

ABSTRACT

CORNEJO, DAVID ALEXANDER. Simulating Individual Choice in Colorectal Cancer Screening. (Under the direction of Dr. Stephen D. Roberts and Dr. Maria E. Mayorga.)

Colorectal cancer is a disease that is very treatable if caught early. Colorectal cancer is caught early when individuals are screened for cancer using effective tests. However, the choice of whether or not to screen is an individual decision. The outcome of this decision may directly affect an individual's long-term survival and health outcome. Public health researchers have recognized that the best way to improve health outcomes for colorectal cancer is to encourage screening by educating individuals. However, observational studies do not follow individuals for a sufficiently long term to see the downstream results of behavioral changes. Because long term studies cannot be conducted in a cost effective manner, researchers have turned to simulation modeling to create detailed models of disease so as to "observe" many individuals for their entire life course. In this dissertation, we develop an approach for optimizing public health interventions within a limited health budget aimed at improving screening behavior. To do this, we first use a generalized logistic response curve to model individuals' behavioral responses to public health programs and incorporate it into a detailed computer simulation model of colorectal cancer progression. To make this model efficient at simulating health gains from behavior changes generated by public health policies, we extend the concept of Common Random Numbers to create a "Common Patient" that is modeled in our aggregate simulation model. We then formulate two different policy design questions as mathematical programming problems and solve these problems using our simulation model. The first question addressed is focused on the allocation of spending across multiple decision periods in individuals' age 50 to 75 screening horizon. A response

surface approach, using kriging to represent the response surface, is proposed as an efficient way of solving the simulation optimization problem. A public health case study using this model suggests it is better to focus public health spending later in an individual's age 50-75 screening horizon. The second policy decision problem modeled is how to allocate spending between multiple interventions. These interventions are described by what populations or test attributes they affect. Using an analytic method, we develop solutions of how budgets should be allocated between different intervention options given individuals response to that spending. Based on the optimization of a quasiconcave objective function, the analytic approach provides easy and intuitive solutions to practical problems. All of these techniques are applied in the context of evaluating public health interventions proposed for use in the State of North Carolina.

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Simulating Individual Choice in Colorectal Cancer Screening

by
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A dissertation submitted to the Graduate Faculty of
North Carolina State University
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

Operations Research

Raleigh, North Carolina

2015

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DEDICATION

To all my classmates, professors, family and friends, thank you for your support on this long journey. To the people of North Carolina, it is my sincere desire that this project will improve your lives.

BIOGRAPHY

David Cornejo is a Ph.D. Student in the Operations Research Graduate Program at North Carolina State University. He was born in Chapel Hill, North Carolina. In May 2010 he graduated Summa Cum Laude from the University of North Carolina-Greensboro with a Bachelor of Arts in Economics and a minor in Mathematics. Immediately after graduation he commenced graduate studies in Economics at the University of Virginia where he graduated with a Master of Arts in Economics in July 2011. David continued his graduate studies, pursuing a Ph.D in Operations Research at North Carolina State University starting in August 2011. While working on his Ph.D. he has served as a research assistant, teaching assistant and course instructor. His research interests include modeling and simulation, optimization, and health outcomes research.

ACKNOWLEDGMENTS

I would like to express my deepest thanks to my advisor, Prof. Stephen Roberts for igniting my interest in the applications of simulation and for his kind support and thoughtful guidance through the long process of completing this dissertation. I am also grateful for the support Dr. Maria E. Mayorga and Dr. Kristen Hassmiller Lich have provided as I tackled the topic of colorectal cancer. Special thanks go to Dr. Jim Wilson for serving on my committee. Funding for this work was provided in part by the National Science Foundation (CMMI-1150732, PI-Mayorga), the Centers for Disease Control and Prevention (CDC-SIP-11-041, PI-Wheeler, Co-PI Hassmiller Lich, Co-PI Mayorga). Special thanks go to my parents, brothers, and sisters who have been a continuous source of support and inspiration during my studies. Finally, I would like to thank the love of my life and fiancée, Virginia Wharton, for allowing me to steal so much time over the last two years to finish this dissertation. Your support made this dissertation possible.

TABLE OF CONTENTS

LIST OF TABLES	viii
LIST OF FIGURES	x
CHAPTER 1 : INTRODUCTION.....	1
CHAPTER 2 : DESCRIPTION OF A SIMULATION MODEL OF COLORECTAL CANCER WITH INDIVIDUAL CHOICE FOR HEALTH POLICY EVALUATION..	8
2.1 Introduction.....	8
2.2 Model Validation.....	23
2.2.1 Statistical Model Validation.....	24
2.2.2 Natural History Model Validation	27
2.3 Extensions and Limitations of Model Presented.....	31
2.4 Conclusion	31
CHAPTER 3 : CREATING THE COMMON PATIENT: SYNCHRONIZING INDIVIDUAL LIFE COURSES.....	33
3.1 Introduction.....	33
3.2 Conclusion	50
CHAPTER 4 : OPTIMIZING TIME-VARYING INTERVENTION POLICIES IN DYNAMIC INDIVIDUAL SIMULATION.....	51
4.1 Introduction.....	51
4.2 Defining the Population Policy Optimization Problem	53
4.3 Defining individual behavior in response to intervention effort.	58
4.3.1 Representing baseline screening behavior.....	58
4.3.2 Modeling how individual choice changes.....	62
4.3.3 Literature on modeling the response of individuals to health interventions	63
4.3.4 The logistic function as a model of individual response to interventions	67
4.3.5 Fitting a Logistic Response Curve for a Mailed Reminder Campaign.....	71
4.3.6 Fitting a Logistic Function Curve for a Mass Media Campaign	75
4.4 Solution Methods to Solve the Population Problem.	80
4.4.1 Simulation Optimization: A Traditional Approach	81
4.4.2 Response Surface Methods Approach to the Population Problem	82
4.4.3 Special Case: Individual Subgroup Solutions	90
4.5 Monte Carlo Simulation Model	92
4.5.1 Estimating the Value of Additional Screening	94
4.6 A Numerical Experiment of the Optimization Procedure	96

4.6.1	Model Parameterization.....	97
4.6.2	Simulation Model Validation.....	104
4.6.3	Numerical Experiment Results.....	107
4.6.4	Robustness of the Solutions to the Population Problem.....	110
4.6.5	Computational Performance Comparison of Solution Methods.....	114
4.7	Results Discussion.....	117
4.8	Conclusion.....	119
CHAPTER 5 : DESIGNING AN OPTIMAL PORTFOLIO OF PUBLIC HEALTH INTERVENTIONS WHEN INDIVIDUAL DECISIONS ARE BASED ON PREFERENCE OF CHOICE ATTRIBUTES.....		121
5.1	Introduction.....	121
5.2	Problem Description.....	123
5.3	Mathematical Model.....	126
5.3.1	Model of Individual Decision-making.....	127
5.3.2	Effecting Changes in the Coefficients via Public Health Programs.....	132
5.3.3	Planner's Intervention Choice.....	135
5.4	Mathematics of the Changing Preferences Through Utility Coefficients.....	139
5.4.1	Example Application of the Required Change in Preferences.....	141
5.5	Properties of a Simplified Mathematical Model.....	147
5.5.1	General form of the solutions.....	153
5.6	Case Studies of Analytic Solutions to the Optimization Problem.....	154
5.7	Case 1: Limited Intervention.....	155
5.7.1	The Effect of Spending.....	156
5.7.2	Objective Function to Solve.....	157
5.7.3	Economic Interpretation of Limited Intervention Model.....	158
5.7.4	Analytic Solution to Limited Intervention: Semi-Log Response Function.....	159
5.7.5	Analytic Solution to Limited Intervention: Modified Exponential Response Function.....	160
5.7.6	Parametrizing and Solving the Model.....	162
5.7.7	Subpopulation Sizes.....	162
5.7.8	Utility Parameter Changes via Intervention Response Function.....	163
5.7.9	Value of Increased Screening.....	165
5.7.10	Optimal Spending Policy for the Limited Intervention Case.....	165
5.7.11	Sensitivity of Limited Intervention Optimal Spending Policy to Differences in Health Benefits.....	167

5.8 Case Study 2: Allocation of Spending on Broad-based Intervention that Affects Two Test Attributes	169
5.8.1 Mathematics of Broad-based Intervention Model	169
5.8.2 Economic Interpretation of Broad-based Intervention Model	170
5.8.3 Analytic Solution to Broad-based Intervention: Semi-log Intervention Response Function	171
5.8.4 Analytic Solution to Broad-based Intervention: Modified Exponential Intervention Response Function	172
5.8.5 Optimal Spending Policy for the Broad-based Intervention Case	174
5.8.6 Sensitivity Analysis of Broad-based Intervention Results	174
5.9 Conclusion	177
CHAPTER 6 : CONCLUSION.....	180
6.1 Contributions of Dissertation Work.....	180
6.2 Future Work.....	184
6.3 Applicability to the Broader Research Community	184
REFERENCES	186
APPENDIX.....	194
Appendix A: The Biology of Colorectal Cancer.....	195

LIST OF TABLES

Table 2-1: Comparison of Adjusted and Unadjusted Compliance Rates in Index Year, 2012	27
Table 2-2: Number of Colorectal Cancer Cases by Stage 2004-2008 (Source: NC Cancer Registry).....	28
Table 2-3: Number of Colorectal Cancer Cases by Race 2004-2008 (Source: NC Cancer Registry).....	29
Table 2-4: Comparison of Modeled Cases to NC Cancer Registry by Stage	30
Table 2-5: Comparisons of Modeled Cases to NC Cancer Registry by Race/Ethnicity.....	30
Table 4-1: Data Used to Parameterize Mailed Reminder Logistic Intervention Response Curve.....	72
Table 4-2: Parameters and Fit Statistics for Logistic Function Response Curve for Mailed Reminder Intervention	74
Table 4-3: Data Used to Parameterize Mass Media Logistic Intervention Response Curve..	78
Table 4-4: Parameters of Fitted Generalized Logistic Function for Mass Media Intervention Data.....	79
Table 4-5: Moment Data for Parameterizing Simulation Model Pearson Rewards Distributions of Life-Years Gained if Cancer is detected at each Decision Period.....	102
Table 4-6: Cost Parameters for Numerical Examples.....	104
Table 4-7: Monte Carlo Simulation Model Validation Comparisons with full CRC Individual Simulation Model.....	105
Table 4-8: Comparison of Results of Validation Policies in CRC Simulation Model vs. Monte Carlo Model	106
Table 4-9: Solutions for the Whole Population Problem.....	108
Table 4-10: Best Budget Allocation Solutions for each Subpopulation over the Decision Periods between the ages of 50-75 as solved by RSM	109
Table 4-11: Subpopulation Benefits from Population and Subpopulation Best Policies	110
Table 4-12: 95% Confidence Interval on Value of Life-Years Gained by Optimal Allocation of Intervention Effort derived though Cross-validation.....	112
Table 4-13: Time-limited Solutions of Direct Simulation Optimization compared to Response Surface Optimal Solution.....	117
Table 5-1: Suggested functional forms for aggregate response functions from the marketing literature (from Albers (2012))	134
Table 5-2: Coefficients of Multinomial Logistic Regression on Impact of CRC Test Factors on Screening Choice Drawn from Results Discrete Choice Experiment Performed by van Dam et al. (2010)	144
Table 5-3: Colorectal Cancer Test Attributes	145
Table 5-4: Baseline Test Choice Probabilities for Different Population Groups from van Dam (2010).....	145
Table 5-5: Raw Utility Function Values for Each Screening Option	146
Table 5-6: Functional Forms Used to Model the Effects of Spending on the Coefficient Related to the Disutility from Pain from Colonoscopy	156
Table 5-7: Case Study Population Size and Proportions	157
Table 5-8: Population Size and Proportions	162

Table 5-9: Health Value of a Percentage Point Increase in Test Modality Compliance	165
Table 5-10: Optimal Budget Allocations between Black Women or Black Men for a Policy that Educates on Pain of Screening.....	166
Table 5-11: Budget Allocation Between Pain and Risk Reduction Intervention Focus.....	174

LIST OF FIGURES

Figure 2-1: Percent of North Carolinians Up-to-date with CRC Screening Adjusted for the Accuracy of Self-report.....	26
Figure 4-1: Density function of statistical model when screening intervals are 1 year and 5 years assuming a constant screening rate over time	62
Figure 4-2: Plot of logistic function.....	68
Figure 4-3: Plot of an instance of generalized logistic function	70
Figure 4-4: Intervention Effect vs. Cost for Mailed Reminder.....	75
Figure 4-5: Intervention Effect vs. Cost Mass Media.....	79
Figure 4-6: 2-D Plot of Latin Hypercube Experimental Design Sample ($N = 200$)	86
Figure 4-7: Latin Hypercube Design Projected onto the Constraint $x_1 + x_2 = 1$	86
Figure 4-8: Histogram of Values of x_1 when LHS Design Projected onto $x_1 + x_2 = 1$	87
Figure 4-9: Plot Disease Incidence by Subpopulation Group.....	99
Figure 4-10: Plot of Probability that an Individual is Alive at a Given Age	99
Figure 4-11: Plot of Baseline Control Policy adjusted for 1, 5, and 10 year Screening Intervals.....	100
Figure 4-12: Plot of Logistic “Effort” Function Used in Experiments.....	101
Figure 4-13: Plots of the Time-variant Reward Distribution of Life-years gained from Cancer Detection over Age for each Subpopulation Group.....	103
Figure 4-14: Connected plot of Population Budget Allocation Solutions from Cross-validation Iterates.....	113
Figure 4-15: Connected plot of Cumulative Budget Allocation over ages for Cross-validation Iterates.....	114
Figure 4-16: Plot of objective value of best solution produced by direct simulation optimization under limited computational budgets vs. the objective value of the solution produced by the RSM with a budget of 2532 seconds.....	117
Figure 5-1: Node-arc Diagram Illustrating the Screening Modality Choice Options Available to Subpopulation Groups Along with the Option of No Screening	132
Figure 5-2: Plot of Semi-logarithmic Intervention Response Function and its Derivative to Show how Value of PAIN Coefficient Changes due to Budget Allocations in Limited Intervention Model.....	164
Figure 5-3: Plot of Modified Exponential Intervention Response Function and its Derivative to Show how Value of PAIN Coefficient Changes due to Budget Allocations in Limited Intervention Model.....	164
Figure 5-4: Plot of Sensitivity of Budget Allocation Percentage to Black Women to a Difference in the Health Benefits of Colonoscopy of Black Women and Black Men	168
Figure 5-5: Plot of Proportion of Budget Allocated to Decreasing Disutility from Pain as the Value of Spending on Risk Reduction Increases	176

CHAPTER 1: INTRODUCTION

The purpose of this dissertation is to provide a set of mathematical and computational tools that will enable public health planners to design intervention policies that generate health gains by influencing individuals' health behavior. A particular focus will be the design of interventions to improve colorectal cancer screening rates and cancer outcomes. Investments in public health programs are significant commitments on the part of governments and non-profit organizations. These organizations would like to see the interventions they fund from their limited budgets generate the greatest health benefits. Disease dynamics and differences in effects between different policy choices make the design of intervention policies complex. Because of the trade-offs inherent in these design choices, applying more structure to these budget allocation decision problems via mathematical optimization is a valuable tool to ensure efficient allocation of spending and design of interventions. To measure the effectiveness of our interventions, we need to "observe" the lifetime outcomes of changes in individual decisions generated by our spending policies. This type of data is extremely time-consuming and expensive to collect through observational studies. To enable rapid evaluation of policies, we utilize a computer simulation model of individual disease progression. This model captures individuals' disease states and the results of screening choices, and records any lifetime effects resulting from their screening decisions. The combination of mathematical formulations of our decision problems and simulation as an evaluative tool enables the analysis of realistic problems that have relevance to public health decision-makers. Each chapter of this dissertation contributes

to this theme by either developing our simulation toolbox or developing and solving a new decision problem related to individual decision-making for colorectal cancer screening.

The value of computer simulation for the evaluation of prospective policies has been made evident by its application in a wide variety of fields and its resultant success in improving decisions in these areas. Simulation involves creating detailed computational models that represent the researcher's understanding of the dynamics of the current system and then calibrating the effects of different proposed policies that would alter this system. Health care applications, and disease modeling in particular, are becoming a common application area for simulation. The medical community has a good understanding of how disease progresses and how policies affect that progression. However, disease processes progress differently between individuals, and individual decisions related to treatment and preventative screenings can substantially impact the progression of disease. The time variant and stochastic aspects of disease progression make these problems a prime candidate for the application of discrete-event simulation techniques. Through modern, object-oriented program design, discrete-event simulation models can capture the stochastics of each component of the disease and decision process producing a high-fidelity, individualized simulation model of a disease process. Simulation models of disease offer a test bed for evaluating different health care policies.

A variety of detailed simulation models have been created and published in the simulation and health policy literature. Various researchers describe detailed models of disease progression for a variety of conditions including heart disease (K. Cooper, Davies, Roderick, & Chase, 2002), diabetes (Zhou et al., 2005), breast cancer (Koscielny et al.,

1985), prostate cancer (Etzioni et al., 2008) and colorectal cancer (Lowe et al., 1999) among others. These models have been traditionally used to optimize intervention policies answering the question “how should individuals behave to best improve outcomes?” Some questions posed in pursuit of this answer are: When should an individual start screening for disease? When should they stop? How often should they screen? With what test should they screen? (see Tejada et al. (2014, 2015), Underwood, Zhang, Denton, Shah, & Inman (2012) and Shechter et al. (2005)). These are all excellent questions to be answered; however, most of the research on these questions does not account for the potentially significant differences between the response of individuals to public policy efforts and individual compliance with recommended health guidelines.

In this dissertation, we seek to leverage data on differences in the preferences and health outcomes of population groups when designing health policies. Public health policies, by improving individual awareness and access to health care, effect individual decisions (“choice”) related to preventative services and treatments. Thus, these policies can have an effect on health outcomes. The question we seek to answer in this dissertation is a reframing/refining of the earlier question: “how do we identify the best intervention policy taking into account individuals’ actual behaviors?” Seeking an answer to this question for the purpose of improving colorectal cancer screening and outcomes drives the work of this dissertation. To answer this question, we 1) develop a model of disease and screening, 2) present necessary simulation methodological innovations, 3) propose a structure for analyzing and optimizing intervention policies, and 4) develop a mathematical model to

determine which attributes of test and intervention options to choose in order to improve and encourage better uptake in screening by the population.

In Chapter 2 we describe the simulation model that forms the core test-bed problem in this dissertation. The model of Chapter 2, developed in collaboration with other researchers at NCSU, UNC and the Renaissance Computing Institute (RENCI), includes both a natural-history model of the progression of colorectal cancer and a statistical model framework that includes individuals' decisions regarding cancer screening test choice and compliance. The natural-history model is based on the well-validated and medically-accepted MISCAN-Colon simulation model. The individual choice components were created specifically to integrate into the natural-history model of colorectal cancer. The individual choice models use logistic regression models to determine person-specific probabilities for choosing among different screening tests and choosing whether or not to screen in allowable decision periods.

In the processes of developing our simulation model and integrating the individual choice components, we identified the need for a very careful approach to simulating individuals' decision events. A careful synchronization of life course events between different scenarios allowed us to take into consideration the many factors that impacted these decision events. Chapter 3 presents the methodology for synchronizing life course events. This approach enables the marginal differences between policies to be evaluated quickly. It also enables an accurate cost-effectiveness analysis of the different intervention policies. The "common patient" that is created by our methodology extends the concept of common random numbers to enable the evaluation of complex simulation models with multiple concurrent "event streams" that need to be synchronized.

Chapter 4 presents a mathematical model to describe the problem of identifying the best way to allocate a limited public health budget over an individual's life course taking into account the individual's responses. The objective is to choose the allocation of public health efforts that maximize the diverse population's health outcomes. This proves to be a difficult optimization problem because we have a large set of feasible solutions from which we can choose to determine the optimal solutions. While we have the full colorectal cancer (CRC) simulation model of Chapter 2 to analyze specific policies, the requirements of the model make it computationally prohibitive to use as a policy-evaluation tool in a search algorithm. Therefore, we develop a simplified, but equivalently calibrated Monte Carlo simulation of our decision problem to evaluate the outcomes of possible policies. Because our objective is defined as a simulation model, we develop a simulation optimization approach to solving this problem. We compare different simulation optimization techniques and find that a response surface optimization technique can find accurate, near-optimal solutions to this problem with relatively little computation effort compared with direct simulation optimization approaches.

Chapter 5 approaches the problem of the design of optimal public health policies from a different perspective. Rather than optimizing how a budget is spent over time on a particular intervention or testing policy as we do in Chapter 4, in Chapter 5 we aim to optimize interventions offered to consumers according to their differing costs and varying benefits to the subpopulations. To do this, we extend our model of individuals' choice behavior to include individual preferences over the attributes of various test/intervention alternatives. We develop a mathematical program to describe this decision problem. This mathematical program helps us allocate spending between intervention policies that affect

individuals' preferences for each of the testing modalities. A Net Health Benefit approach is used to quantify the health benefits of each allocation policy and weigh them against the costs of such a policy. We can show that several cases of the generalized model have closed-form, analytical solutions for optimal spending allocations between intervention policies. This provides us with a way of rapidly using available data to inform decision-making without any special solution algorithms. Case studies demonstrate the simplicity and applicability of this modeling approach.

This thesis contributes to the operations research literature in two ways. First, we describe meaningful modeling methodology improvements that are implemented and tested in the simulation models described in this work. The methodology improvements enable the accurate and repeatable simulations of an individual's life course in simulation models where individual decisions are considered. Accurate and repeatable simulation of an individual's life course is crucial for performing cost-effectiveness analysis on specific populations when interventions influence an individual's decisions. Secondly, we contribute to the literature the formulation of two mathematical models aimed at helping public health planners optimize the expenditure of limited public health budgets with the goal of maximizing health outcomes for their target populations. Each of these mathematical models examines different aspects of the planner's decision-making process. The first model, presented in Chapter 4, explores the optimal allocation of intervention effort to be funded by the budget over a decision time horizon. This is a common tactical concern of planners. The second model, found in Chapter 5, approaches the problem from a more strategic perspective. It focuses on choosing a slate of interventions that are the most cost-effective from all of the ones that

could be designed. Innovative applications of heuristics are presented to solve these difficult optimization problems. These problems are challenging because of the dynamic, stochastic progression of cancer and the high degree of dimensionality introduced by modeling heterogeneous populations. In addition to contributing to the operations research literature, our models, parameterized with detailed data, can offer valuable insight to the public health literature. All of these techniques were developed within the context of analyzing interventions to improve colorectal cancer outcomes. Because of the rich data available for use through our detailed model of colorectal cancer, this is the most immediate application of our techniques. Our numerical examples, which include detailed data, provide valuable knowledge to inform the design and application of public health policy.

CHAPTER 2: DESCRIPTION OF A SIMULATION MODEL OF COLORECTAL CANCER WITH INDIVIDUAL CHOICE FOR HEALTH POLICY EVALUATION

2.1 Introduction

In this dissertation, the methodology contribution focuses on individual simulation and is tested on a simulation model of colorectal cancer progression and the individual choices for colorectal cancer screening. This simulation model was collaboratively developed by researchers at North Carolina State University and The University of North Carolina at Chapel Hill based on a model originally constructed by scientists at the private Research Triangle Institute (RTI) (Subramanian, Bobashev, & Morris, 2009). I have played an important role in the development process of this model, particularly in the implementation of the models of individual choice and implementation of intervention scenarios that impact choice. I do not claim this model to be the result of my work alone; it has truly been a collaborative effort. This section is intended to detail the structure and choice mechanisms developed for the NC-CRC model of colorectal cancer. In later sections of this dissertation, we will improve this core model and develop and demonstrate tools for analyzing individual choice. To describe the model that is used in this dissertation, I have included, in its entirety, a paper published in the 2014 Industrial Systems Engineering Research Conference (ISERC). This paper is co-authored with Professors Maria E. Mayorga of the Department of Industrial & Systems Engineering at North Carolina State University and Kristen Hassmiller Lich from the Gillings School of Public Health at The University of North Carolina at Chapel Hill.

The paper that follows describes the important aspects of the model structure and demonstrates the types of individual choice-changing interventions that can be analyzed. By

way of introduction to this paper, I want to highlight two aspects of this simulation model that make it a particularly good test-bed for methodological and analytic improvements as presented in the following parts of this dissertation. The first feature is its very rich representation of colorectal cancer progression. The NC-CRC model is based on the MISCAN-Colon discrete event simulation model of the natural history of cancer progression. This model incorporates the full range of progression scenarios and differentiates progression based on age, race, and gender. We add more components related to individual choice on top of this from available data. From a health policy perspective, this careful and thorough representation enables us to capture heterogeneity in outcomes based on individual attributes. The inclusion of a new, detailed model of individual choice employing a similar set of individual attributes allows us to examine the interactions of disease progression and individual screening behavior on health outcomes across population groups.

The second reason this model is a good test-bed for methodological and analytic improvements is that our representation of individual choice is flexible. Similar to disease progression, individual choice can be determined by a variety of individual factors/attributes. Therefore, in our model, the representation of how individuals' choice behavior changes over time within the model can be modified without much difficulty. This flexibility opens up new avenues for exploring different models of how individuals behave. Additionally, this model provides a flexible platform for evaluating many type of interventions related to improving individual choice. The design and calibration of new mechanisms/interventions for improving individual choice motivates the development of an analytical model presented in Chapter 4.

The remaining parts in this section are directly from a paper published in the *Proceedings of the 2014 Industrial and Systems Engineering Conference* entitled “Improving Outcomes via Better Choice: Applications in Colorectal Cancer Screening” by David Cornejo, Maria E. Mayorga and Kristen Hassmiller Lich.

Improving Outcomes via Better Choices: Applications in Colorectal Cancer Screening

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Abstract

We present a simulation model of colorectal cancer in a heterogeneous population of individuals. The progression of cancer is modeled and is affected by individuals' characteristics and their screening and mode decisions. A discrete choice model determines these compliance and modality choices. We present a framework for analyzing interventions that affect final outcomes by systematically affecting a change in individual choice. Moreover, recognizing that different sub-populations respond differently to interventions, we present a procedure for choosing the most effective intervention, as defined by outcomes. For this cancer model, we evaluate the cost effectiveness of public health interventions that affect people's choice behavior, using as metrics for cost effectiveness downstream outcomes such as cost of care and life years lost to cancer. We use an original comprehensive synthetic population dataset that represents the population of the State of North Carolina.

Keywords

cancer screening, simulation, individual choice, health systems

1. Introduction

1.1 Background

Colorectal cancer (CRC) is a significant public health issue. CRC is the third most prevalent type of cancer after breast and prostate cancer in US women and men (American Cancer Society, 2013). Deaths related to CRC account for 9% of all cancer-related mortality, making CRC the second leading cause of cancer-related mortality (American Cancer Society, 2013). Despite these grim statistics, CRC is the only cancer for which screening methods can identify pre-cancerous polyps whose removal halts the progression to later cancerous stages with great long term success. When the early stage, localized cancer is identified via screening tests, the 5 year survival rate is 90%, compared to an average survival rate of 64% for cancers found later in diagnostic tests after symptoms have occurred (American Cancer Society, 2013).

Because of the effectiveness of screening protocols in identifying cancer and the excellent outcomes of individuals whose cancer is detected early, the US Preventative Services Task Force (USPSTF) recommends regular screening for colorectal cancer for individuals ages 50-75. Recommended intervals between screenings are dependent on which screening mode is selected. The most common modes are: colonoscopy (10 years), fecal occult blood tests (FOBT, 1 year), and sigmoidoscopy (5 years) with FOBT every 3 years (“Screening for Colorectal Cancer: Recommendation Statement,” 2008).

Screening is a proven method of detecting and halting CRC progression; however, currently only 39% of cancer cases are detected at an early stage (American Cancer Society, 2013) and in 2012, only an estimated 65.1% of individuals in the 50-74 screening window were compliant with screening nationally (Centers of Disease Control and Prevention (CDC), 2012). Therefore, increasing screening rates is a priority for public health planners. The choice of screening modality and compliance with that protocol are fundamentally an individual decision. However, public health authorities can improve awareness of the benefits of screening and improve access to screening tests. Evidence based messaging programs for individual education have been developed to encourage screening (Ko, Reuland, Jolles, Clay, & Pignone, 2013). Additionally, a number of studies have performed Discrete Choice Experiments (DCE) to elicit the aspects of CRC testing (Cheng, Pullenayegum, Marshall, Marshall, & Thabane, 2012) and messaging campaigns (M. Pignone, 2013) that affect individuals’ decisions regarding compliance and modality choice. However, none of these studies take the next step and analyze how better choices improve outcomes. This analysis is complicated because of the varied effectiveness of screening tests, different cancer progression dynamics between races and genders, and a wide variety of individual and geographic factors that affect modality and compliance choice. Computer simulation modeling offers a tool for us to understand the interactions between CRC progression and individual choice of screening and their effect on outcomes.

To analyze the effect of individual decisions we develop an individual-level discrete event simulation (DES) model of cancer progression. We utilize this model to examine the effects of public health campaigns that attempt to affect individuals’ decisions and examine the effect these modified decisions have on outcomes. We provide a ranking of possible public health interventions via cost-effectiveness analysis. Specifically, we analyze the cost-effectiveness of: a colonoscopy free-screening voucher program for the uninsured, mailed reminders for Medicaid/dual insured individuals, and mass-media campaigns targeted at African-Americans while using individual and population health outcomes as our measure of effectiveness. The population on which these interventions are tested is an original, carefully constructed synthetic population that represents the demographic, geospatial distribution and insurance characteristics of the population of the State of North Carolina.

1.2 Relevant Literature

There are many simulation models that model colorectal cancer (Loeve et al., 1999; Roberts, Wang, Klein, Ness, & Dittus, 2007; Vijan et al., 2007). These models either use a Markovian representation of health state transitions or create an individual-level DES model of disease progression. Using a DES model of disease progression allows one to see how a specific screening protocol and individual decision-making affect disease progression and then analyze how the resulting modification of disease progression affects outcomes. Markov Models can include these factors, but this requires enlarging the state space of the problem, often negating the modeling and calibration simplicity of this technique. In the family of DES models, the MISCAN-Colon and SimCRC are the most widely utilized and cited. MISCAN-Colon is especially popular as it is an accepted model in the CISNET program. Our model shares much the same natural history structure and mechanics with the MISCAN-Colon model. Others (Roberts et al., 2007) have created more detailed DES models of CRC, however, these models have so far seen limited applications in the medical literature. A complete discussion on the importance of model structures in modeling CRC can be found in (Kuntz et al., 2011).

The cost effectiveness of different screening protocols has been the traditional research question for which these simulation models were developed. Several screening tests with different sensitivity/specificity ratios and different screening intervals have been analyzed. Most of these papers assume of 100% compliance with the

protocol when presenting their results. This assumption is unrealistic, especially when compared to the observed compliance rates. Roberts et al. (Subramanian et al., 2009) present a model that includes a mechanism for analyzing the effect of compliance rates. However, compliance in their model is limited to capturing a population-level compliance rate that does not take into account differences in compliance between groups of individuals based on individual factors. Outside of DES models of CRC, there has been limited analysis of the interventions to increase rates of compliance with CRC screening using a population-level, system dynamics representation of screening choice (M Hosking, Roberts, Uzsoy, & Joseph, 2012). Our model incorporates a structure where both compliance and modality choices are dynamic and based on individual characteristics through discrete choice logistic regression models.

The remaining portion of this paper is organized as follows. In Section 2 we present our simulation model and the synthetic data we used to populate the model. In Section 3, we introduce the statistical model we utilize to model individual decision making. In Section 4, we describe the interventions that we apply to our populations and explain how they affect individuals' decisions. Section 5 describes the outcome measures tracked in our model. Section 6 presents results of our simulation model. Our conclusions are presented in Section 7.

2. Simulation Model Description

Our simulation model is an individual-level discrete event simulation (DES) model of the natural history of colon cancer progression and includes statistical models to capture the wide range of individual and geographic factors that affect the modality of testing and compliance decisions. Our natural history model of colon cancer progression follows the polyp-adenoma-carcinoma process and is based on the MISCAN-Colon model (Loeve et al., 1999). The transitions parameters of the cancer model were calibrated using national-level data. We used as our test population a representative synthetic population of the State of North Carolina. In this section, we position our model within the literature and highlight important aspects of model structure and describe our unique, synthetic experimental population.

2.1 Model Structure

We implemented our simulation model in AnyLogic (2012). As AnyLogic is a Java-based object-oriented (OO) simulation framework, we implement our natural history model in an OO methodology. Leveraging the OO framework, we represent the modeled population with a `Population` class that is composed of `Person` objects with the `Main` class acting as a controller for statistics collection and input/output. An instance of the `Person` object contains the demographic characteristics of a person from the input population dataset. Each `Person` object also contains a `Test` object instance and one or more `Lesion` object instances. The `Test` object represents the assigned testing modality (FOBT, Colonoscopy etc.) of the individual and controls the frequency and effectiveness of the testing based on the type of screening test it represents. The `Lesion` object represents the opportunity for development of polyps and eventually cancers. A `Lesion` object is not in and of itself a cancer, but encapsulates the natural history progression of cancer. The current state of the `Lesion` object indicates if it is or is not cancer. Figure 1 provides an overview of the structure of our model. Figure 2 presents an overview of the state transition system underlying the natural history model of disease that is encapsulated in the `Lesion` object. The natural history system follows the polyp-adenoma process implemented by the MISCAN-Colon model. In the MISCAN-Colon model, a `Lesion` object may develop to the point where it is a precancerous polyp. This polyp is detectable by screening modalities and removal will halt progression towards cancer. If a polyp is not detected and removed, its size determines the rate at which it is likely to progress to a cancerous stage. If a polyp moves to the Pre-clinical cancer stage, screening will improve outcomes, but not nearly as much as if the cancer is detected in the polyp stage.

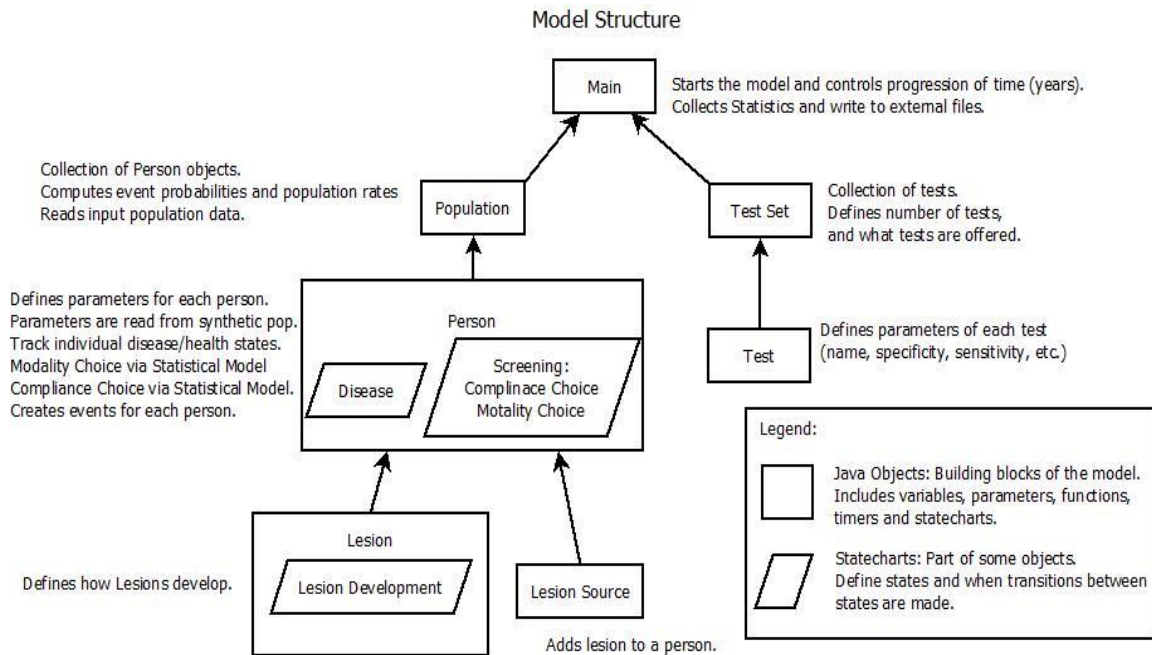


Figure 1: Simulation Model Structure

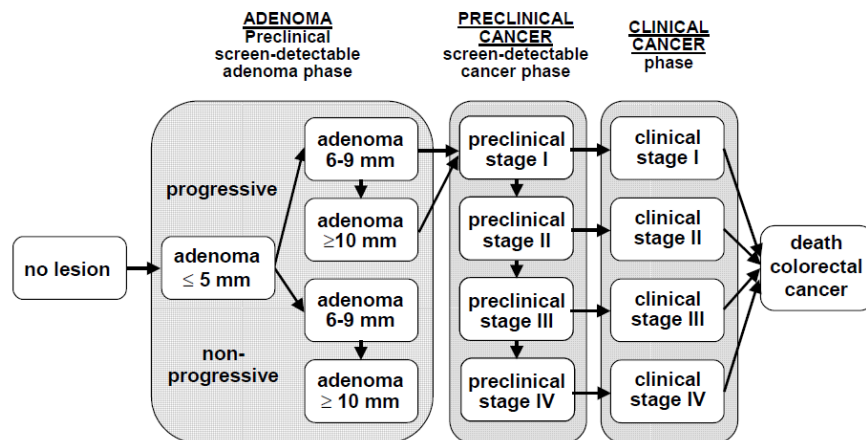


Figure 2: Natural History Transition System (diagram from Lansdorp-Vogelaar et al. (2009b))

To determine the effects of CRC incidence on individual lifetimes and health, we estimate a “cancer-free” lifetime for individuals based on the CDC’s published All-factor Life tables (“Life Tables,” 2009) which depend on race, gender and age-observed. The individuals in the modeled population are assumed to expire by this age. Any other death before that age is attributable to colon cancer or the screening process (there is a small possibility of mortality from colonoscopy screening procedure adverse events).

2.2 Synthetic Population

The population analyzed by this model is a synthetic population of individuals that reflects the demographic trends of the population in the State of North Carolina. The synthetic population is generated from the non-public, micro-level files of the US Census American Community Survey (“American Community Survey,” 2012) observed in 2007. Using appropriate sample weights, a full size population is generated from these non-

public samples (Wheaton et al., 2014). This “smart shuffling” process enables public access and use of the resulting population size files. While the census information contains much useful demographic information, including gender, race, income and geographic locational information, it does not include information about insurance status or an individual’s distance to an endoscopy center. To add insurance information, a logistic regression model was developed (Brown, 2012) that probabilistically assigned insurance status based on the demographic information in the data set. Distance to an endoscopy facility was determined using the zipcode locational information of each individual by measuring from the centroid of an individual’s zipcode to the centroid of an endoscopy center’s zipcode.

The synthetic population is divided into single-age cohorts that are run through the simulation. We run all age-cohorts that will be of eligible screening age (50-75) any time during the intervention window. The results of the simulation runs on each cohort are then aggregated to determine the aggregate response of the population to an intervention in a given calendar year.

3. Choice Models Description

Individual choice of compliance and modality in our model is based on a probability distribution over the possible options available to the individual. These choice probability distributions are generated by a discrete choice, logistic regression model based on observational claims data of individuals enrolled in either a state-sponsored health plan (Medicaid and Medicare) or privately insured through the state’s largest private insurer turning 50 in the years 2005-2008. Because of disease process differences between various demographic groups, including individualized representations of choices through statistical models allows us to investigate targeted interventions that increase the screening rates of disadvantaged groups and examine their health outcome results.

3.1 Logistic Regression

Our statistical models for compliance and modality choice are based on a multi-level, random effects logistic regression. The levels in the model allow individual attributes to have varying impacts between counties in the state of North Carolina. We include county level effects driven primarily by urban/rural county differences as well as income disparities across the state. The specification of our multilevel model can be found in eq. (1), i indexes over individuals, j indexes over counties (100 counties in North Carolina), k is the number of person level characteristics in the model, l is the number of county level characteristics. The linear formulation of the logistic regression value function is converted into a probability by eq. (2).

$$\text{logit}(\pi_{ij}) = Y_{ij} = \beta_{0j} + \sum_k \beta_k X_{ik} + \sum_l \beta_l X_{jl} + \varepsilon_{ij} \quad (1)$$

$$\pi_{ij} = \frac{e^{Y_{ij}}}{1 + e^{Y_{ij}}} \quad (2)$$

Where π_{ij} is the probability for the binary outcome (CRC Screening vs. No Screen or Colonoscopy Choice vs. FOBT) for person i at county j . β_{0j} is the county level intercept X_{ik} and X_{jl} represent the person level (e.g. race, gender) and county level (e.g. distance to endoscopy facility) attributes, respectively. ε_{ij} is the error term which is distributed with a logistic distribution with mean 0 and standard deviation $\frac{\pi}{6}$.

We estimate models for modality choice and compliance choice separately. Both are estimated using the same data set and set of dependent variables. For the compliance model, we estimate the parameters of the linear model using the whole data set. For the modality model, we use the portion of the dataset of people who choose a testing modality in an observed test episode. We choose to estimate modality and compliance choice separately because of opinion that the impacts of demographic factors on compliance and modality are fundamentally different.

3.1 Compliance and Modality Choice Models

The compliance and modality choice model in our simulation has been previously published in (Wheeler et al., 2014). We present a summary of the dependent variables defined in our models in Table 1. For modality choice, we only consider Colonoscopy and FOBT to be the possible modes. This is because very few people in our data set were observed to get screened by the other possible modality, sigmoidoscopy. The results published in (Wheeler et al., 2014) estimate the behavior of individuals over a six year observational time window. We convert these probabilities generated from a model estimated on a six year window to annualized (for FOBT) and decennial (for Colonoscopy) probabilities of compliance assuming a binomial distribution of annual screening probabilities that result in the correct observed cumulative probabilities.

Table1: Variables in Discrete Choice Model

Gender	Female vs. Male		Low-Medium vs Low
Race	Black vs. white	Regional % Non-White	Medium-High vs Low
	Other vs. white		High vs Low
Distance	5-10 vs < 5 miles	Regional Unemployment Rate	Low-Medium vs Low
	10-15 vs < 5 miles		Medium-High vs Low
	15-20 vs < 5 miles		High vs Low
	20-25 vs < 5 miles		1-200 vs 0
	25+ vs < 5 miles		200-400 vs 0
Regional Uninsurance (40-64)	Low-Medium vs Low	Facility Test Volume (per 10,000)	400-600 vs 0
	Medium-High vs Low		600-800 vs 0
	High vs Low	Generalist Count	800+ vs 0
			Above median vs below median

4. Interventions

In this section, we briefly outline the interventions we analyzed using our simulation model as well as present the base case scenario to which they will be compared. The interventions will be henceforth identified as *Free Screening*, *Mailed Reminder* and *Mass Media*. Data to calibrate the effects of these interventions is derived from a review of the medical literature that presents the results of clinical and observational studies measuring the effects of interventions on health behavior. The interventions we model change individual behavior directly by exogenously influencing individual's choice probability distributions. A more complete description of the interventions, as well as citations for their basis in the medical literature, can be found in (Lich, Mayorga, Wheeler, & Pignone, n.d.). These interventions are evaluated over a 10 year time horizon starting in January 1, 2014 and ending December 31, 2023.

4.1 Base Case Scenario Description

The base scenario to which interventions are compared is one where individuals “screen as usual”. This screen as usual behavior is defined by modality and compliance choice being made according to the unaltered statistical models as estimated on the raw data. In contrast to much on the literature that defines a base case of no screening, by defining a data driven base case of screening behavior we can analyze both the incremental health benefits as well as the costs of intervention policies.

4.2 Intervention Description

The *Free Screening* intervention involves a state-wide free screening program in which uninsured individuals who turn 50 in a given year are offered a voucher to cover the cost of an initial colonoscopy. A maximum of 1500 free screening vouchers are offered in a given year. The simulation model determines at random which uninsured individuals receive the screening vouchers. Individuals who receive a voucher are assumed to utilize them in the year they are provided (100% compliance in the year they receive the voucher). The costs for this intervention are the costs of the voucher which covers the cost of the initial colonoscopy as well as expected costs of any resultant diagnostic polypectomy and associated laboratory costs. The cost of treatment is not allocated to this intervention because it is assumed to be covered through charitable organizations or Medicaid if the individual qualifies.

The *Mailed Reminder* intervention consists of mailed reminders sent yearly to Medicaid and Dual insured individuals. We translate results of the study (M. Pignone, 2013) in which individuals were observed to increase their rate of compliance with CRC screening, by generating analogous changes in the behavior of the synthetic Medicaid/Dual population in our model. We increase the probability of these individuals complying with their assigned modality 10 percentage points (with an upper limit on the probability of compliance of 1). The costs of this program are the cost of the mailer as well as limited set-up and personnel costs.

The *Mass Media Campaign* intervention consists of a large-scale mass media campaign targeted to African Americans. This campaign would run yearly for the 10 year experimental window. Based on previous studies of mass media campaigns (Williams, Reinfurt, & Wells, 1996), we expect this intervention to reach 80% of African Americans and increase their compliance rates by 7 percentage points. Recognizing the spillover impacts of mass media messages to non-targeted populations, we estimate a similar 4 percentage point increase in compliance in 40% of non-target individuals. Like the Mailed Reminder intervention, this intervention is implemented in the simulation model by increasing the compliance choice probability of each individual by the appropriate factor. The costs of this program are limited to the direct cost of supporting the mass media campaign.

4.3 Intervention Cost

When assigning cost to each of these interventions, we assume the perspective of the public health planner responsible for spending North Carolina State funds on these interventions. It is important to note that we are taking the perspective of a state health planner vs. a federal planner because of the differences in costs assumed by either of these agents when examining the interventions. For example, in the Medicaid Mailed Reminder program, the State would be responsible for the costs related to the mailed reminder, but they would not be responsible (directly) for the costs incurred in screening these patients since they are covered by federal Medicaid dollars. Table 2 contains a summary of intervention costs relevant to North Carolina public health planners. See Lich et. al. (Lich et al., n.d.) for references and details.

Table 2: Intervention Costs

Free Screen	Colonoscopy cost	\$750	/test
	Programing Development	\$10,000	onetime
Mailed Reminder	Labor/personnel cost	\$4,081	/year
	Material cost	\$0.71	/unit/year
Mass Media	Programing Development	\$368,000	onetime
	Airtime costs	\$332,680	/year

5. Analysis

5.1 Health outcomes measured

The goal of our model is to analyze the effects of higher screening compliance rates and better modality choices on the health outcomes of the whole population. There are many ways to analyze the impact of improved screening decisions on quality of life and health outcomes including mortality. In this section, we explain the outcome measures we use to compare the results of these scenarios. These outcomes are: the number of CRC deaths averted, the number of life years lost to colorectal cancer (*lifelost*), the probability of death due to colorectal cancer given having CRC (either identified or not identified by screening) and the conditional probability of death due to CRC for Medicaid and African-American subpopulations.

The deaths from CRC averted statistic is calculated by comparing the number of deaths due to CRC in the intervention scenarios with the number of deaths due to CRC in the base case “screen as usual” scenario. The *lifelost* outcome is calculated by finding the difference between the predicted lifetime and the actual time of death with any earlier death attributable to CRC. As described in Section 2.2, deaths due to causes other than CRC are captured by the “death age” assigned to each individual at the beginning of model time from the CDC’s All Factor Life-tables. Deaths that occur before that time are due to the modeled lesions (the representation of CRC) progressing to such a state that they can and do transition to the death state before the assigned death age. Because cancer progression is a function of the transition rate parameters for the cancer/lesions states and the choices of individuals to screen (which can halt lesion progression), increased compliance with screening by individuals provides more opportunities to slow and halt lesion progression, hence leading directly to less *lifelost* and more deaths averted from CRC. By calculating the average *lifelost* per person it is possible to derive the number of life years gained from CRC screening since we know the size of the population. We present this more intuitive result in the next section.

The probability of death due to colorectal cancer given CRC statistic is calculated by finding the proportion of people with CRC/CRC precursors that die before their assigned “death age”. This implies death from CRC. Individuals are identified as having CRC/CRC precursors if their lesion objects in the model ever become a polyp. A polyp is a recognized precursor to CRC. Although not all polyps progress to cancerous states, every cancer starts as a polyp. Identifying CRC at the polyp stage is a major goal of CRC screening programs. We identify an individual as having developed a polyp whether that polyp was identified by screening or not. Conditioning the probability of death on the occurrence of the polyp allows us to identify the effect of screening on those it is intended to help most. We compute conditional probabilities of death due to CRC for Medicaid and African-American subpopulations. Using these numbers, we can derive the number of CRC deaths averted by the intervention.

5.2 Cost effectiveness measures

To evaluate the cost effectiveness of the interventions we compute a Cost Effectiveness Ratio (CER) of the cost per CRC death averted. This cost effectiveness ratio is computed using the following formula:

$$CER = \frac{\text{intervention cost}}{\Delta \text{ CRC deaths}} \quad (3)$$

A similar cost effectiveness ratio formula is utilized to calculate a CER for the incremental cost per life year gained in each intervention.

6. Results

Results were obtained by running the model for 10 replications across the whole population (approximately 3.6 million individuals). Each intervention was applied during the experimental window of January 1, 2014 through December 31, 2023. Given the large size of the population and the detailed nature of the natural history model, model runs were performed on a High Performance Computing cluster with 64-core 2.4 GHz processor array with 1 TB of RAM. We were able to leverage all of the cores of the processor because of a parallelization based on the age cohort structure of the model. Each replication population cohort of ~100,000 individual took approximately 10-15 minutes to run on a single processor core. We analyzed 20 age cohorts, aged between 41-75 in 2014; that is, individuals that will be eligible for screening (50-75) any time during the policy window (2014-2023). Given the large number of separate scenarios and replications for each cohort and the number of cohorts, even with computing resources the model takes approximately 4-6 hours to process a complete experiment. In Table 3 we present the results of the simulation runs. All confidence intervals are 95% confidence intervals.

Table 3: Model Results-Cost Effectiveness Ratios

	Cost of Intervention	Number Dead CRC	Cost per CRC Death averted	Life years lost to cancer	Cost per Life year gained
Base Case	N/A	62804	N/A	662098	N/A
		(62,520, 63,088)		(635,209, 688,986)	
		CRC Deaths Averted		Life Years Gained	
Free Screening	\$11,250,000	787	\$14,289.34	4588	\$2,451.81
95% CI	(\$ 11,250,000 , \$11,250,000)	(728, 846)	(\$13,296.20, \$15,442.83)	(1,299, 7,878)	(\$1,428.05, \$8,660.39)
Mailed Reminder	\$2,515,661	391	\$6,440.51	2768	\$908.83
95% CI	(\$ 2,514,857 , \$2,516,355)	(304, 477)	(\$5,267.21, \$8,284.45)	(2,670, 2,866)	(\$877.52, \$942.40)
Mass Media	\$3,694,800	756	\$4,887.95	6914	\$534.39
95% CI	(\$ 3,694,800 , \$3,694,800)	(731, 781)	(\$4,732.54, \$5,053.91)	(6,289, 7,540)	(\$490.05, \$587.55)
All interventions	\$18,460,473	1,739	\$10,614.96	13724	\$1,345.09
95% CI	(\$ 18,459,671 , \$18,461,164)	(1,732, 1,746)	(\$10,572.37, \$10,657.82)	(9,328, 18,121)	(\$1,018.70, \$1,979.12)

Table 4: Effects on Specific Populations

	% Dead CRC given Polyp	Number Dead CRC for Medicaid	Number of Dead CRC for African-American
Base Case	3.6538%	2810	9993
	(3.6373%, 3.6703%)	(2,546, 3,075)	(9,401, 10,585)
		Number of Deaths Averted for Medicaid	Number of Deaths Averted for African-Americans
Free Screening	3.5961%	N/A	122
95% CI	(3.5831%, 3.6092%)		(40, 204)
Mailed Reminder	3.6311%	118	95
95% CI	(3.6164%, 3.6393%)	(114, 123)	(77, 114)
Mass Media	3.6098%	36	236
95% CI	(3.5870%, 3.6172%)	(35, 36)	(285, 186)
All interventions	3.5526%	139	455
95% CI	(3.5146%, 3.5466%)	(132, 146)	(389, 521)

7. Discussion

The most cost-effective intervention in our study overall is the Mass Media Campaign, however, all interventions provide reasonable cost-effectiveness. If we look at the particular sub-groups at which the interventions are targeted, (The uninsured for the Free Screening voucher program, Medicaid/dual insured individuals for the mailed reminder program, and African-Americans for the mass media campaign), the intervention effects are quite significant for each of the targeted sub-groups. These results suggest that all of the interventions are beneficial for resolving known disparities among particular subpopulations. The “All interventions” also provides a cost-effective result, as the three interventions target different sub-groups of the population and hence their combined effect is close to additive.

It is notable from these results that the interventions that affect the largest segments of the population are effective in both absolute and cost effectiveness terms. These results make clear that even small changes in a large portion of the population’s screening behavior can have a significant impact on outcomes. This suggests that large scale messaging campaigns, such as our mailed reminder and mass media interventions, with their wide impact and frequent spillover effects are often a better option than highly effective, but narrowly targeted interventions on specific populations.

From a technical, computing perspective, the long run times despite significant computing power of the model indicate an opportunity for future work that would reduce computation times. If experiment run times were reduced we could investigate more complex implementations of interventions, such as interventions that were focused on specific geographic areas or perform more extensive sensitivity analysis on our results. The individual nature of this simulation model suggests that alternative representation of the distributions of individual outcomes may be possible. These alternative computational approaches are a current active area of work.

8. Conclusion

Building a DES model that captures the natural history process of CRC was an important groundwork for analyzing the effects of user choice on health outcomes. Our model is the first to incorporate user choice of

screening modality and compliance within a simulation model for CRC. The statistical models that determine these decisions are theoretically grounded and include a wide array of variables that are relevant in these decisions. We analyze the effects of public health interventions that effect individual's compliance and modality decisions. In performing this analysis we find that the mass media campaign is the most cost effective program. Additionally, the cost per death averted is relatively low when compared against the costs of cancer and the generally accepted societal willingness-to-pay for health. We showed that interventions that affect wide selections of the population with small individual effects are more effective than interventions that are narrowly focused and affect only a few individual's compliance.

Acknowledgements

Funding for this work was provided in part by the National Science Foundation (CMMI 1150732) for Mayorga and by the Centers for Disease Control 3U48DP001944-03S1 (SIP 11-041) for Hassmiller Lich.

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2.2 Model Validation

Due to the limited word count of the published proceedings paper in this chapter, extensive discussion of model validation was omitted to focus on developing the modeling framework and presenting initial results. Because of the centrality of this simulation model to the empirical work that is described latter in this dissertation, we would like to provide an expanded explanation of the procedure by which the model was validated.

The goal of the NC-CRC simulation model is to replicate cancer progression and individual screening behavior for the purpose of evaluating public health policies that change screening behavior. The NC-CRC model is fully extensible to evaluate public health polices for any given population; however, this work is focused on evaluating public health policies that would be applied to a North Carolina population. Therefore, the NC-CRC model is calibrated to accurately reflect cancer progression and testing behavior of the population of the State of North Carolina. To validate that our model accurately represents North Carolina's situation, we compare the outcomes of the model focusing on estimated cancer cases and cancer outcome against data from the North Carolina cancer registry. The NC-CRC simulation model has two related, but distinct components which were validated: 1) the statistical model of individual screening and compliance choice, and 2) the natural-history component where cancers are generated, progress, and cause death or impairment. The statistical model used to represent modality and screening choice behavior is the primary new component of the NC-CRC model compared with previous models. Thus, validation efforts are primarily be focused on validating the models results as well as validating the integration of this decision-making modeling into the model of cancer progression since how people

make decisions affects the incidence and outcomes of cancer. In the next sections, we describe the data used to validate this model and demonstrate how the comparison of this real-world data with NC-CRC simulation model outputs develops confidence in the empirical results of interventions scenarios evaluated with the model.

2.2.1 Statistical Model Validation

The statistical model components presented in the paper are estimated and tested with claims data from Private, Medicaid, Medicare and Dual-insured individuals (Wheeler et al., 2014). By the nature of the logistic regression modeling methodology, the models produced will be the “best” models given our input data and will generate an average screening rate consistent with the provided data. These models will reflect the heterogeneity in screening observed between different population groups. While our data is sufficient to calibrate the differences between groups during our data collection period, past observational data indicates a long-run secular trend in screening rates. During a ten-year period from the late 1990s to the early 2000s, the average reported colorectal cancer screening rates increased by more than 10%. Incorporating this trend into our choice probabilities is important. As a lifetime model, we need to model individuals’ screening decisions even before the time window of interest (2014-2023). The screening data used for calibrating our statistical models is for the 5-year period, 2004-2008. To account for the trend, we adjust each group’s screening rate by a constant value so that the aggregate screening compliance rate matches the secular trend from 2002-2012.

The observational data used to compare to the model results comes from the NC portion of the Behavior Risk Factor and Surveillance Survey (BRFSS) conducted by the

Centers for Disease Control and Prevention (2012). The BRFSS collects self-reported compliance with screening guidelines. This is measured through a question like “Have you had a Colonoscopy within the last 10 years or an FOBT screen within the last year for colon cancer?” There is extensive literature (see Ezzati, Martin, Skjold, Vander Hoorn, and Murray (2006), Stein, Lederman, and Shea (1993), and Schneider, Clark, Rakowski, and Lapane (2012)) to suggest that self-reported studies, like the BRFSS often have inflated compliance estimates. When the raw BRFSS data is adjusted using adjustments suggested by this literature we have a notable secular trend as seen in Figure 2-1.

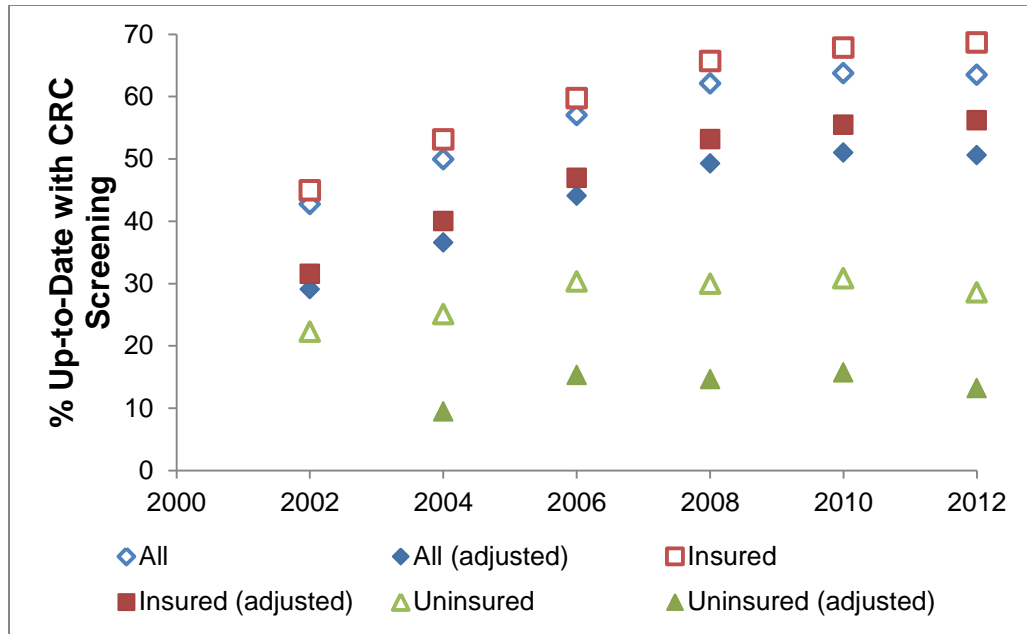


Figure 2-1: Percent of North Carolinians Up-to-date with CRC Screening Adjusted for the Accuracy of Self-report

To achieve a match of our aggregate compliance data to this trend required a 5% point bump to the baseline probabilities produced by our model to match the 2012 aggregate compliance rate. To determine the compliance probabilities for periods before 2012, the 2012 adjusted values were modified so that so that they reflected the same rate of change as the adjusted BRFSS data. Table 2-1 shows the aggregate and subgroup compliance levels with and without the adjustment to bring the model into line with BRFSS.

Table 2-1: Comparison of Adjusted and Unadjusted Compliance Rates in Index Year, 2012

	Adjusted Compliance Rate	Unadjusted Compliance Rate
Year of up-to-date statistics	2012	2012
Overall	53.96%	47.29%
By sex		
Males	55.51%	48.01%
Females	52.99%	45.74%
By race		
Whites	55.42%	47.85%
Blacks	51.95%	44.90%
Others	48.11%	41.86%
By insurance		
Private	57.00%	49.01%
Medicaid	50.29%	42.03%
Medicare	51.97%	45.13%
Dual	44.77%	38.26%
Uninsured	14.57%	14.57%

2.2.2 Natural History Model Validation

The natural-history component of the NC-CRC simulation model seeks to represent the process whereby cancers appear and progress at an individual level. For the sake of our study, we are not primarily interested in validating the polyp stage transition parameters against medical literature. The NC-CRC leverages a deep literature that looks at cancer

progression and estimates polyp formation and transition rates. The general polyp formation and progression parameters in the model are drawn from the MISCAN-Colon model of (Lansdorp-Vogelaar et al., 2009a). However, we are interested in validating that this natural-history component when combined with the statistical decision model represents a cancer stage incidence profile across different demographic groups that is similar to the observed data. From the North Carolina Cancer Registry (2014), we have details on all reported cancers and their stage at diagnosis for the whole population of the State of North Carolina. This data is reported in the five-year interval from 2004-2008. In Table 2-2 we have data on the number of individuals who have cancer by stage of cancer. In Table 2-3 we have data about the racial and ethnic breakdown of cancer cases inclusive of all stages found in Table 2-2.

Table 2-2: Number of Colorectal Cancer Cases by Stage 2004-2008 (Source: NC Cancer Registry)

Stage	COLON/RECTUM
	Cases
0	2,289
I	4,511
II	4,381
III	4,298
IV	3,212
Other/Unknown	2,260

Table 2-3: Number of Colorectal Cancer Cases by Race 2004-2008 (Source: NC Cancer Registry)

	COLON/RECTUM
	Cases
Non-Hispanic Whites	16,169
Non-Hispanic African Americans	4,275
Non-Hispanic Other Races	307
Hispanics	200
All Races and Ethnicities	20,951

The NC-CRC simulation model captures the entire life course of an individual. Additionally, as described in the paper, we use a simulated population of individuals to represent the whole population of the State of North Carolina. By simulating those individuals who are older than 40 (the earliest age at which cancer can appear in the model) during the period 2004-2008 our synthetic population will be statistically reflective of the population that produced these cancer incidence statistics. When the model is instrumented so that we capture just the cancer cases that occur in the years 2004 – 2008 we can compare our model outputs with the Cancer Registry data. Table 2-4 contains a comparison of our model outputs with the Cancer Registry data. Table 2-4 contains a comparison of our model outputs with the registry cancer stage information in Table 2-2. One assumption has been made. Based on discussions with individuals familiar with the collection process for this data, the “Other/Unknown” cases are usually later stage cancers. Therefore we distribute the “Other/Unknown” cases equally to Stages III and IV. Table 2-5 contains a comparison of model outputs with the racial and ethnic cancer incidence breakdown from the cancer registry originally presented in Table 2-3.

Table 2-4: Comparison of Modeled Cases to NC Cancer Registry by Stage

Stage	COLON/RECTUM			
	Actual Cases	Modeled Cases	Number difference	Percent difference
I	4,511	4,249	-262	-5.81%
II	4,381	4,426	45	1.04%
III	4,298	4,520	222	5.17%
IV	3,212	3,677	465	14.46%

Table 2-5: Comparisons of Modeled Cases to NC Cancer Registry by Race/Ethnicity

	COLON/RECTUM		
	Actual Cases	Modeled Cases	Percent Difference
Non-Hispanic Whites	16,169	15,168	-6.2%
Non-Hispanic African Americans	4,275	3,115	-27.1%
Non-Hispanic Other Races	307	538.8	75.5%
Hispanics	200	301.4	50.7%
All Races and Ethnicities	20,951	19,123	-8.7%

Some notes to facilitate comparison of this data, the stage information does not exactly match the categories of our model. Particularly, Stage 0 and the “Other” cancer stages are not reflected directly in the results. From discussion with individuals familiar with the NC Cancer Registry, the Stage 0 represent pre-cancerous adenomas and “other” stages are typically later stage cancer.

The comparisons listed here build confidence that we have modeled the natural history component correctly.

2.3 Extensions and Limitations of Model Presented

The results presented in the preceding paper were based on an early version of the model. Subsequent to the publication of this paper, we substantially improved the methods for simulating individual lifetimes by the application of Common Random Numbers in a way that improved interpretability and the statistical accuracy of the policy comparisons. Hence, the results of this simulation experiment presented in the ISERC paper have changed. In the simulation model presented in the ISERC paper, individual lifetimes were not synchronized between intervention scenarios. When lifetimes are not synchronized, we could not guarantee that the changes in behavior and outcomes were due to the intervention scenario. Instead, the changes in behavior due to the interventions scenario are masked by stochastic noise. To manage these issues, a technique for synchronizing an individual's life course between scenarios in a simulation experiment was required. To this end, we created a so-called "common patient" within our simulation experiment. The methodology to accomplish this effectively is an important contribution of this thesis and is presented in Chapter 3.

2.4 Conclusion

The individual simulation model of colorectal cancer presented in this section provides a detailed, data-driven model of colorectal cancer progression and individual screening behavior for the purpose of evaluating interventions that aim to improve outcomes through changes to individuals' screening behavior. The genesis of this model from the literature of colorectal cancer disease modeling leads to the new components in this model related to individual choice to the larger body of work on evaluating screening policies with simulation. The detailed nature of this model in its description of individual choice and

disease progression will enable analysis of the effects of policies on specific populations, but also necessitates new techniques to correctly and efficiently perform simulation experiments. The flexible representation of individual choice will offer opportunities to evaluate the assumptions surrounding how individuals make screening decisions. These important issues will be addressed in the following sections of this dissertation. All of these methodological tools will provide us with a way to analyze interventions for improving colorectal cancer screening. This model, and the analysis based on it, provides the first real model-driven analysis of screening-promotion programs. The detailed, comprehensive questions that can be answered with this model provide valuable insight to public health planners in their quest to spend their budget for screening promotion in the most cost-effective way possible.

CHAPTER 3: CREATING THE COMMON PATIENT: SYNCHRONIZING INDIVIDUAL LIFE COURSES

3.1 Introduction

Developing individual-based simulation models is a natural way to describe disease progressions that are person specific. Incorporating individual disease progression is also imperative if we wish to determine the effects of individual screening behavior on disease and health outcomes. The most natural way to evaluate changes to individual choice is to perform cohort comparison. In cohort studies, we simulate a base case cohort where each individual's disease progression and choice proceed according to some baseline parameters. This cohort is then compared with the result of running the same cohort of individuals except their behavior changes according to the new rules or parameters defined in the intervention scenario. We expect that the marginal changes in choice behavior will improve health and screening outcomes. These cohort comparisons are based on the assumptions that individuals' disease progression proceeds similarly between the base case and intervention scenario.

Maintaining comparability of life course events has proven difficult because our intervention scenarios are often dynamic (time-varying). The dynamic nature of our intervention scenarios serves to add events to the simulation run in a way that can alter future disease progression if not properly controlled. In this section we will describe the creation of the "common patient" for individual simulation in health policy analysis. This common patient has the interpretability benefits already discussed and substantially increases convergence rates of population statistics compared with naïve methods of individual

modeling. This section describes the need for and the practical application of techniques to improve the modeling of events in an individual's life course.

In Chapter 2, we described an advanced discrete event, individual simulation model of colorectal cancer progression and individual screening choice. The model is individually focused because cancer progresses at different rates in different individuals. Within each representative individual in the model population, there is a discrete event disease model representing the generation and progression of cancers. However, the disease progression process is not one monolithic event generation stream. Leveraging the power of object oriented programming, the model describes the disease process as a hierarchy of event processes that generate events and outcomes we are interested in tracking.

In the remainder of this section, I present a paper, of which I am the primary author, describing and evaluating the issues of synchronization of events within the context of our colorectal cancer simulation. This paper was published in the *Proceedings of the 2014 Winter Simulation Conference*.

CREATING COMMON PATIENTS AND EVALUATING INDIVIDUAL RESULTS: ISSUES IN INDIVIDUAL SIMULATION FOR HEALTH POLICY ANALYSIS

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ABSTRACT

The research direction in modeling complex, chronic conditions for health policy evaluation has been to incorporate individual heterogeneity. This detail makes our models more powerful and relevant. In implementing an individual simulation model of colorectal cancer we have recognized two considerations related to incorporating individual heterogeneity that have not been adequately discussed in the literature. First, there are substantial computational gains and interpretation benefits if an individual's life courses are identical except when differences are directly induced by an intervention. Achieving this is not trivial. We have developed the notion of a "common patient" who is the same between scenarios except for intervention-induced changes. We create the common patient using a careful application of Common Random Numbers (CRN). Second, when we model differentiated individuals we can examine differing impacts of policies on specific sub-groups. This leverages the detail in individual attributes to produce useful results for policy makers.

1 INTRODUCTION

1.1 Simulation for Health Policy Analysis

Over the last several decades, the simulation community has developed techniques and modeling frameworks that have enabled simulation models to contribute to health policy decision-making by creating accurate representations of disease progression and individuals' response to treatment regimes. With these detailed models, policy makers are able to make comparisons regarding the cost-effectiveness of various policies proposed for

implementation and to understand the impact of uncertainty on the robustness of the benefits of various policy options.

To accept a model as valid for the purpose of evaluating policies on the population being analyzed, policy makers have demanded a high degree of fidelity, ensuring the modeled population matches the evaluated population and ensuring that the dynamics of disease are captured accurately by the model. For chronic disease modeling, discrete event natural history models of disease have become the gold standard by which to evaluate policies. These models, often called individual (or micro-) simulation models, incorporate heterogeneity of individuals through differing disease progression.

Utilizing fixed populations of individuals for evaluating health policies has an intuitive appeal, since comparability between individuals in different interventions is assured; an individual in a population dataset will have the same life course over all intervention scenarios except when changes are directly caused by that intervention's impacts. Since individuals in this line of research represent patients in health care settings, we call the person represented by this data a "common patient". The common patient is created using careful synchronization of events in an individual's life course through the implementation of Common Random Numbers on significant event streams. While this concept may appear simple, implementation in complex individual simulation models requires careful design decisions. Using common patients for analyzing interventions is a variance reduction technique that significantly reduces the computational requirements necessary to determine the dominance of interventions under uncertainty. When individual's life courses are comparable, we do not need to "simulate out", via more replications, the stochastic differences in individual life courses when analyzing interventions. The need for such variance reduction techniques becomes particularly apparent when the interventions analyzed have only small effects on individuals. In our model of colorectal cancer, we analyze public health campaign interventions that "nudge" individuals to comply with screening. We demonstrate how using common patients serves as a variance reduction technique.

The fixed population datasets that define our population incorporate a multitude of attributes. Since the simulated individuals defined by this data set are comparable between interventions, we propose that calculating cost-effectiveness at an individual level and calculating individual cost-effectiveness ratios for specific subgroups are beneficial ways of analyzing the distribution of the benefit of an intervention across a population. With this information it is also possible to make qualitative statements about the equity of particular interventions.

2 LITERATURE REVIEW

The concept of Common Random Numbers (see Law (2014)) is a well-known and accepted variance reduction technique that has long been applied in various simulation applications. Leveraging the variance reduction and interpretability of CRN in individual simulation has only recently been recognized as an important methodology in health policy simulations. Shechter et al. (2006) demonstrated that efficiency gains could be achieved by using CRN in a Monte-Carlo simulation of individuals. In their cohort-based, Monte Carlo simulation, they showed that using common random numbers in an individual's event generators produced smaller confidence intervals for any fixed-size cohort. The authors' results also demonstrate that the confidence intervals produced by fairly small cohorts simulated using common random numbers were essentially the same as those produced by cohorts whose size was orders of magnitude larger (large size being an alternative variance reduction technique); thus

substantial computational savings may be achieved by using CRN. Murphy et al. (2013) contributed to the literature relating to CRN in Monte Carlo simulation by investigating the effect of degrees of integration of Common Random Numbers within a simulation model. In their study, fully integrating CRN led to a 93.7% reduction in variance, while partial CRN provided a 5.6% reduction in variance. Additionally, using CRN with Probabilistic Sensitivity Analysis (PSA), the authors demonstrate that these CRN techniques produce substantially tighter dispersions of results from the PSA compared to no CRN, and this results in better identification of the true effects of risk and uncertainty in the model.

The literature presented so far demonstrates the effectiveness of using CRN in Monte Carlo simulation only. These papers, with their focus on Monte Carlo simulation, have not dealt with the details of implementing CRN in more complex discrete event models. Despite the history of CRN as a variance reduction technique (VRT) in discrete event simulation and this support for its effectiveness, CRN is rarely discussed or known to be applied in individual discrete event models of disease progression. A few of the major discrete event models of disease have noted the use of separate random number streams for different life course events (see Roberts et al. (2007) and Goldhaber-Fiebert et al. (2007)). The main work that attempts to provide guidance on how to implement CRN in a discrete event individual simulation model is by Stout and Goldie (2008). Stout and Goldie provide a good overview of important issues faced when implementing CRN in a discrete event model. Particularly, they highlight the need to have multiple random number streams driving the different event streams in a discrete event individual simulation model. Additionally, they recognize the benefits of interpretability of individual level results when CRNs are applied to a detailed model of an individual.

Our work builds directly on Stout and Goldie. Our particular application of disease modeling, however, which models how individual choice affects colorectal cancer progression and hence outcomes, has raised issues beyond those addressed in Stout and Goldie. These new issues require additional approaches to fully implement CRN within a simulation model. Additionally, we extend Stout and Goldie by demonstrating the utility of individual comparability generated by applying CRN in our simulation model.

Having comparable individuals in our simulation model generated by CRN is most useful in that it allows us to make comparisons across groups in our simulated cohort. Subgroup analysis is particularly common in the analysis of medical clinical trials and observational studies. Particularly, there has been a line of work that has highlighted looking at individual cost-effectiveness between subgroups of individuals as the best approach for identifying policy impacts. Ioannidis and Garber (2011) present the notion of an individual cost-effectiveness ratio. They utilize this ratio to highlight differences in impacts to different groups across the population. Differences in impacts should inform our decision making. Pauly (2014) highlights the difficulty in determining the cost effectiveness of an intervention when the benefit is heterogeneous across the population. We intend to show that individual cost-effectiveness is a qualitative tool for making decisions on the cost-effectiveness of interventions even when those effects are heterogeneous.

3 NATURAL HISTORY MODEL OF COLORECTAL CANCER WITH INDIVIDUAL CHOICE

3.1 Description of Model

We have developed an individual-level simulation model of Colorectal Cancer (CRC) which we use to evaluate interventions that affect users' decisions to screen for colorectal cancer.

Their choices can be affected either through their mode choice (between invasive colonoscopy and less invasive Fecal Occult Blood Test (FOBT)) or through their probability of compliance with their chosen mode. The core disease progression model is based on a discrete event, natural history model of colon cancer progression that represents the polyp/adenoma process of colon cancer development. Our discrete event representation is based on the MISCAN-Colon implementation of the polyp-adenoma process (Løve et al., 1999). In this representation; `Lesion` objects are generated based on incidence rates within the population. The lesions either start out as polyps or precancerous objects, then depending on the rate of progression and testing choices, they progress to later stages (or can be removed) as time goes on.

The user choice component of our model is represented by a logistic regression model estimated using claims data from individuals in a state-supported health plan. This includes full information on Medicare, Medicaid and Dually insured populations, as well as individuals covered by a large private insurer in North Carolina (Cornejo, Mayorga, & Hassmiller Lich, 2014).

3.2 Population Evaluated

The population analyzed by this model is a representative synthetic population of individuals in the State of North Carolina in the year 2007. This population is based on data from the non-public, micro-level files of the US Census American Community Survey (“American Community Survey,” 2012) completed in 2007. Using appropriate sample weights, a full size population is generated from these non-public samples (Wheaton et al. 2014). This “smart shuffling” process enables public access and use of the resulting population size files. The census data contains demographic information, including gender, race, income and geographic locational information. Information about insurance status is added by using a logistic regression model (Brown, 2012).

3.3 Interventions to be Evaluated

Using our models of choice and colorectal cancer progression, we intend to evaluate two interventions that affect individual compliance or modality choices. We wish to understand how each of these interventions affects the number of patients up-to-date with screening over time and how these increased screening rates affect individual downstream outcomes like life years lost to cancer (lifelost) and the number of cancer deaths. The two interventions that we evaluate are: A program of mailed reminders to Medicaid and Dually-insured patients and a mass media campaign targeted to African Americans. Each of these interventions will be compared to a baseline scenario of “compliance as usual” in which individual compliance with screening is determined by the baseline statistical models estimated from the data. These interventions change outcomes by changing the probability of compliance with assigned modality. Detailed information about the structure of the interventions can be found in Lich et al.(2014).

4 CREATING A “COMMON PATIENT” USING COMMON RANDOM NUMBERS

In order to make meaningful comparisons of policies, we want to ensure that the individuals we are simulating have the same life course between interventions, except as altered by the intervention policy. We call the individuals who have identical life course between interventions, except for events induced by interventions, “common patients”. By creating a common patient, we are separating the stochastic noise created by the dynamic, stochastic events in an individual’s life course from the uncertainty in the effects of applying the intervention to a particular individual. Eliminating stochastic noise in life courses between interventions reduces the computational effort required to evaluate intervention policies that affect individuals and it also enables the individual analysis presented in the next section. Individual analysis, as previously stated, allows meaningful comparison of individual’s outcomes between intervention policies.

Creating the common patient requires synchronization of simulation events between interventions. Synchronization implies that between interventions in a given replication (replications are differentiated by different random number seeds) individuals will have the same set of events such as cancer onset, screening choices, screening results and death age except as those events are directly affected by the intervention. The well-known variance reduction technique of Common Random Numbers (CRN) is the fundamental way of synchronizing simulation events; it uses identical streams of pseudo-random numbers between interventions (same initial seed in our pseudo-random number generator) to generate the same stream of random variates (draws from a statistical distribution) that then determine simulation events. However, our application of CRN to our colorectal cancer simulation shows that the complexities of discrete event simulation models require more than just a synchronization of the model’s overall random number streams. Many discrete event models of individuals, ours included, are composite models of several discrete event or stochastic systems. For example, in our model of colon cancer, the Disease Progression process consists of two separate event generators, Cancer Creation and Cancer Progression, that must be synchronized. Each of these composite stochastic systems, must be synchronized in order for the individual’s life courses to be comparable. Additionally, some of these event generators interact during the dynamic progression of time in the model. Changes in one process can generate a change in another process, and this can change the path of sampling from its random number stream.

To address the issues discussed above, we have developed a multi-pronged approach to synchronize events in order to create a common patient. First, we classify the events streams that generate events in an individual’s life course and put these event streams on separate streams of Common Random Numbers (CRN). Secondly, we do as much pre-calculation of events in an individual’s life course as possible. This is accomplished either outside the model in a pre-processing step and/or at the beginning of the model run for other events. In the remaining subsections, we provide insight regarding the necessity of synchronizing event streams and address practical considerations in the synchronization of events. Finally, we more fully discuss the advantages of common patients in dealing with uncertainty and in the comparing of results.

4.1 Visualizing the Issues in Synchronizing Event Streams

We have highlighted the issues related to synchronizing life courses to create common patients. We emphasized that it is the multiple event streams in a discrete event model that cause difficulties. In this section, we provide a visual comparison of different levels of event

synchronization with CRN using our CRC model under two different scenarios: 1) no CRN, and 2) CRN for each event stream (the common patient). Referencing our model of colorectal cancer described in Section 2, there are several event streams modeled as objects in our Object Oriented simulation framework. The `Person` objects encapsulate the health states of individuals. Individual health states are primarily determined by the existence of `Lesion` objects which represent cancers. `Lesion` objects only exist when a person has cancer and are generated when a polyp/cancer develops. These polyps are generated and assigned to patients by a `LesionGenerator` object that exists over a person's life course and generates Lesions based on incidence rate tables. Thus `LesionGenerators` exist throughout the whole life course, but lesions only exist when they are created. For this model, lesions can also be removed if the cancer is cured. Each of these objects `Person`, `LesionGenerator` and `Lesion` encapsulate dynamic events that need to be synchronized, thus they will each need an independent random number stream. Figure 1 illustrates the impacts of event synchronization by comparing the No CRN scenario with the Common Patient implementation. This highlights the differences in events in a single individual's life course between interventions. Most notable, it is seen that when no CRN (Figure 1, top two panels) was used we can neither guarantee identical cancer progression nor can we equate estimated lifetimes. This stands in contrast to the common patients model (Figure 1, bottom two panels) where cancer progression and estimated lifetimes are the same except when the patient is influenced by the interventions to pursue more screenings, thus effecting a change in the progression of the disease process.

4.2 Methods for Creating Common Patients

Having established the need for synchronizing event streams within the simulation model, we present several techniques that can be applied alone or in combination to synchronize the events of the simulation model to create a common patient. All of these techniques are fundamentally based on using common streams of random numbers for events. The three techniques that we have found useful include: 1) running each event generator on its own random number stream, 2) determining as many events as possible at the beginning of the model run, and 3) pre-computing states/events outside of the model.

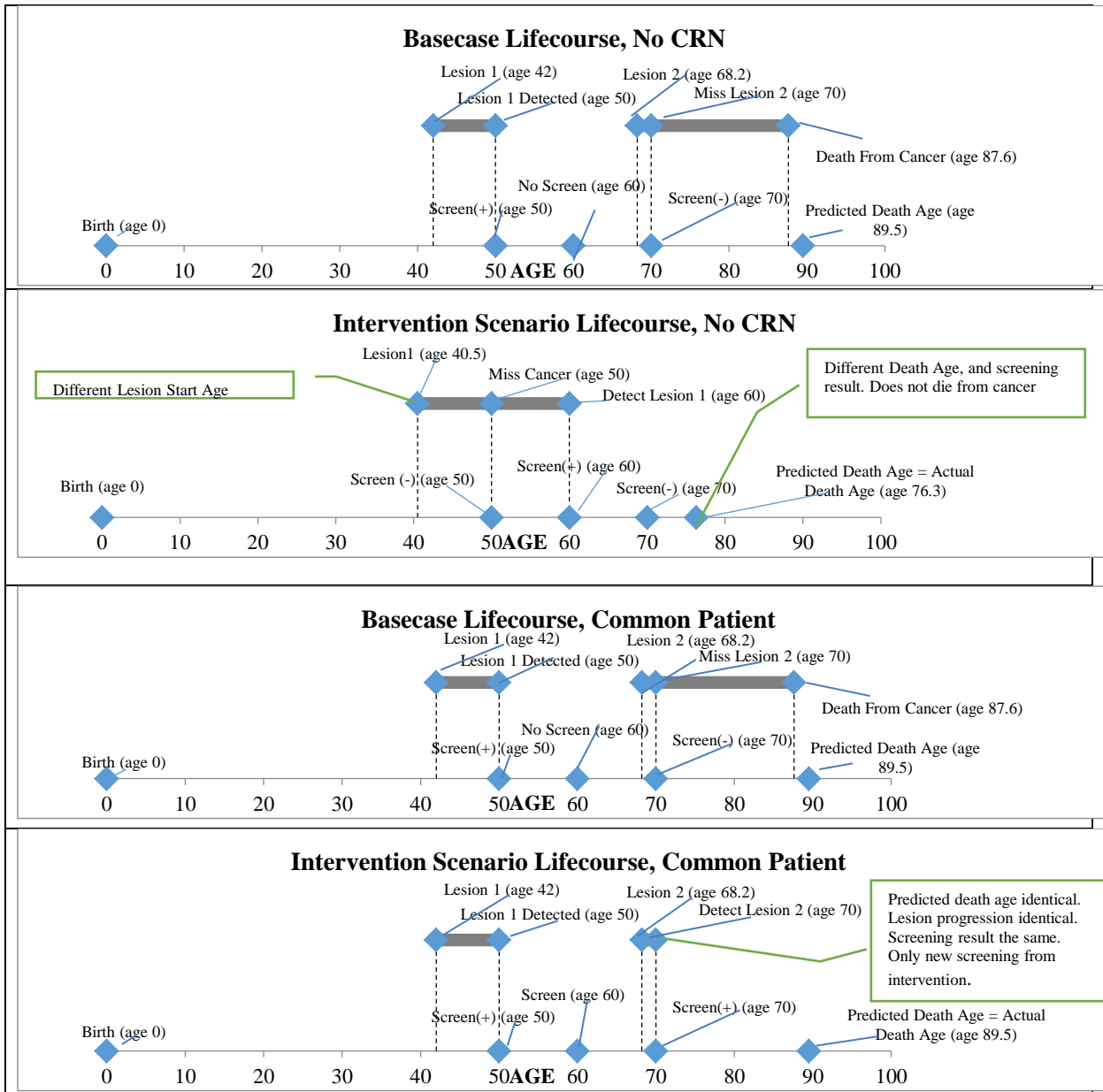


Figure 1: Life courses under different implementations of Common Random Numbers.

4.2.1 Separate Random Number Streams

We have found that there is substantial difficulty synchronizing the events of a simulation model, and hence in creating a common patient, when Common Random Numbers are only used at the model level. Model level random numbers means that the streams between two scenarios (interventions) share the same random number seed, but all random number calls in each of the scenarios use the same random stream. The problem with this design is that if an intervention adds random number calls or causes changes to one or more of the event

processes, all future events will be out of sync between the scenarios from that point in time on. For example, in our model, an intervention adds some random number calls to check whether an individual is eligible to receive the intervention which may or may not induce any real change in behavior and hence disease progression. The fact that we have added some random numbers draws causes all future disease progression and decision events for a given patient to be out of sync because we are sampling at different locations in the random number stream.

Our solution to this difficulty is to have separate random number streams for each major “event-generating process” in the model. We define an important “event-generating process” as a process that we want to progress separately and in sync over time except as it is directly impacted by the intervention. In our model, this meant establishing separate random number streams for our `Person` objects, `LesionGenerator` objects and `Lesion` objects. Additionally, interventions called within the `Person` object were placed on their own random number stream.

In the `Person` object, an individual’s health states are tracked and his/her compliance decisions are made. Within the `Person` object, there are two event streams that need to be coordinated, the compliance decision event stream and the test result event stream. The compliance event stream is synchronized between interventions, ensuring changes in the compliance probabilities from the interventions affects final compliance decisions made. When synchronized, the same uniform random variate is used to determine the compliance decision. This ensures that we are evaluating the marginal impact on decisions resulting from the changed compliance probability. The separate test result stream ensures that the additional tests generated by the intervention do not change the results of future tests. Since FOBT tests have relatively low sensitivity, this is an important issue; we do not want to change the results of the baseline tests (tests that would have been performed regardless of the intervention) when we sample results from the additional tests.

The `LesionGenerator` and `Lesion` object also have their own event streams. The `LesionGenerator` is entirely independent of the compliance decisions and other events in the model. The `Lesion` object’s trajectory should be independent of any other lesion and of the individual’s events except when an individual recognizes and removes a precancerous lesion or polyp.

4.2.2 Compute Events at the Beginning of the Model Run

The dynamic, interactive nature of the components of the simulation model is the main source of difficulty in synchronizing the random number streams. We can avoid many possible issues, and simplify our design by computing as many events related to our new interventions as possible at the beginning of the run. This removes the effects that might be generated by events being reordered over time by the intervention. Model intervention events are candidates for this technique if they are independent of a dynamic model state. For example, in our model, an individual’s decision to screen or not to screen depends only on states that can be pre-determined at the beginning of the model run, therefore, we can pre-determine the sequence of tests, patient compliance with those tests, and the test results (i.e.

whether the cancer is found or not) at the beginning of the model run. Not all events are candidates for this solution. Events that are directly dependent on the state progressions of some model component cannot be computed at the beginning of the model run. Applying this technique carefully can reduce the complexity of applying common random numbers because we can do this processing step with carefully controlled random number streams rather than having to safeguard random number synchronization at every stage.

4.2.3 Pre-compute Events/States Before the Model Run

In a very similar fashion to the process discussed above for computing events at the beginning of the model run, we can pre-compute events/states. When events are computed before the model run in external code, they can be imported into the model by data files as needed during the model run. Almost any event identified as a candidate for pre-computation within the model can be pre-computed outside the model and then imported this way. The main consideration here is a practical one and depends upon the functionality or data structures of the simulation software being used that can make the event computation or storage much easier. For example, we compute individuals' insurance status before and after age 65 and store them in our population input files. This eliminates the need to perform a probabilistic transition between insurance types during the model run.

4.3 Computational Benefits of Common Patients

We have highlighted the issues in event synchronization important for creating a common patient and presented some practical recommendations on how to achieve a truly common patient in a simulation model. In justifying the common patient so far we have focused on comparability of outcomes as the reason for expending this effort in synchronizing simulation events. In this section, we will demonstrate the computational benefits of the common patient using as an example from our individual simulation model of colorectal cancer.

Since we have carefully coordinated the cancer-free lifetimes of individuals between intervention policies, we can confidently isolate the effects of each intervention. To effectively eliminate the stochastic noise if all events were not coordinated would require repeated random runs for a given individual and would require many (about 100) replications of each individual/population cohort. With the common patient concept implemented, we only need to simulate out the stochastic noise associated with the marginal change in compliance probabilities and how that affects individual marginal choice; for this purpose, it is sufficient to do 10-20 replications of the individual/population cohort to understand the effect of the intervention. This represents a significant decrease in computational effort with no loss of accuracy. For our application this means that simulation experiments can be completed in hours, rather than days, because of the high computation time cost of each replication.

4.4 Numerical Example of Common Patient Concept

In the previous discussion, we argued that the common patient gives us comparability between individuals in different scenarios and that this comparability gives us a substantial computational advantage when simulating heterogeneous cohorts of individuals. We conduct several experiments to analyze the effect of the two interventions on two outcome statistics of interest in our model. The first statistic is a time varying statistic that tracks the number of individuals alive in each of the model years 2014 -2033. The second statistic is an output statistic that calculates the average life lost by each individual. We run the model with common patients implemented. By taking the difference between the baseline scenario and each intervention scenario we calculate the number of cancer deaths averted due to improved screening choices. The results for deaths averted is graphed in Figure 2. This figure shows the cumulative number of cancer deaths averted by the intervention. As expected the differences between the baseline and the interventions scenarios is always non-zero and there is a monotonically increasing total number of deaths averted due to screening.

To demonstrate the difficulty in interpreting the deaths averted statistic when the common patient is not implemented, we graph the common patient result against the results of models where common patients are not implemented. To simplify this comparison, we chose one of our interventions, the All ON (free screening, mailed reminder and mass media applied simultaneously). In Figure 3, we compare the results of the common patient scenario with 1, 20 and 50 replications when common patients is not implemented. As we see there is some erratic behavior in the death averted statistic when common patients is not implemented. For low numbers of replications this value may be negative, implying that the intervention scenario may be worse than baseline. As more replications are performed, we see a convergence toward the common patients scenario, as expected, but it is notable that this convergence required an order of magnitude more replications than the common patient scenario.

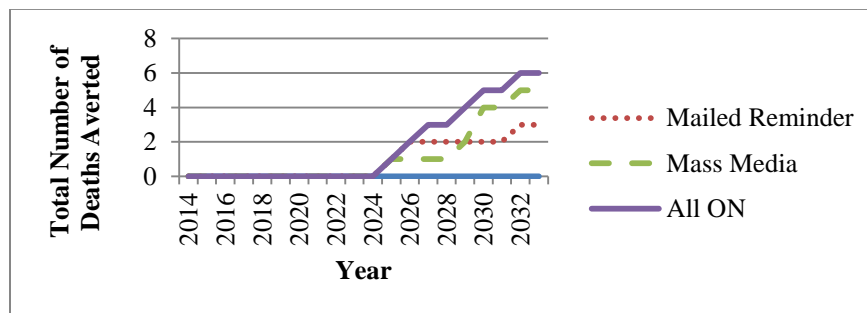


Figure 2: Total Death Averted under each intervention between 2014-2033.

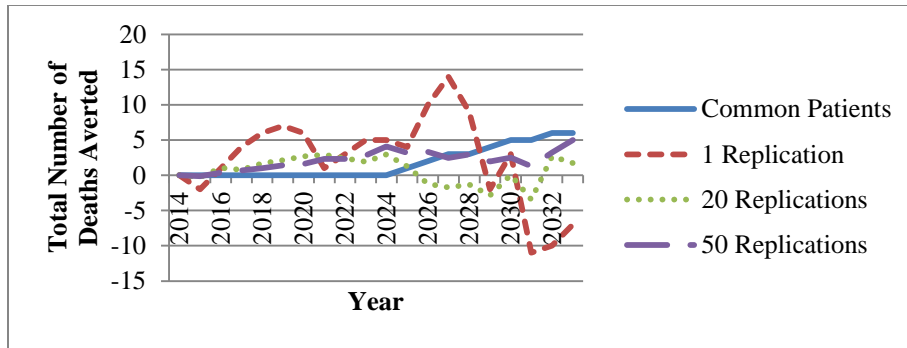


Figure 3: Death Averted for All ON Intervention: Common Patient vs. Standard approach.

In addition to faster convergence of the time varying statistics presented in Figures 2 and 3, the common patient concept also led to faster convergence for output statistics. One output statistic of interest in our model is the number of life years lost to cancer (lifelost). If a person dies from cancer, we compare his death age with his cancer free lifetime determined at the beginning of the model. If there is a difference in their final death age, this is his lifelost. If a person does not die before his natural, cancer-free lifetime due to cancer this value is 0. The individual lifelost values are averaged over the whole population to determine average lifelost at the end of the model run. When the base case and the All ON scenario values of this aggregate lifelost statistic are differenced, we get the life years gained per person. When we compare the results of calculating this statistic using common patients vs. the no CRN approach with 1,20 and 50 replications, we see (Figure 4) a convergence to the common patient produced value as we perform more replications, but again this convergence comes at substantial added computational cost in terms of the number of required replications for convergence when common patient is not used.

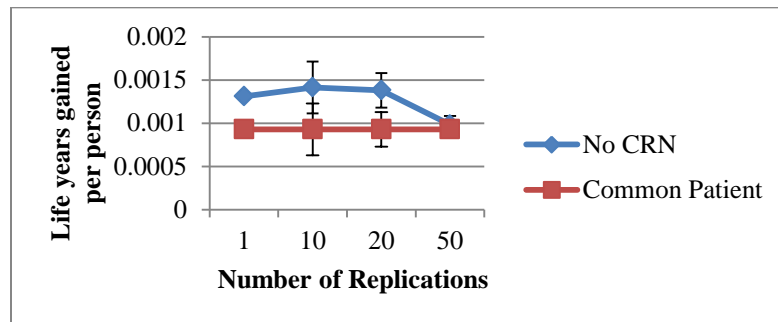


Figure 4: Life years gained convergence: common patient vs. no CRN for the All ON intervention

These numerical examples clearly demonstrate that implementing common patients is very beneficial from a computational point of view.

5 INDIVIDUAL COST-EFFECTIVENESS FOR EQUITY EVALUATION

In our individual simulation model, an individual’s disease progression, compliance and response to treatment are functions of a large array of individual attributes. Having created the common patient, it is possible to directly compare individuals between two scenarios (interventions). Given the low probability of the events being evaluated here, there is often not a substantial benefit to comparing a single individual between interventions, however, each individual has multiple individual attributes. If we average the outcome effects of the intervention for a subgroup of which the individual is a part, we can get a clearer picture of how much a particular individual in that subgroup would stand to benefit from the intervention applied. Because of heterogeneity of disease progression and response to interventions by different groups, the magnitude of the improvement in outcomes can vary significantly between subgroups defined by individual attributes. We believe that incorporating individual level cost-effectiveness information for different subgroups is valuable information for policy makers that can aid in understanding potential disparate impacts of the intervention. Providing information on these disparities provides a qualitative tool for promoting equity in the slate of interventions that are applied to a population.

5.1 Performing Subgroup Analysis

We demonstrate the utility of subgroup analysis by presenting a case study utilizing the results from our simulation model of colorectal cancer. Recall from Section 3 that disease progression in our model varies based on age, race and sex and individual choice varies on a range of attributes including race and sex, but is also driven by individual insurance type. In Table 1 we present the results from the lifelost statistics (described in Section 4.4) grouped by insurance type and sex for the base case and for the free screening, mailed reminder and mass media campaigns as well as an “all on” scenario for the age cohort who will turn 50 in 2014 (this is only a portion of our population).

Table 1: Lifelost statistic by insurance type and sex.

Insurance Type	Sex	Count	Life years lost to cancer				
			Baseline	Free Screening	Mailed Reminder	Mass Media	All ON
Medicaid	Female	4843	0.1682	0.1682	0.1558	0.1508	0.1476
Medicaid	Male	2806	0.1460	0.1460	0.1170	0.1189	0.1170
Uninsured	Female	11595	0.2210	0.2198	0.2210	0.2061	0.2049
Uninsured	Male	13650	0.1635	0.1635	0.1635	0.1508	0.1508
Private	Female	49704	0.1687	0.1687	0.1687	0.1625	0.1625
Private	Male	46360	0.0989	0.0989	0.0989	0.0942	0.0942

Table 1 shows that females have greater average life lost than their male counterparts in all scenarios. When examining results by insurance type, the uninsured individuals have significantly worse outcomes compared to the other insured groups. In examining the cost effectiveness of interventions we will look particularly carefully at this group.

To perform cost effectiveness analysis we must have costs of each intervention. We have developed a cost structure for each of the interventions analyzed and described in Hassmiller (2014). Once these costs have been determined, they can be distributed across the population subgroups proportional to the number of individuals in each of these subgroups. Table 2 contains the individual cost effectiveness ratios for each of the subgroups for the mailed reminder, mass media and all on

interventions.

Table 2: Individual cost-effectiveness ratios.

Insurance Type	Sex	Count	Individual CER on lifelost statistic	
			Mailed Reminder	Mass Media
Medicaid	Female	4843	\$513.34	\$80.83
Medicaid	Male	2806	\$218.97	\$51.64
Uninsured	Female	11595	N/A	\$93.90
Uninsured	Male	13650	N/A	\$110.15
Private	Female	49704	N/A	\$225.81
Private	Male	46360	N/A	\$299.15

From these cost effectiveness results we can see the relative cost effectiveness of the mass media campaign for all population groups. We can also see that the nature of the effects of the mass media campaign does not make it a particularly cost effective intervention to reach privately insured individuals. When we compare these costs of targeting the mailed reminder program to Medicaid/dual insured patients we do not see a significant difference in cost. This suggest that it may be valuable to spend the additional money on Medicaid/dual patients because there are public policy reasons to improve their outcomes and it is equally cost effective to reach this group as compared to privately insured patients.

6 CONCLUSION

Creating individuals that are comparable across interventions is highly desirable for individual disease simulation models. These comparable individuals are created by carefully identifying the different event processes in the model that generate the health events in an individual's life course and running them on separate random number streams that are comparable between interventions. Since the life course thus generated are the same except for differences specifically induced by the interventions, we describe these individuals as common patients. This is a result of the application of Common Random Numbers. However, because of the complex dynamic nature of many models, achieving full individual life time synchronization requires multiple, careful approaches to synchronization of events. We achieve synchronization both by using different random number streams and by determining as many events as possible at the beginning of the model run or in a preprocessing step. As demonstrated with numerical examples from our model of colorectal cancer, the common patient concept has substantial computational benefits.

The use of the common patient enables comparisons to be made between individuals and this opens up a host of possibilities for performing subgroup cost-effectiveness analyses. We performed some of this analysis for subgroups in our model and demonstrated how these analysis can be used as a qualitative tool for the identification of disparities in outcomes and for evaluating the relative cost effectiveness of interventions across subgroups .

ACKNOWLEDGEMENTS

Funding for this work was provided in part by the National Science Foundation (CMMI 1433602) for Mayorga and by the Centers for Disease Control 3U48DP001944-03S1 (SIP 11-041) for Hassmiller Lich.

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3.2 Conclusion

In this section we described a technique for creating a “common patient.” This technique guarantees comparability between individual life courses in different intervention scenarios. This comparability greatly simplifies interpretation of health changes seen as a result of the interventions. Additionally, we have demonstrated the computational benefits derived from our implementation of common patients. Particularly notable is the substantial reduction in the number of replications of each individual’s lifetime required to evaluate each scenario. The size of these replication savings lead to a meaningful reduction in computation time. The reduction in computation time is such that it enables larger, more complex models to be evaluated. For our model of colorectal cancer, a larger model means that a complete, representative, synthetic population of the state of North Carolina can be evaluated. Running large populations is important to accurately gain an understanding of individual effects across geographic areas and within particular demographic subgroups. It is very difficult to scale the results when simulating only a portion of the population, even if it is reflective of the demographic makeup, because of the interactions between geographic and demographic factors. These geographic interactions are lost when only a portion of the population is simulated. The impact of the loss of demographic information is particularly acute when geographic features are defined on a small scale (zipcode level or smaller) as it is in our data. The practice of simulating the whole population also has great appeal to policy makers since they can directly understand the effects of an intervention on the population of interest.

CHAPTER 4: OPTIMIZING TIME-VARYING INTERVENTION POLICIES IN DYNAMIC INDIVIDUAL SIMULATION

4.1 Introduction

A major feature of the simulation model presented in Chapter 2 is the inclusion of a dynamic model of individual choice for screening compliance and screening modality choice where individuals make their screening decision in multiple periods over their lifetime. The purpose of creating a model that includes individual choice related to screening behavior is to enable the evaluation of public health interventions aimed at improving population health outcomes by changing individual decision-making. These interventions were evaluated on a large heterogeneous population of individuals whose disease progression and screening choice behavior was differentiated based on geographic and demographic information. A statistical model is used to represent individual screening choice in each period during the lifetimes simulated by this model. The statistical model, estimated on observational data, reflects how people currently behave with respect to colorectal cancer screening. This approach allowed the modeling of differences in screening behavior between population subgroups. In Chapter 2, several public health interventions were evaluated that had static, fixed effects on individual decision-making probabilities in every period that the intervention was active. The intervention “effect” parameters were based on the estimated effect of a narrowly defined intervention policy. These estimates were based on evidence from intervention case studies and broader observational studies in the public health literature. This approach assumed that the public health budget for a given intervention would be applied evenly over the decision horizon and provided no mechanism for varying the amount of intervention effort allocated to a specific period during the intervention timeframe.

Approaching the problem in this way ignores three important phenomena that are often observed:

- 1) The magnitude of intervention efforts (i.e., the number of messages received in a media campaign, or the amount of cost reduction program) affects individual behavior with regards to the likelihood of screening, and this behavior exhibits varying returns-to-scale behavior.
- 2) The probability of disease incidence and the possible health gains for detecting the disease vary over time, creating time-varying benefits.
- 3) Different population groups vary in their disease dynamics and hence the best policy for improving the health of a group may be different between groups.

The presence of these phenomena suggest the most efficient optimal policy is one where the amount of intervention policy expended in a given period varies across an individual's lifetime and an intervention application time period. This dynamic policy should allow policy makers to more efficiently allocate resources as compared with a static health policy.

Additionally, the heterogeneity of the population subgroups in their disease progression and screening decision-making mentioned in the previous chapters indicates that the best policy for maximizing the whole population's outcomes requires trade-offs between the best time-varying policy for a given subgroup and the population as a whole. This chapter formulates and solves the problem of optimizing the allocation of a public health budget to maximize long-term health outcomes of a heterogeneous population. Because of the complexity of both the disease process and the analysis of the effects of an intervention, we

will resort to modeling the health outcomes using simulation. We begin by exploring several techniques to solve this simulation optimization problem and identify and demonstrate one of them as an efficient method to solve this problem.

This chapter is closely connected to the work in previous chapters related to evaluating policies for improving colorectal cancer outcomes and developing simulation methodologies to improve the evaluation of these policies. The mathematical techniques developed will be formulated within the context of designing policies that improve individual screening for colorectal cancer. The motivating numerical example upon which we will test our solution techniques will be the optimization of a public health policy for colorectal cancer when individuals make screening decisions every 5 years over a 25-year intervention window from ages 50 to 75. The simulation model presented in Chapter 2 will provide data for and determine the structure of a simplified Monte Carlo simulation model used as our simulation engine in this section. The Monte Carlo simulation model described in this section implements the Common Patient methodology presented in Chapter 3 to simulate individual lifetimes for the sake of policy evaluation during optimization to ensure differences in policies can be discriminated using a minimal amount of simulation (computation) effort.

4.2 Defining the Population Policy Optimization Problem

The goal of this chapter is to show how to choose a single allocation of a fixed public health budget to be applied to a heterogeneous population over a finite time horizon in order to maximize population health outcomes. In determining this optimal policy, it is necessary to account for disease dynamics over time and to account for variation in disease progression between groups. In our formulation, we assume there exists a population of D individuals.

This population can be divided into a finite, countable set number of K population subgroups. The size of each of these K population subgroups is the number of individuals in that subgroup. We denote population subgroup size by $w_k, k = 1, \dots, K$. A population subgroup represents a segment of the population defined by its specific attributes. For example, we may be interested in classifying the population by Race (White, African-American or “other”) or Insurance Status (Private, Medicare, Medicaid, or Uninsured) as well as any other attribute available to us. Any of these attributes could also be combined to create more specific population subgroups. Increasing the specificity of the population subgroups increases the size of K .

We desire to evaluate polices on this population and its specific subgroups that change their behavior at specific decision points that are spread out though time. Let T_{min} be the earliest time point (epoch) in a person’s life course at which the individual makes a decision and T_{max} be the latest period in which the individual could make this decision. Let $\mathcal{T} = \{t : T_{min} \leq t \leq T_{max}\}$ be the set of time points where testing is taking place. Each individual in these K population subgroups has variety of parameters that determine disease progression and testing response. These parameters, in general, can vary between population subgroup (indexed by k) with respect to age that corresponds with the observational period (indexed by t). The disease process is defined by the parameter $d_{k,t}$; the probability of disease being present for an individual who is a member of subgroup k at decision time point t . Should cancer be present according to the parameter $d_{k,t}$, the probability of detecting

cancer via test (e.g. test sensitivity) is $s_{k,t}$. We assume that there are a finite number of periods in which individuals make decisions and during which the intervention could be applied to change that decision. The number of decision periods is given by T . Individuals' screening behavior, modeled as the probability of their complying with screening at a given decision epoch, is given by the function $p_k(\cdot)$. This probability is a function because it is dependent on the choice of intervention effort, x_t , at time t . The function, $p_k(\cdot)$, represents a non-linear function that varies with x_t . An expanded explanation of the form of $p_k(\cdot)$ can be found in the next section, Section 4.3. Finally, the "reward" in health savings (life-years gained per individual) from detecting cancer at time t , in population subgroup k is given by the random variable $V_{k,t}$. This random variable is distributed according to the distribution $F(\theta_{k,t})$. It should be noted that the distribution, $F(\theta_{k,t})$, varies among different population groups and over time within a population group. The cost per unit of intervention effort is given by c . The size of the total public health budget that is available to be allocated during the decision periods T is given by B . Budget and cost per unit of effort imply that we have B/c units of effort to allocate during the T decision periods. Given this notation we formulate the problem of maximizing the total reward over the whole population as follows:

$$\begin{aligned}
& \max_{x_t, t=1, \dots, T} \sum_{k=1}^K \sum_{t=1}^T w_k d_{k,t} s_{k,t} p_k(x_t) E[V_{k,t}] \\
& s.t. \\
& \quad c \sum_{t=1}^T x_t \leq B \quad (\text{Budget Constraint}) \\
& \quad x_t \geq 0 \quad \forall t = 1, \dots, T \quad (\text{Non-negativity Constraint})
\end{aligned} \tag{4.1}$$

Where:

- K : Number of population sub-groups
- T : Number of decision epochs in intervention window
- x_t : Units of public health effort chosen to be used at time t
- w_k : The size of the k -th sub-population group
- $V_{k,t}$: Random Variable of the value of detecting disease for the k -th subpopulation
 $V_{k,t} \sim F(\theta_{k,t})$ represents the distribution of life-years saved per individual by detecting disease at time t
- $d_{k,t}$: Probability of disease incidence for individuals in the k -th sub-population at time t
- $s_{k,t}$: Sensitivity of screening test for individuals in the k -th sub-population at time t
- $p_k(\bullet)$: Probability of an individual from the k -th sub-population screening as a function of intervention effort, x_t , at time t
- B : Total public health budget
- c : Cost per unit of public health effort

Sometimes it will be convenient to express the solution of intervention effort, x_t over each of the time periods of the time horizon $t = 1, \dots, T$ as a vector $\mathbf{X} = (x_1, \dots, x_T)$ where at a feasible solution $\|\mathbf{x}\| = B$.

It is important to note that this objective focuses on developing the most efficient solution for maximizing population health given the weights on each population subgroup, w_k given by the size of the population subgroup indexed by k . This stochastic optimization problem does not lend itself to a closed form analytic solution because the rewards from detecting disease, given by the random variable $V_{k,t}$, are distributed according to the general distribution $F(\theta_{k,t})$ whose parameters, denoted by the vector $\theta_{k,t}$, depend on both the

population subgroup and the time period in which we are performing the evaluation.

However, this formulation is an excellent candidate for evaluation using Monte Carlo simulation methods. The objective of the population problem is linear and separable in each of the population subgroups. Thus, we can construct a general simulation model that we parameterize with the particular representation of $d_{k,t}$, $s_{k,t}$ and $p_k(\bullet)$ and the reward

distributions $F(\theta_{k,t})$ for subpopulation k . Thus, each run of the simulation model will sample the events related to testing, disease, and rewards from testing within the lifetime of a cohort of individuals of size N from that a particular subgroup k . Thus, we can use the following Monte Carlo simulation model to estimate the value of our objective function,

$$\max_{x_t, t=1, \dots, T} \sum_{k=1}^K w_k \frac{1}{R} \sum_{r=1}^R \frac{1}{N} \sum_{n=1}^N \sum_{t=1}^T I_{\{U^{n,r} < d_{k,t}^{n,r} s_{k,t}^{n,r} p_k(x_t)\}} V_{k,t}^{n,r}. \quad (4.2)$$

In this simulation model, $n = 1, \dots, N$ indexes the simulated individuals in population subgroup k and $r = 1, \dots, R$ is the number of population (simulation) replications. The Monte Carlo simulation model provides us with an estimate of the average health outcomes of an individual in that population by simulating the health outcomes of each individual in the population group. It does this by simulating every screening decision point and accumulating the appropriate life-years saved (reward) if an individual has disease, screens for it, and that screen is successful. Since several of the components in Equation 4.1 are defined as probabilities where $p_k(x_t)$ is the probability an individual complies with screening as a function of spending, $d_{k,t}^{n,r}$ is the probability disease is present, and $s_{k,t}^{n,r}$ is the probability the test detects the cancer (a.k.a. the sensitivity of the test), we use samples from a uniform

distribution $U^{n,r} \sim \text{Uniform}(0,1)$ and the indicator function $I_{\{U^{n,r} < c\}}$ where $c = d_{k,t}^{n,r} s_{k,t}^{n,r} p_k(x_t)$ to simulate the discrete decision of whether cancer is detected or not. The case when disease is present, an individual complies with screening and the screening test is successful is modeled by $I_{\{U^{n,r} < c\}} = 1$. In this case, the individual accumulates the life-years gained reward $V_{k,t}^{n,r}$ that is sampled from the distribution $F(\theta_{k,t})$.

4.3 Defining individual behavior in response to intervention effort.

An important contribution of this model is its inclusion of a representation of how individual choice changes with respect to changes in the intervention/budget allocation solution, \mathbf{x} . In the formulation of the population problem, this representation was included through the function $p_k(\cdot)$. This function represents the probability of screening in period t given the level, x_t , of intervention effort/budget spent in period t . In this section we elaborate on the functional form this function should take to best model the behavior changes in response to an intervention. Additionally, we discuss how this function can be parameterized using data from observational studies that collect the effects of real-life intervention policies.

4.3.1 Representing baseline screening behavior

In order to estimate the effects of intervention policies in changing an individual's behavior, we must have a good model of how individuals currently behave in regards to their colorectal cancer screening decision-making. We represent the screening choice as a probability of choosing a screening modality in that period. We use a probabilistic structure

for the screening decision because from our perspective as social planners we cannot specify how individuals make the decision. From observational data, we can determine the average rate of screening compliance for specific population groups then use this rate as the probability of screening in our model. Translating this data on screening rates into a useful probability model requires some careful consideration of the context in which the data was collected compared to the specific situation in which it is being applied. In this section, we describe our characterization and parameterization of individuals' time-varying, probabilistic decision-making through a statistical model and how this baseline behavior changes in response to an intervention/public health spending.

We used discrete choice statistical models (multinomial logistic regression) to estimate the baseline probability distribution over the decision options because these models use observed choices of a heterogeneous population to filter the impact population attributes have on choice. The result of estimating a discrete choice model is a probability distribution across the available decision options based on an individual's attributes. In the current model, the decision options are: to Screen or not to Screen. As described in Section 4.1, this statistical model is fundamentally a static model; that is, it returns the probability of choosing each decision choice based on an individual's characteristics. This model can be converted for use as a dynamic representation of individual decision-making by repeatedly applying this model, estimated for a single decision period, over multiple decision periods. Each application of the model at a given decision period gives us a probability based on an individual's current characteristics. We represent the probability of a given choice in a given decision period as a density point. When this is done over multiple decision periods, we

generate a discrete probability density function over time. This is not a properly defined probability mass function (PMF) when viewed across the time dimension (i.e. total density equal to 1) because it represents the probability that a particular decision will be made in that period. For each decision period, the represented probability density point is part of a well-defined probability density defined on the complete set of mutually exclusive decisions that could be made in that period.

By the assumptions of the model, when each decision period is independent and an individual's characteristics are constant over time, we can represent an individual's decision-making as a constant function over time (see Figure 4-1). This assumption is partially mandated by our data since there is a paucity of quality longitudinal data which would be required to estimate correlations between decision periods.

The probability distribution between Screening and Not Screening generated by the logistic regression model is based on the specific time period over which the data is collected. For example if our data is collected over a 6 year interval than the probability distribution produced by logistic regression will return the probability of screening during a six year period. If we wish to define an interval between screenings in our experiment on the model that is different from the interval over which the data was collected, we must adjust the "raw" probabilities produced by the statistical models to account for this variation in timing. We use the following adjustment to convert the probabilities produced by the statistical model when we wish to model other decision intervals:

$$p_{new} = 1 - (1 - p)^{\frac{n}{N}} \quad (4.3)$$

This adjustment equation transforms the probabilities of screening, p , captured over a defined number of periods, N , to the length of each of the T decision epochs in the mathematical model of size n periods. This adjustment for the time period ensures we keep the same rate of compliance over the time period where the data was originally captured. This transformation is based on the assumption that screening decisions in each period are independent of one another. Given this assumption, a Binomial distribution can be used to model the probability of screening over a finite number of periods. Equation 4.3 converts the binomial probability of screening once on N period horizon to the binomial probability of screening once on a n period horizon. Figure 4-1 illustrates the application of this adjustment equation to a model where the baseline decision model is a 50% chance of screening over a 5 year period. It shows the density function of the same probability model expressed when the decision is made every year (in the color red) and when the decision is made every 5 years (in the color blue). We can say that these two rules are equivalent because the total probability of making a screening decision in a 5 year period is the same.

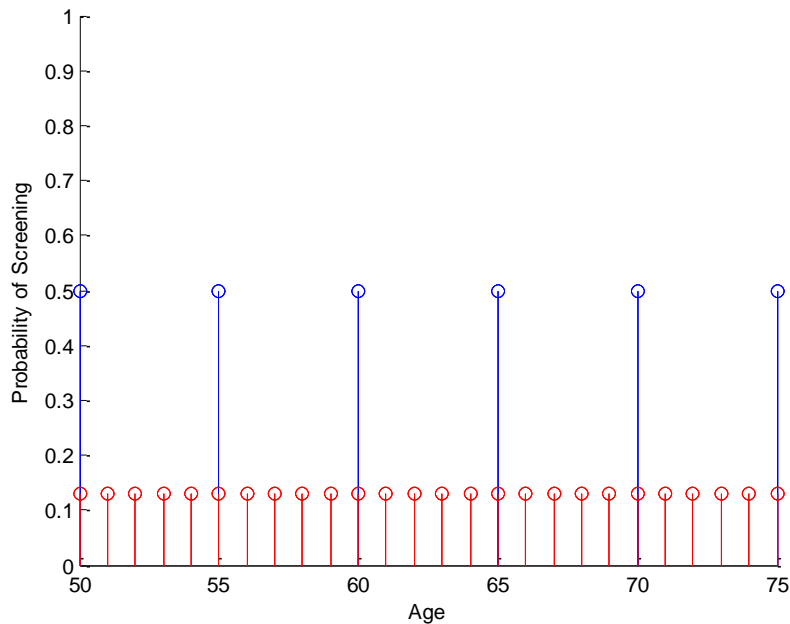


Figure 4-1: Density function of statistical model when screening intervals are 1 year and 5 years assuming a constant screening rate over time

4.3.2 Modeling how individual choice changes

The previous section described a representation of individual’s choice behavior as a probabilistic model. This model represents how individuals screen under the current policy regime. In this section we will often refer to this as the “baseline behavior” model of individuals. In this section we extend this model to incorporate a mechanism for describing how public health efforts translate to changes in individual behavior. This mechanism will incorporate dynamics of individuals’ responses to intervention efforts. It is often observed that individuals see increasing followed by decreasing returns to scale in terms of the change in health behavior in response to an intervention. This non-linear response to intervention effort is the grounds for asserting the existence of a dynamic optimal spending policy on public health interventions across individuals’ life courses. The diseconomies of scale and

the variation in rewards for screening over age represent interactions that can only be evaluated through this holistic, lifetime simulation modeling approach to intervention policy optimization. In the next section we present how the mathematical framework of the logistic function can be used to capture individuals' non-linear response to intervention efforts and how the function can be calibrated to the effects of a possible intervention. The representation of how individuals' behavior changes in response to intervention effort form is an important dynamic function within our simulation model and its form is a major driver in our solutions.

4.3.3 Literature on modeling the response of individuals to health interventions

The public health community has long been interested in designing and evaluating programs to change individuals' health behaviors. Much of this literature has focused on interventions in the clinical context. For example, we have seen papers evaluating individual compliance with different screening tests in Wohl et al. (2011), testing clinical systems of support to increase colorectal cancer screening evaluated in Green et al. (2010), and clinic based behavioral studies evaluating acceptance of colorectal cancer screening in Costanza et al. (2005). More recent literature has evaluated the effect of interventions that are delivered outside the clinic. These so called "mediated" interventions (intervention messages communicated through media vehicles) are becoming an important tool in the public health toolbox for improving colorectal cancer screening (Lewis, Brenner, Griffith, and Pignone, 2008). In the interest of developing meaningful policies, these studies and clinical trials often focused on the effect of a specific designed intervention. The rise of modeling and simulation in this area has opened the door to evaluating a wider range of intervention policies in

computational experiments. Computational experiments leverage data from clinical studies to test a wider range of policies. Often additional theoretical assumptions on individuals' behavior must be made to enable computational analysis. To facilitate computational modeling of the change in individuals' screening behavior due to public health media campaigns, a mathematical model of how individuals respond to information must be chosen. In this section, we explain the grounding of our choice of the logistic function as the model to describe how individuals respond to interventions and provide a context for this methodology within the social science and healthcare literature.

The modeling of individuals' response to social programs has been long studied in the social sciences within the context of understanding and modeling information diffusion. Mahajan and Peterson (1985) provide an early, in-depth comparison of models of information diffusion that are used in various fields of the social sciences. Information diffusion is the concept that the acceptance of new ideas and products has a trajectory of acceptance that is dependent on time and on the intensity of the efforts to spread the idea. Because public health campaigns are promoting an "idea" or "innovation" in thinking about cancer screening, models of information diffusion are a good basis to represent individuals' response to interventions. Since spending allows a wider dissemination of an idea, more spending will bring the "idea" to a large group of people. Mahajan and Peterson (1985) found that information diffusion over time can often be well approximated by sigmoidal functions. The reasons for this sigmoidal shape is the importance of social networks initially in promoting the ideas to "unreached" individual followed by diminishing reach when most population have already been reached by the "idea." The logistic function is a class of

functions which exhibit a sigmoidal shape. We will use a generalized version of the logistic function¹ to model the impact of spending on behavior in our model.

There is a growing body of work in the health community for exploring the varying effects of healthcare interventions with an eye towards developing mathematical models. A current paper implementing the logistic function as a model of health behavior is the work of Chick, Aral, and Grabosch (2014) . In this paper, the authors present a system dynamics model of diabetes progression where the effect of health promotion interventions to improve the health of the at-risk population is modeled as changes in flow probabilities parameterized by logistic functions. The difficulty in applying such models is finding quality data with which to parametrize the functional representation of individuals' response to interventions. In the context of diabetes care, Chick, Aral, and Grabosch (2014) have some population level observational studies of individual behavior in the presence of information about diabetes care. In our context of colorectal cancer, there are comprehensive observational or clinical studies of the effect of the effect of intervention intensity. However, there is a diverse array of more limited clinical and observational studies that examine specific interventions or specific population groups' responses. Additionally, there is a body of literature from similar cancers on the responses of individuals to health promotion campaigns via media. A comprehensive meta-analysis of "mediated" campaigns (those campaigns who delivered there messages though media vs. personal education) by Snyder et al. (2004) provides a grounding of the effectiveness of these campaigns in effecting health behavior for many

¹ It is worth noting that the "Logistic Function" is distinct from "Logistic Regression". The logistic function refers more generally to a functional form. The probabilities generated by logistic regression follow a logistic functional form and this specific functional form is specified by the data.

diseases. At the time of this meta-analysis, there was very limited literature seeking to understand the effectiveness of media campaigns on colorectal cancer screening behavior. More recent studies, such as M. P. Pignone et al. (2014) and M. Pignone (2013), explore specific interventions (notably the mailed reminder campaigns) at a quantitative and granular level. Leveraging such literature, in this section we will describe an approach for modeling health behavior using logistic functions fitted to a diverse group of clinical and observational data on media campaigns aimed at promoting colorectal cancer screening.

Our notion of using the logistic function to determine choice state transition probabilities is very similar to the approach of Chick, Aral, and Grabosch (2014). However, there are two subtle, but notable differences that must be addressed in our modeling context. First, Chick, Aral, and Grabosch (2014) uses the logistic function to determine aggregate rates of flow. This assumption is an inherent part of the systems dynamics modeling paradigm of their model. In our model, we are using an agent-based perspective and while the logistic function will produce a probability, that probability must be used to make a “discrete” decision before any effect can be obtained from an intervention. Second, we fit our logistic curves via nonlinear fitting a two-parameter generalized logistic model, as compared to the single parameter standard logistic function used by Chick, Aral, and Grabosch (2014). This decision is due to theoretical and practical assumptions. From a theoretical point of view, the generalized logistic function allows us to better capture a realistic response curve by enforcing an upper bound on the effect of intervention spending. The lack of this restriction for standard model may lead to extreme solutions where the whole budget is spent in a single period. From a practical point of view, we do not have access to detailed

observational data from each study and must rely on aggregate point estimates reported in the literature. Our fitting approach enables curve fitting with such point estimates. In the next section, we will provide a brief introduction of the logistic function and describe the details of the fitting procedure that we use to parameterize the logistic function.

4.3.4 The logistic function as a model of individual response to interventions

The logistic function provides an intuitive and mathematical representation for how public health intervention efforts are translated into changes in decision-making. The logistic function can translate unit levels of effort into changes to the probability of compliance in each period. The functional form of the standard logistic function is given by:

$$y = \frac{1}{1 + e^{-x}}, \quad x \in \mathbb{R} \quad (4.4)$$

The sigmoidal shape of the logistic function (see Figure 4-2) has several desirable properties that reflect the realities of modeling the translation of effort into behavior changes. First, the bound on the logistic function ensures that the final probabilities remain bounded by zero and one. This ensures that no matter how much intervention effort is applied, the decision probabilities at each period are always well defined. Second, the shape of the function reflects the fact that initially there are increasing returns-to-scale from additional intervention effort, but then at some point there are diminishing returns to scale. These returns-to-scale effects are often observed in practice (see Cutler and Miller (2004)). For example, when implementing mass media messaging campaigns, increasing returns to scale might reflect the fact that in a mass media campaign there has to be a good number of ad spots displayed before many individuals will see and are affected by the campaign. The

diminishing returns to scale at high levels of effort reflects the fact that if a lot of ad spots are already being displayed, an additional ad is going to make relatively less of an incremental change in individual decision-making.

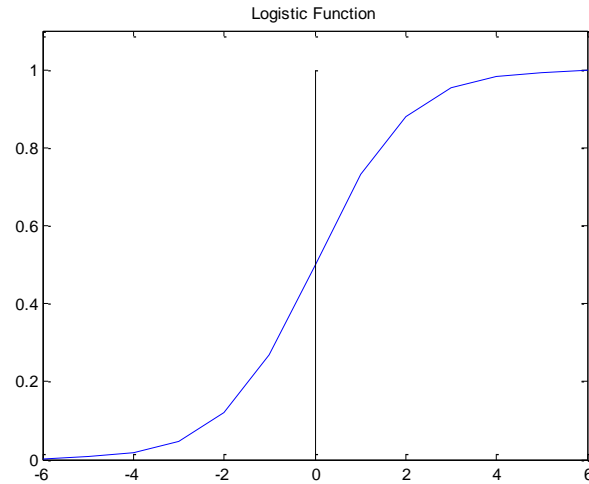


Figure 4-2: Plot of logistic function

The standard logistic function does not give us full control over the rate of change of the function, inflection points or the initial values. Thus, a generalized form of the logistic function, sometime called the Richards curve, is implemented. This specification provides control of the asymptotes and inflection points of the modeled public health intervention. The generalized representation implemented is as follows:

$$f(x) = \frac{K}{(1 + Qe^{-\alpha\nu(x-x_0)})^{1/\nu}}$$

Where

K : is the upper asymptote

(4.5)

$\nu > 0$: affects near which asymptote maximum growth occurs

$$Q = -1 + \left(\frac{K}{f(x_0)} \right)^\nu$$

It is assumed that the lower asymptote of $f(x)$ is zero. Figure 4-3 provides an example of the representation of the generalized logistic function with the parameters

$K = 1, x_0 = 0, f(x_0) = 0.2, \nu = 1,$ and $\alpha = 1$ which can be written in the following functional form:

$$f(x) = \frac{1}{1 + 4e^{-x}} \quad (4.6)$$

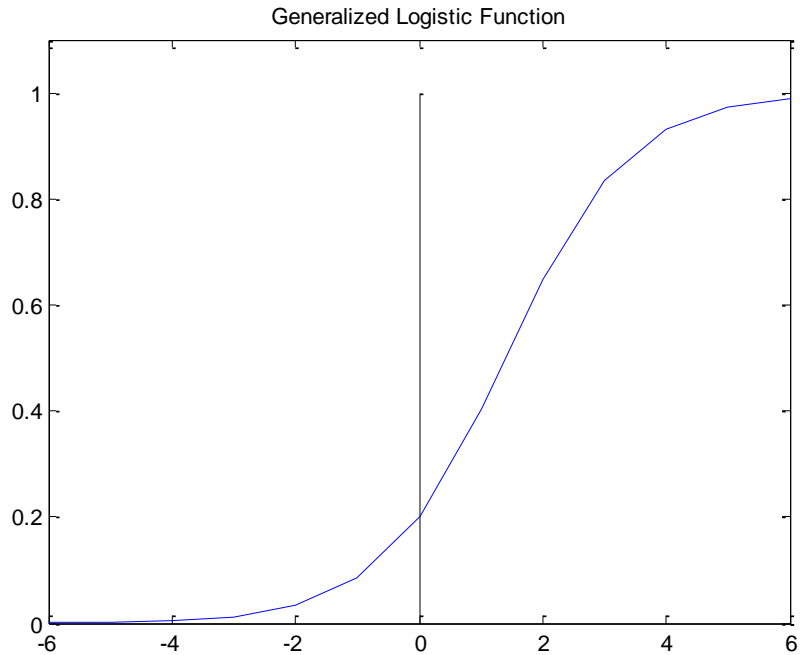


Figure 4-3: Plot of an instance of generalized logistic function

In practice, a value for K , x_0 , and $f(x_0)$ can be estimated from clinical data or expert advice. With these parameters specified we only need to estimate the effect parameter, α , and the asymptote weighting parameter, ν , to have a calibrated logistic intervention response function. This calibration can be done using any data that is available to us with regard to the effectiveness of the intervention. A variety of fitting techniques could be used to find estimates for these functional parameters. We used a technique that chooses the parameters, α, ν to minimize the Mean Square Error of the fitted generalized logistic function. This technique is implemented in Matlab's `nlfitt` procedure which we used to perform the nonlinear fits described here.

4.3.5 Fitting a Logistic Response Curve for a Mailed Reminder Campaign

We now apply the techniques of fitting the logistic function intervention response curves to clinical study data. In this section, we describe the context of each of the clinical studies from which we draw data and produce a fitted logistic function that represents the change in individuals' compliance behavior with screening as a function of spending on the mailed reminder campaign.

We used three primary sources to develop cost and effect estimates for mailed reminder campaigns:

1. The work we completed in the process of developing Chapter 2;
2. A mailed reminder with Fecal Immunochemical Test (FIT) kit sent as a follow-up performed on a population from the Netherlands (van Roon et al., 2011); and
3. A mailed reminder with clinical support intervention at a US-based clinic as detailed in Green et al. (2013).

Additional clinical work by Lewis et al. (2008) informed our analysis.

In Chapter 2 we described a mailed reminder intervention as a mailer that would be sent to individuals once records indicated that they were not up-to-date with screening by either colonoscopy or FOBT. Based on discussions with project collaborator, Mike Pignone, who has extensive experience in investigating mailed reminder interventions for colon cancer in clinical environments, we came up with the effect estimate for this intervention listed in Table 4-1 below. These effect estimates indicate the observed or conjectured percentage point increase in the screening rate over a 10 year screening horizon. This 10-year screening rate would be adjusted using Equation (4.3) to fit the decision epoch length being modeled.

For the cost element of our intervention definition other members of the project team did extensive interviews with program leaders and senior decision-makers at state-level health agencies to understand the costs involved in fully implementing such a program on a statewide basis. The cost estimates we used for the purpose of estimating the intervention response curve include the fixed costs of the intervention distributed across a program of approximately 300,000 yearly mailed reminders. This would be a typical size for a statewide program. The specific cost estimate used can be found in Table 4-1 below.

Table 4-1: Data Used to Parameterize Mailed Reminder Logistic Intervention Response Curve

Cost for effect (per reminder)	Effect	Description	Effect source	Cost source
\$1.00	5.0%		Chapter 2/Cornejo, Hassmiller Lich, Mayorga (2014)	Same
\$4.89	6.3%	Mailed letter and FIT Kit	van Roon et al. (2011)	Same
\$5.37	9.3%	Mailed letter and FIT Kit with reminder letter	van Roon et al. (2011)	Same
\$6.00	15.1%	Automated	Green et al. (2013) Table 2	Same/author estimate
\$10.00	20.5%	Assisted	Green et al. (2013) Table 3	Same/author estimate
\$15.00	25.2%	Navigated	Green et al. (2013) Table 4	same/author estimate

A second source for data about mailed reminder campaigns was a clinical study by van Roon et al. (2011). In this controlled clinical trial taking place in the Netherlands in 2008, individuals were either assigned to a standard care group or an intervention group. The standard care group received an automated notice providing them with a FIT kit and a return envelope. The intervention group received this same kit, but 2 weeks before the kit was sent, they received a letter with additional information on colorectal cancer, the benefits of

screening and information about the present clinical trial. Non-respondents were sent a reminder 6 weeks after the FIT testing kit was sent. We included the FIT kit costs in program costs here because they were an integral part of the intervention policy. The costs and effects for this program are given in Table 4-1.

Finally, we used a second clinical study that evaluated the impact of mailed reminders that were supported by varying degrees of intensity of medical staff follow-up. In the paper by Green et al. (2013), the authors looked at three levels of support that utilized information of screen currency (whether up-to-date or not) from an Electronic Health Record (EHR). The baseline, “usual care” policy was to display screening status in the basic currency report produced by the EHR and sent to the patients on annual basis. This report contained a variety of health information of which colon cancer screening was only one component. The intervention policies involve using the same EHR data, but presenting the colorectal cancer screening information in its own reminder. The “Automated” intervention involved sending a letter via postal mail to an individual near their screening date. The “Assisted” intervention involved sending the same letter, but following up this letter with a call from a Medical Assistant on staff. This medical assistant could answer questions and aid in scheduling colonoscopies and arrange for the delivery of a FIT kit if desired. The “Navigated” intervention followed up the mailed letter with a call from the RN-level nursing staff at the clinic. These individuals encouraged and scheduled colonoscopy procedures and had the ability to arrange for the sending of FIT kits. The costs and effects of this intervention can be found in Table 4-1.

We used this data to estimate generalized logistic function to represent the response curves of the model. We used the five parameter version of the model of (4.5). From our data we can set $x_0 = 1$ and $f(x_0) = 0.05$ which makes our fitted function go through our first data point. We make the assumption that $K = 1.25 * \max \text{EffectData}$ where K is the parameter that controls the maximum effect. Given this data, we can solve for the parameter Q . This leaves the parameters α and ν . We solve for these two parameters using Matlab's `nlfite`. Figure 4-4 compares our fitted function to a connected line plot of our input data. Table 4-2 contains the values of the fitted parameters as well as statistics related to the quality of the fit of our function via Mean Squared Error minimization. Additionally, the fitted curves for the Mailed Reminder and Mass Media interventions are plotted against the raw data in Figure 4-4 and Figure 4-5, respectively.

Table 4-2: Parameters and Fit Statistics for Logistic Function Response Curve for Mailed Reminder Intervention

Mailed Reminder	
Parameters	$\alpha = 2.5, \nu = 0.04$
Mean Squared Error(MSE)	0.00951008
Mean Absolute Error(MAE)	0.189962139

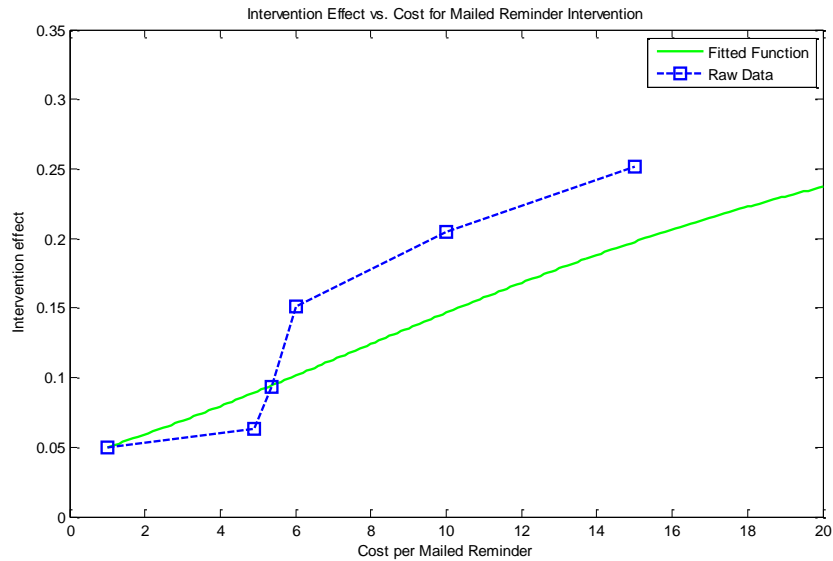


Figure 4-4: Intervention Effect vs. Cost for Mailed Reminder

4.3.6 Fitting a Logistic Function Curve for a Mass Media Campaign Intervention

Mass media campaigns have been popular and effective interventions for a number of cancers and chronic diseases. The authors Wakefield, Loken, and Hornik (2010) perform a comprehensive meta-analysis of the literature evaluating the cost-effectiveness of mass media campaigns to improve health behavior around and awareness of various chronic health conditions. Most relevant for our discussion is that they found moderate evidence of effectiveness of mass media campaign elements that promoted breast and cervical cancer screening. While Wakefield et al. (2010) did not identify any specific literature on the topic of colorectal cancer screening (a.k.a. bowel cancer in their work) there is newer evidence of the effectiveness of mass media health promotion campaigns for colorectal cancer. In this section, we examine the evidence for the effectiveness of mass media campaigns for

colorectal cancer screening promotion and use available information to estimate the costs of such programs.

Any major mass media campaign run by a state-level public health agency would likely be inspired by and conducted under the umbrella of the Centers for Disease Control (CDC) Screen for Life campaign. This ongoing campaign colorectal cancer awareness and screening promotion program was initiated about a decade ago. The Screen for Life campaign is a multimedia campaign that promotes cancer screening via individual brochures, posters and mass media advertisements on radio and TV. Many of these materials feature well known celebrities, most notably Katie Couric, who have had public, personal battles with colon cancer. While the Screen for Life campaign is a national campaign, the campaign has been implemented in different ways and intensities in different states. For example, some states have focused on mass media (radio and TV) advertising while others have focused on developing literature distributed by doctors. This gives us a wide range of implementation intensities to evaluate from both a costs and effectiveness perspective.

There is a large body of work that looks at the development of effective brochures and public service announcements (for example, C. P. Cooper et al. (2005)) that was initiated to validate the efforts of the Screen for Life campaign. Additionally, a number of population and clinical studies have evaluated the indicators for, and barriers to, positive screening behavior (Weitzman, Zapka, Estabrook, & Goins, 2001; Thomas, Lin, & Mun, 2014) with the purpose of using this information to develop effective health promotion campaigns. Additionally, because of the very high profile of some of the Screen for Life spokespeople, most notably Katie Couric, some work has been done to evaluate the effects of “celebrity”

spokespeople in mass media campaigns specifically in the context of colon cancer by Cram et al. (2003). This recent work mirrors the impact of older work that analyzed the effect of Ronald Regan's public episode of colon cancer.

All this work tends to be limited in scope to evaluating a particular material, events or a specific population. The first attempt to understand the impact of the Screen for Life campaigns and associated programs at a population level comes in the work of Ekwueme, Howard, Gelb, Rim, and Cooper (2014). In this study, the authors do a detailed analysis of types of media outlets the Screen for Life materials have been disseminated through and calculate the value of mass media services used to promote the material. Particularly, the authors break down the portion of costs from each type of media (TV, patient educational materials, radio, out-of-home displays (posters), in-kind donated services) and provide estimates of the money spent/value of services in each of these segments. The authors also evaluate the cost-effectiveness of these programs under various effectiveness assumptions. Their estimates of the effect of the Screen for Life programs is between a 0.5% and 10% percentage point increase in screening compliance behavior. We rely on these estimates extensively when developing our cost and effect estimates in Table 4-3.

Table 4-3: Data Used to Parameterize Mass Media Logistic Intervention Response Curve

Description	Effect	Reach	Effect*Reach	Total Program Costs
Small media campaign that relies on radio PSAs that are aired in non-optimal hours	0.5%	50%	0.25%	\$10,000
Small media campaign that relies on well produced radio PSAs that are aired in daytime hours	1.0%	75%	0.75%	\$15,000
Small TV campaign with reliance on PSAs aired overnight	1.0%	50%	0.50%	\$100,000
Small TV campaign with reliance on PSAs aired daytime	1.0%	80%	0.80%	\$150,000
Focused multi-media campaign on African Americans	5.0%	50%	2.50%	\$200,000
Focused multi-media campaign on African Americans with notable celebrities	10.0%	50%	5.00%	\$250,000
Big TV campaign with well-produced advertisement daytime	10.0%	80%	8.00%	\$500,000
Big TV campaign with well-produced advertisement daytime and celebrity spokespeople	15.0%	100%	15.00%	\$700,000

The data in Table 4-3 is used to fit a logistic function using the Matlab `nlfit` function. This methodology is described in Chapter 4.3.4. The parameter estimates from this procedure are given by Table 4-4. Figure 4-5 shows a graph of our fitted function as compared to our data set found in Table 4-4.

Table 4-4: Parameters of Fitted Generalized Logistic Function for Mass Media Intervention Data

Mass Media	
Parameters	$\alpha = 1, \nu = 0.04$
Mean Squared Error(MSE)	0.000793024
Mean Absolute Error(MAE)	0.062352917

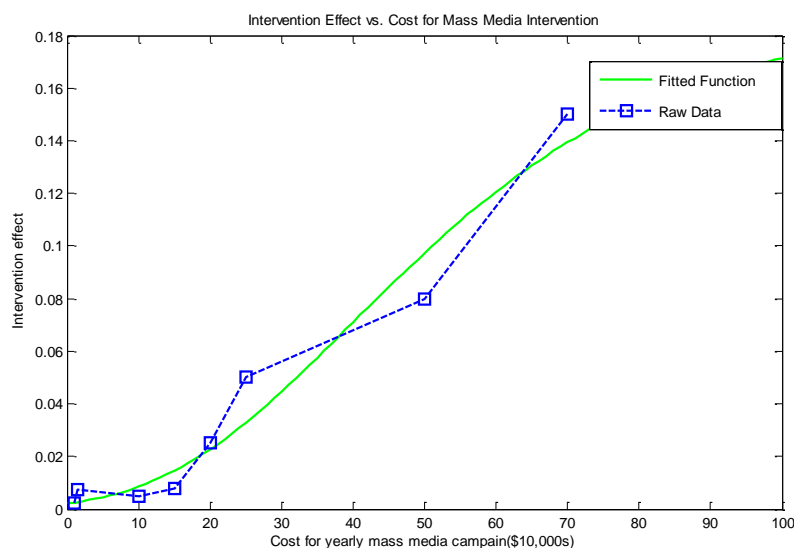


Figure 4-5: Intervention Effect vs. Cost Mass Media

Additional sources that were helpful in developing effect estimates of a mass media program came from the broader work of Kelly, Niederdeppe, and Hornik (2009) on the impact of “scanned information” on health behaviors in the context of colon cancer. Mass media campaigns by their nature are trying to change health behaviors of individuals who are not necessarily looking for health information. The work of Kelly et al. (2009) clarifies the

impact of different magnitudes of campaigns via their empirical evaluation of individuals' responses to "scanned information" received through a campaign such as the Screen for Life program.

The most difficult component of evaluating a mass media program is assessing the cost of the program. The literature mentioned previously provides a good example of past practices for mass media campaigns. Because the exact cost of a program depends on its particular scale and focus, our cost estimates are based on some limited historical experience and best estimates of the costs of programs of various intensities.

4.4 Solution Methods to Solve the Population Problem.

In this section, we describe and demonstrate techniques for solving the population problem shown in equation (4.1). We will define and compare two methods for solving this simulation optimization problem. The first method is a traditional simulation optimization approach that performs non-linear optimization on the simulation model. These techniques can produce good solutions; however, they may only arrive at these solutions after substantial computational effort. Because of this limitation, we propose and compare a second optimization approach to this problem that produces very good solutions with a fraction of the computational effort. The optimization technique we use is a Response Surface Method. This method will be benchmarked against standard simulation optimization approaches to demonstrate its time savings. Additionally, we will highlight the utility of the response surfaces created by this method for interpretability and sensitivity analysis.

As discussed in the previous section, the population problem presented in equation (4.1) is most appropriately reformulated as a simulation optimization problem for the sake of

relevant specific solutions. There are two components that add complexity to this problem: 1) the dimension of the choice space, and 2) the number of population subgroups. The dimensionality of our choice space is defined by the number of decision time periods T . This choice of solution space represents all possible distributions of a fixed public health budget to the decision epochs defined during the time horizon T . Each possible population solution generated during the solution process must be evaluated for each of the K subpopulation groups. This requires K simulation experiments in which the candidate solution is evaluated on each subpopulation. Increases in size of either dimension will increase the computational time requirement to solve this problem. Expansion in the number of time periods, T , means each simulation experiment takes longer. Expansion in the number of subpopulations, K , will increase of the number of simulation models that must be evaluated for each candidate solution. Each simulation experiment can be quite time consuming. A good solution algorithm will economize on the number of simulation runs (experiments) required to reduce the computational time required to find a solution. However, fewer runs must be balanced with effective exploration of the solution space to avoid getting “stuck” at a local optimum.

4.4.1 Simulation Optimization: A Traditional Approach

A traditional approach to solving this continuous simulation optimization problem is to apply a non-linear optimization algorithm. The objective function evaluations required by the algorithm would be simulation runs of the Monte Carlo model. This approach offers great appeal in its simplicity of implementation and intuitive appeal of utilizing the simulation

model directly. However, non-linear optimization algorithms typically require a substantial number of objective evaluations, and hence simulation runs, as it determines the best path through the solution space. This is very time consuming. Additionally, most non-linear solution methods have good performance at finding local minima, but require augmentation to generate good global solutions. To find a good global solution, the non-linear solution algorithm must be forced to explore other regions of the solution space. This can be done by having a fixed number of different initial solutions from which the algorithm is started; alternatively, the algorithm can be forced to “jump away” from its current solution path occasionally to better explore the solution space. Both of these methods increase computational time because of the increased number of simulation runs required.

4.4.2 Response Surface Methods Approach to the Population Problem

An alternative methodology for simulation optimization that has found increasing use in the simulation literature is the Response Surface Methods (RSM). In this section we define what a response surface is, describe how it is estimated, and demonstrate how it can be used to solve our population problem.

A response surface is a representation of the fundamental input-output (I/O) function of the system that the simulation model encapsulates. A response surface is an abstraction of the simulation model; it is estimated using data from the simulation model for an initial estimation step. Successive evaluations of solutions using the RSM, however, do not require simulation model runs. A response surface is created by running simulation experiments at a finite number of points in the solution space. Each run produces an estimate of the model’s output statistic of interest (along with estimates of the accuracy of that solution via variance

estimates). Using statistical techniques, this data can be used to estimate a model that we call our response surface. Using this response surface, we can apply non-linear optimization techniques to find solutions. The accuracy and speed of this method depends on the response surface being a good representation of the underlying simulation model.

Two factors in particular are decisions on the part of the modeler that greatly influence the quality of the response surface model: 1) the design of the experiment to determine which points in the solution space are to be evaluated by the simulation model; and 2) the appropriateness of the statistical technique being applied to this data to estimate the surface. In the next section, we will describe the choices made in this area and discuss the considerations that went into these decisions.

4.4.2.1 Experimental Design for Response Surface Methods

Experimental design is an area that receives much attention within the field of statistics. Statisticians are often in a position to design what data is collected for further analysis. A design could specify that we collect data for every possible scenario in our experiment: a full factorial experiment. However, in practice, it is only feasible for a select few scenarios to be evaluated and data collected. The data collected can then be used to estimate a statistical model for the prediction of results for the other scenarios not tested. The goal of experimental design is to collect a dataset that will enable good predictions by the statistical model at points not evaluated in the experiment. Experimental designs in statistics typically fall into two categories: 1) discrete experimental designs that evaluate scenarios consisting of either High and Low scenario value code for each control variable; and 2) continuous scenarios where the experimental variable can vary continuously. The control

variate in the population problem is the choice of intervention effort over the decision horizon, and thus is a continuous variable in each period. When the points in a design in continuous space are being constructed for the purpose of response surface modeling of the whole domain, designs that “cover” the design space well are to be preferred. Designs that have these characteristics are called “space filling designs.”

In the response surface optimization approach we propose to use a space filling design similar to a Latin Hypercube Sample (LHS) experimental design. The Latin Hypercube Sampling procedure distributes points into each quadrant of the hypercube and then uses an iterative procedure to improve these points such that the space is well covered. Figure 4-6 is a graphical example of a two-dimensional space - the points represent the sample points in an instance of a Latin Hypercube design with 200 points. A limitation of the basic Latin Hypercube procedure is that it is designed to fill an unconstrained design space, for example the 1×1 design space illustrated in Figure 4-6.

However, our design space is limited by the linear budget constraint of the population problem. In fact, we can guarantee that the solution to our problem will lie on the budget constraint plane. Thus, for our application, we modified the basic Latin Hypercube design to take into account this information. The design utilized in our optimization procedure utilizes the points generated by a LHS design, but then projects those points onto the linear budget constraint. This approach ensures that the design points we simulate contribute the most information to finding an optimal intervention effort allocation that satisfies the budget constraint.

Figure 4-7 presents a graphical representation of this projection procedure for the points in our two-dimensional example, contained in Figure 4-6. The points are projected onto a linear constraint $x_1 + x_2 = 1$. We do an orthogonal projection of design points in the rectangular design region onto the linear design space defined by the budget constraint. An orthogonal projection will assign a design point to the point on the (linear) budget constraint where it could be defined by an orthogonal vector emanating from that linear plane. This newly projected experimental design will not have a uniform distribution of the number of experimental design points across the budget constraint design space because of the varying number of points on/near any given orthogonal vector in the rectangular design region.

Figure 4-8 contains a histogram of the count of the number of design points in the projected design at each value of x_1 . The non-uniform distribution with central mass may have some outlier weight but that weight may actually have the benefit in increasing the accuracy of our design surface according to Hosking (2014). Hosking empirically compares designs that place their design point emphasis on the central region of the design space with designs that place their sampling weight towards the edges of the design space. He finds that designs that focus on the center are better when the system's optimal performance is likely to be on the interior of the design space and edge designs are better when the system behaves poorly at the margins. In our case we do not know a priori what type of behavior to expect from our solution. Thus, the current design that balances points on the interior and edges of the design space should enable better predictions.

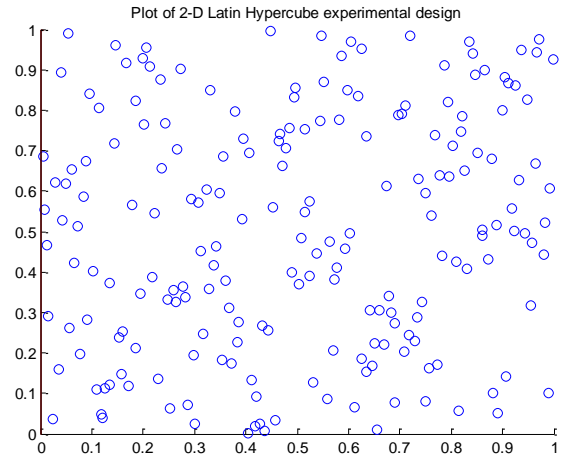


Figure 4-6: 2-D Plot of Latin Hypercube Experimental Design Sample ($N = 200$)

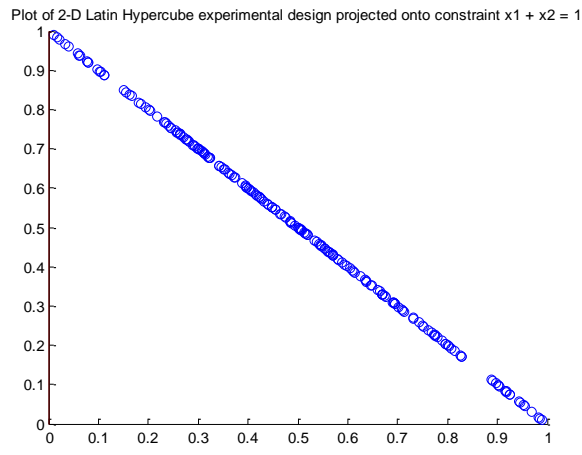


Figure 4-7: Latin Hypercube Design Projected onto the Constraint $x_1 + x_2 = 1$

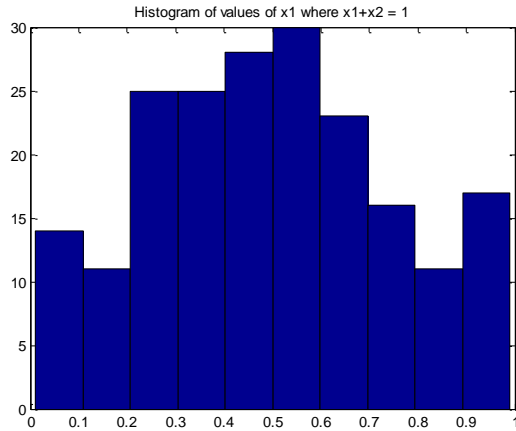


Figure 4-8: Histogram of Values of x_1 when LHS Design Projected onto $x_1 + x_2 = 1$

4.4.2.2 Statistical Methods for Estimation of the Response Surface

The previous section presented the experimental design approach we use to determine what design points that are evaluated in the simulation model. The purpose in this experimental design was to choose points that are then used to estimate a response surface that represents the I/O function encapsulated by the simulation model. In the previous section, there was discussion of choosing points that would be good data for the response surface fitting technique utilized. In this section, we describe the use of a technique called kriging to fit the response surface and describe why it was chosen to model the response surface. We will elaborate on specific design decisions that affected the applicability and performance of kriging models on the population problem.

The response surface fitting technique known as “kriging” is used to estimate the response surface representing simulation model. Kriging is an exact interpolator and is known to be a good model for non-linear I/O functions represented by simulation models.

Kriging provides better predictions when estimated on data produced from space-filling designs. Kriging has a history of being used for estimating response surfaces in higher-dimensional simulation problems because it is very flexible. It consistently performs better than other response surface estimation methods for simulation meta-modeling and rarely performs worse than a naïve linear regression model according to extensive benchmarking by Hosking (2014). Other methods of response surface modeling have much greater variability in their ability to consistently identify near-optimal solutions. These methods require more knowledge of a particular problem's structure in order to find an effective solution.

We utilized ordinary kriging to estimate our models. Kriging models are spatial statistical models meaning that they use the values at sampled design points to influence the predictions of the model at “nearby” points. The influence a particular data point has on estimation at a given point is determined by the Euclidean distance from a sampled data point to the estimation point and the covariance between all of the sampled data points. The rate of decay with respect to distance of a data point on a prediction point is determined by the so called covariance function. The choice of covariance function can have a significant impact on the ability of the response surface to effectively capture the complexities of the represented simulation I/O function. Standard forms of the covariance function include an exponential and Gaussian covariance function. These basic forms sometimes have difficulty representing complex surfaces. Instead of these covariance functions, we use a version of the Matern covariance function. In our example the Matern covariance function has been seen to do a substantially better job allowing the response surface to accurately represent our simulation model's I/O function. All of the estimation of our kriging response surfaces is

performed using the ooDACE toolbox (Couckuyt, Forrester, Gorissen, De Turck, & Dhaene, 2012). More details on kriging as a response surface modeling technique for simulation response surface modeling can be found in Jack P. C. Kleijnen (2008). For a comprehensive treatment of kriging as a statistical technique see Cressie (1993).

4.4.2.3 The Response Surface Reformulation of the Population Problem Objective

With this understanding of the fundamentals of the response surface methodology, we now reformulate the population problem that is solved by this technique and clearly note how this approach is incorporated to solve the problem shown in Equation (4.1). The population problem's objective function is a weighted linear average of health outcomes for each sub-population. The health behavior and health progression of each sub-population is independent of the other populations. Therefore, the linear objective is separable in each of the subpopulations. We leverage this separation of the subpopulations to estimate a response surface for each subpopulation separately. For each subpopulation k , we represent the response surface model estimated for that population subgroup as $\hat{g}_k(\cdot)$. Since this model replaces the need for simulation experiments and will return an estimate of the simulation models performance at any vector, \mathbf{x} , in the solution space, we reformulate the population problem as follows:

$$\begin{aligned}
 \max_{\mathbf{x}=(x_1, \dots, x_T)} \quad & \sum_{k=1}^J w_k \hat{g}_k(\mathbf{x}) \\
 \text{s.t.} \quad & c\mathbf{x}\mathbf{1} \leq B \\
 & \mathbf{x} \geq \mathbf{0}^T,
 \end{aligned} \tag{4.7}$$

where: $\mathbf{x} = [x_1, \dots, x_T]$ is a T -dimensional row vector; $\mathbf{1} = [1, \dots, 1]^T$ is a T -dimensional column vector with all entries equal to 1; and $\mathbf{0} = [0, \dots, 0]^T$ is a T -dimensional column vector with all entries equal to 0.

4.4.2.4 Optimization of the Population Problem with Response Surface Models

As explained in our introduction to this section, after the response surfaces for each of the subpopulations are estimated, optimization of the reformulated population problem is straightforward. The response surface is a statistical evaluator that can be evaluated at a candidate solution point in a fraction of the time the simulation model could be evaluated. Thus, the response surface models can be used as the evaluators for a non-linear optimization procedure. Because we cannot guarantee convexity of our problem, it is best to use heuristics for global non-linear optimization. A multi-start procedure often works well at producing intuitive and implementable solutions when a “good” set of starting points is provided to the algorithm. One possible “good” set of starting points are the solutions to the individual population problems. We discuss what these solutions are and how they are obtained in the next section.

4.4.3 Special Case: Individual Subgroup Solutions

As noted in the previous section, the linear objective of the population problem is a linear combination of the individual subpopulation models. Each of these subpopulation models is separable. This has important implications because it enables us to construct separate and independent simulation models and response surfaces for those simulation models. In the population problem each of the individual subpopulation functions is weighted

using the population size weights and the problem is solved to find solutions that maximize population health outcomes. The population solutions determined using this method will not necessarily maximize the outcomes of each subpopulation when viewed separately. This “individual solution” is the intervention effort/budget allocation that maximizes health outcomes for a representative individual in that group. There is value in determining the optimal solutions of each of the population subgroups separately. Two benefits of determining budget allocation solutions for individual subpopulation separately are:

- 1) Providing a sense of how disease progression and individual choice dynamics differ across the population subgroups.
- 2) Allowing the efficient solution to be adjusted for equity considerations.

Because the objective of both the simulation model representation and the response surface representation of the population problem is separable in the models representing each of the subpopulations, solving the individual problem is as simple as optimizing using either a simulation model representing a subpopulation or the response surface model representing that simulation model. This problem is relatively easy to solve because it eliminates the other $K - 1$ subpopulations and the non-linearities found in the full population weighted objective as a result of combining all K subpopulations. When we present results in the numerical experiments, we will also present the individual solution results.

While obtaining individual solutions is not the primary goal of the population problem, having the solutions for the individual subgroups has three benefits. First, the individual subgroup solutions are useful to public health planners in understanding the optimal effort allocation for a particular subpopulation. Second, this extra knowledge could

be used to modify the solutions produced in solving the population problem so equity considerations could be included. The population problem as framed in Equation (4.1) does not take into account any equity considerations. If the population solution is changed to be similar to a specific subpopulation individual solution, then these targeting/equity considerations could be improved. Finally, as mentioned in the previous section, these individual solutions form a “good” set of starting points for the global non-linear optimization procedure used to solve the population problem. Additionally, since each of the subpopulations models must be estimated before the population problem can be solved using response surfaces; it is a simple matter to optimize each of the individual models before tackling the population problem.

4.5 Monte Carlo Simulation Model

Ideally, optimization of intervention policies would take place by evaluating the policy produced by an intervention within the full simulation model presented in Chapter 2 and sequentially optimizing the timing and magnitude of intervention efforts over time. However, the full model as presented in Chapter 2 is computationally expensive. The relative low incidence of colorectal cancer and the relatively small marginal policy changes evaluated necessitates large simulated populations to be run to distinguish between policy alternatives. Given these large population cohort sizes, a single replication of a single population cohort takes 5-20 minutes to run on a 2.4 GHz single-core of a 64-core virtual machine with 1 TB of RAM. Since multiple population age cohorts must be simulated to capture the population that is eligible for screening, and multiple replications must be performed for each cohort for statistical significance all of which is repeated under multiple policy scenarios, performing a

simple experiment requires computational time on the order of hours or even days. For example, the five simple scenarios evaluated in Chapter 2 took 8 hours to run on a 64-core, 1 TB RAM, virtual machine with parallel processing enabled on all 64-cores. This means that the significant number of runs required by a standard optimization algorithm on the full NC-CRC model is all but computationally intractable. To overcome this challenge, a Monte Carlo model of the screening choice process has been created. This Monte Carlo model uses data from simulated lifetimes generated by the full discrete event CRC simulation model to parametrize the dynamics of cancer overtime and the rewards for an additional screen detecting that cancer. In this section, we describe in greater detail the Monte Carlo simulation model that represents an individual's choice to screen, disease process and the benefits from screening.

To be methodologically correct and computationally efficient, the Monte Carlo simulation model developed here draws on the methodology of Chapter 3 for creating a common patient. In the context of this model, implementing the common patient involved determining the outcomes of baseline screening behavior in terms of disease preventions and comparing it with the new behavior induced by the policy interventions when determining the marginal health benefit of the policies.

The key inputs of the Monte Carlo simulation model are: the probability of being alive at a given age, the probability of detectable cancer being present at each age, the health value of identifying the disease at each age in terms of life-years gained in each decision year, and the probability that an individual will screen in a given decision period. Each of

these components will be statistical representations of the source data for that feature of the model.

The model of disease progression and value of additional screenings will use lifetimes generated by runs of the full CRC simulation model to create probabilistic models and estimate distributions or health benefits, respectively. The probabilistic model of individual choice will be based on probabilities from the logistic regression model used to model individual choice in the CRC simulation model of Chapter 2. The disease progression and screening are relatively straightforward to obtain from data produced by the runs of the full CRC simulation model. The process by which data was obtained to represent the value of additional screens is not as simple. The procedure we have developed to capture the value of additional screenings provides value by distilling complicated information into accessible data formats. In the next section we describe in further detail the format and estimation process used to create the representation of the value of additional screens.

4.5.1 Estimating the Value of Additional Screening

The value of testing and disease detection at each age in terms of long-term outcomes (life-years gained) will be represented by age-varying “reward distributions.” These distributions are parameterized by output data created by running the full scale simulation model of Chapter 2 for a particular population subgroup. From the lifetimes generated by the simulation runs, the value of screenings, in terms of life-years saved, can be observed. Empirical estimates of the first four central moments (average, variance, skewness, and kurtosis) of the life-years saved by a test can be estimated.

The typical life-years gained from a test will decrease with age. The test is administered because other factors cause mortality to come into play as individuals' age. To account for this, we leverage the fact that the lifetimes generated by CRC simulation model runs contain the year of cancer onset. We use this information to “bin” our data so that we have just the life gained by detecting cancer should cancer appear at a given age. Because of this, we bin our data on the number of years lost to cancer by age of cancer detection. A set of moments can be estimated in each of these bins to understand how the value of tests changes with age of testing. These empirical moments generated by this procedure are used to parameterize a sequence of Pearson distributions that are sampled by the Monte Carlo model to estimate the life-years gained by detecting cancer in an additional screening. The particular shape and parameters of these distributions vary with age because the value of detecting cancer in terms of life-years saved decreases with age due to mortality for natural causes and other disease.

Because of data limitations imposed by the computational time requirements of the full CRC model, it is only possible to generate estimates of moments at 3-5 specific ages. However, we may need to evaluate the benefit of additional screenings for any of the 25 years during which individuals are eligible to screen. This requires knowledge of the parameters of the distribution at the particular year being evaluated. We alleviated this problem by applying interpolation to the moments data that we have. Given estimates of the moments of the health benefits reward distribution at specific ages, we can interpolate the value of the moments of this distribution at another age. This flexibility is enabled by the moment driven parametrization of the Pearson distribution.

The distributional representation of life-years gained health rewards from additional screenings is an important tool that enables computationally efficient evaluations of policies using the Monte Carlo simulation model. Our approach enables detailed model data to be encapsulated via the central moments of the data. Additionally, our data formatting and abstraction of a distribution from its moments enable flexibility in analysis that typical Monte Carlo models lack.

We have now completed the discussion of the mechanics of how we represent the model and how we represent individual decision-making. In the next sections, we will use these tools in a series of numerical experiments. The goal of these experiments is to find an optimal intervention to improve individual's decision-making via public health efforts under a limited budget.

4.6 A Numerical Experiment of the Optimization Procedure

In this section we present numerical test examples of the methods presented in the Sections 4.1-4.5. This illustrative example will explore the optimal effort allocation across six decision periods spaced exactly five years apart between the ages of 50-75 for a population with four different subgroups. These subgroups are white females, white males, black females, and black males. These subgroups will represent relevant population segments to understand the trade-offs in program targeting decisions. These subgroups are differentiated in the value of screening in terms of life-years gained. The different-shaped distributions of value of screening reflect differing disease progression and other-cause mortality between subpopulation groups. Each of these components must be parameterized, and these representations will be input data for our simulation model of each subpopulation.

4.6.1 Model Parameterization

The three inputs into the Monte-Carlo simulation model of each subpopulation that need to be parameterized for this numerical experiment are: 1) how disease progresses as people age, 2) the likelihood of detecting disease if it is present and 3) the value of detecting disease. Additionally, the subpopulation sizes need to be specified to determine the weights needed to solve the population problem. While our particular problem specifies that the decisions are exactly five years apart, our representations of these various probabilities could be extended to shorter decision intervals. To allow the representation of different decision-interval lengths, our parameterization of these inputs is structured so as to capture the time varying nature of their values.

The four subpopulations we test are parts of a whole population of 2,198,196 individuals. This population represents the size of the age eligible population during the screening window from 2014-2023. An individual is age eligible if they are between the ages of 50-75 during that period. This total population is divided into four subpopulations are analyzed in detail in our case study: black women (205,036 individuals or 9.3% of the population), black men (172,536 individuals or 7.9% of the population), white women (948,012 individual or 43.1%), and white men (872,612 individuals or 39.7% of the population).

We plot the probability of disease being present and the probability of being alive for each of the subgroups and represent the probability of disease being present and the sensitivity of a test over time as cubic splines. The product of realized values from these splines with respect to age is given in Figure 4-9. The probability, c , represents the

probability of individuals screening in each of the six decision periods. This probability is adjusted from the raw probability of screening that is calibrated to lead to an average screening rate of 63%. Figure 4-11 provides a plot of the probability of screening in each of the six decision periods over the 25 year horizon from 50-75.

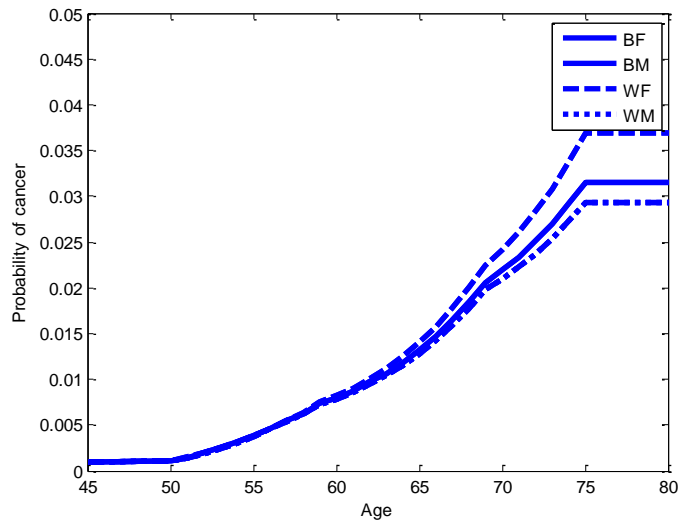


Figure 4-9: Plot Disease Incidence by Subpopulation Group

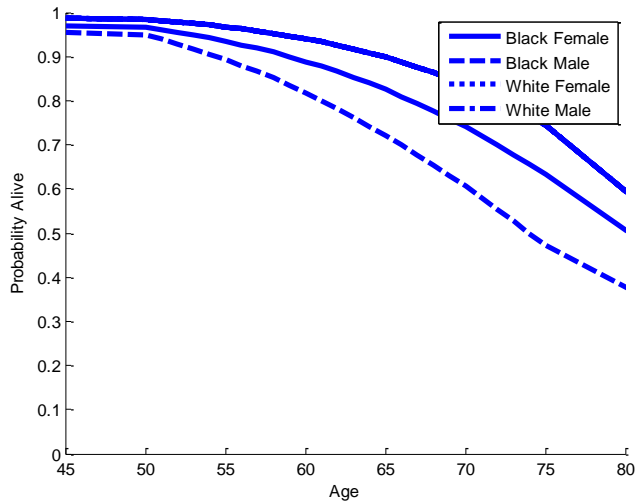


Figure 4-10: Plot of Probability that an Individual is Alive at a Given Age

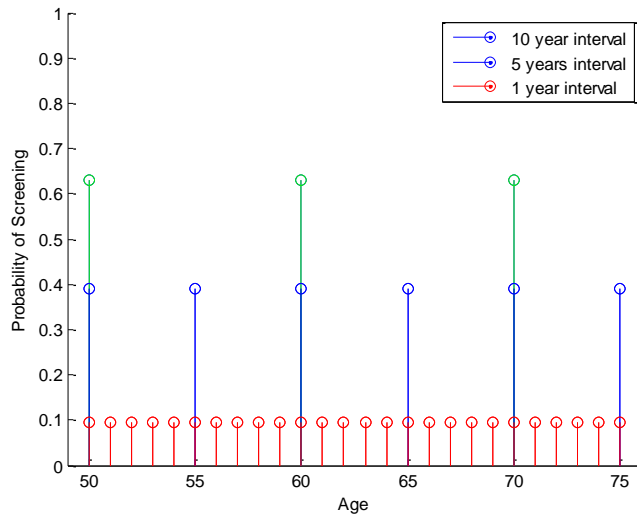


Figure 4-11: Plot of Baseline Control Policy adjusted for 1, 5, and 10 year Screening Intervals

To model how effort affects this baseline representation of individuals' behavior, we utilize a generalized logistic function whose functional form is described in Section 4.3 with the parameters $K = 0.315$, $x_0 = 1$, $f(x_0) = 0.05$, $\nu = 0.04$, $\alpha = 2.5$. Since this logistic function just models the change in individuals' choice probabilities with respect to spending, the value of this function must be added to individuals' baseline probability of screening, which is 63% in this case. A graph of the generalized logistic function with this parameterization added to individuals' baseline screening rate is found in Figure 4-12.

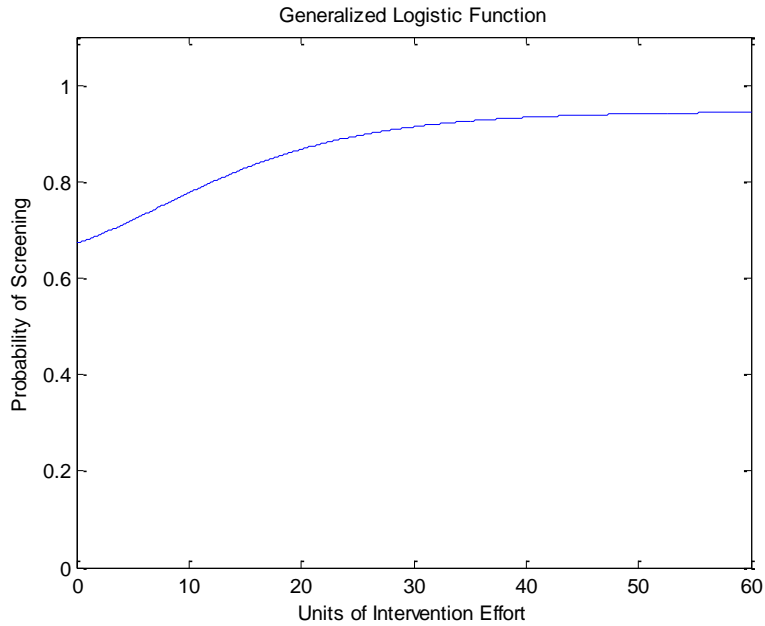


Figure 4-12: Plot of Logistic “Effort” Function Used in Experiments

To model the rewards for identifying disease, distributions for the reward of detecting at each age in life-years gained were parameterized. These shapes of these reward distributions, as defined by the moments, vary over time for each subpopulation. The moments of the data used to parameterize these distributions are given by

Table 4-5. These moments are used to parameterize a Pearson IV distribution. These moments were found by gathering simulated lifetimes data from large runs of the synthetic cohort of North Carolina residents aged 43 in 2007. From each of these sets of run we observed when cancers first appeared and measured the amount of life lost attributable to these cancers. By separating by age when these cancers first formed, we can estimate the life-years saved should that cancer have been detected at that early stage.

Table 4-5: Moment Data for Parameterizing Simulation Model Pearson Rewards Distributions of Life-Years Gained if Cancer is detected at each Decision Period

Age	Black Women				Black Men			
	Mean	Std. Dev.	Skewness	Kurtosis	Mean	Std. Dev.	Skewness	Kurtosis
50	21.04	11.63	0.14	2.02	17.23	10.88	0.21	2.10
55	17.21	9.86	0.14	2.10	14.43	8.62	0.30	2.25
60	15.07	9.56	0.44	2.47	13.03	8.58	0.66	2.75
65	13.17	7.83	0.31	2.18	10.79	6.94	0.47	2.44
70	10.86	7.64	0.49	2.26	9.54	6.79	0.61	2.46
75	8.08	5.36	0.71	2.88	5.98	5.01	0.94	2.93

Age	White Women				White Men			
	Mean	Std. Dev.	Skewness	Kurtosis	Mean	Std. Dev.	Skewness	Kurtosis
50	21.35	12.33	0.08	1.88	19.53	11.29	0.09	1.99
55	20.00	9.22	-0.06	2.16	16.24	9.15	0.10	2.08
60	15.22	9.68	0.40	2.32	13.62	9.14	0.45	2.42
65	13.88	7.83	0.20	2.20	11.82	7.18	0.36	2.26
70	11.57	7.48	0.42	2.13	9.95	6.97	0.50	2.32
75	8.09	5.32	0.61	2.76	6.66	4.83	0.80	2.98

To better understand how these differing moments reflect differences in subpopulation groups life lost distribution we plot samples from the Pearson IV distribution that these moments parameterize. Figure 4-13 displays histogram plots of 200 samples from the Pearson IV distribution that defines the life lost distribution at each 5-year age increment, 50, 55, ..., 75. Because this is color intensity based histogram plot of a finite number of samples, hotter colors indicate a relatively high number of the 200 samples with a given life lost value.

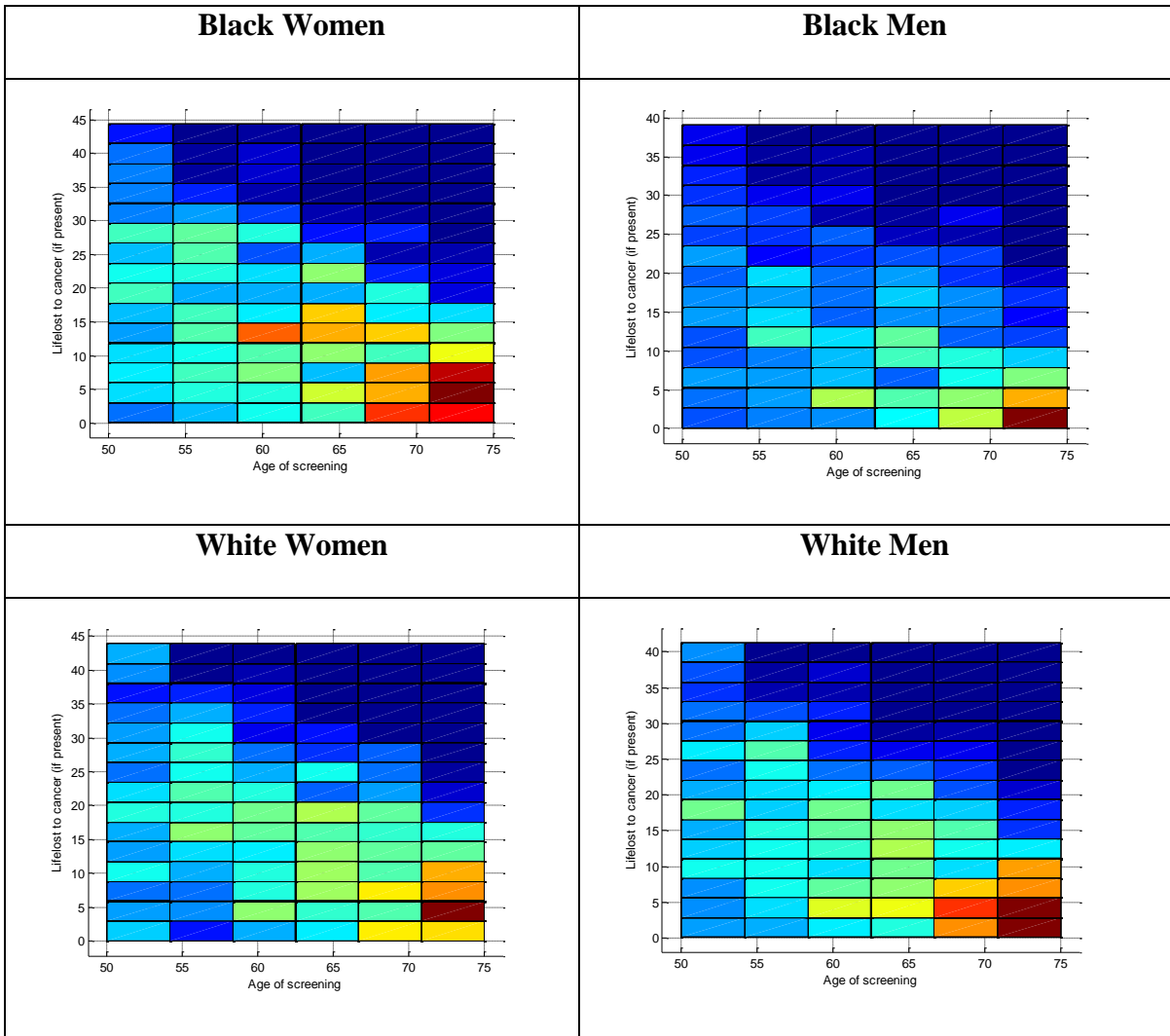


Figure 4-13: Plots of the Time-variant Reward Distribution of Life-years gained from Cancer Detection over Age for each Subpopulation Group

Looking at the trends in Figure 4-13 we note that the distribution of life-years that could be saved by detection is very wide at early screening ages. When individuals screen at later ages, the amount of life-years saved should cancer be detected at that age diminishes significantly. This trend is largely generated by the impact of other cause mortality factors what weighs heavily on the benefits from screening as individuals age. Additionally, from

these histograms we can visually identify the differences between men and women and blacks and whites. These differences are significant. This suggests that incorporating this heterogeneity in the rewards for screening will be an important factor in the solution to our problem.

The cost parameters that are relevant to our numerical experiment are presented in Table 4-6. It is notable that we include both the direct cost of our intervention policies, as well as the test costs generated by the additional screenings our intervention policies produce. All costs are given as a per person cost or a fixed cost for reaching the entire 2.4 million age-eligible individuals in North Carolina.

Table 4-6: Cost Parameters for Numerical Examples

Parameter Name	Cost
Test Cost (each)	\$750
Total Budget 25 year budget Mailed Reminder (per person)	\$50
Average yearly budget Mailed Reminder (total)	\$8,792,784
Average yearly budget for Mass Media Campaign	\$1,000,000

4.6.2 Simulation Model Validation

In the previous section, we presented the structure and data required to parameterize the Monte Carlo simulation model that is used to evaluate policies that improve individuals health behavior. This model has been tested and compared against data from runs of the CRC simulation model to determine the validity of the Monte Carlo model as a summary of the CRC simulation model. In this section we present specific data utilized in the verification

process. We will present data on the validation results for white females specifically in our numerical examples.

4.6.2.1 Disease Process Validation

It is important that our disease process accurately represent the disease process. Table 4-7 compares the difference between the probabilities of disease in our Monte Carlo simulation population of 1,000,000 simulated individuals with the probability of disease as observed in the CRC modeled population.

Table 4-7: Monte Carlo Simulation Model Validation Comparisons with full CRC Individual Simulation Model

Age	CRC Model Disease Probability	MC Model Disease Probability	Percent Difference
50	0.001107634	0.001095	1.14%
60	0.007872843	0.007873	0.00%
70	0.020961598	0.021023	-0.29%

We notice that these probabilities are almost exactly the same, lending confidence that the disease generation and associated process of determining if a person is alive in a given period (since they must be alive for disease to be present) are modeled correctly

4.6.2.2 Outcomes Results Validation

To verify the correct outcomes would be produced by the simulation model, we compared the results of the full CRC model with various constant intervention scenarios applied with the results of an identical scenario run in the Monte Carlo model. We compared the results across 4 different spending polices on mailed reminder campaigns. These 4

campaigns generated the change in the 10 year screening rate displayed in the second column of Table 4-8. Using these probabilities to make a decision of whether to screening with colonoscopy at 50, 60, and 70. These results where then compared to applying the same policy in the Monte Carlo simulation. Table 4-8 contains the results.

Table 4-8: Comparison of Results of Validation Polices in CRC Simulation Model vs. Monte Carlo Model

Policy	Average Screening Rate Increase over 10 years	Estimate of Life-Years Gained CRC Simulation Model	Estimate of Life-Years Gained Monte Carlo Model	Percent Difference
\$10 spending	14.66%	0.01563	0.01599	2.34%
\$15 spending	19.75%	0.01997	0.02123	6.30%
\$20 spending	23.71%	0.02367	0.02555	7.95%
\$25 spending	26.50%	0.02600	0.02870	10.38%

We conclude that the Monte Carlo simulation model produced results that are within a small percentage of our full simulation models results in the important policy regions. In our applications, we will never find that it is optimal to spend a significant amount (more than \$15) in any given decision period so we always operate in areas where the Monte Carlo model is a good match with the NC-CRC model. The differences in the estimates of the NC-CRC model and the Monte Carlo model that do arise as the amount of money allocated to the intervention increases are a product of the fact that our Monte Carlo model does not model the follow-on surveillance policies that are captured in the full NC-CRC model.

4.6.3 Numerical Experiment Results

The data in the previous section can be used to calibrate the simulation models of each of the subpopulations. With this information we can optimize the model using simulation optimization procedures or via a response surface model. Either of these techniques will return a solution to the population problem which is an allocation of our budget across each of the screening ages. These solutions can then be tested in the simulation model to estimate the number of life-years that will be saved by each budget allocation solution.

Because of the time-consuming nature of the simulation model, the computational performance of a solution methodology is important. While the simulation optimization routine will probabilistically converge to the correct solution, this convergence may take a substantial amount of time/computing effort. Our response surface approach offers an opportunity to improve the quality of solutions generated under a small computing budget. Table 4-9 shows the budget allocation solutions, the resulting life-years gained from that allocation and the computational time required to achieve the solution for the response surface method compared with the simulation optimization approach under two different computing time budgets (4000 seconds and 24,000 seconds). We can see that the response surface method solution and the long-time budget (24,000 seconds) simulation optimization solution are almost indistinguishable. However, note the substantial computational time savings (approximately 90%!) reaped from applying the response surface optimization procedure.

Table 4-9: Solutions for the Whole Population Problem

Solution Method	Budget Percentage Allocation Solution (by age)						Life-Years Saved (95% CI)	Percentage Difference from RSM Solution	Computational Time
	50	55	60	65	70	75			
RSM Optimization	8.30%	14.91%	17.20%	21.23%	19.45%	18.89%	32,007 (31,824 32,190)	0.00%	2,535
Simulation Opt. (24,000 sec)	7.92%	17.27%	19.97%	18.32%	18.23%	18.14%	32,315 (32,204 32,387)	0.96%	24,000
Simulation Opt. (4,000 sec)	0.01%	10.74%	0.05%	14.24%	18.27%	56.58%	25,765 (25,673 26,010)	-19.50%	4,000

The solutions presented in Table 4-9 represent the best solution to be applied to the population to maximize life-years gained from the spending program given the size of each subpopulation. It is expected that this population policy may not be the myopic policy that is best for each subpopulation group. These subpopulation myopic policies may differ because of differences in the dynamics of disease or screening in specific subpopulation groups. Because the objective function of the population model is a linear combination of subpopulation models, it is straightforward to compute the individual subpopulation solutions. Using the response surface approach, these solutions can be obtained in almost no computational time.

The kriging model of the subpopulation already exists and can be optimized like any non-linear function in a matter of (milli-)seconds. No such time saving would be realized in the simulation optimization approach. Optimization of the subpopulation solutions would require proportional levels of effort to solving the whole population problem. Table 4-10 shows the best budget allocation solution found via the response surface optimization approach should we chose to design our intervention to primarily affect that subpopulation

group. The objective in this optimization is to maximize the predicted life-years gained from that budget allocation solution. Each of the optimal budget allocations produced by the response surface method optimization is evaluated via the simulation model to find its simulated health value. This procedure is repeated for each of the four risk subpopulations in the experiment: black women, black men, white women, white men. Confidence intervals of the number of life-years saved are provided since they are obtained via simulation.

Table 4-10: Best Budget Allocation Solutions for each Subpopulation over the Decision Periods between the ages of 50-75 as solved by RSM

Population	Budget allocation percentage by age						Population Size	Estimate of life-years saved	95% CI	
	50	55	60	65	70	75				
Black Women	7.80%	13.03%	20.02%	19.80%	20.29%	18.98%	205,036	2,957	(2,938	2,976)
Black Men	3.95%	15.60%	18.05%	22.35%	19.43%	20.50%	172,536	1,900	(1,892	1,907)
White Women	5.28%	15.96%	18.99%	20.18%	20.32%	19.21%	948,012	15,190	(15,118	15,261)
White Men	6.24%	15.51%	19.54%	20.28%	19.95%	18.38%	872,612	11,985	(11,900	12,070)
							Total	2,198,196	32,031	

To understand how these subpopulation best policies found in Table 4-10 perform, they need to be compared to the population policies found in Table 4-9. To do this, we break out the benefits to each subpopulation group of the population problem solutions. The results, found in Table 4-11 show that the subpopulation policies usually improve the population solutions. In most cases, the difference is not that great. The confidence intervals of these effect estimates overlap for the relevant subpopulations. This leads to the conclusion that while there are significant health disparities between population subgroups, there would be

little benefit to overly focus the spending allocation solution to one specific subpopulation group as opposed to implementing the population best policy.

Table 4-11: Subpopulation Benefits from Population and Subpopulation Best Policies

Population	Population Size	RSM Solution	Estimate of Life-years saved		
			Sim Opt. (24,000 seconds)	Sim Opt. (4,000 sec)	Myopic policy
Black Women	205,036	2,974	2,993	2,389	2,957
95 % CI		(2955, 2993)	(2974, 3012)	(2372, 2405)	(2938, 2976)
Black Men	172,536	1,904	1,916	1,514	1,900
95 % CI		(1896, 1912)	(1908, 1924)	(1506, 1521)	(1892, 1907)
White Women	948,012	15,173	15,262	12,317	15,190
95 % CI		(15101, 15244)	(15191, 15333)	(12244, 12390)	(15118, 15261)
White Men	872,612	11,956	12,032	9,622	11,985
95 % CI		(11872, 12041)	(11948, 12117)	(9551, 9693)	(11900, 12070)

4.6.4 Robustness of the Solutions to the Population Problem

The population problem as evaluated through a Monte Carlo simulation model does not have the analytical conditions required to guarantee a unique, optimal solution. Because of this, the optimization procedures presented are not guaranteed to converge to the global optimal solution. The response surface optimization procedure in particular is theoretically sensitive to the data points that are used to estimate the response surface model. Different data points will lead to a different response surface model. These different models could produce different budget allocation solutions and hence different life-years gained. To promote confidence in these solution techniques, we can evaluate the robustness of the solutions produced during our experiments. In this section, we describe the methods used to

examine the robustness of the solution produced via the response surface optimization technique.

The optimization via response surface literature (Dellino, Kleijnen, & Meloni, 2012) has developed a procedure to quantify our confidence in the solution produced by our optimization on the response surface. The procedure uses the technique of cross validation, most commonly applied to evaluate model fit, to also estimate the quality of the response surface for optimization. The kriging type of response surface utilized in this application is an exact interpolator, meaning that the predicted response at simulated points will be identical to the actual data collected. However, if that data point is dropped from the data used to estimate the model, the newly estimated model may provide a different prediction at that dropped design point. The methodology of dropping data points and re-estimating the model is commonly known as cross validation. In our application, we are not interested in how this change affects our whole model fit, but if there is a change in prediction due to dropping a design point. This could occur if we do not have enough design points in a region around the optimal value.

Any number of points could be removed in each iteration where the model is re-estimated. We choose to perform “leave-five-out” cross validation, meaning that on each iteration five design points are left out during the model re-estimation process. This is a standard choice in the response surface model literature (Kleijnen, 2012). When each of these new models is re-optimized, we get new solution vectors. In a similar fashion to how we examined the variation in the simulation optimization method from different initial points, we can examine variation in the objective values of optimal solutions and variation in the

optimal effort resource allocations between these models produced during our leave-five-out cross validation procedure.

We perform 30 iterations of the leave-five-out cross validation (there were 60 design points to begin with). Table 4-12 shows the mean and the 95% confidence interval on the optimal value produced during 30 iterations of the cross-validation procedure.

Table 4-12: 95% Confidence Interval on Value of Life-Years Gained by Optimal Allocation of Intervention Effort derived through Cross-validation

95% CI Lower Bound	Average	95% CI Upper Bound
32,110	32,129	32,148

Since each new optimal objective value was produced by a different budget allocation solution, it is valuable to examine these solutions to ensure consistency in allocations between the cross validation iterations. A great variation in solutions between cross validation iterates would be a cause for concern as it would suggest that the model is very sensitive to the data selected. We visualize the variation of solutions in Figure 4-13. This connected line plot maps the trajectory of each solution in the percentage of the total budget allocated to each five year decision window. At each of the five year marks there is not great variation in the optimal percentage of the budget to be allocated to each decision period. Additionally, for any one particular solution there is not a great degree of variation in allocation between decision periods.

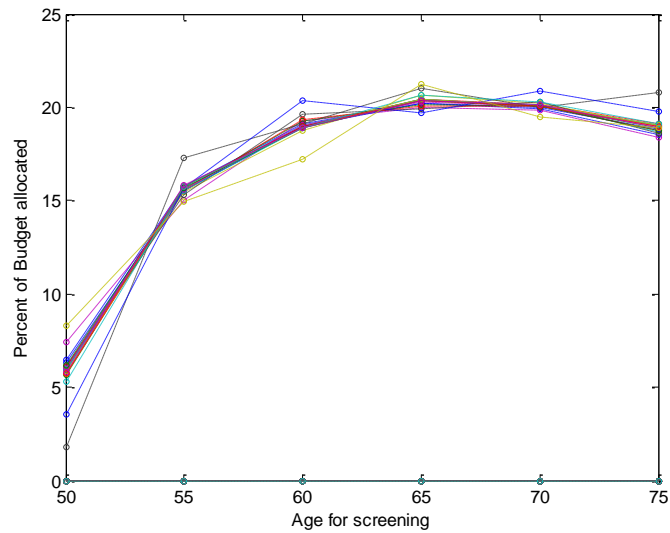


Figure 4-14: Connected plot of Population Budget Allocation Solutions from Cross-validation Iterates.

An alternative way of visualizing the same set of solutions is to look at those solutions in terms of the cumulative amount of the budget expended by a given age. Figure 4-15 presents a connected line plot. This plot reinforces the conclusion that the response surface model is a good representation of the underlying I/O function because our solutions are unresponsive to the specific data points used to estimate the response surface models.

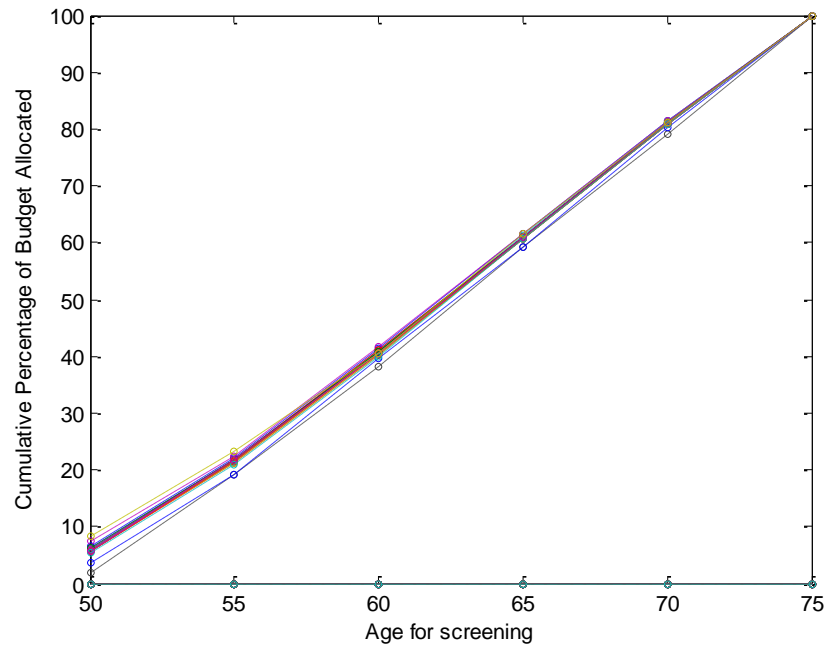


Figure 4-15: Connected plot of Cumulative Budget Allocation over ages for Cross-validation Iterates.

4.6.5 Computational Performance Comparison of Solution Methods

The previous section presented and compared the results of optimizing the population problem with the direct simulation method and with the Response Surface method. The ability of each of these solutions methods to discover the global minimum is to a greater or lesser degree dependent on the amount of computational time allocated to the solution method. The theory behind the simulation optimization techniques utilized states that as more computational time is allocated to each of these methods, the solutions produced should improve and increase the probability of convergence to the global optimum (Andradóttir, 2015). For the direct simulation optimization technique particularly, we have assumed that this model has a global optimum, therefore, if enough computer time is allocated it will be

discovered. For the response surface model, more computational time would allow us to compute more values of the simulation model at more design points and create a better representation of the simulation I/O function as a result. In this section, we present a comparison of the rate of improvement of the solutions of the two methods with respect to increased computation expenditure.

We examine this issue by comparing the time required to identify a solution with as good or better value for the population objective with the direct simulation optimization approach as compared to the response surface method. We fix the time/effort that is to be expended on the response surface method to a total of 60 design points in each of the four population groups solution spaces. Simulating at 60 design points was sufficient to saturate the design space and minimize sensitivity of optimization results to the choice of design points. Evaluating 60 points requires a total of 2532 seconds to simulate and optimize the response surface model using these points. The value of the objective produced by a optimizing on a response surface created using this fixed computational budget is compared with the best solution found by direct simulation optimization over a range of computational budgets. Table 4-13 shows the evolution of the budget allocation solutions as well as the convergence of the simulation optimization life-years gained estimate to the result of the response surface as the simulation time budget is increase. We do this over a range of computational time budgets from 4,000 to 24,000 seconds on the direct simulation optimization and a fixed time budget of 2532 seconds for the response surface optimization method.

Figure 4-16 plots the objective values produced by the solutions produced under each of the computing time budgets. This demonstrates the convergence of the solutions only after substantial computational time.

Table 4-13: Time-limited Solutions of Direct Simulation Optimization compared to Response Surface Optimal Solution

Direct simulation optimization results with increasing computer budget							
Time (seconds)	Life-years gained	x ₁	x ₂	x ₃	x ₄	x ₅	x ₆
4000	25,765	0.01%	10.74%	0.05%	14.24%	18.27%	56.58%
8000	26,487	0.24%	0.00%	12.77%	13.97%	14.57%	58.31%
12000	31,327	4.89%	15.22%	16.14%	17.97%	17.19%	28.44%
16000	31,692	14.30%	16.19%	16.25%	17.59%	17.62%	18.04%
20000	31,898	13.84%	15.88%	16.47%	18.25%	17.94%	17.44%
24000	32,315	7.92%	17.27%	19.97%	18.32%	18.23%	18.14%
Response Surface Model optimization results							
Time (seconds)	Life-years gained	x ₁	x ₂	x ₃	x ₄	x ₅	x ₆
2535	32,227	6.24%	15.94%	18.89%	20.05%	19.94%	18.73%

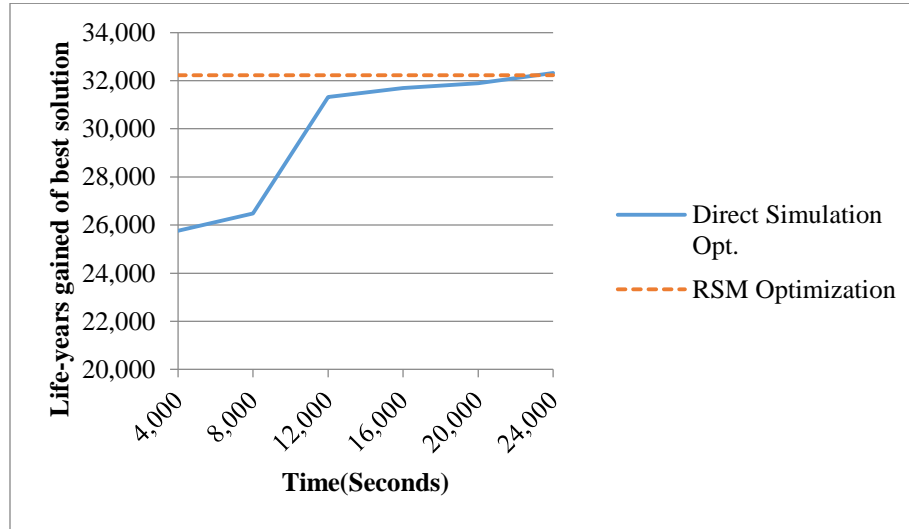


Figure 4-16: Plot of objective value of best solution produced by direct simulation optimization under limited computational budgets vs. the objective value of the solution produced by the RSM with a budget of 2532 seconds

4.7 Results Discussion

The results of these experiments show that it is possible to develop a single population screening policy that takes into account the heterogeneous response and benefits of a diverse population. The heuristics developed to solve the problem leverage the solutions

and the solution methodologies developed for the individual sub-population problems. The solutions produced by these methods incorporate the most pertinent characteristics of each of the individual sub-population solutions when creating the single solution for the whole population.

The optimal solution for each subpopulation is driven by the interactions between decreasing rewards from screening with age and increasing disease prevalence with age. In our numerical experiments, for a populations with a large average benefit of detecting cancer at an early age and if this reward was distributed such that there was a high probability of significant gains in life-years, then screening effort was allocated early in the age 50-75 screening window. When the reward distributions between two decision periods were very similar, the optimal solution was to allocate more effort to the later period due to the fact that disease prevalence was increasing with age.

All of the solutions to the population problem in our numerical experiment exhibit the feature that it is best to allocate all of the intervention effort in a few periods rather than spread it out equally across the entire decision horizon. This is likely partially due to our assumptions that there are increasing returns to public health effort in encouraging individual response. While this may be intuitive based on the structure of our model, this work is the first to present a comprehensive approach to identify this intervention “sweet spot” using data on both individuals’ response to interventions as well as detailed information about disease progression and outcomes. These insights can be very valuable to policy makers as they target their limited public health funds.

Additionally, via the response surface optimization procedure we were able to estimate the best myopic policies for each of the subpopulations. While in this case study the improvements gained from the best myopic policies for each subpopulation were not that significant, our solution procedure verified this fact in a fast easy manner, requiring almost no additional computational time. In the case of other interventions, it may be valuable to explore these myopic policies in more detail.

4.8 Conclusion

In this section, we have presented a comprehensive, data-driven approach to allocate a limited public health budget over multiple decision periods with the goal of maximizing population health outcomes. Public health spending enabled programs that encouraged individuals to screen. Through these additional screenings, cancers were detected that would have eventually caused death. Because these individuals' cancers were caught early, the individuals gained life-years that otherwise would have been lost to cancer. To model the magnitude of the change in individuals' behavior due to increasing levels of intervention effort, a logistic function representation was proposed. The logistic function captures characteristics such as initially increasing returns to effort that eventually turn into decreasing returns to additional effort. This model of individual behavior was incorporated into a Monte Carlo simulation model of cancer incidence and enabled the estimation of the number of life-years gained from a given screening policy. With this simulation model we could then compare different intervention effort/budget allocations that affect the screening decisions of the individuals. To find the optimal intervention effort allocation, we solved this simulation optimization problem with response surface methods. The response surface methods provide

allow for an optimization heuristic where optimization is performed on the response surface. The benefit of this is that it produces good solutions the population problem in a reasonable amount of time. A direct simulation optimization can produce a better (optimal) answer, but in our experiments we found this time to be excessive compared to the time required for the response surface method.

CHAPTER 5: DESIGNING AN OPTIMAL PORTFOLIO OF PUBLIC HEALTH INTERVENTIONS WHEN INDIVIDUAL DECISIONS ARE BASED ON PREFERENCE OF CHOICE ATTRIBUTES

5.1 Introduction

In the previous sections, we presented the structure of individual choice within simulation using an empirical approach. Our structure of individual choice decisions has been based on a probabilistic choice model whereby choice probabilities are determined via discrete choice statistical models. The inclusion of a framework of individual choice into a detailed model of disease allows the estimation of the effects of interventions aimed at improving long-term health outcomes via better choices. Some questions related to this have already been evaluated in this thesis. Chapter 2 and Chapter 4 evaluated the improvement in health outcomes resulting from a specific public health intervention that was assumed to change health behaviors. Individual baseline, pre-intervention, screening choice behavior was modeled by the discrete choice statistical models. These models parsed the significance of an individual's demographic and geographic characteristics in his/her screening modality choices. Given this baseline model of individual choice, Chapter 2 evaluated a few specific interventions. Each of these interventions was assumed to modify baseline choices at a specific rate. The differences in health outcomes between the screen-as-usual baseline scenario and each intervention policy were analyzed. This enabled cost-effectiveness ratios (and incremental cost effectiveness ratios) of these specific policies to be discovered.

In Chapter 4, the scope of policies evaluated was enlarged to examine the effect of varying levels of spending over an individual's life course on their health outcomes. To enable this analysis, the discrete choice model was supplemented with a logistic function to

model the change in an individual's screening choice behavior as a function of spending. The focus in that chapter was an in-depth exploration of the impact of varying levels of spending on a specific intervention over time. This approach was unique in its exploration of how different levels of intensity affected choices. In order to do this with the limited data available, our approach abstracted the effect of an intervention and implemented a change in choice probabilities as a direct impact of spending levels. The limitation of this approach is that it forced us to assume that the intervention had the same impact across broadly defined population groups.

In this chapter, we develop an analytical framework to guide the decision as to which interventions from a set of multiple interventions should be implemented based on analysis of how those interventions affect specific factors relevant to the choices each individual makes. This more detailed analysis to discriminate between intervention policies is enabled by an expanded formulation of each individual's utility function. The expanded utility function explicitly includes factors in each individual's utility function that describe an individual preference for each attribute of a screening test. Intervention effects can be described and these effects change the factors that describe individuals' preferences. Understanding how much we have to change preferences for an intervention to be effective can help guide policy makers understand the amount of effort required for a public health policy to be effective.

In the next section, we consider the literature relevant to this problem and discuss how it can inform the formulation of our problem.

5.2 Problem Description

Our goal is to allocate a limited budget of public health spending across multiple population groups and multiple intervention options in order to increase health the most. We do this within the context of multiple alternative intervention options, with varying degrees of effectiveness. Individuals make choices between these options based their preferences for different attributes of the testing modalities. The planner's goal is to use his spending on interventions to influence the preference of individuals in order to generate the most societal gain in health. All of this takes place under uncertainty regarding the choices of individuals and the rewards generated by these choices. To address this problem, we draw from a wide range of literature across the fields of Operations Research, Management Science, Economics and Public Health to provide the groundwork for the following components of our approach: 1) A model of individual decision-making, 2) an understanding of individual response to intervention spending, 3) a health benefit optimization objective, and 4) non-linear solution approaches to solve the objective function. In this section, we ground our use of each of these components from the existing literature.

The inclusion of individual preferences and the allowance of variation in these preferences across the population is an important component of our model. Individuals have beliefs about and preferences for different attributes of colorectal cancer screening tests. Examples of beliefs and preferences important in colorectal cancer screening are beliefs about pain associated with the testing procedure, the amount of preparation required before a testing procedure (often quite extensive for colonoscopy), and a desire for the risk reduction possible from participating in the screening test. To parse out the impact of each of these

factors on individuals' decision-making, researchers often conduct discrete choice experiments or values elicitation studies to determine relative preferences of individuals across these test attributes. Discrete choice experiments are the most common source of data for quantitative analysis. In a discrete choice experiment, individuals are led through a sequence of choice scenarios where they are asked to choose between several screening options. Each of these test options is described by the characteristics of the test options, for example, the testing modalities level of pain during the procedure, the preparation required, effectiveness of the test modality in reducing cancer risk, etc. By randomizing these attributes and offering repeated choice scenarios several times for each individual in the study group, it is possible to elicit individuals' relative utilities for different test attributes. Multinomial logistic regression and its variants are often used to estimate the coefficients of a linear utility model and these coefficients indicate the relative utility/disutility of each test attribute using data produced by such experiments. Results of such discrete choice experiments are commonly published in the public health literature often comparing the choices of specific populations such as comparisons between screening naïve individuals vs individuals who have screening experience (van Dam et al., 2010) . Additionally, a variety of studies have evaluated the impact of various statistical methods on the conclusions of the analysis of data from such experiments (Cheng et al., 2012). We use the data and methodologies from this body of work to determine individual baseline preferences for testing modality attributes that will then be changed as a result of our intervention spending.

The discrete choice models provide us with a relative weighting of the test attributes and their importance in individual decision-making. The discrete choice model implies that if

utility or disutility weight for a particular choice attribute changes then the probabilistic weight between all of the offered choices will change across the population. Such changes in preferences for different choice attributes could come via spending on public health programs. However, discrete choice models do not inherently provide the ability analyze how spending affects utility coefficients. To enable this analysis, we need to describe the mathematical relationship that exists between intervention spending and changes in the relative utility of each test attribute. We utilize the concept of aggregate response models from the marketing literature to model these changes (see Albers (2012)). The aggregate response models in marketing are used to evaluate the effectiveness of advertising effort to change the purchasing habits of targeted individuals. A variety of non-linear, concave models are utilized in the marketing literature and it has been shown that they can be easily parametrized from the data and incorporated into optimization models. The concavity of these models incorporates the assumption that there are decreasing returns to scale from intervention efforts.

The discrete choice component and the intervention response modeling component are the basis for describing individual decision-making behavior and how they change in response to spending. Our goal is to maximize the health of the population to which interventions could be applied. In the context of colorectal cancer, we measure this by the estimated number of life-years saved as a result of the intervention policies implemented. We want to weigh the benefits of a given policy against its costs. In previous sections, we took a cost-effectiveness ratio approach to consider the costs and benefits of various polices. This cost-effectiveness ratio approach works well when comparing specific, static intervention

policies. But for our purposes, we need to take into account the non-linear response of our target populations to spending and the fact that we need to test and optimize a wide variety of intervention policies. In this context, the non-linear ratio-based objective function of a cost-effectiveness objective becomes intractable for optimization. Because of this, we turn to a Net Health Benefits (NHB) based objective function to model the planner intervention optimization problem. The NHB approach linearizes the objective function while still weighing increases in benefits against increases in cost.

5.3 Mathematical Model

The objective of our mathematical model is to identify the optimal allocation of spending across a broad set of public health policies where the spending affects individuals' preferences for screening modalities. Health gains occur as a result of additional screenings; additional screenings are sought because individual preferences were modified via public health spending. The solution of the mathematical model based on these concepts leads us to a "portfolio" of interventions that we engage in with varying intensities for any given budget. In this section, we present the notation and formulation of our mathematical model.

We assume that our population of D individuals is composed of N individual subgroups that are indexed by $i = 1, \dots, N$. Each of these N individual population subgroups is differentiated by a set of demographic, socio-economic and geographic attributes which we denote by vector X_i of length m where m is the number of attributes tracked. Examples of the attributes included in X_i in our models include: Race, Gender and Urban/Rural location. The size of each population subgroup i , is denoted by h_i such that the sum of all of these

population group sizes is the total population size $\left(\sum_{i=1}^N h_i = D\right)$. The members of all the population subgroups are assumed to have access to a set of $J + 1$ choice options. This set of choice options is indexed by $j = 0, 1, \dots, J$. In the colon cancer context, our “choice” options are the testing modality options. The choice option indexed by $j = 0$ will represent the choice that we do not want individuals to make. In the case of colon cancer screening this is the no screen option. The other $j = 1, \dots, J$ choice options represent choices that lead to positive benefits for the individual. In the case of colorectal cancer, the screening tests Fecal Occult Blood Test (FOBT) and colonoscopy will be available to individuals. Other screening tests such as sigmoidoscopy, computer tomography and barium enemas exist, but only make up a tiny fraction of observed tests and so are excluded in our analysis. These tests could be handled in the model if better data were available for these options. Each of the choice options has certain attributes associated with it denoted by the vector W_{ij} of length p where p is the number of attributes of the test that an individual incorporates into his decision-making. These attributes are choice (test) dependent. Examples of the attributes included in this W_{ij} vector in the colorectal cancer application include pain of the test modality, preparation required, and expense to the individual.

5.3.1 Model of Individual Decision-making

Using this information we can formulate a model of individual decision making across the $J + 1$ choices. We use a model of individual decision-making based on a multinomial discrete choice framework. A good introduction to the concepts of the discrete choice

framework can be found in Train (2000). We use a multinomial logistic regression model to model individual choice between testing modalities. The main benefit of the multinomial logistic regression (aka MNL) is that it can be used to quantify the systematic preference variation that can be accounted for by observed factors. In our formulation of the MNL model, these factors will be found in the X_i and W_{ij} vectors. We can apply the MNL model because our formulation of the choice set of the testing modality options will meet the two conditions for applying multinomial logistic regression. The necessary conditions for the application of MNL is that the choice set is 1) *complete* –i.e., the choice set includes all of the choices available at a given decision period; and 2) *mutually exclusive*; meaning only one choice can be chosen per decision period. This choice enumerates the complete set of choice options for a given decision period. In the context of colorectal cancer screening, this means that our choice set includes screening tests like colonoscopy and FOBT, as well as the option to not screen at all.

There are some important limitations, however, inherent in MNL models. First, the MNL model cannot take into account “random” taste variations that are not accounted for by observed factors. Since in our modeling context we are specifically interested in the impact of observed factors, this is not a limitation. Second, MNL generates proportional substitutions between alternatives. If we increase the probability of one outcome occurring, we will decrease the probability of the other outcomes occurring by an equal proportion. This means that if we have a 10% percentage point increase in colonoscopy screening we will have a 5% percentage point decrease in FOBT screening and 5% percentage point decrease in the no screening rate. If our policies were known to primarily change people’s modality of

screening from FOBT to colonoscopy this would pose a problem. However, in our environment it seems reasonable to make this proportional substitution assumptions since there is no evidence that a particular substitution effect exists between colorectal cancer screening tests.

Discrete choice models are parametrized by comparing the observed set of characteristics X_i and W_{ij} with the observed choices of individuals from the $J + 1$ choice options. In the discrete choice framework, it is assumed that the individual makes the choice, j of the $J + 1$ choice options that has the highest utility for him; that is $\{j: U_{ij} > U_{ik} \forall k \neq j\}$. An individual utility for a given choice, U_{ij} , is a function of the values of observed factors (X_i, W_{ij}) as well as unobserved factors contained in ε_{ij} , the error term. These factors are components in determining an individual's relative utility for a given choice. We will use a linear representation of an individual's utility as a function of these factors, (X_i, W_{ij}) . This linear representation of the utility function is given in Equation (5.1).

$$U_{ij} = \beta_j^0 + \beta_j^1 X_i + \gamma W_{ij} + \varepsilon_{ij} \quad (5.1)$$

Where β_j^0 is a scalar intercept for each of the j testing modality choice options, vector β_j^1 is a $1 \times m$ vector of coefficient weight for each of the demographic variables that differ between subpopulations indexed by i and γ is a $1 \times p$ vector of coefficient weighting the utility attributes of each of the j choice options as viewed by the i^{th} subpopulation. Since we only

have the observed values from (X_i, W_{ij}) . Let V_{ij} be the part of utility we can account for with (X_i, W_{ij}) .

$$V_{ij} = U_{ij} - \varepsilon_{ij} \quad (5.2)$$

The ε_{ij} represents the component of utility that cannot be identified by the factors (X_i, W_{ij}) .

We do not know the values of the unobserved components that affect an individual's "true" utility. Thus, we assume the "error" component, ε_{ij} , varies across individuals and between choices by the joint distribution $f(\varepsilon_i)$ where $\varepsilon_i = [\varepsilon_{i,0}, \varepsilon_{i,1}, \dots, \varepsilon_{i,J}]$. Because of the assumption of independence underlying multinomial logistic regression, the joint distribution $f(\varepsilon_i)$ can be expressed as $f(\varepsilon_i) = f(\varepsilon_{i,0})f(\varepsilon_{i,1})f(\varepsilon_{i,2}) \cdots f(\varepsilon_{i,J})$. The probability that decision-maker in subpopulation i chooses alternative j is the probability that their "true" utility from choosing choice j , U_{ij} , is better than any other choice. While we cannot determine "true" utility because of other factors that will be contained in the error term ε_{ij} , we do have our estimate of the utility to the individual of each option based on (X_i, W_{ij}) ,

$$V_{ij} = U_{ij} - \varepsilon_{ij}.$$

To estimate the coefficients of the linear utility model, V_{ij} , we take our observed data of individuals' choices and the attributes of those individuals and choices. An individual only makes a choice j if he has the highest "true" utility from that choice. Since unobserved

factors that are part of individuals “true” utility will prevent us from finding a set of coefficients that will predict these choices perfectly for every heterogeneous individuals in the observational population, we find the set of coefficients that maximizes the prediction probability. As the derivation in equation (5.3) shows, this problem simplifies to finding the probability that the difference if error terms is less than the difference in observed utilities.

$$\begin{aligned}
 x_{ij} &= \text{Prob}(U_{ij} > U_{ik} \quad \forall k \neq j) \\
 &= \text{Prob}(V_{ij} + \varepsilon_{ij} > V_{ik} + \varepsilon_{ik} \quad \forall k \neq j) \\
 &= \text{Prob}(\varepsilon_{ik} - \varepsilon_{ij} < V_{ij} - V_{ik} \quad \forall k \neq j) \\
 &= \int \cdots \int_{\varepsilon_i} I(\varepsilon_{ik} - \varepsilon_{ij} < V_{ij} - V_{ik} \quad \forall k \neq j) f(\varepsilon_i) d\varepsilon_i
 \end{aligned} \tag{5.3}$$

When we assume the distribution of each the of error terms follows the Type I Generalized Extreme Value distribution, $\varepsilon_{ij} \stackrel{iid}{\sim} GEV(\theta)$, it can be shown that the difference in two random variables that are Type I Generalized Extreme Value is distributed according to the Logistic distribution (see Train (2000)). Based on these assumptions it can be shown that x_{ij} , the probability choice probability estimates generated by logistic regression of individual i choosing choice j , is calculated as:

$$x_{ij} = \frac{\exp(V_{ij})}{\sum_{k=0}^J \exp(V_{ik})} \quad i \in N \tag{5.4}$$

To visualize the idea of population groups choosing between different alternatives, Figure 5-1 shows a node-arc diagram of the options available to the different population subgroups. As specified by Equation (5.4), these weights are a function of the subpopulation attributes, X_i , as well as the attributes of the testing modalities, W_j .

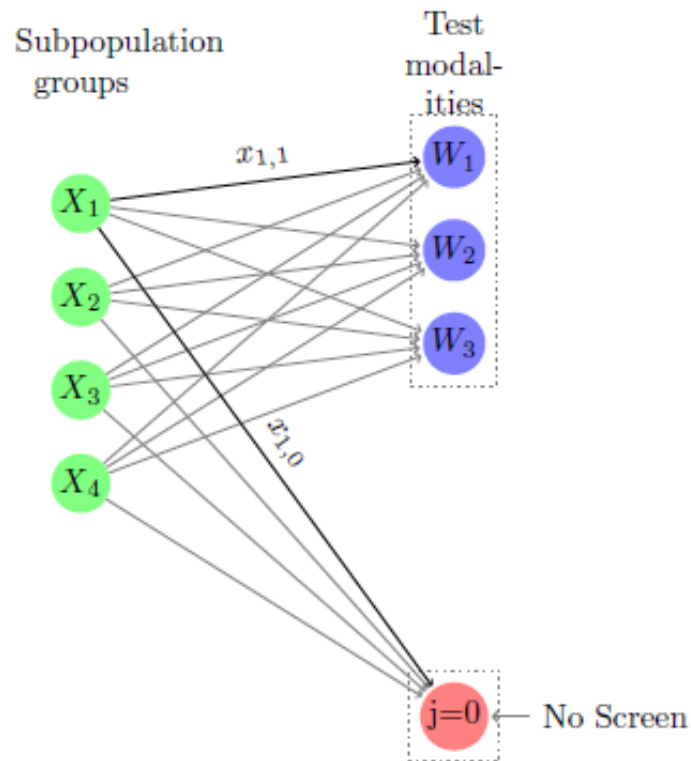


Figure 5-1: Node-arc Diagram Illustrating the Screening Modality Choice Options Available to Subpopulation Groups Along with the Option of No Screening

Having defined how individuals make choices across available test opportunities at any given decision period, we now need to develop a model for planner’s decisions regarding spending on public interventions that may impact individuals’ preferences for test options. In this component of the model, we define the costs and benefits of these choices in the process of developing the planner perspective model.

5.3.2 Effecting Changes in the Coefficients via Public Health Programs

In the previous sections we elaborated on the mathematics and interpretation of changes in the utility model coefficients that determine individuals’ screening test choices. In

this framework, it was hypothesized that changes in preferences, modeled through changes in coefficients, would lead to changes in behavior. In the previous section, there was no development of specific pathways by which this change could be affected. Additionally, we did not account for the intensity of public health interventions that are designed to generate change in individuals' preferences that would bring about positive health outcomes. In this section, we describe several models for how spending could be modeled in order to change the coefficients, and we compare their applicability in this problem setting.

The marketing literature has long studied the question of how individuals respond to sales interventions with the goal of predicting the response of consumers to sales efforts for the purpose of optimizing their spending on marketing campaigns. Viewing the public health planner's effort to change individual screening preferences as an analogous problem, we draw on this marketing literature to propose several functional forms to model the effects of spending on preferences through changes in the coefficients of the individual's linear utility function. Detailed descriptions and applications of each of these function forms can be found in several standard marketing decision modeling textbooks including Lilien, Kotler, and Moorthy (1992) and Wittink, Wedel, and Naert (2000). Albers (2012) summarizes the functional forms that he observed to be commonly used in the marketing literature. Table 5-1 is reproduced from his paper.

Table 5-1: Suggested functional forms for aggregate response functions from the marketing literature (from Albers (2012))

Name	Function	Elasticity
Quadratic	$y = a + bx + cx^2$	$(bx + 2cx^2) / y$
Constant Elasticity (or log-log)	$y = ax^b$	b
Semi-logarithmic	$y = a + b \ln(x)$	b / y
Modified Exponential	$y = a(1 - e^{-bx})$	$\frac{(a - y)}{y} bx$
Log-reciprocal	$y = \exp((a + b) / (1 + x))$	$-\frac{xa}{(1 + x)^2}$

The functions are good models of individuals' utility response to intervention spending because their concave functional form reflects decreasing returns to scale from intervention spending. Decreasing returns to scale (a.k.a. dis-economies of scale) imply that the first dollar of public health spending produces a greater effect on individuals' preferences than the last dollar of public health spending. Translating this to intervention policies, the first television advertisement on colorectal cancer has more impact on your knowledge and preferences than the 50th television advertisement viewed. In addition, these concave functions can be calibrated by estimating as few as a single parameter. This enables calibration even with limited data sets.

5.3.3 Planner's Intervention Choice

Having described individuals' baseline choice behavior and how their preferences change in response to intervention we need to use these tools to make optimal intervention investment choices as a public health planner. The goal of the public health planner is to assemble a "portfolio" of public health interventions to implement with his limited budget, B . We will assume that we have L intervention options indexed by $l = 1, \dots, L$. Each of these l intervention options is applied to one or more of the population subgroups. Let \mathbb{S} represent the set of all population subgroups, $\mathbb{S} = \{i, i = 1, \dots, N\}$. We will denote the subset of population subgroups covered/affected by intervention l by $\mathbb{S}_l \subseteq \mathbb{S}$. The number of individuals in \mathbb{S}_l is given by $|\mathbb{S}_l| = \sum_{i \in \mathbb{S}_l} h_i$. Each of these intervention options has a fixed cost, f_l , that indicates the cost fixed (often the startup costs) of implementing an intervention regardless of the size of the population reached. An example of this fixed cost in the colorectal cancer policy arena would be the cost of developing a media campaign. Additionally, we let c_l denote the per person cost of implementing an intervention. This cost is incurred on the relevant population which is defined as the individuals that are in the population subgroups in \mathbb{S}_l . For example, this could be the per-unit cost of a mailed reminder in such a mailing campaign. As an example of a subset of the population to which this intervention might be applied, we could limit the mailed reminder campaign only to Medicare patients. In this case, the variable costs of sending the mailer would only be incurred over the number of Medicare patients.

In addition to the costs of screening, the public health planner is concerned about the benefits of a particular chosen screening test to the population. We will denote the benefit of a percentage point increase in the screening rate for each test j chosen by population group i as G_{ij} . The estimates of the value of this increased screening rate are obtained via model runs of the NC-CRC Individual simulation model.

The benefit obtained from various intervention policies must be weighed against the costs of the intervention policies. To meaningfully compare health benefits with cost, assumptions must be made on the dollar value per unit of health gained. This is commonly referred to as the Willingness To Pay (WTP) for health. In the context of colorectal cancer, this requires that we assume a value for life-years gained from colorectal cancer screenings. In the literature, the value of \$50,000 is commonly accepted as the WTP amount for an additional Quality-Adjusted Life-Year (QALY). While our metric of life-years gained does not adjust for quality, this WTP value of \$50,000 per QALY provides a good baseline for our analysis.

The dollars spent on a public health intervention policy change individuals' preferences for different test attributes about a given test. We denoted individual preferences by the value function defined by Equation (5.1), therefore we denote the impacts of our intervention spending as changes to one or more coefficients in the vector γ ($\gamma = \langle \gamma_1, \dots, \gamma_p \rangle$ _{$1 \times p$}). These coefficients represent the relative impact on an individual's utility of each attribute in a specific test modality. Larger values of these coefficients indicate relatively more important attributes to an individual. Positive coefficients signify utility for and attribute.

Negative coefficients indicate disutility for a given attribute. Thus, implementing a given intervention l will mean individuals are now making decisions with a new parameter, $\hat{\gamma}, \hat{\gamma} \neq \gamma$ that describes their preferences across test specific attributes. This change in preferences is a function of spending on these interventions, $\hat{\gamma} = f(\mathbf{s}, \gamma)$. We denote spending on intervention l , by s_l , $\mathbf{s} = (s_1, \dots, s_L)$. Our total budget for spending is given by

B . By definition our spending constraint will be $\sum_{l=1}^L s_l = B$. From the social planner's perspective, we want to find the set of intervention spending across interventions that maximizes the public health value of the budget B .

Given this setup to the population problem, we use a Net Health Benefit (NHB) framework to evaluate and compare policies and assumptions on the value of health. The NHB approach was first proposed by Stinnett and Mullahy (1998). This approach uses a linear model that compares the effectiveness of an intervention, E , with its dollar cost, C , appropriately normalized by an assumed Willingness To Pay factor, λ . Total Net Health Benefit for an intervention can be described by:

$$\text{NHB} = E - \frac{C}{\lambda}. \quad (5.5)$$

In the next section, we will describe how to formulate the planner problem as one maximizing NHB.

5.3.3.1 Net Health Benefit Formulation to the Planners Problem

The basic concept of this formulation is to only initiate and spend money on interventions that will bring about positive health benefit and then allocate our limited public

health resources between different intervention options. To set up our problem, we need to define our specific decision variables. We define a decision variable y_l in Equation (5.6) that indicates a specific intervention is implemented.

$$y_l = \begin{cases} 1, & \text{if intervention } l \text{ is implemented,} \\ 0, & \text{otherwise.} \end{cases} \quad (5.6)$$

If an intervention l is chosen, $y_l = 1$, then the fixed cost for that intervention, f_l , is incurred. Putting all of these components together, we develop the following formulation of our mathematical model:

$$\begin{aligned} \max_{\mathbf{s}=(s_1, \dots, s_L)} \sum_{i \in \mathbb{S}_l} \sum_{j=0}^J G_{ij} h_i x_{ij}(\mathbf{s}) - \frac{\sum_{l=1}^L \left[f_l + \sum_{i \in \mathbb{S}_l} c_i h_i \right] y_l}{\lambda} & \quad (a) \\ \text{where } x_{ij}(\mathbf{s}) = \frac{\exp(V_{ij}(\mathbf{s}))}{\sum_{k=0}^J \exp(V_{ik}(\mathbf{s}))} \quad i \in N \quad j \in \{0, \dots, J\} & \quad (b) \\ V_{ij}(\mathbf{s}) = \beta_0^j + \beta_1^j X_i + \gamma_i(\mathbf{s}) W_{i,j} & \quad (5.7) \\ \text{s.t.} & \\ \sum_{l=1}^L s_l \leq B & \quad (c) \\ (s_l - f_l) y_l \geq 0 \quad \forall l = 1, \dots, L & \quad (d) \\ \left(f_l + \sum_{i \in \mathbb{S}_l} c_i h_i - s_l \right) y_l = 0 \quad \forall l = 1, \dots, L & \quad (e) \\ s_l \geq 0 \quad y_l \in \{0, 1\} & \quad (f) \end{aligned}$$

The objective function (a) in Equation (5.7) is our net health benefits objective function. Equation (b) defines the multinomial choice probabilities of the population groups across the screening tests and the no screening option. These probabilities are determined by the value of the linear utility model for the given population group. Our choice of spending

changes coefficient values and these choices propagate into changes in our objective function. Constraint (c) is our budget constraint. Constraints (d) and (e) ensure that the fixed and variable costs are being covered if and intervention is implemented and that no more money than is necessary is being expended.

5.4 Mathematics of the Changing Preferences Through Utility Coefficients

Central to an understanding of our model is the notion that changes in the coefficient vector as a function of spending $\gamma_i(\mathbf{s})$, which denotes the preferences of individuals for different attributes of a given choice j at a given level of spending, \mathbf{s} , lead to positive outcomes by increasing individuals screening rates for tests such as FOBT and colonoscopy that reduce their cancer risks and so bring lifetime health benefits. Public health planners on the other hand do not usually specify policy goals in terms of changes in specific choices, but in terms of aggregate screening rates. In this section, we develop some mathematical relationships to see how to interpret standard public health goals in terms of changes to the vector of preference coefficients.

The vector function $\gamma_i(\mathbf{s})$ is included in our model through the linear utility function $V_{ij}(\mathbf{s}) = \beta_j^0 + \beta_j^1 X_i + \gamma_i(\mathbf{s}) W_{ij}$. This function determines individual's relative choices through the function

$$x_{ij}(\mathbf{s}) = \frac{\exp(V_{ij}(\mathbf{s}))}{\sum_{k=0}^J \exp(V_{ik}(\mathbf{s}))} \quad i \in N \quad (5.8)$$

When spending money on an intervention, our utility weights, modeled though $\gamma_i(\mathbf{s})$, change.

This causes an adjustment in the probability of choosing each of the j choice options. Mathematically, this provides us with a new set of choice probabilities across the j choice options $x_{ij}(\mathbf{s})$. This is because changes in the choice parameter vector through $\gamma_i(\mathbf{s})$ affects the value function defined in equation (5.2). Intuitively, the $\gamma_i(\mathbf{s})$ parameter represents the relative importance of test attributes on an individual's decision; however, it is not immediately obvious how to specify or interpret changes to this $\gamma_i(\mathbf{s})$ parameter as a function of spending. In this section, we develop an intuitive definition for the relation between current choices and new preferences generated by spending on public health intervention. This relation will provide a mathematical link from a desired change in observed choice behavior with individual's preferences for different choice attributes.

Public health planners usually express their goals for public health programs in terms of a certain level of absolute improvement. For example, the CDC's Colorectal Control Program (CRCCP, 2015) stated goal is to improve colorectal cancer screening rates from about 64% to 80% in 5 years. Measures of absolute improvement have the most interpretability for policy makers and the public at large. Any absolute improvement gain can also be specified as a relative improvement or improvement percentage. For example, the goal of the CRCCP could also be stated as aiming to have 25% more people screened than are currently screened. The concept of elasticity from economics allows us to express mathematically how much a percentage change in a particular factor has occurred to achieve a certain outcome. In our case, we desire to know the (percentage) change in the impact of

different choice attributes required to achieve a percentage change in rate of choosing a given test.

To derive this relationship we simplified our utility function. Let $V_{ij} = b_{ij} + g_{ij}$ be a simplified version of our utility function specified in Equation (5.2), where $b_{ij} = \beta_j^0 + \beta_j^1 X_i$ and $g_{ij} = \gamma_i W_{ij}$. Our expression of the rate at which individuals choose each of the general choice options, denoted by x_{ij} , is then given by Equation (5.8). The expression for the elasticity, or responsiveness, of the choice probabilities, x_{ij} to changes in test choice attributes total utility weight, given by g_{ij} , is:

$$\frac{\% \Delta x_{ij}}{\% \Delta g_{ij}} = \frac{dx_{ij}}{dg_{ij}} \frac{g_{ij}}{x_{ij}} \quad (5.9)$$

From our expression of the choice rates in equation (5.8) and our simplified utility functions, we can express the derivative component of equation (5.9) as follows:

$$\frac{\partial x_{ij}}{\partial g_{ij}} \left(\frac{e^{b_{ij} + g_{ij}}}{\sum_{\forall k} e^{b_{ij} + g_{ik}}} \right) = \frac{e^{g_{ij}} \sum_{\forall k \neq j} e^{g_{ik}}}{\left(\sum_{\forall k} e^{g_{ik}} \right)^2} \quad (5.10)$$

5.4.1 Example Application of the Required Change in Preferences

A study by van Dam et al. (2010) looked at the preferences of individuals for different aspects of a screening test on their choice of test. Data for the study was collected through a discrete choice experiment in which individuals were offered a group of three test options with their attributes spelled out. Analysis of the chosen test option in each choice

scenario allowed a weighting of individuals' preferences for each attribute. In the study, two different population groups were analyzed—a screening “naïve” group who had never tested for CRC and the screening aware group who had previously undergone CRC screening. This study evaluated seven attributes of colorectal cancer screening test/modalities that the authors believed to be important to individuals. These attributes are:

1. the level of pain associated with the test procedure
2. the risk of complications from the test procedure
3. The locations where the test procedure must take place
4. The preparation required before the test procedure
5. The duration of the test procedure
6. The recommended interval for screenings via the given modality
7. The relative risk reduction from the test procedure

The meaning of most of these factors is immediately obvious. The relative risk reduction factor, however, deserves a better explanation. Relative risk reduction refers to the percentage decrease in the aggregate death rate from colon cancer. For example, if the death rate from colorectal cancer is 3%, following relative risk reductions would result from the specified changes:

- 3% → 2.7% (10% relative risk reduction)
- 3% → 1.8% (40% relative risk reduction)
- 3% → 1.2% (60% relative risk reduction)
- 3% → 0.3% (90% relative risk reduction)

Individual preferences for screening modalities based on these factors were analyzed for two groups in this study: screening naïve individuals and screening participants. The

difference between these two groups is that the screening naïve group had never received a colon cancer test before participating in this choice experiment, whereas the screening participant group had. Comparisons between these two groups may help identify for which factors preferences can be changed and to what extent we can expect them to change. Table 5-2 presents the estimated coefficients of the linear utility model for different levels of each of these factors for the two population groups analyzed in the study. These coefficient estimates will be a primary data source for the case studies analyzed in this chapter.

Table 5-2: Coefficients of Multinomial Logistic Regression on Impact of CRC Test Factors on Screening Choice Drawn from Results Discrete Choice Experiment Performed by van Dam et al. (2010)

Levels	Screening Naïve			Participants		
	coefficient	95%-CI		coefficient	95%-CI	
Constant (screening)	0.25	0	0.5	0.62	0.35	0.9
<i>Pain</i>						
No pain(ref)						
Mild pain	-0.31	-0.42	-0.2	-0.23	-0.34	-0.11
<i>Risk of complications</i>						
None(ref)						
Small	-0.16	-0.28	-0.05	-0.13	-0.25	-0.01
<i>Location</i>						
At home(ref)						
Hospital	-0.09	-0.2	0.02	-0.01	-0.13	0.1
<i>Preparation</i>						
None(ref)						
Enema(no fasting)	-0.37	-0.57	-0.16	-0.23	-0.45	-0.02
Drinking 0.75l of fluid and 12 hr. fasting	-0.51	-0.72	-0.29	-0.22	-0.45	0.01
Drinking 4l of fluid and 18 hr. fasting	-0.98	-1.18	-0.77	-0.88	-1.1	-0.67
<i>Duration</i>						
None (ref)						
Per 10 min spent in screening process	-0.03	-0.05	-0.01	-0.03	-0.06	-0.01
<i>Interval</i>						
1x in 10 years (ref)						
2x in 10 years	0.28	0.11	0.45	0.24	0.06	0.42
5x in 10 years	0.4	0.21	0.59	0.33	0.13	0.53
10x in 10 years	0.33	0.18	0.49	0.27	0.1	0.44
<i>Risk reduction of death from CRC</i>						
None(ref)						
Per relative 10% reduction in risk	0.32	0.29	0.35	0.26	0.24	0.29

We will assume that there are two colorectal cancer screening tests available, colonoscopy and FOBT, along with an alternative option of No Screening for every decision period that has attributes specified in Table 5-3.

Table 5-3: Colorectal Cancer Test Attributes

Test Name	Pain	Complications	Location	Preparation	Duration(x10 minutes)	Frequency	Risk Reduction (10% points)
Colonoscopy	Mild	Small	Hospital	Drinking 4l of fluid and 18 hr. fasting	4	1x10years	4
FOBT	None	None	Home	Enema	1	10x10years	1
No Screen	None	None	Home	None	0	10x10years	0

Based on these baseline test attributes, we can develop the following baseline probability of choosing each of these testing options for the screening naïve and screening aware populations. These percentages are given in Table 5-4:

Table 5-4: Baseline Test Choice Probabilities for Different Population Groups from van Dam (2010)

Test Name	Screening Naïve	Screening Aware
Colonoscopy	20.36%	21.53%
FOBT	38.23%	55.08%
No Screen	41.41%	55.08%

This test probability distribution of Table 5-4 is based on the raw relative utility function values for each test option calculated by applying the coefficient values in Table 5-2

to the levels of each test given in Table 5-3. These raw utility values are given in Table 5-5.

These are the values g_{ij} that will be evaluated for change.

Table 5-5: Raw Utility Function Values for Each Screening Option

Test Name	Screening Naïve	Screening Aware
Colonoscopy	-0.13	0.29
FOBT	0.50	0.89
No Screen	0.58	0.89

5.4.1.1 Demonstrating a Specific Example

Suppose we want to improve the rate at which screening naïve individuals screen for CRC with colonoscopy by 2.3% points from 20.04% to 22.34%. This absolute increase translates into a relative 10% increase in the number/rate of CRC screening with colonoscopy. From the equations in the previous section, the derivative is 0.16 and the ratio of utility to original choice probabilities is 0.607. This gives an elasticity value of 0.1108. The derivation in equation (5.11) shows that to achieve a 10% improvement in colonoscopy choice ($\% \Delta x_{ij} = 10$) rate, we need an approximately 90% increase in the raw utility of the colonoscopy choice.

$$\frac{\% \Delta x_{ij}}{\% \Delta g_{ij}} = 0.1108 \Rightarrow \frac{10}{\% \Delta g_{ij}} = 0.1108 \Rightarrow \% \Delta g_{ij} = 90.25\% \quad (5.11)$$

This means our raw utility of colonoscopy from Table 5-5 would have to increase from -0.13 to about -0.013. This change could be effected by changing individuals'

preferences for any one of the attributes for colonoscopy in Table 5-3 as measured by a change in the coefficient values in Table 5-2. For example, this 90% increase the raw relative utility could be achieved by a reduction in the disutility from the risk of complications from a coefficient value of -0.16 to a value of -0.144 and a reduction in the disutility of drinking 4 liters of fluid as a colonoscopy preparation from a coefficient of -0.98 to -0.88. Another mechanism to effect this change would be to decrease the coefficient representing the disutility from pain from the procedure from -0.31 to -0.193. Multiple other combinations of factors could be used to explain how the increase in utility (or reduction in disutility) could occur.

5.5 Properties of a Simplified Mathematical Model

The full general model in Equation (5.7) incorporates fixed costs as well as variable costs in the costing component of the model. It is valuable to include these components in a generalizable model, but these components complicate the mathematical analysis of the model. The fixed costs complicate the mathematics by making our solution discontinuous with respect to changes in spending. Additionally, our formulation of variable cost only allows spending in discrete amounts. Because of the complications introduced by this structure we solve a simplified model that relaxes these concerns. The two assumptions we make that differentiate this simplified model are: 1) there are no fixed costs ($f_i = 0$), and 2) the variable costs are described by proportionally distributing the budget B across the relevant subpopulations and interventions ($s_l \in [0,1], \sum_{l=1}^L s_l = 1$). A choice variable, $s_l = 0$, implies that the intervention will not be implemented/utilized. These assumptions mean that

the right-hand side cost component of the NHB objective in Equation (5.7) will never change making it unimportant to the analysis of this simplified model. With this simplified model several general theorems can be derived. In this section, we will the simplification of the mathematical model presented in Equation (5.12).

$$\begin{aligned}
& \max_{\mathbf{s}=(s_1, \dots, s_L)} \sum_{i \in \mathbb{S}_l} \sum_{j=0}^J G_{ij} h_i x_{ij}(\mathbf{s}) & (a) \\
& \text{where } x_{ij}(\mathbf{s}) = \frac{\exp(V_{ij}(\mathbf{s}))}{\sum_{k=0}^J \exp(V_{ik}(\mathbf{s}))} \quad i \in N \quad j \in \{0, \dots, J\} & (b) \\
& V_{ij}(\mathbf{s}) = \beta_0^j + \beta_1^j X_i + \gamma_i(\mathbf{B}\mathbf{s})W_{i,j} & (5.12) \\
& \text{s.t.} \\
& \sum_{l=1}^L s_l = 1 & (c) \\
& s_l \geq 0 \quad \forall l \in \{1, \dots, L\} & (d)
\end{aligned}$$

Based on this simplified mathematical model, we can develop the following results that guarantee the solvability of this problem and yield a closed form solution and a unique maximum.

The first result we aim to prove is that the objective function in Equation 5.12 is sufficiently smooth to apply optimization techniques with a guarantee of finding a global solution. We do this by showing that the objective function is quasiconcave along its whole domain. We use the following proposition to characterize an optimal solution when the function is quasiconcave:

Proposition 1 (Avriel, Diewert, Schaible, and Zang, (1988) Proposition 3.3 pg. 58): Let

f be a quasiconcave function defined on convex set $C \subset \mathbb{R}^n$. If $x^* \in C$ is a strict local maximum of f , then x^* is also a strict global maximum of f on C . The set of points at which f attains its global maximum over C is a convex set.

Proof: Suppose that $x^* \in C$ is a strict local maximum- that is, there is a $\delta > 0$ such that for every $x \neq x^*$ in the set $C \cap N_\delta(x^*)$, where

$$N_\delta(x^*) = \{x : x \in \mathbb{R}^n, \|x - x^*\| < \delta\}, \quad (5.13)$$

we have

$$f(x^*) > f(x). \quad (5.14)$$

If x^* is not a strict global maximum of f then there exists and $\bar{x} \in C, \bar{x} \neq x^*$ such that

$$f(\bar{x}) \geq f(x^*); \quad (5.15)$$

and by the quasiconcavity of f

$$f(\lambda\bar{x} + (1-\lambda)x^*) \geq f(x^*) \quad (5.16)$$

for all $0 \leq \lambda \leq 1$. But for sufficiently small λ it follows that

$x = (\lambda\bar{x} + (1-\lambda)x^*) \in C \cap N_\delta(x^*)$, contradicting $f(x^*) > f(x)$. The convexity of the global maximizing set follows from the convexity of the upper-level sets of quasiconcave functions.

Q.E.D.

With Proposition 1 characterizing the nature of the optimal solution(s) of a quasiconcave function, we now go about showing our objective function is quasiconcave. As our objective function is a composition of multiple functions, we can show the objective

function is quasiconcave if quasiconcavity is preserved under the composition operations we have defined. Avriel et al. (1988) provide a proposition that details the conditions under which composition is a quasiconcavity preserving operation. We present their result in Proposition 2.

Proposition 2 (Avriel et al. (1988) Proposition 5.1 pg. 154): Let ϕ be a quasiconcave function defined on $C \subset \mathbb{R}^n$ and let f be a nondecreasing function on $D \subset \mathbb{R}$, containing the range of ϕ . Then the composite function $f(\phi(x))$ is also quasiconcave on C .

While Proposition 2 may be sufficient for some problems, more generally we will need to show that composition preserves quasiconcavity for the composition of m -functions because $\gamma_i(s)$ may be slightly different for each population group or attribute. We get this result from Avriel et al., (1988) and replicate their proposition and proof here.

Proposition 3(Avriel et al. (1988) Proposition 5.3 pg. 155): Let ϕ_1, \dots, ϕ_m be concave functions on $C \subset \mathbb{R}^n$ and let f be a nondecreasing quasiconcave function on $D \subset \mathbb{R}^m$.

Suppose that D contains the range of $\phi = (\phi_1, \dots, \phi_m)$. Then the composite function $f(\phi_1(x), \dots, \phi_m(x))$ is quasiconcave on C .

Proof: Let $x^1 \in C, x^2 \in C$ such that $f(\phi(x^1)) \neq f(\phi(x^2))$. Since ϕ_1, \dots, ϕ_m are concave and f is nondecreasing, we have for every, $\lambda, 0 < \lambda < 1$

$$f(\phi(\lambda x^1 + (1-\lambda)x^2)) \geq f(\lambda\phi(x^1) + (1-\lambda)\phi(x^2)) \quad (5.17)$$

By quasiconcavity of f it follows that

$$f(\lambda\phi(x^1) + (1-\lambda)\phi(x^2)) \geq \min[f(\phi(x^1)), f(\phi(x^2))] \quad (5.18)$$

Combining these two results gives us the result. **Q.E.D.**

With all of these supporting propositions in place we can now show our main result of this section, that the objective function is quasiconcave.

Theorem 1: If an individual's baseline utility model, V_{ij} , has a linear form and $V_{ij} \geq 0$, estimated via logistic regression, and the intervention response function $\gamma_i(\mathbf{s})$ describing how these coefficients change with respect to spending is concave, then the objective function is

$$\sum_{i=1}^N \sum_{j=0}^J G_{ij} h_i x_{ij}(\mathbf{s}) \text{ quasiconcave in } \mathbf{s} \text{ for any concave function } \gamma_i(\mathbf{s}) \text{ where } \gamma_i(\mathbf{0}) = \gamma.$$

Proof:

Given that that x_{ij} and V_{ij} are defined as:

$$x_{ij}(\mathbf{s}) = \frac{\exp(V_{ij}(\mathbf{s}))}{\sum_{k=0}^J \exp(V_{ik}(\mathbf{s}))}, \quad (5.19)$$

$$V_{ij}(\mathbf{s}) = \beta_0^j + \beta_1^j X_i + \gamma_i(\mathbf{s})W_{i,j}, \quad (5.20)$$

The function V_{ij} is by definition a nondecreasing function in the values of the parameter vector γ_i when $V_{ij} \geq 0$. This is attained when $W_{i,j} \geq 0$. Therefore for any concave family of functions $\gamma_i(\mathbf{s})$, $V_{ij}(\mathbf{s}) = \beta_0^j + \beta_1^j X_i + \gamma_i(\mathbf{s})W_{i,j}$ is a quasiconcave function that maps the intervention allocations $\mathbf{s} \in \mathbb{R}_+^I \rightarrow \mathbb{R}_+$ by Proposition 3.

Since x_{ij} is a multivariate form of the logistic function that is nondecreasing in V_{ij} for any $i = \{1, \dots, N\}$, $j = \{0, \dots, J\}$. The composition function $x_{ij}(\mathbf{s})$ defined as

$$x_{ij}(\mathbf{s}) = \frac{\exp(V_{ij}(\mathbf{s}))}{\sum_{k=0}^J \exp(V_{ik}(\mathbf{s}))} \quad (5.21)$$

That maps the $range(V_{ij}(\mathbf{s}))$ is quasiconcave by Proposition 2. The final step of show the objective function is quasiconcave comes from a second application of Proposition 2 to get the fact that the linear combination of quasiconcave function is also quasiconcave. **Q.E.D**

With the quasiconcavity of our objective function established, we know to find global solutions to our problem, we need to identify local solutions. Local solutions can be identified via first-order conditions for a differentiable function. The functions we are dealing with here is differentiable so we propose analytical solutions to this problem defined by the

first-order conditions. We derive these first-order conditions in the next section for the case when there are only two intervention options. In this case, the problem reduces to a univariate problem.

5.5.1 General form of the solutions

Given that the objective function is a quasiconcave function, the optimum can be found by taking the derivative of the objective function and finding its zeros. If the function

$f(s) = \sum_{i=1}^N \sum_{j=0}^J G_{ij} h_i x_{ij}(s)$ in the case where $s \in \mathbb{R}$ the first-order optimality condition is:

$$\frac{\partial f}{\partial s} = \sum_{i=1}^N \sum_{j=0}^J G_{ij} h_i \frac{\partial x_{ij}}{\partial s} = 0 \quad (5.22)$$

Likewise, the second-order optimality condition is defined as:

$$\frac{\partial^2 f}{\partial s^2} = \sum_{i=1}^N \sum_{j=0}^J G_{ij} h_i \frac{\partial^2 x_{ij}}{\partial s^2} < 0 \quad (5.23)$$

In the case of independent and dependent interventions, this method can be applied to derive a meaningful analytical result when the function that translates spending into intervention responses is concave. This optimality condition has an economic interpretation. While this interpretation will be specific to the particular problem context, the optimality condition fundamentally explores the trade-offs in spending between interventions that increase the screening rates of testing modalities that are beneficial to health. The assumption of decreasing returns-to-scale on intervention polices implies each marginal dollar will be spent on the policy that brings the greatest marginal health gain.

5.6 Case Studies of Analytic Solutions to the Optimization Problem

In the previous section, we established that the objective function for the simplified objective is smooth and that in many cases it will have a unique solution(s) because the objective function is quasiconcave. In proving these properties we did not need to make extensive assumptions about the properties of the function $\gamma(\mathbf{s})$ that models the impact of intervention spending on preferences for different test attributes other than it was a concave function. In modeling specific intervention policies, $\gamma(\mathbf{s})$ will take on one of two specific forms depending on the design of the intervention policy. We will evaluate two case studies of intervention designs:

1. A **limited intervention** where spending on an intervention will affect the coefficients of a specific subgroup
2. A **broad-based intervention** where spending on an intervention will affect multiple subgroup simultaneously

Each of these two types of intervention policies will imply different a formulation for the function $\gamma(\mathbf{s})$. This is because the tradeoff modeled is different in structure. In the first case it is deciding how to spend between population groups. In the broad-base intervention case it is examining the tradeoffs between multiple interventions. In the following sections, we present analytical solutions to the optimization problem for both the limited and broad-based intervention cases. We then use these solutions to evaluate specific case studies involving the application of relevant public health intervention.

5.7 Case 1: Limited Intervention

We will first examine the case of an intervention that can be applied to one specific population group or another. Spending on one population group will not affect the other group. Examples of these types of “limited” intervention policies would include mailed reminder campaigns or targeted clinical education campaigns where the only individuals to receive the message are the specific targeted population. The population groups are differentiated by the health benefits achieved through additional CRC screens. The population groups we analyze are black women and black men. The screening modalities available to individuals are colonoscopy, FOBT and no screening (alternate option). Each of these population groups is assumed to have the same baseline preferences for modality attributes for different CRC screening modalities. The relative preferences for each of the modality attributes is taken from van Dam et al. (2010) and is presented in Table 5-2 in the previous section. We assume for this case study that our individuals are members of the screening naïve group.

The goal of our policy is to increase the rate of screening for CRC with colonoscopy. Thus, our intervention will be targeted at factors that positively impact individuals’ propensity to choose colonoscopy. For this case study, we will examine an intervention that affects the utility (disutility) from the pain individuals believe comes from colonoscopy. Because pain is a factor for colonoscopy choice, any increase in the utility (or a decrease in the disutility) from pain will always increase the colonoscopy screening rate.

5.7.1 The Effect of Spending

Every dollar spent on one population or the other affects the coefficient that estimates the impact of pain involved with colonoscopy on total utility. We will compare the results of our analysis based on two different assumptions on the rate of impact of spending on this coefficient value. We will apply the Semi-log and Modified Exponential functional forms to model how spending affects these coefficients. We choose these two functional forms from the larger list of functional forms in Table 5-1 is because these functional forms can be easily simplified to a concave function with a single parameter. The single parameter version of the Semi-log and modified exponential functions that we use in this example are given in Table 5-6.

Table 5-6: Functional Forms Used to Model the Effects of Spending on the Coefficient Related to the Disutility from Pain from Colonoscopy

Name	Function	Elasticity
Semi-logarithmic	$y = b \ln(x)$	b / y
Modified Exponential	$y = a(1 - e^{-x})$	$\frac{(a - y)}{y} x$

The parameters of these functions are calibrated such that if the full budget is allocated to one population, the maximum benefit that can be obtained is a 90% reduction in disutility from pain. For this specific model this means that pain's disutility decreases from -0.31 to -0.031 if all spending were to be allocated to one population.

The size of each of these population groups and their proportion of the relevant population (African-Americans) is given in Table 5-7.

Table 5-7: Case Study Population Size and Proportions

	Population Size	Percentage of Total
Black Women	205,036	54.30%
Black Men	172,536	45.70%

5.7.2 Objective Function to Solve

The particular version of the objective we need to solve in this case is a special case of Equation (5.12). Based on the notational structure of the model in Equation (5.12), the first index i notates the subpopulation groups. In this case, $i = \{1, 2\}$ where $i = 1$ indicates black women and $i = 2$ indicates black men. The second index j , denotes the testing modality. Index $j = 0$ denotes the alternative of No screening, $j = 1$ indexes FOBT, and $j = 2$ denotes colonoscopy. In this two population case, we can reduce the problem to a univariate solution by assuming a budget of 1 and requiring the entire budget to be spent. The solution that we are finding the optimal percentage of the budget that is spent on the black women.

$$\max_s \sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(1-s) \quad (a)$$

$$\text{where } x_{ij}(s) = \frac{\exp(V_{ij}(s))}{\sum_{k \in \{0,1,2\}} \exp(V_{ik}(s))} \quad i \in N \quad (b)$$

$$\begin{aligned} V_{1j}(s) &= \beta_0^j + \beta_1^j X_i + \gamma(s) PAIN_j + \gamma W_{i,j} \\ V_{2j}(s-1) &= \beta_0^j + \beta_1^j X_i + \gamma(1-s) PAIN_j + \gamma W_{i,j} \end{aligned} \quad (5.24)$$

s.t.

$$s + (1-s) = B = 1 \quad (c)$$

$$s \geq 0 \quad (d)$$

The general form of our optimality condition is given by Equation (5.25).

$$\frac{d}{ds} \left(\sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(1-s) \right) = \sum_{j \in \{0,1,2\}} G_{1j} h_1 \frac{dx_{1j}}{ds} \Big|_s + \sum_{j \in \{0,1,2\}} G_{2j} h_2 \frac{dx_{2j}}{ds} \Big|_{1-s} \quad (5.25)$$

5.7.3 Economic Interpretation of Limited Intervention Model

The optimality condition presented in Equation (5.25) has an intuitive, economic interpretation. This problem is fundamentally about evaluating tradeoffs in health benefits between two screening groups. Increased spending on any one group will make them more likely to screen with a screening mortality (colonoscopy) that has significant health benefits and correspondingly decrease their use of alternative, less beneficial options. However, decreasing returns to scale on the behavioral impacts of spending imply that it may be beneficial to have a mixed allocation of spending between two population groups. It will always be the case that the population with the largest health benefits from the screening tests will get the first and largest portion of the budget. A mixed allocation between populations will occur if the difference in health benefit for an additional percentage point screened

between two population groups is small enough. The smaller the differences the more equal the allocation between the two population groups.

5.7.4 Analytic Solution to Limited Intervention: Semi-Log Response Function

When the intervention response function is assumed to follow the semi-log functional form), we can find a closed-form expression of the optimality condition in Equation (5.25).

Given that the derivatives of the linear utility function including the intervention response function components can be calculated as follows under the assumption that $\gamma(s) = b \ln(1+s)$

$$\frac{\partial}{\partial s} (V_{1j}(s)) = \frac{\partial}{\partial s} (\beta_0^j + \beta_1^j X_i + b \ln(1+s) PAIN_j + \gamma W_{i,j}) = \frac{b}{1+s} \quad (5.26)$$

$$\frac{\partial}{\partial s} (V_{2j}(1-s)) = \frac{\partial}{\partial s} (\beta_0^j + \beta_1^j X_i + b \ln(2-s) PAIN_j + \gamma W_{i,j}) = \frac{b}{s-2} \quad (5.27)$$

The derivatives of the choice probabilities with respect to spending allocation can easily be calculated as follows:

Group 1:

$$\begin{aligned} \frac{\partial x_{1j}}{\partial s_1} &= \frac{\partial V_{1j}}{\partial s_1} x_{1j} (1-x_{1j}) = \frac{b}{1+s} x_{1j} (1-x_{1j}) \text{ for } j=2 \text{ colonoscopy} \\ \frac{\partial x_{1k}}{\partial s_1} &= -\frac{\partial V_{1k}}{\partial s_1} x_{1j} x_{1k} = -\frac{b}{1+s} x_{1j} x_{1k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}} \end{aligned} \quad (5.28)$$

Group 2:

$$\begin{aligned} \frac{\partial x_{2j}}{\partial s_2} &= \frac{\partial V_{2j}}{\partial s_2} x_{2j} (1-x_{2j}) = \frac{b}{s-2} x_{2j} (1-x_{2j}) \text{ for } j=2 \text{ colonoscopy} \\ \frac{\partial x_{2k}}{\partial s_2} &= -\frac{\partial V_{2k}}{\partial s_2} x_{2j} x_{2k} = -\frac{b}{s-2} x_{2j} x_{2k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}} \end{aligned} \quad (5.29)$$

Thus, our optimality equation is as follows

$$\begin{aligned}
& \frac{d}{ds} \left(\sum_{j=0}^2 G_{1j} h_1 x_{1j}(s) + \sum_{j=0}^2 G_{2j} h_2 x_{2j}(1-s) \right) = \\
& \underbrace{G_{12} h_1 \frac{b}{1+s} x_{12}(1-x_{12})}_{\text{Colonoscopy Group 1}} + \underbrace{G_{11} h_1 \left(-\frac{b}{1+s} x_{12} x_{11} \right)}_{\text{FOBT Group 1}} \\
& + \underbrace{G_{22} h_2 \frac{b}{s-2} x_{22}(1-x_{22})}_{\text{Colonoscopy Group 2}} + \underbrace{G_{21} h_2 \left(-\frac{b}{s-2} x_{22} x_{21} \right)}_{\text{FOBT Group 2}} = 0
\end{aligned} \tag{5.30}$$

The general form of our optimality condition is given by Equation (5.31).

$$\begin{aligned}
& \underbrace{G_{12} h_1 \frac{b}{1+s} x_{12}(1-x_{12})}_{\text{Colonoscopy Group 1}} + \underbrace{G_{22} h_2 \frac{b}{s-2} x_{22}(1-x_{22})}_{\text{Colonoscopy Group 2}} = \underbrace{G_{11} h_1 \left(\frac{b}{1+s} x_{12} x_{11} \right)}_{\text{FOBT Group 1}} + \underbrace{G_{21} h_2 \left(\frac{b}{s-2} x_{22} x_{21} \right)}_{\text{FOBT Group 2}}
\end{aligned} \tag{5.31}$$

To find the optimal allocation budget allocation to black women, s , and by implication an allocation $1-s$ to black men we just need to specify the values of screening with the different modalities, G_{ij} , the population proportions, h_i , original screening rates across testing modalities, x_{ij} , and the calibrated parameter b of the intervention response function. All of this data will be calibrated in the next sections and an optimal allocation for this case will be determined.

5.7.5 Analytic Solution to Limited Intervention: Modified Exponential Response Function

When the intervention response function is assumed to follow the semi-log functional form (i.e. $\gamma(s) = a(1 - e^{-x})$), we can find a closed-form expression of the optimality condition in Equation (5.25).

Given that the derivatives of the linear utility function including the intervention response function components can be calculated as follows under the assumption that

$$\gamma(s) = a(1 - e^{-x})$$

$$\begin{aligned} \frac{\partial}{\partial s} (V_{1j}(\mathbf{s})) &= \frac{\partial}{\partial s} (\beta_0^j + \beta_1^j X_i + a(1 - e^{-s}) PAIN_j + \gamma W_{i,j}) = ae^{-s} \\ \frac{\partial}{\partial s} (V_{2j}(\mathbf{s})) &= \frac{\partial}{\partial s} (\beta_0^j + \beta_1^j X_i + a(1 - e^{-(1-s)}) PAIN_j + \gamma W_{i,j}) = -ae^{(s-1)} \end{aligned} \quad (5.32)$$

The derivatives of the choice probabilities with respect to spending allocation can easily be calculated as follows:

Group 1:

$$\begin{aligned} \frac{\partial x_{1j}}{\partial s_1} &= \frac{\partial V_{1j}}{\partial s_1} x_{1j} (1 - x_{1j}) = ae^{-s} x_{1j} (1 - x_{1j}) \text{ for } j=2 \text{ colonoscopy} \\ \frac{\partial x_{1k}}{\partial s_1} &= -\frac{\partial V_{1k}}{\partial s_1} x_{1j} x_{1k} = -ae^{-s} x_{1j} x_{1k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}} \end{aligned} \quad (5.33)$$

Group 2:

$$\begin{aligned} \frac{\partial x_{2j}}{\partial s_2} &= \frac{\partial V_{2j}}{\partial s_2} x_{2j} (1 - x_{2j}) = -ae^{(s-1)} x_{2j} (1 - x_{2j}) \text{ for } j=2 \text{ colonoscopy} \\ \frac{\partial x_{2k}}{\partial s_2} &= -\frac{\partial V_{2k}}{\partial s_2} x_{2j} x_{2k} = ae^{(s-1)} x_{2j} x_{2k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}} \end{aligned} \quad (5.34)$$

Thus, our optimality equation is as follows

$$\begin{aligned} \frac{d}{ds} \left(\sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(1-s) \right) &= \\ \underbrace{G_{12} h_1 ae^{-s} x_{12} (1 - x_{12})}_{\text{Colonoscopy Group 1}} + \underbrace{G_{11} h_1 (-ae^{-s} x_{12} x_{11})}_{\text{FOBT Group 1}} & \\ + \underbrace{G_{22} h_2 (-ae^{(s-1)}) x_{22} (1 - x_{22})}_{\text{Colonoscopy Group 2}} + \underbrace{G_{21} h_2 (ae^{(s-1)} x_{22} x_{21})}_{\text{FOBT Group 2}} &= 0 \end{aligned} \quad (5.35)$$

And our optimality condition is:

$$\overbrace{G_{12} h_1 a e^{-s} x_{12} (1-x_{12})}^{\text{Colonoscopy Group 1}} + \overbrace{G_{22} h_2 (-a e^{(s-1)}) x_{22} (1-x_{22})}^{\text{Colonoscopy Group 2}} = \overbrace{G_{11} h_1 (a e^{-s} x_{12} x_{11})}^{\text{FOBT Group 1}} + \overbrace{G_{21} h_2 (-a e^{(s-1)} x_{22} x_{21})}^{\text{FOBT Group 2}} \quad (5.36)$$

5.7.6 Parametrizing and Solving the Model

Now that we have a closed form solution for these problems, we can solve this model for the optimal spending allocation given values for the various parameters. In this section, we describe how we obtain estimates of these parameters and describe solutions to the model using these parameter values.

5.7.7 Subpopulation Sizes

In our numerical case study we analyze the black women and black men subpopulations. The population size of these groups consists of all North Carolina residents who are between the ages of 50-75 in any of the years 2014-2023. The size of each of these population groups and their proportion of the relevant population (African-Americans) is given in Table 5-8 .

Table 5-8: Population Size and Proportions

	N	Percentage
Black Women	205,036	54.30%
Black Men	172,536	45.70%

5.7.8 Utility Parameter Changes via Intervention Response Function

This limited intervention is hypothesized to affect individuals' preferences for pain from the testing procedure. The way this intervention is designed intervention spending on one group will not affect the other group. Since we are only analyzing two population groups in our case study, black women and black men, we can reduce the problem to finding the allocation we spend on one population group. We define our choice variable to be choosing the proportion of the budget that we spend on black women. Figure 5-2 and Figure 5-3 below show how much the utility parameter will change as we spend varying percentages on black women. We do this for both intervention response functions. Figure 5-2 shows the how the coefficients change under the semi-logarithmic functional form assumption. Figure 5-3 show how the coefficients change under the modified exponential functional form assumption. The left panel of both figure show the absolute change in the pain utility parameter for each population group under a given budget allocation to black women. The right panel of these figures shows the derivatives of these functional forms for the intervention response function. These derivatives are important because they come into the closed form solutions to our problems.

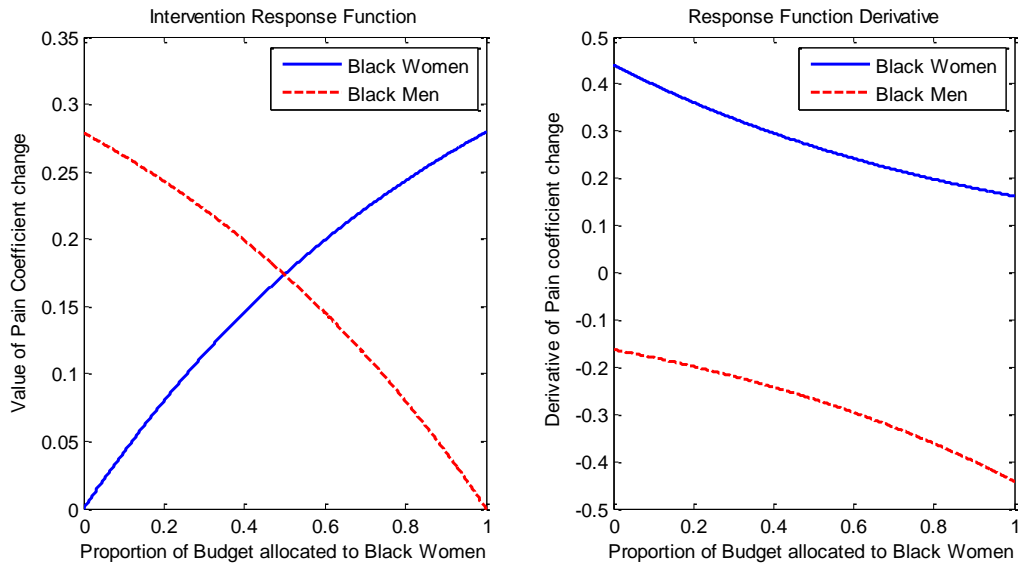


Figure 5-2: Plot of Semi-logarithmic Intervention Response Function and its Derivative to Show how Value of PAIN Coefficient Changes due to Budget Allocations in Limited Intervention Model

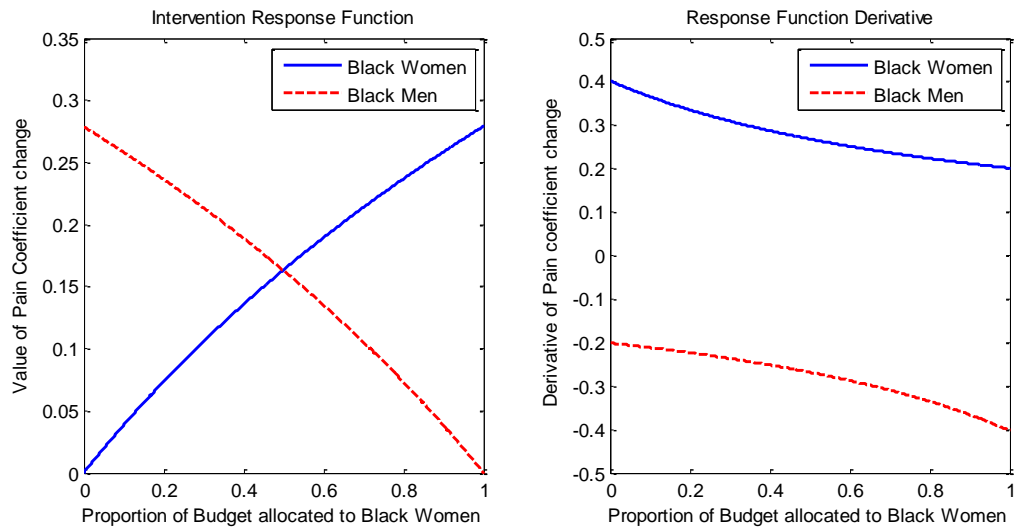


Figure 5-3: Plot of Modified Exponential Intervention Response Function and its Derivative to Show how Value of PAIN Coefficient Changes due to Budget Allocations in Limited Intervention Model

5.7.9 Value of Increased Screening

In the objective function, rewards are obtained from increasing the screening rate from colonoscopy and FOBT. Every increase in the screening rate for colonoscopy or FOBT will find some additional cancers in the population. To estimate the impact of this change, we ran the full CRC simulation model for several units of increase in the CRC screening rate for colonoscopy and FOBT separately. We averaged the marginal increase caused by a 1% point increase to arrive at the value in life-years gained from a percentage point increase in the colonoscopy screening rate. The estimates of the health value of a one (absolute) percentage point increase in screening rates for colonoscopy and FOBT are given in Table 5-9. Because these values are derived from simulation model runs, confidence intervals are included.

Table 5-9: Health Value of a Percentage Point Increase in Test Modality Compliance

	Life-years gained per percentage point increase in annual screening rate per 100,000 population	
	Colonoscopy	FOBT
Black Women	782.3	129.8
95% CI	(528 ,1,036)	(100 ,160)
Black Men	487.3	76.2
95% CI	(302 ,673)	(60 ,92)

5.7.10 Optimal Spending Policy for the Limited Intervention Case

Using the data described above we can solve for the optimal percentage of the budget that should be allocated to each of the independent population groups. Table 5-10 contains

the optimal proportion of the budget to be allocated to each of the two subpopulations considered, black women and black men. Results are presented for both the semi-log and modified exponential functional form assumptions on the intervention response function

Table 5-10: Optimal Budget Allocations between Black Women or Black Men for a Policy that Educates on Pain of Screening

	Black Women	Black Men
Semi-Log	100%	0%
Modified Logarithm	82%	18%

With the semi-log function, it is apparently always beneficial to focus exclusively on the women with intervention spending. This makes sense based on women’s significantly higher benefits from a percentage point increase in screening rates. However, it is notable the difference between the policies generated under the semi-log and modified exponential functional form assumptions. The different functional forms have different rates of decrease in the value of additional expenditures. These differences are great enough that it leads to different solutions. This result of seeing different results under different assumptions of the intervention response curve matches what is often observed in the marketing literature where these functional forms were drawn from. Due to the limited data available to us, we were not able to explore which of these functional forms most accurately captures the rate individuals response. In lieu of this extensive analysis, we report all of our results for both functional forms.

5.7.11 Sensitivity of Limited Intervention Optimal Spending Policy to Differences in Health Benefits

In the results of the specific case study we noted that black women received the largest budget allocation. Moreover we noted that this was largely due to the significantly higher health benefits for an additional percentage point screened accrued to black women as compared to black men. To analyze the significance of this health benefits gap we perform sensitivity analysis on our optimal solutions. For this sensitivity analysis we will fix our value of the benefits of a percentage point increase in colonoscopy screening for black men. We will then vary the benefits assumed to accrue to black women for a percentage point increase in colonoscopy for black women base on a multiple of the value of colonoscopy screening to black men. Figure 5-4 plots the results of the sensitivity analysis. Our solution is the proportion of the budget allocated to black women. Our value to black women of colonoscopy screening is assumed to be a multiple between 1 and 3 of the value of colonoscopy to black men. We report these results for both the semi-log and modified exponential intervention response functions.

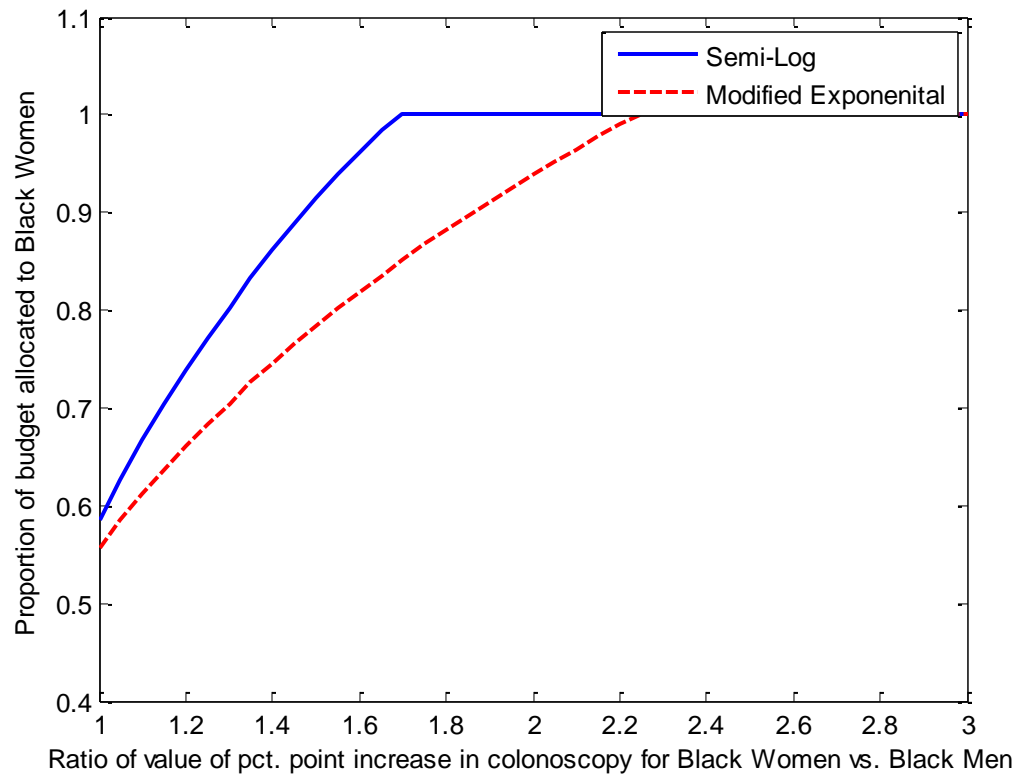


Figure 5-4: Plot of Sensitivity of Budget Allocation Percentage to Black Women to a Difference in the Health Benefits of Colonoscopy of Black Women and Black Men

From this plot we can see that when the gap in health benefits of colonoscopy screening between black women and black men is small (close to 1) then there is a near 50-50 split of the budget between black men and black women. As the gap increase the proportion of the budget allocated to black women increases. The difference in the rate of change of our budget allocation solution between the intervention functional forms becomes apparent in this analysis.

5.8 Case Study 2: Allocation of Spending on Broad-based Intervention that Affects Two Test Attributes

In this second case study, we consider how to optimally allocate spending between two interventions that affect different attributes of a single test. Spending on each of these interventions is assumed to affect populations rather than just one specific population or another. Again our population groups will be black women and black men. The two intervention policies we will analyze are 1) an intervention that increases the utility from risk reduction and 2) a policy that reduces disutility from pain. Because these interventions are assumed to affect both subpopulations, the messages of these campaigns would likely be delivered by a mass media vehicle such as television or radio advertisements or other widely distributed media. An example of an intervention that would increase utility of risk reduction is a campaign highlighting the mortality rates of CRC. Many of the American Cancer Society's communications focus on the risk of mortality from CRC and the benefits of screening; these communications would increase individuals' value for the risk reduction achieved by cancer screening. An example intervention that would decrease the disutility from pain would be a media program demonstrating the simplicity and minimal discomfort associated with the test procedure. Supporting television programs that show celebrities getting colonoscopies (such as Dr. Oz on his show of the same name) would be examples of such programs.

5.8.1 Mathematics of Broad-based Intervention Model

The problem formulation of the two intervention model shares many of the same aspects of the formulation with the two population (independent intervention) case. Problem

notation remains the same. The first index i notates the subpopulation groups. First index $i = \{1, 2\}$ where $i = 1$ indicates black women and $i = 2$ indicates black men. Second index j , denotes the testing modality. Index $j = 0$ denotes the alternative of No screening, $j = 1$ indexes FOBT, and $j = 2$ denotes colonoscopy. The main modification of the two intervention model is that all of the tradeoffs take place between parameters of the linear utility model $V_{ij}(s)$ of each population group and intervention as opposed to across population groups. This leads to the following formulation of the mathematical programming problem:

$$\max_s \sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(s) \quad (a)$$

$$\text{where } x_{ij}(s) = \frac{\exp(V_{ij}(s))}{\sum_{k \in \{0,1,2\}} \exp(V_{ik}(s))} \quad i \in N \quad j \in \{0,1,2\} \quad (b)$$

$$V_{ij}(s) = \beta_0^j + \beta_1^j X_i + \gamma(s) \text{PAIN}_j + \gamma(1-s) \text{RR}_j + \gamma W_{i,j} \quad (5.37)$$

s.t.

$$s + (1-s) = B = 1 \quad (c)$$

$$s \geq 0 \quad (d)$$

The general form of our optimality condition is given by Equation (5.38).

$$\frac{d}{ds} \left(\sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(1-s) \right) = \sum_{j \in \{0,1,2\}} G_{1j} h_1 \frac{dx_{1j}}{ds} \Big|_{x_{1j}(s)} + \sum_{j \in \{0,1,2\}} G_{2j} h_2 \frac{dx_{2j}}{ds} \Big|_{x_{2j}(s)} \quad (5.38)$$

5.8.2 Economic Interpretation of Broad-based Intervention Model

The optimality condition of the broad-based intervention model has an economic interpretation. Like the limited intervention model, the optimality conditions examine the

tradeoffs of inherent in our optimal spending policy. Here the tradeoff is between allocating spending on messaging campaigns that focus on different screening test attributes. Because this tradeoff takes place within an individual's utility function the equilibrium spending allocation will be simple. Spending will be allocated so that the greatest increase in raw utility is obtained. This can be achieved by first focusing on the attribute that has the largest absolute increase in raw utility should the full budget be allocated toward that attribute. Budget should be allocated to the other intervention attribute when the marginal increase in raw utility for the next dollar allocated to this first intervention is less than the change in raw utility from the first dollar of the other attribute. This can/will occur due to the assumption of decreasing returns to scale from our intervention.

5.8.3 Analytic Solution to Broad-based Intervention: Semi-log Intervention Response Function

When our intervention response function is the semi-logarithmic function, $\gamma(s) = b \ln(1 + s)$, then the derivatives of our utility function as a function of spending allocation can be determined. These derivatives are given in Equation (5.39) for change in colonoscopy raw utility due as budget allocations change and Equation (5.40) for the change in FOBT raw utility as budget allocations change. Equation (5.40) only considers the budget allocated to risk reduction since this is the only factor that affects FOBT choice.

$$\begin{aligned} \frac{d}{ds} V_{ij}(s) &= \frac{d}{ds} \left(\beta_0^j + \beta_1^j X_i + b_1 \ln(1 + s) PAIN_j + b_2 \ln(2 - s) RR_j + \gamma W_{i,j} \right) = \\ &= \frac{b_1}{1 + s} PAIN_j + \frac{b_2}{s - 2} RR_j \end{aligned} \quad (5.39)$$

$$\frac{d}{ds} V_{ij}(s) = \frac{d}{ds} \left(\beta_0^j + \beta_1^j X_i + b_2 \ln(2 - s) RR_j + \gamma W_{i,j} \right) = \frac{b_2}{s - 2} RR_j \quad (5.40)$$

Given these derivatives of the linear utility functions, we can parameterize the derivatives of the choice probabilities between colonoscopy, FOBT and no screening. These derivatives are given in Equation (5.41):

$$\begin{aligned}
\frac{\partial x_{ij}}{\partial s} &= \frac{\partial V_{ij}}{\partial s} x_{1j}(1-x_{1j}) = \left(\frac{b_1}{1+s} PAIN_j + \frac{b_2}{s-2} RR_j \right) x_{1j}(1-x_{1j}) \text{ for } j=2 \text{ colonoscopy} \\
\frac{\partial x_{ij}}{\partial s} &= \frac{\partial V_{ij}}{\partial s} x_{1j}(1-x_{1j}) = \left(\frac{b_2}{s-2} RR_j \right) x_{1j}(1-x_{1j}) \text{ for } j=1 \text{ FOBT} \\
\frac{\partial x_{ik}}{\partial s} &= -\frac{\partial V_{ik}}{\partial s} x_{1j}x_{1k} = -\left(\frac{b_1}{1+s} PAIN_j + \frac{b_2}{s-2} RR_j \right) x_{1j}x_{1k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}}
\end{aligned} \tag{5.41}$$

Using these choice probability derivatives we can specify the optimality condition of our particular case. This optimality condition is given by Equation (5.42).

$$\begin{aligned}
\frac{d}{ds} \left(\sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(s) \right) &= \\
\underbrace{\sum_{i=(1,2)} G_{i2} h_i \left(\frac{b_1}{1+s} PAIN_2 \right) x_{i2}(1-x_{i2})}_{\text{Colonoscopy Pain}} &+ \underbrace{\sum_{i=(1,2)} G_{i1} h_i \left(-\left(\frac{b_1}{1+s} PAIN_2 \right) x_{i2}x_{i1} \right)}_{\text{FOBT Pain}} \\
+ \underbrace{\sum_{i=(1,2)} G_{i2} h_i \left(\frac{b}{s-2} RR_2 \right) x_{i2}(1-x_{i2})}_{\text{Colonoscopy Risk Reduction}} &+ \underbrace{\sum_{i=(1,2)} G_{i1} h_i \left(\frac{b}{s-2} RR_1 \right) x_{i1}(1-x_{i1}) + \sum_{i=(1,2)} G_{i1} h_i \left(\left(-\frac{b}{s-2} RR_2 \right) x_{i2}x_{i1} \right)}_{\text{FOBT Risk Reduction}} \\
&= 0
\end{aligned} \tag{5.42}$$

5.8.4 Analytic Solution to Broad-based Intervention: Modified Exponential Intervention Response Function

When our intervention response function is the semi-logarithmic function, $\gamma(s) = a(1 - e^{-x})$, then the derivatives of our utility function as a function of spending allocation can be determined. These derivatives are given in Equation (5.43) for change in colonoscopy raw utility due as budget allocations change and Equation (5.44) for the change

in FOBT raw utility as budget allocations change. Equation (5.44) only considers the budget allocated to risk reduction since this is the only factor that affects FOBT choice.

$$\begin{aligned} \frac{d}{ds} V_{ij}(s) &= \frac{d}{ds} \left(\beta_0^j + \beta_1^j X_i + a_1(1 - e^{-s})PAIN_j + a_2(1 - e^{s-1})RR_j + \gamma W_{i,j} \right) = \\ &= a_1 e^{-s} PAIN_j + a_2 e^{s-1} RR_j \end{aligned} \quad (5.43)$$

$$\frac{d}{ds} V_{ij}(s) = \frac{d}{ds} \left(\beta_0^j + \beta_1^j X_i + a_2(1 - e^{s-1})RR_j + \gamma W_{i,j} \right) = a_2 e^{s-1} RR_j \quad (5.44)$$

Given these derivatives of the linear utility functions, we can parameterize the derivatives of the choice probabilities between colonoscopy, FOBT and no screening. These derivatives are given in Equation (5.45):

$$\begin{aligned} \frac{\partial x_{ij}}{\partial s} &= \frac{\partial V_{ij}}{\partial s} x_{1j}(1 - x_{1j}) = \left(a_1 e^{-s} PAIN_j + a_2 e^{s-1} RR_j \right) x_{1j}(1 - x_{1j}) \text{ for } j=2 \text{ colonoscopy} \\ \frac{\partial x_{ij}}{\partial s} &= \frac{\partial V_{ij}}{\partial s} x_{1j}(1 - x_{1j}) = \left(a_2 e^{s-1} RR_j \right) x_{1j}(1 - x_{1j}) \text{ for } j=1 \text{ FOBT} \\ \frac{\partial x_{ik}}{\partial s} &= -\frac{\partial V_{ik}}{\partial s} x_{1j} x_{1k} = -\left(a_1 e^{-s} PAIN_j + a_2 e^{s-1} RR_j \right) x_{1j} x_{1k} \text{ for } k=0,1 \text{ \{No Screen, FOBT\}} \end{aligned} \quad (5.45)$$

Using these choice probability derivatives we can specify the optimality condition of our particular case. This optimality condition is given by Equation (5.46).

$$\begin{aligned} \frac{d}{ds} \left(\sum_{j \in \{0,1,2\}} G_{1j} h_1 x_{1j}(s) + \sum_{j \in \{0,1,2\}} G_{2j} h_2 x_{2j}(s) \right) &= \\ \underbrace{\sum_{i=\{1,2\}} G_{i2} h_i \left(a_1 e^{-s} PAIN_2 \right) x_{i2}(1 - x_{i2})}_{\text{Colonoscopy Pain}} &+ \underbrace{\sum_{i=\{1,2\}} G_{i1} h_i \left(-\left(a_1 e^{-s} PAIN_2 \right) x_{i2} x_{i1} \right)}_{\text{FOBT Pain}} \\ + \underbrace{\sum_{i=\{1,2\}} G_{i2} h_i \left(a_2 e^{s-1} RR_2 \right) x_{i2}(1 - x_{i2})}_{\text{Colonoscopy Risk Reduction}} &+ \underbrace{\sum_{i=\{1,2\}} G_{i1} h_i \left(a_2 e^{s-1} RR_1 \right) x_{i1}(1 - x_{i1}) + \sum_{i=\{1,2\}} G_{i1} h_i \left(-\left(a_2 e^{s-1} RR_2 \right) x_{i2} x_{i1} \right)}_{\text{FOBT Risk Reduction}} \\ &= 0 \end{aligned} \quad (5.46)$$

5.8.5 Optimal Spending Policy for the Broad-based Intervention Case

The results of solving this problem under the in the semi-log and modified exponential intervention response function can be found in Table 5-11. For both functional forms it was assumed that spending the entire budget on a given attribute could achieve a change in the utility parameter for pain of 90% of original parameter value and 25% for Risk reduction. Sensitivity analysis on these assumptions is performed in the next section to evaluate the impacts of these assumptions

Table 5-11: Budget Allocation Between Pain and Risk Reduction Intervention Focus

	Percentage of budget allocated towards test attribute	
	Pain	Risk Reduction
Semi-Log	34%	66%
Modified Logarithmic	39%	61%

These results demonstrate the bulk of spending should be focused on promoting the risk reduction aspects of colorectal cancer screening. Under the calibration assumptions in the baseline model spending a substantial amount of money on changing individuals' disutility from pain does not bring enough change to justify a lot of spending on these interventions.

5.8.6 Sensitivity Analysis of Broad-based Intervention Results

As noted in the presentation of the results in the previous section, our beliefs on the impact of our spending on individuals' preference parameter drives the solutions that our

model produced. To evaluate the degree of variation in our budget allocation solutions induced by different assumptions in these response parameter we perform sensitivity analysis. We will analysis how the percentage of budget allocated toward reducing disutility for pain changes with respond to the degree of impact of budgetary spending on risk reduction. We will do this analysis by assuming varying the proportion of the maximal effect the risk reduction intervention is assumed to have. As a baseline the risk reduction intervention was assumed to double the individuals' utility preference for risk reduction. Figure 5-5 plots the proportion of the budget allocated to pain as the impact of spending on risk reduction increases. We do this for both the semi-log and modified exponential intervention response functions.

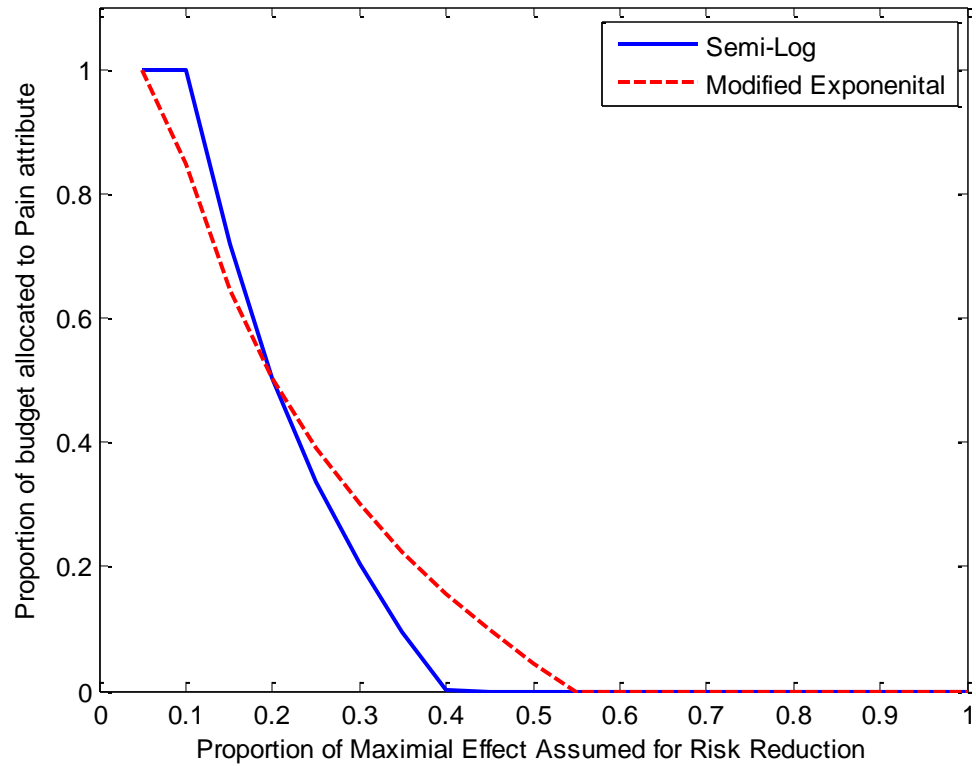


Figure 5-5: Plot of Proportion of Budget Allocated to Decreasing Disutility from Pain as the Value of Spending on Risk Reduction Increases

The trends we observe in Figure 5-5 match our intuition. As the values of spending on risk reduction increase the proportion of the budget allocated to pain decreases. It is notable that there is a wide variation in the budget allocations solutions that appears over a relatively narrow range of parameter assumption. This highlights the importance of correctly estimating the parameter values when attempting to analyze the tradeoffs between two intervention attributes.

5.9 Conclusion

In this section, we have detailed a modeling methodology that can aid planner's decision-making on the design of and allocation of spending on intervention policies and target populations. This optimal "portfolio" of intervention spending provides the most health benefit from a limited public health budget. The policies in this portfolio are optimized while incorporating the dynamic response of individuals to their policy actions. The model of individuals' dynamic behavior used in this chapter is uniquely focused on how individuals view and respond to the attributes of the testing modality. With this level of detail we can model the specific avenues through which interventions make their impact. This methodology contributes to the field of public health decision modeling in three ways: 1) it provides an avenue for positive statements about the design of public health policies based on discrete choice data; 2) it introduces and interprets intervention response function to model the impact of spending on choice data; and 3) it describes a mathematical programming formulation of the decision problem and provides closed form solutions for many practical case examples.

In the public health literature, discrete choice experiments are a common avenue for normatively understanding the factors that influence individual behaviors. The relative utility weights provided by coefficients estimated via a statistical methodology such as logistic regression using discrete choice experiment data enable much to be learned about the relative value of test modality attributes to individual decision-makers. Usually, the public health literature is content with static, comparative analysis of these results. Our approach demonstrates a new, dynamic use of results of discrete choice experiment data to analyze interventions that are hypothesized to affect an individual's utility/disutility for a particular

test attribute. With some additional assumptions on how these utility weights change in response to spending, optimal spending between interventions that affect the utility of different test attributes can be discovered.

The result of basic logistic regression is an estimate of the probability of an individual choosing a given testing modality. The coefficients of a utility model specify the relative impact of test modality attributes in determining these choice probabilities. The public health planner is primarily interested in changing aggregate screening choices to get individuals to choose beneficial interventions. Intuitively, these choices probably would change as a result of changes in individual preferences for different test modality attributes. We mathematically model how our public health polices change screening choices rates via analysis of changes in preferences for specific test attributes. Sales response functions from the marketing literature are repurposed and reinterpreted as intervention response functions to enable this analysis. These functions provide a theoretically sound tool to translate data on intervention effects into calibrated function to enable intervention decision-making.

The components analyzing individual behavior are then incorporated in a mathematical model that describes the planner objective of allocating spending across interventions to maximize population health. Using a Net Health Benefit approach the cost and benefits from intervention policies are weighted to determine the best spending allocation. We show that under limited conditions, most of which are met in practical case applications, this mathematical model has closed-form solutions. This enables rapid solution of this problem once all parameters have been specific. Additionally, the closed-form

solution enables sensitivity analysis on the parameters should some of the parameters not be known with certainty.

Finally, we concluded the section with several case examples to demonstrate the application of these techniques to realistic decision scenarios using detailed data gathered from the large scale NC-CRC simulation model. These policies case studies demonstrate the value of distributing spending across interventions and population groups in many real cases.

CHAPTER 6: CONCLUSION

6.1 Contributions of Dissertation Work

This dissertation provides tools for the design and analysis of public health interventions that improve health via changing choice behavior of individuals. We have demonstrated the applicability of these tools to the design of public health messaging campaigns to improve colorectal cancer screening outcomes. The tools we have developed are both predictive and proscriptive. By advancing the development of an individual simulation model of colorectal cancer progression, we developed an ability to evaluate the impact of prospective policies. The particular innovations in this simulation model came in the detailed description of individual cancer screening behavior and in being able to differentiate according to a wide degree of geographic and socio-demographic factors. Long run-times initially limited the usability of this model for analysis. Innovations that we implemented in the sampling procedure for individual life-course events enabled robust results from a smaller set of experiments which reduced run times and expanded the types of policies that could be evaluated with the model. Using this simulation model as an evaluation tool, we optimized interventions designed to change individuals' screening behavior. We developed mathematical optimization formulas for two decision problems; the first optimizes the allocations of a budget across an individual's 25-year colorectal cancer screening horizon, and the second optimizes the allocations of the budget across the "portfolio" of multiple intervention designs. Each chapter of this dissertation contributes to this theme of improving decision-making for colorectal cancer screening.

The simulation model of colorectal cancer progression and individual screening behavior described in Chapter 2 forms the basis of, and inspiration for, the problems addressed in this dissertation. The model of Chapter 2 extends the well-validated MISCAN-Colon model of cancer natural history to include individuals' screening behavior. This model of screening behavior is data-driven and incorporates differences in screening rates between population groups observed in the data. The model is calibrated and evaluated on a synthetic population representative of the population of North Carolina. Using a population representative of the State of North Carolina ensures that our case study results are relevant and interpretable to a public health audience. Simple interventions were evaluated with this model. The effects of static policies, like sending a mailed reminder when individuals are not up-to-date, broad-based mass media campaigns, voucher programs, and screening locations subsidies, were tested and their results reported. Of these interventions, mass media campaigns and mailed reminder programs showed the most promise for cost-effective improvements in health.

In the original implementation of the model used in Chapter 2, we faced some computational difficulties. The way life course events were sampled between intervention policies initially prevented direct comparison of individuals' life courses due to stochastic noise. We found that this noise could be overcome by large numbers of simulation model runs, but numerous runs also added greatly to the computational time required to run the model to evaluate policies. A solution was found by reevaluating how individual life courses were simulated and synchronizing the sampling of life course events between policy evaluation runs as this enabled significantly fewer model runs to be used to produce accurate

results. . The technique we used to synchronize life course events was the careful application of the concept of Common Random Numbers to each of the multiple “event streams” generating samples that determined events like cancer progression, other-cause mortality, and cancer screening decisions. Because we applied this to an individual simulation model, we coined the term “Common Patient” to describe our synchronization. The architecture of our model necessitated a multi-pronged approach for implementing the Common Random Number concept. Numerical experiments using the colorectal cancer simulation model demonstrated the substantial reduction in computational time and accuracy that can be achieved by implementing Common Patients.

The work of Chapter 2 and Chapter 3 advanced the development of a sophisticated simulation model to test policies that affect individuals’ screening behavior and enabled this analysis in a computationally efficient manner. While simple static policies were developed, tested and compared in Chapter 2, these policies ignored the lifetime dynamics of individuals and the fact that multiple intervention policies are often applied simultaneously. Chapter 4 and Chapter 5 developed mathematical tools to aid in decision-making for these problems and utilized the simulation model of Chapter 2 to provide data for policy optimization and analysis.

Chapter 4 proposed and solved a mathematical model aimed at optimizing the allocation of an intervention budget over time with the goal of maximizing its benefits to the population. This is common tactical approach of public health planners once a particular intervention has been identified for implementation. Solving this problem requires the application of simulation optimization techniques. This dissertation presents a response

surface optimization approach that enables good solutions to this problem to be found with a reasonable amount of computing effort. This technique was used to find the optimal allocation of a limited public health budget for a mailed reminder intervention to the population of North Carolina. Our results demonstrated the value of focusing the bulk of spending on mailings to the 60-70 age group rather than very early or very late in the age 55-75 screening interval.

The mathematical decision model developed in Chapter 5 strives to address the strategic question of how best to design interventions to offer to the population and how to allocate spending for these interventions in order to optimize the health outcome. To enable this analysis, we specify a more extensive utility function for individuals' choices between interventions. The expanded utility function weights each attribute of the testing modality according to the impact it has on an individual's decision making. This detailed utility function then enables us to analyze interventions that hypothesize changes to the utility/disutility experienced by individuals in specific test attributes such as pain, or risk reduction achieved by the test. This knowledge enables us to allocate our spending between different population groups and different test attributes when designing public health programs. The closed-form solutions we prove for several cases of the optimization problem provide a generalizable solution to the problem. With the input of data from specific problem instances, a result can be determined. We demonstrated this fact by applying our results to the design of a mailed reminder campaign and a mass media campaign.

6.2 Future Work

The main opportunity for advancement of this work would be to develop a more sophisticated, data-driven model of the individual screening behavior component as well as using data drawn from US-based discrete choice studies. The model of individual behavior is the core element in this type of model. Describing this behavior accurately is crucial for accurate results. The model of individual behavior we utilized was as sophisticated as our limited data sets allowed. Collecting more data was substantially out of scope for this dissertation since observational studies for colorectal cancer screening require observational periods on the order of years to collect the necessary data. The main element missing from our data was the time-dependent behavior in an individual's decision-making. How someone acted earlier in his screening interval will affect his behavior later in that interval. Our data did not capture this information, so we were forced to assume independence of each decision over time. We attempted to proxy for this behavior change by changing insurance status with age, but this likely does not capture the complete picture of the nature of the time dependence of screening behavior. Additionally, we recognize that there are population and behavioral differences that exist between US and European populations in regards to colorectal cancer screening. Future data collection would be focused on US population rather than European populations.

6.3 Applicability to the Broader Research Community

The techniques and methods developed in this dissertation within the colorectal cancer screening context have applicability to questions that are much broader than this context. The computational techniques and the optimization models both have applicability outside of the

colorectal cancer context. The notion of improving outcomes by changing individuals' choices has wide applicability in many public health contexts, including smoking cessation, family planning decisions, and obesity prevention policy. The computational technique of creating Common Patients has broad applicability for health care policy simulations where effects are generated by marginal individual choices. The means of computationally implementing common patients enables a broad applicability of our techniques across modeling platforms and paradigms. The mathematical structure of the budget allocation over an individual's screening horizon can be parameterized so as to solve this allocation for additional intervention policies and other problem contexts.

The model of Chapter 5 has potential for applications to general marketing problems in addition to health care problems. If a marketer needs to make a decision about how to spend his budget to influence consumer preferences to increase revenue when his product mix is fixed, then this mathematical optimization formulation can aid his decision.

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APPENDIX

APPENDIX A: THE BIOLOGY OF COLORECTAL CANCER

Colorectal cancer refers to benign and malignant growths in the large intestine (colon) and rectal area. There are several types of tumors that can occur in the colon. They are classified based on the location from which the abnormal cells originate. By far the most common type of tumor is an Adenocarcinoma, accounting for 95% of all colon tumors. Adenocarcinoma refers to abnormalities that occur in cells having secretory properties; many of them are involved in the production of the mucous lining of the colon although they do not necessarily need to be part of a gland to be included in this classification. The mucus lining of the colon is shed regularly and these cells are normally expunged along with the normal lining cells, however, sometimes the body responds to these abnormal cells by encasing them, creating a growth that becomes attached to wall of the colon. When these cells are not cancerous, this growth is called a polyp. Some of these polyps will never grow much and will remain benign for the remainder of a person's life. However, if a polyp is not detected or removed, these cells can, overtime, mutate, become malignant and begin to invade further into the wall of the colon. As the cancer invades further into the colon wall, it gains access to the colon's network of blood vessels and the lymphatic system, both contained within the colon wall. These provide avenues for malignant cancer cells to metastasize beyond the colon and to produce cancers in other areas of the body. This metastatic process is what has the most profound effect on the survivability of late stage CRC.

Testing for CRC can be accomplished in a variety of ways. CRC tests attempt to either identify growths (which can either be pre-cancerous polyps or cancers) or to look for

markers of cancer in waste. Tests that seek to identify growths include: Colonoscopy, sigmoidoscopy, barium enemas and CT Tomography. Colonoscopy is the gold standard screening test for CRC. It is the most effective at detecting CRC and offers the ability to immediately remove small polyps and biopsy larger ones. Even when other screening methods are used, colonoscopies are often required to diagnose or follow up on abnormal findings from these other screening methods. A colonoscopy is performed by inserting an endoscope into the colon through the rectum. As the endoscope is moved through the colon, a doctor is able to visually examine the walls of the colon for polyps and abnormalities. Doctors can insert instruments through the endoscope to remove polyps and perform biopsies. A colonoscopy is usually performed by a gastroenterologist under sedation in an outpatient setting. Sigmoidoscopy is very similar to a colonoscopy. It is differentiated by the fact that a shorter endoscope is used, and thus can be performed at a doctor's office without sedation. However, the shorter length means that a relatively shorter length of colon can be examined during a sigmoidoscopy and this results in diminished effectiveness for this test. Additionally, since it is typically performed without sedation, tissue cannot be removed during the procedure. Sigmoidoscopy is not commonly performed in the US due to patients' preference for sedation and gastroenterologists' practice preference for colonoscopy. Two less often used cancer visual identification tests are barium enemas and CT Tomography. In a barium enema, X-ray images of the colon are taken after the colon has been flushed with barium. In CT Tomography, the colon is flushed with air and afterwards, a series of CT images are taken of the colon. These images are reviewed by a radiologist to determine if abnormal growths are present. In the event abnormalities are identified, this would trigger the

need for a colonoscopy for further examination. These last two tests are used infrequently because of gastroenterologists practice preferences and the minimal reduction in the invasiveness of the exam compared to standard colonoscopy. There is some risk of side effects with any of these tests. For colonoscopy, there is a very small risk of perforating the colon which may require surgical intervention to fix; in rare cases, perforation can lead to death. For the image-based colon cancer screening, a small dose of radioactive elements are used. For most patients this risk is insignificant, however some patients must be mindful of their cumulative radiation dosages.

The previous tests all allow complete visual examination of the colon for both cancers and cancer precursors. Each of these tests is invasive to some degree or another and tend to decrease patient willingness to screen. To encourage wider participation in screening programs, three cancer screening tests have been developed that look for markers of cancer in a stool sample. These test are: the Fecal Occult Blood test (FOBT), Fecal immunochemical test (FIT) and fecal DNA test. The FOBT and FIT test seek to identify blood in the stool sample through chemical reactions. Because colon polyps often bleed into the colon, blood in the stool may be an indicator of colon cancer even though this blood may not visible to the naked eye. The difficulty with these tests is that many other conditions can also cause blood in the stool and it is impossible to distinguish the source of blood in the stool from this test. While these fecal analysis tests have no significant side effects or risks, they cannot detect pre-cancerous polyps and have very low sensitivity and specificity. The sensitivity rate (rate of positive tests for cancer when it is present) is particularly low for early stage cancers. The frequent testing interval of 1 year is designed to overcome this limitation, but these tests still

do a poor job at early detection. A new fecal DNA test offers some promise of overcoming these problems. This new test looks for DNA markers of cancer in a stool sample. Early studies have shown this test to be more effective than existing fecal based screening methods, however, it is not yet widely available because it is almost as expensive as a colonoscopy and is still markedly less effective.

Treatment for colon cancer involves removing the abnormal or cancerous cells. Polyps and early stage cancers can usually be removed during a colonoscopy procedure and typically do not require any follow-up surgeries or procedures. For later stage cancer which have invaded the colon wall, treatment involves resecting (removing) the affected part of the colon. This resection can be quite aggressive and may require long-term lifestyle changes such as wearing an ostomy pouch to collect waste if a significant amount of the colon is removed. Additionally, as mentioned earlier, later stage cancers, because of their access to the circulatory and lymphatic systems, often metastasize to other areas of the body, necessitating chemotherapy or possibly additional surgeries to extinguish all forms of cancer.