number of attributes and levels and are often too large and unnecessary.

In addition to using resolution III and V designs to construct DCEs, we propose the use of less commonly used resolution IV designs for constructing DCEs. There are two advantages for considering a resolution IV design. With a resolution IV design all main effects are clear and can always be estimated unbiasedly. Therefore, with a resolution IV design we do not need to assume any two-factor interactions negligible to (clearly) estimate the main effects. Second, with many resolution IV designs, in addition to being able to estimate all main effects, we also can estimate some clear two-factor interactions.

Table 4.3 shows the corresponding run sizes for resolution III, IV, and V designs for $k = 4, \ldots, 9$ factors or attributes. The run sizes for resolution IV designs, primarily fall between the resolution III and V designs. For $k = 4$ attributes, a resolution III and IV design may have the same number of runs, but a resolution

Table 4.3: Run sizes for resolution III, IV, and V designs; $k = 4, \ldots, 9$ attributes

k:	4	5	6	7	8	9
III	8	8	8	8	16	16
IV	8	16	16	16	16	32
V	-	16	32	64	64	128

IV design has the added advantage that all main effects are clear. Comparing resolution IV and V designs, all except for $k = 5$ attributes, resolution IV designs have half, or even less than half, the runs of a resolution V design.

4.3 Blocked factorial designs for discrete choice experiments

4.3.1 Blocked factorial designs

To construct a blocked fractional factorial design we deliberately confound, i.e., confuse, an interaction effect with a block effect, limiting the ability to estimate the two effects separately in exchange for higher precision because the differences associated between blocks are eliminated (Box, Hunter, and Hunter 2005). For a blocked fractional factorial design, a main effect or two-factor interaction is said to be *clear* if it is not aliased with any other main effects, two-factor interactions, or confounded with any block effects (Wu and Hamada 2009). A clear effect can be estimated under the weak assumption that all three-factor interactions and higher are considered negligible.

To block a 2^{k-p} fractional factorial design in 2^q blocks defined by q independent contrasts (blocking variables) we have two defining contrast subgroups: one for defining the fraction and the other for the blocking scheme, known as the treatment defining contrast subgroup and the block defining contrast subgroup,

respectively. All effects, including any aliased effects, which are associated with these blocking variables, are confounded with the blocks (Wu and Hamada 2009).

To illustrate the concept of blocked fractional factorial designs consider the following example. Begin with a $2^{4-1} = 8$-run resolution IV ($k = 4$ and $p = 1$) fractional factorial design in 2^2 blocks ($q = 2$). Each block is of size 2 (2^{k-p-q}). This design has 1 treatment generator: $x_4 = x_1x_2x_3$ and 2 block generators: $b_1 = x_1x_2$ and $b_2 = x_1x_3$. The equation $I = x_1x_2x_3x_4$ is called the treatment defining contrast subgroup, which consists of each treatment generator and the product of the treatment generators. The block defining contrast subgroup is: $b_1 = x_1x_2$, $b_2 = x_1x_3$, and $b_3 = b_1b_2 = x_2x_3$. The block effect b_1 is confounded with the two-factor interaction x_1x_2. Additionally, b_1 is confounded with the two-factor interaction x_3x_4 because we multiply each word within the treatment defining contrast subgroup by b_1; denoted as $b_1 = x_1x_2 = x_3x_4$. Similarly for b_2 and b_3. In this design, all 4 main effects are clear. This blocked fractional factorial design can then be used to construct a DCE. In this example each of the $2^q = 2^2 = 4$ blocks corresponds to a choice set and the size of the block $2^{k-p-q} = 2^{4-1-2} = 2$ represents the size of the choice set, i.e., the number of options within each choice set.

We should point out that fractional factorial designs are constructed under the usual general linear model $y = X\beta + \epsilon$, where the error ϵ is normally distributed. The design properties are determined by the usual information matrix $X'X$. As mentioned earlier, for DCEs we employ a MNL model with an extreme value error distribution and the information matrix is $C = X'\Lambda X$. Nevertheless, under the null hypothesis of no difference between the treatments, there is a close connection between $X'X$ and C. For instance, consider a blocked $2^{4-1} = 8$-run resolution IV ($k = 4$ and $p = 1$) fractional factorial design in 2^1 blocks ($q = 1$). This design has 1

treatment generator: $x_4 = x_1x_2x_3$ and 1 block generator: $b_1 = x_1x_2$. The defining contrast subgroup is $I = x_1x_2x_3x_4$. Since this design is of resolution IV all 4 main effects are clear; however, each two-factor interaction is aliased with another two-factor interaction, i.e., $x_1x_2 = x_3x_4, x_1x_3 = x_2x_4$, and $x_1x_4 = x_2x_3$. The block effect, b_1, is confounded with the interactions x_1x_2 and x_3x_4, i.e., $b_1 = x_1x_2 = x_3x_4$. Table 4.4 shows the scaled information matrices $X'X$ and C as an unblocked design and blocked DCE design. Notice that both matrices are block diagonal and the sub-matrices for the four main effects are diagonal so that the main effects are clear and can be estimated independent of each other and any two-factor interactions. The two matrices differ in rows and columns x_1x_2 and x_3x_4. As an unblocked design, we can estimate x_1x_2 if x_3x_4 is negligible or vice verse. As a blocked DCE design, we cannot estimate either x_1x_2 or x_3x_4 because they are confounded with the block effect.

Table 4.4: Scaled information matrices as an unblocked and blocked 2^{4-1} design

(a) $X'X/8$

	x_1	x_2	x_3	x_4	x_1x_2	x_1x_3	x_1x_4	x_2x_3	x_2x_4	x_3x_4
x_1	1	0	0	0	0	0	0	0	0	0
x_2	0	1	0	0	0	0	0	0	0	0
x_3	0	0	1	0	0	0	0	0	0	0
x_4	0	0	0	1	0	0	0	0	0	0
x_1x_2	0	0	0	0	1	0	0	0	0	1
x_1x_3	0	0	0	0	0	1	0	0	1	0
x_1x_4	0	0	0	0	0	0	1	1	0	0
x_2x_3	0	0	0	0	0	0	1	1	0	0
x_2x_4	0	0	0	0	0	1	0	0	1	0
x_3x_4	0	0	0	0	1	0	0	0	0	1

(b) $C = X'\Lambda X$

	x_1	x_2	x_3	x_4	x_1x_2	x_1x_3	x_1x_4	x_2x_3	x_2x_4	x_3x_4
x_1	1	0	0	0	0	0	0	0	0	0
x_2	0	1	0	0	0	0	0	0	0	0
x_3	0	0	1	0	0	0	0	0	0	0
x_4	0	0	0	1	0	0	0	0	0	0
x_1x_2	0	0	0	0	0	0	0	0	0	0
x_1x_3	0	0	0	0	0	1	0	0	1	0
x_1x_4	0	0	0	0	0	0	1	1	0	0
x_2x_3	0	0	0	0	0	0	1	1	0	0
x_2x_4	0	0	0	0	0	1	0	0	1	0
x_3x_4	0	0	0	0	0	0	0	0	0	0

In a blocked factorial design, any effect that is not confounded with a block effect can be estimated in the usual way, i.e., an effect can be estimated if its alias is assumed negligible. However, we cannot estimate an effect that is confounded with a block effect. The following theorem illustrates this result for the general 2-level blocked fractional factorial design.

Theorem 1. *A blocked 2^{k-p} design in 2^q blocks can be used to construct a DCE experiment with $n = 2^q$ choice sets of $m = 2^{k-p-q}$ options, where each block forms a choice set. An effect that is not confounded with any block effects is estimable under the assumption that all of its alias are negligible.*

The proof of Theorem 1 can be found in the Appendix. As a result, the concept of aliasing and clear effects from the area of traditional fractional factorial designs directly translates over to the area of DCEs. This founding was also reported by Grossmann et al. (2002) for the paired DCEs with $m = 2$ options. Hence, compared to other construction methods, by using blocked factorial designs we have the advantage of knowing the precise aliasing structure for the entire DCE. All DCEs constructed using a blocked factorial design for the estimation of the clear effects are always D-optimal and 100% efficient.

4.3.2 Estimating main effects

Consider the modified trans-Atlantic airline example and we want to construct a DCE with choice sets of size 4 for the estimation of the main effects using a blocked factorial design.

Example 1. *Begin with a blocked 2^{7-3} ($k = 7$, $p = 3$) fractional factorial design in 2^2 blocks ($q = 2$) of resolution IV. We have 4 blocks, or choice sets, and block sizes of 4 (2^{7-3-2}), or 4 options for each choice set. This design has treatment*

Table 4.5: Blocked factorial design for main effects only and choice sets of size 4

Blocks	x_1	x_2	x_3	x_4	x_5	x_6	x_7
1	0	1	1	0	0	1	1
1	0	1	1	1	0	0	0
1	1	0	0	0	1	1	1
1	1	0	0	1	1	0	0
2	0	1	0	0	1	1	0
2	0	1	0	1	1	0	1
2	1	0	1	0	0	1	0
2	1	0	1	1	0	0	1
3	0	0	1	0	1	0	1
3	0	0	1	1	1	1	0
3	1	1	0	0	0	0	1
3	1	1	0	1	0	1	0
4	0	0	0	0	0	0	0
4	0	0	0	1	0	1	1
4	1	1	1	0	1	0	0
4	1	1	1	1	1	1	1

generators: $x_5 = x_1x_2x_3, x_6 = x_1x_2x_4$, *and* $x_7 = x_1x_3x_4$ *and block generators:* $b_1 = x_1x_2$ *and* $b_2 = x_1x_3$ *and is presented in Table 4.5. Blocks 1 through 4 correspond to the 4 choice sets, and the size of the blocks, 4, represents the number of options within each choice set. For example, block 1, represents the first choice set (0110011, 0111000, 1000111, 1001100). Since this design has resolution IV, the main effects are not aliased with any two-factor interactions and thus all seven main effects are clear and can be independently estimated.*

In comparison, using the Street and Burgess method, to estimate main effects begin with a starting design F of at least resolution III and a set of generators G.

Example 2. *Let the starting design F be the* 2^{7-4} *fractional factorial design in 8 runs, or choice sets. This design has treatment generators* $x_4 = x_1x_2, x_5 =$

Table 4.6: Street and Burgess design for main effects only and choice sets of size 4

F	F+g_2	F+g_3	F+g_4
0000000	0000111	1111000	1111111
1010101	1010010	0101101	0101010
0110011	0110100	1001011	1001100
1100110	1100001	0011110	0011001
0001111	0001000	1110111	1110000
1011010	1011101	0100010	0100101
0111100	0111011	1000100	1000011
1101001	1101110	0010001	0010110

$x_1x_3, x_6 = x_2x_3$, *and* $x_7 = x_1x_2x_3$. *Since the smallest word in the treatment defining contrast subgroup is of length 3 this design is said to be of resolution III. The 8 treatment combinations for this particular design are presented under the column F of Table 4.6. This fraction then becomes the profiles presented in option 1 for each choice set. To obtain choice sets each with 4 options we need* $m = 4$ *generators:* g_1, g_2, g_3, g_4, *where* $g_1 = (0000000)$. *Let* G *be the set of generators:* $G = (g_1, g_2, g_3, g_4)$, *such that the differences in the difference vector sum to* $\frac{m^2k}{4} = 28$ *(Street and Burgess 2007). One such set of generators is* $G = (0000000, 0000111, 1111000, 1111111)$ *(Street and Burgess 2007, page 272). Therefore, the 8 choice sets are constructed as* $(F, F + g_2, F + g_3, F + g_4)$, *where the addition is performed modulo 2. These choice sets are presented in Table 4.6, where each row represents a choice set and each column represents options 1 through 4. With this Street and Burgess design, we have the ability to estimate all 7 main effects under the assumption that all two-factor interactions are negligible.*

Comparing these two examples, it is clear that the blocked factorial design in Example 1 has half the number of choice sets as the Street and Burgess design in

Example 2. The former has 4 choice sets each with 4 options, while the latter has 8 choice sets each with 4 options.

Now consider choice sets of size 2 for the estimation of main effects using a blocked factorial design.

Example 3. *Begin with the same blocked* 2^{7-3} *factorial design used in Example 1, but now arrange it into* 2^3 *blocks* ($q = 3$) *with one additional block generator:* $b_3 = x_1x_4$. *The additional block generator splits the 4 blocks of size 4 into 8 blocks of size 2. Each of 8 blocks consists of a foldover pair. For example, one of block consists of pair (0111000, 1000111); another block consists of pair (0110011, 1001100). All seven main effects are clear.*

Similarly, we can construct a DCE using the Street and Burgess method for choice sets of size 2.

Example 4. *Using the same starting design F in Example 2, we can construct a DCE for the estimation of main effects in choice sets of size 2 with a set of generators* $G = (0000000, 1111111)$. *That is, we pair each row with its foldover. This DCE also has 8 choice sets each with 2 options.*

Considering choice sets of size 2, Examples 3 and 4 are directly comparable in terms of the number of choice sets. However, there are some exceptions where a blocked factorial design may reduce the number of choice sets in comparison to the Street and Burgess designs for choice sets of size 2. Consider the blocked 2^{4-1} factorial design in 2^2 blocks presented in Section 4.3.1, this DCE has 4 choice sets each of size 2. In comparison, the Street and Burgess method would require 8 choice sets each of size 2 if the starting design is a resolution III design. By using the blocked factorial design, we reduce the number of choice sets by half, while

still estimating the same number of effects. Other small optimal paired DCEs for the estimation of main effects only can be found in Grasshoff et al. (2004).

4.3.3 Estimating main effects plus some two-factor interactions

Designs that consider the interactions between attributes allow the researcher to see which attributes depend on the levels of other attributes. To illustrate, in the trans-Atlantic airline example consumers might classify their airline choice based on price, but it may also depend on the departure time, the planeload, or other attributes. That is, the consumer may have a specific price set in their mind when going to purchase their airfare, but also takes into account other factors, such as the time in which their plane departs, etc.

However, more commonly, DCEs are designed for the estimation of main effects. While designs for the estimation of main effects plus all two-factor interactions are available, these designs require a starting design of at least resolution V and are often too large in terms of the number of choice sets and place a cognitive burden on the respondent. Researchers are exploring various way to construct DCEs that allow the estimation of main effects plus some pre-specified two-factor interactions, while reducing the number of choice sets. For example, Chen and Chitturi (2011) consider the estimation of subsets of interactions inclusive of one factor for 2^n and 3^n plans based on Pareto optimal choice sets.

In this section we propose the use of blocked factorial designs of at least resolution IV to estimate main effects plus some selected two-factor interactions, while reducing the number of choice sets. The use of designs of at least resolution IV allow all main effects to be clear plus select two-factor interactions are also clear. These designs present the respondent with either the same, or even less, choice sets than current construction techniques.

Consider the 7 two-level attributes in the modified trans-Atlantic airline example. To construct a DCE for the estimation of main effects plus some two-factor interactions, with choice sets of size 4, we begin with a $2^{7-2} = 32$ run ($k = 7, p = 2$) resolution IV fractional factorial design in 2^3 ($q = 3$) blocks each of size 4 (2^{k-p-q}). This design has treatment generators: $x_6 = x_1x_2x_3$ and $x_7 = x_1x_2x_4x_5$ and block generators: $b_1 = x_2x_3x_4$, $b_2 = x_2x_3x_5$, and $b_3 = x_1x_3x_4x_5$. With this design we have 8 choice sets each with 4 options, and seven clear main effects as well as 12 clear two-factor interactions: $x_1x_4, x_1x_5, x_1x_7, x_2x_4, x_2x_5, x_2x_7, x_3x_4, x_3x_5, x_3x_7$, x_4x_6, x_5x_6, and x_6x_7. As a result of using the blocked factorial design we have the ability to estimate each of the seven attributes presented in Table 4.1 as well as 12 of their interactions. When considering which flight to book the consumer would typically focus on the interaction between the plane departure time and the price of the airfare (x_1x_4), or the departure time and the arrival time (x_1x_5). With this design we have the ability to clearly estimate these interaction effects.

The number of choice sets in this example, a blocked factorial design, is the same as the number of choice sets in Example 2, a Street and Burgess design. The Street and Burgess design in Example 2 is indeed identical to a blocked 2^{7-2} fractional factorial design in 2^3 blocks with treatment generators $x_6 = x_1x_2x_5$ and $x_7 = x_1x_3x_5$ and block generators $b_1 = x_1x_2, b_2 = x_1x_3, b_3 = x_1x_4$. This identical design is of resolution IV and all 7 main effects are clear plus 3 clear two-factor interactions: x_4x_5, x_4x_6, and x_4x_7. However, the blocked factorial design presented here has 9 more clear two-factor interactions than the identical Street and Burgess design.

Hence, the number of clear two-factor interactions depends on the design generators and block generators or the starting design F and the generator G. Different fractions and generators lead to different designs with different numbers of clear

two-factor interactions. The blocked factorial designs we present in the next subsection are optimal in the sense that they always have the maximum number of clear two-factor interactions.

4.3.4 Tables of blocked factorial designs for discrete choice experiments

To construct a paired DCE design, a simple method exists (Xu 2006): use an even design and pair each run with its foldover; see Example 5 in Section 4.3.2. A design is called an even design if all words in its treatment defining contrast subgroup have even lengths.

Table 4.7 presents blocked fractional factorial designs to construct DCEs for choice sets of size 4 ($m = 4$) and $k \leq 9$ attributes. Five sizes of choice experiments each with 4 options are given in Table 4.7: 2 choice sets, 4 choice sets, 8 choice sets, 16 choice sets, and 32 choice sets. Presented in Table 4.7 are: k - the number of attributes, p - the number of treatment (or design) generators, q - the number of block generators, design generators, block generators, and clear effects — main effects and/or two-factor interactions. Note that the design generators and block generators are in terms of single numbers rather than the subset x notation previously being used, i.e., $x_1, x_2, \ldots$. For example, instead of using $x_1, x_2, \ldots, x_k$, to represent the attributes, we now use numbers: $1, 2, 3, 4, \ldots$ to define each attribute. Table 4.7 is adapted from Appendices 4A and 5B of Wu and Hamada (2009). Blocked factorial designs with $k > 9$ attributes are available in Xu and Lau (2006) and Xu and Mee (2010).

Table 4.7: Blocked DCEs with $m = 4$ options.
Note: ME's (main effects) and 2fi's (two-factor interactions).

k	p	q	Design generators	Block generators	Clear effects
2 choice sets					
3	0	1	—	$b_1 = 123$	all 3 ME's plus all 3 2fi's
4	1	1	4=123	$b_1 = 12$	all 4 ME's
5	2	1	4=12, 5=13	$b_1 = 23$	none
6	3	1	4=12, 5=13, 6=23	$b_1 = 123$	none
4 choice sets					
4	0	2	—	$b_1 = 134$, $b_2 = 234$	all 4 ME's plus all 2fi's except: 12
5	1	2	5=1234	$b_1 = 12$, $b_2 = 13$	all 5 ME's, 14, 15, 24, 25, 34, 35,45
6	2	2	$5 = 12, 6 = 134$	$b_1 = 13$, $b_2 = 14$	3, 4, 6, 23, 24, 26, 35, 45, 56
7	3	2	$5 = 123, 6 = 124, 7 = 134$	$b_1 = 12$, $b_2 = 13$	all 7 ME's
8	4	2	$5 = 123, 6 = 124, 7 = 134, 8 = 234$	$b_1 = 12$, $b_2 = 13$	all 8 ME's
9	5	2	$5 = 12, 6 = 13, 7 = 14, 8 = 234, 9 = 1234$	$b_1 = 23$, $b_2 = 24$	none
8 choice sets					
5	0	3	—	$b_1 = 135$, $b_2 = 235$, $b_3 = 1234$	all 5 ME's plus all 2fi's except: 12, 34
6	1	3	6=12345	$b_1 = 135$, $b_2 = 235$, $b_3 = 145$	all 6 ME's plus all 2fi's except: 12, 34, 56
7	2	3	6=123, 7=1245	$b_1 = 234$, $b_2 = 235$, $b_3 = 1345$	all 7 ME's, 14, 15, 17, 24, 25, 27, 34, 35, 37, 46, 56, 67
8	3	3	$6 = 123, 7 = 124, 8 = 1345$	$b_1 = 13$, $b_2 = 23$, $b_3 = 14$	all 8 ME's, 15, 18, 25, 28, 35, 38, 45, 48, 56, 57, 58, 68, 78
9	4	3	$6 = 123, 7 = 124, 8 = 134, 9 = 2345$	$b_1 = 12$, $b_2 = 13$, $b_3 = 14$	all 9 ME's, 15, 19, 25, 29, 35, 39, 45, 49, 56, 57, 58, 59, 69, 79, 89
16 choice sets					
6	0	4	—	$b_1 = 136$, $b_2 = 1234$, $b_3 = 3456$, $b_4 = 123456$	all 6 ME's plus all 2fi's except: 12, 34, 56
7	1	4	7=12345	$b_1 = 12$, $b_2 = 34$, $b_3 = 135$, $b_4 = 16$	all 7 ME's plus all 2fi's except: 12, 16, 26, 34, 57
8	2	4	7=1234, 8=1256	$b_1 = 13$, $b_2 = 14$, $b_3 = 25$, $b_4 = 26$	all 8 ME's plus 12, 15, 16, 17, 18, 23, 24, 27, 28, 35, 36, 37, 38, 45, 46, 47, 48, 57, 58, 67, 68
9	3	4	$7 = 123, 8 = 1245, 9 = 1346$	$b_1 = 12$, $b_2 = 13$, $b_3 = 14$, $b_4 = 56$	all 9 ME's plus 15, 16, 18, 19, 25, 26, 28, 29, 35, 36, 38, 39, 45, 46, 48, 49, 57, 58, 59, 67, 68, 69, 78, 79
32 choice sets					
7	0	5	—	$b_1 = 1236$, $b_2 = 12347$, $b_3 = 12456$, $b_4 = 134567$, $b_5 = 234567$	all 7 ME's plus all 2fi's except: 12, 13, 23, 45, 67
8	1	5	8=123456	$b_1 = 12$, $b_2 = 13$, $b_3 = 45$, $b_4 = 46$, $b_5 = 147$	all 8 ME's plus all 2fi's except: 12, 13, 23, 45, 46, 56, 78

9	2	5	8=12345, 9=12367	$b_1 = 123$, $b_2 = 14$, $b_3 = 25$, $b_4 = 16$, $b_5 = 27$	all 9 ME's plus all 2fi's except: 14, 16, 25, 27, 38, 39, 46, 67, 89

Consider an example and suppose that we have 9 attributes each with two levels and we want choice sets of size 4. Using Table 4.7 we have 4 blocked fractional factorial designs to choose from. The design choice can be made depending on the problem of interest. First, consider the estimation of main effects only. For the estimation of main effects begin with a resolution III 2^{9-5} fractional factorial design in 2^2 blocks ($k = 9, p = 5, q = 2$). This design has 4 choice sets each with 4 options. With treatment generators $x_5 = x_1x_2, x_6 = x_1x_3, x_7 = x_1x_4, x_8 = x_2x_3x_4, x_9 = x_1x_2x_3x_4$, or using the new notation $5 = 12, 6 = 13, 7 = 14, 8 = 234, 9 = 1234$, and block generators $b_1 = 23$ and $b_2 = 24$. In this particular design none of the main effects are clear and we can only estimate the main effects under the assumption that all two-factor interactions aliased with the main effects are assumed to be negligible. In comparison to a Street and Burgess design with 9 attributes and choice sets of size 4 for the estimation of main effects, the smallest such starting design F of resolution III, is a 16-run fractional factorial design. This design requires a DCE with 16 choice sets. Consequently by using a blocked fractional factorial design to construct a DCE, we reduce the number of choice sets to one-quarter of the size of a Street and Burgess design, while estimating the main effects with the same amount of precision.

For each main effect to be clear for 9 attributes and choice sets of size 4, we need to consider designs with at least resolution IV. To illustrate, using Table 4.7 we have 3 choice experiment sizes to consider. We may either construct a DCE with 8 choice sets, 16 choice sets, or 32 choice sets. Since all 3 of these designs are of at least resolution IV, then all main effects are clear. In addition these designs

Table 4.8: Cost saving in terms of the number of choice sets

k	Blocked factorial designs	Street and Burgess designs
4	2	8
5	2	8
6	2	8
7	4	8
8	4	16
9	4	16

Note: For the estimation of main effects and $m = 4$ options.

have an added benefit of clearly estimating some two-factor interactions. The 8, 16, and 32 choice sets each have 15, 24, and 27 clear two-factor interactions, respectively.

By using a blocked factorial design with choice sets of size 4, the number of choice sets presented to the respondent is much smaller than previously constructed two-level choice experiments. Table 4.8 shows that for estimating main effects only the number of choice sets presented to the respondent by using blocked factorial designs is generally one-quarter of the size in comparison to the Street and Burgess designs. Except for $k = 7$, where the number of choice for a blocked factorial design is half the size of the number of choice sets for a Street and Burgess design. Therefore, by using a blocked fractional factorial design to construct a DCE, with 4 options, we have the ability to substantially decrease the number of choice sets presented to the respondent, while estimating the same number of effects with equal precision and 100% efficiency.

4.4 Extensions

In the previous section, we have focused on constructing discrete choice experiments using blocked fractional factorial designs for binary attributes. The methodology and procedures described for binary attributes can easily be extended for

three level attributes as well as asymmetric attributes.

To construct a blocked factorial design for three-level attributes is merely identical to the binary case. Appendix 6B of Wu and Hamada (2009) gives efficient blocking schemes for 9-, 27-, and 81- run designs. These designs can then be used to construct DCEs for three-level attributes and the estimation of main effects. For example, suppose that a researcher is interested in 9 attributes each with three levels and wants to construct choice sets of size 3. We can find a $3^{9-6} = 27$-run design of resolution III in $3^2 = 9$ blocks each of size $3^{9-6-2} = 3$. This design has treatment generators: $4 = 12, 5 = 123, 6 = 12^2 3, 7 = 13^2, 8 = 23^2$, and $9 = 12^2 3^2$ and block generators: $b_1 = 12^2$ and $b_2 = 23$. Here $9 = 12^2 3^2$ represents $x_9 = x_1 + 2x_2 + 2x_3 \pmod 3$, see Wu and Hamada (2009) for generating three-level blocked factorial designs. This design presents the respondent with 9 choice sets each of size 3. However, a comparable Street and Burgess design would require 27 choice sets each of size 3, 3 times the blocked factorial design. Typically, for the estimation of main effects for three-level attributes and choice sets of size 3, blocked factorial designs require only one-third of the Street and Burgess designs. We shall point out that in Appendix 6B.2 of Wu and Hamada (2009) there is a typo in the treatment generators. The generator should be $G = AC^2$ not $G = AB^2$ (or in our notation $7 = 13^2$ not $7 = 12^2$) for $k = 8$ and 9. The correct generators can be found in Cheng and Wu (2002).

Now consider the estimation of main effects for asymmetric attributes. Mixed-level orthogonal arrays (Wu and Hamada 2009, Chapter 8), with the addition of the block effect, can be used for the construction of asymmetric DCEs because of their run size economy and great flexibility. There are various methods for constructing mixed level orthogonal arrays, see Wu and Hamada (2009), Dey (1985), Wang and Wu (1991), and Hedayat et al. (1999). To construct a mixed level or-

thogonal array, with the addition of the block effect, for asymmetric attributes we use the following notation: $OA(N, B^1 s_1^{n_1} s_2^{n_2} \dots s_j^{n_j}, t)$, where N is the total number of runs in the design, B^1 is the total number of blocks/choice sets, $s_1^{n_1}, \dots, s_j^{n_j}$ are the levels of the $k = n_1 + \dots + n_j$ attributes, and t is the strength of the design. To estimate main effects only we use orthogonal arrays of strength 2, equivalently designs of resolution III. To ensure that all main effects are clear, orthogonal arrays of strength 3 are useful.

Consider the following example, suppose that we have 7 two-level attributes and 2 four-level attributes and we want choice sets of size 4. A mixed level orthogonal array can be constructed in 32 runs, with 8 blocks: $OA(32, 8^1 4^2 2^7, 2)$. The first column from the orthogonal array is used to define the 8 blocks or choice sets each of size 4 for the 9 mixed level attributes. For this mixed level orthogonal array we present the respondent with 8 choice sets each of size 4 and all 9 main effects can be estimated independently with 100% efficiency. Commonly, with the use of mixed level orthogonal arrays, the number of choice sets and, or, the size of the choice sets can increase quickly. In these situations we recommend the use of nearly orthogonal arrays or orthogonal main-effect plans. Unlike the blocked factorial designs we present in this paper, these designs are not 100% efficiency for estimating the main effects.

4.5 Summary

We have provided a novel application of blocked fractional factorial designs for designing smaller optimal discrete choice experiments. Our method provides 100% efficiency for the estimation of all clear effects. An illustrative example for flight preference was provided for binary attributes and we proposed the use of resolution

IV designs to guarantee all main effects are clear and in some situations some two-factor interactions are clear. There are some restraints on the construction of DCEs using blocked factorial designs. For example, our approach relies on the availability of previously constructed blocked factorial designs. However, given the available blocked factorial designs we have shown that we can substantially decrease the number of choice sets presented to the respondent. Overall, for binary attributes and choice sets of size 4, we have the ability to reduce the number of choice sets by one-half or three quarters, compared with the Street and Burgess designs. In addition, we described how the approach for binary attributes can be extended to three-level attributes; generally decreasing the number of choice sets by two-thirds.

Appendix

Proof of Theorem 1. Let X be the model matrix of (some or all) effects that are not confounded with any block effects. We can arrange X according to the choice sets as $X = (X_1', \ldots, X_n')'$, where X_i is the corresponding model matrix for the ith choice set. With this arrangement, the matrix of the second derivatives Λ is a block diagonal matrix, i.e., $\Lambda = (m^2 n)^{-1}\text{diag}(mI_m - J_m, \ldots, mI_m - J_m)$, where I_m is the $m \times m$ identity matrix and J_m is an $m \times m$ matrix of 1. Then the information matrix is

$$C = X'\Lambda X = (X_1', \ldots, X_n')\Lambda(X_1', \ldots, X_n')' = (m^2 n)^{-1} \sum_{i=1}^{n} X_i'(mI_m - J_m)X_i.$$

Because none of the columns of X is confounded with any block effect, each column of X_i is a contrast and $J_m X_i = 0$. Then $C = (m^2 n)^{-1} \sum_{i=1}^{n} mX_i'X_i = (mn)^{-1}X'X$. In particular, if X contains at most one effect from each alias set,

$X'X$ is of full rank and so does C. This completes the proof. $\square$

CHAPTER 5

Discussion

This dissertation has focused on the development of new methodologies motivated by real world applications. With these real world applications arose new challenges, and with new challenges emerged innovative construction techniques. The goal of this dissertation was to construct efficient and optimal factorial designs in the fields of biomedical science and marketing survey research. In Chapters 2 and 3, we motivated the need for the research by presenting current techniques for drug combination determination using the feedback system control and discussed their challenges to quantify drug contributions and drug interactions. We introduced the sequential use of two- and three- level factorial designs to determine potential optimal drug dosages. This lead to the construction of a new class of composite designs effective for factor screening. These designs are shown be a good trade-off between estimation efficiency and run size economy, and can be used as an alternative to the popular and existing composite designs. In addition, we presented an overview of discrete choice experiments and the application of blocked fractional factorial designs for constructing smaller optimal choice sets. While many of the developed methods offer significant improvements, there are numerous extensions for the construction and application of factorial designs.

Continuing research on optimal drug combination determination, there is a growing demand for identifying drug combinations for a large number of drugs,

ranging from 10-50. Currently, we are working on determining optimal drug combinations with minimum additive dosages to treat KB oral caner. We consider 11 drugs based on prior pilot studies. Typically, high dosages of these individual drugs are promising for treating KB oral cancer; however, high dosages of these individual drugs can be very toxic to normal tissue cells. Rather than study the individual drugs at high dosages, we study lower dosages of these individual drugs and focus on the drug-drug interactions between these anti-cancer drugs. We propose to study the 11 drugs, each with 3 dosage levels, in an 81-run blocked fractional factorial design. With this design we can clearly estimate the drug by drug interactions. By understanding the complex drug-drug interactions and drug-cell interactions, we hope to identify optimal drug combinations with minimum additive dosages in order to treat this oral cancer.

Additionally, further consideration should be given to the application of factorial designs in the field of DCEs. Researchers in the area of DCEs have been branching out and developing resources for practitioners in healthcare on the implementation of a DCE. For example, Lancsar and Louviere (2008) develop a user's guide for conducting DCEs to inform healthcare decision making. The objective is to provide an overview of the basics of DCE principles and guidance on the key factors to consider when undertaking and assessing the quality of a DCE. A comprehensive review on DCEs in health economics can be found in De Bekker-Grob et al. (2010). In this review, the current use of DCEs in the field of health economics is illustrated. It also shows the limitations that exist within their applications. Out of the 114 papers considered in the review, 37% (42) did not report the source of the experimental design, and 28% (32) did not report sufficient details on how choice sets were created. Additionally, the designs typically focused on the estimation of main effects (89%), and only 5% of designs

stated main effects plus two-factor interactions were estimable. This provokes the need for a resource on how to design DCEs for practitioners in field of healthcare. In particular, this resource should outline details on how to construct an efficient and optimal DCE, as well as focus on the identification of which model effects are estimable; i.e., main effects, or main effects plus two-factor interactions. The goal is to provide a resource for practitioners in the field of public health on the construction, and design, of a DCE using blocked fractional factorial designs, for the estimation of main effects and the estimation of main effects plus some two-factor interactions.

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