INCREASING AND ASSESSING THE IMPACT OF PATIENT CHOICE IN LIVER TRANSPLANTATION

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In 2009, almost 1,500 Americans died of end-stage liver disease (ESLD), which is the twelfth leading cause of death in the U.S. As liver transplantation is the only possible therapy for ESLD and there is a considerable difference between the number of donated organs and patients, it is important to manage donor-patient match and investigate alternative treatments to transplantation.

Every patient lists in at least one waiting list (OPO) in order to be eligible for a donated organ. However, patients may list in additional OPOs. This practice is called multiple listing. Currently, multiple listing is one of the most debated topics in organ allocation.

Although transplantation is a successful procedure, it may not be available on time due to the massive shortage of donated organs. Therefore, an alternative therapy to transplantation is needed. Liver Assist Devices (LADs) are an emerging therapy for ESLD that aim to stabilize a patient until transplantation or her own organ recovers.

In this dissertation, we discuss three models that are related to ESLD. In the first model, we optimize the three-stage decision process faced by a single patient. The patient decides her geographic location, in which OPOs to multiple list, and which organ offers to accept. This problem is formulated as a continuous-time Markov Decision Process (MDP). We derive structural properties of this model and solve it using clinical data.

The second model analyzes multiple listing from the societal perspective. Utilizing an existing simulation of the U.S. liver allocation system, we give every patient the flexibility to multiple list. Therefore, we evaluate the effects of multiple listing on every wait-listed

patient, rather than on a single patient. We also study the same problem where multiple listing is a more widespread practice in the U.S.

The third model considers a hypothetical system in which an internal LAD is available. So, in addition to the liver accept/reject decision, patients can decide to accept an LAD. This model aims to help manufacturers by estimating potential demand for an LAD. We model this problem as a discrete-time MDP and give sufficient conditions under which an LAD will be worthwhile.

Keywords: End-stage liver disease, liver transplantation, multiple listing, liver assist device, Markov decision processes.

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To my wonderful family,

especially to my grandfather Mehmet Yazıcı.

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1.0 INTRODUCTION

The United States (U.S.) spends more on health per capita than any other country [121], and health expenditures have been increasing as a percentage of gross domestic product (GDP) (see Figure 1.1). Based on U.S. Bureau of Labor Statistics (BLS), health care is one of the largest industries in the U.S.[21]

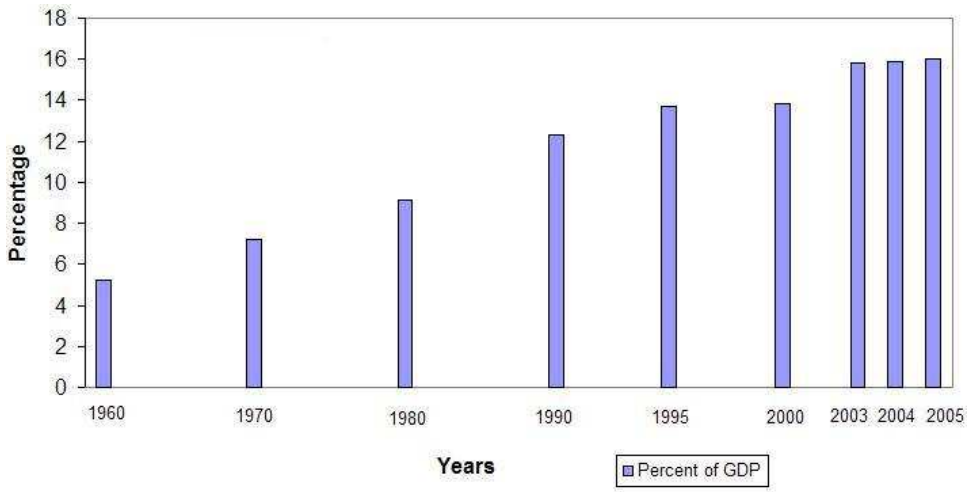

Figure 1.1: National health expenditures as a percentage of GDP [120]

Considering the health care industry's increasing share of GDP, even a small increase in the efficiency of the health care system, including an increase in the life expectancy of patients, may result in a substantial improvement in the U.S. economy, thus making informed medical decision making crucial. Optimization techniques have been applied to different health care issues over the last few decades. According to the National Center for Health Statistics [122], health measures provide essential information for assessing how the nation's resources should be directed toward improving its population's health. Some health care optimization models consider allocating or scheduling healthcare resources, and some

examples of these models include personnel scheduling [79, 111, 189], ambulance location [22, 24], operating room scheduling [16, 41] and emergency room scheduling [34, 95]. Therapeutic optimization is another available stream of health care research. Operations research (OR) studies in cancer treatment [14, 31, 53, 92, 98, 139, 200], HIV treatment [161], diabetes treatment [89], sepsis treatment [88] and optimal organ allocation [3, 7, 8, 9, 38, 39, 65, 86, 143, 153, 173, 202, 203] are among the studies in this area.

This dissertation focuses on patient decisions in organ allocation. According to the U.S. Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients (SRTR), there were 183,222 persons living with a functioning transplanted organ in the U.S. as of the end of 2007 [198]. This number reflects an increase of 1.7% over the prior year and a 56.6% increase since 1999. Unfortunately, there were also approximately 100,597 people registered on organ waiting lists at the end of 2008, a 3.8% increase over the number of people waiting for an organ at the end of 2007 [198]. The percentage of patients who remain on the waiting list for multiple years is increasing, in large part because of lack of availability of organs. Given the scarcity and perishability of donated organs, and the increasing number of patients waiting for an organ transplant, policy making about organ allocation is very controversial.

This dissertation will specifically focus on end-stage liver disease (ESLD), such as primary biliary cirrhosis and hepatitis B, the twelfth-leading cause of death in the U.S. (see Table A1 in Appendix A). For patients with ESLD, liver transplantation is the only therapy that is currently being used, unlike other diseases such as end-stage renal disease (ESRD), for which dialysis is an alternative therapy. However, new liver assist devices may hold some promise as alternative therapies. ESLD patients can obtain livers for transplantation through two sources: living donors and cadaveric donors. Most patients, including many of those with living donors, join one or more waiting lists in order to be eligible for cadaveric liver offers. Currently, there are nearly 16,000 patients waiting for a liver in the U.S.

A comparison of Table 1.1 with Figure 1.2 reveals that, although the number of organ donors and transplants increased between 2001 and 2009, the decrease in the number of deaths could not keep pace with the number of waiting list registrations. Therefore, either an allocation mechanism matching the donated organ and the ESLD patient or an alternative

Table 1.1: U.S. liver data between 2001 and 2007 [180]

	2001	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**
Donors	5,630	5,657	6,004	6,642	7,016	7,305	7,202	7,001	6,957
Cadaveric	5,106	5,294	5,682	6,319	6,693	7,017	6,936	6,752	6,738
Living	524	363	322	323	323	288	266	249	219
Transplants	5,196	5,332	5,673	6,171	6,444	6,651	6,494	6,319	6,320
Cadaveric	4,672	4,969	5,351	5,848	6,121	6,363	6,228	6,070	6,101
Living	524	363	322	323	323	288	266	249	219

therapy to transplantation is needed so that the organ wastage and the number of deaths are reduced. The United Network for Organ Sharing (UNOS), a non-profit organization, is responsible for managing the national organ donation and allocation system. UNOS facilitates the organ-patient match, and develops organ transplantation policy.

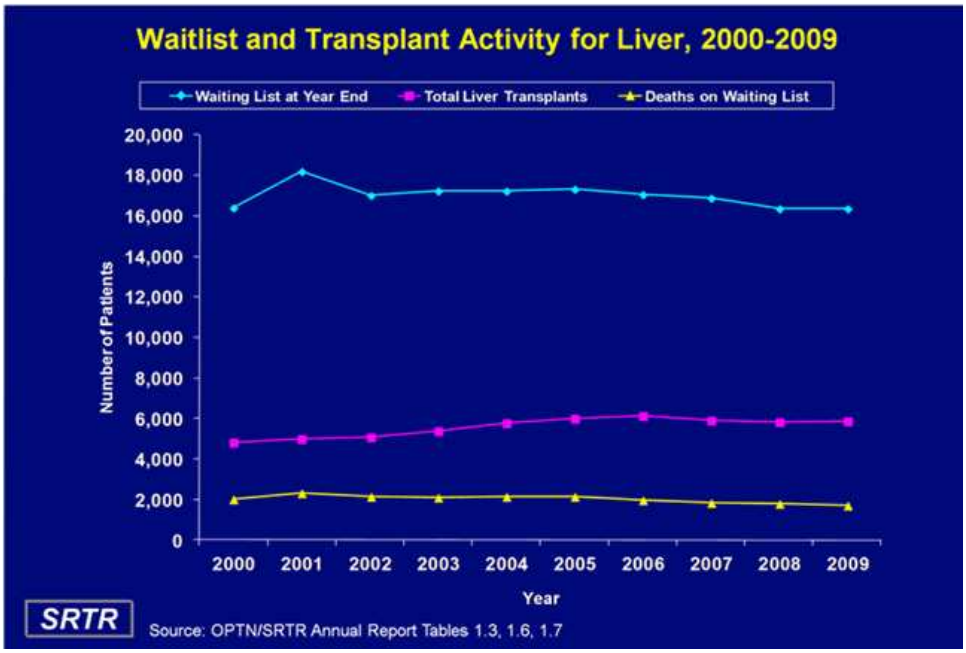

Figure 1.2: Number of ESLD patients waiting for, registered to receive, and died while waiting for a transplant between 2001 and 2007 [180]

1.1 CURRENT LIVER ALLOCATION SYSTEM

UNOS divides the U.S. into approximately 60 local organizations, called Organ Procurement Organizations (OPOs), through which it administers the organ allocation process. OPOs are responsible for identifying donors, retrieving organs for transplantation, encouraging organ donation in their designated geographical areas, and maintaining local waiting lists. The geographical area of an OPO varies in size, ranging from a certain part of a state to a collection of states. Each ESLD patient must join at least one OPO waiting list in order to be eligible for cadaveric liver offers.

UNOS divides the U.S. into 11 regions which are comprised of OPOs. These regions are designed to facilitate organ allocation so as to decrease geographical disparities. Once an OPO procures an organ, UNOS tries to find a potential recipient based on geographical location (patient and organ OPO, as well as patient and OPO region), medical urgency of the patient, blood type and waiting time. Physical proximity of the patient to the organ is considered in addition to the medical urgency, since livers are perishable. Cold ischemia time (CIT) is the time interval that begins when an organ is cooled with a cold perfusion solution after organ procurement surgery and ends when the organ is implanted [165]. The maximum CIT for a liver is 18-24 hours. Although 18-24 hours appears to be enough time to be able to transport a liver anywhere within the U.S., a liver's viability declines as it spends more time outside of a human body [168]. Moreover, each refusal tends to increase the CIT.

UNOS classifies patients as either "Status 1" or assigns them a "Model for End-Stage Liver Disease" (MELD) score for the purpose of allocating livers. Without a liver transplant, Status 1 candidates have a life expectancy of less than seven days [73]. Status 1 candidates constitute less than 1% of all liver transplant candidates [182]. MELD is a score for chronic liver disease [77, 97, 197] that estimates the probability of candidate death and is derived from a mortality risk score corresponding to the degree of medical urgency [133]. If a patient is not classified as a Status 1, then she is assigned a MELD score, which is a function of total bilirubin, creatinine and prothrombin time (INR). Bilirubin measures how effectively the liver excretes bile, INR measures the liver's ability to make blood clotting factors, and

creatinine measures kidney function [182]. The following formula, adapted from Wiesner et al. [197], is used by UNOS to calculate the MELD score of a patient:

$$\begin{aligned}\text{MELD} \quad = \quad & 10 * \ \text{round}\Big(0.957 * ln(\text{creatinine mg/dL}) + 0.378 * ln(\text{bilirubin mg/dL}) + \\ & 1.120 * ln(\text{INR}) + 0.643 + (\text{constant based on liver disease etiology})\Big).\end{aligned}$$

Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation. The maximum serum creatinine considered within the MELD score equation is 4.0 mg/dl [181]. For patients who have had dialysis twice within the last week, the creatinine value is automatically set to 4.0 mg/dl [181]. The MELD score of a patient ranges between 6 and 40, with higher scores corresponding to sicker health states. MELD scores greater than 40 are rounded down to 40. The liver policy based on MELD was approved by the UNOS/OPTN Board of Directors in November 2001 and went into effect in February 2002 [182], although multiple modifications have been made since then.

UNOS has different liver allocation algorithms for adult and pediatric patients. This dissertation considers the adult patients only, and therefore presents the three-tiered adult liver allocation algorithm as follows [133]:

1. ***Local:*** Status 1 candidates,
2. ***Regional:*** Status 1 candidates,
3. ***Local:*** Candidates with MELD Scores ≥ 15 in descending order of MELD Scores,
4. ***Regional:*** Candidates with MELD Scores ≥ 15 in descending order of MELD Scores,
5. ***Local:*** Candidates with MELD Scores < 15 in descending order of MELD Scores,
6. ***Regional:*** Candidates with MELD Scores < 15 in descending order of MELD Scores,
7. ***National:*** Status 1 candidates,
8. ***National:*** All other candidates in descending order of MELD Scores.

Patients are stratified within each MELD score by blood type similarity. If two patients cannot be distinguished by geography, medical urgency, or blood type, then waiting time at the current health or sicker is used to break ties.

Once an organ offer is made, the potential recipient is given one hour to accept or reject it without penalty. If a patient rejects an organ, it is then offered to other patients as long

as the liver is viable. Organs are frequently declined due to low quality. Howard [66] reports that 45% of livers are rejected by the first patients to whom they are offered.

UNOS allows ESLD patients to change the waiting list in which they are registered by relocating. UNOS also allows ESLD patients to be registered in more than one waiting list. In this case, if a patient receives a transplant or dies while waiting for a transplant, she will be removed from all the waiting lists she joined. As mentioned before, there are very few Status 1 candidates compared to MELD patients. Therefore, this study is restricted to MELD patients.

1.2 AN EMERGING ALTERNATIVE THERAPY

Although liver transplantation improves patient survival, the number of patients dying while waiting for a liver transplant increases due to the shortage of livers. In addition, many patients with hepatic failure do not qualify for transplantation because of metastatic cancer, concomitant infection, active alcoholism, drug abuse, or concurrent medical problems [78]. The regenerative capacity of the liver is substantial and some ESLD patients, especially those with toxic insult and viral hepatitis, have the potential for spontaneous recovery [78]. Therefore, as an alternative to liver transplantation, researchers have been working toward the goal of developing a fully functional artificial liver [117].

The development of an artificial liver is challenging, since the liver has multiple functions essential to maintaining life, such as carbohydrate metabolism, synthesis of proteins, amino acid metabolism, urea synthesis, lipid metabolism, drug biotransformation, and waste removal. The development of an artificial heart, lung, or kidney is perhaps less demanding, since each has only one primary mechanical function [78].

In the last two decades, a new generation of extracorporeal liver assist devices (LADs) has been developed. Some of these devices are tested on animals, and some of them are tested in clinical trials, providing encouraging results for the future [150]. Generally, internal organ support devices are preferable to external devices [195]. An internal LAD has not been de-

veloped yet [135]. We propose a model that can be used to estimate the clinical impact of a hypothetical LAD.

1.3 PROBLEM STATEMENT

As noted above, patients have the right to relocate to change the waiting list in which they are registered or to join the waiting lists of several OPOs, a practice referred to as "multiple listing". In Chapter 3, a single patient's relocation, multiple listing, and organ offer accepting decisions are optimized. The model described in this chapter gives patients the autonomy to choose the waiting list(s) they join. This chapter analyzes the question of where a patient should list in order to maximize expected life years subject to an upper bound on the number of waiting lists she can join or total distance she is allowed to travel in order to multiple list. The patient still faces the liver acceptance decision after she determines where she will register, and this model captures this decision as well.

Historically, multiple listing has been a controversial topic because of its potential effects on equity in access to transplantation. Indeed, multiple listing was prohibited during part of 1988 [107], and it is still forbidden for kidney transplant candidates in New York State [191]. There were legal disputes about proposed bans on multiple listing within UNOS in 1988 and again in 1994, but the issue never came to a final vote [183, 184, 185]. The controversy stems from the fact that if multiple listing is prohibited, some patients may be obliged to list at an OPO with poor access to organs [12], which might then increase the geographical disparities. On the other hand, if multiple listing is allowed, patients who multiple list may gain an unfair advantage, since multiple-listed patients have, on average, a 195% greater transplantation rate than other patients [107]. Currently, every OPO in the U.S. accepts multiple-listed ESLD patients. [107].

Surprisingly, only 3.3% of ESLD patients multiple list, either because they are not aware of the option, or because of various costs and restrictions [107]. For example, third-party insurers will usually provide coverage at only one OPO [159]. Also, since increased travel time may result in a decrease in organ quality, the recipient must be able to reach the OPO

quickly once an organ is available. Therefore, geographical constraints may prevent some patients from multiple listing. Lastly, most transplant centers require a personal visit from the patient and a separate evaluation, which are both time-consuming and expensive. Some centers require that all or part of the tests be repeated using their staff and equipment [37]. White, younger, privately insured, and higher-educated patients are currently more likely to multiple list in the U.S. [107]. In our analysis of multiple-listed patients, we cannot differentiate whether all the multiple registrations correspond to multiple listing (patients being actively registered at more than one waiting list) or to relocation (patients are removed from one list and registered at another). According to our analysis, almost every multiple-listed patient lists in two OPOs, and the maximum number of OPOs in which any ESLD patient list is four. Among the multiple-listed patients, approximately 3.60% list in three OPOs and 0.23% list in four OPOs. Also, 30% of all multiple-listed patients list only in one region.

Opponents of multiple listing believe that it gives an unfair advantage to patients who do so, and this advantage tends to benefit more educated, wealthier patients. In 2005, almost 20% of adults reported they did not receive needed health-related services in the past 12 months because they could not afford them [122]. However, having equal access to health care services does not guarantee that necessary services will be received or that outcomes will be optimal. Not everyone who has access to services receives them when needed, and people who live in areas with few services may still obtain them, in spite of their scarcity [72].

Chapter 4 investigates the multiple listing problem from the societal perspective. From this perspective, it is not only possible to assess the benefit of multiple listing to multiple-listed patients, but also to measure any of its drawbacks for single-listed patients. This analysis builds on the U.S. liver allocation simulation model of Shechter et al. [162] by probabilistically deciding whether an ESLD patient in the simulation chooses to multiple list or not. Chapter 4 also performs sensitivity analysis on the percentage of patients who multiple list.

Chapter 5 of this dissertation explores an emerging therapy in ESLD, the aforementioned liver assist devices (LADs). This chapter investigates the optimal time to start using an LAD,

and by doing this it adds insight to current LAD design efforts. This chapter also considers a hypothetical, internal LAD. This model increases the number of actions available to the patient. In addition to the simple liver accept/reject decision process, patients are given the choice of an alternative therapy in each period. This study assumes that once a patient chooses to be treated with an LAD, she stays on this therapy until she dies or receives a transplant.

1.4 CONTRIBUTIONS

Models described in Chapters 3 and 5 contribute to the patient perspective in medical decision making and generalize Alagoz et al.'s model [8] by adding additional decisions or actions. The model described in Chapter 4 contributes to the societal perspective and improves Shechter et al.'s [162] model by incorporating multiple listing into the current liver allocation system.

The remainder of this dissertation is organized as follows: Chapter 2 provides background information on the major modeling methodology used throughout this dissertation. It also reviews the literature concerning primary application areas for the major modeling framework, the organ allocation and organ support devices. Chapter 3 develops the optimization problem faced by a single multiple-listed ESLD patient. Chapter 4 extends this model such that it analyzes the multiple listing decision from a societal perspective, utilizing a simulation framework. Chapter 5 considers an emerging technology in ESLD, an organ support device, which would act like a bridge therapy to transplantation, or to liver regeneration. We discuss conclusions, limitations, and future extensions of the dissertation in Chapter 6.

2.0 LITERATURE REVIEW

2.1 MARKOV DECISION PROCESSES

The problems described in Chapters 3 and 5 are modeled as a Markov Decision Process (MDP). An MDP is an appropriate technique to model sequential decisions under uncertainty, considering both the outcomes of current decisions and future decision making opportunities [141]. The notation in this section is based on Puterman [141].

The five components of an MDP are sets of decision epochs, states, actions, rewards, and transition probabilities. *Decision epochs* can be discrete ($T = 1, \cdots, N$) or continuous ($T = [0, N]$). If N is infinite, the decision problem will be called a *infinite-horizon* problem ($T = [0, \infty)$). The system occupies a *state* (s) at each decision epoch. Throughout this dissertation S denotes the set of states. The decision maker chooses an *action* a from $\mathcal{A}_s$, the set of actions available in state s. Based on the action taken in state s at decision epoch t, the decision maker receives an immediate *reward* of $r_t(s, a)$ and the system transitions into a subsequent state determined by the *probability distribution* $P_t(\cdot|s, a)$. We refer the collection of objects $\{T, S, A_s, r_t(s, a), P_t(\cdot|s, a)\}$ as an MDP [141]. A *decision rule*, d_t, specifies the action selection in each state at a specified decision epoch. It suffices to consider Markovian (i.e., d_t depends on previous system states and actions only through the current state of the system) and deterministic (i.e., d_t chooses an action with certainty) decision rules. A *policy* specifies the decision rules to be used at all decision epochs. In other words, a policy π, is a sequence of decision rules, $\pi = \{d_1, d_2, \cdots, d_{N-1}\}$. A policy is a stationary policy if $d_t = d$ for all $t \in T$. At a specified point in time, upon observing the state of the system, the decision maker either receives an immediate reward and leaves the system, or based on

the decision maker's action, the system transitions to a new state according to a probability distribution [141].

In this dissertation we consider infinite-horizon, discounted MDPs, so that $N = \infty$ and future rewards are discounted by a multiplier $0 \leq \lambda \leq 1$. We focus on the expected total discounted reward criterion, although other criteria may be used [141]. The objective of an MDP is to find an optimal policy d^* that maximizes one of these criteria. Let $u(s)$ be the total discounted expected reward obtained in state s. Then the following form will characterize values and optimal policies in discounted infinite-horizon models, finite state and action spaces, and an expected total discounted reward objective:

$$u(s) = \max_{a \in \mathcal{A}_s} \left\{ r(s,a) + \sum_{j \in S} \lambda P(j|s,a) u(j) \right\}. \tag{2.1}$$

(2.1) are referred to as the *optimality equations* or *Bellman equations*. It can also be shown that there is a unique solution to the following optimality equations giving the optimal policy [141].

$$V(s) = \max_{a \in \mathcal{A}_s} \left(r(s,a) + \sum_{j \in S} \lambda P(j|s,a) V(j) \right) \text{ for } s \in S,$$

where $V(s)$ is the optimal value of the MDP at state s. The policy maximizing this set of equations is the optimal policy.

One use of MDPs is to establish the existence of optimal policies with appealing structure. These policies are easy to implement and they enable efficient computation. Assuming an ordered state space, a control limit policy is a deterministic Markov policy composed of decision rules of the form

$$d_t(s) = \begin{cases} a_1, & s < s^*, \\ a_2, & s \geq s^*, \end{cases}$$

where s^* is a *control limit*. If the state of the system is less than the control limit, then it is optimal to take action a_1. Otherwise, the decision maker should take action a_2. In Chapter 5 we show the sufficient conditions for the existence of optimal control limit policies.

Value iteration [20, 141, 160], policy iteration [18, 67] and linear programming [42] are the most common techniques used to solve MDPs. Other techniques include modified policy

iteration [115], relative value iteration [192] and approximate methods such as neuro-dynamic programming [19].

MDPs have been applied to various areas including maintenance and inspection [47, 48, 58, 63, 163, 193], inventory and production [25, 59, 76, 83], finance [26, 106, 128, 151], agriculture [131], and sports [84, 127]. More applications of MDPs are discussed in a survey by White [194].

MDPs have also been applied to different healthcare topics. Schaefer et al. [155] describe MDP modeling in the context of medical treatment and discuss when MDPs are an appropriate technique. They review selected successful applications of MDPs to treatment decisions in the literature. Lefevre [93] utilizes an MDP model in order to decide a quarantine level and medical treatment level. The states at each decision epoch are the number in the population who are infected and can transmit the disease. The new states at the next decision epoch depend upon disease propagation rates and on the decisions made. Magni et al. [96] model optimal timing of intervention for treating hereditary spherocytosis disease as an MDP. They use an objective that maximizes Quality Adjusted Life Years (QALYs), a class of utility functions widely used in the medical literature. Shechter et al. [161] utilize MDPs to model the optimal timing of HIV therapy. Kreke et al. [88] model hospital discharge policies of sepsis patients as an MDP. Kurt et al. [89] model the optimal time to start therapy for diabetes patients and Chhatwal et al. [31] model optimal policies for biopsy decision-making in breast cancer using MDPs. MDPs have been used to model organ allocation decisions in literature [7, 8, 9, 86, 153]; these studies will be discussed in Section 2.2.

Another class of problems that is solved using MDPs is optimal stopping problems. They describe situations in which the decision maker's goal is to decide when to stop the process so as to maximize the total expected reward or minimize the total expected cost [33]. If there is more than one possible stop to the decision process, then the optimal stopping problem is said to have multiple stops. In Chapter 5, we discuss an optimal stopping problem with multiple stops and we model this problem as an MDP. Therefore, we summarize applications of MDPs with multiple stops in different settings.

Haggstrom [60] considers an optimal stopping problem in which the decision maker tries to maximize her gain by observing a sequence of random variables and deciding when to stop this sequence and start observing another one. Similarly, in the LAD model, the patient should decide when to accept an LAD which stops a decision problem and starts another decision problem. Allaart and Monticino [11] analyze optimal single and multiple stopping rules for a class of correlated random walks that provides an elementary model for processes exhibiting momentum or directional reinforcement behavior. Similar to transaction costs complicating their simple buy/sell model, the nature of the decision of accepting a device complicates our multiple stopping problem. The patient cannot simply accept/reject an LAD at every decision epoch since she should also consider the fact that once she accepts an LAD, she stays with an LAD. Other practical applications requiring a generalization of the optimal stopping problem to possibly multiple stops include [27, 99, 104, 118, 166, 176].

2.2 ORGAN TRANSPLANTATION MODELS

In this dissertation, we develop organ transplantation models that consider either a societal perspective similar to studies [39, 143, 148, 149, 167, 202, 203], or a patient's perspective similar to studies such as [3, 7, 8, 9, 38, 65, 66].

The societal perspective considers all of the patients and distributes organs to patients according to some societal metric, but without considering patient preferences. Many papers in this area make strong assumptions such as the number of organs is more than the number of patients, organs are not offered to more than one patient and so on. Among examples from the literature, Righter [143] considers a resource allocation problem with a finite number of activities but does not consider the effect of the waiting list on the organ arrival rates and does not provide any computational results. David and Yechiali [39] consider allocating multiple organs to multiple patients, but assume that patient health is static and do not consider the waiting list.

The patient's perspective only considers a single patient and models how this patient should accept/reject organs. Although patient's perspective may be implementable right

away given the necessary data, its impacts may be limited. Howard [66] models the problem of when to decline a cadaveric liver and provides statistical results, but does not provide any numerical solutions or structural insights. David and Yechiali [38] make limiting assumptions such as the number of organs is equal to the number of transplant candidates, and that the patient will receive less frequent organ offers as time progresses. Ahn and Hornberger [3], and Hornberger and Ahn [65] use simple and static models of patient health and do not consider the waiting list. Alagoz et al. [7, 9] consider the problem of optimally timing a living-donor (cadaveric-donor) liver transplant to maximize a patient's total life expectancy. They seek a policy describing the health states in which the living-donor (cadaveric-donor) liver transplantation should occur and those where waiting is the optimal action. Alagoz et al. [8] consider a decision problem faced by the patient where possibly both a living-donor and a cadaveric-donor are available. They are able to find optimal control-limit type policies in all models. Although Alagoz et al. [7, 8, 9] models are the most relevant to our models, they calibrate their models such that liver offers to a patient only depend on the region in which she is listed. Sandikci et al. [153] model the optimal time to transplant using an explicit model of the waiting list. By doing so, they are able to estimate the price of privacy in liver transplantation. In our models, we assume an implicit model of the waiting list similar to Alagoz et al.'s models [7, 8, 9].

There are a small number of studies that combine the societal and patient's perspectives. Su and Zenios [172, 173] integrate both perspectives where they consider the problem of globally allocating kidneys to transplant candidates who have the right to refuse the organs. Although they are able to integrate both perspectives, they make limiting assumptions such as there are no patient arrivals, patients can't die before a transplant, kidneys may be offered to only one patient, patient health does not change, all patients are homogeneous and organs do not deteriorate. We relax each of these assumptions in our models.

Alagoz et al. [10] present a detailed review of the kidney and liver allocation system as well as previous research on organ allocation. Major differences of the models discussed above from the models described in this dissertation are that they assume that patients are singly listed and that an organ support device does not exist.

2.3 PREVIOUS SIMULATION MODELS ON LIVER ALLOCATION SYSTEM

In Chapter 4, we discuss and build on a previous simulation model on the U.S. liver allocation system by Shechter et al. [162] in order to estimate the effect of multiple listing on the entire waiting list. In this section, we present several other discrete-event simulation models that have been developed to estimate the effect of various allocation policies.

The UNOS Liver Allocation Model (ULAM) is a simulation of the cadaveric liver allocation system in the U.S. ULAM permits the comparison of multiple liver allocation policies in the proposal phase so that policies can be tested prior to implementation [61]. ULAM uses either historical or simulated data streams for both patient listings and donor arrivals. Another liver allocation simulation is developed by the CONSAD Corporation [36]. A potential flaw in both of these modeling efforts is that the description of natural history was estimated entirely through probability distributions that describe how patients move through the existing priority scheme for allocation, preventing an unbiased analysis of any organ allocation scheme significantly different than the current mechanism [87].

Shechter et al. [162] describe a discrete event simulation model of the national liver allocation system that differs from previous modeling efforts in that it considers the natural history of the disease independently of any particular patient priority scheme. The model provides various outputs such as patient survival, and the number of wasted organs. Alagoz et al. [6] create a discrete-event simulation model that represents the biology of end-stage liver disease and the health care organization of transplantation in the U.S. They design the simulation model to test proposed changes in allocation policies. At the individual level, Alagoz et al. [6] use mathematical models of disease progression and post-transplant survival to track patients health.

2.4 HOW CAN A PATIENT OVERCOME GEOGRAPHIC DISPARITIES IN ORGAN ALLOCATION?

As described in Chapter 1, UNOS considers the geographic location as well as the medical urgency of patients when offering organs. Geographic location of a patient is important since the viability of organs decrease by time. However, prioritizing patients based on their location causes geographical disparities. Among patients who received a transplant in San Francisco bay area between July 1, 2008 and June 30, 2009, 35% of them had a MELD score between 31-40 at the time of the transplant. However, all of the patients who received a transplant in Sacramento between July 1, 2008 and June 30, 2009 were healthier at the time of transplant. Indeed 37.5% of patients in Sacramento had a MELD score between 21-30 at the time of transplantation [165]. In general, there is a significant disparity in MELD scores in liver transplant recipients in small versus large OPOs [196]. According to Trotter and Osgood [179], of the 4,798 cadaveric-donor liver transplantations performed between February 28, 2002, and March 31, 2003, 8.3% were transplanted in small OPOs. Also, the rate of transplantation was 2.5-fold higher for patients listed in small OPOs [179]. Although there is an apparent geographical disparity within organ allocation, there are several ways through which an ESLD patient can change the geographical disparity to her benefit. In this section, we elaborate on two autonomies that are available to ESLD patients.

2.4.1 Relocating in Organ Allocation

In Chapter 3, we construct a model that gives an ESLD patient the autonomy to relocate and register at another OPO. There are ESLD patients who utilize this opportunity available to them. For example, ELSD patients move from Massachusetts to Florida in order to increase their chances of receiving organ offers [57, 105, 126, 130]. This is a reasonable decision because in terms of harvesting livers, New England is chronically short on organs but Florida has a relatively large supply [57]. One would assume that it is better for an ESLD patient to live in a city renowned for its hospitals, and especially transplant centers

like Boston. However, because of the long waiting times in Boston, it is better for ESLD patients to move to Jacksonville and live next to Mayo Clinic in Jacksonville, Florida [57, 105, 130].

Medical literature in relocation for an organ transplant is limited and mostly considers the psychological aspects of relocation such as putting life on hold, experiencing diminished emotional support, and worrying about money [44, 171, 188]. Although the relocation choice is currently being practiced by patients [57, 105, 126, 130, 140, 177], according to our knowledge of the literature, there is no study in the OR literature that focuses on it.

2.4.2 Multiple Listing in Organ Allocation

We construct models of multiple listing in liver transplantation in Chapters 3 and 4. We present previous studies form the medical literature because there does not exist an OR model that focuses on multiple listing in organ transplantation. Although there are several studies about multiple listing in kidney transplantation [13, 107, 112, 134, 190, 191], to the best of our knowledge, Merion et al. [107] is the only existing study on multiple listing in liver transplantation.

The ethics of multiple listing have been a focus of several studies in literature such as [12, 32]. According to Ankeny [12], although the organ allocation system appears to be a national system, it actually is a complex regionalized system that in turn causes disparities for candidates under certain conditions. Therefore, Ankeny [12] believes that the debate over multiple listing shouldn't be perceived as competing principles such as autonomy and equity. Rather, it should be recognized as a problem of inequity of the allocation system. Childress [32] provides an ethical analysis and assessment of various actual and proposed policies of organ procurement and distribution. Concentrating on policies being developed in the UNOS, Childress [32] examines the point system for cadaveric kidneys, the access of foreign nationals to organs donated in the U.S., and the multiple listings of patients seeking transplants. The ethics of multiple listing has also been a focus in the popular media recently [125]. A wealthy candidate receiving a transplant through relocating and multiple listing arisen concerns on the moral principles of U.S. allocation policy.

Other studies in the literature quantify the effects of multiple listing in access to transplantation. Miller [112] explores the social and ethical issues raised by multiple listing, contrasting policies adopted at the national level with those implemented in New York State. (Recall that multiple listing is prohibited in New York State for kidney candidates). He examines the implications of the debate for broader questions about entitlement and access to health care. White et al. [191] study the effectiveness of a 1990 ban by New York State on multiple listing for a cadaver kidney transplant, and the impact of the ban on equity in access to transplantation. They use multivariate hazard models to estimate the impact of the ban on the overall odds of multiple listing and on the odds of multiple listing at instate and out-of-state transplant centers. They also utilize simulation techniques to estimate the effects of a complete multiple listing ban on group waiting time differentials. They conclude that although the ban reduced the number of multiple-listed patients, the results suggest that banning multiple listing is not likely to result in large improvements in equity in access to transplantation. Merion et al. [107] examine the practices and outcomes of multiple listing using data on 26,260 liver candidates registered over a five-year period. They develop a logistic regression model to evaluate candidate and OPO characteristics associated with whether or not a candidate was ever multiple listed. They assume that every ESLD patient is listed in at most two OPOs and consider a static waiting list. They use a Kaplan-Meier approach to determine the expected time until liver transplant and establish time-dependent Cox regression models of access to liver transplantation and waiting list mortality. Our studies are more similar to the studies by White et al. [191] and Merion et al. [107] since we quantify the effects of multiple listing on a particular multiple-listed patient, as well as on the entire waiting list. The modeling framework we use and the additional decisions we model distinguish our models from theirs.

2.5 ORGAN SUPPORT DEVICES

Medical researchers have been trying to develop artificial organs for the last few decades. An increasing number of patients waiting for an organ transplant and the scarcity of cadaveric

donors are common to all organs. Organ devices can be classified into external and internal devices. In this section, we review various organ support devices and the current stage of liver assist devices.

Many patients with end-stage congestive heart failure who are awaiting transplantation receive mechanical circulatory-support devices. (See [17, 23, 35, 43, 50, 74, 108, 145, 201] for technical descriptions of various artificial hearts). DeVries et al. [43] report their first experience with the use of an artificial heart in a human being, a 61 year-old male with chronic congestive heart failure. In their study, the patient survives for 112 days and the artificial heart functions well for the entire postoperative course. Zareba [201] discusses a successful implantation of a fully implantable replacement heart, called AbioCor. It is an advanced medical system developed to fully sustain the body's circulatory system and closely mimic the function of the human heart it replaces. Copeland et al. [35] conduct a nonrandomized, prospective study in order to assess the safety and efficacy of an artificial heart called CardioWest Total Artificial Heart in transplant-eligible patients. The authors note that implantation of the total artificial heart improves the rate of survival to cardiac transplantation and survival after transplantation. Rose et al. [145] experiment the long-term use of a left ventricular assist device and conclude that the use of this device in patients with advanced heart failure results in a clinically meaningful survival benefit and an improved quality of life.

The development of an artificial kidney has a great importance since dialysis is still suboptimal in terms of morbidity and mortality for patients with acute renal failure [69, 103]. An artificial kidney was developed as early as 1926 [94]. According to Kolff [85], the artificial kidney increases the lives of experimental animals and of human beings lacking renal function. More contemporary studies in this area include [68, 70, 71, 152, 178, 187]. Vanholder [187] discusses some of the problems for artificial kidney, such as dialysis patients' being prone to vascular disease and being immobilized throughout the treatment. Humes [68] summarizes the current state of a renal tubule assist device and a cell therapy device development that have the promise to be combined to produce a wearable or implantable bioartificial kidney for full renal replacement therapy. Humes et al. [70] develop an extracorporeal bioartificial kidney. The durability of their device is sustained for up to 24 hours of continuous use.

Humes et al. [71] also discuss the development of a tissue-engineered bioartificial kidney for patients in the intensive care unit. They are able to demonstrate maintenance of cell viability and functionality and also cardiovascular stability. Lee and Zenios [91] model the problem of optimal dialysis initiation from a policy-maker's perspective. They model the problem as an MDP and they examine both equity-based and efficiency-based criteria. They use an approximate policy iteration algorithm to solve the model numerically. Although dialysis is not an artificial organ, this study is similar to ours as it considers the optimal timing of an alternative therapy to transplantation using an MDP framework.

Although clinical trials are underway, artificial and bioartificial livers as either bridge or permanent interventions are not yet clinical reality. Also, clinical research for an artificial liver is not yet as advanced as other artificial organ support devices since unlike other organs, the liver has multiple functions. Attempts to develop an artificial liver started in the 1950s [81, 82, 90, 129, 156]. These earlier studies (nonbiologic support) are analogous to hemodialysis in patients with acute renal failure [157], however they do not show any improvement of survival [75, 81]. Extracorporeal liver support have been performed since the 1960s [1, 2, 29, 49, 52]. These devices are connected to the circulation of the patient and they even have bridged several patients to recovery or transplantation.

Matsumura et al. [101] develop a clinically applied bioartificial liver device, which uses rabbit liver cells. The Extracorporeal Liver Assist Device (ELAD) [64, 169, 174, 175] is the only liver assist device in which human liver cells are used. Several patients are successfully bridged to transplantation within a phase I trial. There are other artificial livers such as the HepatAssist System [40, 170], the TECA-Hybrid Artificial Liver Support System [30, 199], the Bioartificial Liver Support System [102, 138], the Radial Flow Bioreactor [113, 114], the Liver Support System [56, 116], The AMC-Bioartificial Liver [51, 164], the Bioartificial Hepatic Support system [46], and the Hybrid-Bioartificial Liver [45]. More detailed information on the characteristics of eight different artificial liver systems, the associated clinical outcomes and recent advances in clinical practice are available in [28, 80, 158].

3.0 IN WHICH OPOS SHOULD AN END-STAGE LIVER DISEASE PATIENT LIST?

3.1 INTRODUCTION

As discussed in Chapter 1, each ESLD patient joins a waiting list in an OPO in order to be eligible for cadaveric liver offers, and an ESLD patient may list in more than one OPO. The set of OPOs that a patient joins determines the quality and frequency of organs offered to her. Furthermore, as illustrated in Figure 3.1, the volume of transplants, waiting list additions, and sizes of the waiting lists differ across the 11 regions. These observations raise an important question from the patient's perspective, namely, *"In which OPOs should she list?"*

We model the decision problem faced by the patient in three stages. The "home OPO" refers to the original waiting list in which the patient is listed. In other words, home OPO refers to the geographic location of the patient. In the first stage, the patient chooses her home OPO. That is, in the first stage, the patient is allowed to relocate, and therefore, join the waiting list at any OPO. The first-stage problem is called the "home OPO selection" problem. If relocation is not an option for a patient, then we can fix the home OPO and decide optimal policies for this patient in subsequent stages. In the second stage, called the "listing" problem, the patient chooses additional OPOs in which to list. These additional OPOs may depend on the home OPO. We use a cardinality constraint and a budget constraint to restrict multiple listing. In the third stage, after the patient has listed in a specific set of OPOs, she decides to accept or reject organ offers as they are made. The third-stage problem is called the "liver acceptance" problem and was studied by Alagoz et al. [9]. The differences of our model from Alagoz et al.'s are presented in Section 3.2.

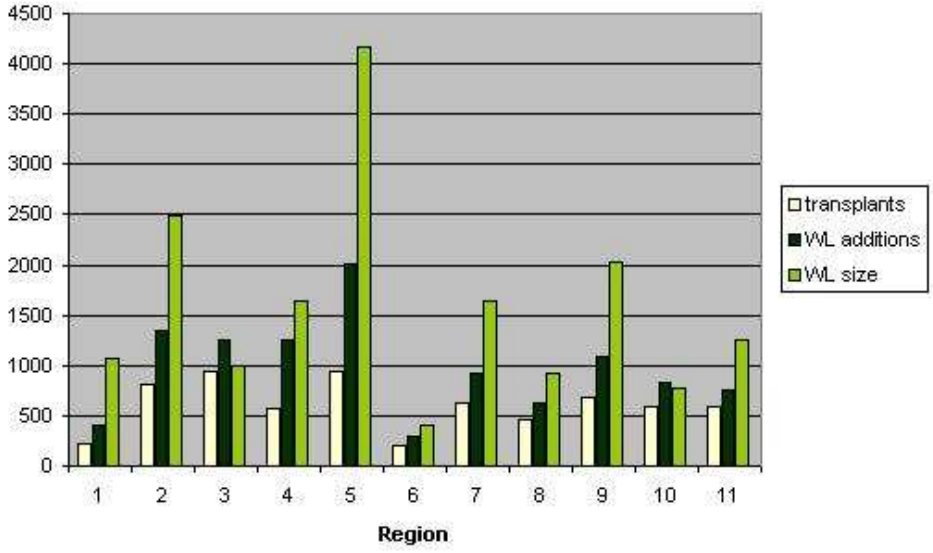

Figure 3.1: Transplant volumes and the number of waiting list additions per U.S. region in 2006

This chapter's approach considers patient perspective decision making in organ allocation, which is similar to existing studies such as [7, 8, 9] that are discussed in Chapter 2. These models, however, only consider the third-stage organ acceptance problem. Among them, Alagoz et al. [9] is the most relevant to this study. They model the third-stage decision as a discrete-time Markov decision process (MDP). They calibrate their model such that the frequency and quality of organ offers to a patient are determined based on the (single) region and not the OPO in which she is listed. However, OPOs belonging to the same region may have very different organ harvesting frequencies. A comparison of the number of organs harvested in Norcross,GA and Metairie,LA between the years 2003 and 2008 reveals that Norcross,GA harvested 30% more livers than Metairie,LA [132], despite the fact that both OPOs belong to Region 3. Therefore, estimating the frequency of organ offers to a patient based on her region is not a reliable representation of the current liver allocation system. Moreover, other studies do not consider neither the practice of multiple listing nor relocation in their models. They also assume that a patient receives only one offer during any time period. Our model relaxes all of these assumptions.

Section 3.2 formulates a mathematical model of the three-stage decision problem faced by the patient under a cardinality constraint and a total distance (budget) constraint. Section 3.3 establishes several structural properties of the cardinality-constrained model described in Section 3.2. Section 3.4 is a discussion of the computational approach for the cardinality-constrained model, and Section 3.5 is an analysis of the numerical results. Section 3.6 draws conclusions and presents ideas for future research.

3.2 MODEL FORMULATION

In the first stage of the decision process, the patient selects a home OPO $b \in \mathcal{I}$, where $\mathcal{I}$ represents the entire set of OPOs.

In the second stage, the patient selects a set of additional OPOs in which to list based on the home OPO picked in the first stage. As discussed in Chapter 1, there are geographical and other constraints that prohibit the patient from being listed in every OPO in $\mathcal{I}$. We model the second-stage listing problem first by using a cardinality constraint, and then by using a total distance constraint to represent those restrictions.

In the third stage of the decision process, the patient either accepts or rejects the organs offered to her over time. If she accepts an offer, she is removed from every waiting list she has joined and she quits the process. Otherwise, she stays in the process with the hope of receiving future organ offers. The process may also terminate with the pre-transplant death of the patient.

Although the patient faces the decision problems in consecutive stage order, we consider them in the opposite order. That is, we begin by solving the liver acceptance problem that is farthest downstream and then move upstream.

3.2.1 Liver Acceptance Problem

3.2.1.1 Continuous-time MDP Formulation Similar organ acceptance decision models, such as [7, 9], consider organ offers to patients in a single OPO or in a region, and model

the liver acceptance decision as a discrete-time MDP. However, we consider the organ offers to patients listed in different sets of OPOs. Therefore, there is a need to calculate the total organ offer frequency that a patient would see when listed in a set of OPOs. Modeling the third-stage liver acceptance problem in continuous time facilitates the estimation of the total organ offer frequency at a set of OPOs, as shown in Section 3.5.2.

The objective of the continuous-time MDP is to maximize the patient's total expected discounted reward (e.g., the patient's expected survival in terms of life days). We denote the set of OPOs in which the patient is listed by O. $\mathcal{R}(i)$ represents the region to which OPO i belongs and $\mathcal{R}(O)$ stands for the set of regions to which OPOs in set O belong, i.e. $\mathcal{R}(O) = \bigcup_{i \in O} \mathcal{R}(i)$. According to this definition, $\mathcal{R}(\mathcal{I})$ represents the entire set of regions. States, actions, rewards and transition rates of the continuous-time MDP are as follows:

States: We characterize the state $s \in S$ of the process as the health state of the patient, $h \in S_H$, and the quality of the liver currently being offered to the patient, $\ell \in S_L$; $S_H = \{1, \ldots, H+1\}$, where $H+1$ represents death, $H < \infty$, and $S_L = \{1, \ldots, L+1\}$, where $L+1$ represents the case that no liver is currently being offered, $L < \infty$, so that $S = S_H \otimes S_L$. We define $S'_H = S_H \setminus \{H+1\}$ and $S'_L = S_L \setminus \{L+1\}$. We assume that there exists a complete ordering of patient health states as well as of liver qualities.

Actions: The patient can either reject the current offer and continue the process (action 'W') or she can accept the offer and quit the process (action 'T'). We define $a^*(s)$ as the optimal decision in state s and $\mathcal{A}_s$ as the action space for state s; i.e.,

$$\mathcal{A}_s = \begin{cases} \{T, W\}, & \text{if } h \in S'_H, \ell \in S'_L, \\ \{W\}, & \text{if } h \in S'_H, \ell = L+1, \\ \emptyset, & \text{if } h = H+1. \end{cases}$$

Rewards: The patient receives an expected post-transplant lump sum reward $r_T(h, \ell)$ if she accepts a liver of type ℓ while in health state h. We assume that $r_T(h, L+1) = r_T(H+1, \ell) = 0$. Note that although $r_T(h, \ell)$ is also a function of the patient type (gender and blood type), we suppress this dependency for notational convenience as these factors are fixed. The patient accrues reward at rate $r_W(h)$ while in health state h. Similarly, we assume that $r_W(H+1) = 0$. We assume that the reward functions are stationary.

Transition rates: A transition in the process occurs when either the health state of the

patient changes or the patient is offered an organ. We assume that the transition rates are stationary. Let $\mu(h'|h)$ be the transition rate from health state h to health state h'. Let $\nu_O(\ell|h)$ be the type ℓ organ offer rate to a patient in health state h who is listed in OPO set O and $\omega_j(\ell|h)$ be the type ℓ organ offer rate to a singly-listed patient in health state h who is listed in OPO j.

We refer to the rate of an organ offer arrival as "local", if the donor and the recipient are in the same OPO; "regional", if the donor and the recipient are not in the same OPO but in the same region; or "national" if the donor and the recipient are in different regions. The national sharing of livers is very low compared to local and regional sharing. According to Gerber et al. [55], the local, regional and national sharing of transplanted livers is approximately 69.03%, 23.36% and 7.61%, respectively. Also, the percentage of national sharing has been decreasing. Moreover, the national organ offer arrival rate complicates our model immensely due to extensive data needs. Consequently, we do not consider national offers in this dissertation.

From every OPO in every region in which the patient is listed, she receives either a stream of local offers or a stream of regional offers. Let $\xi_i(\ell|h)$ be the rate of a type ℓ organ offer from OPO i to a patient in MELD score h, who is listed in OPO i, and $\theta_i(\ell|h)$ be the rate of a type ℓ organ offer from OPO i to a patient in MELD score h, who is listed in one of the OPOs in region to which OPO i belongs. In other words, $\xi_i(\ell|h)$ $(\theta_i(\ell|h))$ represents the rate of local (regional) offers of organs harvested in OPO i. Therefore, we characterize $\nu_O(\ell|h)$ and $\omega_j(\ell|h)$ as a function of $\xi_i(\ell|h)$ and $\theta_i(\ell|h)$ as follows:

$$\nu_O(\ell|h) = \sum_{R\in\mathcal{R}(O)} \left[\left(\sum_{i\in O,\mathcal{R}(i)=R} \xi_i(\ell|h) + \sum_{j\notin O,\mathcal{R}(j)=R} \theta_j(\ell|h) \right) \right], \tag{3.1}$$

and

$$\omega_j(\ell|h) = \xi_j(\ell|h) + \sum_{m\in\mathcal{I},\mathcal{R}(m)=\mathcal{R}(j)} \theta_m(\ell|h). \tag{3.2}$$

According to (3.1) and (3.2), the arrival rate of organ offers to a patient depends not only on the OPOs in which she is listed but also on the other OPOs in the region(s) in which she is listed.

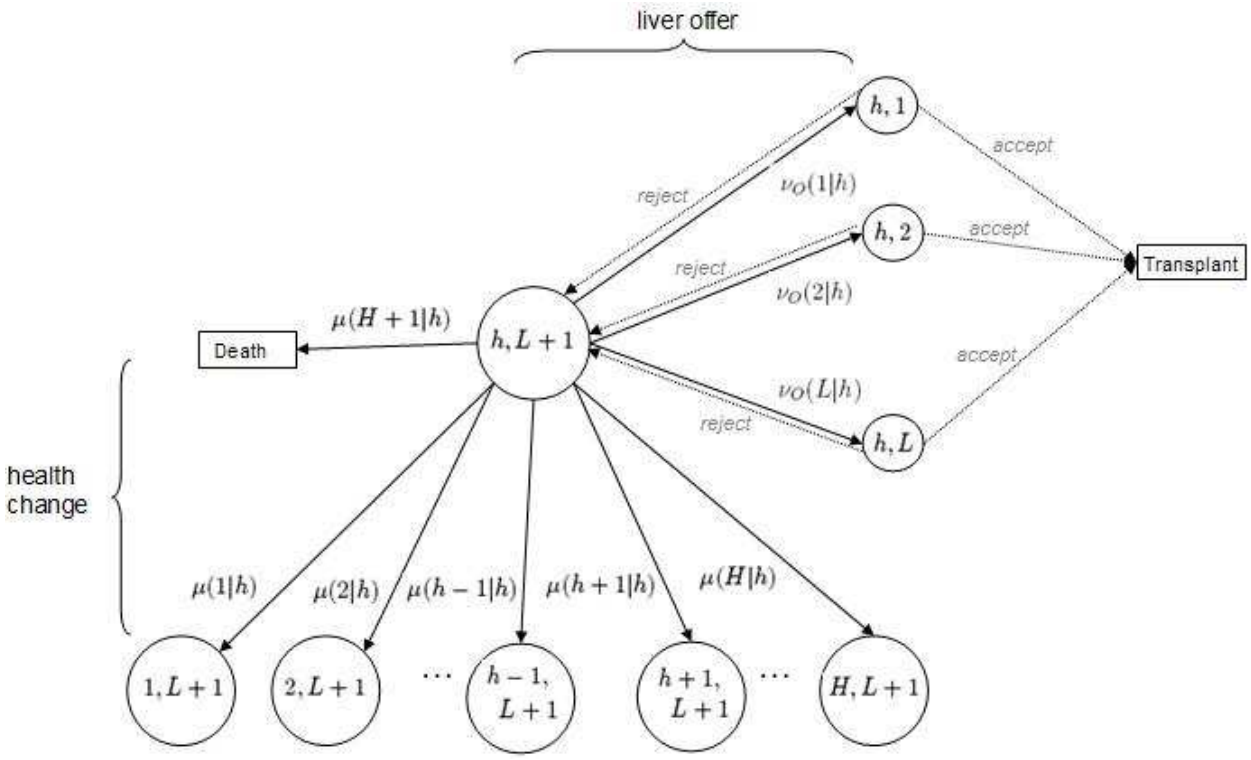

Figure 3.2: Continuous-time Markov chain governing the third-stage liver acceptance decision faced by the patient.

Note that states (h, ℓ), $h \neq H+1$ and $\ell \neq L+1$, are instantaneous states [146] and immediately return the patient to state $(h, L+1)$ or transition the patient to state *"transplant"* after an action is taken. If $a^*(s) =$'T', the patient accepts the organ offer and instantly quits the process. Otherwise, $a^*(s) =$'W', the patient rejects the offer and instantly enters state $(h, L+1)$. One or the other of these events occurs each time an offer is received. Figure 3.2 demonstrates the possible transitions in the process.

Because the transition rate out of an instantaneous state is infinitely large and the transition rate out of the terminal death state is zero, we only specify the total transition rates out of the remaining states as follows:

$$\gamma_O(h, L+1) = \sum_{\ell' \in S'_L} \nu_O(\ell'|h) + \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h), \quad h \in S'_H.$$

Discount rate: We denote the continuous discount rate by $\alpha > 0$.

3.2.1.2 Uniformizing the continuous-time MDP

An equivalent discrete-time MDP model can be formulated through uniformization of the continuous-time model. Based on Bertsekas' [19] definitions, additional notation is presented in order to formulate the equivalent discrete-time problem. We define a uniform transition rate λ_{max} as the maximum total transition rate out of any non-instantaneous state, $\lambda_{max} = \max_{h \in S_H} \gamma_O(h, L+1)$. The discount rate of the uniform process, $\tilde{\alpha}$, is therefore $\tilde{\alpha} = \frac{\lambda_{max}}{\lambda_{max}+\alpha}$. We uniformize the rate of reward associated with waiting in health state h by defining $\tilde{r}_W(h) = \frac{r_W(h)}{\lambda_{max}+\alpha}$. We determine the transition probability matrix as follows:

$$\tilde{P}_O(h', \ell'|h, \ell) = \begin{cases} \frac{\nu_O(\ell'|h)}{\lambda_{max}}, & h' = h, h \in S'_H, \ell' \in S'_L, \\ \frac{\mu(h'|h)}{\lambda_{max}}, & h' \in S'_H \setminus \{h\}, \ell' = L+1, \\ 1 - \sum_{h' \in S_H \setminus \{h\}} \frac{\mu(h'|h)}{\lambda_{max}} - \sum_{\ell' \in S'_L} \frac{\nu_O(\ell'|h)}{\lambda_{max}}, & h' = h, h \in S'_H, \ell' = L+1, \\ 0, & \text{otherwise.} \end{cases}$$

Optimality equations: The patient can either accept or reject the organ offer in state (h, ℓ). If she accepts the offer, she receives a reward of $r_T(h, \ell)$ and leaves the process. If she rejects the offer, she receives an intermediate reward of $\tilde{r}_W(h)$ and transitions into state (h', ℓ') with probability $\tilde{P}_O(h', \ell'|h, \ell)$. Let $V_O(h, \ell)$ be the maximum total expected discounted reward that the patient can attain when her health state is h, the current liver offered to her is ℓ, and she is listed in OPOs specified by O. The optimal solution to this problem can be found by solving Bellman's equations [141] as follows:

$$V_O(h, \ell) = \max \left\{ r_T(h, \ell), \tilde{r}_W(h) + \tilde{\alpha} \sum_{(h', \ell') \in S} \tilde{P}_O(h', \ell'|h, \ell) V_O(h', \ell') \right\} \forall (h, \ell) \in S. \quad (3.3)$$

The optimality equations (3.3) are analogous to those of Alagoz et al.'s [9].

3.2.2 Listing Problem

3.2.2.1 Cardinality-constrained listing problem

In this section, we use a cardinality-constrained framework to model the second-stage listing decision. Restricting the number of OPOs in which a patient can list is justifiable given that no patient has ever listed in more than four OPOs.

In the cardinality-constrained model, geographical restrictions on multiple listing are captured using an *admissible set*. An admissible set A_b for home OPO b is the set of OPOs, including b, in which the patient can list. The model allows a flexible characterization of the admissible set in practice. It could be comprised of the OPOs in which the patient has family or OPOs that have a direct flight from the home OPO or OPOs that are within a prescribed distance of b. If there were no other costs or restrictions associated with multiple listing besides the geographical constraints, then the patient would list in every OPO in the admissible set. To reflect the additional costs and restrictions discussed in Chapter 1, we impose an upper bound K on the number of waiting lists the patient can join. This model is called the "cardinality-constrained multiple listing problem". The patient's cardinality-constrained listing decision is represented by $O(b, K)$, which is the set of OPOs in which she has decided to list.

The second-stage listing problem is solved for a specific home OPO and the corresponding admissible set. In this stage, we compare different subsets of K admissible OPOs. The OPO set that yields the highest total life expectancy corresponds to the optimal listing decision.

For an initial state $(h, L+1)$ and home OPO b, the patient chooses a set of OPOs in which to list (O) based on the following optimization problem:

$$\max_{O \in A_b} \Big\{ V_O(h, L+1) \Big\} \tag{3.4}$$

$$|O| \leq K. \tag{3.5}$$

$$b \in \mathcal{I}. \tag{3.6}$$

3.2.2.2 Total distance constrained listing problem In the cardinality-constrained model, we define an admissible set to represent the geographical restrictions on multiple listing and impose a cardinality constraint to capture the rest of the restrictions. In the total distance constrained model, we characterize all of the restrictions on multiple listing (geographical and non-geographical) through a budget-type framework. In other words, we relax the admissible set restriction, and we impose a restriction on the total cost (distance) of being listed in a certain OPO set. Instead of differentiating between those OPOs which are in the admissible set and those which are not, we associate a cost (c_{bi}) with every OPO

(i) based on its distance from the home OPO b. The patient can list in any OPO set as long as the cost of being listed in that set does not exceed her limited budget (B). In other words, rather than comparing individual OPOs within the home OPO's admissible set for every upper bound K, we compare OPO sets such that the cost of being listed in them is within a certain budget for a fixed home OPO.

For an initial state $(h, L+1)$ and home OPO b, the patient chooses a set of OPOs in which to list (O) based on the following optimization problem:

$$\max_{O \in \mathcal{I}} \left\{ V_O(h, L+1) \right\} \tag{3.7}$$

$$\sum_{i \in O} c_{bi} \leq B, \tag{3.8}$$

$$b \in \mathcal{I}. \tag{3.9}$$

The budget-constrained model captures the essence of the multiple listing problem better than the cardinality-constrained model, because it is a more general model. If we assume $B = K$, $c_{bi} = 1$ for those OPOs in the admissible set, and $c_{bi} = K + 1$ for those OPOs that are not in the admissible set, the budget model transforms to the cardinality-constrained model. However, the budget-constrained model requires more data and it is harder to solve.

3.2.3 Home OPO Selection Problem

Although the home OPO selection problem does not apply to the majority of patients on the waiting list, there are patients who wish to relocate, as described in Chapter 2, in order to decrease their waiting times. Our model optimizes the home OPO selection decision for these patients. However, our model might also ignore the first-stage decision problem for patients who cannot change their home OPOs and optimize the second- and third-stage decisions of such patients.

In order to determine the best home OPO, we solve the optimization problems (3.4)-(3.6) and (3.7)-(3.9) for every OPO $b \in \mathcal{I}$ and take the maximum. In other words, we add $\max_b$ to the objective functions (3.4) and (3.7). Figure 3.3, modified from the Institute of Medicine's Organ Procurement and Transplantation report [73], illustrates potential outcomes of home OPO selection and listing problems for the cardinality-constrained model.

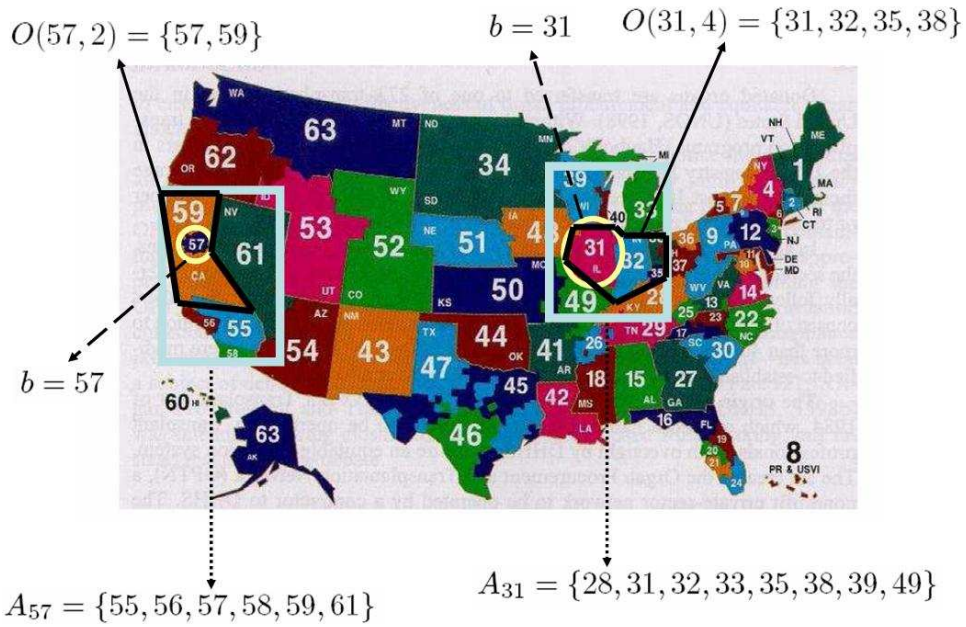

Figure 3.3: Two examples of the *home OPO selection* and *listing* decisions.

3.3 STRUCTURAL PROPERTIES FOR THE CARDINALITY-CONSTRAINED MODEL

In this section, we develop some structural properties of the model described in Section 3.2. We define $S_L(O,h,T)$ as the set of livers a patient should optimally accept uniquely given that she is listed in OPO set O, i.e., $S_L(O,h,T) = \left\{ \ell \in S'_L \middle| a^*(h,\ell) = \text{`}T' \right\}$. We also assume that $r_T(h,\ell)$ is nonincreasing in h and ℓ (Assumption 1). That is, as the patient gets sicker or as the quality of the liver offered to her decreases, her post-transplant reward does not increase.

Remark 3.1 states that given O, the maximum total expected discounted reward that the patient can attain in state (h,ℓ) is greater than or equal to the total expected discounted reward she can receive in that health state when no organ is offered to her. Another result that follows from Remark 3.1 is that if the post-transplant reward associated with accepting the offer is less than the total expected discounted reward in health state h when no organ is offered to the patient, then it is optimal for her to reject the offer.

Remark 3.1 *If we use the value iteration algorithm to solve the optimization problem (3.3), at any step n of the algorithm $V_O^n(h,\ell) \geq V_O^n(h,L+1), \forall \ell \in S_L$ holds.*

Proof. $V_O^n(h,L+1)$ is defined as the total expected discounted reward the patient can attain when she is not offered an organ or she rejects an organ offer. Therefore, $V_O^n(h,\ell) = \max\Big\{r_T(h,\ell), V_O^n(h,L+1)\Big\}$. So, $V_O^n(h,\ell) \geq V_O^n(h,L+1)$. Note from this definition that, if $r_T(h,\ell) < V_O^n(h,L+1)$, then $V_O^n(h,\ell) = V_O^n(h,L+1)$. □

Definition 3.1 modifies the dominance relationship characterized by Alagoz et al. [7] in order to compare the uniformized organ offer arrival rates at different OPO sets.

Definition 3.1 *Let O_1 and O_2 be sets of OPOs. O_2 dominates O_1 if*

$$\sum_{\ell=k}^{L+1} \frac{\nu_{O_2}(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\nu_{O_1}(\ell|h)}{\lambda_{max}}, 1 \leq k \leq L+1, 1 \leq h \leq H+1.$$

According to Definition 3.1, the following equations follow:

$$\sum_{\ell=1}^{k-1} \frac{\nu_{O_2}(\ell|h)}{\lambda_{max}} \geq \sum_{\ell=1}^{k-1} \frac{\nu_{O_1}(\ell|h)}{\lambda_{max}}, 1 \leq k \leq L+1, 1 \leq h \leq H+1.$$

If $k = L+1$, then

$$\begin{aligned} &\sum_{\ell=1}^{L} \frac{\nu_{O_2}(\ell|h)}{\lambda_{max}} \geq \sum_{\ell=1}^{L} \frac{\nu_{O_1}(\ell|h)}{\lambda_{max}}, 1 \leq h \leq H+1, \\ \Longrightarrow \quad &\sum_{\ell \in S'_L} \nu_{O_2}(\ell|h) \geq \sum_{\ell \in S'_L} \nu_{O_1}(\ell|h), 1 \leq h \leq H+1. \end{aligned}$$

Proposition 3.1 *Let O_1, O_2 and O_3 be sets of OPOs. If O_1 dominates O_2, and O_2 dominates O_3, then O_1 dominates O_3.*

Proof. Let

$$\lambda_{max} = \max_{h \in S_H} \Big(\gamma_{O_1}(h,L+1), \gamma_{O_2}(h,L+1), \gamma_{O_3}(h,L+1)\Big).$$

From Definition 3.1, if O_1 dominates O_2, and O_2 dominates O_3, then the following equations hold for $k \in S_L, h \in S_H$:

$$\sum_{\ell=k}^{L+1} \frac{\nu_{O_1}(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\nu_{O_2}(\ell|h)}{\lambda_{max}}, \tag{3.10}$$

$$\sum_{\ell=k}^{L+1} \frac{\nu_{O_2}(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\nu_{O_3}(\ell|h)}{\lambda_{max}}, \tag{3.11}$$

$$\Rightarrow \sum_{\ell=k}^{L+1} \frac{\nu_{O_1}(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\nu_{O_3}(\ell|h)}{\lambda_{max}}. \tag{3.12}$$

From Definition 3.1 and (3.12), O_1 dominates O_3. In other words, the dominance relationship is transitive. □

Proposition 3.2 *Let i, j, k be OPOs in the same region and $O_1 = \{i\}$, $O_2 = \{i, j\}$, $O_3 = \{i, k\}$, $O_4 = \{i, j, k\}$. If O_2 dominates O_1, then O_4 dominates O_3.*

Proof. As $i, j,$ and k belong to the same region, organ offer arrival rates at OPO sets $O_1, O_2, O_3,$ and O_4 can be written as follows:

$$\begin{aligned}
\nu_{O_1}(\ell|h) = &\ \omega_i(\ell|h), h \in S_H, \ell \in S'_L, \\
\nu_{O_2}(\ell|h) = &\ \omega_i(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h), h \in S_H, \ell \in S'_L, \\
\nu_{O_3}(\ell|h) = &\ \omega_i(\ell|h) + \xi_k(\ell|h) - \theta_k(\ell|h), h \in S_H, \ell \in S'_L, \\
\nu_{O_4}(\ell|h) = &\ \omega_i(\ell|h) + \xi_j(\ell|h) + \xi_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h), h \in S_H, \ell \in S'_L.
\end{aligned}$$

Let $\lambda_{max} = \max_{h \in S_H} \Big(\gamma_{O_4}(h, L+1)\Big)$. If O_2 dominates O_1, then the following equations hold for $k \in S_L, h \in S_H$:

$$\sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h)}{\lambda_{max}}, \tag{3.13}$$

$$\Rightarrow \sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h) - \omega_i(\ell|h)}{\lambda_{max}} \leq 0, \tag{3.14}$$

$$\Rightarrow \sum_{\ell=k}^{L+1} \frac{\xi_j(\ell|h) - \theta_j(\ell|h)}{\lambda_{max}} \leq 0. \tag{3.15}$$

If O_4 dominates O_3, then the following equations hold for $k \in S_L, h \in S_H$:

$$\sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h) + \xi_j(\ell|h) + \xi_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h)}{\lambda_{max}} \leq \sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h) + \xi_k(\ell|h) - \theta_k(\ell|h)}{\lambda_{max}}, \tag{3.16}$$

$$\Rightarrow \sum_{\ell=k}^{L+1} \frac{\omega_i(\ell|h) + \xi_j(\ell|h) + \xi_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h) - \omega_i(\ell|h) - \xi_k(\ell|h) + \theta_k(\ell|h)}{\lambda_{max}} \leq 0, \tag{3.17}$$

$$\Rightarrow \quad \sum_{\ell=k}^{L+1} \frac{\xi_j(\ell|h) - \theta_j(\ell|h)}{\lambda_{max}} \leq 0. \tag{3.18}$$

As apparent from (3.13)-(3.15) and (3.16)-(3.18), if O_2 dominates O_1, then the condition for O_4 to dominate O_3 is satisfied automatically. Therefore, if O_2 dominates O_1, then O_4 dominates O_3. □

Theorem 3.1 proves that a patient's total life expectancy does not decrease as she lists in additional OPOs.

Lemma 3.1 *$V_O(h,\ell)$ is monotonically nonincreasing in ℓ, $\ell \in S'_L, h \in S_H$.*

Proof. To show that $V_O(h,\ell)$ is monotonically nonincreasing in ℓ, we consider the two values $V_O(h,\ell+1)$ can obtain. If $V_O(h,\ell+1) = r_T(h,\ell+1)$, then $V_O(h,\ell) \geq V_O(h,\ell+1)$ because $V_O(h,\ell) \geq r_T(h,\ell) \geq r_T(h,\ell+1)$ by Assumption 1 and (3.3). If $V_O(h,\ell+1) = V_O(h,L+1)$, then $V_O(h,\ell) \geq V_O(h,\ell+1)$ because $V_O(h,\ell) \geq V_O(h,L+1)$ by (3.3). □

Theorem 3.1 *Consider any two sets of OPOs, $O_1 \subseteq O_2 \subseteq \mathcal{I}$. If O_2 dominates O_1, then $V_{O_1}(h,\ell) \leq V_{O_2}(h,\ell)$, for all $(h,\ell) \in S$.*

Proof. We apply the value iteration algorithm to solve the two problems simultaneously and also show that at any iteration of the algorithm $V^i_{O_1}(h,\ell) \leq V^i_{O_2}(h,\ell)$ is preserved for all $(h,\ell) \in S$. Since the value iteration algorithm converges [141], the result will then follow.

For the base case, assume that the value iteration algorithm starts with a value of 0 for each state for both problems. Then:

$$V^1_{O_1}(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, \forall (h,\ell) \in S,$$

$$V^1_{O_2}(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, \forall (h,\ell) \in S.$$

So, the result holds for the base case.

Now assume that for iterations 2 through n the result holds, i.e., $V^i_{O_1}(h,\ell) \leq V^i_{O_2}(h,\ell)$, $\forall (h,\ell) \in S, i = 2,\ldots,n$. Then, for any state $(h,\ell) \in S$,

$$V^{n+1}_{O_1}(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right.$$

$$+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_1}(\ell'|h)}{\lambda_{max}+\alpha}\cdot V^n_{O_1}(h,L+1)$$
$$+\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)\cdot V^n_{O_1}(h',L+1)}{\lambda_{max}+\alpha}+\sum_{\ell'\in S'_L}\frac{\nu_{O_1}(\ell'|h)\cdot V^n_{O_1}(h,\ell')}{\lambda_{max}+\alpha}\Bigg\}, \tag{3.19}$$

and

$$V^{n+1}_{O_2}(h,\ell)=\max\Bigg\{r_T(h,\ell),\frac{r_W(h)}{\lambda_{max}+\alpha}$$
$$+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_2}(\ell'|h)}{\lambda_{max}+\alpha}\cdot V^n_{O_2}(h,L+1)$$
$$+\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)\cdot V^n_{O_2}(h',L+1)}{\lambda_{max}+\alpha}+\sum_{\ell'\in S'_L}\frac{\nu_{O_2}(\ell'|h)\cdot V^n_{O_2}(h,\ell')}{\lambda_{max}+\alpha}\Bigg\}. \tag{3.20}$$

If $r_T(h,\ell)\geq$

$$\frac{r_W(h)}{\lambda_{max}+\alpha}+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_1}(\ell'|h)}{\lambda_{max}+\alpha}\cdot V^n_{O_1}(h,L+1)$$
$$+\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)\cdot V^n_{O_1}(h',L+1)}{\lambda_{max}+\alpha}+\sum_{\ell'\in S'_L}\frac{\nu_{O_1}(\ell'|h)\cdot V^n_{O_1}(h,\ell')}{\lambda_{max}+\alpha}$$

then, $V^{n+1}_{O_1}(h,\ell)=r_T(h,\ell)$ and because $V^{n+1}_{O_2}(h,\ell)\geq r_T(h,\ell)$ by (3.3), and the result follows. Otherwise, as a result of Remark 3.1 we can replace $V^{n+1}_{O_1}(h,\ell)$ with $V^{n+1}_{O_1}(h,L+1)$ to obtain the following:

$V^{n+1}_{O_2}(h,\ell)-V^{n+1}_{O_1}(h,\ell)=V^{n+1}_{O_2}(h,\ell)-V^{n+1}_{O_1}(h,L+1)$

$$\geq \frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_2}(\ell'|h)}{\lambda_{max}+\alpha}V^n_{O_2}(h,L+1)$$
$$-\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_1}(\ell'|h)}{\lambda_{max}+\alpha}V^n_{O_1}(h,L+1)$$
$$+\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)V^n_{O_2}(h',L+1)}{\lambda_{max}+\alpha}-\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)V^n_{O_1}(h',L+1)}{\lambda_{max}+\alpha}$$
$$+\sum_{\ell'\in S'_L}\frac{\nu_{O_2}(\ell'|h)V^n_{O_2}(h,\ell')}{\lambda_{max}+\alpha}-\sum_{\ell'\in S'_L}\frac{\nu_{O_1}(\ell'|h)V^n_{O_1}(h,\ell')}{\lambda_{max}+\alpha}, \tag{3.21}$$

$$\geq \frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_2}(\ell'|h)}{\lambda_{max}+\alpha}V^n_{O_1}(h,L+1)$$

$$
\begin{aligned}
&-\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O_1}(\ell'|h)}{\lambda_{max}+\alpha}V^n_{O_1}(h,L+1)\\
&+\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)V^n_{O_1}(h',L+1)}{\lambda_{max}+\alpha}-\sum_{h'\in S_H\setminus\{h\}}\frac{\mu(h'|h)V^n_{O_1}(h',L+1)}{\lambda_{max}+\alpha}+\\
&+\sum_{\ell'\in S'_L}\frac{\nu_{O_2}(\ell'|h)V^n_{O_1}(h,\ell')}{\lambda_{max}+\alpha}-\sum_{\ell'\in S'_L}\frac{\nu_{O_1}(\ell'|h)V^n_{O_1}(h,\ell')}{\lambda_{max}+\alpha},
\end{aligned}
\tag{3.22}
$$

$$
\begin{aligned}
&= \frac{\sum_{\ell'\in S'_L}\Big(\nu_{O_2}(\ell'|h)-\nu_{O_1}(\ell'|h)\Big)\Big(V^n_{O_1}(h,\ell')-V^n_{O_1}(h,L+1)\Big)}{\lambda_{max}+\alpha},\\
&\geq 0.
\end{aligned}
\tag{3.23}
$$

We replace $V^n_{O_2}(h,\ell)$ by $V^n_{O_1}(h,\ell), \forall (h,\ell)\in S$ in (3.21) without violating the inequality because $V^n_{O_2}(h,\ell)\geq V^n_{O_1}(h,\ell), \forall (h,\ell)\in S$ by the induction hypothesis. As $\sum_{\ell'\in S'_L}\Big(\nu_{O_2}(\ell'|h)$ $-\nu_{O_1}(\ell'|h)\Big)\geq 0$ by Definition 3.1, $V^n_{O_1}(h,\ell')$ is nondecreasing in ℓ' by Lemma 3.1 and $V^n_{O_1}(h,\ell')\geq V^n_{O_1}(h,L+1)$ by Remark 3.1, (3.23) ≥ 0 is a direct result from Lemma 4.7.2 in Puterman [141]. □

Satisfaction of Theorem 3.1 depends on the super OPO set (O_2) dominating the sub OPO set (O_1). According to the organ offer arrival rate definition, a patient sacrifices regional offer arrival rates in order to benefit from local offer arrival rates, if she is listed in OPOs that belong to the same region. However, if she is listed in OPOs in different regions, she does not sacrifice any regional offers; i.e., she is offered organs as if she is singly listed in all of the OPOs in which she is listed. Therefore, the dominance condition in Theorem 3.1 holds trivially when OPOs in $O_2\setminus O_1$ belong to regions to which OPOs in O_1 do not belong. Hence, we are interested in investigating instances where regions to which OPOs in $O_2\setminus O_1$ belong include at least one of the regions in $\mathcal{R}(O_1)$.

From Proposition 3.2 and without loss of generality, O_2 dominates O_1 if $\{(O_2\setminus O_1)\cup i\}$ dominates $\{i\}, i\in O_1$. From Proposition 3.1, $\{(O_2\setminus O_1)\cup i\}$ dominates $\{i\}, i\in O_1$ if $\{i,k\}$ dominates $\{i\}$ and $\{(O_2\setminus O_1)\cup i\}$ dominates $\{i,k\}, i\in O_1, k\in (O_2\setminus O_1)$. Again from Proposition 3.2 $\{(O_2\setminus O_1)\cup i\}$ dominates $\{i,k\}$ if $\{(O_2\setminus O_1)\cup i\}\setminus\{k\}$ dominates $\{i\}, i\in O_1, k\in (O_2\setminus O_1)$. Iteratively utilizing Propositions 3.2 and 3.1 as above leads to the

observation that ensuring if the dominance relationship holds between two OPO sets such that $O_1 = \{i\}, O_2 = \{i, j\}, \mathcal{R}(i) = \mathcal{R}(j)$ represents checking if the dominance relationship holds between all possible pairs of OPO sets such that $O_1 \subseteq O_2$. In other words, the numerical experiments in which $O_1 = \{i\}, O_2 = \{i, j\}, \mathcal{R}(i) = \mathcal{R}(j)$ are representative of the dominance relationships between all possible OPO sets based on Proposition 3.1 and Proposition 3.2. There are 103 instances in which $O_1 = \{i\}, O_2 = \{i, j\}, \mathcal{R}(i) = \mathcal{R}(j)$. The dominance condition is satisfied approximately 96% of those instances. Therefore, we conclude that assuming that an OPO set dominates its subsets is valid.

For the rest of this chapter, we assume that if $O_1 \subseteq O_2$, then O_2 dominates O_1. Therefore, we assume that Theorem 3.1 holds for the rest of this chapter.

Corollary 3.1 shows that the patient becomes more selective if she lists in additional OPO(s). That is, if a patient receives more frequent, higher-quality liver offers from a particular OPO, then being listed in that OPO, she accepts fewer higher-quality livers.

Corollary 3.1 *Consider any two sets of OPOs,* $O_1 \subseteq O_2 \subseteq \mathcal{I}$. *Then* $S_L(O_1, h, T) \supseteq S_L(O_2, h, T)$.

Proof. Note that $S_L(O_1, h, T) = \left\{\ell \in S'_L \middle| r_T(h, \ell) > V_{O_1}(h, L+1)\right\}$ and that $S_L(O_2, h, T) = \left\{\ell \in S'_L \middle| r_T(h, \ell) > V_{O_2}(h, L+1)\right\}$. From Theorem 3.1, $V_{O_1}(h, L+1) \leq V_{O_2}(h, L+1)$ because $O_1 \subseteq O_2$. So, if $\ell \in S_L(O_2, h, T)$, then $\ell \in S_L(O_2, h, T)$. Therefore, $S_L(O_1, h, T) \supseteq S_L(O_2, h, T)$. □

3.3.1 Submodularity

In this section, we explore the submodularity of the value function. Definition 3.2 presents the definition of submodularity [124] in terms of value functions attained through being listed in different OPO sets. Theorem 3.2 establishes a submodularity result for the value function under certain conditions.

Note that submodularity (subadditivity) is defined differently for MDPs in general. Puterman [141] defines submodularity in terms of the states of the MDP. However, in this dissertation, we study the submodularity of the value function for different listing decisions rather than for different health states and liver qualities. In other words, we consider the

notion of submodularity as it is defined in the context of discrete optimization [124]. It is in a sense a discrete analogue of convexity.

Definition 3.2 *Let O be a set of OPOs. $V_O(h,\ell)$ is submodular if $V_{O\cup\{j\}}(h,\ell) - V_O(h,\ell) \geq V_{O\cup\{j,k\}}(h,\ell) - V_{O\cup\{k\}}(h,\ell)$ for all $(h,\ell) \in S$.*

Intuitively, submodularity can be regarded as the diminishing returns property; and therefore, it states that the patient's life expectancy would increase more by listing in an additional OPO if she is currently listed in a smaller OPO set.

$V_O(h,\ell)$ is not submodular in general. This can be shown by illustrating that it may be optimal to transplant when the patient is listed in $O, O\cup\{j\}$ and/or $O\cup\{k\}$ but it is optimal to wait when she is listed in $O\cup\{j,k\}$, an OPO set that is a superset of $O, O\cup\{j\}$ and $O\cup\{k\}$. We show these cases numerically in Section 3.5.3.

Lemma 3.2 *Consider any set of OPOs $O \subset \mathcal{I}$ and $j,k \in \mathcal{I}\setminus O$. Then*

$$\nu_{O\cup\{j\}}(\ell|h) + \nu_{O\cup\{k\}}(\ell|h) \geq \nu_O(\ell|h) + \nu_{O\cup\{j,k\}}(\ell|h), \;\; h \in S_H, \ell \in S'_L. \tag{3.24}$$

Proof. Recall the following definitions for an OPO set O, OPO j, health state $h \in S_H$ and liver type $\ell \in S'_L$:

$$\nu_O(\ell|h) = \sum_{R\in\mathcal{R}(O)} \left[\left(\sum_{i\in O, \mathcal{R}(i)=R} \xi_i(\ell|h) + \sum_{m\notin O, \mathcal{R}(m)=R} \theta_m(\ell|h) \right) \right], \tag{3.10}$$

$$\omega_j(\ell|h) = \xi_j(\ell|h) + \sum_{m\in\mathcal{I}, \mathcal{R}(m)=\mathcal{R}(j)} \theta_m(\ell|h). \tag{3.11}$$

Based on the regions to which OPOs i and j belong, there are five cases to consider.
Case 1: $\mathcal{R}(j), \mathcal{R}(k) \notin \mathcal{R}(O)$ and $\mathcal{R}(j) \neq \mathcal{R}(k)$: In this case, by adding OPO j and/or OPO k to OPO set O, a patient receives organ offers from OPO j and/or OPO k as if she is singly listed in those OPOs. This is due to the fact that neither OPO j nor OPO k belong to one of the regions in which she is listed and also OPO j and OPO k belong to different regions. Therefore,

$$\nu_{O\cup\{j\}}(\ell|h) = \nu_O(\ell|h) + \omega_j(\ell|h), h \in S_H, \ell \in S'_L,$$

$$\nu_{O\cup\{k\}}(\ell|h) = \nu_O(\ell|h) + \omega_k(\ell|h), h \in S_H, \ell \in S'_L,$$
$$\nu_{O\cup\{j,k\}}(\ell|h) = \nu_O(\ell|h) + \omega_j(\ell|h) + \omega_k(\ell|h), h \in S_H, \ell \in S'_L.$$

So, $\nu_{O\cup\{j\}}(\ell|h) + \nu_{O\cup\{k\}}(\ell|h) - \nu_O(\ell|h) - \nu_{O\cup\{j,k\}}(\ell|h)$

$$\begin{aligned} = \quad & \nu_O(\ell|h) + \omega_j(\ell|h) + \nu_O(\ell|h) + \omega_k(\ell|h) \\ & -\nu_O(\ell|h) - \Big(\nu_O(\ell|h) + \omega_j(\ell|h) + \omega_k(\ell|h)\Big), h \in S_H, \ell \in S'_L, \\ = \quad & 0. \end{aligned}$$

Case 2: $\mathcal{R}(j), \mathcal{R}(k) \notin \mathcal{R}(O)$ *and* $\mathcal{R}(j) = \mathcal{R}(k)$: In this case, by adding OPO $j(k)$ to OPO set O, a patient receives organ offers from OPO $j(k)$ as if she is singly listed in OPO $j(k)$. Suppose the patient lists in $O \cup \{j\}$ ($O \cup \{k\}$). Then, by listing in OPO k (j) additionally, she will sacrifice the regional offers she used to receive from OPO k (j). Note that since OPO j and OPO k are in the same region, by adding OPO k (j) to her listing set, she is additionally eligible for organs harvested locally in OPO k (j). So,

$$\begin{aligned} \nu_{O\cup\{j\}}(\ell|h) = \quad & \nu_O(\ell|h) + \omega_j(\ell|h), h \in S_H, \ell \in S'_L, \\ \nu_{O\cup\{k\}}(\ell|h) = \quad & \nu_O(\ell|h) + \omega_k(\ell|h), h \in S_H, \ell \in S'_L, \\ \nu_{O\cup\{j,k\}}(\ell|h) = \quad & \nu_O(\ell|h) + \omega_j(\ell|h) + \omega_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h) \\ & - \sum_{m\notin\{j,k\}, \mathcal{R}(m)=\mathcal{R}(j)} \theta_m(\ell|h), h \in S_H, \ell \in S'_L. \end{aligned}$$

So, $\nu_{O\cup\{j\}}(\ell|h) + \nu_{O\cup\{k\}}(\ell|h) - \nu_O(\ell|h) - \nu_{O\cup\{j,k\}}(\ell|h)$

$$\begin{aligned} = \quad & \nu_O(\ell|h) + \omega_j(\ell|h) + \nu_O(\ell|h) + \omega_k(\ell|h) \\ & -\nu_O(\ell|h) - \Big(\nu_O(\ell|h) + \omega_j(\ell|h) + \omega_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h) \\ & - \sum_{m\notin\{j,k\}, \mathcal{R}(m)=\mathcal{R}(j)} \theta_m(\ell|h)\Big), h \in S_H, \ell \in S'_L, \\ \geq \quad & 0. \end{aligned}$$

Case 3: $\mathcal{R}(j) \in \mathcal{R}(O), \mathcal{R}(k) \notin \mathcal{R}(O)$: In this case, by adding OPO j to OPO set O, a patient receives organ offers from OPO j with a local rate, instead of a regional rate, because OPO j is in one of the regions in which she is listed. However, if she lists in OPO k in addition to

OPO set O, then she receives organ offers from OPO k as if she is singly listed in OPO k. So, the organ offer arrival rates at different OPO sets are characterized as follows:

$$\begin{aligned}
&\nu_{O\cup\{j\}}(\ell|h) = \nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h), h \in S_H, \ell \in S'_L,\\
&\nu_{O\cup\{k\}}(\ell|h) = \nu_O(\ell|h) + \omega_k(\ell|h), h \in S_H, \ell \in S'_L,\\
&\nu_{O\cup\{j,k\}}(\ell|h) = \nu_O(\ell|h) + \xi_j(\ell|h) + \omega_k(\ell|h) - \theta_j(\ell|h), h \in S_H, \ell \in S'_L.
\end{aligned}$$

Therefore, $\nu_{O\cup\{j\}}(\ell|h) + \nu_{O\cup\{k\}}(\ell|h) - \nu_O(\ell|h) - \nu_{O\cup\{j,k\}}(\ell|h)$

$$\begin{aligned}
= \;& \nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h) + \nu_O(\ell|h) + \omega_k(\ell|h)\\
& -\nu_O(\ell|h) - \Big(\nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h) + \omega_k(\ell|h)\Big), h \in S_H, \ell \in S'_L,\\
= \;& 0.
\end{aligned}$$

Case 4: $\mathcal{R}(j) \notin \mathcal{R}(O), \mathcal{R}(k) \in \mathcal{R}(O)$: This case is identical to *Case 3* and therefore omitted.

Case 5: $\mathcal{R}(j), \mathcal{R}(k) \in \mathcal{R}(O)$: If both OPOs are in one of the regions to which OPOs in O belong, then by listing in OPO j and/or OPO k, a patient receives organ offers from OPO j and/or OPO k with a local rate instead of a regional rate. Therefore,

$$\begin{aligned}
&\nu_{O\cup\{j\}}(\ell|h) = \nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h), h \in S_H, \ell \in S'_L,\\
&\nu_{O\cup\{k\}}(\ell|h) = \nu_O(\ell|h) + \xi_k(\ell|h) - \theta_k(\ell|h), h \in S_H, \ell \in S'_L,\\
&\nu_{O\cup\{j,k\}}(\ell|h) = \nu_O(\ell|h) + \xi_j(\ell|h) + \xi_k(\ell|h) - \theta_j(\ell|h) - \theta_k(\ell|h), h \in S_H, \ell \in S'_L.
\end{aligned}$$

So, $\nu_{O\cup\{j\}}(\ell|h) + \nu_{O\cup\{k\}}(\ell|h) - \nu_O(\ell|h) - \nu_{O\cup\{j,k\}}(\ell|h)$

$$\begin{aligned}
= \;& \nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h) + \nu_O(\ell|h) + \xi_k(\ell|h) - \theta_k(\ell|h)\\
& -\nu_O(\ell|h) - \Big(\nu_O(\ell|h) + \xi_j(\ell|h) - \theta_j(\ell|h) + \xi_k(\ell|h) - \theta_k(\ell|h)\Big), h \in S_H, \ell \in S'_L,\\
= \;& 0. \;\square
\end{aligned}$$

Lemma 3.3 *Consider any set of OPOs $O \subset \mathcal{I}$. Then*

$$V_O(h, L+1) \geq \mathcal{B}(h), h \in S_H, \tag{3.25}$$

where,

$$\mathcal{B}(h) = \frac{r_W(h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) r_T(h, \ell')}{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) + \alpha}.$$

Proof. From Equation (3.3) and Remark 3.1, $V_O(h, L+1) =$

$$\frac{r_W(h)}{\lambda_{max} + \alpha} + \frac{\lambda_{max} - \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) - \sum_{\ell' \in S'_L} \nu_O(\ell'|h)}{\lambda_{max} + \alpha} V_O(h, L+1) + \frac{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) V_O(h', L+1)}{\lambda_{max} + \alpha} + \frac{\sum_{\ell' \in S'_L} \nu_O(\ell'|h) V_O(h, \ell')}{\lambda_{max} + \alpha}, \tag{3.26}$$

So, $\left(1 - \frac{\lambda_{max} - \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) - \sum_{\ell' \in S'_L} \nu_O(\ell'|h)}{\lambda_{max} + \alpha}\right) V_O(h, L+1) =$

$$\frac{r_W(h)}{\lambda_{max} + \alpha} + \frac{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) V_O(h', L+1)}{\lambda_{max} + \alpha} + \frac{\sum_{\ell' \in S'_L} \nu_O(\ell'|h) V_O(h, \ell')}{\lambda_{max} + \alpha}, \tag{3.27}$$

$$\Rightarrow \left(\frac{\alpha + \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h)}{\lambda_{max} + \alpha}\right) V_O(h, L+1) =$$

$$\frac{r_W(h)}{\lambda_{max} + \alpha} + \frac{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) V_O(h', L+1)}{\lambda_{max} + \alpha} + \frac{\sum_{\ell' \in S'_L} \nu_O(\ell'|h) V_O(h, \ell')}{\lambda_{max} + \alpha}, \tag{3.28}$$

Therefore, $V_O(h, L+1) =$

$$\frac{r_W(h) + \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) V_O(h', L+1) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) V_O(h, \ell')}{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) + \alpha}, \tag{3.29}$$

$$\geq \frac{r_W(h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) V_O(h, \ell')}{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) + \alpha} \tag{3.30}$$

$$\geq \frac{r_W(h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) r_T(h, \ell')}{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) + \sum_{\ell' \in S'_L} \nu_O(\ell'|h) + \alpha} = \mathcal{B}(h). \tag{3.31}$$

As removing nonnegative terms do not increase the overall value, (3.29) $\geq$ (3.30). From Equation (3.3), $V_O(h, \ell) \geq r_T(h, \ell)$, so (3.31) follows. □

Theorem 3.2 *Consider any set of OPOs $O \subset \mathcal{I}$ and $j, k \in \mathcal{I} \setminus O$. $V_O(h, \ell)$ is submodular if the following condition holds:*

$$r_T(h, \ell) \leq \frac{\lambda_{max} - \sum_{h' \in S_H \setminus \{h\}} \mu(h'|h)}{\lambda_{max} + \alpha} \mathcal{B}(h) + \frac{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h) \mathcal{B}(h')}{\lambda_{max} + \alpha}$$

$$+\frac{r_W(h)}{\lambda_{max}+\alpha},\ \ h \in S_H, \ell \in S_L. \tag{3.32}$$

where $\mathcal{B}(h)$ is the ratio of total reward in health state h (sum of the immediate reward and the expected post-transplant reward over all liver qualities) to the total rate out of state $(h, L+1)$.

Proof. We apply the value iteration algorithm to solve MDPs corresponding to all OPO sets $(O, O\cup\{j\}, O\cup\{k\}, O\cup\{j,k\})$ simultaneously, and show that at any iteration of the algorithm $V_{O\cup\{j\}}(h,\ell) - V_O(h,\ell) \geq V_{O\cup\{j,k\}}(h,\ell) - V_{O\cup\{k\}}(h,\ell)$ is preserved for all $(h,\ell) \in S$. We assume that $\lambda_{max} = \max_{h\in S_H} \gamma_{O\cup\{j,k\}}(h, L+1)$.

For the base case, assume that the value iteration algorithm starts with a value of 0 for each state for all problems, i.e.,:

$$V_O^1(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, (h,\ell) \in S,$$
$$V_{O\cup\{j\}}^1(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, (h,\ell) \in S,$$
$$V_{O\cup\{k\}}^1(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, (h,\ell) \in S,$$

$$V_{O\cup\{j,k\}}^1(h,\ell) = \max\left\{r_T(h,\ell), \frac{r_W(h)}{\lambda_{max}+\alpha}\right\}, (h,\ell) \in S.$$

So, the result holds for all $(h,\ell) \in S$ for the base case.

Now assume that $V_{O\cup\{j\}}^i(h,\ell) - V_O^i(h,\ell) \geq V_{O\cup\{j,k\}}^i(h,\ell) - V_{O\cup\{k\}}^i(h,\ell), \forall (h,\ell) \in S, i = 2,\ldots,n$. Then, there are two cases based on the optimal decision in $O\cup\{j,k\}$.

Case 1: $V_{O\cup\{j,k\}}^{n+1}(h,\ell) = r_T(h,\ell)$ (i.e. transplant in $O\cup\{j,k\}$ on iteration $n+1$ of value iteration)

For any (h,ℓ), if $V_{O\cup\{j,k\}}^{n+1}(h,\ell) = r_T(h,\ell)$, then $V_O^{n+1}(h,\ell) = V_{O\cup\{j\}}^{n+1}(h,\ell) = V_{O\cup\{k\}}^{n+1}(h,\ell) = r_T(h,\ell)$, because $r_T(h,\ell) \geq V_{O\cup\{j,k\}}^{n+1}(h, L+1)$ by Remark 3.1 and $V_{O\cup\{j,k\}}^{n+1}(h, L+1) \geq V_O^{n+1}(h, L+1)$, $V_{O\cup\{j,k\}}^{n+1}(h, L+1) \geq V_{O\cup\{j\}}^{n+1}(h, L+1)$, $V_{O\cup\{j,k\}}^{n+1}(h, L+1) \geq V_{O\cup\{k\}}^{n+1}(h, L+1)$ by Theorem 3.1. So, $V_O(h,\ell)$ is submodular.

Case 2: $V^{n+1}_{O\cup\{j,k\}}(h,\ell) = V^{n+1}_{O\cup\{j,k\}}(h, L+1)$ *(i.e. wait in* $O\cup\{j,k\}$ *on iteration n+1 of value iteration)*

By Remark 3.1,

$$\begin{aligned} & V^{n+1}_{O\cup\{j\}}(h,\ell) - V^{n+1}_{O}(h,\ell) - V^{n+1}_{O\cup\{j,k\}}(h,\ell) + V^{n+1}_{O\cup\{k\}}(h,\ell) \\ = \; & V^{n+1}_{O\cup\{j\}}(h,\ell) - V^{n+1}_{O}(h,\ell) - V^{n+1}_{O\cup\{j,k\}}(h, L+1) + V^{n+1}_{O\cup\{k\}}(h,\ell) \end{aligned}$$

Now there are two cases to consider based on the optimal decision in O.

Case 2.1: $V^{n+1}_{O}(h,\ell) = V^{n+1}_{O}(h, L+1)$ *(i.e. wait in* O *on iteration n+1 of value iteration)*

In this case, $V^{n+1}_{O\cup\{j\}}(h,\ell) = V^{n+1}_{O\cup\{j\}}(h, L+1)$ because $V^{n+1}_{O\cup\{j\}}(h, L+1) \geq V^{n+1}_{O}(h, L+1) \geq r_T(h,\ell)$. Similarly, $V^{n+1}_{O\cup\{k\}}(h,\ell) = V^{n+1}_{O\cup\{k\}}(h, L+1)$. Therefore,

$$\begin{aligned} & V^{n+1}_{O\cup\{j\}}(h,\ell) - V^{n+1}_{O}(h,\ell) - V^{n+1}_{O\cup\{j,k\}}(h, L+1) + V^{n+1}_{O\cup\{k\}}(h,\ell) \\ = \; & V^{n+1}_{O\cup\{j\}}(h, L+1) - V^{n+1}_{O}(h, L+1) - V^{n+1}_{O\cup\{j,k\}}(h, L+1) + V^{n+1}_{O\cup\{k\}}(h, L+1) \end{aligned}$$

$$\begin{aligned} = \; & \frac{r_W(h)}{\lambda_{max}+\alpha} + \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) - \sum_{\ell'\in S'_L} \nu_{O\cup\{j\}}(\ell'|h)}{\lambda_{max}+\alpha} V^n_{O\cup\{j\}}(h, L+1) \\ & + \frac{\sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) V^n_{O\cup\{j\}}(h', L+1)}{\lambda_{max}+\alpha} + \frac{\sum_{\ell'\in S'_L} \nu_{O\cup\{j\}}(\ell'|h) V^n_{O\cup\{j\}}(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.33) \\ & - \frac{r_W(h)}{\lambda_{max}+\alpha} - \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) - \sum_{\ell'\in S'_L} \nu_{O}(\ell'|h)}{\lambda_{max}+\alpha} V^n_{O}(h, L+1) \\ & - \frac{\sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) V^n_{O}(h', L+1)}{\lambda_{max}+\alpha} - \frac{\sum_{\ell'\in S'_L} \nu_{O}(\ell'|h) V^n_{O}(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.34) \\ & - \frac{r_W(h)}{\lambda_{max}+\alpha} - \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) - \sum_{\ell'\in S'_L} \nu_{O\cup\{j,k\}}(\ell'|h)}{\lambda_{max}+\alpha} V^n_{O\cup\{j,k\}}(h, L+1) \\ & - \frac{\sum_{h'\in S_H\setminus\{h\}} \mu(h'|h) V^n_{O\cup\{j,k\}}(h', L+1)}{\lambda_{max}+\alpha} - \frac{\sum_{\ell'\in S'_L} \nu_{O\cup\{j,k\}}(\ell'|h) V^n_{O\cup\{j,k\}}(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.35) \end{aligned}$$

$$+\frac{r_W(h)}{\lambda_{max}+\alpha}+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_{O\cup\{k\}}(\ell'|h)}{\lambda_{max}+\alpha}V^n_{O\cup\{k\}}(h,L+1)$$

$$+\frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)V^n_{O\cup\{k\}}(h',L+1)}{\lambda_{max}+\alpha}+\frac{\sum_{\ell'\in S'_L}\nu_{O\cup\{k\}}(\ell'|h)V^n_{O\cup\{k\}}(h,\ell')}{\lambda_{max}+\alpha} \tag{3.36}$$

We rewrite $\nu_{O\cup\{j\}}(\ell|h)=\nu_{O\cup\{j\}}(\ell|h)-\nu_O(\ell|h)+\nu_O(\ell|h)$, $\nu_{O\cup\{k\}}(\ell|h)=\nu_{O\cup\{k\}}(\ell|h)-\nu_O(\ell|h)+\nu_O(\ell|h)$, and $\nu_{O\cup\{j,k\}}(\ell|h)=\nu_{O\cup\{j,k\}}(\ell|h)-\nu_O(\ell|h)+\nu_O(\ell|h)$ and rearrange terms to obtain the following:

$$\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)-\sum_{\ell'\in S'_L}\nu_O(\ell'|h)}{\lambda_{max}+\alpha}\Big(V^n_{O\cup\{j\}}(h,L+1)-V^n_O(h,L+1)$$
$$-V^n_{O\cup\{j,k\}}(h,L+1)+V^n_{O\cup\{k\}}(h,L+1)\Big) \tag{3.37}$$
$$+\frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)}{\lambda_{max}+\alpha}\Big(V^n_{O\cup\{j\}}(h',L+1)-V^n_O(h',L+1)-V^n_{O\cup\{j,k\}}(h',L+1)$$
$$+V^n_{O\cup\{k\}}(h',L+1)\Big) \tag{3.38}$$
$$+\frac{\sum_{\ell'\in S'_L}\nu_O(\ell'|h)\Big(V^n_{O\cup\{j\}}(h,\ell')-V^n_O(h,\ell')-V^n_{O\cup\{j,k\}}(h,\ell')+V^n_{O\cup\{k\}}(h,\ell')\Big)}{\lambda_{max}+\alpha} \tag{3.39}$$
$$+\frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{j\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{j\}}(h,\ell')-V^n_{O\cup\{j\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} \tag{3.40}$$
$$+\frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{k\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{k\}}(h,\ell')-V^n_{O\cup\{k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} \tag{3.41}$$
$$-\frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{j,k\}}(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha}. \tag{3.42}$$

Due to the inductive hypothesis (3.37)+(3.38)+(3.39) ≥ 0. Therefore, we get rid of these equations without violating the inequality. So, (3.37)-(3.42)

$$\geq \frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{j\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{j\}}(h,\ell')-V^n_{O\cup\{j\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} \tag{3.43}$$
$$+\frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{k\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{k\}}(h,\ell')-V^n_{O\cup\{k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} \tag{3.44}$$
$$-\frac{\sum_{\ell'\in S'_L}\Big(\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)\Big)\Big(V^n_{O\cup\{j,k\}}(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha}. \tag{3.45}$$

We decompose (3.43),(3.44) and (3.45) into two sets of summations as $\ell \in S_L(O\cup\{j,k\},h,T)$ and $\ell \notin S_L(O\cup\{j,k\},h,T)$. Note that if $\ell \notin S_L(O\cup\{j,k\},h,T)$, then $V^n_{O\cup\{j,k\}}(h,\ell) = V^n_{O\cup\{j,k\}}(h,L+1)$. If $\ell \in S_L(O\cup\{j,k\},h,T)$, then $V^n_{O\cup\{j,k\}}(h,\ell) = r_T(h,\ell)$, and therefore, $V^n_{O\cup\{j\}}(h,\ell) = V^n_{O\cup\{k\}}(h,\ell) = r_T(h,\ell)$ by Remark 3.1 and Theorem 3.1. Therefore, (3.43)-(3.45) is rewritten as:

$$
\begin{aligned}
= & \frac{\sum_{\ell'\notin S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(V^n_{O\cup\{j\}}(h,\ell')-V^n_{O\cup\{j\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.46)\\
& +\frac{\sum_{\ell'\notin S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{k\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(V^n_{O\cup\{k\}}(h,\ell')-V^n_{O\cup\{k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.47)\\
& -\frac{\sum_{\ell'\notin S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)]}{\lambda_{max}+\alpha}\Big(V^n_{O\cup\{j,k\}}(h,L+1)-V^n_{O\cup\{j,k\}}(h,L+1)\Big) && (3.48)\\
& +\frac{\sum_{\ell'\in S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(r_T(h,\ell')-V^n_{O\cup\{j\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.49)\\
& +\frac{\sum_{\ell'\in S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{k\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(r_T(h,\ell')-V^n_{O\cup\{k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.50)\\
& -\frac{\sum_{\ell'\in S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(r_T(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha}. && (3.51)
\end{aligned}
$$

As (3.48) $= 0$ and (3.46) ≥ 0, (3.47) ≥ 0 by Equation (3.3), these terms can be removed without violating the inequality. Let $\bar{V}^n(h,L+1) = \max\left\{V^n_{O\cup\{j\}}(h,L+1), V^n_{O\cup\{k\}}(h,L+1)\right\}$, $h \in S_H$. In (3.49) and (3.50), $V^n_{O\cup\{j\}}(h,L+1)$ and $V^n_{O\cup\{k\}}(h,L+1)$ can be replaced with $\bar{V}^n(h,L+1)$. Then it is clear that (3.52) $\leq$ (3.49)+(3.50). Therefore, (3.46)-(3.51)

$$
\begin{aligned}
\geq & \frac{\sum_{\ell'\in S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j\}}(\ell'|h)+\nu_{O\cup\{k\}}(\ell'|h)-2\nu_O(\ell'|h)]\Big(r_T(h,\ell')-\bar{V}^n(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.52)\\
& -\frac{\sum_{\ell'\in S_L(O\cup\{j,k\},h,T)}[\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)]\Big(r_T(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} && (3.53)
\end{aligned}
$$

From Lemma 3.2, $[\nu_{O\cup\{j\}}(\ell'|h)+\nu_{O\cup\{k\}}(\ell'|h)-2\nu_O(\ell'|h)] \geq [\nu_{O\cup\{j,k\}}(\ell'|h)-\nu_O(\ell'|h)]$, $h \in S_H, \ell \in S_L(O\cup\{j,k\},h,T)$ and $\Big(r_T(h,\ell')-\bar{V}^n(h,L+1)\Big) \geq \Big(r_T(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)$ because $\bar{V}^n(h,L+1) \leq V^n_{O\cup\{j,k\}}(h,L+1)$ by Theorem 3.1. Then (3.52) + (3.53) ≥ 0. So, the value function is submodular in this case.

Case 2.2: $V_O^{n+1}(h,\ell) = r_T(h,\ell)$ (i.e. transplant in O on iteration $n+1$ of value iteration)
Note that if $V_{O\cup\{j\}}^{n+1}(h,\ell) = r_T(h,\ell)$ and/or $V_{O\cup\{k\}}^{n+1}(h,\ell) = r_T(h,\ell)$, then the value function is not submodular. Therefore, we need to impose a strong condition for the value function to be submodular in this case.

$$\begin{aligned} & V_{O\cup\{j\}}^{n+1}(h,\ell) - V_O^{n+1}(h,\ell) - V_{O\cup\{j,k\}}^{n+1}(h,L+1) + V_{O\cup\{k\}}^{n+1}(h,\ell) \\ \geq\ & V_{O\cup\{j\}}^{n+1}(h,L+1) - r_T(h,\ell) - V_{O\cup\{j,k\}}^{n+1}(h,L+1) + V_{O\cup\{k\}}^{n+1}(h,L+1) \end{aligned}$$

$$\begin{aligned} =\ & \frac{r_W(h)}{\lambda_{max}+\alpha} + \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}}\mu(h'|h) - \sum_{\ell'\in S_L'}\nu_{O\cup\{j\}}(\ell'|h)}{\lambda_{max}+\alpha} V_{O\cup\{j\}}^n(h,L+1) \\ & + \frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)V_{O\cup\{j\}}^n(h',L+1)}{\lambda_{max}+\alpha} + \frac{\sum_{\ell'\in S_L'}\nu_{O\cup\{j\}}(\ell'|h)V_{O\cup\{j\}}^n(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.54) \\ & - r_T(h,\ell) - \frac{r_W(h)}{\lambda_{max}+\alpha} - \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}}\mu(h'|h) - \sum_{\ell'\in S_L'}\nu_{O\cup\{j,k\}}(\ell'|h)}{\lambda_{max}+\alpha} V_{O\cup\{j,k\}}^n(h,L+1) \\ & - \frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)V_{O\cup\{j,k\}}^n(h',L+1)}{\lambda_{max}+\alpha} - \frac{\sum_{\ell'\in S_L'}\nu_{O\cup\{j,k\}}(\ell'|h)V_{O\cup\{j,k\}}^n(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.55) \\ & + \frac{r_W(h)}{\lambda_{max}+\alpha} + \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}}\mu(h'|h) - \sum_{\ell'\in S_L'}\nu_{O\cup\{k\}}(\ell'|h)}{\lambda_{max}+\alpha} V_{O\cup\{k\}}^n(h,L+1) \\ & + \frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)V_{O\cup\{k\}}^n(h',L+1)}{\lambda_{max}+\alpha} + \frac{\sum_{\ell'\in S_L'}\nu_{O\cup\{k\}}(\ell'|h)V_{O\cup\{k\}}^n(h,\ell')}{\lambda_{max}+\alpha} \qquad (3.56) \\ =\ & \frac{r_W(h)}{\lambda_{max}+\alpha} - r_T(h,\ell) + \frac{\lambda_{max} - \sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)}{\lambda_{max}+\alpha}\Big(V_{O\cup\{j\}}^n(h,L+1) \\ & \qquad - V_{O\cup\{j,k\}}^n(h,L+1) + V_{O\cup\{k\}}^n(h,L+1)\Big) \qquad (3.57) \\ & + \frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)\Big(V_{O\cup\{j\}}^n(h',L+1) - V_{O\cup\{j,k\}}^n(h',L+1) + V_{O\cup\{k\}}^n(h',L+1)\Big)}{\lambda_{max}+\alpha} \qquad (3.58) \\ & + \frac{\sum_{\ell'\in S_L'}\nu_{O\cup\{j\}}(\ell'|h)\Big(V_{O\cup\{j\}}^n(h,\ell') - V_{O\cup\{j\}}^n(h,L+1)\Big)}{\lambda_{max}+\alpha} \qquad (3.59) \end{aligned}$$

$$+\frac{\sum_{\ell'\in S'_L}\nu_{O\cup\{k\}}(\ell'|h)\Big(V^n_{O\cup\{k\}}(h,\ell')-V^n_{O\cup\{k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha} \tag{3.60}$$

$$-\frac{\sum_{\ell'\in S'_L}\nu_{O\cup\{j,k\}}(\ell'|h)\Big(V^n_{O\cup\{j,k\}}(h,\ell')-V^n_{O\cup\{j,k\}}(h,L+1)\Big)}{\lambda_{max}+\alpha}. \tag{3.61}$$

Equations (3.59), (3.60), (3.61) can be decomposed into two sets of sums as $\ell \in S_L(O\cup\{j,k\},h,T)$ and $\ell \notin S_L(O\cup\{j,k\},h,T)$. Similarly to *Case 1*, (3.59)+(3.60)+(3.61) is nonzero because $\nu_{O\cup\{j\}}(\ell|h)+\nu_{O\cup\{k\}}(\ell|h)\geq\nu_{O\cup\{j,k\}}(\ell|h)$, $h\in S_H,\ell\in S'_L$ by Lemma 3.2 and $V^n_{O\cup\{j\}}(h,L+1)\leq V^n_{O\cup\{j,k\}}(h,L+1), V^n_{O\cup\{k\}}(h,L+1)\leq V^n_{O\cup\{j,k\}}(h,L+1)$ by Remark 3.1. In Equation (3.57), $\Big(V^n_{O\cup\{j\}}(h,L+1)-V^n_{O\cup\{j,k\}}(h,L+1)+V^n_{O\cup\{k\}}(h,L+1)\Big)$ can be replaced with $V^n_O(h,L+1)$ by the inductive argument. Similarly, in Equation (3.58), $\Big(V^n_{O\cup\{j\}}(h',L+1)-V^n_{O\cup\{j,k\}}(h',L+1)+V^n_{O\cup\{k\}}(h',L+1)\Big)$ can be replaced with $V^n_O(h',L+1)$. So, (3.57)-(3.61)

$$\begin{aligned}
&\geq \frac{r_W(h)}{\lambda_{max}+\alpha}-r_T(h,\ell)\\
&\quad+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)}{\lambda_{max}+\alpha}V^n_O(h,L+1)+\frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)V^n_O(h',L+1)}{\lambda_{max}+\alpha} &(3.62)\\
&\geq \frac{r_W(h)}{\lambda_{max}+\alpha}-r_T(h,\ell)\\
&\quad+\frac{\lambda_{max}-\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)}{\lambda_{max}+\alpha}\mathcal{B}(h)+\frac{\sum_{h'\in S_H\setminus\{h\}}\mu(h'|h)\mathcal{B}(h')}{\lambda_{max}+\alpha} &(3.63)\\
&\geq 0. &(3.64)
\end{aligned}$$

Equation (3.63) follows from Lemma 3.3 and (3.64) follows from Condition (3.32).□

3.3.2 Complexity

We are interested in exploring the complexity of the multiple listing problem as it is a large-scale combinatorial optimization problem. In this section, we show the NP-hardness of a slight variant of the problem described in Section 3.2. In this modification, the regional offer arrival rates are estimated based on the harvesting OPO as well as the OPO to which the organ is offered.

3.3.2.1 ***NP*-hardness Proof of the Multiple Listing Problem** The decision problem version of the optimization problem (3.4)-(3.6) with a different representation of regional offer arrival rates can be written as follows. We refer to this problem as MULTIPLE LISTING (ML).

MULTIPLE LISTING (ML)

INSTANCE: Given a set of OPOs $\mathcal{I}$, a set of regions $\mathcal{R}$, sets of health states and liver qualities S_H, S_L, a set of coefficients $\mathcal{R}(i) \in \mathbb{Z}_+^{|\mathcal{I}|}$ for each $i \in \mathcal{I}$, which indicates the region to which OPO i belongs, health state transition rates $\mu(h,h') \in \mathbb{R}_+^{|S_H|*|S_H|}$ for each $h, h' \in S_H$, organ arrival rates $\omega_{ij}(\ell|h) \in \mathbb{R}_+^{|\mathcal{I}|*|\mathcal{I}|*|S_H|*|S_L|}$ for each $i,j \in \mathcal{I}, h \in S_H, \ell \in S_L$, an admissible set A_i for each $i \in \mathcal{I}$, post-transplant rewards $r_T(h,\ell)$ for each $h \in S_H, \ell \in S_L$, immediate rate of rewards $r_W(h)$ for each $h \in S_H$ and $K, M \in \mathbb{Z}_+^1$.

QUESTION: Is there a selection of a home OPO $b \in \mathcal{I}$ and a set of OPOs $O \in \mathcal{I}$ of cardinality at most K such that $b \in O, j \in A_b$ for $j \in O$ and the total life expectancy, $V_O(h,\ell)$ given by (3.3), is at least M?

Proposition 3.3 *ML is NP-complete.*

Proof. We reduce the MAX BISECTION problem, which is known to be NP-complete [54], to solving SML (which is shown to be a restricted version of ML in Appendix B).

SIMPLIFIED MULTIPLE LISTING (SML)

INSTANCE: Given a set $\mathcal{I}$ of indices with $|\mathcal{I}|$ even, and $\omega_{ij} \in \mathbb{R}_+^{|\mathcal{I}|*|\mathcal{I}|}$ of coefficients for each $i,j \in \mathcal{I}$ such that $\omega_{ii} = \omega_{jj}$, $\omega_{jj} > \max_i \sum_{k \neq i} \omega_{ik}$, and $\omega_{jk} = \omega_{kj}, i,j,k \in \mathcal{I}$, rewards r_T, r_W such that $r_T > (r_W/\alpha)$ and $M \in \mathbb{Z}_+$.

QUESTION: Is there is a partition of $\mathcal{I}$ into disjoint sets $\mathcal{I}_1$, $\mathcal{I}_2$ such that $|\mathcal{I}_1| = |\mathcal{I}_2|$ and $\sum_{i \in \mathcal{I}_2} \sum_{i \in \mathcal{I}_1} \omega_{ij}$ is at least M?

MAX BISECTION

INSTANCE: Graph $G = (\mathcal{V}, \mathcal{E})$ with $|\mathcal{V}|$ even, weight $w(e) \in \mathbb{Z}_+$ for each $e \in \mathcal{E}$, and $M \in \mathbb{Z}_+$.

QUESTION: Is there a partition of $\mathcal{V}$ into disjoint sets $\mathcal{V}_1$ and $\mathcal{V}_2$ such that $|\mathcal{V}_1| = |\mathcal{V}_2|$, and the sum of the weights of the edges from $\mathcal{E}$ that have one endpoint in $\mathcal{V}_1$ and other endpoint in $\mathcal{V}_2$ is at least M?

It is easy to see that MAX BISECTION remains NP-complete if $w(e) \in \mathbb{R}^1_+$ for each $e \in \mathcal{E}$. Consider an instance of MAX BISECTION. If there is no edge (i, j), then we create an edge (i, j) with a zero weight. The solution of a MAX BISECTION instance is independent of the weights of the edges that describe a self-loop. Therefore, changing the diagonal entries in the weight matrix does not change the solution. Consequently, we set weights of all of the edges that describe a self-loop the same and higher than the maximum weight among all edges that do not describe a self-loop. As a result, the weight matrix of the MAX BISECTION instance becomes diagonally dominant. This transformation of the weight matrix is polynomial. We then construct an instance of SML such that $\mathcal{I}$ is the set of indices that correspond to the vertices in $\mathcal{V}$, set of coefficients $\omega_{ij} = w(e)$, and consider the same positive integer M. This transformation is also polynomial.

Given a bisection $\mathcal{V}_1, \mathcal{V}_2$ that solves MAX BISECTION, create $\mathcal{I}_1, \mathcal{I}_2$ such that $\mathcal{I}_1 = \mathcal{V}_1$ and $\mathcal{I}_2 = \mathcal{V}_2$. Since $|\mathcal{V}_1| = |\mathcal{V}_2|$ from the definition of MAX BISECTION, $|\mathcal{I}_1| = |\mathcal{I}_2|$. The weight of an edge $w(e)$ in set $\mathcal{E}$ will correspond to the coefficients ω_{ij}. Note that $\sum_{i \in \mathcal{I}_2} \sum_{i \in \mathcal{I}_1} \omega_{ij} \geq M$.

Given a partition of OPOs $\mathcal{I}_1, \mathcal{I}_2$ that solves SML, create $\mathcal{V}_1, \mathcal{V}_2$ such that $\mathcal{V}_1 = \mathcal{I}_1$ and $\mathcal{V}_2 = \mathcal{I}_2$. Since $|\mathcal{I}_1| = |\mathcal{I}_2|$ from the definition of SML, $|\mathcal{V}_1| = |\mathcal{V}_2|$. The arrival rate of organ offers, ω_{ij}, will correspond to coefficients $w(e)$ in MAX BISECTION. Note that the sum of coefficient $w(e)$ such that one endpoint (v_j) of e is in $\mathcal{V}_1$ and other (v_i) in $\mathcal{V}_2$ is at least M.

So, SML decision problem is NP-complete. SML decision problem is a restricted version of ML decision problem (See Appendix B) and it is NP-complete. Therefore, ML is NP-complete.

ML decision problem is no harder than the ML optimization problem (3.4)-(3.6). Therefore, (3.4)-(3.6) is NP-hard [54]. □

3.3.2.2 Greedy Algorithm Nemhauser and Wolsey [123] show that among different algorithms, the greedy algorithm is the best suited for maximizing a nondecreasing submodular function subject to a cardinality constraint. Therefore, by Theorem 3.1 and Theorem 3.2 under Condition (3.32), the greedy algorithm should work well for (3.4)-(3.6). Moreover, the previous section proves that it is extremely difficult to find a computationally efficient

algorithm that captures the specific structure of our model. Both of these ideas suggest that the greedy solution should be a very good approximation of the optimal solution.

The greedy algorithm makes the locally optimal choice at every stage and never reconsiders its previous choices. In that sense, the greedy solution for this model is achieved by selecting the best OPO given the OPOs selected so far. As listing in an additional OPO provides positive life expectancy to the patient, she always chooses to list in more OPOs if she can. Therefore, $O(b,k) \subset O(b,k+1),\ k < K$ is true for the greedy solution constructed for this model. However, this is not necessarily true for the optimal solution. The patient might optimally list in a completely different set of OPOs if she is allowed to list in one more OPO. Intuitively, if a patient is already listed in a bigger OPO set, then the marginal benefit of listing in one more OPO should be smaller. The submodularity maximization supports this intuition. Therefore, we believe that the greedy solution should perform well compared to the optimal solution and will discuss it further in Section 3.5.3.

3.4 COMPUTATIONAL APPROACH FOR THE CARDINALITY-CONSTRAINED MODEL

We structure the second-stage listing decision faced by the patient as a branch-and-bound tree. Recall that the patient has selected b as her home OPO in the first stage and therefore A_b is the admissible set of OPOs (including OPO b) in which she can list.

The number of OPOs in which the patient lists beyond the home OPO is the depth of a node in the branch-and-bound tree. That is, there are at most $|A_b| - 1$ levels including the root node where the level of the root node is assumed to be 0. The root node represents the case that the patient is listed only in the home OPO (i.e., she is singly listed). A node at level k represents the selection of a particular OPO to be listed in as k^{th} OPO in addition to the home OPO. We index OPOs from $0, \cdots, (|\mathcal{I}| - 1)$ arbitrarily, with the home OPO's index at 0. Every node of the branch-and-bound tree corresponds to the set of OPOs selected so far, and the index of the node is the same as the index of the OPO selected most recently. Each node of the branch-and-bound tree constitutes a different instance of the liver acceptance

problem faced in the third stage, i.e., a different set of OPOs. Figure 3.4 illustrates the listing decision by an example branch-and-bound tree. In this figure, the admissible set includes 4 OPOs, and therefore the highest level of the branch-and-bound tree is 3. The figure also shows that different nodes of the tree are different OPO sets. Therefore, a different MDP is developed for every node. We use value iteration [141] to solve the decision problem at each node.

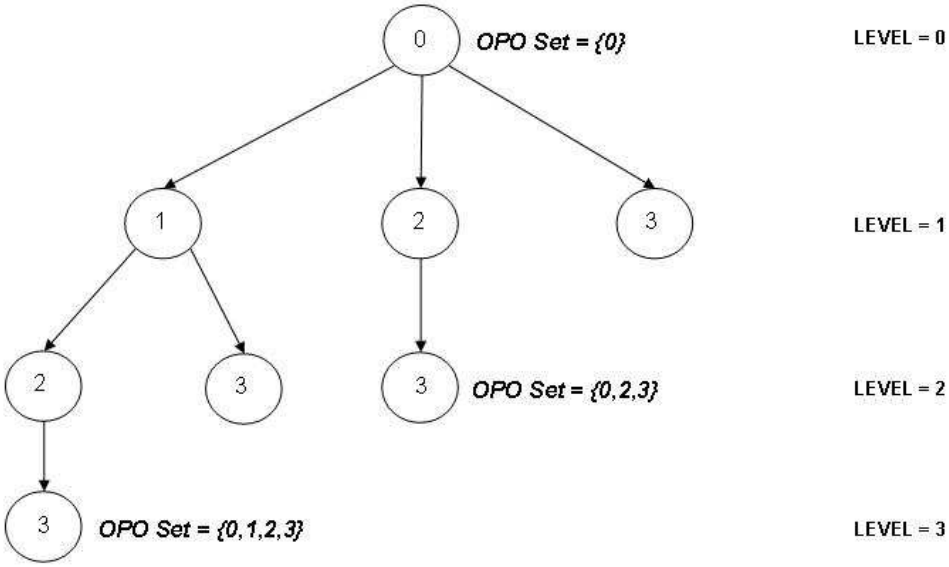

Figure 3.4: Branch-and-bound tree constructed for $A_0 = \{0, 1, 2, 3\}$.

During the branch-and-bound algorithm, we employ a depth-first strategy due to its relatively low memory requirements. Every node in the admissible set is indexed from 0 (home OPO) to $|A_b| - 1$, and lower indexed nodes are explored earlier in the branch-and-bound algorithm.

A general upper bound for the second-stage listing problem is the solution to the optimization problem in (2) with choosing $O = A_b$ where b is the home OPO. While there is a single upper bound, we calculate a general lower bound for each level. The value of the parent node will be a lower bound on the value of its child nodes by Theorem 3.1.

Let $n(k)$ refer to node n at level k and $P^j(n(k))$ refer to $n(k)$'s ancestor at level j. According to this definition, $P^0(n(k)) = 0$ (home OPO), $P^k(n(k)) = n$ (the OPO itself). Recall that the set of OPOs in which the patient lists changes her total life expectancy. Given $n(k)$, $O_{UB(n(k))}$ is defined as the OPO set which maximizes the total life expectancy

of the patient who lists in it. $O_{LB(n(k))}$ is the set of OPOs the patient is listed in so far at $n(k)$. $UB(n(k))$ ($LB(n(k))$) represents the upper (lower) bound on $n(k)$.

Proposition 3.4 *An upper bound for node $n(k)$ is obtained by solving the MDP attained through a set of OPOs specified by $O_{UB(n(k))}$. Therefore, we set $UB(n(k)) = V_{O_{UB(n(k))}}(h, L+1)$ where:*

$$O_{UB(n(k))} = \left\{ \bigcup_{j=0}^{k} P^j(n(k)) \right\} \bigcup \left\{ \bigcup_{i=n+1}^{|A_b-1|} i \right\}. \tag{3.65}$$

Proposition 3.5 *A lower bound for node $n(k)$ is obtained by solving the MDP attained through a set of OPOs specified by $O_{LB(n(k))}$. Therefore, we set $LB(n(k)) = V_{O_{LB(n(k))}}(h, L+1)$ where:*

$$O_{LB(n(k))} = \left\{ \bigcup_{j=0}^{k} P^j(n(k)) \right\}. \tag{3.66}$$

Let $n'(k)$, $n(k)$ be two nodes such that their ancestors are the same up to level $k-1$, i.e., $P^j(n(k)) = P^j(n'(k))$ for $j = 0, \cdots, k-1$. If the upper bound on $n(k)$ is less than the lower bound on $n'(k)$, then $n(k)$ will be explored no further. According to the fathoming rule, two MDPs are solved (lower and upper bounds) at each node.

Lemma 3.4 *Let $n(k), n'(k)$ be nodes such that their ancestors are the same up to level $k-1$. If $n(k) > n'(k)$, then upper bound on $n(k)$ is less than upper bound on $n'(k)$.*

Proof. From the definitions of OPO sets that facilitate the upper bounds:

$$O_{UB(n(k))} = \left\{ \bigcup_{j=0}^{k-1} P^j(n(k)) \right\} \bigcup \Big\{ n, n+1, \cdots, |A_b - 1| \Big\},$$

$$O_{UB(n'(k))} = \left\{ \bigcup_{j=0}^{k-1} P^j(n'(k)) \right\} \bigcup \Big\{ n', n'+1, \cdots, |A_b - 1| \Big\},$$

because their ancestors are the same up to level $k-1$, $\left\{\bigcup_{j=0}^{k-1} P^j(n(k))\right\} = \left\{\bigcup_{j=0}^{k-1} P^j(n'(k))\right\}$. Also, because $n > n'$, $\Big\{n, n+1, \cdots, |A_b-1|\Big\} \subseteq \Big\{n', n'+1, \cdots, |A_b-1|\Big\}$. So, $O_{UB(n(k))} \subseteq O_{UB(n'(k))}$. Then $UB(n(k)) \leq UB(n'(k))$ because $V_{O_{UB(n(k))}}(h, L+1) \leq V_{O_{UB(n'(k))}}(h, L+1)$ by Theorem 3.1. □

Theorem 3.3 states that if a node will not be explored further due to the fathoming rule, then the remaining nodes that have the same ancestors at the same level and higher indices also will not be explored further.

Theorem 3.3 *Let $n(k), n'(k), n''(k)$ be nodes such that their ancestors are the same up to level $k-1$ and $n'' > n'$. Then, if lower bound on $n(k)$ is greater than upper bound on $n'(k)$, the branch following $n'(k)$ and $n''(k)$ can be fathomed.*

Proof. From Lemma 3.4, $UB(n''(k)) \leq UB(n'(k))$ because $n'' > n'$. According to the theorem, $LB(n(k)) \geq UB(n'(k))$, so that $n'(k)$ can be fathomed. Because $UB(n''(k)) \leq UB(n'(k))$, $n''(k)$ can be fathomed as well. □

The home OPO corresponds to the root node of the branch-and-bound tree. Therefore, the root node differs for every home OPO. In other words, a different branch-and-bound tree is constructed for each possible home OPO. Any OPO can potentially be the home OPO. Therefore, we execute a branch-and-bound algorithm $|\mathcal{I}|$ times where the root node (and therefore the admissible set) changes each time; i.e., we perform an exhaustive enumeration.

We implement the bounds described in this section. In order to calculate the bounds, we solve an extra MDP at every node of the branch-and-bound tree. The savings in the computational time gained by the fathoming rule should exceed the additional time it takes to solve the extra MDP at each node for the bounds to be implemented. Unfortunately, the bounds are ineffective based on the computational experiments performed. It is possible that this is due to our implementation, and more sophisticated data structures would render these bounds effective. We leave this for future research.

3.5 NUMERICAL RESULTS

3.5.1 Data Sources

There are four data sources utilized in the computational experiments. We use the post-transplant rewards estimated by Roberts et al. [144]. In their study, Roberts et al. [144] use a

publicly available dataset from UNOS (UNOS1). In order to estimate health state transition rates, we employ the health state transition probabilities of Alagoz et al. [5], which are estimated using a dataset obtained from the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center (UPMC). We transform the probabilities estimated by Alagoz et al. [5] to health state transition rates by the method described in Section 3.5.2. The third data source (UNOS2) is also a publicly available dataset provided by UNOS. This data was collected between February 1, 2002, and March 31, 2005. UNOS2 includes more up-to-date data of more patients than UNOS1. There are 44,930 patients in UNOS2.

UNOS2 includes patient information such as region, OPO, MELD scores, age, blood type, gender, race, and disease type and organ information such as gender, cause of death, age, region number, and the date of the offer. UNOS2 is used to estimate organ offer rates. The fourth data source (UNOS3) is also provided by UNOS. It includes all organs that are transplanted in the U.S. between the years 1996 and 2003. The number of transplants performed in an OPO by the OPO in which the organ is harvested is available from UNOS3. UNOS3 is used as a substitute for the number of organ offers made in an OPO by the harvesting OPO. Therefore, UNOS3 is utilized to determine the proportion of local and regional organs offered to patients in each OPO.

3.5.2 Parameter Estimation

Post-transplant rewards, health state transition rates, the offer arrival rates at the OPO level as well as the intra-regional level are estimated using the above-mentioned four clinical data sets. Alagoz et al. [7, 9, 10] give a detailed description of post-transplant reward and health state transition probability estimations.

In their models, Alagoz et al. [7, 9, 10] consider the expected intermediate reward of waiting as 1 day given the lack of quality-adjusted data. Similarly, we assume that the rate of immediate reward of rejecting an organ offer or not being offered an organ is one day per day.

To facilitate the estimation of health state transition rates, we exploit the study undertaken by Alagoz et al. [7, 9, 10] and utilize the health state transition probabilities estimated by them. Miller et al. [110] showed how to convert a probability over a period of time to a (constant) instantaneous rate by using the following formula:

$$r = -[ln(1-p)]/t, \tag{3.67}$$

where r is the rate, p is the probability and t is the time period that the probability is calculated over. In their studies, Alagoz et al. [7, 9, 10] calculate daily probability of health state transitions, and therefore t is 1. In summary, we use probabilities estimated by Alagoz et al. [7, 9, 10] and adopt Miller et al.'s [110] method to convert health state transition probabilities to health state transition rates. Health state transition probabilities achieved through uniformization is different from that of Alagoz et al.'s [7, 9, 10], because Alagoz et al. [7, 9, 10] estimate daily health state transition probabilities whereas the health state transition probabilities obtained by uniformization depend on λ_{max}.

The continuous discount rate is calculated by setting $e^{\alpha} = \lambda$, where λ denotes the discrete-time discount rate [141].

In order to estimate offer arrival rates, we discretize the liver quality and classify the liver types similarly to [4]. As a result, there are a total of 28 categories for liver types. Because the data are sparse, we aggregate the liver types and MELD scores so that we use 14 and 18 categories for livers and MELD scores, respectively. Liver Type 1 (14) corresponds to the highest (lowest) quality liver. Employing UNOS2, we count the number of days each patient who is listed in a given OPO spends in a given MELD score, and for each MELD score and OPO, we count the number of times a specific liver type is offered. In other words, we consider as if a patient is singly listed in every OPO in which she is listed. This is a reasonable assumption as very few patients multiple list in practice [107]. Let $W_i^k(h)$ and $N_i^k(h,\ell)$ be the number of days patient k waits in MELD score h in OPO i and the number of times liver ℓ is offered to patient k at MELD score h who is listed in OPO i, respectively.

Then the liver ℓ offer arrival rate to a singly-listed patient in OPO i, with MELD score h is obtained using the following formula:

$$\omega_i(\ell|h) = \frac{\sum_k N_i^k(h,\ell)}{\sum_k W_i^k(h)}, \quad h \in S'_H, \ell \in S'_L. \tag{3.68}$$

Recall our assumption that the patient does not benefit from offers at the national level, since national offers are very few compared to local and regional offers. Therefore, we assume that this rate includes offers of organs harvested in all OPOs in the same region as OPO i as well as the organs harvested in OPO i. In order to differentiate between offers of organs harvested in OPO i and those harvested in other OPOs in the same region, we define $P(j,i)$ and operationalize $\xi_i(\ell|h)$, which is defined in Section 3.2.1.1. The fraction of liver transplants in OPO i involving an organ harvested in OPO j is represented by $P(j,i)$, and the rate of offers from OPO i to a patient listed in OPO i (local offers) is represented by $\xi_i(\ell|h)$. Then $\xi_i(\ell|h)$ can be calculated as follows:

$$\xi_i(\ell|h) = P(i,i) \cdot \omega_i(\ell|h), \quad h \in S'_H, \ell \in S'_L. \tag{3.69}$$

It would be ideal for $P(j,i)$ to represent the fraction of organ offers rather than the fraction of organ transplants in OPO i involving an organ harvested in OPO j. However, the fraction of organ offers is not available and the UNOS dataset (UNOS3) contains the number of organs transplanted in the U.S. between the years 1996 and 2003 by the harvest and transplant OPOs.

Let n_R be the number of OPOs in region R. Regional organ offer arrival rate for a specific $(h,\ell), \ h \in S_H, \ell \in S'_L$ for OPOs in region R ($|n_R|$ unknowns) could be calculated by solving the following $|n_R|$ equations:

$$\omega_i(\ell|h) = \xi_i(\ell|h) + \sum_{j \neq i, \mathcal{R}(i)=\mathcal{R}(j)} \theta_j(\ell|h), \quad i \in \mathcal{I}, \mathcal{R}(i) = R. \tag{3.70}$$

Equations (3.70) yield the following formula for the regional organ offer arrival rates for a specific $(h,\ell), \ h \in S_H, \ell \in S'_L$:

$$\theta_i(\ell|h) = \frac{\sum_{j \neq i, \mathcal{R}(j)=R} (\omega_j(\ell|h) - \xi_j(\ell|h)) - (n_R - 2)(\omega_i(\ell|h) - \xi_i(\ell|h))}{n_R - 1}, \quad i \in \mathcal{I}, \mathcal{R}(i) = R. \tag{3.71}$$

The estimation of $\xi_i(\ell|h)$ and $\theta_i(\ell|h)$ are shown numerically in Appendix C.1. As demonstrated in this appendix, solving equations (3.71) may yield negative estimates of regional organ offer arrival rates. We believe that this is due to employing the fraction of transplants performed as a proxy for the fraction of organ offers made.

3.5.2.1 LP model: As the data on the fraction of organ offers made is not available and utilizing the fraction of transplants performed does not act as a good alternative for every OPO and (h,ℓ), we perturb the $P(i,i)$ estimates as less as possible that leads to nonnegative estimates of regional organ offer arrival rates. Consequently, for region R and an $(h,\ell),\ h \in S'_H, \ell \in S'_L$, we solve the following LP:

$$
\begin{aligned}
&\min \sum_{i\in\mathcal{I},\mathcal{R}(i)=R} |x(i,i,h,\ell) - P(i,i)| \\
&x(i,i,h,\ell)\omega_i(\ell|h) + \sum_{j\neq i} \theta_j(\ell|h) = \omega_i(\ell|h),\ \ \mathcal{R}(i)=\mathcal{R}(j)=R, i,j\in\mathcal{I}, \\
&0 \le x(i,i,h,\ell) \le 1,\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\theta_i(\ell|h) \ge 0,\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\epsilon \ge 0.
\end{aligned}
$$

where $x(i,i,h,\ell)$ corresponds to the fraction of liver offers made in OPO i involving an organ harvested in OPO i for state (h,ℓ). We define two sets of variables $\alpha_i, \beta_i,\ \ i\in\mathcal{I}, \mathcal{R}(i)=R$ where $x(i,i,h,\ell) - P(i,i) = \alpha_i - \beta_i$ and the objective is $\alpha_i + \beta_i$. So, the LP is rewritten as follows:

$$
\begin{aligned}
&\min \sum_{i\in\mathcal{I},\mathcal{R}(i)=R} (\alpha_i + \beta_i) \\
&\alpha_i\omega_i(\ell|h) - \beta_i\omega_i(\ell|h) + \sum_{j\neq i} \theta_j(\ell|h) = (1-P(i,i))\omega_i(\ell|h),\ \ \mathcal{R}(i)=\mathcal{R}(j)=R, i,j\in\mathcal{I}, \\
&\alpha_i - \beta_i \le 1 - P(i,i),\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\beta_i - \alpha_i \le P(i,i),\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\theta_i(\ell|h) \ge 0,\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\alpha_i \ge 0,\ \ \mathcal{R}(i)=R, i\in\mathcal{I}, \\
&\beta_i \ge 0,\ \ \mathcal{R}(i)=R, i\in\mathcal{I}.
\end{aligned}
$$

We use the optimal solutions attained through solving the LPs constructed above as the estimates for local and regional offer arrival rates. An example LP is built numerically in Appendix C.2.

3.5.2.2 Solving the LP Model: We solve the LP model described in Section 3.5.2.1 and obtain the fraction of local offers, that are closest to the fraction of local transplants, for every OPO and (h, ℓ). Table 3.1 displays the average percentage perturbation in the fraction of local transplants required in order to achieve nonnegative regional rates for every OPO and (h, ℓ). The average percentage perturbation in $P(i, i)$ is defined as follows:

$$\frac{\sum_{i\in\mathcal{I}}\sum_{h\in S'_H}\sum_{\ell\in S'_L}\Big(|P(i,i)-x(i,i,h,\ell)|/P(i,i)\Big)}{|\mathcal{I}|*|S'_H|*|S'_L|}*100. \tag{3.72}$$

Average perturbation for region R is defined as:

$$\frac{\sum_{i\in\mathcal{I},\mathcal{R}(i)=R}\sum_{h\in S'_H}\sum_{\ell\in S'_L}\Big(|P(i,i)-x(i,i,h,\ell)|/P(i,i)\Big)}{|n_R|*|S'_H|*|S'_L|}*100. \tag{3.73}$$

From Table 3.1, Regions 3, 8, 10 and 11 have higher percentage perturbations than the remaining regions. An analysis of the OPOs in these regions suggest that Gainesville in Region 3, Omaha in Region 8, Cincinnati in Region 10 and Memphis in Region 11 are the OPOs that cause high percentage perturbations. It is interesting that the fraction of local transplants performed in these OPOs are much lower than other OPOs. In other words, a high percentage of the transplants performed in these OPOs involve an organ harvested in another OPO. However, it is not necessarily true that among all offers made to patients listed in these OPOs, offers of organs harvested in other OPOs have a much higher percentage than local organs. According to the allocation policy of UNOS, organs are offered to local patients first. Therefore, we believe that the reason for high values of perturbation is due to higher differences between the offers made to local patients and the transplants performed with local organs.

Table 3.1: Average percentage change in $P(i, i)$.

Region	Number of OPOs	Perturbation
1	2	0.00
2	5	4.76
3	6	19.13
4	4	2.10
5	6	4.69
6	3	0.93
7	4	0.84
8	5	15.28
9	2	0.00
10	6	29.75
11	7	28.02
ALL	50	12.65

3.5.3 Optimal Policy Examples for the Cardinality-Constrained Model

In this section, we investigate the optimal liver acceptance, listing, and home OPO selection strategies of two patients for the cardinality-constrained model. Patient 1 is a 45-year-old female hepatitis patient who has blood type A. Patient 2 is a 45-year-old female patient with biliary cirrhosis disease, who has blood type O. Initially, we consider that both patients are from Chicago, IL. Therefore Chicago, IL is the home OPO of both patients. Both patients have cytomegalovirus (CMVGR), no encephalopathy and no previous transplant. In the numerical examples, we use an annual discount rate of 0.99, and therefore the continuous discount rate is 0.01005.

3.5.3.1 Liver Acceptance In this section, we conduct analysis and draw conclusions on optimal liver acceptance decisions.

Recall that the liver acceptance decision is modeled as a continuous-time MDP and then uniformized. The uniformized discrete-time MDP is equivalent to the problem explored in Alagoz et al.[9]. Figure 3.5 presents the optimal liver acceptance policy for a 40 year-old female patient with blood type A, no previous transplant, who is listed in every OPO in Region 1 and has hepatitis disease. We compare the optimal liver acceptance policy of this patient provided in Alagoz et al. [9] to that of ours, in order to check whether the optimal policy attained in our model is consistent with the optimal policy achieved by Alagoz et al. [9].

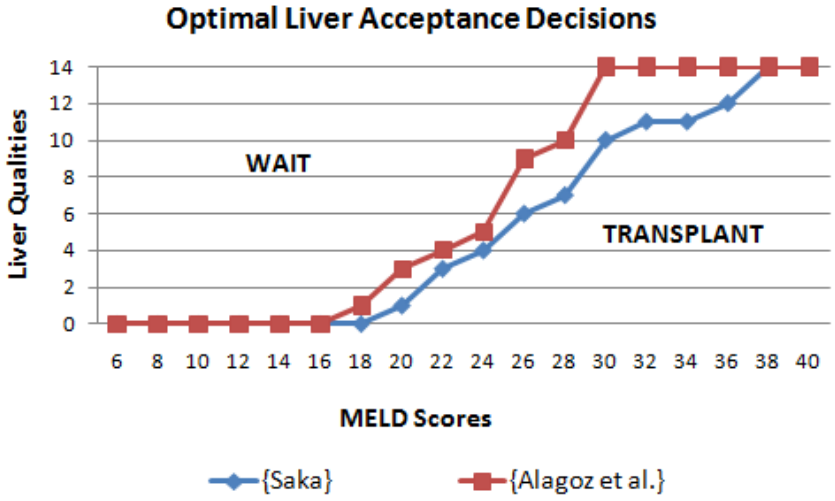

Figure 3.5: Optimal liver acceptance decisions of a 40 year-old female patient with hepatitis.

Liver acceptance policies in Figure 3.5 suggest that the patient is less willing to accept offers if our model is utilized. This difference can be partially explained by the fact that the dataset we use to estimate organ arrival rates is newer and bigger than the dataset Alagoz et al. [9] use. In order to compare the organ arrival rates in our model to organ arrival probabilities in Alagoz et al., we convert Alagoz et al.'s organ arrival probability estimates for Region 1 to rates using (3.67). For every MELD score ($h \in S'_H$), we compare the maximum rate of receiving an offer over all liver types ($\max_{\ell \in S'_L} \nu_O(\ell|h)$). The comparison demonstrates that in 67% of MELD scores, our estimates yield a higher maximum rate of receiving an offer than that of Alagoz et al's and at the same time the offer corresponds to a higher-quality liver. This result is reasonable as Alagoz et al. assume that a patient is

offered at most one organ on any given day. In other words, they do not consider multiple offers to a patient. However, we do not ignore any organ offer. Therefore, the patient waits for higher-quality livers in more health states according to our optimal policy because she is being offered higher-quality organs with higher frequency. Consequently, the difference in the optimal liver acceptance policies depicted in Figure 3.5 is expected.

Figure 3.6 displays the optimal liver acceptance policies, under our model, of Patient 1 and Patient 2 when the patients are singly listed in Chicago, IL. According to this figure, Patient 2 starts accepting organs sooner. That is, Patient 2 accepts lower quality organs compared to Patient 1, whereas Patient 1 waits for higher quality organs.

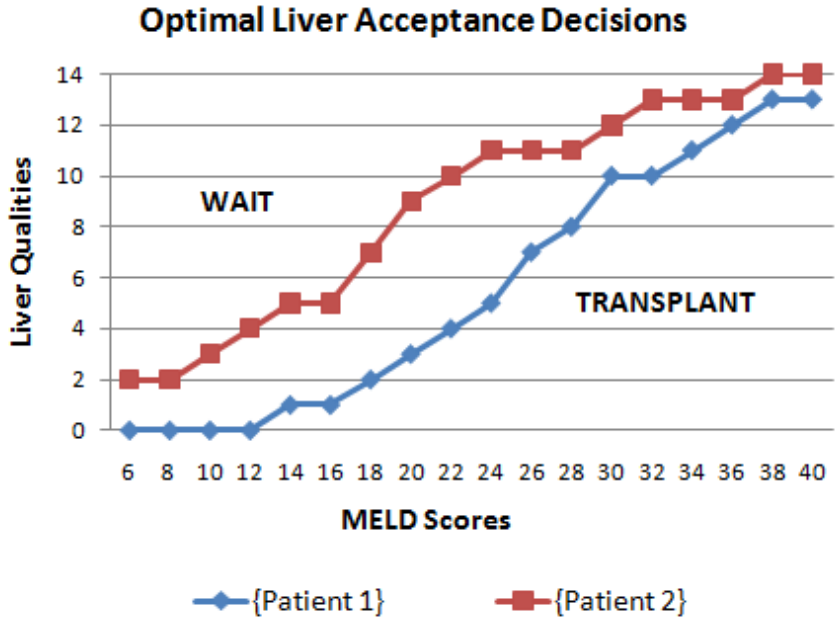

Figure 3.6: Optimal liver acceptance decisions of Patient 1 and Patient 2 when they are singly listed in Chicago, IL.

Different etiologies for ESLD can result in different liver acceptance policies. For Patient 1, the etiology is hepatitis, and cirrhosis causes ESLD in Patient 2. We compare the health state transition rates for hepatitis and cirrhosis. We compute the mean sojourn time in every health state $\left(t(h) = \frac{1}{\sum_{h' \in S_H \setminus \{h\}} \mu(h'|h)}, h \in S'_H\right)$. Utilizing the MELD score distribution at a random point in time on the waiting list, that is specific to disease type $(p(h))$ from UNOS [180], we calculate the weighted average of transition rate into a sicker health state $\left(\frac{\sum_{h \in S'_H} \sum_{h' > h} p(h) \cdot \mu(h'|h) \cdot t(h)}{|S'_H|}\right)$ and the weighted average of transition rate to death

$\left(\frac{\sum_{h\in S'_H} p(h)\cdot\mu(H+1|h)\cdot t(h)}{|S'_H|}\right)$ for both diseases. According to these calculations, the weighted average of transition rate into a sicker health state is approximately 4.05% higher if the underlying cause of ESLD is cirrhosis than it is if the cause is hepatitis. Similarly, the weighted average of transition rate to death is approximately 57.14% higher if the underlying cause of ESLD is cirrhosis. Therefore, we conclude that cirrhosis is a more aggressive disease than hepatitis. For the remainder of this chapter, we will refer to these differences between the health transition rates as Patient 2 having a more aggressive disease than Patient 1.

Another explanation for the different liver acceptance policies emerges due to the diverse post-transplant rewards. On average, when a same quality liver is offered in the same health state, Patient 2 has a total post-transplant life expectancy that is 63% longer than Patient 1. Therefore, it is reasonable for Patient 2 to accept livers that Patient 1 does not accept.

Figure 3.7 exhibits the optimal liver acceptance policies of Patient 1 and Patient 2 for different OPO sets. Based on this figure, the optimal liver acceptance policies appear to be different for different OPO sets. It is optimal for Patient 1 to reject a Type 2 organ offer in MELD score 18 when she is listed in Chicago and Louisville. However, it is optimal for her to accept the same offer in that MELD score when she is listed in Chicago only. In general, Figure 3.7 leads us to the conclusion that if a patient accepts a particular liver offer in a particular MELD score when she is listed in Chicago and Louisville, she will accept the offer when she is listed in Chicago only. In other words, Figure 3.7 illustrates Corollary 3.1 for both patients. Also, patients' liver acceptance policy changes with their listing decision.

The optimal liver acceptance decision of Patient 2 when she is listed in Chicago and Louisville exemplifies a nonmonotonic policy. According to this policy, for MELD score 32, the worst quality liver that Patient 2 would accept is a Type 10 liver and for MELD score 34, the worst quality liver that she would accept is a Type 9 liver. In other words, she accepts higher quality livers even if her health gets worse. As Alagoz et al. [9] convey, it is an intuitive result due to the U.S. allocation policy. Allocation policy states that the likelihood of receiving a liver offer increases as a patient gets sicker. Therefore, if the frequency that a patient receives an organ offer increases in a considerable amount as she gets sicker, then it may be optimal to wait until she gets higher quality livers. For every home OPO and $K = 1, 2, 3, 4$, we compare the worst quality liver patients would accept in health state

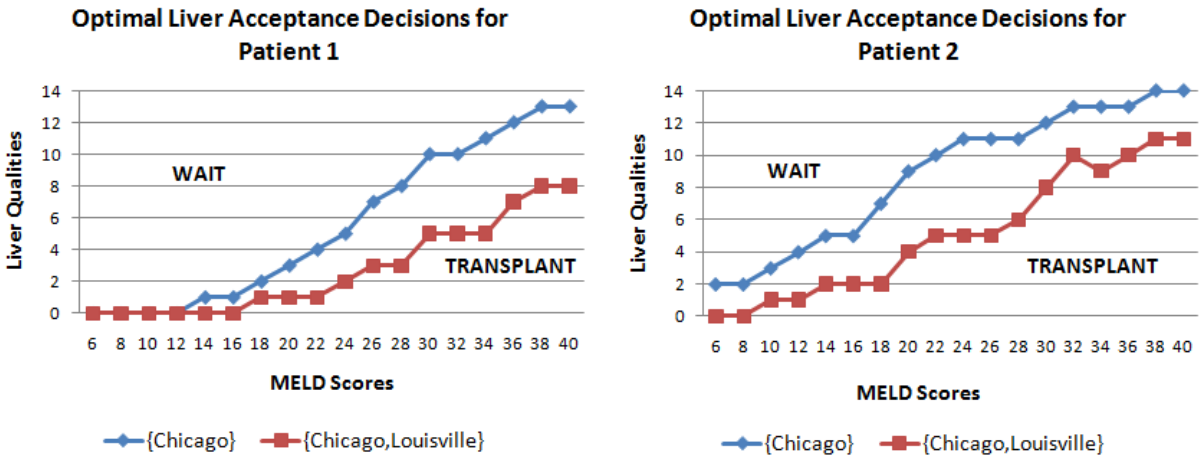

Figure 3.7: Optimal liver acceptance decisions of Patient 1 and Patient 2 for different OPO sets.

h to that of $h+1$. According to this analysis, Patient 1 (Patient 2) has a nonmonotonic liver acceptance policy approximately 4.64% (10.36%) of the instances tested. Patient 2 has more nonmonotonic policies than Patient 1 and this might be a result of the fact that her underlying disease is more aggressive.

Submodularity of the Value Function: In this section, we demonstrate numerically that $V_O(h,\ell)$ is not submodular in general. Let O be the home OPO, Chicago, OPO j be St. Louis and OPO k be Maumee (Figure 3.8). When being offered a Type 2 liver in MELD score 12, it is optimal for Patient 2 to accept the offer if she is listed in {Chicago}, {Chicago, St. Louis} or {Chicago, Maumee} (life expectancy is 5590 days). However, if the patient is listed in {Chicago, St. Louis, Maumee}, then it is optimal for her to wait as the total life expectancy she attains by waiting is 5633 days. When being offered a Type 3 liver in MELD score 14, it is optimal for Patient 2 to accept the offer if she is listed in {Chicago} or {Chicago, Maumee} (life expectancy is 5411 days). However, if the patient is listed in {Chicago, St. Louis} (life expectancy is 5425 days) or {Chicago, St. Louis, Maumee} (life expectancy is 5485 days), then it is optimal for her to wait. When being offered a Type 7 liver in MELD score 24, it is optimal for Patient 2 to accept the offer if she is listed in {Chicago} or {Chicago, St. Louis} (life expectancy is 4549 days). However, if the patient is listed in

{Chicago, Maumee} (life expectancy is 4584 days) or {Chicago, St. Louis, Maumee} (life expectancy is 4702 days), then it is optimal for her to wait. All of these numerical examples yield a negative value for $V_{O\cup\{j\}}(h,\ell) - V_O(h,\ell) - V_{O\cup\{j,k\}}(h,\ell) + V_{O\cup\{k\}}(h,\ell)$, and therefore $V_O(h,\ell)$ is not submodular.

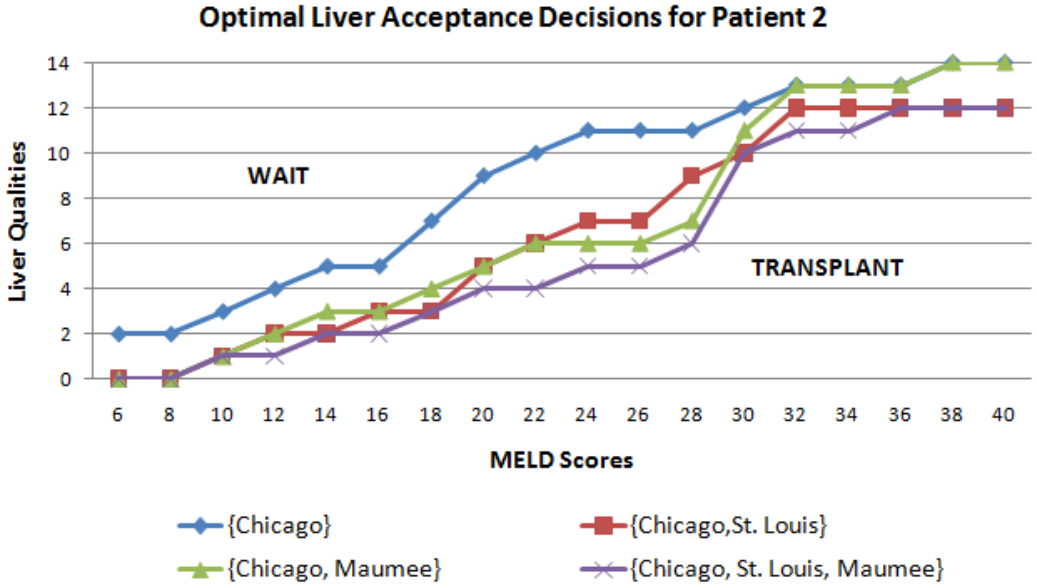

Figure 3.8: Optimal liver acceptance decisions of Patient 2.

According to Theorem 3.2, $V_O(h,\ell)$ is submodular under condition (3.32). We numerically test 270 states (18 health states, 14 liver qualities as well as a no offer state) for 36 sets of OPOs (Table D2). The OPO sets in Table D2 are constructed such that O is the home OPO, Chicago, and j and k are OPOs that are within 350 miles of Chicago. Results indicate that (3.32) is satisfied in approximately 20.36%, and the value function ($V_O(h,\ell)$) is submodular in approximately 84.20% of the instances tested.

As the objective is to maximize $V_O(h, L+1)$, it would be interesting to investigate the submodularity of $V_O(h, L+1)$. We inspect OPO sets such that O is any home OPO and i and j are OPOs that are within 350 miles of the home OPO (Table D3). As there are 679 such sets of OPOs, and 18 health states (we only consider the no offer state, $L+1$), we examine the submodularity of $V_O(h, L+1)$ for 12,222 instances. Among those instances, $V_O(h, L+1)$ is submodular approximately 99% of the time. Another appealing fact that worths mentioning is that (3.32) is satisfied for $(h, L+1)$ states, because $r_T(h, L+1) = 0$.

3.5.3.2 Listing Decision In this section, we discuss and compare the optimal listing decisions for both patients when the admissible set includes OPOs that are within 350 miles of Chicago. We present the optimal listing policies when the admissible set includes OPOs within 250 miles of Chicago in Appendix E. The admissible sets include the OPOs specified in Table 3.2.

Table 3.2: Different admissible sets for Chicago, IL (Region 7).

OPOs within (0,250] miles	**OPOs within (250,350] miles**
Indianapolis, IN (Region 10)	Ann Arbor, MI (Region 10)
Madison, WI (Region 7)	Cincinnati, OH (Region 10)
Milwaukee, WI (Region 7)	Louisville, KY (Region 11)
North Liberty, IA (Region 8)	Maumee, OH (Region 10)
	St. Louis, MO (Region 8)

We compute the optimal decisions for every MELD score in general. However, as the median MELD score when a patient joins the list is 10-12 [147], MELD score 12 is one of the initial MELD scores for which the optimal multiple listing policies are displayed in Tables E1, 3.3, E2 and 3.4. Home OPOs in Tables E1, 3.3, E2 and 3.4 are italicized and fixed to Chicago, because the home OPO selection decision has already been made.

It is worth mentioning conclusions that apply to both patients first. Those conclusions include that the optimal OPO sets in which patients list differ for different initial health states, K and admissible set. Another observation reveals that higher total life expectancies are attained in healthier initial states and with a relaxed geographical constraint. Patients' total life expectancies also increase as they are allowed to list in more OPOs. However, the average increase in total life expectancy, over initial MELD scores, by listing in an additional OPO decreases if patients are currently listed in more OPOs. This is an intuitive result as it ties back to submodularity and the diminishing returns ideas discussed in Section 3.3.

A further conclusion is that, as the upper bound on the number of OPOs patients can list in (K) increases, patients mostly list in OPOs that belong to one of the regions in which they have not listed yet. This reflects the fact that patients are not only offered organs

harvested in one of the OPOs in which they are listed, but also those harvested in other OPOs in one of the regions in which they are listed.

Table 3.3 illustrates the optimal listing decisions for Patient 1, when she can list in OPOs within 350 miles of Chicago. According to this table, when K is 2, the patient lists in Louisville in addition to Chicago when her initial MELD score is 12. However, she lists in Cincinnati in addition to Chicago when her initial MELD score is 30.

Louisville is in Region 11 and Chicago is in Region 7. Therefore, the rate of additional offers Patient 1 receives by listing in Louisville beyond Chicago is equal to the rate of offers she would receive if she were singly listed in Louisville. In other words, the patient does not sacrifice any regional offers by listing in Louisville, because Louisville and Chicago do not belong to the same region. Same argument holds for Cincinnati and Chicago. Therefore, we compare the organ offer arrival rates to a singly-listed patient in Louisville to that of Cincinnati's.

The arrival rate of the highest quality liver to a singly-listed patient in MELD score 12 (i.e., $\omega_i(1|12)$) in Louisville is approximately 53.04% higher than that of a singly-listed patient in Cincinnati. However, in MELD score 30, a singly-listed patient in Cincinnati is offered an organ of any type with approximately 52.74% higher rate on average $\left(\frac{\sum_{\ell \in S'_L} \omega_i(\ell|30)}{|S'_L|}\right)$ than a singly-listed patient in Louisville. These results suggest that it is more reasonable for a patient to list in a riskier OPO, an OPO that has a higher offer arrival rate of organs of the highest-quality but a lower overall offer arrival rate of any liver type, if she is healthier and in a safer OPO if she is sicker.

The average increase based on the distribution of the initial MELD scores for hepatitis, over initial MELD scores and every home OPO, in total life expectancy Patient 1 achieves by listing in an additional OPO is 7.02%, 2.16%, and 1.07% when she is currently listed in 1,2, and 3 OPOs respectively and she is allowed to list in OPOs that are within 350 miles of the home OPO.

Comparison of Listing Decisions: In this section, we compare the optimal listing decisions of Patient 1 and Patient 2. Table 3.4 depicts the optimal listing decisions for Patient 2, when she can list in OPOs within 350 miles of Chicago.

Table 3.3: Optimal listing decisions for Patient 1 for different initial health states, K, and when admissible set includes OPOs within 350 miles of Chicago.

Initial health state (MELD score)	***K***	**Optimal OPO set**	**Optimal region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	1	*Chicago, IL*	{7}	2759	
	2	*Chicago, IL* Louisville, KY	{7,11}	3041	10.22
	3	*Chicago, IL* Louisville, KY Ann Arbor, MI	{7,10,11}	3101	1.97
	4	*Chicago, IL* Louisville, KY Ann Arbor, MI Madison, WI	{7,10,11}	3141	1.29
30	1	*Chicago, IL*	{7}	1356	
	2	*Chicago, IL* Cincinnati, OH	{7,10}	1585	16.89
	3	*Chicago, IL* Cincinnati, OH Louisville, KY	{7,10,11}	1665	5.05
	4	*Chicago, IL* Cincinnati, OH Louisville, KY North Liberty, IA	{7,8,10,11}	1698	1.98

For initial MELD score 30, when K is 4, and admissible set includes OPOs within 350 miles of Chicago, the first patient lists in Cincinnati, Louisville, and North Liberty, IA in addition to Chicago and the second patient lists in Cincinnati, Louisville, and Indianapolis in addition to Chicago. In other words, when her MELD score is 30, the first patient chooses North Liberty, IA, whereas the second patient chooses Indianapolis. The region to which North Liberty, IA belongs is not one of the regions to which Cincinnati, Louisville and Chicago belong. However, Indianapolis belongs to the same region with Cincinnati. So, by listing in Indianapolis, the second patient sacrifices the regional offers from Indianapolis. Consequently, we compare the organ offer arrival rate to a singly-listed patient in North Liberty, IA ($\omega_{North\ Liberty}(\ell|h)$) to the tradeoff between the local and regional organ offer arrivals in Indianapolis ($\xi_{Indianapolis}(\ell|h) - \theta_{Indianapolis}(\ell|h)$).

Comparison of organ offer arrival rates at North Liberty, IA to that of the tradeoff rate at Indianapolis reveals that the rate of receiving the highest-quality liver in MELD score 30 ($i.e., \omega_{North\ Liberty}(1|30)$) is approximately 50.78% higher in North Liberty, IA. However, the average rate of receiving an offer of any organ type in MELD score 30 is approximately 27.02% higher in Indianapolis $\left(\frac{\sum_{\ell \in S'_L}(\xi_{Indianapolis}(\ell|30) - \theta_{Indianapolis}(\ell|30))}{|S'_L|}\right)$. In summary, we conclude that the patient with a more aggressive disease (Patient 2) lists in a safer OPO, which promises more offers in any quality. However, the patient with a less aggressive disease (Patient 1) lists in a riskier OPO, which promises more offers of the highest quality organ but less offers in general.

Similar to Patient 1, we conduct an analysis on the average increase based on the distribution of the initial MELD scores for cirrhosis, over initial MELD scores and every home OPO, in total life expectancy by listing in an additional OPO for Patient 2, when she can list in OPOs that are within 350 miles of the home OPO. According to this analysis, the average increase in total life expectancy by listing in an additional OPO is 7.09%, 1.88%, and 0.94% when she is currently listed in 1,2, and 3 OPOs respectively.

Performance of the Greedy Solution: In this section, we compare greedy and optimal listing strategies with a specific example and present numerical analysis on how the greedy algorithm performs in general.

Table 3.4: Optimal listing decisions for Patient 2 for different initial health states, K, and when admissible set includes OPOs within 350 miles of Chicago.

Initial health state (MELD score)	***K***	**Optimal OPO set**	**Optimal region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	1	*Chicago, IL*	{7}	5338	
	2	*Chicago, IL* Louisville, KY	{7,11}	5644	5.73
	3	*Chicago, IL* Louisville, KY St. Louis, MO	{7,8,11}	5692	0.85
	4	*Chicago, IL* Louisville, KY St. Louis, MO Ann Arbor, MI	{7,8,10,11}	5715	0.40
30	1	*Chicago, IL*	{7}	3529	
	2	*Chicago, IL* Cincinnati, OH	{7,10}	4168	18.11
	3	*Chicago, IL* Cincinnati, OH Louisville, KY	{7,10,11}	4341	4.15
	4	*Chicago, IL* Cincinnati, OH Louisville, KY Indianapolis, IN	{7,10,11}	4425	1.94

Table 3.5 compares the first patient's optimal multiple listing strategy to her greedy multiple listing strategy in MELD score 12 if her home OPO were Milwaukee.

Table 3.5: Optimal and greedy listing decisions for Patient 1 when admissible set includes OPOs within 350 miles of Milwaukee.

Initial health state (MELD score)	***K***	**Optimal OPO set**	**Optimal region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	2	*Milwaukee, WI* Ann Arbor, MI	{7,10}	3001	
	3	*Milwaukee, WI* Indianapolis, IN Maumee, OH	{7,10}	3076	2.50
Initial health state (MELD score)	***K***	**Greedy OPO set**	**Greedy region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	2	*Milwaukee, WI* Ann Arbor, MI	{7,10}	3001	
	3	*Milwaukee, WI* Ann Arbor, MI Madison, WI	{7,10}	3069	2.27

Table 3.5 shows that the greedy approach does not always produce the optimal solution. When K is 2, it is optimal for the patient to list in Milwaukee and Ann Arbor. However, if the patient is allowed to list in an additional OPO, then it is not optimal for her to simply add another OPO to the set of OPOs in which she is already listed. Instead, it is optimal for her to unregister from Ann Arbor and list in Indianapolis and Maumee. Although it is obvious from Table 3.5 that the greedy algorithm does not always provide the optimal solution, the observations presented in Tables E1, 3.3, E2 and 3.4 lead to the conclusion that the greedy solution is a very good approximation of the optimal solution. This is an expected result as

Nemhauser and Wolsey [123] show that the greedy algorithm is a very good approximation for maximizing a nondecreasing submodular function subject to a cardinality constraint, and we numerically show that the value function ($V_O(h, L+1)$) is almost always submodular and we maximize the nondecreasing value function based on a cardinality constraint.

We analyze the optimal listing decisions of Patient 1 and Patient 2 for every initial MELD score and potential home OPO, when the admissible set includes OPOs that are within 250 or 350 miles of the home OPO. We assume that the home OPO is fixed because the patient has already made the home OPO selection decision in the previous stage. Therefore, we do not compare the optimal listing decisions when K is 1 to K is 2. However, we compare the listing decisions when K is 3 to K is 2 and K is 4 to K is 3. The number of comparisons is determined based on the home OPO, and the number of OPOs in the admissible set depending on the admissible set. For example, there are 4 (5) OPOs in Birmingham's admissible set of 250 (350) miles. Note that the admissible sets include Birmingham. Therefore, we are able to compare listing decisions when K is 3 to K is 2 and K is 4 to K is 3 for the 350 mile admissible set. However, we are only able to compare listing decisions when K is 3 to K is 2 if the admissible set includes OPOs within 250 miles of Birmingham. Table 3.6 presents the percentage of instances for which the greedy solution is optimal.

Table 3.6: Percentage of instances for which the greedy solution is optimal.

	250 miles		**350 miles**	
	Patient 1	**Patient 2**	**Patient 1**	**Patient 2**
Comparing $K = 3$ to $K = 2$	77.27%	55.88%	73.53%	50.00%
Comparing $K = 4$ to $K = 3$	46.67%	57.14%	46.43%	53.33%
Overall	64.86%	56.45%	61.29%	51.35%

According to Table 3.6, the greedy solution is optimal approximately 65% (%61) and 56% (%51) of the time for Patient 1 and Patient 2 respectively, when the admissible set includes OPOs within 250 (350) miles of the home OPO. As the cardinality constraint is relaxed, the admissible set includes more OPOs, and therefore the number of greedy solutions decrease. For both patients, the total expected discounted reward attained by listing in the greedy

OPO set is within 1% of the total expected discounted reward attained by listing in the optimal OPO set.

3.5.3.3 Home OPO Selection In this section, we convey the optimal home OPO selection decisions for both patients when the admissible set includes OPOs that are within 350 miles of the home OPO. We display the optimal home OPO selection policies when the admissible set includes OPOs within 250 miles of the home OPO in Appendix E. We use the terms optimal home OPO and best home OPO interchangeably. The best home OPOs are italicized.

As shown in Tables E3, 3.7, E4 and 3.8, the optimal home OPO patients choose differ for different initial health states, K and admissible set. Similar to conclusions reached at the previous section, we can mention here that higher total life expectancies are attained in healthier initial states and with a relaxed geographical constraint. Patients' total life expectancies also increase as they are allowed to list in more OPOs.

Table 3.7 represents the optimal home OPO selection decisions for Patient 1 for different initial health states, K, and when the admissible set includes OPOs within 350 miles of the home OPO. In this table, when K is 2, both OPOs in which the patient is listed could be the optimal home OPO. Therefore, there are multiple optimal home OPOs. However, when K is 4, Gainesville for initial MELD score 12 is the unique optimal home OPO. This is due to the fact that the distances between Norcross and Tampa, and Norcross and Miami, exceed 350 miles. Note that the patient relocates in order to increase her total life expectancy.

Table 3.8 displays the optimal home OPO selection decisions for Patient 2 for different initial health states, K, and when the admissible set includes OPOs within 350 miles of the home OPO. Similar to the optimal home OPOs for Patient 1, when K is 2, both OPOs in which the patient is listed could be the optimal home OPO, because the distance between these OPOs is less than 350 miles. In Table 3.8, when K is 4 and initial MELD score is 30, all OPOs in {Cincinnati, Louisville, Indianapolis, Ann Arbor} could be an optimal home OPO. We reach this conclusion because the distance between every pair of OPOs in this set is less than 350 miles. In Table E4, Cincinnati is the unique home OPO among the same set of OPOs because the admissible set includes OPOs within 250 miles of the home OPO.

Table 3.7: Home OPO selection decision for Patient 1 for different initial health states, K, and when admissible set includes OPOs within 350 miles of the home OPO.

Initial health state (MELD)	***K***	**Best home OPO**	**Total life expectancy in best home OPO**	**% gain in life expectancy over worst home OPO**
12	1	*Tampa, FL*	3053	12.28
	2	*Tampa, FL* *Gainesville, FL*	3123	8.97
	3	*Tampa, FL* *Gainesville, FL* *Miami, FL*	3154	5.61
	4	*Gainesville, FL* Tampa, FL Miami, FL Norcross, GA	3169	4.99
30	1	*Cincinnati, OH*	1522	33.38
	2	*Cincinnati, OH* *Louisville, KY*	1642	19.98
	3	*Cincinnati, OH* *Louisville, KY* *Indianapolis, IN*	1676	10.92
	4	*Indianapolis, IN* Cincinnati, OH Louisville, KY Madison, WI	1701	10.29

Table 3.8: Home OPO selection decision for Patient 2 for different initial health states, K, and when admissible set includes OPOs within 350 miles of the home OPO.

Initial health state (MELD)	***K***	**Best home OPO**	**Total life expectancy in best home OPO**	**% gain in life expectancy over worst home OPO**
12	1	*Westwood, KS*	5673	7.16
	2	*Westwood, KS* *St. Louis, MO*	5704	4.56
	3	*St. Louis, MO* Westwood, KS Louisville, KY	5739	2.84
	4	*St. Louis, MO* Westwood, KS Louisville, KY Memphis, TN	5749	2.64
30	1	*Cincinnati, OH*	3984	47.14
	2	*Cincinnati, OH* *Louisville, KY*	4273	21.34
	3	*Cincinnati, OH* *Louisville, KY* *Indianapolis, IN*	4386	10.08
	4	*Cincinnati, OH* *Louisville, KY* *Indianapolis, IN* *Ann Arbor, MI*	4440	9.01

In Table 3.7 and Table 3.8, we quantify the difference, in terms of total life expectancy, between listing in the best and the worst home OPOs. As K increases and the initial MELD score decreases, the percentage gain attained by selecting the best home OPO instead of the worst home OPO decreases. In these tables, the worst home OPO has at least K OPOs in its admissible set. In other words, the worst home OPO at level K is selected among those OPOs that have at least K OPOs in their admissible sets. However, if we consider every OPO when selecting the worst home OPO, then the percentage gain attained by selecting the best home OPO instead of the worst home OPO increases. For example, if a patient ichooses Denver as the home OPO, then she can not list in an additional OPO since Denver's admissible set includes only itself. In this case, for every level K, we compare the total life expectancy attained by listing in the best home OPO set (of cardinality K) to the total life expectancy attained by listing in Denver only. As K increases, the the total life expectancy attained by listing in the best home OPO set increases, but the total life expectancy attained by listing in Denver stays the same. Therefore, the difference between the corresponding total life expectancies increase.

For every initial MELD score, we consider optimal home OPOs when K is 1,2,3, and 4 and when the admissible set includes OPOs that are within 350 miles of the home OPO. According to our results, Gainesville and Louisville appear to be the best home OPOs, as at least one of them is selected as an optimal home OPO approximately 38% and 32% of the instances tested for Patient 1 and Patient 2 respectively. Gainesville is the best OPO in terms of the overall rate of an organ offer to a singly-listed patient. More specifically, we compute the overall rate of an offer arrival to a singly-listed patient for all OPOs. Gainesville is the OPO with the highest overall offer arrival rate according to this comparison. Therefore, it is reasonable for patients to choose Gainesville as one of the best home OPOs. Based on this comparison, Louisville is the eighth best. This result alone, it is not very intuitive why patients select Louisville as one of the best home OPOs.

In Appendix G, we present the map of U.S. transplant regions, transplant OPOs as well as the set of regions that are within 350 miles of Louisville. As apparent from Figure G3, Louisville is close to the border of Region 11 and therefore patients listed in Louisville have close proximity to organs harvested in other regions. That is, once listed in Louisville and

allowed to list in OPOs that are within 350 miles of Louisville, patients have a chance to list in OPOs in regions 7, 8, 10, and 11. There are 10 OPOs in Louisville's admissible set. Although it would have been preferable to list in other OPOs if patients were singly listed, according to the optimal policies we consider, Louisville emerges as one of the best home OPOs because patients can list in as many as 4 OPOs.

3.5.4 Optimal Policy Examples for the Total Distance Constrained Model

In this section, we investigate the optimal listing and home OPO selection strategies of the same two patients considered in the previous section.

We represent the cost of being listed in an OPO (c_{bi}) by the distance of that OPO from the home OPO. Consequently, the budget is the upper bound on the sum of the distances of individual OPOs in an OPO set from the home OPO.

3.5.4.1 Listing In this section, we discuss optimal policies when the maximum total distance patients can travel from the home OPO is 800 miles. We present optimal listing results for a total distance of 400 miles for both patients in Appendix F. The home OPOs are italicized and fixed to Chicago, because the home OPO selection decision has already been made.

Tables 3.9 and F1 illustrate the optimal listing decisions of Patient 1 for different total distances traveled. Similarly, Tables 3.10 and F2 report the optimal listing decisions for Patient 2. Initial assessment of these tables reveal that the optimal OPO sets that the patients list in differ by initial health state and the total distance traveled. Higher total life expectancies are attained in healthier initial states and with a higher maximum total distance. In other words, as the total distance the patient is allowed to travel in order to multiple list increases, so does her total life expectancy. However, similar to the cardinality-constrained model, the increase diminishes for higher budgets. Another observation is that as the maximum total distance increases, patients mostly list in OPOs that belong to regions in which they have not listed yet.

Table 3.9: Optimal OPO sets for Patient 1 for different initial health states, and when the total distance traveled from Chicago cannot exceed 800 miles.

Initial health state (MELD)	**Optimal OPO set**	**Region**	**Total life expectancy attained by a total distance of 800 miles (days)**	**Percentage gain in life expectancy attained over a total distance of 700 miles**
12	*Chicago, IL*	7	3141	0.35
	Ann Arbor, MI	10		
	Louisville, KY	11		
	Madison, WI	7		
30	*Chicago, IL*	7	1693	0.95
	Cincinnati, OH	10		
	Louisville, KY	11		
	Madison, WI	7		

Table 3.9 summarizes the optimal listing decisions for Patient 1, when she can travel at most 800 miles in total from Chicago. According to this table, Patient 1 lists in O_1={Chicago, Ann Arbor, Louisville, Madison} when her MELD score is 12 and she lists in O_2={Chicago, Cincinnati, Louisville, Madison} when her MELD score is 30. In order to understand the rationale behind her listing decision, we compare the organ offer arrival rates to a multiply-listed patient in O_1 to that of O_2. This comparison suggests that the average probability of receiving an organ offer in MELD score 12 $\left(i.e., \frac{\sum_{\ell \in S'_L} \nu_O(\ell|12)}{|S'_L|}\right)$ is approximately 3.85% higher if the patient is listed in the first set and the average probability of receiving an organ offer in MELD score 30 $\left(i.e., \frac{\sum_{\ell \in S'_L} \nu_O(\ell|30)}{|S'_L|}\right)$ is approximately 25.38% higher if the patient is listed in the second set. Therefore, in addition to Chicago, Louisville, and Madison, it is reasonable for Patient 1 to list in Ann Arbor when her MELD score is 12 and in Cincinnati when her MELD score is 30.

The patient's total life expectancy increases 12.29% for the first 500 miles she is allowed to travel in total in order to multiple list, if her initial MELD score is 12. However, the additional increase is only 1.94% if she is allowed a total distance of 1,000 miles rather than 500 miles. If the patient is sicker, she benefits more by increasing total distance. Namely, in initial MELD score 30, her total life expectancy increases by 20.50% and 5.26%, if the total distance is 500 and 1,000 miles, respectively. Figure 3.9 depicts the total life expectancies that both patients attain by listing in OPOs that are within 100 to 1,000 miles of the home OPO. A budget of zero miles refers to the case where a patient is singly listed.

Table 3.10 displays the optimal listing decisions for Patient 2, when she can travel a total of 800 miles from Chicago. Similar to Patient 1, we calculate the increase in the second patient's total life expectancy by a 500 mile increase in the total distance. In initial MELD score 12, her total life expectancy increases approximately 6.20% and 1.23% for the first and the second additional 500 miles in total distance. If her initial MELD score is 30, the corresponding percentages are 20.88% and 4.74%. That is, the patient's total life expectancy increases more by multiple listing if she is sicker.

Comparison of the optimal listing decisions of both patients when their initial MELD score is 12 reveals that Patient 1 lists in O_1={Chicago, Ann Arbor, Louisville, Madison} and Patient 2 lists in O_2={Chicago, Louisville, Maumee, North Liberty}. We evaluate the

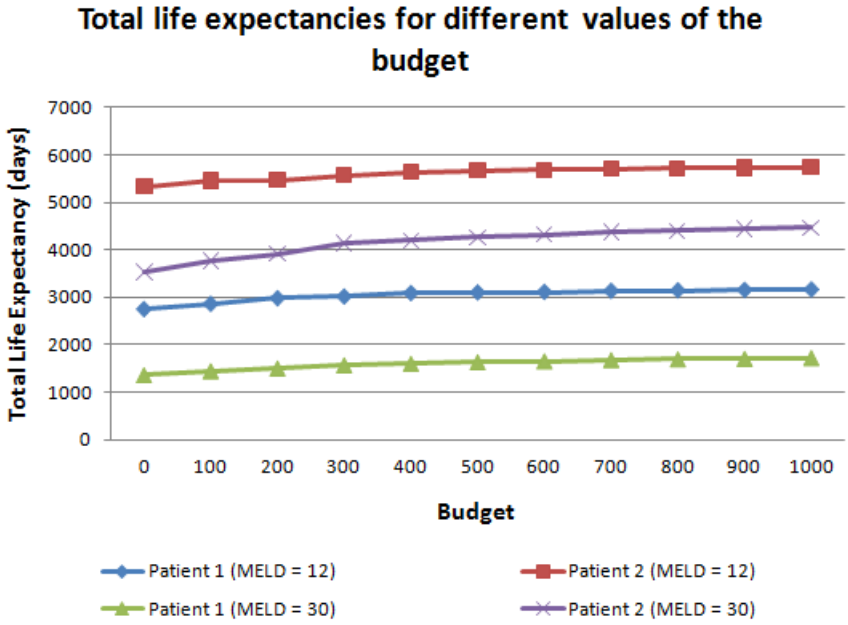

Figure 3.9: Total life expectancy for different budgets.

average rate of receiving an organ of any type in MELD score 12 $\left(i.e., \frac{\sum_{\ell \in S'_L} \nu_O(\ell|12)}{|S'_L|}\right)$ for a patient multiply listed in both sets. According to this evaluation, the average rate is approximately 3.58% higher for the second set. However, the rate of receiving the highest-quality liver in MELD score 12 ($i.e., \nu_O(1|12)$) in O_1 is approximately 14.33% higher. In other words, we attain the same conclusion as in the cardinality-constrained model. That is, as Patient 2 has a more aggressive disease, she prefers to list in an OPO set that has a higher overall organ offer arrival rate. By listing in this safer set, Patient 2 sacrifices the higher rate of receiving the highest-quality liver.

Comparison of optimal listing decisions in Table 3.3 to those in Table 3.9, as well as comparison of optimal listing decisions in Table F2 to those in Table E2 reveal that given the same initial MELD score and K, the cardinality-constrained and the budget-constrained models yield different optimal policies.

3.5.4.2 Home OPO Selection In this section, we touch on the optimal home OPO selection decisions for both patients, when patients can travel a total of 800 miles from the home OPO. Similar to the previous section, the optimal policies corresponding to the

Table 3.10: Optimal OPO sets for Patient 2 for different initial health states, and when the total distance traveled from Chicago cannot exceed 800 miles.

Initial health state (MELD)	**Optimal OPO set**	**Region**	**Total life expectancy attained by a total distance of 800 miles (days)**	**Percentage gain in life expectancy attained over a total distance of 700 miles**
12	*Chicago, IL*	7	5713	0.11
	Louisville, KY	11		
	Maumee, OH	10		
	North Liberty, IA	8		
30	*Chicago, IL*	7	4404	0.57
	Cincinnati, OH	10		
	Indianapolis, IN	10		
	North Liberty, IA	8		

maximum total distance of 400 are displayed in Appendix F. The best home OPOs are italicized.

Optimal home OPO selection decisions shown in this section as well as those presented in Appendix F exhibit that initial health state and the total distance patients are allowed to travel in order to multiple list change their home OPO selection decision. As expected, patients achieve higher total life expectancies in healthier states and as they are allowed to travel higher maximum total distances.

Table 3.11: Optimal home OPO selection decision for Patient 1 for different initial health states, and when the total distance traveled from the home OPO cannot exceed 800 miles.

Initial health state MELD score	**Best home OPO and optimal OPO set**	**Region**	**Total life expectancy in best home OPO**	**Gain in life expectancy over worst home OPO (%)**
12	*Gainesville, FL*	10	3159	11.55
	Tampa, FL	10		
	Charleston, SC	11		
30	*Louisville, KY*	11	1720	36.40
	Cincinnati, OH	10		
	Indianapolis, IN	10		
	Memphis, TN	11		
	Nashville, TN	11		

In Table 3.11, in order to determine if there is more than one home OPO in which the patient can optimally multiple list, we calculate the total distance between a particular OPO and the remaining OPOs in which the patient lists. If it does not exceed the total distance the patient is allowed to travel, then that OPO can be an optimal home OPO. Based on this rationale, in Table 3.11, Gainesville and Tampa are optimal home OPOs when the first patient's MELD score is 12. Also, Louisville is the unique optimal home OPO when the patient's initial MELD score is 30.

Table 3.12: Optimal home OPO selection decision for Patient 2 for different initial health states, and when the total distance traveled from the home OPO cannot exceed 800 miles.

Initial health state MELD score	**Best home OPO and optimal OPO set**	**Region**	**Total life expectancy in best home OPO**	**Gain in life expectancy over worst home OPO (%)**
12	*St. Louis, MO*	8	5749	5.97
	Louisville, KY	11		
	Memphis, TN	11		
	Westwood, KS	8		
30	*Louisville, KY*	11	4486	40.76
	Cincinnati, OH	10		
	Indianapolis, IN	10		
	Memphis, TN	11		
	Nashville, TN	11		

Table 3.12 represents the optimal home OPO selection decisions for Patient 2. According to this table, Patient 2 has to relocate to St. Louis so as to reach the highest total life expectancy in MELD score 12. Moreover, she has to relocate to Louisville in MELD score 30.

For every initial MELD score and total distances 100 through 1,000, we consider the optimal home OPOs for both patients, including the multiple optimal ones. For Patient 1 (Patient 2), at least one of Cincinnati or Gainesville is selected as an optimal home OPO for approximately 45% (35%) of the instances tested. As discussed before, Gainesville is the best OPO in terms of the average rate of receiving an organ offer. Therefore, it is selected as one of the best home OPOs in the budget-constrained model as well. In the cardinality-constrained model, we just consider the number of OPOs in a particular home OPOs's admissible set. In this section, the distance of an OPO from a particular home OPO has more importance. Therefore, we calculate the average distance from a particular home OPO b over all OPOs in $\mathcal{I} \setminus \{b\}$. According to this evaluation, the average distance from Cincinnati is the lowest. Recall from our previous discussions that listing in an OPO from another region is important. Therefore, we compute the average distance from a particular home OPO b over all OPOs that are in another region. In other words, we are looking for a home OPO that is closest to OPOs in other regions. This computation yields that Cincinnati is the fourth best in terms of average distance from an OPO in another region. We believe that the results discussed here set the reason why these two OPOs are selected as a best home OPO more frequently.

3.6 CONCLUSIONS

The model described in this chapter increases and optimizes patient autonomy in liver transplantation by giving patients the flexibility to relocate, choose the waiting list(s) they join and accept or reject organ offers. This model is the first OR model which considers relocation and multiple listing aspects of U.S. organ allocation scheme. Another aspect of this model that differentiates it from other OR models of liver transplantation in the literature is that

it models the liver acceptance decision as a continuous-time MDP. This enables us to relax several unrealistic assumptions made in those other models.

An important finding of this chapter is that the liver acceptance value function for different cardinality-constrained listing decisions is nondecreasing and submodular under certain restrictions. Moreover, we prove that a slight variation of the cardinality-constrained listing decision is NP-hard. Therefore, greedy algorithm is a very good approximation to the optimal listing decision under the cardinality-constrained model.

Illustration of our model using clinical data demonstrates that patients with a more aggressive disease and higher expected post-transplant rewards start accepting organ offers sooner and the organ offers that they accept are of lower quality.

Numerical results also indicate that patients should practice multiple listing if they can, because it increases total life expectancy. Also, as patients list in more OPOs, they tend to decline more organ offers in the hope of receiving better offers in the future. According to the numerical results, each patient should list in OPOs based on her individual needs and demographics. For example, a patient with a less aggressive disease increases her total life expectancy more by listing in a riskier OPO. That is, those patients should list in OPOs that do not promise a high offer arrival rate, but give patients a higher chance of receiving good quality offers.

Our results also suggest that when selecting the home OPO, patients should consider the frequency of organ offers at OPOs as well as the proximity of the home OPO to other OPOs, especially OPOs from other regions. Based on our results, Gainesville is one of the best alternatives for the home OPO because it has the highest average frequency of organ offers. Other good candidates for being the best home OPO are Louisville and Cincinnati. Both Louisville and Cincinnati are close to many other OPOs, both in the region to which they belong and in other regions. According to our numerical results, OPOs in California (Region 5) are never selected as a home OPO. Therefore, it is especially important for patients in California to either relocate or to multiple list, preferably in Regions 10 or 11. Recently, Steve Jobs of Apple Inc. received a liver transplant in Memphis, TN (Region 11), although he was originally located in California (Region 5). It is argued that listing in Tennessee in addition to or instead of listing in California decreased his waiting time [125]. Steve Jobs'

decision is also very reasonable based on the numerical results of the decision model built in this dissertation.

In summary, the decisions made in all three stages are important, because the life expectancy of patients depend on the home OPO they choose, where they multiple list, and which organ offers they accept. The total life expectancy of patients increase as they are allowed to list in more distant OPOs or they are given a higher total distance to travel.

In this dissertation, we consider in which OPOs a patient should list, but we do not consider when should a patient list in an additional OPO. This question remains as an interesting future work. Moreover, we do not consider the organs shared at the national level when estimating the organ offer arrival rates. Inclusion of national sharing of offers requires solving $|n_R|$ equations of type (3.70) for region R with $|\mathcal{I}|$ unknowns, and therefore complicates the current organ offer arrival rate estimation. This is also left for future research.

4.0 ASCERTAINING THE SOCIETAL EFFECT OF MULTIPLE LISTING

4.1 INTRODUCTION

The model formulated in Chapter 3 analyzes the multiple listing problem from a single patient's perspective, assuming the equilibrium doesn't change. That is, the model optimizes the patient's multiple listing decision under the assumption that her multiple listing does not change the optimal policies of other patients in the waiting list. However, this is a restrictive assumption, because the nature of the liver allocation process is competitive. In this chapter, we relax this assumption and investigate the liver allocation process from the societal perspective. We only consider the listing and liver acceptance decisions.

The problem discussed in this chapter could be modeled as a stochastic game. However, given the number of players, it is extremely challenging to calculate the equilibria numerically. In other words, we would like to determine an optimal multiple listing and a liver acceptance policy simultaneously for every patient, but it is unrealistic to represent the problem as a stochastic game because there are approximately 16,000 ESLD patients. As more patients list at a certain OPO, the organ offer rates to patients listed in that OPO will decrease, making this problem very complex. The other difficulties associated with this model are that it is nonzero-sum and asymmetric. Such a large-scale, discounted, nonzero-sum stochastic game is likely to remain intractable for the foreseeable future. Recent studies included in the literature can solve various stochastic games for only three [204, 205], four [100] or six players [62]. Therefore, we utilize the simulation model of Shechter et al. [162] in order to simulate the waiting list and the allocation process. We model the problem in which every patient in the waiting list multiple lists under a certain probability distribution, given that the waiting list is dynamic.

In Section 4.2 we discuss the history of multiple listing in the U.S., and in Section 4.3, we review Shechter et al.'s [162] simulation model. Section 4.4 presents the incorporation of multiple listing to the existing simulation model. Section 4.5 studies the computational approach. Section 4.6 exhibits the computational results. We state our concluding remarks in Section 4.7.

4.2 HISTORY OF PATIENTS WHO MULTIPLE LIST

In this section, we touch on the specific facts about patients who multiple list. The UNOS data set (UNOS4) we use is available at UPMC and covers a time frame from the year 1988 to the year 2002. UNOS4 includes data for 89,364 patients who listed in one or more OPOs to receive cadaveric liver offers between the specified years. UNOS4 consists of patient characteristics such as age, gender, race, employment status, home OPO, disease type, number of previous transplants, and insurance type.

We assume that patients who appear to be multiple listed are actually patients who relocated and relisted at another OPO if the distance between the OPOs in which they were listed is at least 1,500 miles. We make this assumption because 1,500 miles is presumably too far to travel in the time required to respond to an organ offer, and we do not have data identifying patients who leave one OPO and register at another. Therefore, these patients are regarded as single listed. According to UNOS4, 2.99% of all ESLD patients multiple list. Among them, 96.17% list in two OPOs, 3.60% list in three OPOs, and 0.23% list in four OPOs. No patient lists in more than four OPOs. The average age of patients who multiple list is 43. 3.24% of all female ESLD patients and 3.56% of all male ESLD patients multiple list. The average distance patients travel in order to multiple list is about 500 miles.

Patients who are originally listed in Pennsylvania, New York, and California are most likely to multiple list. Regionwise, patients from Region 1 (Connecticut, Maine, Massachusetts, New Hampshire and Rhode Island), Region 4 (Oklahoma and Texas), and Region 10 (Indiana, Michigan and Ohio) have a higher propensity for multiple listing.

Table 4.1 shows the pairs of OPOs in which patients multiple list the most, including the number of patients listed in these OPO sets and the regions in which these OPOs are located.

Table 4.1: Most popular OPO pairs in terms of multiple listing.

OPO pair	**Region set**	**Number of patients**
Sacramento, CA; San Francisco, CA	{5}	97
Arlington, VA; Baltimore, MD	{2}	85
Boston, MA; New York,NY	{1, 9}	59
Los Angeles,CA; San Francisco, CA	{5}	52
Jersey City, NJ; New York, NY	{2, 9}	51
New York City, NY; Pittsburgh, PA	{2, 9}	40
Miami, FL; Pittsburgh, PA	{2, 3}	37
Miami, FL; New York City, NY	{3, 9}	36
Charlotte, NC; Pittsburgh, PA	{2, 11}	35
Boston, MA; Hartford, CT	{1}	31

4.3 EXISTING SIMULATION MODEL OF THE LIVER ALLOCATION PROCESS

Shechter et al. [162] build a biologically based discrete event simulation model of the national liver allocation system. Their simulation model includes a patient generator, an organ generator, pre-transplant natural history, matching algorithm, and post-transplant survival. With these modules, they are able to simulate the complex allocation process in which patients and organs arrive with certain characteristics and patient health changes over time. Throughout the simulation model, a patient either receives a transplant, dies while waiting for a transplant, is discharged because her health gets better, is removed from the model due to other reasons (such as a living-donor liver transplant), or remains in the waiting list.

If the patient receives a transplant, she then either dies post-transplant or she is relisted depending on the graft and patient survival. That is, if the expected survival time of the graft is shorter than the expected survival time of the patient, then she is relisted. Otherwise, the patient dies post-transplant. Shechter et al. [162] represent the current liver allocation policy of UNOS by offering organs generated locally, then regionally, and then nationally.

4.4 INCORPORATING PATIENTS' MULTIPLE LISTING CHOICES INTO THE SIMULATION

Although the existing simulation model is a good illustration of the current allocation process, it does not give patients the autonomy to multiple list. In the Shechter et al. [162] model, patients are assigned a home OPO when they are generated, and it is assumed that they will only be listed in this home OPO throughout the process. According to our analysis of historical data, approximately 3% of all ESLD patients multiple list. Also, based on our numerical results in Chapter 3, a patient can increase her life expectancy by multiple listing. Therefore, we give the flexibility to multiple list to every patient generated in the simulation.

The patient generator module of Shechter et al. [162] assigns several characteristics to each patient, such as race, gender, region, OPO, disease group, and MELD score. In our model, additionally, we determine if the generated patient multiple lists; and if so, in which OPOs. We do not utilize the optimization model described in Chapter 3 to decide in which OPOs a generated patient lists. Instead, we define a probability distribution, as described in more detail in Section 4.5.2. We associate new variables for the second, third, and fourth OPOs in which the patient lists accordingly. Since no ESLD patient lists in more than four OPOs, patients generated in the simulation list in four OPOs or fewer. A generated patient is eligible for local and regional offers through each of the OPOs in which she is listed. If the patient leaves the model for any of the reasons discussed in Section 4.3, we delete her from every waiting list she joined.

If a patient is offered an organ that is harvested in neither her original OPO nor in one of the other OPOs in her original region, but either in one of the additional OPOs in which

she is listed or in one of the other OPOs in the additional regions, then the offered organ will possibly wait for her for a longer time. In other words, the travel time required to reach the harvesting OPO is longer for the patient, which increases CIT. The viability of the organ, i.e., the expected survival time of the graft, decreases as the CIT increases. However, the simulation model, and therefore our results, do not reflect the fact that the CIT increases and the viability of the organ decreases if the patient is not offered an organ that is harvested in her original OPO.

By incorporating the patient's choice of multiple listing into the simulation model, we are able to investigate the effect of multiple listing on the entire waiting list. Comparing the expected number of transplants and pre-transplant deaths, as well as the expected survival of patients after receiving a transplant within our model to those same expectations within that of Shechter et al. [162] enables us to assess the influences of multiple listing on both single- and multiple-listed patients.

We modify the simulation model for different percentages of patients who multiple list. That is, we conduct a sensitivity analysis on the percentage of patients who multiple list in order to evaluate the potential outcomes if multiple listing becomes a more widespread practice in the U.S. As more patients multiple list, as an expected outcome, patient heterogeneity among OPO waiting lists would decrease. In an extreme case, if every ESLD patient lists in every OPO, there would be in effect a single, national waiting list. Also in that case, some patients would benefit from the single national list, but not from multiple listing. If a single patient decided not to multiple list, then she would be disadvantaged. Based on this rationale, we expect the benefit of multiple listing to decrease as more patients choose that option. Since multiple listing is a problem which is currently under debate within the organ allocation community, the results from this model could potentially help UNOS with its policy decisions.

4.5 COMPUTATIONAL CONSIDERATIONS

In this section, we discuss the computational approach undertaken in order to determine the OPO set in which every generated patient lists. To facilitate this, we first determine the probability that a particular patient generated within the simulation multiple lists, and we then establish which OPO list(s) she joins.

4.5.1 Constructing Patient Groups

According to Merion et al. [107], the probability that a patient multiple lists depends on race, gender, insurance type, and education level, but does not depend on age. When determining the probability of multiple listing for every generated patient, we consider the patient's gender, and race. We also consider her disease type, because a patient's disease type is a significant determinant in predicting whether she multiple lists or not (Appendix H). However, we do not consider education level and insurance type, because UNOS4 does not include values corresponding to them for many patients. Also, education level and insurance type are not features assigned to a patient upon generation within the simulation model. Altogether, then, we construct patient groups based on gender, race, and disease group and we determine the probability of multiple listing for each group. Since there are two possible genders, and race codes and diseases are grouped into five classes, there are a total of 50 patient groups.

4.5.2 Determining the Probability to Multiple List

We calculate the probability that a generated patient multiple lists by building a logistic regression model. We run the logistic regression model using SAS 9.1 [154] and UNOS4 as our input data. We define binary variables for gender ($female$), every race category, and every disease group as predictor variables of the logistic regression model. As every patient belong to only one disease group, for a particular patient, only one of the binary variables that correspond to disease groups is one. The same is true for binary variables corresponding to race categories. There are five race categories. White patients constitute race category

1 ($de1$), black patients are in race category 2 ($de2$). Race category 3 ($de4$) corresponds to Hispanic patients, race category 4 ($de5$) corresponds to Asian patients, and race category 5 ($de8$) incudes all other patients. There are five disease groups. Disease group 1 ($dd1$) includes primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease, and autoimmune disorder. Disease group 2 ($dd2$) includes hepatitis C virus, and hepatitis B virus. Acute liver failure is referred to as disease group 3 ($dd3$). All cancers are included in disease group 4 ($dd4$). Disease group 5 ($dd5$) consists of metabolic disorders and other chronic diseases. We run the logistic regression model with only one predictor variable and with combinations of predictor variables present. A patient's gender does not appear to be significant. When considered alone, every disease group and every ethnicity category is significant in predicting the multiple listing indicator. When all ethnicity categories are present, the category "white" predicts the multiple listing indicator alone. In Appendix H, p-values of the logistic regression models are presented.

We include the binary variables for gender, every disease group, and ethnicity category in the logistic regression model. That is, we define 11 predictor variables. Let β_0 be the intercept and $\beta_1, \cdots, \beta_{11}$ be the predictor coefficients of x_1(gender), $\cdots$, x_{11} (disease group five) respectively. Further, let $\mu(g, r, d)$ be the probability that a patient multiple lists, such that she belongs to patient group (g, r, d), where g represents gender, r represents race, and d represents disease group. Then:

$$\mu(g, r, d) = \frac{1}{1 + e^{-z}} \text{ where } z = \beta_0 + \beta_1 x_1 + \cdots + \beta_{11} x_{11}.$$

Based on $\mu(g, r, d)$, we determine if the generated patient multiple lists or not. In order to increase the probability of multiple listing associated with every patient group, so as to increase the number of multiple-listed patients, we multiply the predictor coefficients $\beta_0, \beta_1, \cdots, \beta_{11}$ with the same constant.

4.5.3 Establishing the Set of OPO(s) for Multiple Listing

If the generated patient multiple lists, then we find out which additional OPO(s) in which she should list within the simulation model. For every home OPO, we create a probability

distribution of the additional OPOs in which patients multiple list based on UNOS4. So once a generated patient decides to multiple list, based on her home OPO and the historical data of patients who multiple listed from the same home OPO, we determine the additional OPOs in which she lists. If UNOS4 does not include a record of a multiple listing from a certain home OPO, then we assume that a generated patient from this home OPO single lists.

4.6 COMPUTATIONAL RESULTS

In its original form, the model simulates the national liver allocation system between the years 1999 and 2002. However, more than 30% of patients who are generated between those years remain in the waiting list at the end of 2002. Therefore, we model a "cool down" period, at the end of which approximately 1% of the patients who are generated between 1999 and 2002 remain in the waiting list.

We run the simulation model in this case where multiple listing is prohibited and where it is allowed. We compare the rates of transplantation, the number of patients who die while waiting for an organ, the number of of patients who survive at least one and five years after receiving a transplant. We also compare the average time to death while waiting for an organ, the average time to receive a transplant for a transplanted patient, and the average post-transplant survival of transplanted patients.

Our results correspond to the average of 20 replications of the simulation. Recall that patients leave the simulation model if they die, receive a transplant, are discharged or if they are removed for other reasons. Therefore, the average percentages of the number of patients transplanted and the number of patients who die while waiting for an organ do not add up to the number of patients generated. The number of discharges and removals in the simulation add up to approximately 20%, which is substantially high. Also, since the expected remaining lifetime is unknown for patients who are discharged or removed, or for those who stay in the waiting list at the end of the cool down period, we do not consider those patients when calculating the statistics. A patient may receive multiple transplants

within the simulation, similar to the actual liver allocation system. However, we only collect the statistics for the first transplant.

Table 4.2: Percentage of patients as an average of 20 replications when 2.48% of all ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML prohibited	ML allowed		
	all patients	all patients	sl patients	ml patients
generated			97.52%	**2.48**%
transplanted	57.12%	56.99%	56.58%	73.13%
died while waiting	23.89%	24.00%	24.21%	15.75%
survived 1 year	83.44%	83.59%	83.55%	84.94%
survived 5 years	48.36%	48.50%	48.46%	49.78%

Table 4.2 illustrates two cases where multiple listing is prohibited, and when 2.48% of all ESLD patients in the waiting list multiple list. The average percentage of transplanted patients do not seem to be equal for the two cases. However, we perform a paired t-test for the average number of patients transplanted for 20 replications, and the average percentages are not equal for a type 1 error of 0.01. So there is no evidence that the average percentage of patients transplanted under these two cases is different. However, the difference between the percentage of multiple- and single-listed patients transplanted is considerable. When multiple listing is allowed, we observe a slight overall increase in the average percentage of patients who die while waiting for a transplant. However, the average percentage of multiple-listed patients who die while waiting for an organ is far less than the that of single-listed patients. In other words, although multiple-listed patients benefit in terms of survival while waiting for an organ, single-listed patients, and society as a whole are disadvantaged. Although multiple-listed patients appear to be at an advantage in terms of one-year and five-year survivals, the benefit they gain by multiple listing is not substantial.

Table 4.3 demonstrates the average post-transplant survival of transplanted patients, average time to death before a transplant, and average time to transplant for transplanted

Table 4.3: Average time in years when 2.48% of ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML prohibited	ML allowed (2.48%)		
	all patients	all patients	sl patients	ml patients
post-transplant survival	7.22	7.24	7.23	7.45
time to death while waiting	3.22	3.20	3.21	2.22
time to transplant	2.75	2.75	2.78	1.93

patients. According to Table 4.3, although multiple listing benefits patients in terms of their post-transplant survival, that benefit is not statistically significant. Multiple-listed patients die much earlier than those who are single listed. There may be several reasons for this result. For one, it may suggest that sicker patients tend to multiple list, a conclusion which Merion et al. [107] mentioned as well. Also, the results mentioned in Table 4.3 show the average time to death of patients who died while waiting; i.e., they are conditional averages. Therefore, a smaller average time to death for multiple-listed patients might be due to the fact that their transplants occur sooner. Table 4.3 also shows that the average time to transplant is much shorter for multiple-listed patients. There are two possible causes for this. One, since multiple-listed patients are registered in more than one waiting list, they are eligible for organs harvested in more than one OPO, which possibly increases their chances of receiving a transplant. Also, since sicker patients may be more likely to multiple list, they are more likely to be offered organs than healthier patients.

4.6.1 What if More Patients Multiple List?

The probability that a patient who belongs to patient group $\mu(g, r, d)$ multiple lists when more patients multiple list is calculated as follows for $k > 0$:

$$\mu(g, r, d) = \frac{1}{1 + e^{-z}} \text{ where } z = k * \beta_0 + k * \beta_1 x_1 + \cdots + k * \beta_{11} x_{11}.$$

Tables 4.4 and 4.5 depict the average percentages of patients who were transplanted, died while waiting for an organ, and survived for at least one and five years, when the number of multiple-listed patients increase. We obtained the increased percentages of multiple-listed patients by augmenting the regression coefficients. On average, as more patients multiple list, fewer single- and multiple-listed patients receive a transplant, and multiple-listed patients still receive more transplants. A similar statement can be made about the number of deaths while waiting for an organ. As before, there is no significant difference between the percentage of patients who survive for at least one and five years. Similar to the previous case, we perform paired t-tests for the average number of patients transplanted in both cases, where 5.79% and 12.61% of patients multiple list for 20 replications, and the average percentages are not equal for a type 1 error of 0.05.

Table 4.4: Percentage of patients as an average of 20 replications when 5.79% of all ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML allowed		
	all patients	sl patients	ml patients
generated		94.21%	**5.79**%
transplanted	56.97%	56.06%	71.77%
died while waiting	24.06%	24.54%	16.29%
survived 1 year	83.42%	83.33%	84.51%
survived 5 years	48.53%	48.48%	49.12%

Tables 4.6 and 4.7 demonstrate the different times associated with multiple listing when it becomes a more prevalent practice. As more patients multiple list, the average time to transplant for transplanted patients increases for single- and multiple-listed patients. This is an intuitive result since, as mentioned before, as more patients multiple list, the waiting list converges to a single national list. We do not observe a greater difference related to with regard to the average post-transplant time for transplanted patients.

Table 4.5: Percentage of patients as an average of 20 replications when 12.61% of all ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML allowed		
	all patients	sl patients	ml patients
generated		87.39%	**12.61**%
transplanted	56.97%	55.12%	69.77%
died while waiting	23.97%	24.91%	17.44%
survived 1 year	83.63%	83.46%	84.54%
survived 5 years	48.41%	48.29%	49.09%

4.6.2 Statistical Averaging of Multiple-Listed Patients

In this section, we consider all patients in UNOS4, rather than just the multiple-listed ones. We calculate statistical averages for the percentage of single- and multiple-listed patients, and for all patients who were generated, transplanted, died while waiting for an organ, survived for one year and survived for five years. We also calculate statistical averages for post-transplant survival time, time to death while waiting for an organ, and time to transplant

Table 4.6: Average time in years when 5.79% of ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML allowed (5.79%)		
	all patients	sl patients	ml patients
post-transplant survival	7.24	7.23	7.30
time to death while waiting	3.21	3.24	2.39
time to transplant	2.75	2.81	2.00

Table 4.7: Average time in years when 12.61% of ESLD patients multiple list.

ML = multiple listing, sl = single-listed, ml=multiple-listed

	ML allowed (12.61%)		
	all patients	sl patients	ml patients
post-transplant survival	7.22	7.20	7.34
time to death while waiting	3.20	3.27	2.49
time to transplant	2.75	2.87	2.13

for transplanted patients. Tables 4.8 and 4.9 show the corresponding results.

Table 4.8: Percentage of patients as a statistical average of patients in UNOS4.

sl = single-listed, ml=multiple-listed

	all patients	sl patients	ml patients
generated		96.57%	3.43%
transplanted	57.72%	57.18%	73.06%
died while waiting	17.26%	17.41%	13.13%
survived 1 year	70.02%	69.65%	80.44%
survived 5 years	26.14%	26.16%	25.47%

The percentage of multiple-listed patients in Table 4.2 is lower than that in Table 4.8. Recall that a patient designated as multiple listed based on the probability distribution is assumed to be single listed if a history of multiple listing from a multiple-listed patient's home OPO does not exist. The number of patients transplanted are similar in Tables 4.2 and 4.8. According to these two tables, simulation overestimates the number of deaths while waiting for an organ and the number of patients survived for one and five years after transplantation. Comparing the post-transplant survival time and time to transplant of single- and multiple-listed patients in Tables 4.3 and 4.9, we realize that the corresponding times are longer in Table 4.3.

Table 4.9: Average time in years as a statistical average of patients in UNOS4.

sl = single-listed, ml=multiple-listed

	all patients	sl patients	ml patients
post-transplant survival	3.68	2.16	3.74
time to death while waiting	0.86	0.83	1.72
time to transplant	3.68	3.74	2.16

4.7 CONCLUSIONS

In this chapter, we study the consequences of the practice of multiple listing among ESLD patients. Our research is motivated by the current debates about multiple listing within UNOS [183, 184, 185]. According to our knowledge of the literature, our model is the first one that analyzes possible outcomes of multiple listing as more patients are educated about multiple listing and list in additional OPOs.

The primary contribution of this chapter is its conclusion that, in the current form of practice where only approximately 3% of all ESLD patients multiple list, multiple-listed patients have a much higher transplantation rate and a much lower mortality rate while waiting for an organ than single-listed patients. However, the post-transplant mortality rates and the post-transplant survival do not differ significantly when patients multiple list. These observations agree with the conclusions reached by Merion et al. [107].

Another conclusion we reach through the computational results is that, as more patients multiple list and it becomes a more widespread practice in the U.S., advantageous patients would be those who gain more benefit from a single national waiting list than from multiple listing. Multiple listing has a small overall effect when we consider all patients on the waiting list, without classifying them as single-listed or multiple-listed.

There are some restrictions regarding the model described in this chapter. We probabilistically determine which patients multiple list based on historical data. This restricts the simulation to the current OPO sets rather than optimal OPO sets of different patients.

Solving a game-theoretic framework of the liver allocation system where patients are allowed to multiple list is left for future research.

5.0 INVESTIGATING THE DEMAND FOR A LIVER ASSIST DEVICE

5.1 INTRODUCTION

New technological advances can prevent, treat, or ameliorate conditions and diseases that were once thought untreatable [122]. Although liver transplantation is currently the only therapy for ESLD patients and it has an overall successful survival rate, it may not always be available due to organ shortages. Because of the increasing waiting times and mortality rates, there has been interest in techniques for providing liver support to stabilize patients [80].

An external liver assist device (LAD) serves as liver support for a patient with ESLD, keeping her alive until her own liver can recover or until a suitable organ becomes available for transplantation [186]. This type of therapy involves connecting external LADs to the circulation of a patient, and it is predicated upon the idea that acute liver failure can be stabilized or reversed with active detoxification [137]. So far, very few different external LADs have been applied clinically. However, the persistence of survival with external LADs has been shown in animal studies, increasing expectations for their clinical application [80]. Unlike with other artificial organ technologies, external LAD development is in its infancy; therefore, engineering requirements for an external LAD have yet to be understood, identified or developed [136]. There are also several disadvantages of an external LAD. For instance, the patient cannot resume her daily activities while she is on the therapy, and infection may develop in the areas that are connected to the device [201]. Because of these disadvantages, an implantable internal LAD is preferred for patients; however, an internal LAD has not been developed yet [135].

In this chapter, we consider the optimal timing of an LAD. Our model may serve as a tool for manufacturers to use to understand the demand for a device. To determine the type of the LAD to model, we assume that an internal LAD possesses similar features to an external LAD, although as an internal LAD has not been developed yet. Although an external LAD keeps an ESLD patient alive until her own liver can recover or until a suitable organ becomes available for transplantation, we assume that an internal LAD only keeps the patient alive until transplantation. Since an internal LAD would be implantable in the patient and would not help the patient's own organ to recover, once a patient accepted an internal LAD, it would remain implanted until she died or received a transplant. Therefore, an internal LAD implant would be a one-time decision, whereas a patient might be treated with an external LAD at multiple times (similar to dialysis treatment for patients with renal disease). Hence, a model that is uniquely applicable to an internal LAD is a special case of a model that is applicable to an external LAD. The study described in this chapter is the first one to consider mathematical modeling of an LAD. We assume that the priority of a patient on the waiting list does not change after accepting an LAD in our model. That is, even if a patient accepts an LAD, she is still regarded as a MELD patient. This assumption contradicts UNOS's heart allocation rule, because according to that rule, a patient with a ventricular assist device (VAD) is considered in the highest urgency status [142], and the longer she has the VAD, the more her priority in the waiting list increases [142]. In other words, an earlier heart transplantation of VAD patients is encouraged. Similarly, we assume that an LAD behaves in a nonstationary manner. That is, once an LAD is implanted in a patient, her health improves for a while and then her health gets worse. Therefore, her priority in the waiting list should eventually increase. However, we do not consider this fact for simplicity.

Since an internal LAD has not been developed yet, we continue to utilize known facts about an external LAD when modeling a hypothetical internal LAD. Although initial clinical trials confirm the positive effect of an external LAD, patient tolerance for external LAD therapy is not well understood. In other words, the fact that external LADs have been shown to support patients does not necessarily confirm that they should accept the devices early. Although the patient's health typically improves while using an external LAD, the benefit of using it might be worse than not using it, since a patient's tolerance to continuous external

LAD therapy is largely unknown at this time [136]. Also, there may be other complications associated with using both types of LADs, similar to dialysis patients' predisposition to vascular disease [187] and the increased incidence of complications ranging from clotting to stroke in patients with artificial hearts [201]. We assume that these characteristics of an external LAD apply to the internal LAD discussed in our model. Our model considers this tradeoff and considers the conditions under which an ESLD patient should start or stop using an internal LAD. Therefore, our model will help manufacturers estimate the demand for a particular internal LAD.

The remainder of the chapter considers only internal LADs. We present the formulation of this model in Section 5.2 and discuss the structural properties we analyze in Section 5.3. We provide a numerical example in Section 5.4, and we present conclusions in Section 5.5.

5.2 MODEL FORMULATION

We formulate this model as two nested optimal stopping problems. The first one (OSP1) corresponds to the decision problem faced by the patient before accepting an LAD, and the second one (OSP2) corresponds to the decision problem faced by the patient while she is using an LAD. Both problems are formulated as discrete-time, infinite-horizon MDPs, with an objective of maximizing expected discounted reward (e.g., patient's expected survival in terms of life days). In the discrete-time MDP models, we assume the set of stages to be infinite, $\{1, \cdots, \infty\}$. We define λ as the discount factor with $0 < \lambda < 1$. States, actions, rewards, transition probabilities and optimality equations of the discrete-time MDP corresponding to the first optimal stopping problem are as follows:

States of OSP1: We identify state of the process at time t, $s_t \in S$ as the health state of the patient at time t, $h_t \in S_H$, and the quality of the liver offered to the patient at time t, $\ell_t \in S_L$. $S_H = \{1, \cdots, H+1\}$ where $H+1$ represents death, $H < \infty$, $S_L = \{1, \cdots, L, L+1\}$ where $L+1$ represents the "no offer" state, $L < \infty$. Therefore, $S = S_H \otimes S_L$. Note that the state space is the same as that of Alagoz et al. [7]. We assume that there exists a complete ordering of both the patient health states and liver qualities.

Actions of OSP1: At any time period, the patient can accept the offer and quit the process (action 'T'), or she can reject the current offer but accept an LAD and continue the process with an implanted LAD (action 'D'), or she can reject both the current offer and an LAD and continue the process (action 'W'). We define $a^*(s_t)$ as the optimal decision in state s at time t and $\mathcal{A}_{s_t}$ as the action space for state s at time t for the first optimal stopping problem; i.e.,

$$\mathcal{A}_{s_t} = \begin{cases} \{T, D, W\}, & \text{if } s = (h, \ell) \text{ s.t. } h \neq H+1, \ell \neq L+1, \\ \{D, W\}, & \text{if } s = (h, L+1) \text{ s.t. } h \neq H+1, \\ \emptyset, & \text{if } s = (H+1, \ell). \end{cases}$$

Rewards of OSP1: We assume that the rewards are stationary. The patient receives an expected post-transplant reward $r_T(h, \ell)$ if she accepts a liver of type ℓ while in health state h. We assume that $r_T(h, L+1) = r_T(H+1, \ell) = 0$. That is, the patient does not receive a post-transplant reward if she dies or if she does not receive an organ offer. The patient receives an expected immediate reward $r_D(h)$ if she rejects the current organ offer but accepts an LAD in health state h, and the patient accrues an expected immediate reward of $r_W(h)$ while in health state h if she rejects the current offer and an LAD. (Recall that currently she is not using an LAD.) Similarly, we assume that $r_D(H+1) = r_W(H+1) = 0$.

Transition probabilities of OSP1: Unless a patient either accepts an organ offer or dies, her health changes during the process based on the health state transition probability matrices $\mathcal{H}_D$ (if she accepts an LAD) and $\mathcal{H}_W$ (if she rejects an LAD). $\mathcal{H}_D = [\mathcal{H}_D(h^{'}|h)]$ is the probability that the patient will be in health state $h^{'}$ at time $t+1$, given that her health state is h at time t, and she accepts an LAD at time t, $h^{'}, h \in S_H$. Similarly, $\mathcal{H}_W = [\mathcal{H}_W(h^{'}|h)]$ is the probability that the patient will be in health state $h^{'}$ at time $t+1$, given that her health state is h at time t, and she rejects an LAD at time t, $h^{'}, h \in S_H$. We define $\mathcal{H}_D(H+1|H+1) = \mathcal{H}_W(H+1|H+1) = 1$, indicating that death is an absorbing state. We assume that the probability of an organ offer to a patient depends only on her current health state. We define $\mathcal{L}$ as the organ arrival probability matrix, i.e., $\mathcal{L} = [\mathcal{L}(\ell|h)]$ is the probability that the patient will receive liver offer ℓ at time t, given that her health state is h at time t. We set $\mathcal{L}(L+1|H+1) = 1$, so that the patient does not receive any liver offer after she dies. Then the transition probability matrix of the process is $\mathcal{P} = [\mathcal{P}(s'|h)], s' \in S$,

and $h \in S_H$ where $\mathcal{P}((h',\ell')|h) = \mathcal{H}_D(h^{'}|h)\mathcal{L}(\ell'|h')$, $h, h' \in S_H, \ell \in S_L$ if the patient rejects the organ offer and accepts an LAD. $\mathcal{P}((h',\ell')'|h) = \mathcal{H}_W(h^{'}|h)\mathcal{L}(\ell'|h')$, $h, h' \in S_H, \ell \in S_L$ if the patient rejects the organ offer and rejects an LAD.

Optimality equations of OSP1: In state (h,ℓ) the patient selects one of at most three actions available to her: she may accept the liver offer to transplant, reject the liver offer but accept an LAD, or reject both the liver offer and an LAD. Figure 5.1 represents the state transition diagram of the LAD model.

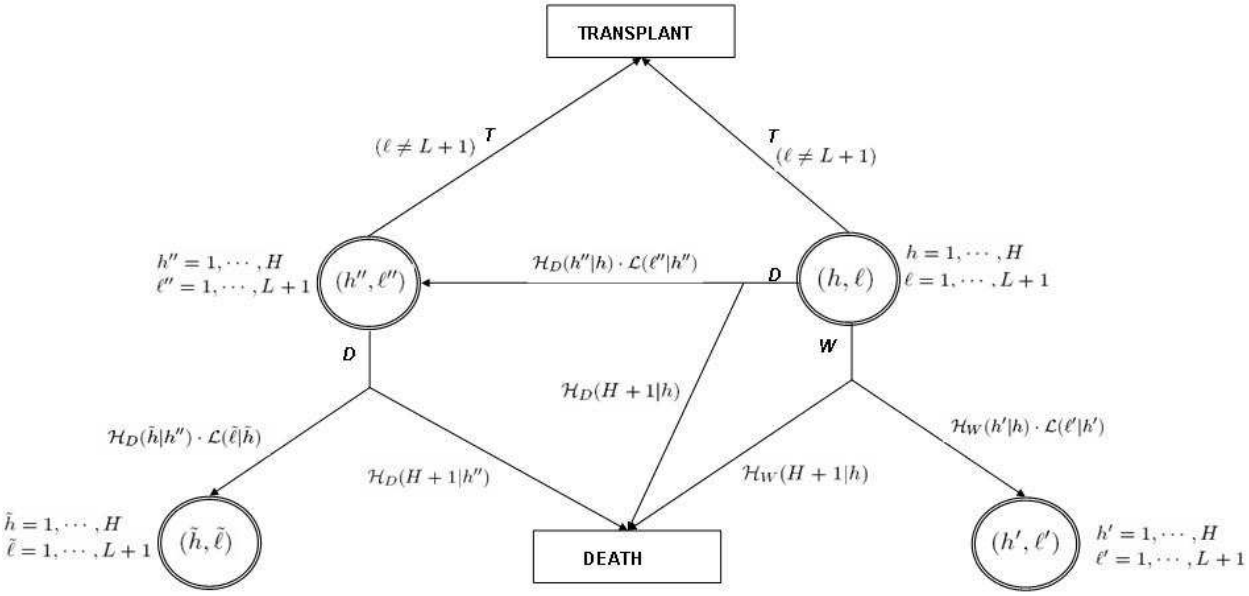

Figure 5.1: State transition diagram of the LAD Model.

We define $V(h,\ell)$ as the maximum total discounted expected reward that the patient can attain when her current health state is h, the quality of the current liver offer is ℓ, and the patient is not currently using an LAD. If the patient accepts the organ offer, she receives a reward of $r_T(h,\ell)$ and leaves the process. If she rejects the offer but accepts an LAD, she receives an expected reward of $r_D(h)$ and transitions into state (h',ℓ') with probability $\mathcal{H}_D(h^{'}|h)\mathcal{L}(\ell'|h')$. If she rejects both options and decides to wait for another period, she receives an intermediate reward of $r_W(h)$ and transitions into state (h',ℓ') with probability $\mathcal{H}_W(h^{'}|h)\mathcal{L}(\ell'|h')$. If the patient dies without receiving a transplant, she transitions to the terminal death state.

There are multiple stops to the first optimal stopping problem. If the patient accepts the current liver offer, the first optimal stopping problem ends without the second optimal

stopping problem being reached. If the patient accepts an LAD, the wait action is no longer available to her, since she has to stay with an LAD. Therefore, accepting an LAD terminates the first optimal stopping problem and initiates the second one.

States of OSP2: States are the same as those of OSP1.

Actions of OSP2: The patient is currently using an LAD, so she cannot take action 'W' anymore. We define $b^*(s_t)$ as the optimal decision in state s at time t and $\mathcal{B}_{s_t}$ as the action space for state s at time t for OSP2; i.e.,

$$\mathcal{B}_{s_t} = \begin{cases} \{T, D\}, & \text{if } s = (h, \ell) \text{ s.t. } h \neq H+1, \ell \neq L+1, \\ \{D\}, & \text{if } s = (h, L+1) \text{ s.t. } h \neq H+1, \\ \emptyset, & \text{if } s = (H+1, \ell) \end{cases}$$

Rewards of OSP2: Although the patient cannot receive the immediate reward $r_W(h)$, the definition of $r_D(h)$ and $r_T(h, \ell)$ stay the same.

Transition probabilities of OSP2: Transition probabilities that correspond to 'W' action are not applicable in this case.

Optimality equations of OSP2: In state (h, ℓ), the patient can either accept the organ offer or she can reject the organ offer and stay with an LAD implanted. We define $U(h, \ell)$ as the maximum total discounted expected reward that the patient can attain when her current health state is h, the quality of the current liver offer is ℓ, and she is currently using an LAD, where

$$U(h,\ell) = \max\left\{ r_T(h,\ell), r_D(h) + \lambda \left(\sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_D(h'|h) \mathcal{L}(\ell'|h') U(h', \ell') \right) \right\}, \\ h = 1, \cdots, H+1, l = 1, \cdots, L+1. \tag{5.1}$$

Then the optimality equations of OSP1 can be written as:

$$V(h,\ell) = \max\left\{ r_T(h,\ell), r_D(h) + \lambda \left(\sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_D(h'|h) \mathcal{L}(\ell'|h') U(h', \ell') \right), \right. \\ \left. r_W(h) + \lambda \left(\sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_W(h'|h) \mathcal{L}(\ell'|h') V(h', \ell') \right) \right\}, \\ h = 1, \cdots, H+1, l = 1, \cdots, L+1. \tag{5.2}$$

We set $V(H+1,\ell) = U(H+1,\ell) = 0$ for $\ell \in S_L$ because the total expected reward associated with the death state is 0.

From (5.1) and (5.2), $V(h,\ell)$ can be rewritten as:

$$V(h,\ell) = \max\left\{\max\left\{r_T(h,\ell), r_D(h) + \lambda\left(\sum_{h'\in S_H}\sum_{\ell'\in S_L}\mathcal{H}_D(h'|h)\mathcal{L}(\ell'|h')U(h',\ell')\right)\right\},\right.$$
$$\left. r_W(h) + \lambda\left(\sum_{h'\in S_H}\sum_{\ell'\in S_L}\mathcal{H}_W(h'|h)\mathcal{L}(\ell'|h')V(h',\ell')\right)\right\},$$
$$h = 1,\cdots,H+1, l = 1,\cdots,L+1, \quad (5.3)$$

or

$$V(h,\ell) = \max\left\{U(h,\ell), r_W(h) + \lambda\left(\sum_{h'\in S_H}\sum_{\ell'\in S_L}\mathcal{H}_W(h'|h)\mathcal{L}(\ell'|h')V(h',\ell')\right)\right\},$$
$$h = 1,\cdots,H+1, l = 1,\cdots,L+1. \quad (5.4)$$

(5.4) is equivalent to the model described in Alagoz et al. [9] with $r_T(h,\ell)$ replaced by $U(h,\ell)$. Although the patient faces the first stopping problem (OSP1) and then the second stopping problem (OSP2), we solve the system in the reverse order. That is, we solve OSP2 first, as output of it is an input to OSP1.

5.3 STRUCTURAL PROPERTIES

5.3.1 Definitions

Definition 5.1 *[15] A Markov chain is said to be increasing failure rate (IFR) if its rows are in increasing stochastic order; that is,*

$$z(i) = \sum_{j=h}^{H+1} P(j|i)$$

is nondecreasing in i for all $h = 1,\cdots,H+1$.

Definition 5.2 *The reward of continuing the first optimal stopping problem is defined as:*

$$R_W(h,\ell) = r_W(h) + \lambda \left(\sum_{h'} \sum_{\ell'} \mathcal{H}_W(h'|h) \mathcal{L}(\ell'|h') V(h',\ell') \right) \tag{5.5}$$

The reward of initiating/continuing the second optimal stopping problem is defined as:

$$R_D(h,\ell) = r_D(h) + \lambda \left(\sum_{h'} \sum_{\ell'} \mathcal{H}_D(h'|h) \mathcal{L}(\ell'|h') U(h',\ell') \right) \tag{5.6}$$

According to Definition 5.2, $V(h,\ell)$ and $U(h,\ell)$ are

$$V(h,\ell) = \max \Big\{ r_T(h,\ell), R_D(h,\ell), R_W(h,\ell) \Big\}, \quad (h,\ell) \in S, \tag{5.7}$$

$$U(h,\ell) = \max \Big\{ r_T(h,\ell), R_D(h,\ell) \Big\}, \quad (h,\ell) \in S. \tag{5.8}$$

5.3.2 Assumptions

In order to derive the structural properties of the LAD model, we make use of the following assumptions:

As1: $r_T(h,\ell)$ is nonincreasing in h and ℓ. That is, as the patient gets sicker or as the quality of the liver offered to her decreases, her post-transplant discounted quality-adjusted expected life days do not increase.

As2: $r_D(h)$ and $r_W(h)$ are nonincreasing in h. That is, as the patient gets sicker, the immediate reward she receives by waiting and using an LAD do not increase.

As3: $r_W(h) \geq r_D(h)$ for all health states. That is, there is a discomfort level associated with using an LAD, and therefore the immediate reward of waiting is greater than the immediate reward of using an LAD for every health state.

As4: $\mathcal{H}_D$ and $\mathcal{H}_W$ are IFR. That is, as the patient gets sicker, the probability of her moving to sicker health states increases if she waits or uses an LAD.

5.3.3 Monotonicity and Control-Limit Theorems

Remark 5.1 *(a)* $R_W(h,\ell) = R_W(h,\ell+1)$, $\ell = 1,\cdots,L$.
(b) $R_D(h,\ell) = R_D(h,\ell+1)$, $\ell = 1,\cdots,L$.

The proof of Remark 5.1 is obvious, and therefore omitted. According to this remark, $R_W(h,\ell)$ and $R_D(h,\ell)$ do not depend on ℓ. Therefore, we will refer to them as $R_W(h)$ and $R_D(h)$ respectively for the rest of the chapter.

Lemma 5.1 states that, for both optimal stopping problems, the maximum total expected discounted reward that the patient can attain in state (h,ℓ) is at least as high as the total expected discounted reward she can receive in health state h when no organ is offered to her. The proof of this lemma is very similar to the proof of Remark 3.1 and is therefore omitted.

Lemma 5.1 *(a) If we use the value iteration algorithm to solve the optimization problem (5.7), at any step n of the algorithm* $V^n(h,\ell) \geq V^n(h,L+1)$ *holds. Also, if* $r_T(h,\ell) < R_W(h)$ *and* $R_D(h) < R_W(h)$ *hold for state* (h,ℓ)*, then* $V^n(h,\ell) = V^n(h,L+1)$.
(b) If we use the value iteration algorithm to solve the optimization problem (5.8), at any step n of the algorithm $U^n(h,\ell) \geq U^n(h,L+1)$ *holds. Also, if* $r_T(h,\ell) < R_D(h)$ *holds for state* (h,ℓ)*, then* $U^n(h,\ell) = U^n(h,L+1)$.

Theorem 5.1 provides the sufficient conditions to establish the monotonicity of the value functions of both optimal stopping problems ($V(h,\ell)$ and $U(h,\ell)$) in ℓ. That is, the total life expectancy of the patient does not increase as the quality of the liver offer decreases both before and after accepting the device therapy under assumption *As1*. Alagoz et al. [9] also show the monotonicity of the value function of their model in the quality of liver offered to the patient. Although Alagoz et al.'s [9] model is a special case of (5.2), by rewriting it as two different optimal stopping problems, we are able to represent both (5.7) and (5.8) as special cases of Alagoz et al.'s model [9]. Therefore, $V(h,\ell)$ and $U(h,\ell)$ are also monotonic in the quality of liver offered to the patient.

Theorem 5.1 *Under As1, the value functions* $V(h,\ell)$ *and* $U(h,\ell)$ *are monotonically non-increasing in* ℓ, $\ell \in S_L \setminus \{L+1\}$, $\forall h \in S_H$.

Proof. To show that $U(h,\ell)$ is monotonically nonincreasing in ℓ, $\ell \in S_L \setminus \{L+1\}$, $\forall h \in S_H$, we consider the two values $U(h,\ell+1)$ can obtain. If $U(h,\ell+1) = r_T(h,\ell+1)$, then $U(h,\ell+1) \leq U(h,\ell)$ because $r_T(h,\ell+1) \leq r_T(h,\ell)$ by *As1* and $r_T(h,\ell) \leq U(h,\ell)$ by (5.8). If $U(h,\ell+1) = R_D(h)$, then $U(h,\ell+1) \leq U(h,\ell)$ because $R_D(h) \leq U(h,\ell)$. The proof of the monotonicity of $V(h,\ell)$ in ℓ is similar and omitted. □

Theorem 5.2 gives sufficient conditions for the monotonicity of value functions of both optimal stopping problems ($V(h,\ell)$ and $U(h,\ell)$) in the health state of the patient. Theorem 5.2 makes use of *As2* and *As4*. We present two lemmas before presenting Theorem 5.2.

Alagoz et al. [9] show the monotonicity of value function of their model by assuming that the health state transition matrix is IFR and Condition (5.9) is satisfied. Although the action space of our model includes more actions than Alagoz et al.'s, we are able to show monotonicity of both value functions in the health state of the patient under the same conditions. As Alagoz [4] interprets it, Condition (5.9) means that for any given liver type, as the patient gets sicker, the increase in the probability of receiving a liver offer must be smaller than the reduction in the benefit of total expected discounted post-transplant reward.

Lemma 5.2 *Let $V^i(h,\ell)$ and $U^i(h,\ell)$ be the value functions of the first and second optimal stopping problems at the i^{th} iteration of the value iteration algorithm. Let $z^i(h) = \sum_{\ell \in S_L} \mathcal{L}(\ell|h) V^i(h,\ell)$. If $V^i(h,\ell)$ is nonincreasing in h and ℓ and*

$$\frac{\mathcal{L}(\ell|h+1)}{\mathcal{L}(\ell|h)} \leq \frac{r_T(h,\ell)}{r_T(h+1,\ell)} \text{ for } h = 1,\cdots,H-1 \text{ and } \ell = 1,\cdots,L. \tag{5.9}$$

Then $z^i(h)$ is nonincreasing in h under As2 and As4.

Proof. Let $S^i_{L_{T_1}} = \{\ell \in S_L : a^{*i}(h+1,\ell) = \text{`}T', \mathcal{L}(\ell|h+1) \geq \mathcal{L}(\ell|h)\}$, $S^i_{L_{T_2}} = \{\ell \in S_L : a^{*i}(h+1,\ell) = \text{`}T', \mathcal{L}(\ell|h+1) < \mathcal{L}(\ell|h)\}$, $S^i_{L_D} = \{\ell \in S_L : a^{*i}(h+1,\ell) = \text{`}D'\}$, and $S^i_{L_W} = \{\ell \in S_L : a^{*i}(h+1,\ell) = \text{`}W'\}$. Then

$$z^i(h) - z^i(h+1) = \sum_{\ell \in S^i_{L_{T_1}}} [\mathcal{L}(\ell|h)V^i(h,\ell) - \mathcal{L}(\ell|h+1)V^i(h+1,\ell)] \tag{5.10}$$

$$+ \sum_{\ell' \in S^i_{L_{T_2}}} [\mathcal{L}(\ell'|h)V^i(h,\ell') - \mathcal{L}(\ell'|h+1)V^i(h+1,\ell')] \tag{5.11}$$

$$+ \sum_{\ell'' \in S^i_{L_D} \cup S^i_{L_W}} [\mathcal{L}(\ell''|h)V^i(h,\ell'') - \mathcal{L}(\ell''|h+1)V^i(h+1,\ell'')] \quad (5.12)$$

We can eliminate (5.10) by Condition (5.9), and (5.11) can be replaced with

$$\sum_{\ell' \in S^i_{L_{T_2}}} [\mathcal{L}(\ell'|h)V^i(h+1,L+1) - \mathcal{L}(\ell'|h+1)V^i(h+1,L+1)]$$

without increasing the right-hand side value because $V^i(h,\ell)$ is nonincreasing in h, ℓ and $\mathcal{L}(\ell'|h+1) < \mathcal{L}(\ell'|h)$ by definition. Then

$$\begin{aligned} z^i(h) - z^i(h+1) \geq & \sum_{\ell \in S^i_{L_{T_2}}} [\mathcal{L}(\ell|h)V^i(h+1,L+1) - \mathcal{L}(\ell|h+1)V^i(h+1,L+1)] && (5.13)\\ & + \sum_{\ell' \in S^i_{L_D} \cup S^i_{L_W}} \mathcal{L}(\ell'|h)V^i(h,\ell') && (5.14)\\ & - \sum_{\ell'' \in S_{L_D}} \mathcal{L}(\ell''|h+1)V^i(h+1,\ell'') && (5.15)\\ & - \sum_{\ell''' \in S_{L_W}} \mathcal{L}(\ell'''|h+1)V^i(h+1,\ell''') && (5.16) \end{aligned}$$

In (5.14), $V^i(h,\ell')$ can be replaced with $V^i(h+1,L+1)$ because $V^i(h,\ell)$ is nonincreasing in h and ℓ. In (5.15), $V^i(h+1,\ell'')$ can be replaced with $U^i(h+1,L+1)$ because the patient accepts the device. It can further be replaced with $V^i(h+1,L+1)$ because $V^i(h+1,L+1) \geq U^i(h+1,L+1)$. In (5.16) $V^i(h+1,\ell''')$ can be replaced with $V^i(h+1,L+1)$ because the patient decides to wait. Then we obtain

$$\begin{aligned} z^i(h) - z^i(h+1) \geq & \sum_{\ell \in S^i_{L_{T_2}}} [\mathcal{L}(\ell|h)V^i(h+1,L+1) - \mathcal{L}(\ell|h+1)V^i(h+1,L+1)] && (5.17)\\ & + \sum_{\ell' \in S^i_{L_D} \cup S^i_{L_W}} [\mathcal{L}(\ell'|h) - \mathcal{L}(\ell'|h+1)]V^i(h+1,L+1) && (5.18)\\ = & \sum_{\ell \notin S^i_{L_{T_1}}} [\mathcal{L}(\ell|h) - \mathcal{L}(\ell|h+1)]V^i(h+1,L+1) && (5.19) \end{aligned}$$

(5.19) is nonnegative by the definition of $S^i_{L_{T_1}}$ and nonnegativity of $V^i(h{+}1, L{+}1)$. Therefore, $\sum_{\ell \in S_L} \mathcal{L}(\ell|h)V^i(h,\ell)$ is nonincreasing in h.

Lemma 5.3 *[4] Let $\mathcal{H}$ be an IFR transition probability matrix and $V(h)$ be a nonincreasing function. Then the following hold:*

$$\sum_{h' \le h} \Big[\mathcal{H}(h'|h) - \mathcal{H}(h'|h+1)\Big] V(h') \ge \sum_{h' \ge h} \Big[\mathcal{H}(h'|h) - \mathcal{H}(h'|h+1)\Big] V(h),$$
$$\sum_{h'' > h} \Big[\mathcal{H}(h''|h) - \mathcal{H}(h''|h+1)\Big] V(h'') \ge \sum_{h'' > h} \Big[\mathcal{H}(h''|h) - \mathcal{H}(h''|h+1)\Big] V(h+1).$$

Theorem 5.2 *If As4 and (5.9) hold, then the value functions $V(h,\ell)$ and $U(h,\ell)$ are monotonically nonincreasing in h, $h \in S_H$, $\forall \ell \in S_L$.*

Proof. The monotonicity of $U(h,\ell)$ in h, $h \in S_H$, $\forall \ell \in S_L$ follows from Theorem 6.2 of Alagoz [4] because $\mathcal{H}_D$ is an IFR matrix (by *As4*) and (5.9) holds.

We show the monotonicity of $V(h,\ell)$ in h, $h \in S_H$, $\forall \ell \in S_L$ by induction. Let $V^i(h,\ell)$ be the total life expectancy of the patient in state (h,ℓ) at i^{th} iteration of the value iteration algorithm. We show that if we apply the value iteration algorithm to solve the problem, at any iteration of the algorithm $V^i(h,\ell) \ge V^i(h{+}1,\ell)$ is preserved for $h \in S_H \backslash \{H{+}1\}, \ell \in S_L$. The result follows from the convergence of the value iteration algorithm [141].

For the base case, assume that the value iteration algorithm starts with a value of 0 for each state for both problems, i.e., $V^1(h,\ell) = \max\Big\{U(h,\ell), r_W(h)\Big\}$ and $V^1(h+1,\ell) = \max\Big\{U(h+1,\ell), r_W(h+1)\Big\}$, for $h \in S_H \setminus \{H+1\}, \ell \in S_L$. Then the result holds for the base case, because $U(h,\ell) \ge U(h+1,\ell)$ by the monotonicity of $U(h,\ell)$ in h and $r_W(h) \ge r_W(h+1)$ $\forall h \in S_H \setminus \{H+1\}$ by *As2*.

Now assume that for iteration n, the result holds, i.e., $V^n(h,\ell) \ge V^n(h+1,\ell)$, $h \in S_H \setminus \{H+1\}, \ell \in S_L$. If $V^{n+1}(h+1,\ell) = U(h+1,\ell)$, then $V^{n+1}(h,\ell) \ge V^{n+1}(h+1,\ell)$, because $U(h,\ell) \ge U(h+1,\ell)$ and $V^{n+1}(h,\ell) \ge U(h,\ell)$. Otherwise,

$$\begin{aligned} V^{n+1}(h,\ell) - V^{n+1}(h+1,\ell) \ge r_W(h) + \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_W(h'|h)\mathcal{L}(\ell'|h')V^n(h',\ell') \\ - r_W(h+1) - \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_W(h'|h+1)\mathcal{L}(\ell'|h')V^n(h',\ell') \end{aligned} \quad (5.20)$$

$$\geq \lambda \sum_{h' \leq h} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1)\Big] z^n(h') + \lambda \sum_{h'' > h} \Big[\mathcal{H}_W(h''|h) - \mathcal{H}_W(h''|h+1)\Big] z^n(h'') \quad (5.21)$$

(5.21) follows from *As2*. From the induction assumption and Lemma 5.2, $z^n(h)$ is monotonic. So, we can replace $z^n(h')$ with $z^n(h)$ for $h' \leq h$ and $z^n(h'')$ with $z^n(h+1)$ for $h'' > h$, by Lemma 5.3. Then we obtain the following inequality:

$$\begin{aligned} &\geq \lambda \left(\sum_{h' \leq h} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1)\Big] z^n(h) + \sum_{h'' > h} \Big[\mathcal{H}_W(h''|h) - \mathcal{H}_W(h''|h+1)\Big] z^n(h+1) \right) \\ &= \lambda \left(\sum_{h' \leq h} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1)\Big] \Big[z^n(h) - z^n(h+1)\Big] \right) \quad (5.22) \\ &\geq 0. \end{aligned}$$

$z^n(h) - z^n(h+1) \geq 0$ by the induction assumption and Lemma 5.2, $\sum_{h' \leq h} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1)\Big]$ is nonnegative by *As4*. Therefore, $V(h, \ell)$ is monotonic in h. □

Definition 5.3 *[4] A liver-based control limit policy establishes a threshold liver quality ℓ for a particular health state h such that if the optimal action is to "accept" the liver offer for the threshold liver quality ℓ, then the optimal action stays the same if the quality of the liver offered is $1, 2, \ldots, \ell - 1$. Furthermore, if the optimal action is either to "wait" or "accept an LAD" for the threshold liver quality, then the optimal action is still "wait" or "accept an LAD" for the states corresponding to liver qualities $\ell + 1, \ldots, L$.*

Theorem 5.3 proves that a threshold liver quality exists for both optimal stopping problems ($(V(h, \ell))$ and $(U(h, \ell))$) such that the optimal action is to accept the organ offer if the quality of the liver is higher than the threshold and reject the liver otherwise. Theorem 5.3 is an immediate consequence of Remark 5.1 and *As1*, and therefore the proof is omitted.

Theorem 5.3 *There exists a liver-based control limit policy for both optimal stopping problems ($V(h, \ell)$ and $U(h, \ell)$) for a fixed health state, $h = 1, \cdots, H$ and $\ell = 1, \cdots, L - 1$ if As1 holds.*

Definition 5.4 *[4] A health-based control limit policy establishes a health state h for a particular liver quality ℓ such that if the optimal action is to "transplant" (accept the liver offer of quality ℓ) for the threshold health state h, then the optimal action stays the same for sicker health states, i.e., $h+1, h+2, \ldots, H$.*

Theorem 5.4 proves the existence of an optimal health-based control limit policy for the first optimal stopping problem. Theorem 5.4 makes use of *As2* and *As4*. Alagoz et al. [9] prove the existence of an optimal health-based control limit policy for their problem under conditions similar to (5.23) and (5.25). However, our model includes two different health state transition probability matrices. Therefore, we need two sets of each condition Alagoz et al. [9] define.

Conditions (5.23) and (5.24) state that for both health transition probability matrices $(\mathcal{H}_D, \mathcal{H}_W)$, the sum of health transition probabilities to sicker states are higher if the patient's current health state is sicker. Conditions (5.25) and (5.26) state that for both health transition probability matrices $(\mathcal{H}_D, \mathcal{H}_W)$, as the patient gets sicker, the decrease in the expected post-transplant reward is less than the increase in her probability of death. In order to prove this theorem, we use techniques similar to those of Alagoz [4].

Theorem 5.4 *If As2, As4 and (5.9) hold,*

$$\sum_{k=j}^{H} \mathcal{H}_D(k|h) \leq \sum_{k=j}^{H} \mathcal{H}_D(k|h+1), j = h+1, \cdots, H, h = 1, \cdots, H, \tag{5.23}$$

$$\sum_{k=j}^{H} \mathcal{H}_W(k|h) \leq \sum_{k=j}^{H} \mathcal{H}_W(k|h+1), j = h+1, \cdots, H, h = 1, \cdots, H, \tag{5.24}$$

$$\frac{r_T(h,\ell) - r_T(h+1,\ell)}{r_T(h+1,\ell)} \leq \lambda \left\{ \mathcal{H}_D(H+1|h+1) - \mathcal{H}_D(H+1|h) \right\}, h = 1, \cdots H, \tag{5.25}$$

and

$$\frac{r_T(h,\ell) - r_T(h+1,\ell)}{r_T(h+1,\ell)} \leq \lambda \left\{ \mathcal{H}_W(H+1|h+1) - \mathcal{H}_W(H+1|h) \right\}, h = 1, \cdots H, \tag{5.26}$$

hold, then a health-based control limit policy exists for the first optimal stopping problem for a fixed liver state.

Proof. In order to prove this theorem, we consider two cases:

Case 1: Suppose there exists a state (h, ℓ) *such that* $a^*(h, \ell) =$ 'T' *but* $a^*(h+1, \ell)$ *is uniquely* 'W'*:*

As $a^*(h, \ell) =$ 'T',

$$r_T(h, \ell) \geq r_W(h) + \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_W(h'|h) \mathcal{L}(\ell'|h') V(h', \ell'), \tag{5.27}$$

and $a^*(h+1, \ell) =$ 'W' uniquely,

$$r_T(h+1, \ell) < r_W(h+1) + \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_W(h'|h+1) \mathcal{L}(\ell'|h') V(h', \ell'). \tag{5.28}$$

Then

$$\begin{aligned} r_T(h, \ell) - r_T(h+1, \ell) > \quad & r_W(h) - r_W(h+1) + \\ & \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1) \Big] \mathcal{L}(\ell'|h') V(h', \ell') \end{aligned} \tag{5.29}$$

$$\begin{aligned} \geq \qquad & \lambda \left(\sum_{h' \leq h} \mathcal{H}_W(h'|h) z(h') + \sum_{h'' > h} \mathcal{H}_W(h''|h) z(h'') \right) \\ & -\lambda \left(\sum_{h' \leq h} \mathcal{H}_W(h'|h+1) z(h') + \sum_{h'' > h} \mathcal{H}_W(h''|h+1) z(h'') \right), \end{aligned} \tag{5.30}$$

$$\begin{aligned} = \quad & \lambda \left(\sum_{h' \leq h} \Big[\mathcal{H}_W(h'|h) - \mathcal{H}_W(h'|h+1) \Big] z(h') + \right. \\ & \left. + \sum_{h''=h+1}^{H} \Big[\mathcal{H}_W(h''|h) - \mathcal{H}_W(h''|h+1) \Big] z(h'') \right), \end{aligned} \tag{5.31}$$

(5.30) follows from *As2*. (5.31) follows by $z(H+1)=0$. By Lemma 5.3, $z(h')$ can be replaced with $z(h)$ and $z(h'')$ can be replaced with $z(h+1)$ because $\mathcal{H}_W$ is IFR and $z(h)$ is nonincreasing in h by Condition (5.9).

$$\begin{aligned} \geq \quad & \lambda \left(\left[1 - \sum_{h''=h+1}^{H} \mathcal{H}_W(h''|h) - \mathcal{H}_W(H+1|h) \right] \right. \\ & \left. - \left[1 - \sum_{h''=h+1}^{H} \mathcal{H}_W(h''|h+1) - \mathcal{H}_W(H+1|h+1) \right] \right) z(h) \\ & + \lambda \left(\sum_{h''=h+1}^{H} \Big[\mathcal{H}_W(h''|h) - \mathcal{H}_W(h''|h+1) \Big] z(h+1) \right), \end{aligned} \tag{5.32}$$

$$\begin{aligned} = \quad & \lambda \left(\left[\sum_{h''=h+1}^{H} \left[\mathcal{H}_W(h''|h+1) - \mathcal{H}_W(h''|h) \right] \right] \left[z(h) - z(h+1) \right] \right) \\ & + \lambda \left(\Big[\mathcal{H}_W(H+1|h+1) - \mathcal{H}_W(H+1|h) \Big] z(h) \right), \end{aligned} \tag{5.33}$$

$\left[\sum_{h''=h+1}^{H} [\mathcal{H}_W(h''|h+1) - \mathcal{H}_W(h''|h)] \right] \geq 0$ by Condition (5.24), so we can delete this term without increasing the right-hand side and obtain,

$$r_T(h,\ell) - r_T(h+1,\ell) > \quad \lambda \left(\Big[\mathcal{H}_W(H+1|h+1) - \mathcal{H}_W(H+1|h) \Big] z(h) \right), \tag{5.34}$$

$z(h)$ can be replaced with $r_T(h+1,\ell)$ without increasing the right-hand side because $z(h) \geq V(h,L+1) \geq V(h+1,L+1) > r_T(h+1,\ell)$. The last inequality follows because $a^*(h+1,\ell)$ is uniquely 'W'. Then (5.34) becomes

$$r_T(h,\ell) - r_T(h+1,\ell) > \quad \lambda \left(\Big[\mathcal{H}_W(H+1|h+1) - \mathcal{H}_W(H+1|h) \Big] r_T(h+1,\ell) \right), \tag{5.35}$$

However, (5.35) contradicts Condition (5.26). Therefore, if $a^*(h,\ell) =$ 'T', $a^*(h+1,\ell) \neq$ 'W'.

Case 2: Suppose there exists a (h,ℓ) *such that* $a^*(h,\ell) =$ 'T' *but* $a^*(h+1,\ell)$ *is* 'D' *or* 'W'*:* If $a^*(h+1,\ell)$ is 'W', then the contradiction discussed in the previous case stays valid.

Otherwise, $a^*(h+1,\ell)$ is 'D'. Because $a^*(h,\ell) =$ 'T',

$$r_T(h,\ell) \geq r_D(h) + \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_D(h'|h)\mathcal{L}(\ell'|h')U(h',\ell'), \tag{5.36}$$

and $a^*(h+1,\ell) =$ 'D' implies

$$r_T(h+1,\ell) < r_D(h+1) + \lambda \sum_{h' \in S_H} \sum_{\ell' \in S_L} \mathcal{H}_D(h'|h+1)\mathcal{L}(\ell'|h')U(h',\ell'). \tag{5.37}$$

This part of the theorem is very similar to *Case 1*. By *As2*, the assumption that $\mathcal{H}_D$ is IFR, the monotonicity of $\sum_{\ell \in S_L} \mathcal{L}(\ell|h)U(h,\ell)$ by Lemma 5.2, Conditions (5.9), (5.23) and (5.25), a similar argument shows that if $a^*(h,\ell) =$ 'T', $a^*(h+1,\ell) \neq$ 'D'. Because $a^*(h+1,\ell) \neq$ 'W' and $a^*(h+1,\ell) \neq$ 'D', $a^*(h+1,\ell) =$ 'T' when $a^*(h,\ell) =$ 'T'. □

Theorem 5.5 compares the optimal liver-based control limits for the two optimal stopping problems. The proof is based on the idea that if a patient accepts a particular quality of organ offered to her in health state h before accepting an LAD, then she will accept the same quality of organ offer in the same health state after accepting an LAD. Basically, if the patient has more choices, she will be more selective. Let $\Omega_1(h)(\Omega_2(h))$ be the optimal liver-based control limit for health state h for the first (second) optimal stopping problem.

Theorem 5.5 $\Omega_1(h) \leq \Omega_2(h)$ *for every health state.*

Proof. $a^*(h,\Omega_1(h))$ ='T' because $\Omega_1(h)$ is the threshold liver quality such that the patient accepts the organ offer. Therefore, $V(h,\Omega_1(h)) = r_T(h,\Omega_1(h))$, and $r_T(h,\Omega_1(h)) \geq R_D(h), r_T(h,\Omega_1(h)) \geq R_W(h)$ by (5.7). From (5.8) and $r_T(h,\Omega_1(h)) \geq R_D(h)$, $b^*(h,\Omega_1(h)) =$ 'T'. That is, every acceptable liver in OSP1 is also acceptable in OSP2. So, $\Omega_1(h) \leq \Omega_2(h)$. □

5.4 A NUMERICAL EXAMPLE

In this section, we numerically solve the model described earlier in this chapter a hypothetical internal LAD. In other words, data to estimate the health state transition probability

matrices for an LAD as well as the immediate rewards associated with using it are not available. Therefore, we use hypothetical data in our numerical experiments. More specifically, we validate our model numerically by using existing health state transition matrices corresponding to different disease groups.

Data sources used to estimate the parameters in this chapter are either obtained from the data sources used in Section 3.5.1 or from Alagoz [4]. The expected post-transplant rewards used in Chapter 3 are directly used in this chapter as well. We assume that the immediate reward of waiting is one day similar to existing studies in the literature [7, 8, 9, 153]. Since there is a discomfort level associated with using an LAD, we assume that the immediate reward associated with using it is less than one day.

We do not use the liver arrival rates estimated in Section 3.5.2 because we are interested in liver arrival probabilities in this chapter. Therefore, we utilize the liver arrival probabilities estimated by Alagoz [4] using UNOS data. The UNOS dataset Alagoz [4] uses to estimate liver arrival probabilities is not one of the datasets we use in Chapter 3. This data set was collected between February 27, 2002, and May 31, 2003, and it includes information such as region, MELD scores, age, blood type, gender, race, and disease type for 25,810 patients waiting for a liver transplant. It also includes information for the cadaveric organ offers.

Alagoz [4] utilizes UPMC data in order to estimate health state transition probability matrices $\mathcal{H}$ for different disease groups. Ideally, $\mathcal{H}$ matrices that Alagoz [4] estimates should correspond to $\mathcal{H}_W$ in our model. However, we assume that $\mathcal{H}$ matrices that Alagoz [4] estimates for different disease groups correspond to both $\mathcal{H}_W$ and $\mathcal{H}_D$ in our model. More specifically, we consider the health state transition probability matrix for disease group one (primary biliary cirrhosis) as $\mathcal{H}_W$ and the health state transition probability matrix for disease group two (hepatitis) as $\mathcal{H}_D$. We make this selection because disease group two is a more stable disease than disease group one, as discussed in Chapter 3. That is, the patient's health deteriorates faster under disease group one. This is a reasonable selection of disease groups for corresponding actions, because, by accepting an LAD, we assume that the patient's disease progression becomes more stable.

We consider the optimal policies for a 60-year-old, female patient with primary biliary cirrhosis who has blood type A. We use an annual discount rate of 0.97. We either refer

to Alagoz et al. [7, 9] or calculate the maximum violation of the IFR assumption and the sufficient conditions presented in Section 5.3.3. According to Alagoz et al. [7], the maximum violation of $As4$ for 'W' and 'D' actions are calculated as follows:

$$\epsilon_1 = \max_{j,h} \left\{ 0, \sum_{k=j}^{H+1} \mathcal{H}_W(k|h) - \mathcal{H}_W(k|h+1) \right\} \text{ for } j = 1, \cdots, H+1, \text{ and } h = 1, \cdots H-1,$$

$$\epsilon_2 = \max_{j,h} \left\{ 0, \sum_{k=j}^{H+1} \mathcal{H}_D(k|h) - \mathcal{H}_D(k|h+1) \right\} \text{ for } j = 1, \cdots, H+1, \text{ and } h = 1, \cdots H-1.$$

The maximum violation of Condition (5.9) [9]:

$$\epsilon_3 = \max_{h,\ell} \left\{ 0, \frac{\mathcal{L}(\ell|h+1)}{\mathcal{L}(\ell|h)} - \frac{r_T(h,\ell)}{r_T(h,\ell+1)} \right\} \text{ for } h = 1, \cdots, H-1, \text{ and } \ell = 1, \cdots L.$$

The maximum violations of Conditions (5.23) and (5.24) [7]:

$$\epsilon_4 = \max_{j,h} \left\{ 0, \sum_{k=j}^{H} \mathcal{H}_D(k|h) - \mathcal{H}_D(k|h+1) \right\} \text{ for } j = h+1, \cdots, H, \text{ and } h = 1, \cdots H,$$

$$\epsilon_5 = \max_{j,h} \left\{ 0, \sum_{k=j}^{H} \mathcal{H}_W(k|h) - \mathcal{H}_W(k|h+1) \right\} \text{ for } j = h+1, \cdots, H, \text{ and } h = 1, \cdots H.$$

The maximum violations of Conditions (5.25) and (5.26):

$$\epsilon_6 = \max_{h} \left\{ 0, \frac{r_T(h,\ell) - r_T(h+1,\ell)}{r_T(h+1,\ell)} - \lambda \left\{ \mathcal{H}_D(H+1|h+1) - \mathcal{H}_D(H+1|h) \right\} \right\} \text{ for } h = 1, \cdots, H.$$

$$\epsilon_7 = \max_{h} \left\{ 0, \frac{r_T(h,\ell) - r_T(h+1,\ell)}{r_T(h+1,\ell)} - \lambda \left\{ \mathcal{H}_W(H+1|h+1) - \mathcal{H}_W(H+1|h) \right\} \right\} \text{ for } h = 1, \cdots, H,$$

The values for $\epsilon_1, \cdots, \epsilon_7$ are 0.0234, 0.021, 0.64, 0.0021, 0.0038, 0.532, and 0.0278, respectively.

Figure 5.2 illustrates the optimal policies when the immediate reward of accepting an LAD is assumed to be 0.3 days. According to this figure, there is a liver-based and a health-based control limit in terms of the transplant action as proved in Theorems 5.3 and 5.4. For a particular health state, the Wait/Device decision does not change with the quality of the organ offered, because the rewards of waiting and accepting an LAD do not depend on it, as stated in Remark 5.1. Also, according to Figure 5.2, the set of acceptable livers for OSP1 is a subset of the set of acceptable livers for OSP2.

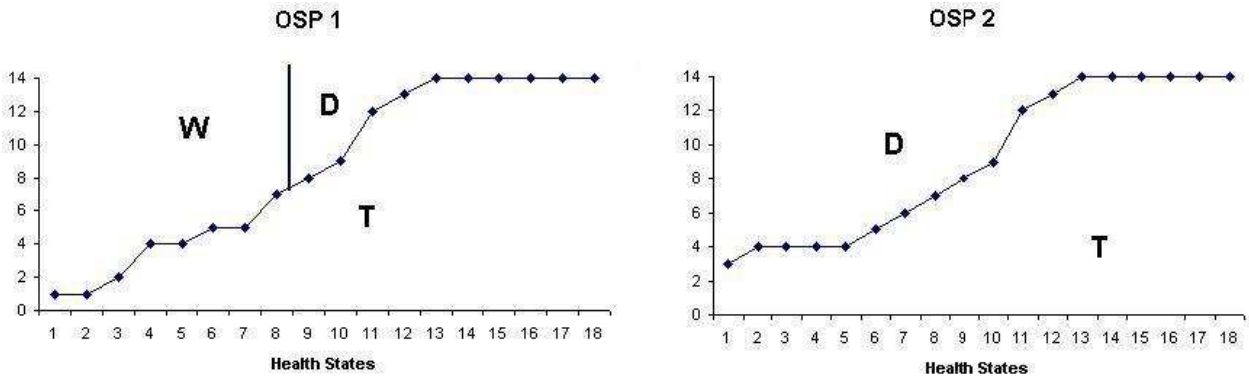

Figure 5.2: Example optimal LAD policies.

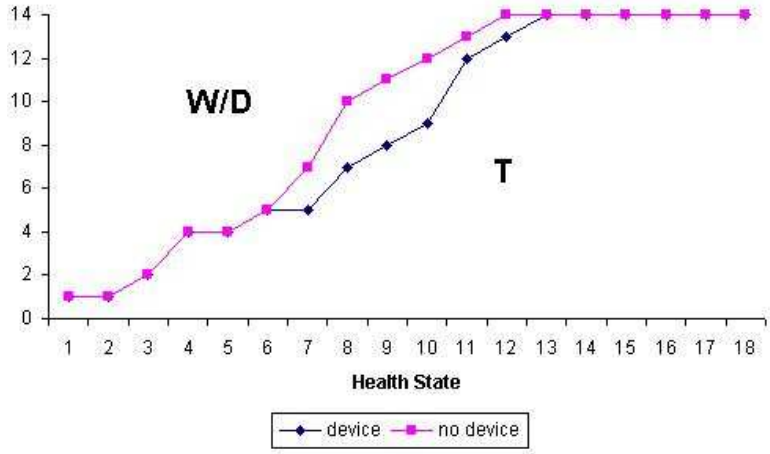

Figure 5.3: Comparing optimal policies when an LAD is available and when an LAD is not available.

Figure 5.3 compares the optimal policies when an LAD is available to the patient and when it is not available to the patient. In other words, we compare the optimal policies of the model described in this section to that of Alagoz et al.'s [9]. This figure shows that the patient accepts fewer, higher quality livers if an LAD is available to her.

5.5 CONCLUSIONS

Currently, transplantation remains the only therapy for ESLD patients. Present efforts toward improving the donor pool by split-liver and living-donor transplantations still do not decrease considerably the number of patients who die while waiting for an organ. Therefore, an intermediate therapy, that will either support the patient while she is waiting for a transplant or replace the function of a liver, is needed.

In this chapter, we model an emerging type of treatment for ESLD, a hypothetical LAD, which would eliminate the concerns discussed above. We also present sufficient conditions for a patient to accept a transplant both before and after accepting an LAD and for different health states and liver offers. Since we model our problem as two nested optimal stopping problems and classify both as special cases of the model presented in Alagoz et. al. [9], the structural properties we discuss resemble their model.

Our model is based on the assumption that the immediate reward of accepting an LAD and the health state transition probability matrices while using one both are known. However, the data regarding that reward and those matrices while using an LAD do not exist. Therefore, our model considers hypothetical data, and in order for it to be practical, they should be calibrated. Even if the data regarding the health state transition matrices while using an LAD were within reach, we still would have to modify our model such that a patient's health initially improves while she is using an LAD, and then gets worse.

If the ongoing research on LADs satisfies the conditions presented in this chapter, and a new generation of LADs is designed based on those conditions, then the number of patients who die while waiting for a liver should decrease, and the patients' total life expectancy should increase.

6.0 CONCLUSIONS AND FUTURE RESEARCH

6.1 CONCLUSIONS

This dissertation applies mathematical techniques to address fundamental and emerging questions in ESLD. Three models discussed in this dissertation increase and ascertain patient autonomy in liver transplantation, either by investigating patients' flexibility to choose the waiting list(s) they join, or by investigating a patient's choice regarding the optimal timing of the use of an emerging liver assist device therapy.

The first two models concentrate on multiple listing, which is one of the most controversial issues within organ transplantation. This dissertation is the first study to introduce an optimization model of multiple listing in liver transplantation. We establish two different models of multiple listing in liver transplantation through which we are able to consider a single multiple-listed patient's perspective as well as the societal perspective. Critically analyzing the results of both perspectives, we add insight to existing debate about multiple listing.

In Chapter 3, we assess the impact of relocation and multiple listing on a single patient. We analyze decisions faced by an ESLD patient beyond the simple liver accept/reject decision. The patient decides in which home OPO to list, in which additional OPOs to list, and then which organs to accept. We model the liver accept/reject decision as an infinite horizon continuous-time MDP model. We solve the multiple listing decision using a branch-and-bound technique in which each node of the tree corresponds to a different OPO set. We construct a separate branch-and-bound tree for each home OPO. We analyze this problem under two constraints: a cardinality constraint that restricts the number of OPOs in which

a patient can list, and a budget constraint that restricts the total distance a patient can travel in order to multiple list.

Considering the societal perspective in Chapter 4, we evaluate the potential benefits and disadvantages of multiple listing to the entire waiting list. However, we do not present a game-theoretic model due to the intractability given the number of players, the asymmetry of the game, and a nonzero-sum reward structure. Therefore, we solve the problem utilizing Shechter et al.'s simulation model [162]. We model the current liver allocation system in which approximately 3% of all ESLD patients multiple list, and we also explore sensitivity with respect to this value. We compare our findings to the case where multiple listing is prohibited, i.e., to Shechter et al.'s [162] results.

All of the previous models in liver transplantation optimization consider an organ transplant as the only treatment option available to ESLD patients [7, 8, 9, 153]. Iin Chapter 5, we consider an additional treatment option: a hypothetical, internal LAD. We model the problem as a nested, infinite horizon discrete-time MDP. We derive the structural properties of that model, including sufficient conditions that ensure the existence of control-limit policies. We provide a numerical example using hypothetical data. Through our model and the sufficient conditions we provide, we assist researchers and manufacturers in their development guidelines.

6.2 FUTURE RESEARCH

Solving the listing and home OPO selection decisions multiple times: In Chapter 3, we model the decision problem faced by the patient in three stages. The problems faced in the first stage (home OPO selection), and the second stage (multiple listing) are one-time decisions and the third-stage (liver acceptance) is a sequential decision process that depends on the first two stages. As the health state of the patient changes, her optimal first- and second-stage decisions change as well. Therefore, the patient should be given the flexibility to change the decisions she made in the first two stages. Currently, we solve the first two stages for the patient's initial health state. However, we can modify the model so that it is

possible for her to change her home OPO or listing decision as her health changes. Instead of solving the third-stage decision for specific home OPO and listing decisions, we would have to solve the decision problems at every stage at every decision epoch.

Patients listing in their optimal OPO sets within the simulation: In Chapter 4, we determine the probability of multiple listing and the set of OPOs based on historical data. A possible extension of this model includes finding the optimal OPO set for every patient and incorporating this decision into the simulation. In other words, running the optimization problem described in Chapter 3 (excluding the first-stage decision) and the simulation model described in Chapter 4 together. In doing so, we may restrict every patient generated in the simulation with a different cardinality/total distance constraint based on race, gender, and disease group. Since the optimization problem assumes that the multiple listing of a single patient does not change the organ arrival rates to other patients, we are aware that this would yield sub-optimal results.

Selecting the home OPO within the simulation: In its current form, the home OPO selection decision is left out of the simulation model described in Chapter 4. If we run the simulation model based on the results from the optimization problem, we can also incorporate the home OPO selection decision into the societal framework.

Modeling the listing decision as a congestion game: The listing and liver acceptance decisions can also be incorporated within a societal framework such that the listing decision is modeled as a *congestion game*. In a congestion game, the payoff a player receives for playing a particular strategy depends on the total number of players utilizing the same strategy and decreases by that number [109]. Similarly, a patient would receive more frequent organ offers that are harvested in one of the OPOs in which she is listed if fewer patients were listed in that OPO. By iteratively running the simulation model for a specific listing for every patient, thereby revising the liver arrival rates, and resolving the congestion game (listing decision) with the revised arrival rates, we should obtain the equilibrium listing and liver acceptance decisions.

Possible extensions to the liver assist device model: We do not provide an extensive numerical study for the model described in Chapter 5, since we consider a hypothetical LAD. However, showing numerically that the structural properties discussed in Chapter 5 hold is an interesting research opportunity for the future. Also, a very important consideration in liver support system design is the issue of how much human liver tissue from deceased/living donors is needed to provide adequate bioactive support [78]. The tradeoff stems from the fact that more human liver tissue would enable prolonged survival; however, it is a scarce resource. This idea of finding the optimal amount of liver cells is a current consideration in LAD development research.

APPENDIX A

LEADING CAUSES OF DEATH

Table A1: Leading causes of death in the U.S. in 2004 [119]

Rank	Cause of death	Number	Percent
...	All causes	2,397,615	100.0
1	Diseases of heart	652,486	27.2
2	Malignant Neoplasms	553,888	23.1
3	Cerebrovascular diseases	150,074	6.3
4	Chronic lower respiratory diseases	121,987	5.1
5	Accidents (unintended injuries)	112,012	4.7
6	Diabetes mellitus	73,138	3.1
7	Alzheimer's disease	65,965	2.8
8	Influenza and pneumonia	59,664	2.5
9	Nephritis, nephrotic syndrome and nephrosis	42,480	1.8
10	Septicemia	33,373	1.4
11	Intentional self-harm (suicide)	32,430	1.4
12	Chronic liver disease and cirrhosis	27,013	1.1
13	Essential (primary) hypertension and hypertensive renal disease	23,076	1.0
14	Parkinson's disease	17,989	0.8
15	Assault (homicide)	17,357	0.7
...	All other causes (residual)	414,674	17.3

APPENDIX B

OBTAINING SML THROUGH A RESTRICTION ON ML

In this appendix, we consider a special case of ML, which we call simplified multiple listing (SML). We formally define SML as follows:

SIMPLIFIED MULTIPLE LISTING (SML)
INSTANCE: Given a set $\mathcal{I}$ of indices with $|\mathcal{I}|$ even, and $\omega_{ij} \in \mathbb{R}_+^{|\mathcal{I}|*|\mathcal{I}|}$ of coefficients for each $i, j \in \mathcal{I}$ such that $\omega_{ii} = \omega_{jj}$, $\omega_{jj} > \max_i \sum_{k \neq i} \omega_{ik}$, and $\omega_{jk} = \omega_{kj}, i, j, k \in \mathcal{I}$, rewards r_T, r_W such that $r_T > (r_W/\alpha)$ and $M \in \mathbb{Z}_+$.
QUESTION: Is there a partition of $\mathcal{I}$ into disjoint sets $\mathcal{I}_1$, $\mathcal{I}_2$ such that $|\mathcal{I}_1| = |\mathcal{I}_2|$ and $\sum_{i \in \mathcal{I}_2} \sum_{i \in \mathcal{I}_1} \omega_{ij}$ is at least M?

SML is a specific class of ML. In this restricted problem, there are even number of OPOs ($|\mathcal{I}|$ even). If $|\mathcal{I}|$ is odd, then we add a dummy OPO with zero organ offer arrival rate. There is only one region ($|\mathcal{R}| = 1$), so $\mathcal{R}(i)$ are the same for all $i \in \mathcal{I}$. $K \in \mathbb{Z}_+$ in this problem is defined as $K = |\mathcal{I}|/2$. So, the cardinality constraint restricts the patient to list in at most half of the OPOs. There is only one health state ($|S_H| = 1$) and a single liver quality ($|S_L| = 1$). Therefore, $\mu(h, h')$ for $h, h' \in S_H$ is not defined, while r_T and r_W are used to represent post-transplant and immediate rewards, respectively. In this specific problem $r_T > (r_W/\alpha)$. Recall that $\nu_O(\ell|h)$ is the organ offer arrival rate at OPO set O and that it is a function of $\omega_{ij}(\ell|h)$. Since $|S_H| = 1$ and $|S_L| = 1$, $\omega_{ij}(\ell|h)$ and $\nu_O(\ell|h)$ can be simply refer-

red to as ω_{ij} and ν_O, respectively. In the simplified problem, every OPO is in the admissible set of the home OPO, i.e. $A_i = \mathcal{I}$. Hence, there is no geographical restriction.

According to the above-mentioned restrictions and Remark 3.1, Bellman's equations can be rewritten as follows:

$$V_O(\ell) = \max\left\{r_T, V_O(L+1)\right\} \tag{B.1}$$

$$V_O(L+1) = \frac{r_W}{\lambda_{max}+\alpha} + \frac{\lambda_{max}-\nu_O}{\lambda_{max}+\alpha}V_O(L+1) + \frac{\nu_O}{\lambda_{max}+\alpha}V_O(\ell). \tag{B.2}$$

From (B.2), it is possible to define $V_O(L+1)$ in terms of $V_O(\ell)$ as:

$$\left(1 - \frac{\lambda_{max}-\nu_O}{\lambda_{max}+\alpha}\right)V_O(L+1) = \frac{r_W}{\lambda_{max}+\alpha} + \frac{\nu_O}{\lambda_{max}+\alpha}V_O(\ell) \tag{B.3}$$

$$V_O(L+1) = \frac{r_W + \nu_O V_O(\ell)}{\alpha+\nu_O}. \tag{B.4}$$

From (B.1), $V_O(\ell)$ is either r_T or $V_O(L+1)$. If $V_O(\ell) = r_T$, then

$$V_O(L+1) = \frac{r_W + \nu_O r_T}{\alpha+\nu_O}. \tag{B.5}$$

If $V_O(\ell) = V_O(L+1)$, then

$$V_O(L+1) = \frac{r_W + \nu_O V_O(L+1)}{\alpha+\nu_O}$$

$$V_O(L+1) = \frac{r_W}{\alpha}. \tag{B.6}$$

From Equation (B.5),

$$V_O(L+1) = \frac{r_W + \nu_O r_T}{\alpha+\nu_O}$$

$$V_O(L+1) = \frac{r_W + \nu_O r_T + \alpha r_T - \alpha r_T}{\alpha+\nu_O}$$

$$V_O(L+1) = \frac{r_W - \alpha r_T}{\alpha+\nu_O} + \frac{r_T(\nu_O+\alpha)}{\alpha+\nu_O}$$

$$V_O(L+1) = \frac{r_W - \alpha r_T}{\alpha+\nu_O} + r_T. \tag{B.7}$$

Since $r_T > (r_W/\alpha)$, $r_W - \alpha r_T < 0$. Therefore, maximizing $V_O(h, L+1)$ in (B.7) is equivalent to maximizing ν_O.

Next from Equation (B.5),

$$\frac{r_W + \nu_O r_T}{\alpha + \nu_O} > \frac{r_W + \nu_O (r_W/\alpha)}{\alpha + \nu_O}$$
$$= \frac{r_W(\alpha + \nu_O)}{\alpha(\alpha + \nu_O)} = \frac{r_W}{\alpha}.$$

Since $r_T > (r_W/\alpha)$, then from (B.5) and (B.6) it follows that in the solution of (3.4)-(3.6) $V_O(\ell) = r_T$. Consequently, maximizing $V_O(L+1)$ is equivalent to maximizing ν_O based on (B.7). Therefore, optimization problem (3.4)-(3.6) is reduced to solving:

$$\max_O \sum_{i \in O} \nu_O \tag{B.8}$$
$$|O| \leq \frac{|\mathcal{I}|}{2}. \tag{B.9}$$

where $\nu_O = \sum_{i \in O} \omega_{ii} + \sum_{i \in O} \sum_{k \notin O} \omega_{ki}$.

Furthermore, we assume that the arrival rate of organs that are harvested and offered in the same OPO is higher than the maximum regional offer rate any OPO can provide ($\omega_{jj} > \max_i \sum_{k \neq i} \omega_{ik}, i, j, k \in \mathcal{I}$). In other words, it is optimal to list in as many OPOs as possible, and therefore receive local organ arrival rates, rather than to list in fewer OPOs, and sacrifice some local rates in order to receive higher regional rates. Consequently, constraint (B.9) should be tight in the optimal solution.

We further assume that the regional arrival rates are the same between the harvesting OPO and the transplant OPO ($\omega_{jk} = \omega_{kj}$, $\forall j, k \in \mathcal{I}$), and the local arrival rates at each OPO is the same ($\omega_{ii} = \omega_{jj}$ for $i, j \in \mathcal{I}$). Therefore, we set $\omega_{ii} = \mathcal{F} > \max_i \sum_{k \neq i} \omega_{ik}, i, k \in \mathcal{I}$.

As optimal O includes exactly half of the OPOs and the local arrival rates are the same for each OPO, $\sum_{i \in O} \omega_{ii}$ becomes $|\mathcal{I}|/2 \cdot \mathcal{F}$. Since constraint (B.9) in (B.8)-(B.9) is tight and $|\mathcal{I}|/2 \cdot \mathcal{F}$ is a constant, the optimization problem (B.8)-(B.9) is reduced to:

$$\max_O \left\{ \sum_{i \in O} \sum_{k \notin O} \omega_{ki} \right\} \tag{B.10}$$
$$|O| = \frac{|\mathcal{I}|}{2}. \tag{B.11}$$

According to (B.10)-(B.11), only regional rates are of interest. The decision problem version of (B.10)-(B.11) is referred to as SIMPLIFIED MULTIPLE LISTING (SML).

APPENDIX C

ESTIMATING ORGAN OFFER ARRIVAL RATES

C.1 CALCULATING LOCAL AND REGIONAL RATES NUMERICALLY

In this section we numerically show the estimation of regional offer rates for OPOs in Region 10 for MELD score 6 and liver type 10.

According to the UNOS datasets utilized in the dissertation, offer arrival rate to a singly-listed patient ($\omega_i(\ell|h)$) in OPOs in Region 10 and the fraction of local transplants ($P(i,i)$) in OPOs in Region 10 are displayed in Table C1.

Table C1: Input Values.

OPO(i)	$\omega_i(\ell = 10\|h = 6)$	$P(i,i)$
Ann Arbor (Ann)	0.001116	0.959383754
Cincinnati (Cin)	0.000824	0.340557276
Cleveland (Cle)	0.00195	0.596707819
Columbus (Col)	0.000077	0.788732394
Indianapolis (Ind)	0.000647	0.900862069
Maumee (Mau)	0.000317	0.652173913

Using the values shown in Table C1, we calculate values in Table C2, which are then utilized in evaluating (3.71).

Table C2:

OPO(i)	$\xi_i(\ell = 10\|h = 6)$	$\omega_i(\ell = 10\|h = 6) - \xi_i(\ell = 10\|h = 6)$
Ann Arbor	0.001070672	0.000045327
Cincinnati	0.000280619	0.000543381
Cleveland	0.00116358	0.00078642
Columbus	0.0000607324	0.000016267
Indianapolis	0.000582858	0.000064142
Maumee	0.000206739	0.000110261

Then the regional rate of organ offers are calculated as follows:

$$\begin{aligned}
\theta_{Ann}(10|6) = & \frac{0.000543381 + 0.00078642 + 0.000016267 + 0.000064142}{5} \\
& + \frac{0.000110261 - 4 * 0.000045327}{5} \\
= & \ 0.000267832. \\
\theta_{Cin}(10|6) = & \frac{0.000045327 + 0.00078642 + 0.000016267 + 0.000064142}{5} \\
& + \frac{0.000110261 - 4 * 0.000543381}{5} \\
= & \ -0.000230221. \\
\theta_{Cle}(10|6) = & \frac{0.000045327 + 0.000543381 + 0.000016267 + 0.000064142}{5} \\
& + \frac{0.000110261 - 4 * 0.00078642}{5} \\
= & \ -0.00047326. \\
\theta_{Col}(10|6) = & \frac{0.000045327 + 0.000543381 + 0.00078642 + 0.000064142}{5} \\
& + \frac{0.000110261 - 4 * 0.000016267}{5} \\
= & \ 0.000296892. \\
\theta_{Ind}(10|6) = & \frac{0.000045327 + 0.000543381 + 0.00078642 + 0.000016267}{5} \\
& + \frac{0.000110261 - 4 * 0.000064142}{5}
\end{aligned}$$

$$= \quad 0.000249018.$$

$$\theta_{Mau}(10|6) = \frac{0.000045327 + 0.000543381 + 0.00078642 + 0.000016267}{5} + \frac{0.000064142 - 4 * 0.000110261}{5}$$

$$= \quad 0.000202899.$$

In our numerical experiments, we do not use the regional organ offer rate estimates as calculated in this section, because the estimation might yield negative regional rates. Therefore, we perturb the percentage of organs transplanted in order to attain nonnegative rate estimates as demonstrated in the following section.

C.2 CONSTRUCTING THE LP NUMERICALLY

We construct the LP to calculate the local and regional offer rates of OPOs in Region 10 for MELD score 6 and liver type 10 as follows:

$$\min \left(\alpha_{Ann} + \beta_{Ann} + \alpha_{Cin} + \beta_{Cin} + \alpha_{Cle} + \beta_{Cle} + \alpha_{Col} + \beta_{Col} + \alpha_{Ind} + \beta_{Ind} + \alpha_{Mau} + \beta_{Mau}\right)$$

s.t.

$$0.001116\alpha_{Ann} - 0.001116\beta_{Ann} + \theta_{Cin} + \theta_{Cle} + \theta_{Col} + \theta_{Ind} + \theta_{Mau} = 0.040616246 * 0.001116,$$

$$0.000824\alpha_{Cin} - 0.000824\beta_{Cin} + \theta_{Ann} + \theta_{Cle} + \theta_{Col} + \theta_{Ind} + \theta_{Mau} = 0.659442724 * 0.000824,$$

$$0.00195\alpha_{Cle} - 0.00195\beta_{Cle} + \theta_{Ann} + \theta_{Cin} + \theta_{Cle} + \theta_{Ind} + \theta_{Mau} = 0.403292181 * 0.00195,$$

$$0.000077\alpha_{Col} - 0.000077\beta_{Col} + \theta_{Ann} + \theta_{Cin} + \theta_{Cle} + \theta_{Ind} + \theta_{Mau} = 0.211267606 * 0.000077,$$

$$0.000647\alpha_{Ind} - 0.000647\beta_{Ind} + \theta_{Ann} + \theta_{Cin} + \theta_{Cle} + \theta_{Col} + \theta_{Mau} = 0.099137931 * 0.000647,$$

$$0.000317\alpha_{Mau} - 0.000317\beta_{Mau} + \theta_{Ann} + \theta_{Cin} + \theta_{Cle} + \theta_{Col} + \theta_{Ind} = 0.347826087 * 0.000317,$$

$$\alpha_{Ann} - \beta_{Ann} \leq 0.040616246,$$

$$\alpha_{Cin} - \beta_{Cin} \leq 0.659442724,$$

$$\alpha_{Cle} - \beta_{Cle} \leq 0.403292181,$$

$\alpha_{Col} - \beta_{Col} \leq 0.211267606,$

$\alpha_{Ind} - \beta_{Ind} \leq 0.099137931,$

$\alpha_{Mau} - \beta_{Mau} \leq 0.347826087,$

$\beta_{Ann} - \alpha_{Ann} \leq 0.959383754,$

$\beta_{Cin} - \alpha_{Cin} \leq 0.340557276,$

$\beta_{Cle} - \alpha_{Cle} \leq 0.596707819,$

$\beta_{Col} - \alpha_{Col} \leq 0.788732394,$

$\beta_{Ind} - \alpha_{Ind} \leq 0.900862069,$

$\beta_{Mau} - \alpha_{Mau} \leq 0.652173913,$

$\theta_{Ann}, \theta_{Cin}, \theta_{Cle}, \theta_{Col}, \theta_{Ind}, \theta_{Mau} \geq 0,$

$\alpha_{Ann}, \alpha_{Cin}, \alpha_{Cle}, \alpha_{Col}, \alpha_{Ind}, \alpha_{Mau} \geq 0,$

$\beta_{Ann}, \beta_{Cin}, \beta_{Cle}, \beta_{Col}, \beta_{Ind}, \beta_{Mau} \geq 0.$

Table C3 shows the optimal $x(i,i,6,10)\Big(\alpha_i - \beta_i + P(i,i)\Big)$, $\xi_i(10|6)\Big(\omega_i(10|6)\cdot x(i,i,6,10)\Big)$ and $\theta_i(10|6)$ values attained by solving the LP built above.

Table C3:

OPO(i)	$x(i,i,6,10)$	$\xi_i(10\|6$	$\theta_i(10\|6)$
Ann Arbor	0.901200	0.001006	0.000000
Cincinnati	0.866188	0.000714	0.000000
Cleveland	0.943456	0.001840	0.000000
Columbus	0.788732	0.000121	0.000078
Indianapolis	0.879541	0.000569	0.000032
Maumee	0.652174	0.000207	0.000000

We use the values presented in Table C3 as the estimates for local and regional offer rates of OPOs in Region 10 for MELD score 6 and liver type 10.

APPENDIX D

NUMERICAL ANALYSIS ON SUBMODULARITY OF THE VALUE FUNCTION

Table D1: OPOs by indices used in numerical submodularity study.

Index	**OPO**	**Index**	**OPO**
0	Birmingham, AL	25	Charlotte, NC
1	Phoenix, AZ	26	Greenville, NC
2	Oakland, CA	27	Omaha, NE
3	Sacramento, CA	28	New Providence, NJ
4	Los Angeles, CA	29	Rochester, NY
5	San Diego, CA	30	New York, NY
6	Denver, CO	31	Cleveland, OH
7	Windsor, CT	32	Maumee, OH
8	Annandale, DC	33	Columbus, OH
9	Miami, FL	34	Cincinnati, OH
10	Gainesville, FL	35	Oklahoma City, OK
11	Tampa, FL	36	Portland, OR
12	Norcross, GA	37	Philadelphia, PA
13	Honolulu, HI	38	Pittsburgh, PA
14	North Liberty, IA	39	Charleston, SC
15	Chicago, IL	40	Nashville, TN
16	Indianapolis, IN	41	Memphis, TN
17	Louisville, KY	42	Houston, TX
18	Metairie, LA	43	San Antonio, TX
19	Waltham, MA	44	Dallas, TX
20	Baltimore, MD	45	Salt Lake City, UT
21	Ann Arbor, MI	46	Virginia Beach, VA
22	St. Paul, MN	47	Bellevue, WA
23	St. Louis, MO	48	Milwaukee, WI
24	Westwood, KS	49	Madison, WI

Table D2: Sets of OPOs that are used to test (3.32).

O	$O \cup \{i\}$	$O \cup \{j\}$	$O \cup \{i, j\}$
{15}	**{15,14}**	**{15,16}**	**{15,14,16}**
{15}	**{15,14}**	**{15,17}**	**{15,14,17}**
{15}	**{15,14}**	**{15,21}**	**{15,14,21}**
{15}	**{15,14}**	**{15,23}**	**{15,14,23}**
{15}	**{15,14}**	**{15,32}**	**{15,14,32}**
{15}	**{15,14}**	**{15,34}**	**{15,14,34}**
{15}	**{15,14}**	**{15,48}**	**{15,14,48}**
{15}	**{15,14}**	**{15,49}**	**{15,14,49}**
{15}	**{15,16}**	**{15,17}**	**{15,16,17}**
{15}	**{15,16}**	**{15,21}**	**{15,16,21}**
{15}	**{15,16}**	**{15,23}**	**{15,16,23}**
{15}	**{15,16}**	**{15,32}**	**{15,16,32}**
{15}	**{15,16}**	**{15,34}**	**{15,16,34}**
{15}	**{15,16}**	**{15,48}**	**{15,16,48}**
{15}	**{15,16}**	**{15,49}**	**{15,16,49}**
{15}	**{15,17}**	**{15,21}**	**{15,17,21}**
{15}	**{15,17}**	**{15,23}**	**{15,17,23}**
{15}	**{15,17}**	**{15,32}**	**{15,17,32}**
{15}	**{15,17}**	**{15,34}**	**{15,17,34}**
{15}	**{15,17}**	**{15,48}**	**{15,17,48}**
{15}	**{15,17}**	**{15,49}**	**{15,17,49}**
{15}	**{15,21}**	**{15,23}**	**{15,21,23}**
{15}	**{15,21}**	**{15,32}**	**{15,21,32}**
{15}	**{15,21}**	**{15,34}**	**{15,21,34}**
{15}	**{15,21}**	**{15,48}**	**{15,21,48}**
{15}	**{15,21}**	**{15,49}**	**{15,21,49}**

Table D2 (continued)

O	$O \cup \{i\}$	$O \cup \{j\}$	$O \cup \{i, j\}$
{15}	**{15,23}**	**{15,32}**	**{15,23,32}**
{15}	**{15,23}**	**{15,34}**	**{15,23,34}**
{15}	**{15,23}**	**{15,48}**	**{15,23,48}**
{15}	**{15,23}**	**{15,49}**	**{15,23,49}**
{15}	**{15,32}**	**{15,34}**	**{15,32,34}**
{15}	**{15,32}**	**{15,48}**	**{15,32,48}**
{15}	**{15,32}**	**{15,49}**	**{15,32,49}**
{15}	**{15,34}**	**{15,48}**	**{15,34,48}**
{15}	**{15,34}**	**{15,49}**	**{15,34,49}**
{15}	**{15,48}**	**{15,49}**	**{15,48,49}**

Table D3: Sets of OPOs that are used to calculate total life expectancy and the submodularity inequality.

{0}	**{0,12}**	**{0,18}**	**{0,12,18}**
{0}	**{0,12}**	**{0,40}**	**{0,12,40}**
{0}	**{0,12}**	**{0,41}**	**{0,12,41}**
{0}	**{0,18}**	**{0,40}**	**{0,18,40}**
{0}	**{0,18}**	**{0,41}**	**{0,18,41}**
{0}	**{0,40}**	**{0,41}**	**{0,40,41}**
{7}	**{7,19}**	**{7,20}**	**{7,19,20}**
{7}	**{7,19}**	**{7,28}**	**{7,19,28}**
{7}	**{7,19}**	**{7,29}**	**{7,19,29}**
{7}	**{7,19}**	**{7,30}**	**{7,19,30}**
{7}	**{7,19}**	**{7,37}**	**{7,19,37}**
{7}	**{7,20}**	**{7,28}**	**{7,20,28}**
{7}	**{7,20}**	**{7,29}**	**{7,20,29}**
{7}	**{7,20}**	**{7,30}**	**{7,20,30}**
{7}	**{7,20}**	**{7,37}**	**{7,20,37}**
{7}	**{7,28}**	**{7,29}**	**{7,28,29}**
{7}	**{7,28}**	**{7,30}**	**{7,28,30}**
{7}	**{7,28}**	**{7,37}**	**{7,28,37}**
{7}	**{7,29}**	**{7,30}**	**{7,29,30}**
{7}	**{7,29}**	**{7,37}**	**{7,29,37}**
{7}	**{7,30}**	**{7,37}**	**{7,30,37}**
{8}	**{8,20}**	**{8,26}**	**{8,20,26}**
{8}	**{8,20}**	**{8,28}**	**{8,20,28}**
{8}	**{8,20}**	**{8,30}**	**{8,20,30}**
{8}	**{8,20}**	**{8,37}**	**{8,20,37}**
{8}	**{8,20}**	**{8,38}**	**{8,20,38}**

Table D3 (continued)

{8}	{8,20}	{8,46}	{8,20,46}
{8}	{8,26}	{8,28}	{8,26,28}
{8}	{8,26}	{8,30}	{8,26,30}
{8}	{8,26}	{8,37}	{8,26,37}
{8}	{8,26}	{8,38}	{8,26,38}
{8}	{8,26}	{8,46}	{8,26,46}
{8}	{8,28}	{8,30}	{8,28,30}
{8}	{8,28}	{8,37}	{8,28,37}
{8}	{8,28}	{8,38}	{8,28,38}
{8}	{8,28}	{8,46}	{8,28,46}
{8}	{8,30}	{8,37}	{8,30,37}
{8}	{8,30}	{8,38}	{8,30,38}
{8}	{8,30}	{8,46}	{8,30,46}
{8}	{8,37}	{8,38}	{8,37,38}
{8}	{8,37}	{8,46}	{8,37,46}
{8}	{8,38}	{8,46}	{8,38,46}
{9}	{9,10}	{9,11}	{9,10,11}
{10}	{10,9}	{10,11}	{10,9,11}
{10}	{10,9}	{10,12}	{10,9,12}
{10}	{10,11}	{10,12}	{10,11,12}
{11}	{11,9}	{11,10}	{11,9,10}
{12}	{12,0}	{12,10}	{12,0,10}

Table D3 (continued)

{12}	**{12,0}**	**{12,25}**	**{12,0,25}**
{12}	**{12,0}**	**{12,39}**	**{12,0,39}**
{12}	**{12,0}**	**{12,40}**	**{12,0,40}**
{12}	**{12,10}**	**{12,25}**	**{12,10,25}**
{12}	**{12,10}**	**{12,39}**	**{12,10,39}**
{12}	**{12,10}**	**{12,40}**	**{12,10,40}**
{12}	**{12,25}**	**{12,39}**	**{12,25,39}**
{12}	**{12,25}**	**{12,40}**	**{12,25,40}**
{12}	**{12,39}**	**{12,40}**	**{12,39,40}**
{14}	**{14,15}**	**{14,22}**	**{14,15,22}**
{14}	**{14,15}**	**{14,23}**	**{14,15,23}**
{14}	**{14,15}**	**{14,24}**	**{14,15,24}**
{14}	**{14,15}**	**{14,27}**	**{14,15,27}**
{14}	**{14,15}**	**{14,48}**	**{14,15,48}**
{14}	**{14,15}**	**{14,49}**	**{14,15,49}**
{14}	**{14,22}**	**{14,23}**	**{14,22,23}**
{14}	**{14,22}**	**{14,24}**	**{14,22,24}**
{14}	**{14,22}**	**{14,27}**	**{14,22,27}**
{14}	**{14,22}**	**{14,48}**	**{14,22,48}**
{14}	**{14,22}**	**{14,49}**	**{14,22,49}**
{14}	**{14,23}**	**{14,24}**	**{14,23,24}**
{14}	**{14,23}**	**{14,27}**	**{14,23,27}**

Table D3 (continued)

{14}	**{14,23}**	**{14,48}**	**{14,23,48}**
{14}	**{14,23}**	**{14,49}**	**{14,23,49}**
{14}	**{14,24}**	**{14,27}**	**{14,24,27}**
{14}	**{14,24}**	**{14,48}**	**{14,24,48}**
{14}	**{14,24}**	**{14,49}**	**{14,24,49}**
{14}	**{14,27}**	**{14,48}**	**{14,27,48}**
{14}	**{14,27}**	**{14,49}**	**{14,27,49}**
{14}	**{14,48}**	**{14,49}**	**{14,48,49}**
{15}	**{15,14}**	**{15,16}**	**{15,14,16}**
{15}	**{15,14}**	**{15,17}**	**{15,14,17}**
{15}	**{15,14}**	**{15,21}**	**{15,14,21}**
{15}	**{15,14}**	**{15,23}**	**{15,14,23}**
{15}	**{15,14}**	**{15,32}**	**{15,14,32}**
{15}	**{15,14}**	**{15,34}**	**{15,14,34}**
{15}	**{15,14}**	**{15,48}**	**{15,14,48}**
{15}	**{15,14}**	**{15,49}**	**{15,14,49}**
{15}	**{15,16}**	**{15,17}**	**{15,16,17}**
{15}	**{15,16}**	**{15,21}**	**{15,16,21}**
{15}	**{15,16}**	**{15,23}**	**{15,16,23}**
{15}	**{15,16}**	**{15,32}**	**{15,16,32}**
{15}	**{15,16}**	**{15,34}**	**{15,16,34}**
{15}	**{15,16}**	**{15,48}**	**{15,16,48}**

Table D3 (continued)

{15}	**{15,16}**	**{15,49}**	**{15,16,49}**
{15}	**{15,17}**	**{15,21}**	**{15,17,21}**
{15}	**{15,17}**	**{15,23}**	**{15,17,23}**
{15}	**{15,17}**	**{15,32}**	**{15,17,32}**
{15}	**{15,17}**	**{15,34}**	**{15,17,34}**
{15}	**{15,17}**	**{15,48}**	**{15,17,48}**
{15}	**{15,17}**	**{15,49}**	**{15,17,49}**
{15}	**{15,21}**	**{15,23}**	**{15,21,23}**
{15}	**{15,21}**	**{15,32}**	**{15,21,32}**
{15}	**{15,21}**	**{15,34}**	**{15,21,34}**
{15}	**{15,21}**	**{15,48}**	**{15,21,48}**
{15}	**{15,21}**	**{15,49}**	**{15,21,49}**
{15}	**{15,23}**	**{15,32}**	**{15,23,32}**
{15}	**{15,23}**	**{15,34}**	**{15,23,34}**
{15}	**{15,23}**	**{15,48}**	**{15,23,48}**
{15}	**{15,23}**	**{15,49}**	**{15,23,49}**
{15}	**{15,32}**	**{15,34}**	**{15,32,34}**
{15}	**{15,32}**	**{15,48}**	**{15,32,48}**
{15}	**{15,32}**	**{15,49}**	**{15,32,49}**
{15}	**{15,34}**	**{15,48}**	**{15,34,48}**
{15}	**{15,34}**	**{15,49}**	**{15,34,49}**
{15}	**{15,48}**	**{15,49}**	**{15,48,49}**

Table D3 (continued)

{16}	**{16,15}**	**{16,17}**	**{16,15,17}**
{16}	**{16,15}**	**{16,21}**	**{16,15,21}**
{16}	**{16,15}**	**{16,23}**	**{16,15,23}**
{16}	**{16,15}**	**{16,31}**	**{16,15,31}**
{16}	**{16,15}**	**{16,32}**	**{16,15,32}**
{16}	**{16,15}**	**{16,33}**	**{16,15,33}**
{16}	**{16,15}**	**{16,34}**	**{16,15,34}**
{16}	**{16,15}**	**{16,40}**	**{16,15,40}**
{16}	**{16,15}**	**{16,48}**	**{16,15,48}**
{16}	**{16,15}**	**{16,49}**	**{16,15,49}**
{16}	**{16,17}**	**{16,21}**	**{16,17,21}**
{16}	**{16,17}**	**{16,23}**	**{16,17,23}**
{16}	**{16,17}**	**{16,31}**	**{16,17,31}**
{16}	**{16,17}**	**{16,32}**	**{16,17,32}**
{16}	**{16,17}**	**{16,33}**	**{16,17,33}**
{16}	**{16,17}**	**{16,34}**	**{16,17,34}**
{16}	**{16,17}**	**{16,40}**	**{16,17,40}**
{16}	**{16,17}**	**{16,48}**	**{16,17,48}**
{16}	**{16,17}**	**{16,49}**	**{16,17,49}**
{16}	**{16,21}**	**{16,23}**	**{16,21,23}**
{16}	**{16,21}**	**{16,31}**	**{16,21,31}**
{16}	**{16,21}**	**{16,32}**	**{16,21,32}**

Table D3 (continued)

{16}	**{16,21}**	**{16,33}**	**{16,21,33}**
{16}	**{16,21}**	**{16,34}**	**{16,21,34}**
{16}	**{16,21}**	**{16,40}**	**{16,21,40}**
{16}	**{16,21}**	**{16,48}**	**{16,21,48}**
{16}	**{16,21}**	**{16,49}**	**{16,21,49}**
{16}	**{16,23}**	**{16,31}**	**{16,23,31}**
{16}	**{16,23}**	**{16,32}**	**{16,23,32}**
{16}	**{16,23}**	**{16,33}**	**{16,23,33}**
{16}	**{16,23}**	**{16,34}**	**{16,23,34}**
{16}	**{16,23}**	**{16,40}**	**{16,23,40}**
{16}	**{16,23}**	**{16,48}**	**{16,23,48}**
{16}	**{16,23}**	**{16,49}**	**{16,23,49}**
{16}	**{16,31}**	**{16,32}**	**{16,31,32}**
{16}	**{16,31}**	**{16,33}**	**{16,31,33}**
{16}	**{16,31}**	**{16,34}**	**{16,31,34}**
{16}	**{16,31}**	**{16,40}**	**{16,31,40}**
{16}	**{16,31}**	**{16,48}**	**{16,31,48}**
{16}	**{16,31}**	**{16,49}**	**{16,31,49}**
{16}	**{16,32}**	**{16,33}**	**{16,32,33}**
{16}	**{16,32}**	**{16,34}**	**{16,32,34}**
{16}	**{16,32}**	**{16,40}**	**{16,32,40}**
{16}	**{16,32}**	**{16,48}**	**{16,32,48}**

Table D3 (continued)

{16}	**{16,32}**	**{16,49}**	**{16,32,49}**
{16}	**{16,33}**	**{16,34}**	**{16,33,34}**
{16}	**{16,33}**	**{16,40}**	**{16,33,40}**
{16}	**{16,33}**	**{16,48}**	**{16,33,48}**
{16}	**{16,33}**	**{16,49}**	**{16,33,49}**
{16}	**{16,34}**	**{16,40}**	**{16,34,40}**
{16}	**{16,34}**	**{16,48}**	**{16,34,48}**
{16}	**{16,34}**	**{16,49}**	**{16,34,49}**
{16}	**{16,40}**	**{16,48}**	**{16,40,48}**
{16}	**{16,40}**	**{16,49}**	**{16,40,49}**
{16}	**{16,48}**	**{16,49}**	**{16,48,49}**
{17}	**{17,15}**	**{17,16}**	**{17,15,16}**
{17}	**{17,15}**	**{17,21}**	**{17,15,21}**
{17}	**{17,15}**	**{17,23}**	**{17,15,23}**
{17}	**{17,15}**	**{17,31}**	**{17,15,31}**
{17}	**{17,15}**	**{17,32}**	**{17,15,32}**
{17}	**{17,15}**	**{17,33}**	**{17,15,33}**
{17}	**{17,15}**	**{17,34}**	**{17,15,34}**
{17}	**{17,15}**	**{17,40}**	**{17,15,40}**
{17}	**{17,16}**	**{17,21}**	**{17,16,21}**
{17}	**{17,16}**	**{17,23}**	**{17,16,23}**
{17}	**{17,16}**	**{17,31}**	**{17,16,31}**

Table D3 (continued)

{17}	**{17,16}**	**{17,32}**	**{17,16,32}**
{17}	**{17,16}**	**{17,33}**	**{17,16,33}**
{17}	**{17,16}**	**{17,34}**	**{17,16,34}**
{17}	**{17,16}**	**{17,40}**	**{17,16,40}**
{17}	**{17,21}**	**{17,23}**	**{17,21,23}**
{17}	**{17,21}**	**{17,31}**	**{17,21,31}**
{17}	**{17,21}**	**{17,32}**	**{17,21,32}**
{17}	**{17,21}**	**{17,33}**	**{17,21,33}**
{17}	**{17,21}**	**{17,34}**	**{17,21,34}**
{17}	**{17,21}**	**{17,40}**	**{17,21,40}**
{17}	**{17,23}**	**{17,31}**	**{17,23,31}**
{17}	**{17,23}**	**{17,32}**	**{17,23,32}**
{17}	**{17,23}**	**{17,33}**	**{17,23,33}**
{17}	**{17,23}**	**{17,34}**	**{17,23,34}**
{17}	**{17,23}**	**{17,40}**	**{17,23,40}**
{17}	**{17,31}**	**{17,32}**	**{17,31,32}**
{17}	**{17,31}**	**{17,33}**	**{17,31,33}**
{17}	**{17,31}**	**{17,34}**	**{17,31,34}**
{17}	**{17,31}**	**{17,40}**	**{17,31,40}**
{17}	**{17,32}**	**{17,33}**	**{17,32,33}**
{17}	**{17,32}**	**{17,34}**	**{17,32,34}**
{17}	**{17,32}**	**{17,40}**	**{17,32,40}**

Table D3 (continued)

{17}	{17,33}	{17,34}	{17,33,34}
{17}	{17,33}	{17,40}	{17,33,40}
{17}	{17,34}	{17,40}	{17,34,40}
{18}	{18,0}	{18,42}	{18,0,42}
{19}	{19,7}	{19,28}	{19,7,28}
{19}	{19,7}	{19,30}	{19,7,30}
{19}	{19,7}	{19,37}	{19,7,37}
{19}	{19,28}	{19,30}	{19,28,30}
{19}	{19,28}	{19,37}	{19,28,37}
{19}	{19,30}	{19,37}	{19,30,37}
{20}	{20,7}	{20,8}	{20,7,8}
{20}	{20,7}	{20,26}	{20,7,26}
{20}	{20,7}	{20,28}	{20,7,28}
{20}	{20,7}	{20,29}	{20,7,29}
{20}	{20,7}	{20,30}	{20,7,30}
{20}	{20,7}	{20,37}	{20,7,37}
{20}	{20,7}	{20,38}	{20,7,38}
{20}	{20,7}	{20,46}	{20,7,46}
{20}	{20,8}	{20,26}	{20,8,26}
{20}	{20,8}	{20,28}	{20,8,28}
{20}	{20,8}	{20,29}	{20,8,29}
{20}	{20,8}	{20,30}	{20,8,30}

Table D3 (continued)

{20}	{20,8}	{20,37}	{20,8,37}
{20}	{20,8}	{20,38}	{20,8,38}
{20}	{20,8}	{20,46}	{20,8,46}
{20}	{20,26}	{20,28}	{20,26,28}
{20}	{20,26}	{20,29}	{20,26,29}
{20}	{20,26}	{20,30}	{20,26,30}
{20}	{20,26}	{20,37}	{20,26,37}
{20}	{20,26}	{20,38}	{20,26,38}
{20}	{20,26}	{20,46}	{20,26,46}
{20}	{20,28}	{20,29}	{20,28,29}
{20}	{20,28}	{20,30}	{20,28,30}
{20}	{20,28}	{20,37}	{20,28,37}
{20}	{20,28}	{20,38}	{20,28,38}
{20}	{20,28}	{20,46}	{20,28,46}
{20}	{20,29}	{20,30}	{20,29,30}
{20}	{20,29}	{20,37}	{20,29,37}
{20}	{20,29}	{20,38}	{20,29,38}
{20}	{20,29}	{20,46}	{20,29,46}
{20}	{20,30}	{20,37}	{20,30,37}
{20}	{20,30}	{20,38}	{20,30,38}
{20}	{20,30}	{20,46}	{20,30,46}
{20}	{20,37}	{20,38}	{20,37,38}

Table D3 (continued)

{20}	**{20,37}**	**{20,46}**	**{20,37,46}**
{20}	**{20,38}**	**{20,46}**	**{20,38,46}**
{21}	**{21,15}**	**{21,16}**	**{21,15,16}**
{21}	**{21,15}**	**{21,17}**	**{21,15,17}**
{21}	**{21,15}**	**{21,31}**	**{21,15,31}**
{21}	**{21,15}**	**{21,32}**	**{21,15,32}**
{21}	**{21,15}**	**{21,33}**	**{21,15,33}**
{21}	**{21,15}**	**{21,34}**	**{21,15,34}**
{21}	**{21,15}**	**{21,38}**	**{21,15,38}**
{21}	**{21,15}**	**{21,48}**	**{21,15,48}**
{21}	**{21,16}**	**{21,17}**	**{21,16,17}**
{21}	**{21,16}**	**{21,31}**	**{21,16,31}**
{21}	**{21,16}**	**{21,32}**	**{21,16,32}**
{21}	**{21,16}**	**{21,33}**	**{21,16,33}**
{21}	**{21,16}**	**{21,34}**	**{21,16,34}**
{21}	**{21,16}**	**{21,38}**	**{21,16,38}**
{21}	**{21,16}**	**{21,48}**	**{21,16,48}**
{21}	**{21,17}**	**{21,31}**	**{21,17,31}**
{21}	**{21,17}**	**{21,32}**	**{21,17,32}**
{21}	**{21,17}**	**{21,33}**	**{21,17,33}**
{21}	**{21,17}**	**{21,34}**	**{21,17,34}**
{21}	**{21,17}**	**{21,38}**	**{21,17,38}**

Table D3 (continued)

{21}	**{21,17}**	**{21,48}**	**{21,17,48}**
{21}	**{21,31}**	**{21,32}**	**{21,31,32}**
{21}	**{21,31}**	**{21,33}**	**{21,31,33}**
{21}	**{21,31}**	**{21,34}**	**{21,31,34}**
{21}	**{21,31}**	**{21,38}**	**{21,31,38}**
{21}	**{21,31}**	**{21,48}**	**{21,31,48}**
{21}	**{21,32}**	**{21,33}**	**{21,32,33}**
{21}	**{21,32}**	**{21,34}**	**{21,32,34}**
{21}	**{21,32}**	**{21,38}**	**{21,32,38}**
{21}	**{21,32}**	**{21,48}**	**{21,32,48}**
{21}	**{21,33}**	**{21,34}**	**{21,33,34}**
{21}	**{21,33}**	**{21,38}**	**{21,33,38}**
{21}	**{21,33}**	**{21,48}**	**{21,33,48}**
{21}	**{21,34}**	**{21,38}**	**{21,34,38}**
{21}	**{21,34}**	**{21,48}**	**{21,34,48}**
{21}	**{21,38}**	**{21,48}**	**{21,38,48}**
{22}	**{22,14}**	**{22,48}**	**{22,14,48}**
{22}	**{22,14}**	**{22,49}**	**{22,14,49}**
{22}	**{22,48}**	**{22,49}**	**{22,48,49}**
{23}	**{23,14}**	**{23,15}**	**{23,14,15}**
{23}	**{23,14}**	**{23,16}**	**{23,14,16}**
{23}	**{23,14}**	**{23,17}**	**{23,14,17}**

Table D3 (continued)

{23}	**{23,14}**	**{23,24}**	**{23,14,24}**
{23}	**{23,14}**	**{23,40}**	**{23,14,40}**
{23}	**{23,14}**	**{23,41}**	**{23,14,41}**
{23}	**{23,15}**	**{23,16}**	**{23,15,16}**
{23}	**{23,15}**	**{23,17}**	**{23,15,17}**
{23}	**{23,15}**	**{23,24}**	**{23,15,24}**
{23}	**{23,15}**	**{23,40}**	**{23,15,40}**
{23}	**{23,15}**	**{23,41}**	**{23,15,41}**
{23}	**{23,16}**	**{23,17}**	**{23,16,17}**
{23}	**{23,16}**	**{23,24}**	**{23,16,24}**
{23}	**{23,16}**	**{23,40}**	**{23,16,40}**
{23}	**{23,16}**	**{23,41}**	**{23,16,41}**
{23}	**{23,17}**	**{23,24}**	**{23,17,24}**
{23}	**{23,17}**	**{23,40}**	**{23,17,40}**
{23}	**{23,17}**	**{23,41}**	**{23,17,41}**
{23}	**{23,24}**	**{23,40}**	**{23,24,40}**
{23}	**{23,24}**	**{23,41}**	**{23,24,41}**
{23}	**{23,40}**	**{23,41}**	**{23,40,41}**
{24}	**{24,14}**	**{24,23}**	**{24,14,23}**
{24}	**{24,14}**	**{24,27}**	**{24,14,27}**
{24}	**{24,14}**	**{24,35}**	**{24,14,35}**
{24}	**{24,23}**	**{24,27}**	**{24,23,27}**

Table D3 (continued)

{24}	{24,23}	{24,35}	{24,23,35}
{24}	{24,27}	{24,35}	{24,27,35}
{25}	{25,12}	{25,26}	{25,12,26}
{25}	{25,12}	{25,39}	{25,12,39}
{25}	{25,12}	{25,46}	{25,12,46}
{25}	{25,26}	{25,39}	{25,26,39}
{25}	{25,26}	{25,46}	{25,26,46}
{25}	{25,39}	{25,46}	{25,39,46}
{26}	{26,8}	{26,20}	{26,8,20}
{26}	{26,8}	{26,25}	{26,8,25}
{26}	{26,8}	{26,39}	{26,8,39}
{26}	{26,8}	{26,46}	{26,8,46}
{26}	{26,20}	{26,25}	{26,20,25}
{26}	{26,20}	{26,39}	{26,20,39}
{26}	{26,20}	{26,46}	{26,20,46}
{26}	{26,25}	{26,39}	{26,25,39}
{26}	{26,25}	{26,46}	{26,25,46}
{26}	{26,39}	{26,46}	{26,39,46}
{27}	{27,14}	{27,24}	{27,14,24}
{28}	{28,7}	{28,8}	{28,7,8}
{28}	{28,7}	{28,19}	{28,7,19}
{28}	{28,7}	{28,20}	{28,7,20}

Table D3 (continued)

{28}	{28,7}	{28,29}	{28,7,29}
{28}	{28,7}	{28,30}	{28,7,30}
{28}	{28,7}	{28,37}	{28,7,37}
{28}	{28,7}	{28,38}	{28,7,38}
{28}	{28,8}	{28,19}	{28,8,19}
{28}	{28,8}	{28,20}	{28,8,20}
{28}	{28,8}	{28,29}	{28,8,29}
{28}	{28,8}	{28,30}	{28,8,30}
{28}	{28,8}	{28,37}	{28,8,37}
{28}	{28,8}	{28,38}	{28,8,38}
{28}	{28,19}	{28,20}	{28,19,20}
{28}	{28,19}	{28,29}	{28,19,29}
{28}	{28,19}	{28,30}	{28,19,30}
{28}	{28,19}	{28,37}	{28,19,37}
{28}	{28,19}	{28,38}	{28,19,38}
{28}	{28,20}	{28,29}	{28,20,29}
{28}	{28,20}	{28,30}	{28,20,30}
{28}	{28,20}	{28,37}	{28,20,37}
{28}	{28,20}	{28,38}	{28,20,38}
{28}	{28,29}	{28,30}	{28,29,30}
{28}	{28,29}	{28,37}	{28,29,37}
{28}	{28,29}	{28,38}	{28,29,38}

Table D3 (continued)

{28}	**{28,30}**	**{28,37}**	**{28,30,37}**
{28}	**{28,30}**	**{28,38}**	**{28,30,38}**
{28}	**{28,37}**	**{28,38}**	**{28,37,38}**
{29}	**{29,7}**	**{29,20}**	**{29,7,20}**
{29}	**{29,7}**	**{29,28}**	**{29,7,28}**
{29}	**{29,7}**	**{29,30}**	**{29,7,30}**
{29}	**{29,7}**	**{29,31}**	**{29,7,31}**
{29}	**{29,7}**	**{29,37}**	**{29,7,37}**
{29}	**{29,7}**	**{29,38}**	**{29,7,38}**
{29}	**{29,20}**	**{29,28}**	**{29,20,28}**
{29}	**{29,20}**	**{29,30}**	**{29,20,30}**
{29}	**{29,20}**	**{29,31}**	**{29,20,31}**
{29}	**{29,20}**	**{29,37}**	**{29,20,37}**
{29}	**{29,20}**	**{29,38}**	**{29,20,38}**
{29}	**{29,28}**	**{29,30}**	**{29,28,30}**
{29}	**{29,28}**	**{29,31}**	**{29,28,31}**
{29}	**{29,28}**	**{29,37}**	**{29,28,37}**
{29}	**{29,28}**	**{29,38}**	**{29,28,38}**
{29}	**{29,30}**	**{29,31}**	**{29,30,31}**
{29}	**{29,30}**	**{29,37}**	**{29,30,37}**
{29}	**{29,30}**	**{29,38}**	**{29,30,38}**
{29}	**{29,31}**	**{29,37}**	**{29,31,37}**

Table D3 (continued)

{29}	{29,31}	{29,38}	{29,31,38}
{29}	{29,37}	{29,38}	{29,37,38}
{30}	{30,7}	{30,8}	{30,7,8}
{30}	{30,7}	{30,19}	{30,7,19}
{30}	{30,7}	{30,20}	{30,7,20}
{30}	{30,7}	{30,28}	{30,7,28}
{30}	{30,7}	{30,29}	{30,7,29}
{30}	{30,7}	{30,37}	{30,7,37}
{30}	{30,8}	{30,19}	{30,8,19}
{30}	{30,8}	{30,20}	{30,8,20}
{30}	{30,8}	{30,28}	{30,8,28}
{30}	{30,8}	{30,29}	{30,8,29}
{30}	{30,8}	{30,37}	{30,8,37}
{30}	{30,19}	{30,20}	{30,19,20}
{30}	{30,19}	{30,28}	{30,19,28}
{30}	{30,19}	{30,29}	{30,19,29}
{30}	{30,19}	{30,37}	{30,19,37}
{30}	{30,20}	{30,28}	{30,20,28}
{30}	{30,20}	{30,29}	{30,20,29}
{30}	{30,20}	{30,37}	{30,20,37}
{30}	{30,28}	{30,29}	{30,28,29}
{30}	{30,28}	{30,37}	{30,28,37}

Table D3 (continued)

{30}	**{30,29}**	**{30,37}**	**{30,29,37}**
{31}	**{31,16}**	**{31,17}**	**{31,16,17}**
{31}	**{31,16}**	**{31,21}**	**{31,16,21}**
{31}	**{31,16}**	**{31,29}**	**{31,16,29}**
{31}	**{31,16}**	**{31,32}**	**{31,16,32}**
{31}	**{31,16}**	**{31,33}**	**{31,16,33}**
{31}	**{31,16}**	**{31,34}**	**{31,16,34}**
{31}	**{31,16}**	**{31,38}**	**{31,16,38}**
{31}	**{31,17}**	**{31,21}**	**{31,17,21}**
{31}	**{31,17}**	**{31,29}**	**{31,17,29}**
{31}	**{31,17}**	**{31,32}**	**{31,17,32}**
{31}	**{31,17}**	**{31,33}**	**{31,17,33}**
{31}	**{31,17}**	**{31,34}**	**{31,17,34}**
{31}	**{31,17}**	**{31,38}**	**{31,17,38}**
{31}	**{31,21}**	**{31,29}**	**{31,21,29}**
{31}	**{31,21}**	**{31,32}**	**{31,21,32}**
{31}	**{31,21}**	**{31,33}**	**{31,21,33}**
{31}	**{31,21}**	**{31,34}**	**{31,21,34}**
{31}	**{31,21}**	**{31,38}**	**{31,21,38}**
{31}	**{31,29}**	**{31,32}**	**{31,29,32}**
{31}	**{31,29}**	**{31,33}**	**{31,29,33}**
{31}	**{31,29}**	**{31,34}**	**{31,29,34}**

Table D3 (continued)

{31}	**{31,29}**	**{31,38}**	**{31,29,38}**
{31}	**{31,32}**	**{31,33}**	**{31,32,33}**
{31}	**{31,32}**	**{31,34}**	**{31,32,34}**
{31}	**{31,32}**	**{31,38}**	**{31,32,38}**
{31}	**{31,33}**	**{31,34}**	**{31,33,34}**
{31}	**{31,33}**	**{31,38}**	**{31,33,38}**
{31}	**{31,34}**	**{31,38}**	**{31,34,38}**
{32}	**{32,15}**	**{32,16}**	**{32,15,16}**
{32}	**{32,15}**	**{32,17}**	**{32,15,17}**
{32}	**{32,15}**	**{32,21}**	**{32,15,21}**
{32}	**{32,15}**	**{32,31}**	**{32,15,31}**
{32}	**{32,15}**	**{32,33}**	**{32,15,33}**
{32}	**{32,15}**	**{32,34}**	**{32,15,34}**
{32}	**{32,15}**	**{32,38}**	**{32,15,38}**
{32}	**{32,15}**	**{32,48}**	**{32,15,48}**
{32}	**{32,16}**	**{32,17}**	**{32,16,17}**
{32}	**{32,16}**	**{32,21}**	**{32,16,21}**
{32}	**{32,16}**	**{32,31}**	**{32,16,31}**
{32}	**{32,16}**	**{32,33}**	**{32,16,33}**
{32}	**{32,16}**	**{32,34}**	**{32,16,34}**
{32}	**{32,16}**	**{32,38}**	**{32,16,38}**
{32}	**{32,16}**	**{32,48}**	**{32,16,48}**

Table D3 (continued)

{32}	**{32,17}**	**{32,21}**	**{32,17,21}**
{32}	**{32,17}**	**{32,31}**	**{32,17,31}**
{32}	**{32,17}**	**{32,33}**	**{32,17,33}**
{32}	**{32,17}**	**{32,34}**	**{32,17,34}**
{32}	**{32,17}**	**{32,38}**	**{32,17,38}**
{32}	**{32,17}**	**{32,48}**	**{32,17,48}**
{32}	**{32,21}**	**{32,31}**	**{32,21,31}**
{32}	**{32,21}**	**{32,33}**	**{32,21,33}**
{32}	**{32,21}**	**{32,34}**	**{32,21,34}**
{32}	**{32,21}**	**{32,38}**	**{32,21,38}**
{32}	**{32,21}**	**{32,48}**	**{32,21,48}**
{32}	**{32,31}**	**{32,33}**	**{32,31,33}**
{32}	**{32,31}**	**{32,34}**	**{32,31,34}**
{32}	**{32,31}**	**{32,38}**	**{32,31,38}**
{32}	**{32,31}**	**{32,48}**	**{32,31,48}**
{32}	**{32,33}**	**{32,34}**	**{32,33,34}**
{32}	**{32,33}**	**{32,38}**	**{32,33,38}**
{32}	**{32,33}**	**{32,48}**	**{32,33,48}**
{32}	**{32,34}**	**{32,38}**	**{32,34,38}**
{32}	**{32,34}**	**{32,48}**	**{32,34,48}**
{32}	**{32,38}**	**{32,48}**	**{32,38,48}**
{33}	**{33,16}**	**{33,17}**	**{33,16,17}**

Table D3 (continued)

{33}	**{33,16}**	**{33,21}**	**{33,16,21}**
{33}	**{33,16}**	**{33,31}**	**{33,16,31}**
{33}	**{33,16}**	**{33,32}**	**{33,16,32}**
{33}	**{33,16}**	**{33,34}**	**{33,16,34}**
{33}	**{33,16}**	**{33,38}**	**{33,16,38}**
{33}	**{33,17}**	**{33,21}**	**{33,17,21}**
{33}	**{33,17}**	**{33,31}**	**{33,17,31}**
{33}	**{33,17}**	**{33,32}**	**{33,17,32}**
{33}	**{33,17}**	**{33,34}**	**{33,17,34}**
{33}	**{33,17}**	**{33,38}**	**{33,17,38}**
{33}	**{33,21}**	**{33,31}**	**{33,21,31}**
{33}	**{33,21}**	**{33,32}**	**{33,21,32}**
{33}	**{33,21}**	**{33,34}**	**{33,21,34}**
{33}	**{33,21}**	**{33,38}**	**{33,21,38}**
{33}	**{33,31}**	**{33,32}**	**{33,31,32}**
{33}	**{33,31}**	**{33,34}**	**{33,31,34}**
{33}	**{33,31}**	**{33,38}**	**{33,31,38}**
{33}	**{33,32}**	**{33,34}**	**{33,32,34}**
{33}	**{33,32}**	**{33,38}**	**{33,32,38}**
{33}	**{33,34}**	**{33,38}**	**{33,34,38}**
{34}	**{34,15}**	**{34,16}**	**{34,15,16}**
{34}	**{34,15}**	**{34,17}**	**{34,15,17}**

Table D3 (continued)

{34}	**{34,15}**	**{34,21}**	**{34,15,21}**
{34}	**{34,15}**	**{34,31}**	**{34,15,31}**
{34}	**{34,15}**	**{34,32}**	**{34,15,32}**
{34}	**{34,15}**	**{34,33}**	**{34,15,33}**
{34}	**{34,15}**	**{34,38}**	**{34,15,38}**
{34}	**{34,15}**	**{34,40}**	**{34,15,40}**
{34}	**{34,16}**	**{34,17}**	**{34,16,17}**
{34}	**{34,16}**	**{34,21}**	**{34,16,21}**
{34}	**{34,16}**	**{34,31}**	**{34,16,31}**
{34}	**{34,16}**	**{34,32}**	**{34,16,32}**
{34}	**{34,16}**	**{34,33}**	**{34,16,33}**
{34}	**{34,16}**	**{34,38}**	**{34,16,38}**
{34}	**{34,16}**	**{34,40}**	**{34,16,40}**
{34}	**{34,17}**	**{34,21}**	**{34,17,21}**
{34}	**{34,17}**	**{34,31}**	**{34,17,31}**
{34}	**{34,17}**	**{34,32}**	**{34,17,32}**
{34}	**{34,17}**	**{34,33}**	**{34,17,33}**
{34}	**{34,17}**	**{34,38}**	**{34,17,38}**
{34}	**{34,17}**	**{34,40}**	**{34,17,40}**
{34}	**{34,21}**	**{34,31}**	**{34,21,31}**
{34}	**{34,21}**	**{34,32}**	**{34,21,32}**
{34}	**{34,21}**	**{34,33}**	**{34,21,33}**

Table D3 (continued)

{34}	**{34,21}**	**{34,38}**	**{34,21,38}**
{34}	**{34,21}**	**{34,40}**	**{34,21,40}**
{34}	**{34,31}**	**{34,32}**	**{34,31,32}**
{34}	**{34,31}**	**{34,33}**	**{34,31,33}**
{34}	**{34,31}**	**{34,38}**	**{34,31,38}**
{34}	**{34,31}**	**{34,40}**	**{34,31,40}**
{34}	**{34,32}**	**{34,33}**	**{34,32,33}**
{34}	**{34,32}**	**{34,38}**	**{34,32,38}**
{34}	**{34,32}**	**{34,40}**	**{34,32,40}**
{34}	**{34,33}**	**{34,38}**	**{34,33,38}**
{34}	**{34,33}**	**{34,40}**	**{34,33,40}**
{34}	**{34,38}**	**{34,40}**	**{34,38,40}**
{35}	**{35,24}**	**{35,44}**	**{35,24,44}**
{37}	**{37,7}**	**{37,8}**	**{37,7,8}**
{37}	**{37,7}**	**{37,19}**	**{37,7,19}**
{37}	**{37,7}**	**{37,20}**	**{37,7,20}**
{37}	**{37,7}**	**{37,28}**	**{37,7,28}**
{37}	**{37,7}**	**{37,29}**	**{37,7,29}**
{37}	**{37,7}**	**{37,30}**	**{37,7,30}**
{37}	**{37,7}**	**{37,38}**	**{37,7,38}**
{37}	**{37,7}**	**{37,46}**	**{37,7,46}**
{37}	**{37,8}**	**{37,19}**	**{37,8,19}**

Table D3 (continued)

{37}	**{37,8}**	**{37,20}**	**{37,8,20}**
{37}	**{37,8}**	**{37,28}**	**{37,8,28}**
{37}	**{37,8}**	**{37,29}**	**{37,8,29}**
{37}	**{37,8}**	**{37,30}**	**{37,8,30}**
{37}	**{37,8}**	**{37,38}**	**{37,8,38}**
{37}	**{37,8}**	**{37,46}**	**{37,8,46}**
{37}	**{37,19}**	**{37,20}**	**{37,19,20}**
{37}	**{37,19}**	**{37,28}**	**{37,19,28}**
{37}	**{37,19}**	**{37,29}**	**{37,19,29}**
{37}	**{37,19}**	**{37,30}**	**{37,19,30}**
{37}	**{37,19}**	**{37,38}**	**{37,19,38}**
{37}	**{37,19}**	**{37,46}**	**{37,19,46}**
{37}	**{37,20}**	**{37,28}**	**{37,20,28}**
{37}	**{37,20}**	**{37,29}**	**{37,20,29}**
{37}	**{37,20}**	**{37,30}**	**{37,20,30}**
{37}	**{37,20}**	**{37,38}**	**{37,20,38}**
{37}	**{37,20}**	**{37,46}**	**{37,20,46}**
{37}	**{37,28}**	**{37,29}**	**{37,28,29}**
{37}	**{37,28}**	**{37,30}**	**{37,28,30}**
{37}	**{37,28}**	**{37,38}**	**{37,28,38}**
{37}	**{37,28}**	**{37,46}**	**{37,28,46}**
{37}	**{37,29}**	**{37,30}**	**{37,29,30}**

Table D3 (continued)

{37}	**{37,29}**	**{37,38}**	**{37,29,38}**
{37}	**{37,29}**	**{37,46}**	**{37,29,46}**
{37}	**{37,30}**	**{37,38}**	**{37,30,38}**
{37}	**{37,30}**	**{37,46}**	**{37,30,46}**
{37}	**{37,38}**	**{37,46}**	**{37,38,46}**
{38}	**{38,8}**	**{38,20}**	**{38,8,20}**
{38}	**{38,8}**	**{38,21}**	**{38,8,21}**
{38}	**{38,8}**	**{38,28}**	**{38,8,28}**
{38}	**{38,8}**	**{38,29}**	**{38,8,29}**
{38}	**{38,8}**	**{38,31}**	**{38,8,31}**
{38}	**{38,8}**	**{38,32}**	**{38,8,32}**
{38}	**{38,8}**	**{38,33}**	**{38,8,33}**
{38}	**{38,8}**	**{38,34}**	**{38,8,34}**
{38}	**{38,8}**	**{38,37}**	**{38,8,37}**
{38}	**{38,20}**	**{38,21}**	**{38,20,21}**
{38}	**{38,20}**	**{38,28}**	**{38,20,28}**
{38}	**{38,20}**	**{38,29}**	**{38,20,29}**
{38}	**{38,20}**	**{38,31}**	**{38,20,31}**
{38}	**{38,20}**	**{38,32}**	**{38,20,32}**
{38}	**{38,20}**	**{38,33}**	**{38,20,33}**
{38}	**{38,20}**	**{38,34}**	**{38,20,34}**
{38}	**{38,20}**	**{38,37}**	**{38,20,37}**

Table D3 (continued)

{38}	{38,21}	{38,28}	{38,21,28}
{38}	{38,21}	{38,29}	{38,21,29}
{38}	{38,21}	{38,31}	{38,21,31}
{38}	{38,21}	{38,32}	{38,21,32}
{38}	{38,21}	{38,33}	{38,21,33}
{38}	{38,21}	{38,34}	{38,21,34}
{38}	{38,21}	{38,37}	{38,21,37}
{38}	{38,28}	{38,29}	{38,28,29}
{38}	{38,28}	{38,31}	{38,28,31}
{38}	{38,28}	{38,32}	{38,28,32}
{38}	{38,28}	{38,33}	{38,28,33}
{38}	{38,28}	{38,34}	{38,28,34}
{38}	{38,28}	{38,37}	{38,28,37}
{38}	{38,29}	{38,31}	{38,29,31}
{38}	{38,29}	{38,32}	{38,29,32}
{38}	{38,29}	{38,33}	{38,29,33}
{38}	{38,29}	{38,34}	{38,29,34}
{38}	{38,29}	{38,37}	{38,29,37}
{38}	{38,31}	{38,32}	{38,31,32}
{38}	{38,31}	{38,33}	{38,31,33}
{38}	{38,31}	{38,34}	{38,31,34}
{38}	{38,31}	{38,37}	{38,31,37}

Table D3 (continued)

{38}	{38,32}	{38,33}	{38,32,33}
{38}	{38,32}	{38,34}	{38,32,34}
{38}	{38,32}	{38,37}	{38,32,37}
{38}	{38,33}	{38,34}	{38,33,34}
{38}	{38,33}	{38,37}	{38,33,37}
{38}	{38,34}	{38,37}	{38,34,37}
{39}	{39,12}	{39,25}	{39,12,25}
{39}	{39,12}	{39,26}	{39,12,26}
{39}	{39,25}	{39,26}	{39,25,26}
{40}	{40,0}	{40,12}	{40,0,12}
{40}	{40,0}	{40,16}	{40,0,16}
{40}	{40,0}	{40,17}	{40,0,17}
{40}	{40,0}	{40,23}	{40,0,23}
{40}	{40,0}	{40,34}	{40,0,34}
{40}	{40,0}	{40,41}	{40,0,41}
{40}	{40,12}	{40,16}	{40,12,16}
{40}	{40,12}	{40,17}	{40,12,17}
{40}	{40,12}	{40,23}	{40,12,23}
{40}	{40,12}	{40,34}	{40,12,34}
{40}	{40,12}	{40,41}	{40,12,41}
{40}	{40,16}	{40,17}	{40,16,17}
{40}	{40,16}	{40,23}	{40,16,23}

Table D3 (continued)

{40}	**{40,16}**	**{40,34}**	**{40,16,34}**
{40}	**{40,16}**	**{40,41}**	**{40,16,41}**
{40}	**{40,17}**	**{40,23}**	**{40,17,23}**
{40}	**{40,17}**	**{40,34}**	**{40,17,34}**
{40}	**{40,17}**	**{40,41}**	**{40,17,41}**
{40}	**{40,23}**	**{40,34}**	**{40,23,34}**
{40}	**{40,23}**	**{40,41}**	**{40,23,41}**
{40}	**{40,34}**	**{40,41}**	**{40,34,41}**
{41}	**{41,0}**	**{41,23}**	**{41,0,23}**
{41}	**{41,0}**	**{41,40}**	**{41,0,40}**
{41}	**{41,23}**	**{41,40}**	**{41,23,40}**
{42}	**{42,18}**	**{42,43}**	**{42,18,43}**
{42}	**{42,18}**	**{42,44}**	**{42,18,44}**
{42}	**{42,43}**	**{42,44}**	**{42,43,44}**
{43}	**{43,42}**	**{43,44}**	**{43,42,44}**
{44}	**{44,35}**	**{44,42}**	**{44,35,42}**
{44}	**{44,35}**	**{44,43}**	**{44,35,43}**
{44}	**{44,42}**	**{44,43}**	**{44,42,43}**
{46}	**{46,8}**	**{46,20}**	**{46,8,20}**
{46}	**{46,8}**	**{46,25}**	**{46,8,25}**
{46}	**{46,8}**	**{46,26}**	**{46,8,26}**
{46}	**{46,8}**	**{46,37}**	**{46,8,37}**

Table D3 (continued)

{46}	**{46,20}**	**{46,25}**	**{46,20,25}**
{46}	**{46,20}**	**{46,26}**	**{46,20,26}**
{46}	**{46,20}**	**{46,37}**	**{46,20,37}**
{46}	**{46,25}**	**{46,26}**	**{46,25,26}**
{46}	**{46,25}**	**{46,37}**	**{46,25,37}**
{46}	**{46,26}**	**{46,37}**	**{46,26,37}**
{48}	**{48,14}**	**{48,15}**	**{48,14,15}**
{48}	**{48,14}**	**{48,16}**	**{48,14,16}**
{48}	**{48,14}**	**{48,21}**	**{48,14,21}**
{48}	**{48,14}**	**{48,22}**	**{48,14,22}**
{48}	**{48,14}**	**{48,32}**	**{48,14,32}**
{48}	**{48,14}**	**{48,49}**	**{48,14,49}**
{48}	**{48,15}**	**{48,16}**	**{48,15,16}**
{48}	**{48,15}**	**{48,21}**	**{48,15,21}**
{48}	**{48,15}**	**{48,22}**	**{48,15,22}**
{48}	**{48,15}**	**{48,32}**	**{48,15,32}**
{48}	**{48,15}**	**{48,49}**	**{48,15,49}**
{48}	**{48,16}**	**{48,21}**	**{48,16,21}**
{48}	**{48,16}**	**{48,22}**	**{48,16,22}**
{48}	**{48,16}**	**{48,32}**	**{48,16,32}**
{48}	**{48,16}**	**{48,49}**	**{48,16,49}**
{48}	**{48,21}**	**{48,22}**	**{48,21,22}**

Table D3 (continued)

{48}	**{48,21}**	**{48,32}**	**{48,21,32}**
{48}	**{48,21}**	**{48,49}**	**{48,21,49}**
{48}	**{48,22}**	**{48,32}**	**{48,22,32}**
{48}	**{48,22}**	**{48,49}**	**{48,22,49}**
{48}	**{48,32}**	**{48,49}**	**{48,32,49}**
{49}	**{49,14}**	**{49,15}**	**{49,14,15}**
{49}	**{49,14}**	**{49,16}**	**{49,14,16}**
{49}	**{49,14}**	**{49,22}**	**{49,14,22}**
{49}	**{49,14}**	**{49,48}**	**{49,14,48}**
{49}	**{49,15}**	**{49,16}**	**{49,15,16}**
{49}	**{49,15}**	**{49,22}**	**{49,15,22}**
{49}	**{49,15}**	**{49,48}**	**{49,15,48}**
{49}	**{49,16}**	**{49,22}**	**{49,16,22}**
{49}	**{49,16}**	**{49,48}**	**{49,16,48}**
{49}	**{49,22}**	**{49,48}**	**{49,22,48}**

APPENDIX E

ADDITIONAL OPTIMAL LISTING AND HOME OPO SELECTION DECISIONS FOR THE CARDINALITY MODEL

Table E1: Optimal listing decisions for patient 1 for different initial health states, K, and when admissible set includes OPOs within 250 miles of Chicago.

Initial health state (MELD score)	***K***	**Optimal OPO set**	**Optimal region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	1	*Chicago, IL*	{7}	2759	
	2	*Chicago, IL* Indianapolis, IN	{7,10}	2983	8.12
	3	*Chicago, IL* Indianapolis, IN Madison, WI	{7,10}	3066	2.78
	4	*Chicago, IL* Indianapolis, IN Madison, WI North Liberty, IA	{7,8,10}	3099	1.08
30	1	*Chicago, IL*	{7}	1356	
	2	*Chicago, IL* Indianapolis, IN	{7,10}	1535	13.20
	3	*Chicago, IL* Indianapolis, IN North Liberty, IA	{7,8,10}	1608	4.76
	4	*Chicago, IL* Indianapolis, IN North Liberty, IA Madison, WI	{7,8,10}	1646	2.36

Table E2: Optimal listing decisions for patient 2 for different initial health states, K, and when admissible set includes OPOs within 250 miles of Chicago.

Initial health state (MELD score)	***K***	**Optimal OPO set**	**Optimal region set**	**Total life expectancy (days)**	**Gain in life expectancy (Percentage)**
12	1	*Chicago, IL*	{7}	5338	
	2	*Chicago, IL* North Liberty, IA	{7,8}	5575	4.44
	3	*Chicago, IL* North Liberty, IA Indianapolis, IN	{7,8,10}	5630	0.99
	4	*Chicago, IL* North Liberty, IA Indianapolis, IN Madison, WI	{7,8,10,11}	5656	0.46
30	1	*Chicago, IL*	{7}	3529	
	2	*Chicago, IL* Indianapolis, IN	{7,10}	4072	15.39
	3	*Chicago, IL* Indianapolis, IN North Liberty, IA	{7,8,10}	4250	4.37
	4	*Chicago, IL* Indianapolis, IN North Liberty, IA Madison, WI	{7,8,10}	4323	1.72

Table E3: Home OPO selection decision for patient 1 for different initial health states, K, and when admissible set includes OPOs within 250 miles of the home OPO.

Initial health state (MELD)	***K***	**Best home OPO**	**Total life expectancy in best home OPO**	**% gain in life expectancy over worst home OPO**
12	1	*Tampa, FL*	3053	12.28
	2	*Tampa, FL* *Gainesville, FL*	3123	8.97
	3	*Indianapolis, IN* Louisville, KY Maumee, OH	3126	5.57
	4	*Cincinnati, OH* Indianapolis, IN Louisville, KY Maumee, OH	3138	4.72
30	1	*Cincinnati, OH*	1522	33.38
	2	*Cincinnati, OH* *Louisville, KY*	1642	19.98
	3	*Cincinnati, OH* *Louisville, KY* *Indianapolis, IN*	1676	12.77
	4	*Cincinnati, OH* Louisville, KY Indianapolis, IN Ann Arbor, MI	1697	11.90

Table E4: Home OPO selection decision for patient 2 for different initial health states, K, and when admissible set includes OPOs within 250 miles of the home OPO.

Initial health state (MELD)	***K***	**Best home OPO**	**Total life expectancy in best home OPO**	**% gain in life expectancy over worst home OPO**
12	1	*Westwood, KS*	5673	7.16
	2	*Westwood, KS* *St. Louis, MO*	5704	4.56
	3	*St. Louis, MO* Westwood, KS Indianapolis, IN	5722	3.44
	4	*Nashville, TN* Birmingham, AL Louisville, KY Memphis, TN	5723	2.83
30	1	*Cincinnati, OH*	3984	47.14
	2	*Cincinnati, OH* *Louisville, KY*	4273	21.34
	3	*Cincinnati, OH* *Louisville, KY* *Indianapolis, IN*	4386	12.18
	4	*Cincinnati, OH* Louisville, KY Indianapolis, IN Ann Arbor, MI	4440	11.06

APPENDIX F

ADDITIONAL OPTIMAL LISTING AND HOME OPO SELECTION DECISIONS FOR THE TOTAL DISTANCE MODEL

Table F1: Optimal OPO sets for Patient 1 (maximum total distance = 400 miles).

Initial health state (MELD)	**Optimal OPO set**	**Region**	**Total life expectancy attained by a total distance of 400 miles (days)**	**Percentage gain in life expectancy attained over a total distance of 300 miles**
12	*Chicago, IL*	7	3085	2.27
	Ann Arbor, MI	10		
	Madison, WI	7		
30	*Chicago, IL*	7	1596	1.94
	Madison, WI	7		
	North Liberty, IA	8		

Table F2: Optimal OPO sets for Patient 2 (maximum total distance = 400 miles).

Initial health state (MELD)	**Optimal OPO set**	**Region**	**Total life expectancy attained by a total distance of 400 miles (days)**	**Percentage gain in life expectancy attained over a total distance of 300 miles**
6	*Chicago, IL*	7	5644	1.24
	Louisville, KY	11		
32	*Chicago, IL*	7	4197	1.36
	Indianapolis, IN	10		
	Madison, WI	7		

Table F3: Optimal home OPO selection decision for Patient 1(maximum total distance = 400 miles).

Initial health state MELD score	**Best home OPO and optimal OPO set**	**Region**	**Total life expectancy in best home OPO**	**Gain in life expectancy over worst home OPO (%)**
12	*Louisville, KY*	11	3132	10.59
	Cincinnati, OH	10		
	Indianapolis, IN	10		
	Nashville, TN	11		
30	*Cincinnati, OH*	10	1692	34.18
	Columbus, OH	10		
	Indianapolis, IN	10		
	Louisville, KY	11		

Table F4: Optimal home OPO selection decision for Patient 2(maximum total distance = 400 miles).

Initial health state MELD score	**Best home OPO and optimal OPO set**	**Region**	**Total life expectancy in best home OPO**	**Gain in life expectancy over worst home OPO (%)**
12	*Louisville, KY*	11	5718	5.40
	Cincinnati, OH	10		
	Indianapolis, IN	10		
	Nashville, TN	11		
30	*Cincinnati, OH*	10	4424	38.81
	Columbus, OH	10		
	Indianapolis, IN	10		
	Louisville, KY	11		

APPENDIX G

MAPS OF US TRANSPLANT REGIONS AND OPOS

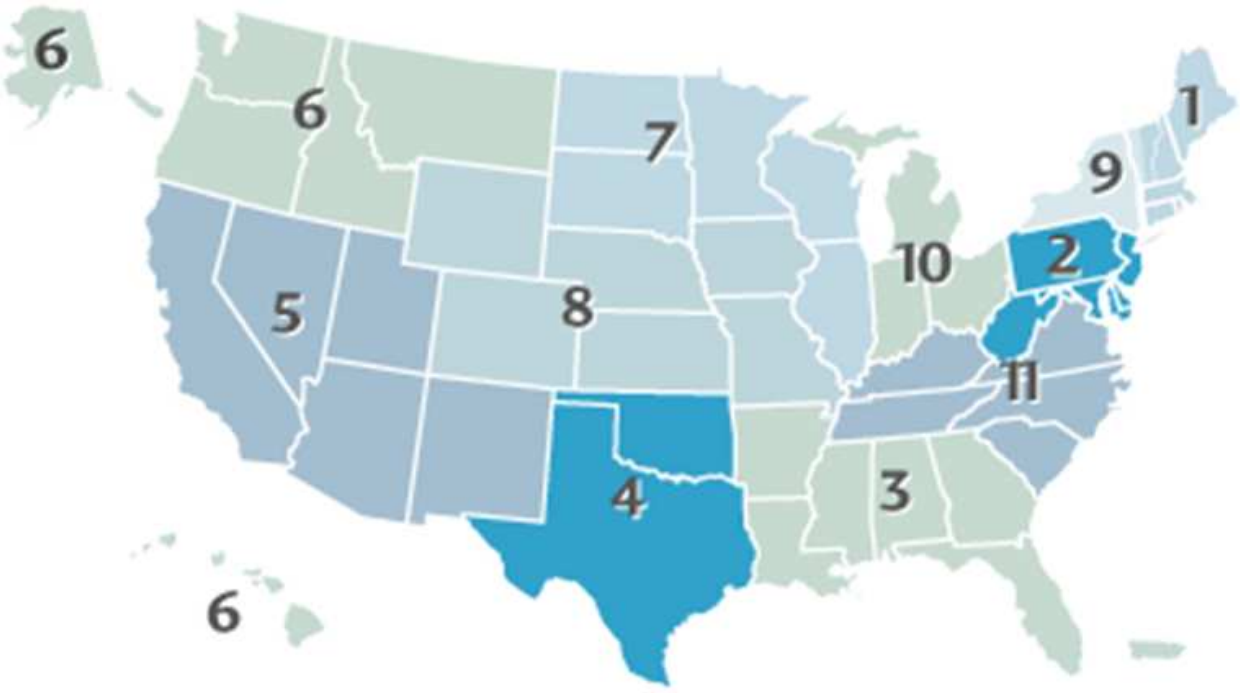

Figure G1: Transplant Regions.

Figure G2: Transplant OPOs.

Figure G3: OPOs within 350 miles of Louisville, KY span Regions 7, 8, 10 and 11.

APPENDIX H

P-VALUES OF THE LOGISTIC REGRESSION MODELS

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4542	0.0260	17592.1908	<.0001
female	1	-0.0612	0.0409	2.2426	0.1343

Gender = Female

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4246	0.0249	18888.3548	<.0001
dd1	1	-0.1496	0.0421	12.6466	0.0004

Disease group 1

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.5263	0.0249	20112.0231	<.0001
dd2	1	0.1402	0.0421	11.0740	0.0009

Disease group 2

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4500	0.0206	28137.3164	<.0001
dd3	1	-0.4968	0.0948	27.4629	<.0001

Disease group 3

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4666	0.0202	29307.6613	<.0001
dd4	1	-0.5744	0.1552	13.7063	0.0002

Disease group 4

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.5356	0.0230	23685.6021	<.0001
dd5	1	0.2608	0.0473	30.4464	<.0001

Disease group 5

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.8791	0.0475	6663.8582	<.0001
de1	1	0.5110	0.0524	94.9932	<.0001

Ethnicity category 1

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4541	0.0207	27791.4424	<.0001
de2	1	-0.3538	0.0838	17.8238	<.0001

Ethnicity category 2

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4421	0.0210	26945.7274	<.0001
de4	1	-0.3797	0.0727	27.2889	<.0001

Ethnicity category 3

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4606	0.0203	29201.6030	<.0001
de5	1	-0.7591	0.1549	24.0043	<.0001

Ethnicity category 4

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.4681	0.0202	29335.4848	<.0001
de8	1	-0.5200	0.1552	11.2211	0.0008

Ethnicity category 5

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept	1	-3.8004	0.1579	579.6045	<.0001
female	1	-0.0299	0.0416	0.5186	0.4714
de1	1	0.6693	0.1558	18.4610	<.0001
de2	1	0.2226	0.1742	1.6326	0.2013
de4	1	0.2133	0.1692	1.5892	0.2074
de5	1	-0.2012	0.2178	0.8532	0.3557
de8	0	0	.	.	.
dd1	1	-0.3488	0.0537	42.1888	<.0001
dd2	1	-0.1159	0.0542	4.5682	0.0326
dd3	1	-0.6445	0.1015	40.3382	<.0001
dd4	1	-0.7492	0.1596	22.0300	<.0001
dd5	0	0	.	.	.

All disease groups, all ethnicity categories, and a binary variable for female is present

Figure H1: p-values of the logistic regression models when only one predictor variable is present and all predictor variables are present.

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