Multi-Objective Two-Stage Stochastic Programming for Adaptive Interdisciplinary Pain Management with Piecewise Linear Network Transition Models

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Abstract

This research uses a two-stage stochastic programming (2SP) approach to optimize personal adaptive treatment strategies for pain management. Transition models are represented by piecewise linear networks (PLN). A multi-objective mixed integer linear program (MILP) is developed to optimize treatment strategies for patients based upon on these transition models. A convex quadratic program (QP) is developed to determine weights for multiple levels of multiple pain outcomes that are consistent with surveys submitted pain management experts.

Keywords: Piecewise Linear Network Model, Mixed Integer Linear Program, Convex Quadratic Programming, Two-Stage Stochastic Programming, Pain Management, Odd's Ratio

1. Introduction

Everyone experiences pain at various times and to varying degrees. Indeed, pain is the most common reason for people to seek medical assistance [1]. "Pain is always something that hurts" [2]. When a patient visits a physician, the most common symptom is pain, which is highly subjective, and the perception of pain involves various brain-peripheral feedback mechanisms.

The pain experience involves three interactive domains: physiological, psychological, and social (i.e., the biopsychosocial model) as shown in Figure 1. Treatment of pain involves dealing with the complex biopsychosocial changes of patients. For example, pain and depression are related to each other; people who have depression report more pain than non-depressed individuals. Therefore, many biopsychosocial factors are involved for treatment when a patient suffering from pain visits a physician. Some of these factors determine the causes of pain, duration, pain intensity, etc. Pain can be short-term or long-term, and its type and level can differ from patient to patient. Short-term pain that lasts a maximum 6 months is also

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known as acute pain. If short-term pain is not appropriately treated, then it can persist and become chronic, which is also known as chronic pain. Research shows that two-thirds of elderly people suffer from at least two chronic conditions [3]. Acute pain is fast, intense, and localized, while chronic pain is slow, diffuse, and prolonged [4]. People with chronic pain require more treatment than patients with acute pain. Chronic pain reduces a person's quality-of-life and working capability [5]. Many patients are somewhat afraid to report pain because they fear: having a surgery; long-term treatment; losing social independence; etc. In some cases, they are unable to verbalize their pain condition to physicians. Surgery, cancer, and bone fractures usually cause acute pain. By contrast, arthritis, cancer, diabetic neuropathy, and back pain syndrome often cause chronic pain [6]. Chronic pain is related to medical and physical conditions as well. In most instances, the best pain management involves coordinated drug and non-drug therapies [7].

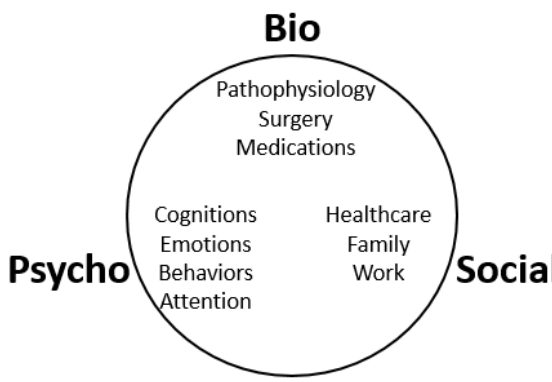


Figure 1: The Three Biopsychosocial Domains of Pain

A total of 65 million people have lower back pain in the United States [8]. In the next 30 years, the number of older adults in the United States is expected to double [9]. Two-thirds of older adults suffer from back pain. For example, Cooner and Amorosi conducted a telephone poll in New York City that showed that almost 50% of elderly people suffer from chronic pain and have taken pain medications. 51.4 million inpatient surgical procedures were performed in 2010 [10], and more than 25 million outpatient surgeries are performed each year in 5300 certified surgery centers in the United States [11]. Many surgeries are conducted on older adults. Among these, 80-85% experience some health problems that cause pain. In order to mitigate this unwanted pain, 45% of older adults visit at least three physicians [12].

Moreover, many traditional pain management therapies have recommended using highly addictive treatments such as opioids. These prescriptions have led to a crisis in the United States [13]. More than 750,000 people have died since 1999 from a drug overdose [14], and two out of three drug overdose deaths in 2018 involved an opioid [15]. Consequently, the National Institutes of Health and the Department of Health and Human Services now recommend physicians treating pain management to alternative less addictive treatments [13].

The Eugene McDermott Center for Pain Management at UT Southwestern Medical Center, which we refer to as the *Center*, administers an interdisciplinary two-stage pain management program for chronic pain. Figure 2 demonstrates that, at the beginning of the program, a patient receives a preliminary *pre-treatment evaluation*, which includes review of past medical records, the patient's demographic information, and biopsychosocial examinations.

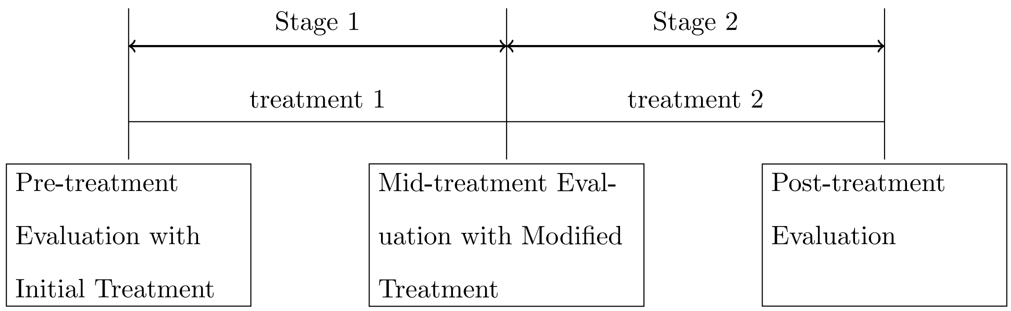


Figure 2: Two-stage Interdisciplinary Pain Management Program at the Center [16]

Based on these evaluations, physicians prescribe a treatment plan for the patient, which is the beginning of Stage 1. After a certain period of time, the patient visits the Center again and receives a *mid-treatment evaluation*. Physicians then review the pain outcomes of the evaluation and prescribe a new set of treatments to the patient if needed, which is the end of Stage 1 and the beginning of Stage 2. The *post treatment evaluation*, where final pain outcomes are measured, ends the two-stage pain management program. Patients receive another evaluation program after one year of this two-stage pain management program. In this research, we will not consider this last evaluation. The time duration between each stage varies from patient to patient but usually ranges from 6 months to 1 year.

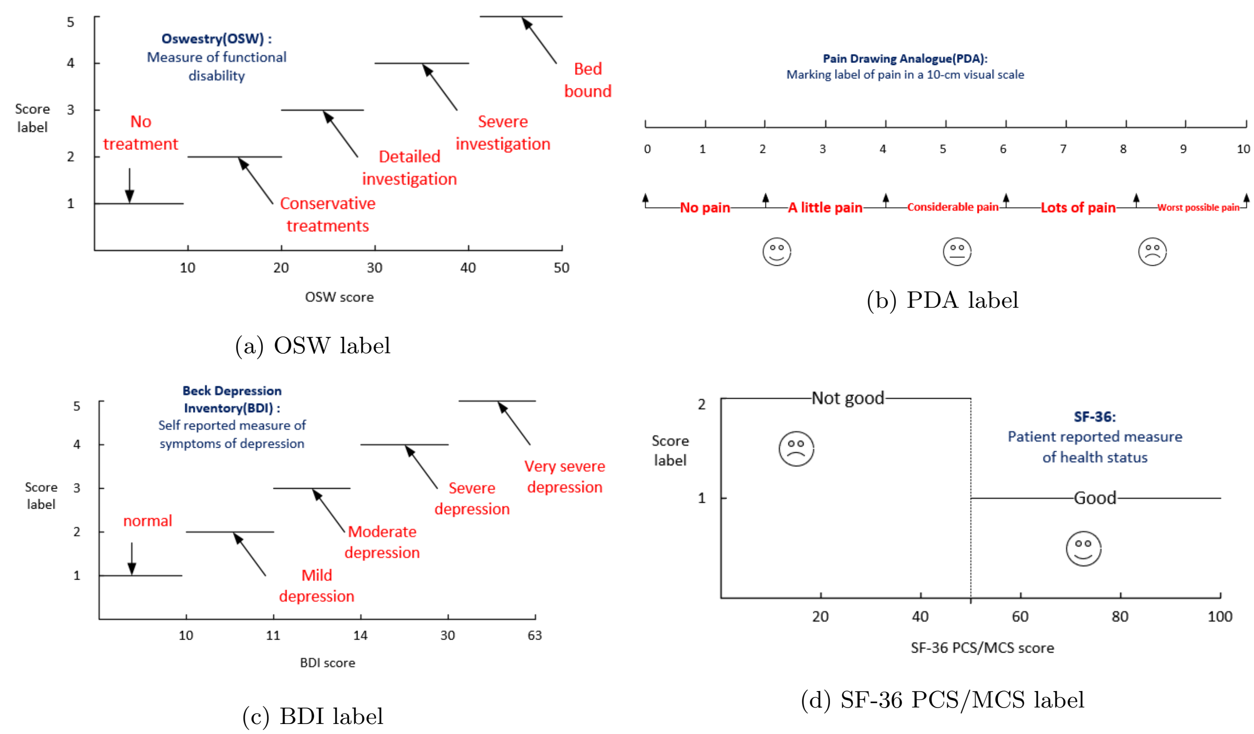
The rest of this paper is organized as follows. In section 2, we describe background of pain outcomes, literature related to multi-objective health care optimization and piecewise linear networks, and the contribution of this research. Section 3 presents a two-stage stochastic programming (2SP) formulation for an adaptive interdisciplinary pain management program, including a mixed integer linear program (MILP) formulation that uses piecewise linear network (PLN) transition models and a convex quadratic program (QP) formulation to determine weights for multiple pain outcomes. In section 4, we discuss a case study, treatment analysis, and final pain outcome comparisons among this research, Wang et al. [17], and observed data in both stages.

2. Background, Literature, and Contribution

In this section, we discuss background on pain outcomes, literature on multi-objective health care optimization, and piecewise linear networks. Finally, we discuss the contribution of this research.

2.1. Background on Multiple Pain Outcomes

The Center uses multiple pain outcome measures to identify pain intensity. These outcome measures include the Beck Depression Inventory (BDI), the Dallas Pain Questionnaire (DPQ), the Oswestry Pain Disability Index (OSW), the Pain Drawing Analogue (PDA), the Multidimensional Pain Inventory (MPI), the 36-item Short Form Survey Physical Component Score (SF-36 PCS), and the 36-item Short Form Survey Mental Component Score (SF-36 MCS). However, the dataset we get from the Center consists of five pain outcome measures, namely OSW, PDA, BDI, SF-36 PCS, and SF-36 MCS. Consequently, we consider these five pain outcome measures in this study, even though the model and general approach are amenable to additional and different outcome measures. .



(a) OSW label

(b) PDA label

(c) BDI label

(d) SF-36 PCS/MCS label

Figure 3: Different pain outcomes and their Labels

OSW is a measure of perceived functional disability caused by pain, and below is a summary from the European Medical Tourist [18]. OSW is the most widely used measure for assessing the disability level from back pain. To determine OSW, a patient submits a survey with 10 sections, and each section has a score range of 0 to 5. Consequently, OSW has a maximum total score of 50. As shown in Firgure 3a, a patient with a raw score between 0 and 10 indicates that the patient has minimal disability and usually no treatment is necessary. A score between 11 and 20 signifies that the patient has mild disability, so a conservative treatment plan is recommended. OSW from 21 to 30 signifies severe disability, so a detailed investigation of the pain is required. OSW in the range of 31 to 40 suggests that the patient has crippling disability, which requires a severe intervention. Patients with an OSW score over 40 are usually bed bound.

For the PDA scale, patients are asked to mark their level of pain on a 10-cm visual analogue scale as shown in Figure 3b. This PDA outcome ranges from 0 to 10 and is classified into five levels. A PDA value between 0 to 2 indicates that the patient essentially has no pain. PDA from 3 to 4 means that the patient is experiencing a little pain. A patient with a PDA score from 5 to 6 means that the patient has considerable pain. A PDA score from 7 to 8 indicates that the patient has a lot of pain. Patients with a PDA of 9 or 10 have the worst possible pain.

BDI is a self-reported measure of symptoms of depression and is determined from a survey 21 of questions. Each question has a score range of 0 to 3, so BDI has a maximum score of 63 as shown in Figure 3c. A BDI score in the range of 0 to 10 signifies normal depression symptoms. A BDI of 11 indicates mild depression, and a BDI from 12 to 14 signifies the patient has moderate depression. A BDI in the range of 15 to 30 signifies severe depression, and over 30 implies very severe depression.

SF-36 PCS and SF-36 MCS scores are both patient-reported health status measures, which range from 0-100. SF-36 PCS and SF-36 MCS scores greater than or equal to 50 indicate that the patient is in good health, as shown in Figure 3d.

In Figure 3, we show the breakpoints of different levels of different pain outcomes. In this research, we consider the *normal level* of pain outcomes for PDA, OSW, and BDI less than 6, less than 12, and less than 13 respectively; a mean score greater than 50 for SF-36 is considered normal. If patients' pain outcomes are in these ranges, then they are assumed to be normal patients with limited pain [7].

2.2. Multi-Objective Health Care Optimization

Several researchers use multi-objective optimization in the literature. Zhang et al. [19] used a multi-objective optimization approach for health-care facility location-allocation problems. They examine where health-care facilities should be located to improve the equity of accessibility, raise the total accessibility for the entire population, reduce the population that falls outside the coverage range, and decrease the cost of building new facilities. A genetic algorithm based multi-objective optimization approach is used to yield a set of Pareto solutions that can be used to find the most practical tradeoffs between the conflicting objectives. Cetin and Sarul [20] used a goal programming formulation as a multi-objective optimization approach to model a blood bank location. They considered three objectives, namely minimizing the total fixed cost of locating blood banks, minimizing total distance between hospitals and blood banks, and minimizing an inequality index as a fairness mechanism for the distances. The objectives are transformed into a single objective via goal programming. Wei et al. [21] developed a bi-objective model that uses interchange algorithms to find optimal locations for preventive health care facilities. The two objectives of their optimization model were efficiency of the facility locations and coverage of patients. Alkhamis [22] developed a framework that uses simulation and optimization. The objective function is to maximize patient throughput and reduce patient waiting time. A deterministic budget constraint and stochastic patient waiting time are used as constraints. Baesler and Sepulveda [23] developed a methodology for a cancer treatment center in Florida, where a simulation model is incorporated into a multi-objective optimization technique. Four objectives are considered in this simulation optimization model. The objectives include minimization of patients waiting time and closing time, and maximization of chairs and nurse utilization.

In this research, we consider the minimization of treatment cost and adverse pain outcomes in our optimization model. The aforementioned five pain outcomes are considered, and they are balanced based upon results from questionnaires. Questionnaires are widely used to identify treatment outcomes in chronic pain. These types of questionnaires may consist of more than 300 questions, which is too long for patients to complete. Huang et al.[24] used machine learning to find out the best subset of questions from the questionnaire. Their classification results shows the subsets have high relationships with treatment outcomes. Thus, they reduce irrelevant questions from the questionnaire for patients with pain. Ali et al. [25] developed an automated delivery system for clinical guidelines (DSCG) to assist physicians in diagnosing and treating patients with chest pain. These guidelines, which are selected from a knowledge based server, are used to improve efficiency in both diagnostic and treatment stages. The delivery system recommends optimal treatment plans based on the most probable diagnosis, which improve patient outcomes. Computer based protocols in emergency departments are used to forecast myocardial infarction. Goldman et al. [26] found that computer based protocols reduce the admission of patients to emergency departments by 11.5%.

2.3. Piecewise Linear Networks and Models

In dynamic systems, state transition models predict how the state of the system evolves, and in this research, we use PLN models to predict how patients and patient outcomes respond to treatments. These PLN models, shown in Figure 4, are developed by Rowat et al. [27]. The decision space is divided into multiple networks, and each network consists of a centroid and a set of linear regression models for the response variables. A weighted distance measure is used to determine the network membership. The weighted L_1 norm distance is used to calculate the distance measure.

Although this is the first research to use PLN models to predict patient outcomes, several researchers have

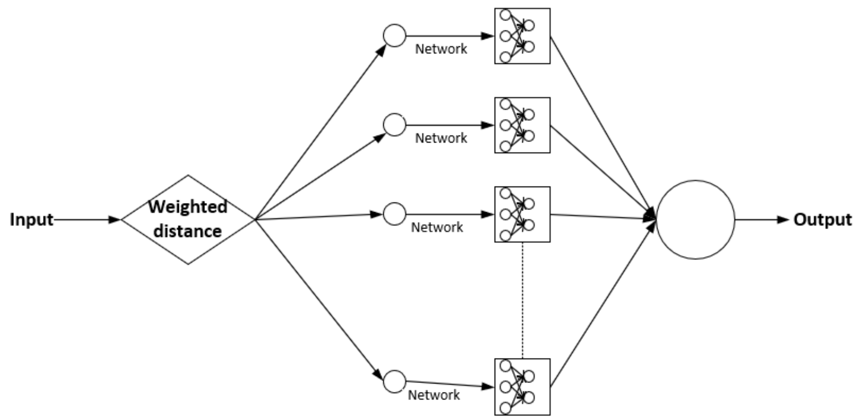


Figure 4: Structure of Piecewise Linear Network [27]

used other general piecewise linear models to do so. Matthews et al. [28] studied the changes in risk factors of coronary heart disease in midlife women using a piecewise linear model, consistent with ovarian aging, and a linear model, consistent with chronological aging. The piecewise linear model provides a better fit. Reynolds and Chiu [29] used a piecewise regression model in their study of understanding thermoregulatory transitions during hemorrhaging in rats.

2.4. Background on Pain Management Optimization Research

Attempts to optimize adaptive treatment strategies for chorinc pain patients have been made in the past. Lin et al. [16] developed a stochastic dynamic programming approach using a statistical design and analysis of computer experiments method developed by Chen et al. [30]. They employed approximate dynamic programming (ADP) solution methods where transition models were constructed empirically, and the future value function was approximated using state space discretization based on a latin hypercube design. By using ADP, they were able to identify a recommended treatment regime, which minimized pain while penalizing excessive costs. They determined treatments using a local optimization solver, even though the problem was a constrained non-convex optimization problem. Consequently, their approach cannot guarantee global optimality.

LeBoulluec et al. [31] developed a method based on the inverse probability of treatment weighted (IPTW) method to mitigate concerns about endogeneity for interdisciplinary pain management data. Endogeneity happens when treatment variables at a previous stage can influence patient variables at the current stage, which will in turn influence the treatments at the following stage [32]. Their proposed IPTW method consists of five steps. Step 1: Build a model to identify significant treatments. Step 2: Check the selected treatments from Step 1 for conditional independence. Step 3: If the treatments are independent of each other, fit a logistic regression model for each treatment. Step 4: Calculate weights based on the fitted models from Step

3. Step 5: Fit the weighted model. This IPTW method eventually removes the bias in estimating the true effect of treatments on the outcomes.

Wang et al. [17] developed a 2SP model for adaptive pain management, where transition models that were used as constraints were non-convex and quadratic. These nonconvex quadratic models were then refitted using a piecewise linear approximation. Prediction accuracy of the refit model (hereafter **S-L2SP model**) was higher than the original model, and at the same time, the S-L2SP model maintained all of the original models assumptions. By using these mathematical models, they found an optimal adaptive treatment strategy for patients. The treatment recommendations generated by the S-L2SP model were better than those from the original non-convex mixed-integer non-linear (MINLP) model in terms of solution quality and time required for optimization. They showed that treatment recommendations generated by the S-L2SP model were 12 times more likely to achieve a normal pain level compared with the treatments in the observed dataset. The objective value achieved by the S-L2SP model in 20 seconds using 4225 scenarios is less than the objective value from the MINLP using 400 scenarios, which required 15 minutes of computational time.

LeBoulluec et al. [31] addressed time varying confounding when treatments are independent in their IPTW method; however, in most cases these treatments exhibit some correlation. Ohol [33] extended the IPTW framework of LeBoulluec et al. [31] to address time varying confounding in a two-stage adaptive interdisciplinary pain management program when treatments exhibit correlation. Most of the literature on handling time varying confounding use methods, such as inverse probability of treatment weighting and g-computation, to obtain consistent estimates for a single treatment. Ohol [33] extended these methods to multiple treatments, and, using a simulation study, highlighted the challenges faced in estimating these treatment effects.

2.5. Contribution

This research proposes a multi-objective 2SP optimization approach to find optimal treatment strategies for adaptive pain management in which the transition models, which are used in constraints, in the multiple pain outcomes model are PLN models. We develop a MILP to integrate these PLN models into the 2SP optimization. To see the relationship between different pain outcomes, we develop a survey, which asks experts to conduct pairwise comparisons between different levels of different pain outcomes. Pain management experts submit the surveys. However, the survey results are not entirely consistent because survey input is subjective and varies from expert to expert. To determine weights to penalize different pain outcomes, we develop a convex quadratic programming (QP) model that attempts to find a consensus within the surveys. We compare the results with observed data, and the S-L2SP model, where Wang et al. [17] used a regression approach to develop transition models on a single pain outcome measure. Finally, we conduct odds ratio analysis to compare the final pain outcomes of the optimization model with observed data and the S-L2SP model.

3. Math Programming Models

In this section, we describe mathematical models to determine adaptive treatment strategies. Section 3.1 shows the two-stage stochastic programming formulation. In section 3.2, we show how a convex quadratic programming formulation is used to determine a set of pain outcome weights that are most consistent with a set of surveys. Section 3.3 discusses a mixed integer linear programming formulation to integrate PLN models into the original 2SP.

3.1. Stochastic Programming Formulation

Similar to this research, the S-L2SP model in Wang et al. [17] described a general two-stage stochastic programming formulation for optimizing treatment in adaptive interdisciplinary pain management program. This S-L2SP model considered only one pain outcome, namely OSW. As described in Section 2.1, pain management physicians and programs usually consider multiple pain outcomes. Consequently, in this section, we modify the S-L2SP model in Wang et al. [17] to consider multiple pain outcomes.

Let I be the set of pain outcomes (indexed by i). As in the S-L2SP model, the objective function consists of two parts—a penalty function on pain outcomes, $P_i(\bullet)$, and a cost function for treatment usage, $C(\bullet)$. The difference between the penalty function $P_i(\bullet)$ in this research and the one in the S-L2SP model is that $P_i(\bullet)$ considers multiple pain outcomes. As in the S-L2SP model, the purpose of the cost function $C(\bullet)$ is to reduce treatment usage to avoid over medication and can be used to reduce the prescription of potentially highly addictive treatments, such as opioids. Similar to the S-L2SP model, the cost function used in this research is from Lin et al. [16]. Parameter ρ is a treatment cost coefficient, which is used to maintain a balance between the pain outcomes and the treatment cost function. Let variables $Y_{i1}(\varepsilon_{i1})$ and $Y_{i2}(\varepsilon_1, \varepsilon_{i2})$ be pain outcome i at stages 1 and 2 with uncertainties ε_{i1} and ε_{i2}, and $Y_1(\varepsilon_1)$ and ε_1 are vectors of with components $Y_{i1}(\varepsilon_{i1})$ and ε_{i1}, $\forall i \in I$. Let s_1 is a constant vector of the patient's state variables at the beginning of stage 1, which could include the patient's entire medical history, s_2 is the vector of state variables at the beginning of stage 2, x_t is the vector of treatment decisions at stage $t = 1, 2$, with component $x_t^{\bar{i}}$ being the dose or usage of treatment $\bar{i}$, Γ_t is the set of feasible treatment decisions, Λ is a set of treatment interaction restrictions, function h_{it} is the state transition model that updates the patient's pain outcome at the end of each stage for all $i \in I$, and random vector ε_t represents the uncertainty in the state transition models.

The general multi-objective 2SP model for this pain management program is shown in model (1).

$$\min \sum_{i\in I} E\Big(P_i(Y_{i2}(\varepsilon_1,\varepsilon_{i2}))\Big) + \rho\Big(C(x_1) + E(C(x_2(\varepsilon_1)))\Big) \tag{1a}$$

subject to:

$$Y_{i1}(\varepsilon_{i1}) = h_{i1}(s_1, x_1, \varepsilon_{i1}) \qquad \forall i \in I; \tag{1b}$$

$$Y_{i2}(\varepsilon_1,\varepsilon_{i2}) = h_{i2}(s_2(\varepsilon_1), x_2(\varepsilon_1), \varepsilon_{i2}) \qquad \forall i \in I; \tag{1c}$$

$$x_1^{\bar{i}} x_1^{\bar{j}} = 0, \quad x_2^{\bar{i}}(\varepsilon_1) x_2^{\bar{j}}(\varepsilon_1) = 0 \qquad \forall (x^{\bar{i}}, x^{\bar{j}}) \in \Lambda \times \Lambda; \tag{1d}$$

$$s_2(\varepsilon_1) = [s_1, x_1, Y_1(\varepsilon_1)]\,; \tag{1e}$$

$$x_1 \in \Gamma_1, x_2(\varepsilon_1) \in \Gamma_2. \tag{1f}$$

Constraint set (1b) shows transition models for all pain outcomes at the end of stage 1, while constraint set (1c) is for transition models at the end of stage 2. Equation (1d) ensures that some treatments that have adverse interaction are not assigned to patients simultaneously. The state variables in stage 2 include the set of stage 1 state variables, stage 1 decision variables, and pain outcomes of stage 1, which is shown in equation (1e). This equation carries information from stage 1 to stage 2. Equation (1f) ensures that the treatment decision variables in both stages 1 and 2 are within a feasible region.

3.2. Convex Quadratic Programming Formulation to Determine Weights

As mentioned previously, we consider five pain outcomes in this research, which are OSW, PDA, BDI, SF-36 PCS, and SF-36 MCS, and we must determine penalty weights that strike a balance among the different pain outcomes. Consequently, we survey pain management experts to determine the relationships among these pain outcomes. The survey is a pairwise comparison of different levels of different pain outcomes, developed by the authors, from which we can derive relative importance measures from these comparisons. Both the survey and the derivation of the relative importance measures are shown in Appendix E. However, survey results may be inconsistent among pain management experts. To determine pain outcome penalty weights that are most consistent with a set of surveys, we use a convex quadratic programming model.

Consider the following sets, parameters, and variables. Let J_i be the set of levels of each pain outcome $i \in I$ (indexed by j). Let u_{ij} be a penalty weight of pain outcome $i \in I$ for level $j \in J_i$. Let K be the set of surveys (indexed by k). Let parameter $\sigma > 1$ be a targeted weight ratio between consecutive levels of the same pain outcome. For each $(i, \hat{i}) \in I \times I, \hat{i} > i, j \in J_i, \hat{j} \in J_{\hat{i}}, k \in K$, let parameter $\omega_{ij\hat{i}\hat{j}k}$ be the relative importance of the j-th level of pain outcome i with the $\hat{j}$-th level of pain outcome $\hat{i}$ from survey k. For each pain outcome $i \in I$ and each level $j \in J_i \setminus \{|J_i|\}$, let variable v_{ij} be the inconsistency of weights between consecutive levels j and $j+1$ of pain outcome i. For each $(i,\hat{i}) \in I \times I, \hat{i} > i, j \in J_i, \hat{j} \in J_{\hat{i}}, k \in K$, let variable $z_{ij\hat{i}\hat{j}k}$ be the inconsistency of the weight between the j-th level weight of pain outcome i and the $\hat{j}$-th level weight of pain outcome $\hat{i}$ derived by survey k.

The convex quadratic program to determine pain outcome penalty weights is given by model (2).

$$\min \sum_{i\in I} \sum_{j\in J_i \setminus \{|J_i|\}} v_{ij}^2 + \sum_{i\in I} \sum_{j\in J_i} \sum_{\substack{\hat{i}\in I \\ :\hat{i}>i}} \sum_{\hat{j}\in J_{\hat{i}}} \sum_{k\in K} z_{ij\hat{i}\hat{j}k}^2 \tag{2a}$$

subject to:

$$u_{i1} \geq 1 \qquad \forall i \in I; \tag{2b}$$

$$u_{i(j+1)} \geq u_{ij} \qquad \forall i \in I, j \in J_i \setminus \{|J_i|\}; \tag{2c}$$

$$u_{i(j+1)} + v_{ij} \geq \sigma u_{ij} \qquad \forall i \in I, j \in J_i \setminus \{|J_i|\}; \tag{2d}$$

$$\omega_{ij\hat{i}\hat{j}k} u_{ij} - u_{\hat{i}\hat{j}} = z_{ij\hat{i}\hat{j}k} \qquad \forall (i,\hat{i}) \in I \times I, \hat{i} > i, j \in J_i, \hat{j} \in J_{\hat{i}}, k \in K; \tag{2e}$$

$$v_{ij} \geq 0 \qquad \forall i \in I, j \in J_i \setminus \{|J_i|\}; \tag{2f}$$

$$z_{ij\hat{i}\hat{j}k} \geq 0 \qquad \forall (i,\hat{i}) \in I \times I, \hat{i} > i, j \in J_i, \hat{j} \in J_{\hat{i}}, k \in K. \tag{2g}$$

The objective (2a) minimizes the inconsistencies of the penalty weights based upon the set of surveys. Constraint set (2b) restricts the lowest level of penalty weights to be greater than or equal to 1. Since the weight for higher levels of pain should be greater than or equal to that of lower levels, constraint set (2c) includes hard constraints that ensure that the weight values between consecutive increasing levels are non-decreasing. Constraint set (2d) includes soft constraints that encourage consecutive pain levels within the same pain outcome to have a ratio of at least σ. When this ratio is unmet, the variable v_{ij} is positive and penalized in the objective function. In the case study, we choose $\sigma = 3$ based upon conversations with domain experts [7]. Constraint set (2e) shows that the j-th level weight of i-th pain outcome is $\omega_{ij\hat{i}\hat{j}k}$ times more important than the $\hat{j}$-th level of the $\hat{i}$-th pain outcome for each survey $k \in K$. This pairwise comparison of different levels of different pain outcomes is treated as a soft constraint. Survey inconsistency penalty $z_{ij\hat{i}\hat{j}k}$ is also included in constraint set (2e) and minimized in the objective funciton. Constraint sets (2f) and (2g) show the lower bounds for decision variables.

Using the penalty weights u_{ij}, $\forall i \in I, j \in J_i$, from model (2), we determine each penalty function, $P_i(\bullet)$, $\forall i \in I$. Because OSW, PDA, and BDI have five levels, while SF-36 PCS and SF-36 MCS have only two levels, their penalty functions have different structure. For OSW, PDA, and BDI pain outcomes, the penalty function passes through the midpoints of the level limits at the u penalty weights, as well as the origin.

Specifically, for pain outcome $i = 1, \ldots, 3$ and level $j \in J_i$, let L_{ij} be the lower limit of pain outcome Y_{2i} at level j as shown in Figures 3a–3c, which are also given in Table 1. In addition, let L_{i6} be the upper limit of outcome i. The penalty function on pain outcome $P_i(\bullet)$ for all $i = 1, ..., 3$ is defined as the step function given in (3).

Table 1: Lower limits for each level of OSW, PDA, and BDI

L_{ij}	OSW($i = 1$)	PDA($i = 2$)	BDI($i = 3$)
L_{i1}	0	0	0
L_{i2}	10	2	10
L_{i3}	20	4	12
L_{i4}	30	6	14
L_{i5}	40	8	30
L_{i6}	50	10	63

$$P_i(Y_{i2}) = \begin{cases} \frac{2u_{i1}}{L_{i2}-2L_{i1}} \left(\lfloor Y_{i2} \rfloor - L_{i1}\right) & L_{i1} \leq Y_{i2} \leq \frac{L_{i2}}{2}; \\ \frac{2(u_{i(j+1)}-u_{ij})}{L_{i(j+2)}-L_{ij}} \left(\lfloor Y_{i2} \rfloor - \frac{L_{ij}+L_{i(j+1)}}{2}\right) + u_{ij} & \frac{L_{ij}+L_{i(j+1)}}{2} < Y_{i2} \leq \frac{L_{i(j+1)}+L_{i(j+2)}}{2}, \forall j = 1, .., 4; \\ \frac{2(u_{i5}-u_{i4})}{L_{i6}-L_{i4}} \left(\lfloor Y_{i2} \rfloor - \frac{L_{i4}+L_{i5}}{2}\right) + u_{i4} & \frac{L_{i5}+L_{i6}}{2} < Y_{i2} \leq L_{i6}. \end{cases} \tag{3}$$

By contrast, the penalty functions for SF-36 PCS and SF-36 MCS are step functions with only single steps at what are considered normal versus abnormal outcomes. Specifically, for pain outcome $i = 4, 5$ the step function is given in (4).

$$P_i(Y_{i2}) = \begin{cases} u_{i1} & 0 \leq Y_{i2} \leq 50; \\ u_{i2} & Y_{i2} > 50. \end{cases} \tag{4}$$

3.3. Mixed Integer Linear Programming for Piecewise Linear Network Models

In this research, we use PLN models to predict transitions. PLN models predict multiple response variables while considering correlations among them. Such multiple response models reduce prediction errors and improve the predictive accuracy as compared to developing individual prediction models of each response variable separately on the same set of predictor variables [34].

State transition models for pain outcomes h_{i1} and h_{i2}, for all $i \in I$, are in constraints (1b) and (1c) in the 2SP model (1). Each network has a centroid and a set of linear regression models for the response variables. To determine the predicted responses for a set of independent variables, a weighted ℓ_1 distance measure determines to which network centroid the set of independent variables is closest. Then the linear regression models within the selected network determine the predicted responses. To incorporate these PLN transition models, in place of h_{i1} and h_{i2}, into our optimization model, we must introduce additional binary and continuous variables and constraints. To simplify the notation in this section, we omit the stage subscript t from 2SP model (1), and we assume that we can represent a state transition model h_i, $\forall i \in I$, with set of general features N (indexed by n), for either a treatment variable x or a state variable s.

Consider the following sets, parameters, and variables. Let Ψ be the set of networks (indexed by ψ). Let parameter $\bar{w}_n^{\psi}$ be the centroid value for network $\psi \in \Psi$ and feature $n \in N$. For each $n \in N$, let decision variable w_n be the value of feature n, and for each $\psi \in \Psi$, let decision variables π_ψ and $\eta_{\psi n}$ be binary variables such that

$$\pi_\psi = \begin{cases} 1 & \text{if } w_n \text{ is in Network } \psi \\ 0 & \text{otherwise;} \end{cases} \qquad \eta_{\psi n} = \begin{cases} 1 & \text{if } w_n \geq \bar{w}_n^{\psi} \\ 0 & \text{otherwise.} \end{cases} \tag{5}$$

For each network $\psi \in \Psi$, each pain outcome $i \in I$, and each feature $n \in N$, let parameter β_{in}^{ψ} be the regression coefficient. Similarly, let β_{i0}^{ψ} be the intercept coefficient for each pain outcome $i \in I$ and each network $\psi \in \Psi$. For each feature $n \in N$, let parameter b_n be the distance measure weight. Let variable Y_i be the outcome of the PLN transition models for each pain outcome $i \in I$, and let parameter M be a big number. For each network $\psi \in \Psi$ and each feature $n \in N$, let variables $w_n^{\psi+}$ and $w_n^{\psi-}$ be the value of decision variable w_n, whether it is greater than or less than the centroid of network ψ, respectively. Let $d_{\psi n}$, defined in equation (6g), be the weighted distance variables for each network $\psi \in \Psi$ and each feature $n \in N$. The MILP transition constraints are formulated by the following:

$$\begin{aligned} -M(1-\pi_\psi) + \beta_{i0}^{\psi} + \sum_{n \in N} \beta_{in}^{\psi} w_n + \varepsilon_i &\leq Y_i \\ \leq \beta_{i0}^{\psi} + \sum_{n \in N} \beta_{in}^{\psi} w_n + \varepsilon_i + M(1-\pi_\psi) & \qquad \forall i \in I, \psi \in \Psi; \end{aligned} \tag{6a}$$

$$\sum_{\psi \in \Psi} \pi_\psi = 1 \tag{6b}$$

$$\sum_{n \in N} d_{\psi n} \leq \sum_{n \in N} d_{\psi' n} + M(1-\pi_\psi) \qquad \forall (\psi, \psi') \in \Psi \times \Psi, \psi' \neq \psi; \tag{6c}$$

$$\bar{w}_n^{\psi} \eta_{\psi n} \leq w_n^{\psi+} \leq M \eta_{\psi n} \qquad \forall \psi \in \Psi, n \in N; \tag{6d}$$

$$-M(1-\eta_{\psi n}) \leq w_n^{\psi-} \leq \bar{w}_n^{\psi}(1-\eta_{\psi n}) \qquad \forall \psi \in \Psi, n \in N; \tag{6e}$$

$$w_n = w_n^{\psi+} - w_n^{\psi-} \qquad \forall \psi \in \Psi, n \in N; \tag{6f}$$

$$d_{\psi n} = b_n(\bar{w}_n^{\psi} - 2\bar{w}_n^{\psi}\eta_{\psi n} + w_n^{\psi +} - w_n^{\psi -}) \qquad \forall \psi \in \Psi, n \in N; \tag{6g}$$

$$\pi_{\psi} \in \{0, 1\} \qquad \forall \psi \in \Psi; \tag{6h}$$

$$\eta_{\psi n} \in \{0, 1\} \qquad \forall \psi \in \Psi, n \in N; \tag{6i}$$

$$\bar{Y}_i = \max\Big(0, Y_i\Big) \qquad \forall i \in I. \tag{6j}$$

If the decision variables w_n, $n \in N$, are in network ψ, then constraint set (6a) ensures the pain outcomes Y_i, $i \in I$, are equal to the regression models within the network ψ; otherwise, the constraints are relaxed (6a). Constraint (6b) guarantees only one network is used. Constraint set (6c) ensures that for each network pair $(\psi, \psi') \in \Psi \times \Psi$ and each feature variable $n \in N$, the sum of the weighted distance variables $d_{\psi n}$, is less than or equal to the sum of the weighted distances of all other networks ψ' where $\psi' \neq \psi$. Consequently, this constraint set determines the selected network. Constraints (6d)–(6f) link the decision variable w_n to variables $w_n^{\psi +}$ and $w_n^{\psi -}$ based upon whether w_n is greater than or less then centroid values $\bar{w}_n^{\psi}$. As in the S-L2SP model, constraint set (6j) makes sure that non-negative pain outcomes are used in the model. Using PLN models for transition model h_i, $\forall i \in I$, we replace constraints (1b) and (1c) with constraints (6a)-(6j) for each stage 1 and 2.

The revised 2SP model, denoted as **M-L2SP**, is shown in (7).

$$\begin{gathered} \min \sum_{i \in I} E\Big(P_i\left(\bar{Y}_{i2}(\varepsilon_{i1}, \varepsilon_{i2})\right)\Big) + \rho\Big(C(x_1) + E(C(x_2(\varepsilon_{i1})))\Big) \\ \text{subject to: } \text{(1d) - (1f), and (6a) - (6j) for each stage 1 and 2.} \end{gathered} \tag{7}$$

4. Case Study

This section details computational results based on the mathematical models discussed in section 3. Section 4.1 describes the data set used in this study, decision variables, and state variables. Analysis of weights from model 2 are discussed in section 4.2. Section 4.3 shows the M-L2SP model parameters used in this research. Treatment analysis comparing the M-L2SP model with that of the S-L2SP model and the observed data in both stages is described in section 4.4. Final pain outcome comparisons among the M-L2SP model, observed data, and the S-L2SP model are given in section 4.5.

4.1. Data

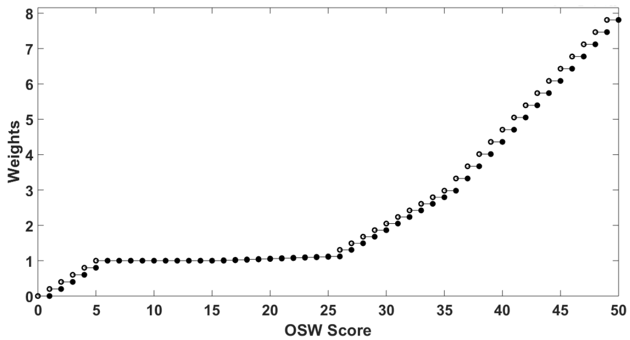
The data set used in this research is from the Eugene McDermott Center for Pain Management at UT Southwestern Medical Center. It has 294 observations, which means 294 patients completed both stage 1 and stage 2. The data are divided into training and testing datasets consisting of 235 and 59 observations, respectively. The data set consists of 62 state variables, 5 mid-pain outcomes, 5 post-pain outcomes, 14 stage 1 decision variables, and 13 stage 2 decision variables. In stage 1, there are 8 pharmaceutical treatment variables and 6 procedural treatment variables, while in stage 2, there are 8 pharmaceutical variables and 5 procedural variables. In Appendix A, we describe these treatment variables in more detail. Procedural variables are binary, while pharmaceutical variables are discrete. We use PDA, OSW, BDI, SF-36 PCS, and SF-36 MCS pain outcomes in this optimization model as described in section 2.1. We use a two-stage feature selection method to find optimal features [27]. We solve the optimization problem to determine treatment policy, and we compare the treatment policy with observed data and policies found in the S-L2SP model. We code all math optimization models in the AMPL modeling language, and we use IBM ILOG CPLEX 12.7.0.0 to solve the M-L2SP model on a NEOS server [35, 36, 37] with the number of threads equal to 1. The program terminates if a relative tolerance on the gap between the best integer objective and the objective of the best node remaining are within 0.01.

4.2. Pain Outcome Penalty Functions

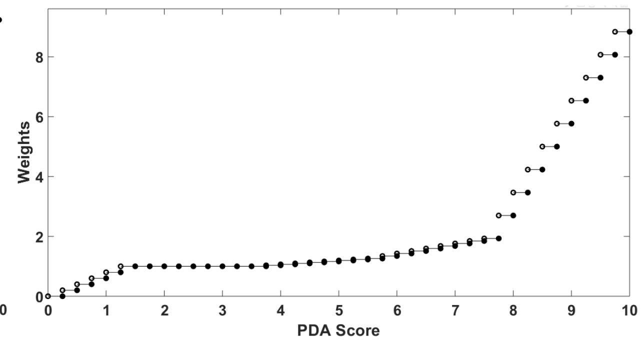
Figure 5 shows piecewise linear penalty functions for all five pain outcomes derived from surveys of two pain management experts and weights from the convex quadratic programming model that is described in section 3.2. From Figures 5a–5c, we observe how higher pain outcomes are penalized more compared to lower scores for OSW, PDA, and BDI. Figures 5d and 5e show that SF-36 scores below 50, which suggests that a patient needs medication, are more penalized than those above 50, which is considered in the normal range of pain. However, the magnitudes of penalties on the SF-36 scores are relatively small compared to those of the other pain outcomes. This is perhaps because the surveyed experts consider OSW, PDA, and BDI more comprehensive measures than the SF-36 scores. In addition, these penalty functions are consistent with our conversations with domain experts [7].

4.3. Study of Parameters of the M-L2SP Model

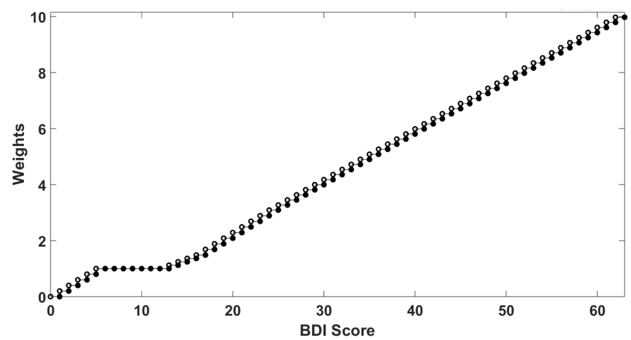
For the M-L2SP model in this research, we conduct a similar study of parameters as the one in the S-L2SP model for a single pain outcome model. The details of this study are given in Appendixes B, C, and D. Specifically, the coefficient parameter ρ in the M-L2SP model objective function (7) balances the cost of treatment with the expected pain outcome penalties described in Figure 5. We use $\rho = 0.05$ in this research as justified in Appendix B. We use the sample average approximation method for two-stage stochastic programming along with discrete sampled scenarios to represent uncertainty [38]. We sampled 900 scenarios, 30 in each stage, to determine solutions using the M-L2SP model. In Appendix C, we calculate the optimality gaps based upon Mak et al. [39] and justify this set of sampled scenarios. Appendix D describes the optimality gap calculations in more detail.



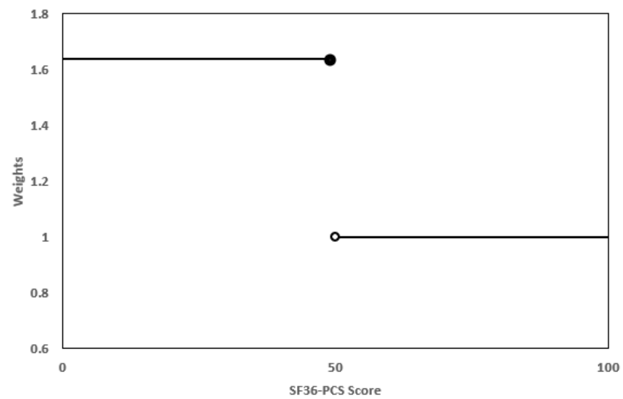
(a) Penalty function for OSW



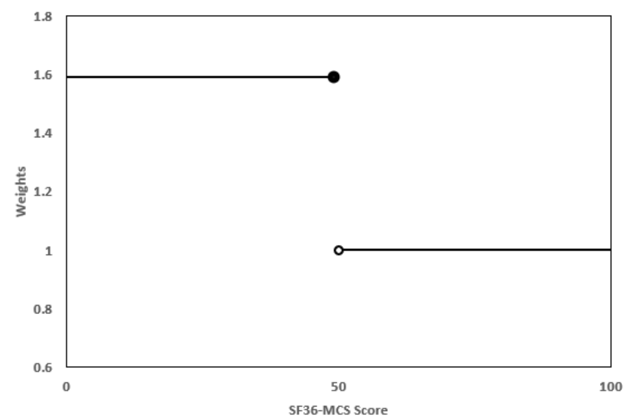
(b) Penalty function for PDA



(c) Penalty function for BDI



(d) Penalty function for SF-36 PCS



(e) Penalty function for SF-36 MCS

Figure 5: Penalty Functions for OSW, PDA, BDI, SF-36 PCS, and SF-36 MCS

4.4. Treatment Analysis

This section compares how often treatments are used in the observed data from the Center with solutions from the M-L2SP and S-L2SP models for the 294 patients.

4.4.1. First Stage Treatment Comparison

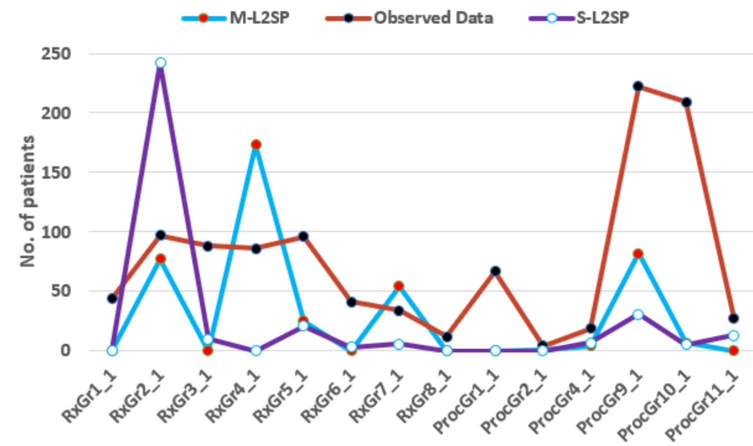


Figure 6: First Stage Treatment Usage Analysis in Observed Dataset, S-L2SP Model, and M-L2SP Model

Figure 6 shows first-stage treatment frequency in the observed data and solutions from the S-L2SP and M-L2SP models. It is clear that there is disagreement in the selected treatments. The most used treatment in stage 1 in the observed dataset is cognitive behavioral therapy (ProcGr9_1), which is recommended to 76% of the patients. This treatment is recommended by the M-L2SP model to 28% of patients. However, the treatment policy from the S-L2SP model recommends this treatment to only 10% of the patients. Physical therapy (ProcGr10_1) is the second most used treatment in the observed data, while it applies to 3% of the patients in the M-L2SP model and only 1.7% of the patients in the S-L2SP model. One thing to notice is that the S-L2SP model from Wang et al. [17] seldom recommends procedural treatments, while the observed data and the M-L2SP model select most of the procedural treatments. The reason is that when a physician recommends treatment to patients, they consider all the aspects of pain. In the M-L2SP model, we also consider five pain outcomes including BDI, which is mostly treated with procedural treatments. As we mentioned earlier, the S-L2SP model considers only OSW, which is why procedural treatments are not recommended in their solutions.

In the M-L2SP model, the most used treatment is muscle relaxants (RxGr4_1), which are given to 30% of patients in the observed data. However, they are never recommended in the S-L2SP model. NSAIDs (RxGr2_1) are the only treatment that are recommended to more than 25% of the patients in solutions of the M-L2SP model (27%). They are given to 33% of patients in the observed data and recommended to 83% of patients in solutions of the S-L2SP model. NSAIDs are particularly useful to reduce functional disability, and the S-L2SP model only considers the OSW pain outcome. Consequently, NSAID's are often recommended in solutions of the S-L2SP model. By constrast, the Center and the M-L2SP model consider other pain outcomes and are more likely to use other treatments instead of just NSAIDs.

4.4.2. Second Stage Treatment Comparison

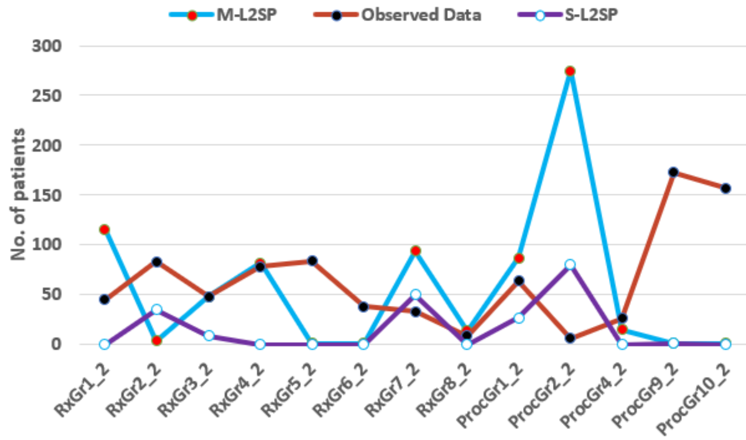


Figure 7: Second Stage Treatment Usage Analysis in Observed Dataset, S-L2SP Model, and M-L2SP Model

The frequencies of treatment usage in the second stage of the observed data and recommendations from the S-L2SP and the M-L2SP models are shown in Figure 7. In the observed dataset, we see that all 13 treatments are recommended to patients. Block procedure (`ProcGr2_2`) is the least frequently used treatment (2%) in the observed dataset, but it is the most frequently used treatment (94%) in the M-L2SP model recommendations. In the S-L2SP model, Block Procedures are the most recommended treatment (27%) as well. Cognitive behavior therapy (`ProcGr9_2`) treatment is most frequently used in the observed dataset, but it is recommended to only one patient by both the M-L2SP and S-L2SP models. Physical therapy (`ProcGr10_2`) is the second most frequently prescribed treatment in the observed dataset, but it is recommended as a treatment to only one patient by the M-L2SP model. However, it is never recommended by the S-L2SP model. Sleeping pills (`RxGr7_2`) are the only treatment that is used with more than 10% of the patients in the observed data and in the M-L2SP and S-L2SP model solutions.

One interesting finding is that both Tramadol (`RxGr1_1`) and Narcotics (`RxGr3_1`) are used in second stage if the M-L2SP solutions, but they are not used in first stage at all. This is because the penalties on these two treatments in the M-L2SP model in this study are not larger than the typical treatment cost. However, these two treatments are highly addictive substances. Since the M-L2SP model has the flexibility of adding new constraints to make sure that these two dangerous substances are not recommended to any patients in any stages, we will examine the affect of these new constraints in treatment policy generation in future research.

4.5. Final Pain Outcome Comparison

We conduct odds ratio analysis to compare the final pain outcomes of the M-L2SP and S-L2SP models with the observed data. Let Q_i be the sets of patients from the observed data that require treatment after pre-evaluation for each pain outcome $i \in I$. Let R_i be the set of patients that achieve normal pain levels after post-evaluation for each pain outcome $i \in I$ in the observed dataset, where $R_i \subseteq Q_i$. The odds of the observed data, $O1_i$, for each pain outcome $i \in I$ is calculated using $O1_i = \left(\frac{|R_i|}{|Q_i|-|R_i|}\right)$. We calculate the odds for each optimization models with the following steps: (1) Let p_{iq} be the probability that a patient's final pain outcome is normal for each pain outcome $i \in I$ and for each patient $q \in Q_i$. (2) The number of patients with a normal level for outcome $i \in I$ from the optimization model is $N\_opt\_normal_i = \sum_{q \in Q_i} p_{iq}$ for each $i \in I$. (3) The odds from the optimization models, $O2_i$, can be estimated using $O2_i = \left(\frac{N\_opt\_normal_i}{|Q_i|-N\_opt\_normal_i}\right)$. Since we want to determine how the optimization models perform over the observed data, for each pain outcome $i \in I$, we use $OR_i = \left(\frac{O2_i}{O1_i}\right)$ to calculate *odds ratios*.

Table 2: Pain Outcome Comparison

			No. of Patients Required trt.	No. of Patients in normal Pain level after trt.	Odds Ratio
PDA	Optimization	M-L2SP	210	156.7	0.61
		S-L2SP	210	154.7	0.57
	Observed data		210	174.0	-
OSW	Optimization	M-L2SP	256	126.8	3.59
		S-L2SP	256	117.5	3.10
	Observed data		256	55.0	-
BDI	Optimization	M-L2SP	145	123.8	4.49
		S-L2SP	145	119.5	3.60
	Observed data		145	82.0	-
SF-36 PCS	Optimization	M-L2SP	264	122.2	2.87
		S-L2SP	264	110.9	2.41
	Observed data		264	61.0	-
SF-36 MCS	Optimization	M-L2SP	134	100.9	1.87
		S-L2SP	134	98.8	1.72
	Observed data		134	80.0	-

We use a Monte Carlo sample size $m = 30$ for each stage with 900 scenarios in model (7) as a first-stage treatment policy generator. Given a first-stage treatment policy, we evaluate the optimal pain outcome using model (8) in Appendix C with sample size $m' = 60$. Table 2 shows the number of patients that require treatment in the beginning of the two-stage pain management program, and the number of patients that achieve a normal pain level at the end of the program for all five pain outcomes. From the observed data, we see that 84, 38, 149, 30, and 160 patients have normal pain levels at the beginning of pain management program for PDA, OSW, BDI, SF-36 PCS, and SF-36 MCS pain outcomes, respectively. We then find the final pain outcomes for the rest of the patients in the observed dataset and optimization results.

Table 2 shows that the M-L2SP model policy gives better outcomes compared to the observed data set in the case of OSW, BDI, SF-36 PCS and SF-36 MCS, while the PDA pain outcome in the observed data is better compared to those results of the M-L2SP model. We also evaluate the S-L2SP model's first-stage treatment policies in our evaluation model (8) to see which treatment policy is better in terms of the number of patients with normal pain outcomes after the pain management program. From Table 2, the M-L2SP model has higher odds ratios for all five pain outcomes than the S-L2SP model. However, the observed data outperforms both the M-L2SP and S-L2SP models in PDA.

Observe that, the M-L2SP model performs better in each pain outcomes metrics, and it outperforms the S-L2SP model in BDI. This is perhaps due to the fact that BDI is fundamentally different from the other measures because it is purely cognitive. BDI is psychological value evaluation, while the other metrics are highly correlated to pain. One of the likely reasons of the M-L2SP model is doing so much better than the S-L2SP model in BDI than the other pain outcomes is because the M-L2SP model is considering patient's psychological state.

5. Conclusions and Future Work

Pain is a major health problem for many people, and pain management is currently innovating because of the opioid crisis in the United State. In this research, we develop a multi-objective 2SP model, where the objective is to minimize adverse pain outcomes and treatment cost as well. We consider five pain outcomes in our optimization model and develop a survey to find penalty weights from the pain management experts. To ensure that weights are consistent, we develop a convex quadratic programming model. State transition models are PLN models, which are used as constraints in the optimization model. To integrate these PLN models into the 2SP model, we develop an MILP, denoted as the M-L2SP model. Finally, we solve the M-L2SP model with AMPL/CPLEX and compare pain outcomes from these solutions with those of the S-L2SP model from Wang et al. [17], which used non-convex quadratic transition models, and with the observed dataset.

In future research, we will generate a survey of treatment preferences for the physicians. Since some physicians prefer some treatments, we want to include those treatment preferences in the optimization model. Moreover, we will study using additional penalties to avoid treatments that can cause addiction, such as Tramadol and other narcotics. We will also develop additional constraints based upon 3-way and 4-way treatment interactions to improve computational efficiency.

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Appendices

A. Description of Treatment Variables

Table 3 shows the description of the treatment variables in stages 1 and 2.

Table 3: Description of the Treatment Variables

Treatment Type	Stage 1		Stage 2	
	Variable Name	Description	Variable Name	Description
Procedural	ProcGr1_1	Injection in Stage 1	ProcGr1_2	Injection in Stage 2
	ProcGr2_1	Block Procedure in Stage 1	ProcGr2_2	Block Procedure in Stage 2
	ProcGr4_1	Stimulation Procedure in Stage 1	ProcGr4_2	Stimulation Procedure in Stage 2
	ProcGr9_1	Cognitive Behavioral Therapy in Stage 1	ProcGr9_2	Cognitive Behavioral Therapy in Stage 2
	ProcGr10_1	Physical Therapy in Stage 1	ProcGr10_2	Physical Therapy in Stage 2
	ProcGr11_1	Number of Additional Procedures in Stage 1		
Pharmaceutical	RxGr1_1	Tramadol in Stage 1	RxGr1_2	Tramadol in Stage 2
	RxGr2_1	NSAIDs in Stage 1	RxGr2_2	NSAIDs in Stage 2
	RxGr3_1	Narcotic in Stage 1	RxGr3_2	Narcotic in Stage 2
	RxGr4_1	Muscle Relaxant in Stage 1	RxGr4_2	Muscle Relaxant in Stage 2
	RxGr5_1	Antidepressant in Stage 1	RxGr5_2	Antidepressant in Stage 2
	RxGr6_1	Tranquilizer in Stage 1	RxGr6_2	Tranquilizer in Stage 2
	RxGr7_1	Sleeping Pills in Stage 1	RxGr7_2	Sleeping Pills in Stage 2
	RxGr8_1	Others in Stage 1	RxGr8_2	Others in Stage 2

B. Treatment Cost Coefficient

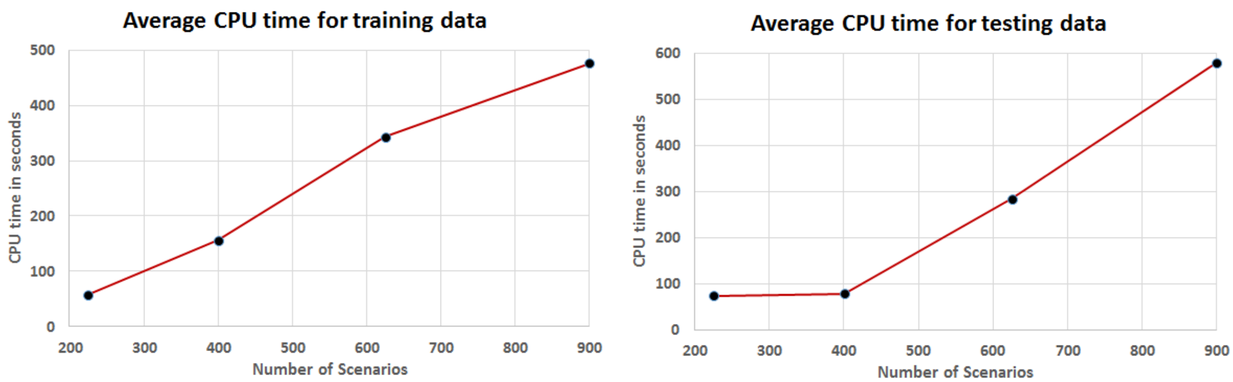
Solving M-L2SP model with $\rho = 0.01$, 0.05, 0.10, and 0.50 yields the average treatment costs and the average pain outcomes given in Table 4.

Table 4: Determination of Treatment Coefficient

	Treatment coefficient, ρ			
	0.01	0.05	0.1	0.5
Treatment Cost	88.67	49.60	33.56	2.52
Avg. PDA	4.86	4.90	5.02	5.90
Avg. OSW	11.27	12.13	12.91	17.08
Avg. BDI	4.42	4.79	5.25	7.99
Avg. SF-36 PCS	41.13	40.24	39.63	34.47
Avg. SF-36 MCS	51.97	50.52	48.79	47.94

Treatment cost decreases with an increasing value of ρ, while average pain outcome scores increase for PDA, OSW, and BDI and decrease for SF-36 PCS and SF-36 MCS (higher scores of SF-36 are better). Based upon these results and conversations with domain experts [7], we choose $\rho = 0.05$.

C. The Case for Using 900 Scenarios



(a) CPU time for Training Dataset (b) CPU time for Testing Dataset

Figure 8: Average CPU time in different scenarios in Training and Testing Datasets

We solve M-L2SP with sample sizes of 15, 20, 25, and 30 for each stage. Average CPU times for different sample sizes for optimizing treatments for both the Training and Testing datasets are shown in Figure 8. The CPU time increases along with increasing number of scenarios (sample size squared). For a small number of scenarios, the CPU time is low. However, these small set of scenarios may not be able to represent the uncertainty in the two-stage stochastic programming model. We choose to use 900 scenarios (sample size $m = 30$), because it takes an average of 10 minutes per patient to get the treatment policy, which is a reasonable waiting time [7].

(a) Objective values for Training Dataset (b) Objective values for Testing Dataset

Figure 9: Average Objectives in different scenarios in Training and Testing Datasets

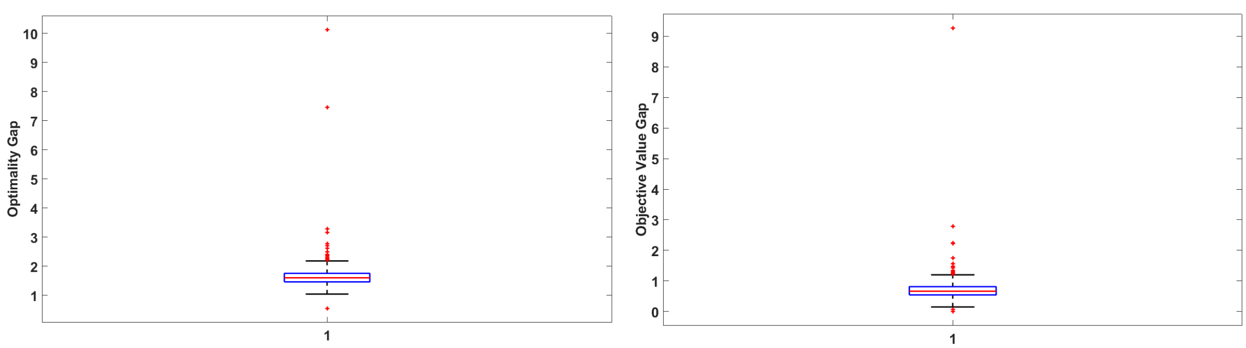
Average objective values for both the Training and Testing dataset in case of policy generation is shown in Figure 9 in the purple color line. We evaluate the quality of the first-stage treatment solution using 2500 and 3600 scenarios. Specifically, let $x^*_{1(30)}$ be the optimal first-stage treatment with sample size 30.

$$\min \sum_{i \in I} E\Big(P_i(\bar{Y}_{i2}(\varepsilon_{i1}, \varepsilon_{i2}))\Big) + \rho\Big(C(x_1) + E(C(x_2(\varepsilon_{i1})))\Big) \tag{8a}$$

$$\text{subject to: } (6a) - (6i), (1d) - (1f), \qquad \text{with sample size of } m'$$

$$x_1 = x^*_{1(30)} \tag{8b}$$

The evaluated objective values are shown in red and green for $m' = 50$ and $m' = 60$, respectively, in Figure 9. We choose 3600 scenarios (sample size $m' = 60$) for evaluation because that gives almost same objective values for 900 scenarios policy generation. Moreover, we calculate optimality gap for all 294 patients using the method given in Mak et al. [39] with $m = 30$ and $m' = 60$. Figure 10a shows a box plot of the upper limits on 99% confidence intervals on the optimality gaps for all of the patients, and Appendix D describes these calculations in more detail from Mak et al. [39]. Note that the average optimally gap for all 294 patients is 1.70, which is practically insignificant from a physician's perspective [7]. Figure 10b shows a box plot for the differences between the evaluated objective value and the first-stage treatment policy objective value for all 294 patients, which averages 0.73.



(a) Box Plot of the Upper Limits on 99% Confidence Intervals of the Optimilaity Gaps

(b) Box Plot of the Average Evaluated Objective Value and First-Stage Treatment Policy Objectives

Figure 10: Box Plots of Optimality Gaps and Objective Value Differences

D. Optimality Gap Calculation from Mak et al. [39]

To calculate an optimality gap using $m = 30$, we run M-L2SP model (7) for 30 different $m = 30$ samples. Let $\bar{z}^{*i}_m$ be the optimal objective value $\forall i = 1, ..., m_l$, where $m_l = 30$. Consider the average of the objective values $\bar{L}(m_l)$, given by

$$\bar{L}(m_l) = \frac{1}{m_l}\sum_{i=1}^{m_l} \bar{z}_m^{*i}.$$

From [39], $\bar{L}(m_l)$ is an expected lower bound on the optimal objective function of model (7). To get an upper bound, we run model (8) with $m' = 60$ samples, and the objective value from this model is denoted by $\bar{U}(m_u)$, where $m_u = 3600$. Let $\bar{s}_l(m_l)$ and $\bar{s}_u(m_u)$ be the sample standard deviation of $\bar{z}_m^{*i}$ and of objective values of all scenarios of model (8), respectively. Let $\tilde{\epsilon}_u = \frac{\bar{t}_{m_u-1,\alpha}\bar{s}_u(m_u)}{\sqrt{m_u}}$ and $\tilde{\epsilon}_l = \frac{\bar{t}_{m_l-1,\alpha}\bar{s}_l(m_l)}{\sqrt{m_l}}$. Finally, we calculate a 99% confidence interval for the optimality gap for each patient using $[0, [\bar{U}(m_u) - \bar{L}(m_l)]^+ + \tilde{\epsilon}_l + \tilde{\epsilon}_u]$, as described in Mak et al. [39].

E. Survey

As discussed in section 3.2, $\omega_{ij\hat{i}\hat{j}k}$ is the relative importance of the j-th level of pain outcome i with the $\hat{j}$-th level of pain outcome $\hat{i}$ from survey k. We get the value of $\omega_{ij\hat{i}\hat{j}k}$ from the surveys that are filled out by pain management experts. An example of a survey is shown in Table 5. This survey shows the pairwise comparison between different levels of two pain outcomes, namely OSW and PDA. Both OSW and PDA consist of five levels which are described in section 2.1.

Parameter $\omega_{ij\hat{i}\hat{j}k}$ has the value of 1, 3, 5, 7, and 9. If j-th level of OSW and $\hat{j}$-th level of PDA are equally important, then $\omega_{ij\hat{i}\hat{j}k}$ equals to 1 for this particular survey k. In this case, a pain management expert will check column 3 of Table 5. However, if the j-th level of OSW is more important than the $\hat{j}$-th level of PDA, then the expert will check column (a). In the next step, the expert will check one of the columns from 4 to 7 to specify how important column (a) compare to column (b). If it is slightly important, then $\omega_{ij\hat{i}\hat{j}k}$ equals to 3. For moderately, strongly, and extremely important, $\omega_{ij\hat{i}\hat{j}k}$ equals to 5, 7, and 9, respectively.

Table 5: Questionnaire for OSW vs. PDA

Objective Pairs	Pain outcome level (a)	Pain outcome level (b)	If pain outcome level (a) and (b) are equally important, then check this column.	If one is important than other one between (a) and (b), then check the important one in pain outcome level column. After that check one of the columns from below to show how important that checked pain outcome level compare to other one. slightly more important	moderately more important	strongly more important	extremely more important
OSW(0-10) vs. PDA	☐ OSW(0-10)	☐ PDA(0-2)	☐	☐	☐	☐	☐
	☐ OSW(0-10)	☐ PDA(3-4)	☐	☐	☐	☐	☐
	☐ OSW(0-10)	☐ PDA(5-6)	☐	☐	☐	☐	☐
	☐ OSW(0-10)	☐ PDA(7-8)	☐	☐	☐	☐	☐
	☐ OSW(0-10)	☐ PDA(9-10)	☐	☐	☐	☐	☐
OSW(11-20) vs. PDA	☐ OSW(11-20)	☐ PDA(0-2)	☐	☐	☐	☐	☐
	☐ OSW(11-20)	☐ PDA(3-4)	☐	☐	☐	☐	☐
	☐ OSW(11-20)	☐ PDA(5-6)	☐	☐	☐	☐	☐
	☐ OSW(11-20)	☐ PDA(7-8)	☐	☐	☐	☐	☐
	☐ OSW(11-20)	☐ PDA(9-10)	☐	☐	☐	☐	☐
OSW(21-30) vs. PDA	☐ OSW(21-30)	☐ PDA(0-2)	☐	☐	☐	☐	☐
	☐ OSW(21-30)	☐ PDA(3-4)	☐	☐	☐	☐	☐
	☐ OSW(21-30)	☐ PDA(5-6)	☐	☐	☐	☐	☐
	☐ OSW(21-30)	☐ PDA(7-8)	☐	☐	☐	☐	☐
	☐ OSW(21-30)	☐ PDA(9-10)	☐	☐	☐	☐	☐
OSW(31-40) vs. PDA	☐ OSW(31-40)	☐ PDA(0-2)	☐	☐	☐	☐	☐
	☐ OSW(31-40)	☐ PDA(3-4)	☐	☐	☐	☐	☐
	☐ OSW(31-40)	☐ PDA(5-6)	☐	☐	☐	☐	☐
	☐ OSW(31-40)	☐ PDA(7-8)	☐	☐	☐	☐	☐
	☐ OSW(31-40)	☐ PDA(9-10)	☐	☐	☐	☐	☐
OSW(41-50) vs. PDA	☐ OSW(41-50)	☐ PDA(0-2)	☐	☐	☐	☐	☐
	☐ OSW(41-50)	☐ PDA(3-4)	☐	☐	☐	☐	☐
	☐ OSW(41-50)	☐ PDA(5-6)	☐	☐	☐	☐	☐
	☐ OSW(41-50)	☐ PDA(7-8)	☐	☐	☐	☐	☐
	☐ OSW(41-50)	☐ PDA(9-10)	☐	☐	☐	☐	☐