MARKOV DECISION PROCESS MODELS FOR IMPROVING EQUITY IN LIVER ALLOCATION

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In the United States, end-stage liver disease (ESLD) patients are prioritized primarily by their Model for End-stage Liver Disease score (MELD) to receive organ offers. Therefore, patients are required to update their MELD score at predefined frequencies that depend on the patient's last reported score. One aim of this dissertation is to mitigate inequities that stem from patients' flexibility regarding MELD score updates. We develop a Markov decision process (MDP) model to examine the degree to which an individual patient can benefit from the updating flexibility, and provide a menu of updating requirements that balance inequity and data processing more efficiently than the current updating requirements. We also derive sufficient conditions under which a structured optimal updating policy exists.

As the coordinator of the harvesting Organ Procurement Organization (OPO) extends offers according to MELD score prioritization, the organ becomes less desirable. To avoid not placing the organ, the OPO coordinator can initiate an expedited placement, i.e., offer the organ to a transplant center, which can then allocate it to *any* of its patients. A second aim of this dissertation is to mitigate inequities induced by the OPO coordinator's premature departure from the prioritized list of patients via an expedited placement.

As a preliminary step to studying the inequity induced by expedited liver placement, we conduct an extensive analysis of the current expedited liver placement practice based on recent data. We investigate different aspects of extending offers, e.g., the number of offers

extended concurrently, and patients' response characteristics. Several of the results from this analysis serve as inputs for a second MDP model that examines how many concurrent offers the OPO coordinator should extend and when the coordinator should initiate an expedited placement. Numerical experimentation reveals a structured optimal policy, and we test the sensitivity of the model outcomes with respect to changes in model inputs. Lastly, we examine how our model outputs compare to the analogous measures observed in current practice and how they can be used to improve current practice.

Keywords: Markov decision processes, dynamic programming, optimal stopping, structured optimal policies, Pareto optimality, sensitivity analysis, medical decision making, organ transplantation, information asymmetry, societal welfare.

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ACKNOWLEDGMENTS

dedicated to my grandparents, Naciye and Melih Sert

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1.0 INTRODUCTION

The health care industry is one of the world's largest and fastest growing industries [24]. Consuming over 10% of gross domestic product (GDP) of most developed nations, health care can form an enormous part of a country's economy. It is one of the biggest industries in the United States (US) and 10 of the 20 fastest growing occupations are health care related [32]. In 2003, health care costs paid to hospitals, physicians, nursing homes, diagnostic laboratories, pharmacies, medical device manufacturers and other components of the health care system consumed 15.3% of the GDP of the US, the largest of any country in the world [21]; in 2006, US health care expenditures totaled $2.2 trillion; and in 2008, health care provided 14.3 million jobs for wage and salary workers [32]. Given the health care industry's upward rising trend, it is projected that its share of the GDP will reach 19.6 % by 2016 [12]. According to the Bureau of Labor Statistics of the US, health care will generate 3.2 million new wage and salary jobs by 2018, more than any other industry, largely in response to rapid growth in the elderly population. These tremendous expenditures have brought pressure on the health care industry not only to minimize cost of services, but also to eliminate some of the services.

This dissertation relates to the ultimate goal of improving the quality of health care services, specifically transplantation of livers, the second most commonly transplanted major organ after the kidney. Other types of organ transplants include the heart, intestine, kidney, lung and pancreas. The organ transplant history started with the first successful kidney transplant in 1954. The first successful pancreas and liver transplants were performed in 1966 and 1967 respectively, followed by the first successful heart transplant in 1968 [22]. A

new name is added to the national waiting list for organs every 13 minutes [22] to be eligible for a potentially life-saving transplant. Currently, there are 111,812 patients nationwide waiting for an organ. However, the total number of transplants was only 28,662 in 2010 [34]. Due to the scarcity of available organs, an average of 18 people die every day in the U.S. waiting for an organ [22].

Liver transplantation is the definitive form of treatment for end-stage liver disease (ESLD) patients. ESLD is an irreversible condition that leads to the complete failure of the liver which can occur rapidly, in a matter of weeks (acute liver failure), or slowly over months and years (chronic liver failure). ESLD has many causes including liver cirrhosis, biliary duct atresia, cystic fibrosis, early-stage liver cancer, hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangitis and Wilson's disease [14], and it is the 12^{th} leading cause of death in the United States [20].

Liver donations come from either deceased or living donors. Living donor transplantation has emerged in recent decades and has modestly helped to alleviate the widespread shortage of deceased donor livers for patients awaiting transplant. Despite the efforts encouraging living donor transplants and the surge in the number of transplant programs, the number of living donor transplants remains very limited compared to the number of deceased donor transplants. In 2010, 282 living donor transplants were recorded, whereas the corresponding number for deceased donor transplants was 6009 (Figure 1.1). As of this writing, 16,278 people are on the national liver transplant waiting list. However, the total number of transplants in 2010 was only 6291, which illustrates the large gap between the supply and demand of transplantable livers (Figure 1.1).

In both living and deceased liver transplantation, the procedure of transplantation involves the replacement of the native, diseased liver by the donor organ in the same anatomic location as the original liver. It typically involves 3 surgeons and 1 anesthesiologist, with up to 4 supporting nurses. The surgical procedure, which can range from 4 up to 18 hours depending on outcome, is very demanding, and it is one of the most expensive treatments in modern medicine. Typical expenses during the first year (everything included from surgery,

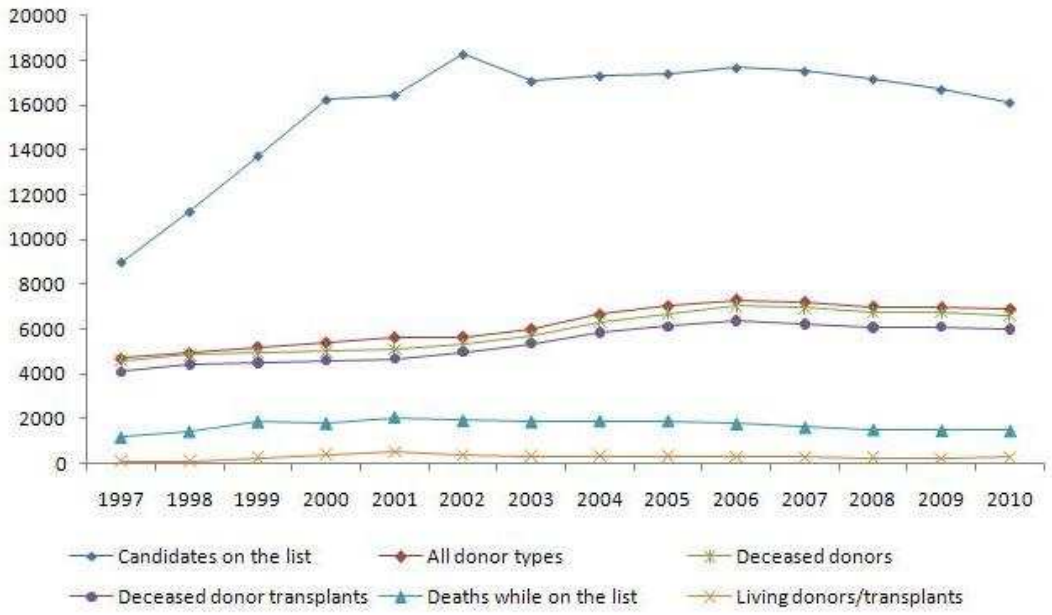


Figure 1.1: Liver transplantation activity between 1997-2010

hospitalization, lab testing, medications) are up to $315,000, excluding insurance or government assistance [25]. The cost is considerably lower in countries like India where a living donor liver transplant typically costs approximately $50,000. This considerably lower cost is one of the driving forces for illegal organ trafficking and for "transplantation tourism," one of the many ethical issues relating organ transplantation.

The combination of (i) the absence of alternative therapies combined with the scarcity of donated livers; (ii) the high organ waste rate (in 2010, the number of liver donations was 6890 while 6291 transplants were made resulting in the waste of nearly 9% of all donations (Figure 1.1)); and (iii) the ethical dilemmas of the allocation procedure underscores the importance of the efficient management of liver donations. Two different perspectives exist in the decision making regarding the management of liver donations. First, there is society's perspective which looks at the entire system and aims to design an allocation mechanism to optimize an objective or combination of objectives. Second, there is patients' perspective

which focuses on how an individual patient with her transplant team should exercise the prerogative decision to accept or decline organs over time. This accept/reject decision making process is a complex optimal stopping problem which we discuss in greater detail in Section 1.1.1.

Operations Research (OR) provides a multitude of decision making tools which can be utilized to assist the policy makers as well as individual patients regarding the management of limited resources. The application of OR techniques dates back to the 1950's and OR tools have been widely applied to many different health care related problems. A recent survey is presented by [11]. In the last decade however, there has been a significant increase in the number of studies focusing on the management of liver transplantation. They primarily take an individual patient's perspective and deal with the optimization of liver accept/decline decisions ([5], [6], [7], [42]). Studies from society's perspective include works by [2], [19] and [44]. Due to the set of realistic assumptions made, this body of literature on liver transplantation has a greater appeal of real world applicability than the existing literature on other organ transplantations which include studies by [1], [5], [6], [7], [16], [27], [28] from the patient's perspective and [17], [18], [37] [40], [47], [50], [51], [52], [53] from society's perspective.

We take both society's and an individual patient's points of views to investigate the deceased donor liver transplantation for adult patients. From the patients' perspective, we provide policies to obtain the maximum possible life expectancy under the current regulations; from society's perspective we attack different sources of inequity and provide suggestions to mitigate their effects. We provide easy to implement guidelines for both the patients and policy makers.

1.1 LIVER ALLOCATION SYSTEM

To structure the nationwide allocation of donated organs, the National Organ Transplant Act (NOTA) of 1984 called for an Organ Procurement and Transplantation Network (OPTN) in charge of (i) increasing and ensuring the effectiveness, efficiency and equity of organ sharing in the national system of organ allocation, and (ii) increasing the supply of donated organs available for transplantation. OPTN, as a unified transplant network, needed to be operated by a private, non-profit organization under federal contract. The United Network for Organ Sharing (UNOS) was awarded the initial OPTN contract in 1986, and has continued to administer the OPTN since then. As part of the OPTN contract, UNOS' main responsibilities are ensuring an organ sharing system that maximizes the efficient use of deceased organs through equitable and timely allocation, maintaining a system to collect, store, analyze and publish data on the patient waiting list, organ matching, and transplants, and informing, consulting and guiding persons and organizations concerned with human organ transplantation in order to increase the number of organs available for transplantation. Recently, UNOS has been improving its operations via the use of the internet; in 1999, it launched UNet, a secure, Internet-based transplant information database system for all organ matching and management of transplant data. In 2006, UNOS launched DonorNet, a secure, Internet-based system in which organ procurement coordinators send out offers of newly donated organs to transplant hospitals with compatible candidates.

To facilitate transplantation, the US is divided into 11 geographic regions represented in Figure 1.2. Each region is further divided into subregions called donation service areas (DSAs) of Organ Procurement Organizations (OPOs). Currently, there are 58 [33] OPOs serving unique areas of varying sizes, population densities, donation rates, and transplantation activities. UNOS handles all its activities through these OPOs which are responsible for approaching families about donation, evaluating the medical suitability of potential donors, and coordinating the recovery, preservation, and transportation of organs donated for transplantation within their harvesting DSA. Within each OPO there are several transplant

centers where eligible candidates register to be considered for donation and transplantation operations are realized. The total number of transplant centers continues to increase and currently there are 254 centers for organ transplants, with 127 transplant centers accommodating liver transplant programs [33].

Region 1:	Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont
Region 2:	Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia
Region 3:	Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico
Region 4:	Oklahoma, Texas
Region 5:	Arizona, California, Nevada, New Mexico, Utah
Region 6:	Alaska, Hawaii, Idaho, Montana, Oregon, Washington
Region 7:	Illinois, Minnesota, North Dakota, South Dakota, Wisconsin
Region 8:	Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming
Region 9:	New York, Western Vermont
Region 10:	Indiana, Michigan, Ohio
Region 11:	Kentucky, North Carolina, South Carolina, Tennessee, Virginia

Figure 1.2: UNOS regions

When an organ is donated, UNOS' centralized computer network, UNet links all OPOs and transplant centers in a real-time environment using the Internet. Then an OPTN computer match program compares data on the organ donor with data on transplant candidates and ranks candidates according to OPTN policies to determine the priority for allocating the donor organ. The prioritization is based on two main factors; a patient's medical urgency, i.e., her level of sickness and a patient's geographic location, i.e., her proximity to the OPO where the organ is harvested.

At the geographical level, the ranking algorithm considers three types of patients: local patients who are registered in the harvesting OPO, regional patients who are registered in an OPO in the harvesting region, and national patients from any other region. The reason patient geography is considered as a determinant is the limited length of time donated organs and tissues can be kept chilled outside the body in the absence of blood supply, i.e., the cold ischemia time (CIT). For livers, CIT is between 12-18 hours [34] beyond which the organs lose their vitality and cannot be used for transplantation. Given this time constraint, local patients are most favorable whereas the national patients are the least favorable.

At the medical urgency level, the prioritization is based on two patient categories: Status 1 patients and Model for End-stage Liver Disease (MELD) score patients. Status 1 patients have fulminant liver failure with a life expectancy without a liver transplant of less than 7 days. The total number of candidates listed as Status 1 has not changed appreciably in past years, representing only 0.1% of the total number of patients on the waiting list [34]. The medical urgency of patients who do not qualify for classification as Status 1 is measured by their MELD score which predicts their probability of pre-transplant death. The integer-valued MELD score is calculated using a regression equation based on three clinical values from the patient (bilirubin, INR and creatinine) and ranges from 6 (less ill) to 40 (gravely ill). Candidates within Status 1 and each MELD score are stratified using "points" which are assigned based on the compatibility of their blood type with the donors blood type.

Because a patient's MELD score can vary over time depending on the status of her disease, and prioritization is based primarily on MELD score, UNOS requires patients to update their clinical lab values at a minimum frequency that depends on their most recently reported MELD score (Table 1.1). Not surprisingly, sicker patients are required to update more frequently than healthier patients. Patients can update more frequently than the guidelines dictate; however, if they fail to update by the required time, then UNOS downgrades their reported MELD score to the healthiest score of 6 until new results are received. The transplant center caring for the candidate is responsible for sending this information to UNOS, who then records it in their database. Processing this data is costly and Roberts et al. [38] estimate the data processing cost at a large transplant center to be approximately $175,000 per year; this figure is likely higher now and does not include the data processing costs incurred by UNOS.

Table 1.1: Frequency of MELD score updates required by UNOS [22]

Last reported MELD score	≤ 10	11-18	19-24	≥ 25
Minimum update frequency (days)	365	90	30	7

Figure 1.3 represents the factors used to create the prioritized candidate list. As seen in Figure 1.3, the combined set of local and regional Status 1 patients tops the priority ranking whereas the set of national candidates, including all levels of medical urgency, comprises the bottom of the prioritization. That is, all local and regional MELD score patients have priority over national Status 1 and MELD score patients combined. For the local and regional MELD score patients, the MELD score spectrum is split at MELD 15 and patients with MELD≥15 are considered first among the local patients that have priority over regional ones. Patients with MELD <15 are considered next, again making the local versus regional distinction. Within each group, patients are ordered in decreasing severity and then by their compatibility with the donor's blood type, indicated by the blue arrows.

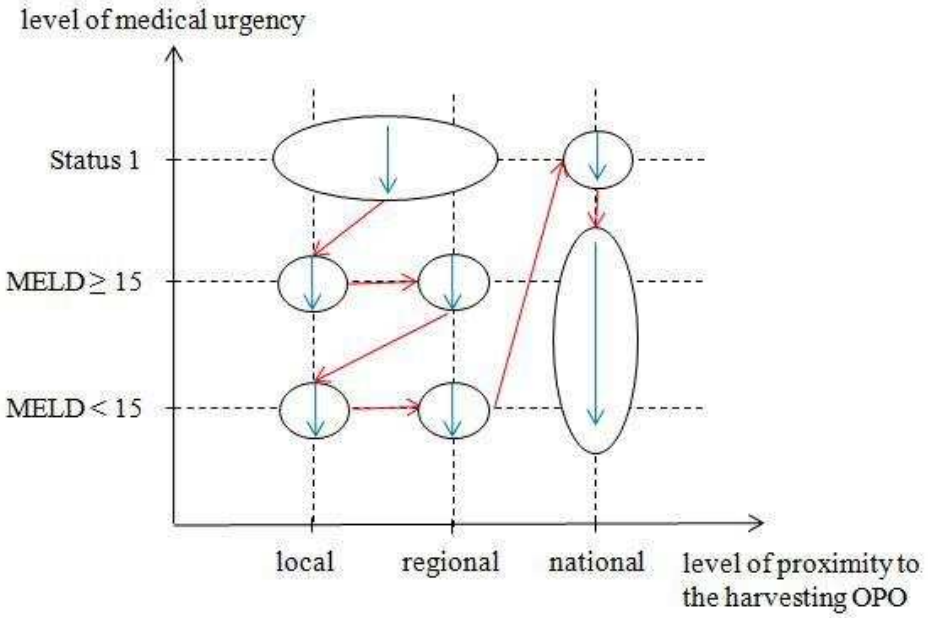


Figure 1.3: Candidate prioritization according to the current liver allocation system

There are a few types of liver disease for which exceptions are made to the MELD scoring system because their prognosis depends upon factors other than liver disease severity. They are termed recognized exceptional diagnoses (REDs) and include hepatocellular carcinoma (HCC), hepatopulmonary syndrome (HPS), familial amyloid polyneuropathy (FAP), and

primary oxaluria. Because the waiting list mortality of patients belonging to this category may not be accurately represented by their MELD score [9], they may be assigned additional MELD points beyond their calculated MELD score. For stage 2 HCC patients, UNOS has a different set of prioritization rules [22]. Also, UNOS has a slightly different scoring mechanism and allocation system for pediatric patients.

1.1.1 Match List Process

Once the prioritized match list is created, the harvesting OPO proceeds through this list by making offers until a successful match is obtained. We refer to the process of following the prioritized match list as the match list process, the offers made according to the match list as "standard" offers and multiple standard offers extended simultaneously represent a "batch" of offers. Initially, organ offers were distributed via fax and numerous phone calls which involved the exchange of large amounts of clinical and biologic information. On April 30, 2007, UNOS launched a web-based system via DonorNet which enables the OPOs to send out offers faster and to multiple transplant centers simultaneously. In the case of local offers, the OPOs set their own limits on the number of concurrently outstanding offers and/or on the number of transplant centers with concurrently outstanding offers. For regional or national offers, offers can be made to an unlimited number of patients up to 3 programs simultaneously for pre-recovery offers and up to 5 programs simultaneously for post-recovery offers. Although the establishment of the DonorNet electronic environment improved the standards of the current practice, organ waste unfortunately still remains high; in 2010, approximately 10% of all donated organs went unused, mainly due to the limited CIT time of livers (Figure 1.1).

Once the electronic offer notification is sent out to a transplant center, the transplant surgeon and/or physician in charge of the candidate has one hour to log into the electronic environment and view the donor's record. Then they have an additional hour to enter the final response to the organ offer which is either an acceptance or a refusal. The transplant surgeon and/or the physician responsible for the care of the patient, and the patient act as

a single decision maker to make the final accept/reject decision which depends on several factors, e.g., the patient's current health, quality of the organ offered, underlying disease, location, rank, presence or absence of a potential living donor.

If the response is an acceptance to the organ offer, responses to outstanding offers for patients with higher priorities (if there are any) need to be taken into account before the OPO makes the ultimate allocation decision. Eventually, the highest ranked patient with an acceptance response receives the organ, and the match list process terminates. If the response is a refusal, it is either in the form of an individual refusal or a range refusal. A range refusal is realized when the surgeon and/or physician rejects the organ offer not only for the patient receiving the offer notification but also for a range of the same transplant center's other patients, i.e., a block of patients from that transplant center's portion of the waiting list to whom the organ would have been offered sometime later in the match list process. In the case of refusals of either type, the patients remain eligible for future offers and their history of rejections does not affect their priority for the new offers. Despite the scarcity of donated organs, almost half of the liver offers are rejected by the first surgeon to whom the offer is made [28] and 60% of all liver offers are rejected [3].

1.1.2 Expedited Liver Placement

Because of the perishable nature of donated livers, the match list process is executed under considerable time pressure. If the procurement coordinator anticipates that proceeding through the match list will not produce a match quickly enough, then the coordinator may opt in to an "expedited placement." The initiation of an expedited placement implies that the coordinator of the harvesting OPO departs from the match list process and offers the organ to a transplant center. If the transplant center receiving the expedited organ offer accepts it, it is free to allocate the organ to any of the patients under its care without any match list constraints. This premature termination of the match list process implies that

some candidates having a higher match list priority than the candidate receiving the expedited placement liver offer, do not receive standard offers for the related organ, i.e., these higher ranked patients are bypassed.

The unpublicized, yet common practice of expedited placement of livers is described as an escape mechanism from the tightly controlled transplant matching process [15] and is intended to alleviate the allocation time constraint. Furthermore, there is a surge in the availability of organs which qualify for expedited placement. O'Connor et al. [31] report that the number of hepatitis C virus (HCV)+ donors and donors after cardiac death (DCD) which are most likely to be considered for an expedited placement, have tripled in Region 1 between 2004 and 2005. Despite the strategic importance of expedited placement livers in decreasing waste of donated organs, currently there are no allocation rules for expedited placement livers. Therefore the coordinators find themselves without much support regarding the timing and recipient of an expedited offer [15].

Recently OPTN/UNOS Liver and Intestinal Organ Transplantation Committee formed the Liver Utilization Working Group tasked with (1) evaluating and assessing the practice of expedited liver placement, and (2) formulating a transparent process for expedited liver placement [22]. As of June 2011, the working group is still in the early phases of information gathering.

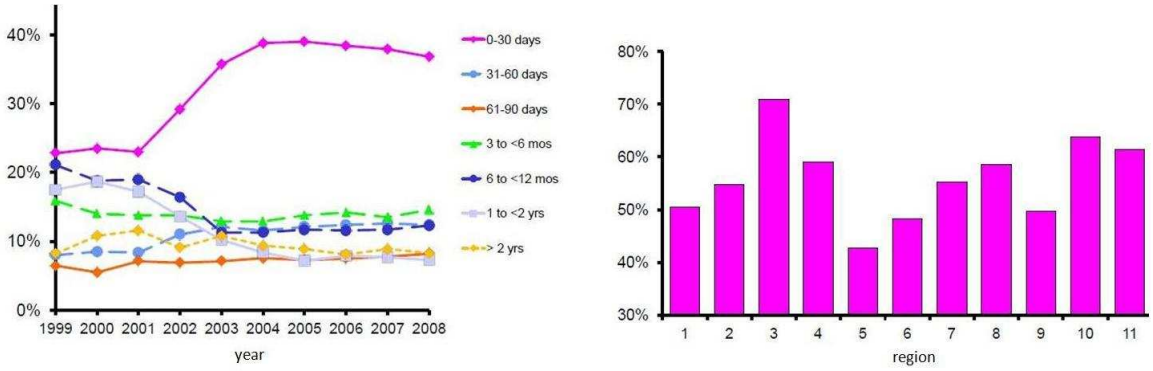
In addition to the absence of regulations for expedited placement livers, there is also a lack of literature about expedited liver placement practice. The most extensive study about expedited liver placement is by O'Connor et al. [31] who study the utilization of expedited placement livers in Region 1 between 2004 and 2005. They report that the percentage of expedited offers that are accepted increased from 18.8% in 2004 to 61.3% in 2005. To our knowledge, no other studies about the expedited liver placement practice exists.

1.2 MOTIVATION, PROBLEM STATEMENT AND CONTRIBUTIONS

Because deceased donor livers are a scarce, lifesaving resource, policies for prioritizing the allocation are of ultimate importance for patients whose lives depend upon liver transplantation. Therefore, the policies regarding the allocation of livers are continuously being refined to target the patients in greatest need and scrutinized for their potential unfairness.

Most notably, there is criticism regarding the currently employed prioritization algorithm, mainly because the definition of the "best" potential recipient cannot be agreed upon. On the one hand, patients with the severest medical urgency should have the greatest priority. However, the current measure of medical urgency, i.e., the MELD scoring system, does not serve all potential liver transplant candidates equally well. On the other hand, proximity needs to be taken into consideration as well because the travel distance of the organ impacts the organ quality and thus the post transplant life expectancy of the recipient. The highly variable densities of the regions and OPOs lead to highly variable patient waiting times (Figure 1.4) and imply that sicker patients in some part of the country may die while waiting on the list while some relatively healthier patients may receive a transplant [43], [48], [49]. To balance the efficiency and equity of the liver allocation system, Demirci et al. [19] and Kong et al. [29] propose redesigning the regional network. Another study by Akan et al. [2] proposes a new set of criteria for patient prioritization based on total quality adjusted life years and the number of unused organs. The outcomes of both studies require major system redesigns, and therefore seem impractical.

Additional proposed modifications to the allocation policy include prohibiting a patient from joining several waiting lists simultaneously (also known as "multilisting") [10], [30], increasing priority for children, developing guidelines to determine admission to the waiting lists which entails a series of medical evaluations by the transplant team, limiting or even banning retransplantation [13], [30], managing direct donations [23].



(a) (b)

Figure 1.4: Time from listing until transplant by year of transplant (a), the proportion of liver transplant recipients with a waiting time of 90 days or less by region (b) [34]

We are interested in mitigating inequities in the current liver allocation system that stem from two sources. The first is induced by patients' ability to game the allocation system by not reporting their MELD score to UNOS whenever their score changes. We measure this inequity by the percentage increase in life expectancy for a patient who is exploiting the flexibility in the current system by not reporting all MELD score changes. Mitigating the resulting inequity by requiring very frequent updates, however, is impractical and would add to the already significant data processing burden. Using a Markov decision process (MDP) model parameterized by clinical data, we examine (i) the degree to which an individual patient can benefit from the updating flexibility, and (ii) how the resulting inequities may be mitigated by revising the updating frequencies without significantly adding to the data processing burden. We provide a menu of updating requirements that balance inequity and data processing more efficiently than the current updating requirements.

The second source of inequity that we consider is induced by the OPO coordinator's premature departure from the match list process via an expedited placement. To gain insight about the mechanics of the current practice of expedited liver placement, we first

conduct an extensive analysis of current liver allocation practices where we specifically focus on the novel aspects of expedited placement activity. Using clinical data from OPTN, we investigate the prevalence of expedited placement livers by region, the timing of expedited offer initiation, the number of patients bypassed due to an expedited placement and the acceptance probabilities of expedited liver offers. We also investigate different aspects of the match list process within the current practice.

Using the insights gained by the assessment of current liver allocation practices, we formulate the match list process, which can possibly culminate in an expedited offer initiation, as an optimal stopping problem. Our model rewards reflect the OPO coordinator's adherence to the match list which is captured by the number of offers extended until a successful match. Using an MDP model, we examine (i) how many standard electronic offers the OPO coordinator should include in a batch during the match list process and (ii) when she/he should depart from the match list process, i.e., initiate an expedited placement. The following trade-off is involved in (i): Extending too many offers is impractical, whereas extending too few offers increases the likelihood of organ waste. And the trade-off involved in (ii) is as follows: Initiating expedited placement too soon implies a low level of adherence to the waiting list and thus is undesirable, whereas a late initiation implies a high risk to waste the donated organ. In our numerical experiments, we use different sets of model input and identify optimal solutions for the related problem instances. Additionally, we test the sensitivity of the model outcomes with respect to model input which we expect to vary across the nation or which depend on model assumptions. Eventually, we examine how our model outputs compare to the analogous measures observed in the current practice and how they can be useful to improve the current practice.

1.3 OVERVIEW OF THE DISSERTATION

The remainder of this dissertation is organized as follows. Chapter 2 presents an MDP model for the accept/reject/update (MELD score) decision problem faced by liver transplantation candidates, given a specific set of updating requirements. First, we analyze structural and numerical results relating to patient decision making. Then, we derive a menu of efficient updating schemes that balance inequity and data processing more efficiently than the current updating requirements. In Chapter 3, we assess the current allocation practice by analyzing OPTN data with a focus on the novel aspects of the match list process, expedited liver placement, and the patients' response mechanism. Chapter 4 presents the results of an MDP formulation for the optimal timing of an expedited liver placement initiation. We present a detailed numerical study parameterized with clinical data from Chapter 3 and conduct sensitivity analyses with respect to model inputs. In Chapter 5, we summarize our results and discuss the underlying limitations as well as possible directions for future research.

2.0 MITIGATING INEQUITIES IN LIVER ALLOCATION VIA REVISED HEALTH REPORTING FREQUENCIES

In Chapter 1, we explained that UNOS prioritizes patients awaiting liver transplantation based primarily on their medical urgency, as measured by their model for end-stage liver disease (MELD) score. Therefore, UNOS requires each patient to report their MELD score at a frequency that depends on their last reported MELD score (the sicker, the more frequent). As a result of this flexibility, patients may conceal changes in their MELD score and "game" the system. Mitigating the resulting inequity by requiring very frequent updates, however, is impractical and would add to the already significant data processing burden. In this chapter, we examine (i) the degree to which an individual patient can benefit from the updating flexibility, and (ii) how the resulting inequities may be mitigated by revising the updating frequencies without significantly adding to the data processing burden. We use a Markov decision process (MDP) model parameterized by clinical data and provide a menu of Pareto-optimal updating policies that balance inequity and data processing and suggest that requiring the sicker (healthier) patients to update more (less) frequently than they must under the current policy can improve both metrics.

The rest of this chapter is organized as follows. In Section 2.1 we present a review of the related literature. We illustrate our model formulation and analyze structural and numerical results relating to patient decision making in Section 2.2. Using this model, we derive a menu of efficient UNOS updating schemes in Section 2.3 before concluding in Section 2.4.

2.1 LITERATURE REVIEW AND MOTIVATION

Several researchers address the liver accept/reject problem from the patient's perspective as defined in Chapter 1. We refer the reader to Sandikci [41] for a detailed discussion of the organ transplantation literature. Within this body of work, the most relevant to our problem is Alagoz et al. [5], which is therefore considered in greater detail.

Alagoz et al. [5] present a discrete-time, infinite-horizon MDP model which maximizes total expected discounted life days associated with the accept/decline decision. The state of the process is described by the current patient health, $h \in S_H = \{1, 2, \ldots, H, H+1\}$ and the current organ quality, $l \in S_L = \{1, 2, \ldots, L, L+1\}$. Increasing values of h and l correspond to sicker health conditions and lower organ qualities, respectively, where $H+1$ and $L+1$ correspond to patient death and no liver offer, respectively. For each possible state (h, l), provided an offer is made, the patient chooses to either accept the offer and transplant, or reject the offer and continue to the next time period. The authors assume however, as do all other studies that examine the liver accept/reject decision process [6, 7, 42], *that UNOS knows the patient's current MELD score at all times.* This assumption implies that unless the patient chooses to transplant in a time period, her current health is reported to UNOS at every time period which correspond to days in Alagoz et al. formulation. If the patient accepts an offer of quality l while in health state h, she receives a total expected post-transplant reward, $R(h, l)$ and the problem terminates. Otherwise, i.e., if the patient decides to wait for another organ when her health state is h, she accrues the expected immediate reward in the current time period, r_h. Then, the maximum total expected discounted reward that the patient can attain starting from state (h, l) is denoted by

$$v(h,l) = \max \begin{cases} R(h,l), \\ r_h + \lambda \sum\limits_{(h',l' \in S_H)} \Pr(h', l'|h) v(h', l') \end{cases} \tag{2.1}$$

for $h \in S_H$ and $l \in S_L$ where λ is a discount factor and $\Pr(h', l'|h)$ is the probability that in the next period the patient will be in health state h' and receive a liver offer of quality l',

given that she is in health state h in the current time period. For this model, the authors derive conditions for a monotone, control-limit policy which states that for a patient at health state h it is optimal to accept an offer of type l if $l \leq l^*(h)$ and decline it otherwise.

Our model relaxes the assumption of updating at every time period and allows a patient to either (i) transplant (if an organ is available), (ii) do nothing, or (iii) update. The update action in our formulation is equivalent to the wait action in Alagoz et al. model. The relaxation of this assumption and inclusion of an explicit do nothing action not only represents the real world setting more accurately, but also enables us to capture a patient's gaming ability by not reporting all MELD score changes.

To illustrate this potential for gaming, consider two hypothetical, extreme situations: (i) continuous MELD score updating and (ii) completely voluntary updating. Under (i), inequity among the patients is eliminated; however, such continuous updating requirements are impractical and would inflate the already costly data processing burden at transplant centers and UNOS. Under (ii), the data processing burden would be minimized; however, patients would be able to game the system to the maximum possible extent. Clearly, there are two ways in which a patient may game the system by not reporting all MELD score changes. First, if the patient's health improves (i.e., her MELD score declines), she increases her likelihood of receiving an offer by not reporting her MELD score change. Secondly, if the patient's health deteriorates (i.e., her MELD score increases), she may choose not to report because updating to a sicker MELD score can leave her with a shorter amount of time until the next required update. Both of these possibilities induce information asymmetry between UNOS and the patient which we measure by the percentage increase in life expectancy for a patient who is exploiting the flexibility in the current system by not reporting all MELD score changes. An ideal updating scheme strikes a balance between these competing objectives, i.e., system inequity and the data processing burden.

2.2 PATIENT DECISION MAKING

2.2.1 Model Formulation

We assume that at the start of each discrete time period the patient knows her current MELD score and chooses to either (i) transplant, T (if an organ is available), (ii) do nothing, (DN), or (iii) update (U), i.e., report her current MELD score to UNOS, so as to maximize her total expected discounted reward. Liver offers of various quality arrive at the end of each time period according to probability distributions that depend on the patient's last *reported* MELD score. If the patient chooses to transplant, she receives a lump sum post-transplant reward as a function of her *current* MELD score and the accepted liver's quality, and the process terminates. If she chooses not to transplant, she obtains a pre-transplant reward that depends on her current MELD score and transitions to a new health state according to a known probability distribution conditional on her current MELD score in the previous period. If the patient does nothing, her last reported MELD does not change and the time until the next required update decreases by one period. If the patient chooses to do nothing with no time remaining, then her reported MELD score is downgraded to the healthiest MELD score. If the patient chooses to update, her last reported MELD is updated to her current score and the time until next required update is reset according to a given updating scheme, e.g., Table 1.1, which dictates the minimum updating requirements for all MELD scores.

We model this problem as an infinite horizon discrete time MDP. The state of the MDP is defined by (h, m, τ, l). In this state definition, $h \in S^{\mathcal{H}} = \{6, 7, \ldots, 40, 41\}$ is the patient's current MELD score, where 41 represents death; $m \in S^{\mathcal{M}} = \{6, 7, \ldots, 40\}$ is the patient's last reported MELD score; $\bar{\tau} : S^{\mathcal{M}} \to \mathcal{R}_+$ is an updating scheme and $\tau \in S^{\bar{\tau}(m)} = \{0, 1, 2, \ldots, \bar{\tau}(m) - 1\}$ is the number of periods remaining until the next required update, where $\bar{\tau}(m)$ is the maximum time allowed between two consecutive MELD updates when the last reported MELD score is m under the given updating scheme, $\bar{\tau}$; $l \in S^{\mathcal{L}} = \{1, 2, \ldots, L, L+1\}$ is the quality of the deceased-donor liver currently offered to

the patient, where lower numbers represent better quality livers and $L+1$ represents no liver offer. Let $A(h, m, \tau, l)$ be the set of actions in state (h, m, τ, l). Then, for all h, m, τ,

$$A(h, m, \tau, l) = \begin{cases} \{\text{T,DN,U}\}, & l < L+1; \\ \{\text{DN,U}\}, & l = L+1. \end{cases}$$

The immediate reward earned when the patient chooses not to transplant with current MELD score h is defined as $r_h \in [0, \infty)$ for $h \leq 40$ and $r_{41} = 0$. The post-transplant reward earned when the patient chooses to transplant with MELD score h given liver quality l is defined as $R(h, l) \in [0, \infty)$ for $h \leq 40$ and $l < L+1$, and $R(41, l) = R(h, L+1) = 0, \forall l, h$. Note that the patient does not accumulate any additional rewards once she is dead.

The transition probability matrix that governs health state changes is denoted by $\mathcal{H}$ where the probability that the patient with current MELD score h transitions to MELD score h' in the next period given that she does not transplant is defined by $\mathcal{H}(h'|h)$ for all h and h'. Note that $\mathcal{H}(41|41) = 1$. The matrix of liver offer probabilities is denoted by $\mathcal{L}$, where the probability that the patient receives a liver offer of quality l given that her last reported MELD score is m is defined by $\mathcal{L}(l|m)$ for all l and m.

Given a discount factor $\lambda \in [0, 1]$, we define $v(h, m, \tau, l)$ as the patient's maximum expected total discounted reward starting from state (h, m, τ, l):

$$v(h, m, \tau, l) = \begin{cases} \max\{v^T(h, l), v^{DN}(h, m, \tau), v^U(h)\}, & \forall h, m, \tau \text{ and } l < L+1; \\ \max\{v^{DN}(h, m, \tau), v^U(h)\}, & \forall h, m, \tau \text{ and } l = L+1, \text{ where} \end{cases} \tag{2.2}$$

$$v^T(h, l) = R(h, l), \forall h, l < L+1, \tag{2.3}$$

$$v^{DN}(h, m, \tau) = r_h + \lambda \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v(h', m, \tau - 1, l') \right), \forall h, m, \text{ and } \tau > 0, \tag{2.4}$$

$$v^{DN}(h, m, 0) = r_h + \lambda \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(6) - 1, l') \right), \forall h, m, \tag{2.5}$$

$$v^U(h) = r_h + \lambda \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v(h', h, \bar{\tau}(h) - 1, l') \right), \forall h. \tag{2.6}$$

Note that $v(41, m, \tau, l) = 0$ for $\forall m, \tau, l$.

2.2.2 Structural Results

In this section, we establish several structural properties of the MDP model presented in Section 2.2.1. Specifically, we identify conditions on the model parameters that guarantee structured value functions and optimal policies. These results may provide deeper insight into the overall problem and help devise computationally faster solution approaches. The corresponding proofs can be found in Appendix B.

Lemma 1 states that if the last reported MELD score is the healthiest score, then the remaining time to the next required update, τ, is irrelevant.

Lemma 1. *For all h, l, $v(h, 6, \tau, l)$ is constant in τ.*

We make use of the following three assumptions, As1, As2 and As3 throughout the remainder of this section.

As1. *The post-transplant rewards, $R(h, l)$, are decreasing in h and l.*

As2. *The intermediate reward, r_h, is decreasing in h.*

As3. *The rows of the liver transition probability matrix $\mathcal{L}$ are in decreasing stochastic order, i.e., $\sum_{l=k}^{L+1} \mathcal{L}(l|m) \geq \sum_{l=k}^{L+1} \mathcal{L}(l|m+1), \forall m$ and $1 \geq k \geq L+1$.*

As1 implies that the post-transplant reward does not increase as the patient deteriorates and/or the quality of the liver degrades. Similarly, As2 implies that the intermediate reward of waiting does not increase as the patient deteriorates. Finally, As3 implies that the greater the last reported MELD score of a patient, the greater her chance of being offered a high quality liver.

Proposition 1 illustrates the intuitive facts that it is better to (a) be offered a higher-quality organ, (b) have a higher MELD score in the UNOS system, and (c) have more time until the next required MELD update.

Proposition 1.

(a) Under As1, $v(h, m, \tau, l)$ is decreasing in l for all h, m and τ.

(b) Under As1 and As3, $v(h, m, \tau, l)$ is increasing in m for each h, l, τ.

(c) Under As1 and As3, $v(h, m, \tau, l)$ is increasing in τ for each h, m, l.

Corollary 1 illustrates that (a) when no time remains, updating is always better than doing nothing; (b) updating is always better than doing nothing if the reported MELD score is the healthiest; (c) if the current MELD score is the healthiest and the last reported score is not, then doing nothing is always better than updating; and (d) if the reported MELD score and the current MELD score are equivalent, then updating is always better than doing nothing.

Corollary 1. *Under As1 and As3,*

(a) $v^U(h) \geq v^{DN}(h, m, 0), \quad \forall h, m, l.$

(b) $v^U(h) \geq v^{DN}(h, 6, \tau), \quad \forall h, l, \tau.$

(c) $v^{DN}(6, m, \tau) \geq v^U(6), \quad \forall l, \tau$ *and* $m > 6.$

(d) $v^U(m) \geq v^{DN}(m, m, \tau), \quad \forall m, l, \tau.$

Reporting a greater MELD score than the last reported score involves a tradeoff between increasing the chance of obtaining an offer and decreasing the amount of time until the next required MELD update. Clearly, this tradeoff is irrelevant if after updating the patent would have a greater number of periods until the required update. Proposition 2 establishes this result.

Proposition 2. *Under As3, for $h > m$ and $\bar{\tau}(h) \geq \tau$, $v^U(h) \geq v^{DN}(h, m, \tau)$ for all l.*

Definition 1. *[26, 46] An $n \times n$ matrix $\mathcal{P}$ is called* upper Hessenberg *if $\forall i = 1, \ldots, n-1$, it satisfies $\sum_{j=1}^{i-1} \mathcal{P}(j|i+1) = 0$.*

In the context of our model, if $\mathcal{H}$ is uppertriangular, i.e., patient health never improves, then τ is irrelevant and updating always yields a larger value than doing nothing. If $\mathcal{H}$ is upper Hessenberg, then a patient's MELD score may improve by at most one per period, i.e., improvements in health occur gradually (if at all). Our estimation of $\mathcal{H}$ nearly satisfies the upper Hessenberg condition; see Section 2.2.3. Proposition 3 shows that if the rows of $\mathcal{L}$ are in decreasing stochastic order and $\mathcal{H}$ is upper Hessenberg, then updating is better than doing nothing when the patient is sicker than the reported MELD score indicates.

Proposition 3. *Under As3 and if $\mathcal{H}$ is upper Hessenberg, then $v^U(h) \geq v^{DN}(h, m, \tau)$ for $h > m$, $\forall l, \tau$.*

The intuition behind Proposition 3 is that under an upper Hessenberg $\mathcal{H}$, after the patient updates in some state with $h > m$, if the patient's health improves, then the patient will always have the opportunity to update when their current health is m. That is, the MELD score cannot "jump over" m and force the patient to report a healthier score.

Alagoz et al. [5] define a liver-based control-limit optimal policy to be a policy among the optimal policies that, for a given health state h distinguishes a critical liver state l^* and prescribes transplantation for all livers $l \leq l^*$ and doing nothing for all livers $l > l^*$. Analogously we define and establish the existence of control-limit optimal policies based on the liver quality, number of periods remaining until the next required update and the patient's last reported MELD score in Proposition 4.

Proposition 4.

(a) Under As1, for a given h, m, τ there exists a liver quality l^* such that transplanting is optimal for $l \leq l^*$ and doing nothing or updating is optimal otherwise.

(b) Under As1 and As3, for a given h, m, l there exists a time remaining until next required update τ^* such that doing nothing is optimal for $\tau \leq \tau^*$ and transplanting or updating is optimal otherwise.

(c) Under As1 and As3, for a given h, τ, l there exists a MELD score m^* such that doing nothing is optimal for $m \leq m^*$ and transplanting or updating is optimal otherwise.

Lastly, in Proposition 5 we prove that any non-continuous updating scheme, i.e., anything other than updating in every period, results in more discriminating patients in terms of the liver offers they are willing to accept.

Proposition 5. *Consider the updating scheme A in which* $\bar{\tau}(h) = 1, \forall h$*, and another updating scheme B in which* $\bar{\tau}(h) > 1$ *for at least one* h*. Let the critical liver state to transplant be* l_A^* *and* l_B^* *for updating scheme A and B, respectively. Then,* $l_B^* \leq l_A^*$ *for all* h*,* m*.*

2.2.3 Numerical Results

In this section, we provide several numerical examples that provide additional insight. First, we discuss parameter estimation and the scope of the numerical experimentation. Second, we examine how the current updating scheme affects patient behavior and illustrate how patients can benefit from this flexibility.

We define each period to be one day and consider the objective of maximizing the patient's total expected remaining lifetime. Therefore, we set $r_h = 1$, and estimate the patient-specific total expected post-transplant life days, $R(h, l), \forall h, l < L+1$ using the post-transplant survival model of [39]. The data set used is described in Alagoz et al. [5]. We note that these estimates satisfy Assumptions As1 and As2.

To estimate $\mathcal{H}$, we follow Alagoz et al. [5]. Because there is no large, multi-center study that regularly collects data on the natural history of liver disease, they estimate health transition probability matrices for different disease groups using the natural history model (NHM) ([4]). The NHM is an empirical stochastic model which uses cubic spline functions to estimate incomplete lab values needed for MELD score calculations. In this model patients are stratified by disease group and patient location, i.e., for each disease group, cubic splines are sampled at daily intervals for patients in the hospital and in the intensive care unit (ICU), and at monthly intervals for patients at home to obtain a complete longitudinal history of each patient. Then, MELD scores are calculated using the simulated lab values which are validated using historical patient records, and are proven to be a fair approximation of the real disease progression.

We exclude Status 1 patients and consider only adult ESLD patients who are classified by their MELD score. We consider Disease Groups 1 and 2 which include primary biliary cirrhosis, primary sclerosing cholongitis, alcoholic liver disease, autoimmune disorders, and hepatitis B and C, respectively. Due to sparsity of the available data, Alagoz et al. [5] represent patient health by MELD scores aggregated in groups of two. We use a slightly different aggregation scheme than [5] in order to facilitate computational tractability. More specifically, the healthiest five MELD scores (6-10) are aggregated into one group and the following eight MELD scores are aggregated into two groups of four (11-14 and 15-18). For the remainder of the MELD scores, like [5], we aggregate in groups of two. We quantify the violation of Definition 1, i.e., the upper Hessenberg property of $\mathcal{H}$ using the following metric:

$$\epsilon_1 = \max_i \left\{ \max\{0, \sum_{j=1}^{i-2} H(j|i)\} \right\}, \text{ for } i = 3, \ldots, H+1. \tag{2.7}$$

The maximum violations are 0.0287 and 0.0081 for Disease Group 1 and 2, respectively and the histograms of the corresponding ϵ_1 values are displayed in Figure 2.1.

To estimate $\mathcal{L}$, we also follow the liver quality classification scheme of [5], which considers 14 liver qualities as determined by the age, race, and gender of the donor [39]. The data used in the estimations are obtained from UNOS and contain information about the patient characteristics and deceased donor liver offers over a 15-month period. Detailed descriptions of the liver quality assignment scheme is provided in [5]. We quantify the violation of As3 using the following metric:

$$\epsilon_2 = \max_{k,m} \left\{ \max\{0, \sum_{l=k}^{L+1} L(l|m+1) - L(l|m)\} \right\}, \tag{2.8}$$

for $k = 1, \ldots, L+1$ and $m = 1, \ldots, H-1$. The violation of As3 is only observed for two rows of $\mathcal{L}$ and the maximum violation is 0.0128.

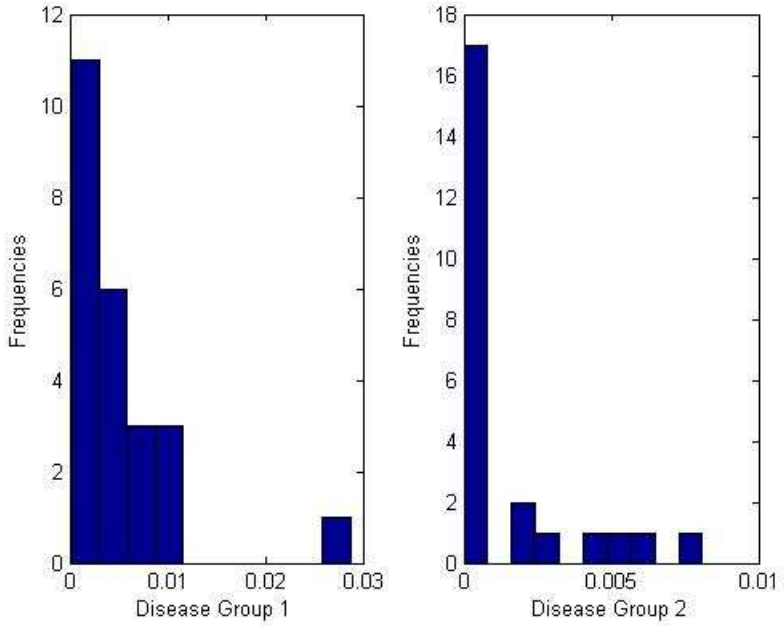


Figure 2.1: Histogram of the violations of the upper Hessenberg property on $\mathcal{H}$

We use an annual discount rate of 0.97, which translates into a daily discount rate, λ=0.999917, and solve problem instances of the model presented in Section 2.2.1 using policy iteration [35]. As in previous studies [5, 6, 7, 42], this approach determines an optimal accept/reject/update policy for a single patient assuming that all other patients behave as they do now.

Given these parameter estimates, we conduct our numerical experiments using data corresponding to patients of three different ages: 22, 40 and 60 years old. Other patient characteristics are fixed to those values most commonly occurring in the population, namely caucasian patients, with no prior transplants, no cytomegalovirus (CMVGR) and no encephalopathy. We consider both genders and both disease groups. Of the patients we consider, the most likely is a 60-year old male from Disease Group 1 (in 2008, males comprised 60.7% of the active waiting list, more than 70% of all patients were in Disease Group 1 and

62.5% of all the patients were between ages 50-64 [34]). For this reason, the majority of our results are for this age, gender and disease group combination. First, we examine how the current UNOS updating scheme affects patient decision making. We compare the optimal policy for a 60-year old male from Disease Group 1 under the current scheme to the optimal policy for the same patient under the continuous (i.e., daily) updating scheme as in [5]. This benchmarking illustrates the deviation in patient behavior from the case in which UNOS has perfect patient information. To facilitate this comparison, we restrict our attention to states in which $\tau = 0$ and the optimal action is therefore either update or transplant (Corollary 1(a)). Figure 2.2 illustrates that under the current UNOS updating requirements, the patient's optimal liver threshold does not increase, i.e., the patient is no more likely to accept livers of lesser quality, compared to the threshold under daily updating. For example, for MELD score 24, under the current scheme the patient optimally switches from update to transplant at liver quality 7, whereas she optimally switches from do nothing to transplant at liver quality 8 for the same MELD score under the daily updating scheme.

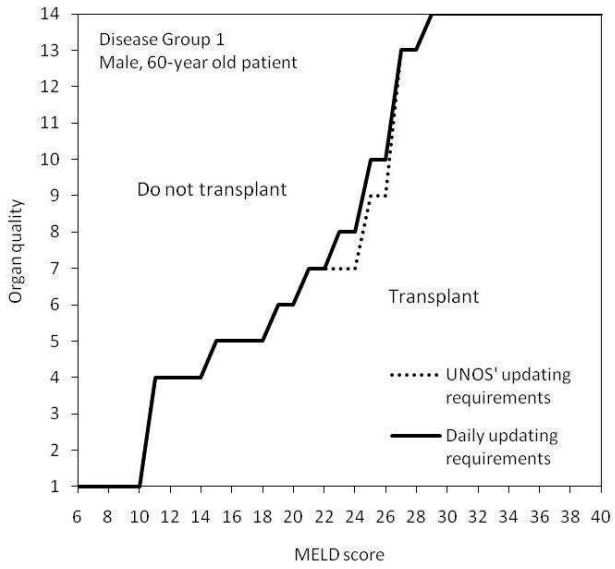


Figure 2.2: Optimal transplant behavior under UNOS updating for $\tau = 0$ as compared to daily updating

Next, we consider the degree to which a patient can benefit from the current updating scheme. To do so, we evaluate the increase in total expected lifetime and the decrease in the number of expected updates as compared to the same measures under the daily updating scheme. For a patient with MELD score h at the time of listing who does not receive an offer at that time, we calculate the percentage increase in expected lifetime under the current scheme as compared to daily updates as

$$\omega(h) = \frac{v(h, h, \bar{\tau}(h), L+1) - v_{daily}(h, L+1)}{v_{daily}(h, L+1)} \times 100, \tag{2.9}$$

where $v_{daily}(h, L+1)$ represents the total expected reward of the patient with MELD h at the time of listing under the daily updating scheme [5]. The decrease in the expected number of updates is calculated similarly using

$$\mu(h) = \frac{U_{daily}[h, L+1] - U[h, h, \bar{\tau}(h), L+1])}{U_{daily}[h, L+1]} \times 100, \tag{2.10}$$

where $U[h, h, \bar{\tau}(h), L+1]$ denotes the expected number of times a patient with MELD score h with no liver offer at the time of listing updates while on the list and $U_{daily}[h, L+1]$ is the analogous value under the daily updating scheme.

Figure 2.3 shows these metrics as a function of initial MELD score averaged over male patients of ages 22, 40 and 60 for Disease Groups 1 and 2. For both disease groups, patients with relatively healthy and relatively sick initial MELD scores benefit less than patients with mid-range initial MELD scores in both measures. The intuition behind this observation is that MELD scores typically change slowly over time. That is, patients who are initially healthy typically spend a fair amount of time having a MELD score in which they are unlikely to receive offers, regardless of whether or not they report minor improvements in their MELD score as they occur. Similarly, patients who are initially very ill are very close to death and receive frequent organ offers, leaving them little room to benefit. Furthermore, patients in Disease Group 2 experience a greater improvement in both measures than their counterparts in Disease Group 1. The intuition behind this result is that the diseases in Disease Group 2 are less aggressive than those in Disease Group 1, which leads patients

in this group to benefit more from not reporting improvements in their MELD scores than those in Disease Group 1. Our results for female patients are analogous and display the same trends. As a final note, the bumpiness of the curves is due to data sparsity.

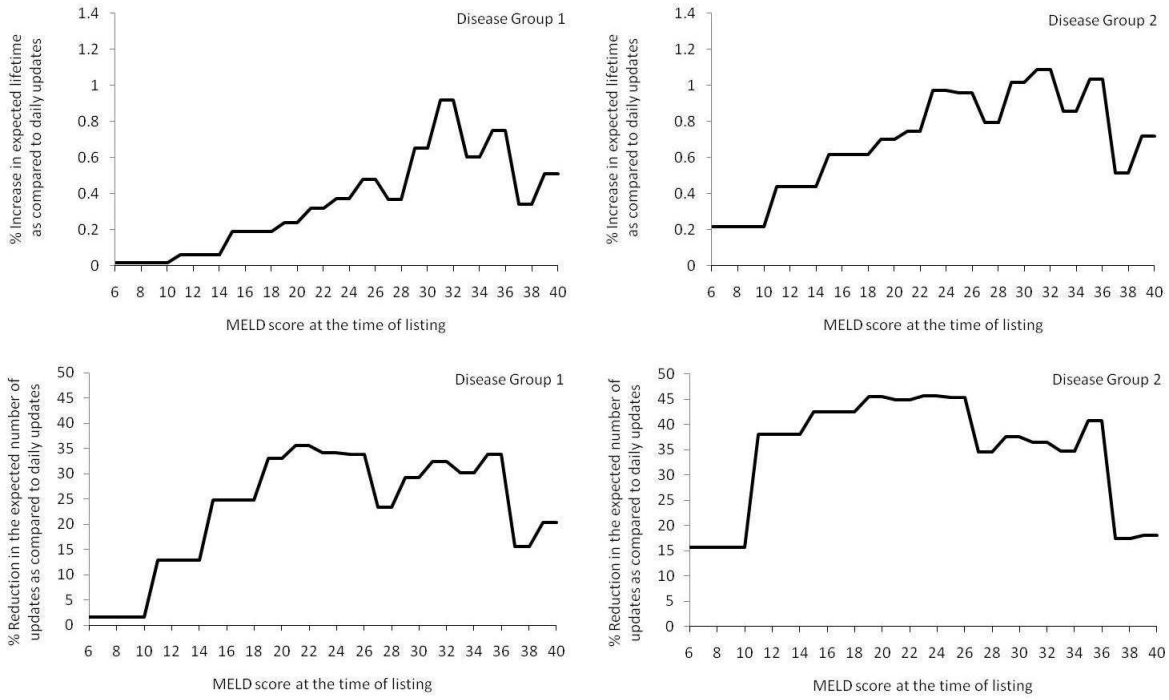


Figure 2.3: Patient benefits under UNOS updating: Increase in the expected patient life and decrease in the expected number of updates

In summary, the results presented in this section indicate that UNOS' current updating scheme results in more discriminating patients with respect to organ quality. Our findings suggest that by exploiting the updating flexibility, a typical patient can increase his life expectancy by up to 1% (Figure 2.3) and his updating burden can decrease by up to 40% as compared to daily updates (Figure 2.3).

2.3 APPROXIMATING THE EFFICIENT FRONTIER OF UPDATING SCHEMES

As demonstrated in Section 2.2.3, by exploiting the inherent flexibility in UNOS' current updating scheme, patients can increase their life expectancy and reduce their expected number of updates. However, such increases in life expectancy can be interpreted as increases in system inequity because when one patient uses this flexibility to improve their chances of receiving a high quality organ, another patient who has a greater priority under the current allocation algorithm, may suffer. Therefore, in this section we investigate improved updating requirements which outperform the current UNOS requirements with respect to system equity without resulting in an increased data processing burden, or vice versa.

For a specific updating scheme $\bar{\tau}$ with updating frequencies $\bar{\tau}(h), h = 1, \ldots, 40$, we calculate the average percentage increase in system inequity as compared to daily updating scheme using the weighted average of the $\omega(h)$ values given by (2.9) over all MELD scores at the time of listing, h, by

$$\gamma(\bar{\tau}) = \sum_{h=6}^{40} \omega(h) \times p(h), \tag{2.11}$$

where $p(h)$ represents the probability that a patient has MELD score h at the time of listing. We estimate the $p(h)$ probabilities using data provided by UNOS for the 27,866 patients who joined the list between 2001-2008. The average percentage decrease in the data processing burden is calculated similarly, using $\mu(h)$ defined in (2.10), i.e.,

$$\delta(\bar{\tau}) = \sum_{h=6}^{40} \mu(h) \times p(h). \tag{2.12}$$

Finding an updating scheme $\bar{\tau}(h)$ for all h, that optimizes some combination of these two objectives, is computationally burdensome. Therefore, we implement a heuristic approach that conducts a local search over a collection of intuitive and easy-to-implement updating schemes. We restrict ourselves to monotone updating schemes, i.e., $\bar{\tau}(h)$ decreasing in h.

Moreover, to be consistent with UNOS' current updating scheme, we restrict the updating frequencies (in days) to the set $\{1, 3, 7, 14, 30, 60, 90, 180, 365\}$ and fix the updating breakpoints as specified in Table 1.1, i.e., at MELD scores $\{10, 18, 24\}$. (Numerical experimentation on schemes with different MELD score breakpoints showed no significant improvement. See Appendix A for details.)

Table 2.1 represents the complete set of lexicographically ordered updating schemes evaluated on a 32-bit version operating system with Intel Core 2 Duo CPU, 3.00 GHz Processor and 2.00 GB of RAM. In Figure 2.4(a) we provide the evaluation results for the updating schemes in Table 2.1 for a 60-year old male from Disease Group 1. Also included in the figure are the points corresponding to a continuous (daily) updating scheme, the current UNOS scheme and a completely voluntary scheme. From this set of updating schemes, we identify the set of *dominant* or *efficient* schemes as displayed by the black points in Figure 2.4(a). The entries corresponding to efficient updating schemes are shaded in light gray and numbered in Table 2.1 in the order in which they appear on the efficient frontier from left to right. (The dark grey entries are addressed laster in this section.)

In Figure 2.4(b), we illustrate how changes in the updating frequency requirement for specific MELD scores affect the performance measures. We observe that changes in frequencies corresponding to higher MELD scores (corresponding to sicker health states) have a greater impact as evidenced by a steeper trend both in the increase in system inequity as well as in the reduction in data processing burden. This observation is consistent with the observation that patients with relatively lower initial MELD scores benefit less from the updating flexibility than patients with higher initial scores (Figure 2.3).

Figure 2.5 provides the outcomes of the same set of 40 updating schemes for male patients of all ages across disease groups. The results for females are analogous. We note that the set of efficient policies does not significantly vary with patient type or disease group. However, for Disease Group 2 we observe a greater increase in system inequity and a greater reduction in data processing burden for a specific updating scheme, i.e.,

Table 2.1: List of the updating schemes evaluated

	MELD Score			
Updating Scheme	6-10	11-18	19-24	25-40
1	30	30	1	1
1'	30	30	7	1
	30	30	14	1
	30	30	30	1
	30	30	30	7
	60	60	30	7
2	90	90	1	1
2'	90	90	7	1
	90	90	7	7
	90	90	14	1
	90	90	30	1
	90	90	30	7
15	90	90	90	60
	180	90	30	7
	365	60	30	7
	365	90	14	7
	365	90	30	1
	365	90	30	3
	365	90	30	14
	365	90	60	1

	MELD Score			
Updating Scheme	6-10	11-18	19-24	25-40
	365	90	60	3
	365	90	60	7
	365	90	90	1
	365	90	90	7
4	365	180	7	1
	365	180	7	7
	365	180	14	1
	365	180	14	3
	365	180	14	7
7	365	180	30	1
10	365	180	30	3
11	365	180	30	7
3	365	365	1	1
5	365	365	7	1
6	365	365	14	1
9	365	365	14	3
8	365	365	30	1
12	365	365	30	7
13	365	365	30	14
14	365	365	30	30

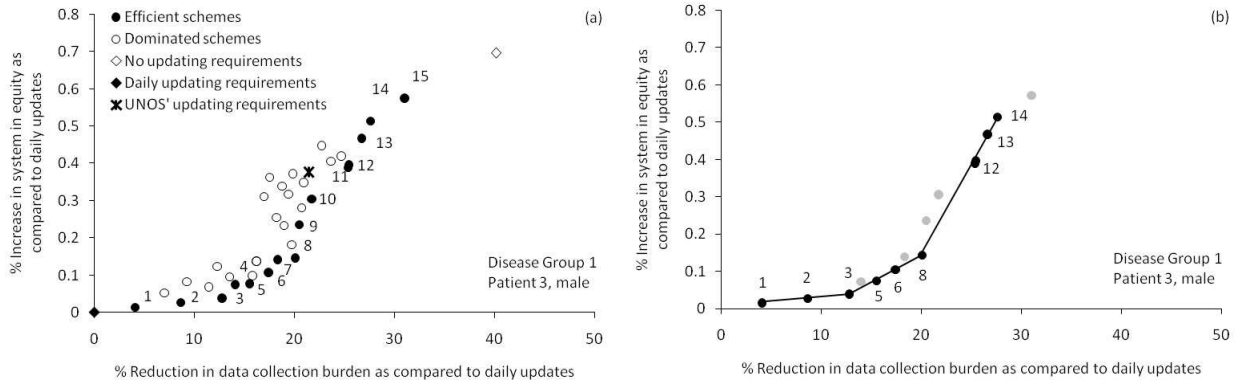


Figure 2.4: Evaluation of different updating schemes (a), sensitivity of the performance measures to changes in frequency requirements (b)

a shift of the complete set towards the upper right corner. This observation is driven mainly by the fact that Disease Group 2 is less aggressive than Disease Group 1, giving patients in Disease Group 2 more opportunity to benefit from the updating flexibility.

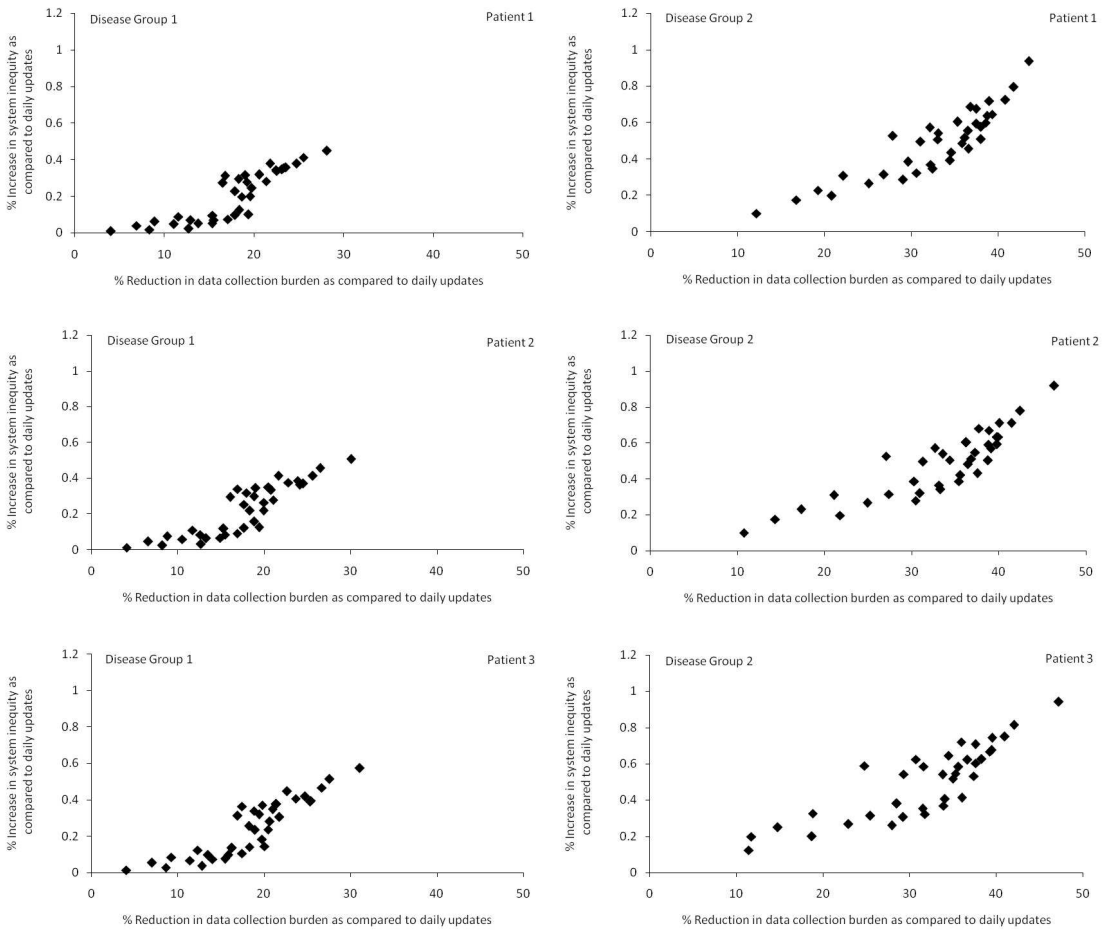


Figure 2.5: Evaluation of updating schemes for all male patients considered

Next, consider the weighted averages of the performance measures over all patient types for both disease groups (Figure 2.6). We observe that the updating schemes that are efficient for Disease Group 1 are also efficient for Disease Group 2 which is the same set of schemes identified to be efficient in Figure 2.4(a). The only deviation occurs in updating schemes $1'$

and $2'$ which are efficient for Disease Group 2, but not for Disease Group 1 and they are highlighted in darker gray in Table 2.1. Note that the current UNOS updating scheme is not efficient and the menu of 15 efficient updating schemes improves both performance measures, i.e., decreases the system inequity and decreases the data processing burden, by adjusting the updating frequencies.

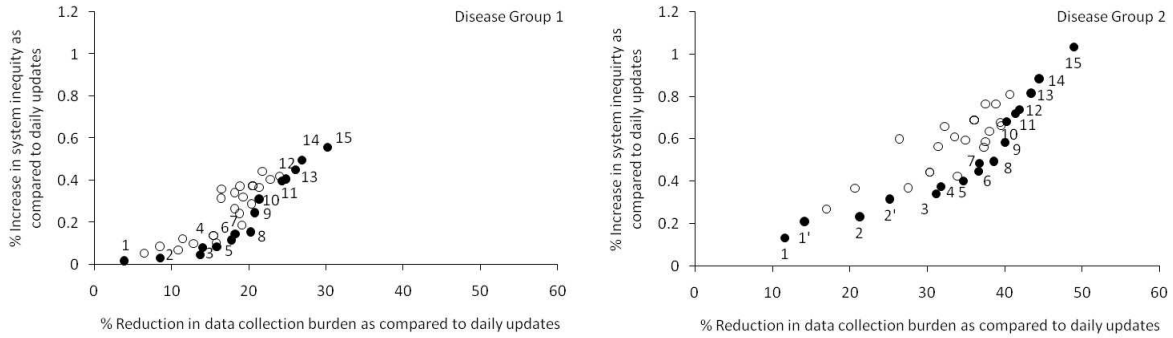


Figure 2.6: The performance of the updating schemes considering averages of all male and female patients for each disease group

Note that schemes 5, 6 and 8 perform relatively better with respect to both objectives (being "closest" to the lower right corner). If we consider the frequencies of these updating schemes, we observe a common characteristic: The allowable time between required updates for MELD scores 19 and greater is less than or equal to those dictated by the current scheme, whereas the allowable time between required updates for MELD scores 18 and smaller is greater than or equal to those dictated by the current scheme. That is, our results suggest that *relatively healthy (sick) patients should be required to update less (more) frequently than the current requirements dictate*. One potential explanation for this finding is that the national average MELD score at transplantation is 20 [22]. Our results suggest that tracking patients with MELD scores below 20 (above 20) less closely (more closely) may avoid significant increases in inequity while achieving a relatively low data processing burden.

2.4 CONCLUSION

In this chapter, we examine the current health reporting requirements for ESLD patients from the individual patient's and from UNOS' perspective. We quantify the degree to which patients can increase their life expectancy by optimally choosing when to update their MELD scores with UNOS. We construct a menu of 15 updating schemes that render the current UNOS updating scheme inefficient with respect to an increase in system inequity versus a decrease in the data processing burden (Table 2.1). This menu suggests that requiring the sicker (healthier) patients to update more (less) frequently than they must under the current policy can improve both metrics. This menu appears to be insensitive to patient characteristics. Furthermore, the resulting schemes are readily implementable by UNOS and easily followed by patients. Related future research directions are discussed in Chapter 5.

3.0 ASSESSMENT OF THE CURRENT PRACTICE OF EXTENDING OFFERS AND RESPONDING TO OFFERS

In Chapter 1 we explained how the current liver allocation system works and we highlighted the significance of the appropriate management of donated organs. Also, we pointed out the lack of regulations for expedited placement livers which is accompanied by the lack of existing literature about the expedited liver placement practice. The goal of this chapter is to analyze various novel aspects of the current allocation practice using clinical OPTN data. Most importantly, we aim to investigate the trends involved in expedited offer making which have remained unexplored to date.

The rest of this chapter is organized as follows. In Section 3.1 we introduce a new measure for organ availability which is used to explain our findings presented in the remainder of this chapter. The clinical OPTN data are described in Section 3.2, and in Section 3.3 we analyze various performance measures of the current practice of extending standard electronic offers during the match list process. In Section 3.4 we investigate the current mechanics of the expedited offer placement practice where we present how many expedited offers are initiated by harvesting regions and how many expedited offers are accepted by recipient regions. The distribution of the number of bypassed patients involved in an expedited offer allocation is also explored within this section. Then in Section 3.5 we focus on the individual transplant center/patient perspective and explore the distribution of the response times and acceptance/rejection probabilities for standard and expedited offers.

3.1 DONOR DENSITY

In this section we define a measure for organ neediness at a regional level which is utilized to explain our findings in the following sections. The number of donors in a region during a specific time interval is certainly an indicator of the organ availability. Therefore, we consider the number of donors in a specific region in conjunction with the number of waiting list additions in that region during the time interval between $\underline{t}$ and $\bar{t}$ and define a new metric, *donor density*, $\xi_i(\underline{t}, \bar{t})$ as a measure of the level of organ shortage in Region i:

$$\xi_i(\underline{t}, \bar{t}) = \frac{\text{number of donors in Region } i \text{ between } \underline{t} \text{ and } \bar{t}}{\text{number of waiting list additions in Region } i \text{ between } \underline{t} \text{ and } \bar{t}}$$

Table 3.1 illustrates the number of donors, the number of waiting list additions for $\underline{t} =$ 01/01/2008 and $\bar{t} =$ 12/31/2008, and the corresponding donor densities in decreasing order for all regions.

Table 3.1: Calculation of donor density for regions in 2008

Region number	Number of donors	Number of wait list additions
1	190	488
2	863	1351
3	1181	1276
4	590	1249
5	923	1900
6	202	247
7	532	891
8	509	668
9	320	879
10	620	824
11	822	900

$\Longrightarrow$

Region number	Donor density
3	0.93
11	0.91
6	0.82
8	0.76
10	0.75
2	0.64
7	0.60
5	0.49
4	0.47
1	0.39
9	0.36

We observe that Region 3 has the highest number of donors as well as the highest donor density value. However, consider Region 6 which has the second smallest number of donors but its donor density indicates that the small number of donors is scaled down by the small number of waiting list additions. Region 11 is the second region with the most generous supply of livers relative to the waiting list additions while Region 9 has the least supply.

3.2 DATA SOURCES

Throughout this chapter we use clinical OPTN data obtained from Donornet. The data covers all liver match runs between May 1, 2007 and February 28, 2009, a total of 16883 match runs and 68816 batches of offers. The match runs are further broken down into the individual offers made where there are 428255 records of electronic offers after the elimination of manual offers and range refusals as defined in Chapter 1.

For each match run, the data contain the unique donor and match identification numbers, date and time of the match run, and the region number of the recovering OPO. Within each match run, we have the following information about each individual electronic offer: the sequential order/rank and the distinct center identification number of the candidate receiving the offer, the identification number and the limits of the corresponding batch of offers, date and time the transplant center receives the offer, batch number when transplant center enters a response, date, time and type of the response to the offer. We use this information to estimate the distribution of patient response times, the acceptance probabilities to standard offers, the number of electronic offers in each batch, the time between sequential batches of offers and the length of a match run.

If an offer recipient responded with refusal, or if a waiting list candidate was bypassed, the data provide information regarding the so-called refusal codes for the corresponding offers. The refusals can be due to candidate-related reasons such as the candidate being too ill and/or unavailable for a transplant, histocompatibility-related reasons such as unacceptable antigens, program-related reasons such as when the response time of the patient exceeds one hour, or donor-related reasons such as an anatomically damaged organ. A patient is bypassed due to policy related reasons such as a directed donation or other reasons such as the initiation of an expedited placement. We are interested in the match runs which terminate due to the initiation of an expedited offer and use the information regarding the refusal codes to identify the specific set of match runs culminating in expedited offers.

If a match run terminated with a successful allocation via a standard offer or an expedited offer, the data display the sequential order/rank of the organ recipient. In the case of a match run which terminates without allocation, there is simply no indication. We use this information to identify the expedited liver recipients and, subsequently, to estimate the number of bypassed patients due to the expedited placement, as well as the acceptance rates for expedited offers.

We mention in Chapter 1 that the electronic organ allocation environment was launched on April 30, 2007. Therefore, the data we discuss here relate to the early implementation era and some data inaccuracies exist because of the recording errors during this adaptation phase.

3.3 THE PRACTICE OF EXTENDING ELECTRONIC OFFERS

Once an organ is harvested, the harvesting OPO coordinator is responsible for its allocation by either extending a batch of standard electronic offers according to the prioritized match list or by initiating an expedited placement. In this section, we are interested in the practice of extending electronic offers during the match list process. Motivated by the lack of guidelines as how long the OPOs should/can wait before proceeding to extending the next batch of electronic offers and how many offers to include in a local batch, we aim to identify the patterns underlying the standard offer making practice. To this end, we investigate the distribution of the number of offers in a batch and the time between sequential batches. Also, we provide an analysis of the total length of match runs and the average number of batches per match, respectively.

3.3.1 Length of a Match Run

As we mentioned before, liver match runs are inherently limited by the CIT of livers, 18-24 hours. Therefore, the timely allocation of the donated organ is critical and the OPOs are under significant time pressure. In this section, we analyze the distribution of the match length to gain insight about the time frame of organ allocation.

Figure 3.1 displays the histogram of the lengths of match runs. Because donated livers are inviable after 18 hours of CIT [22], we suspect that data corresponding to match runs longer than 18 hours are recorded incorrectly and thus excluded from this analysis. The average, median, the 75^{th} and 90^{th} quantiles for the match runs are 4.36, 3, 6 and 11 hours, respectively. The observed frequencies are almost monotone decreasing in the number of hours, and the probability that a match run exceeds 11 hours is 0.1. These findings imply that the majority of match runs terminate relatively quickly and much earlier than the time limit imposed by liver CIT.

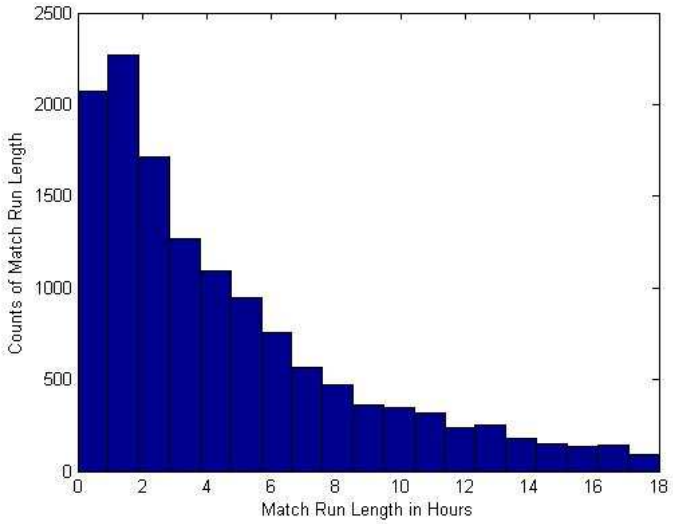


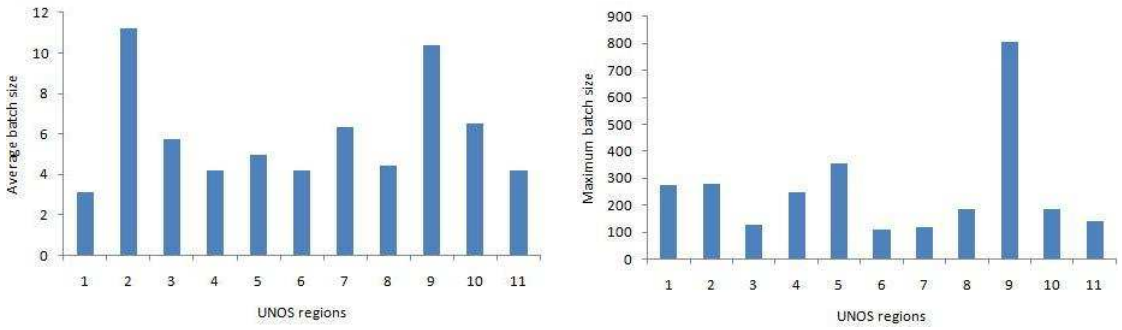
Figure 3.1: Histogram of match run lengths in hours

3.3.2 Offer Batching

In this section, we explore the average number of batches per match as well as the distribution of the number of electronic offers per batch, i.e., the batch size, for every region. Table 3.2 illustrates the average number of batches per match, average number of offers per batch and the maximum observed batch size by region and Figure 3.2 displays the plots of the average (a) and maximum batch size (b) by region. The average number of batches per match and the average batch size over all regions is 4.18 and 5.94, respectively. Equality of the mean batch sizes across regions is tested via t-tests assuming unequal variances at a 5% level of significance. Among 55 pairwise comparisons, only the null hypothesis of equal means in Region 1 and 2 is rejected.

Table 3.2: Average number of batches per match, average number of offers per batch and maximum observed batch size

Region number	Total number of matches	Total number of batches	Average number of batches per match	Average number of offers per batch	Maximum observed batch size
1	546	3028	5.55	3.13	273
2	2098	9376	4.47	11.19	280
3	2846	9841	3.46	5.71	125
4	1555	4346	2.79	4.21	246
5	2260	9310	4.12	4.98	353
6	596	2210	3.71	4.21	111
7	1312	3496	2.66	6.34	117
8	1191	5435	4.56	4.43	183
9	948	4799	5.06	10.39	805
10	1619	7114	4.39	6.53	185
11	1911	9861	5.16	4.17	139



(a) (b)

Figure 3.2: Average number (a), and maximum number (b) of offers in a batch for all regions

Next, we examine the distribution of batch size. Figure 3.3 displays the corresponding histograms which illustrate that the batch size distribution does not significantly change by region. We test the equality of the batch size distributions via Kolmogorov-Smirnov tests at a 5% level of significance. Among 55 pairwise comparisons, the null hypothesis of equal distributions is rejected between Region 1 and 2, 9, 10, Region 2 and 4, 6, 7, 8, 9, and Region 6 and 7, 9, 10, 11.

For all regions, the frequency of the observations significantly decreases with increasing batch size and there is a spike in the frequencies corresponding to batches of 10 to 14 offers. We explain this pattern as follows: Under the current regulations which are explained in detail in Chapter 1, the limits on simultaneous local offers are determined by the harvesting OPO and UNOS cites over 60% of all offers are allocated locally [34]. Therefore, the OPOs start the match list process by extending smaller local batches of offers. This pattern is intuitive because a match is relatively likely to terminate quickly with a local allocation, and thus extending too many offers slows down the process. If the local centers are exhausted without a successful allocation, then the OPOs proceed to making regional and national offers. The current maximum number of non-local simultaneous offers is 10 and we observe higher frequencies of 10 to 14 batch sizes. Therefore, we conclude

that the batch size increases when the match list process proceeds to the non-local level and in fact, OPOs seem to extend as many non-local offers at once as the current limits allow.

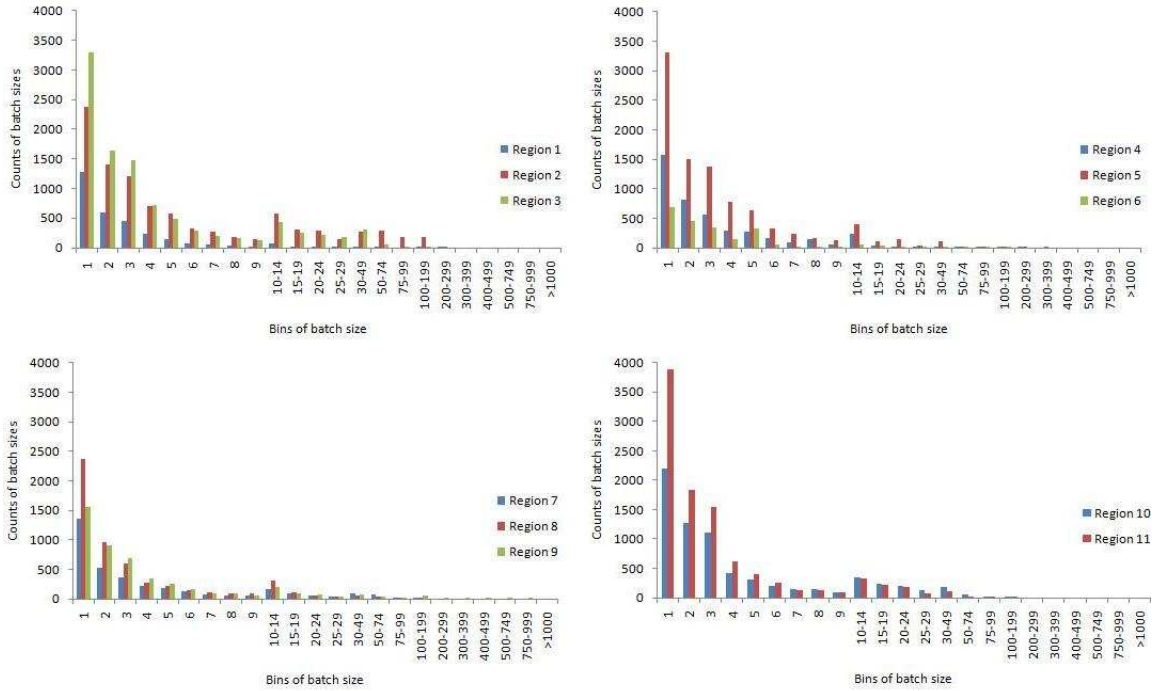
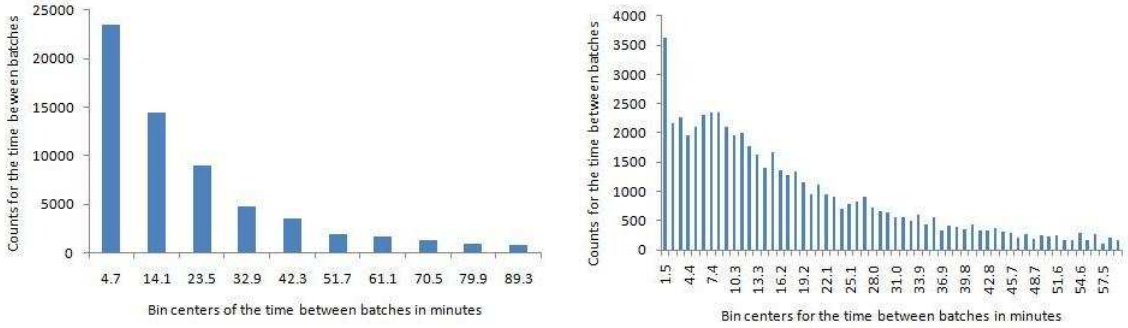


Figure 3.3: Histograms of batch size by region

3.3.3 Time between Sequential Batches of Offers

In this section, we are interested in the distribution of the time between sequential batches of electronic offers. We have examined all batch records included in the data sets and find that the time between sequential batches of offers can be as small as 1 minute and as large as 16 hours. We calculate the median, the 75^{th} and the 90^{th} quantiles as 16, 37 and 94.3 minutes respectively. Because the probability that the time between two sequential batches of offers exceeding 94.3 minutes is relatively low, we view the records greater than 94.3 minutes as outliers and eliminate them from further consideration.

Figure 3.4 (a) displays the histogram of the recorded times between batches of offers after the elimination of outliers and Figure 3.4 (b) considers only the batches which are extended sequentially in less than an hour. We can conclude from this analysis that the OPOs tend to extend sequential offers rather frequently, which is compatible with intuition given the time constraint nature of the liver allocation process.



(a) (b)

Figure 3.4: The histograms of the duration between sequential batches of offers considering when match lengths are less than 94.3 minutes (a), when match lengths are less than 60 minutes (b)

3.4 THE PRACTICE OF EXPEDITED PLACEMENT

As we mentioned in Chapter 1, the initiation of an expedited placement indicates the termination of the match list process and implies that the harvesting OPO is free to direct the expedited offer to any transplant center. Therefore, the decisions involved in an expedited offer, specifically when to initiate the offer or which transplant center to direct it to, can vary significantly by the harvesting OPO. In this section, we explore how these decisions regarding an expedited offer are made in the current practice and provide novel insight into the expedited placement process.

3.4.1 Expedited Placement Activity by Region

We identify a match as an expedited match when it includes at least one candidate who is bypassed with the refusal code representing an expedited placement attempt. We find that the total number of expedited matches between May 1, 2007 and February 28, 2009 is 534 which implies that 3.16% of all match runs culminated in an attempted expedited placement. In this section we explore how the expedited placements are distributed over regions.

Table 3.3 illustrates the number of expedited offers by the region initiating the placement and by the region receiving and accepting the offer. First, we consider the expedited offer placement activity. Table 3.3 displays that Region 3 and 11 initiate most of the expedited placements, i.e., 54.31% of all expedited offers combined whereas Region 5 is a distant third. This finding is intuitive because Regions 3 and 11 have the two highest donor densities as defined in Section 3.1 among all regions.

Table 3.3: The frequency of expedited offers by region

		Region of the Expedited Offer Recipient											Total Number of Expedited Offer Attempts
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Region of the Harvesting OPO	**1**	3	3					1		1			12
	2		6			1		7		14	1		41
	3	1	5	15	1	1	1	5		39	12	6	133
	4				7	1				3	2		23
	5			1		27		5		3	2		64
	6						4	1		1	1		14
	7		2					12		1	1		24
	8		2	1				4	6	7	5		34
	9		3					3		4	1		23
	10		1					1			4		9
	11	1	4	20	2	1		3		34	15	15	157
Total Number of Expedited Acceptances		5	26	37	10	31	5	42	6	107	44	21	

Next, we consider the expedited offer acceptance activity. For each harvesting region, the region which accepts the largest number of expedited offers initiated by that harvesting region is shaded gray in Table 3.3. The reason we consider the number of accepted expedited offers is that we only have the region information of the recipient of an expedited placement

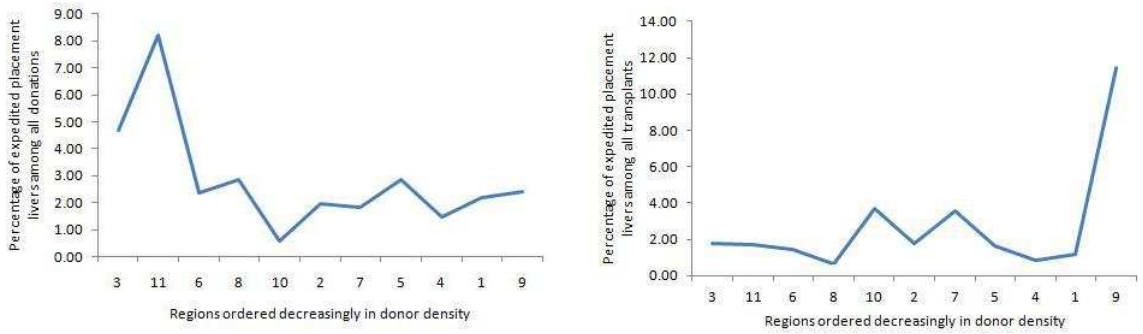
resulting in an acceptance. We believe that the number of accepted expedited offers is positively correlated to the total number of expedited offers received by that region. The strongly diagonal pattern displayed in Table 3.3 suggests that expedited offers are mostly directed to transplant centers within the boundaries of the harvesting region. This pattern is only violated by Region 9 which in fact accepts the largest number of expedited offers from all regions, i.e., 32.4% of all expedited offers. This finding is also intuitive because Region 9 has the lowest donor density and thus the greatest organ shortage among all regions.

To further explore the relation between the donor density and expedited placement activity, we calculate the percentage of match runs which culminated in an expedited placement and the percentage of transplants using expedited placement livers for all regions. The corresponding values are illustrated in Table 3.4 and plotted in Figure 3.5.

Table 3.4: Percentage of expedited placement livers among all donations and transplants

Region number	Percentage of expedited placement livers	
	among all donations	among all transplants
1	4.67	1.78
2	8.22	1.71
3	2.35	1.45
4	2.85	0.66
5	0.56	3.67
6	1.95	1.74
7	1.83	3.55
8	2.83	1.67
9	1.48	0.85
10	2.20	1.21
11	2.43	11.47

If donor density is an appropriate predictor for expedited offer placement tendency, we expect to see a monotone decreasing trend implying a positive correlation in Figure 3.5 (a) and a monotone increasing trend implying a negative correlation in Figure 3.5 (b). We calculate the respective correlation coefficients, and obtain 0.532 (-0.406) indicating a positive (negative) correlation between donor density and the percentage of expedited placement livers among all donations (transplants). Also, we observe that a general decreasing (increasing) trend exists in Figure 3.5 (a) (in Figure 3.5 (b)). These findings confirm that donor density is one of the driving factors behind the initiation and acceptance of expedited placement livers.



(a) (b)

Figure 3.5: Percentage of expedited placement livers among all donations (a) and among all transplants (b) for regions ordered in decreasing donor density

3.4.2 Initiating Expedited Placement

Here we investigate when an expedited placement is initiated in terms of clock time and the number of standard offers made. First we consider how long into a match run process expedited placements are initiated. Figure 3.6 displays the histogram of expedited offer initiation times in hours. Data indicating an expedited placement initiated beyond 18 hours is not included in the analysis. The average, median, the 75^{th} and 90^{th} quantiles for the times of initiation are 6.65, 5, 11 and 14.5 hours, respectively.

Although the average time to initiate an expedited placement is greater than the average match run length reported in Section 3.3.1, Figure 3.6 reveals that the majority of expedited matches are initiated relatively early during a match run, i.e., within the first 5 hours. This histogram strongly suggests that the expedited organs are mostly those which the OPO coordinator is anticipating not being able to place.

Next we explore the time to initiate an expedited placement as a function of the total number of standard offers made. The reason we consider cumulative standard offer number extended as opposed to the rank of the last patient receiving a standard offer is the frequent

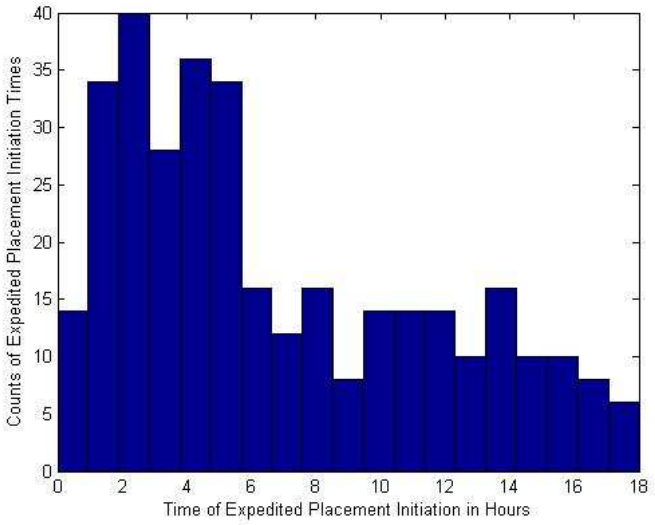


Figure 3.6: Histogram of expedited offer initiation times in hours

occurrence of range refusals. That is each time a range refusal is issued, the corresponding portions of the waiting list get eliminated from further consideration, i.e., the rank of candidates remaining on the list may shift up as a result of a range refusal. Figure 3.7 illustrates the corresponding histogram with 10 equally spaced bins. The average offer number after rounding to the next integer is 47.2 and we observe that the majority of the expedited placements are initiated by the time the 100^{th} standard offer is extended. This finding is compatible with our previous finding which states that the great majority of expedited offers are initiated within the early hours of a match run.

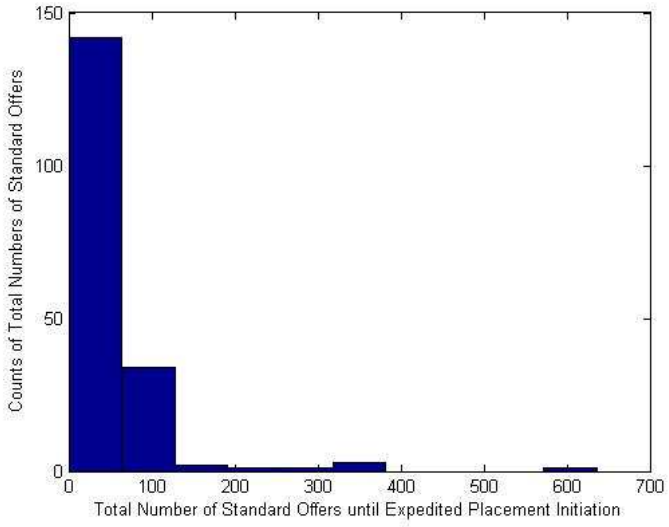
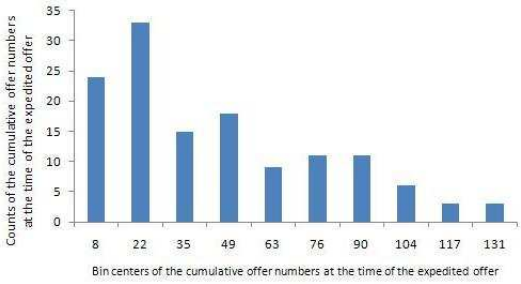


Figure 3.7: Total number of standard offers until expedited placement initiation

To gain more insight about the relation between expedited offer initiation and offer number, we refine our binning scheme by decreasing the bin sizes. To eliminate the possibility that regional patterns cancel each other resulting in the national histogram of offer numbers presented in Figure 3.7, we take our analysis to the regional level. Because more than 50% of all expedited offers originate from OPOs in Regions 3 and 11, and the data regarding expedited match runs in the rest of the regions is rather scarce to reveal any pattern, we restrict our attention to Regions 3 and 11. Figure 3.8 displays the frequency counts of the total number of standard offers until expedited placement initiation and the corresponding histograms for Region 3 and 11. Both histograms are decreasing in the number of offers made and confirm that expedited offers are mostly initiated after a relatively small number standard offers.

	Bin centers of offer numbers									
10 equally spaced bins	8	22	35	49	63	76	90	104	117	131
Number of expedited offers	24	33	15	18	9	11	11	6	3	3
Number of acceptances	18	20	12	12	4	5	7	4	2	2
Number of refusals	6	13	3	6	5	6	4	2	1	1

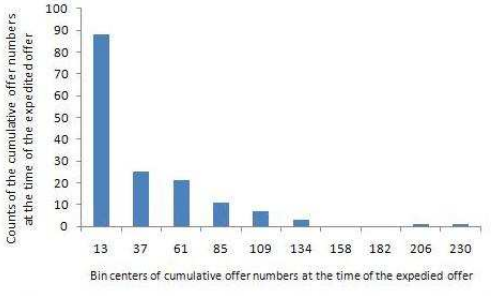
(a)



(b)

	Bin centers of offer numbers									
10 equally spaced bins	13	37	61	85	109	134	158	182	206	230
Number of expedited offers	88	25	21	11	7	3	0	0	1	1
Number of acceptances	68	12	2	3	1	2	0	0	1	1
Number of refusals	20	13	19	8	6	1	0	0	0	0

(c)



(d)

Figure 3.8: The counts of total number of standard offers until expedited placement initiation for Region 3 (a) and Region 11 (c), the corresponding histograms for Region 3 (b) and Region 11 (d)

3.4.3 Distribution of the Number of Bypassed Patients

A transplant center receiving and accepting an expedited offer is free to allocate the organ to any candidate under its care which may involve bypassing some patients ranked higher in the prioritized match list. Here, we are interested in the distribution of the number of bypassed patients due to an expedited placement.

First, we consider all expedited offers nationwide, and Figure 3.9 displays the histogram of the number of bypassed patients using 30 equally-spaced bins. This histogram illustrates that in a significant majority of expedited offers, the number of bypassed patients is less

than 200. Specifically, the mean number of bypassed patients is 631.8 and the median is 127.5. However, we observe that in a few instances the number of bypassed patients can be as much as 9000.

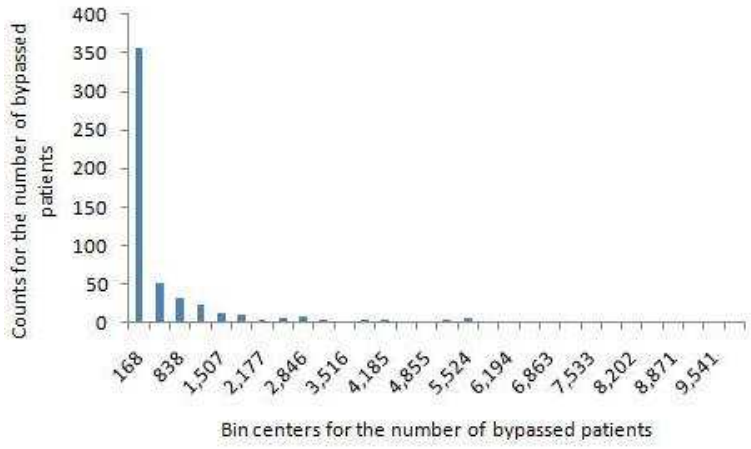


Figure 3.9: Histogram of the number of bypassed patients due to an expedited placement attempt using 30 equally spaced bins

Figure 3.10 further investigates the variability in the number of bypassed patients and displays a histogram with manually adjusted bins where the bin widths increase with increasing number of bypassed patients. We observe again that the number of bypassed patients is likely to be less than 200.

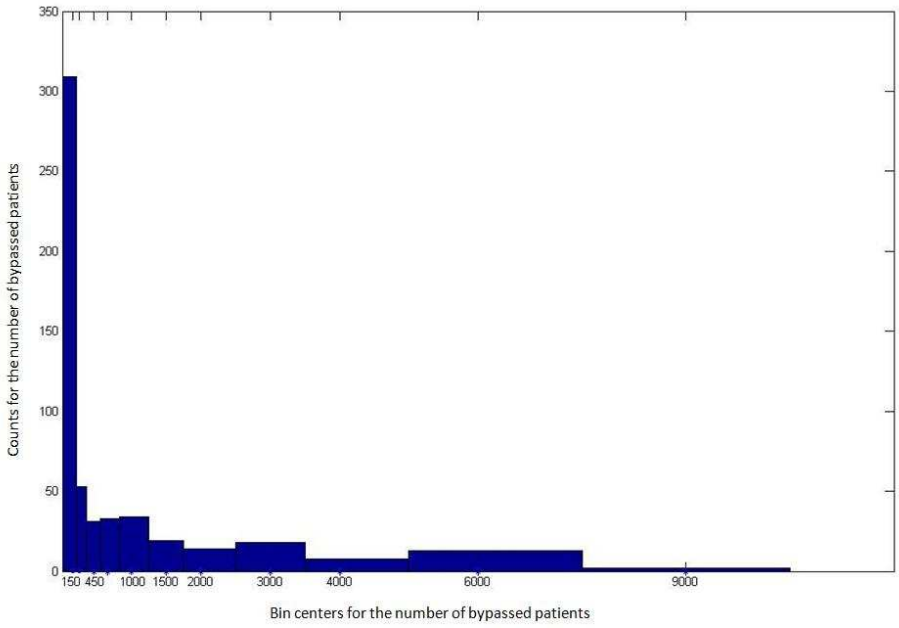


Figure 3.10: Histogram of the number of bypassed patients due to an expedited placement attempt with manually adjusted bins

Next we question whether a functional relation between the number of bypassed patients and the cumulative number of standard offers exists. Therefore, we create a scatter plot of these pairs of cumulative standard offer numbers and bypassed patient numbers for expedited matches in increasing order of the cumulative offer number. Figure 3.11 (a) displays the scatter plot of these pairs of numbers for all expedited match runs nationwide while Figure 3.11 (b) and (c) display the scatter plots of expedited match runs in Regions 3 and 11, respectively.

None of these plots reveals a significant pattern which is confirmed by the calculation of respective correlation coefficients; 0.003 for all expedited match runs, 0.03 for expedited match runs in Region 3 and -0.014 for expedited match runs in Region 11. This outcome is expected because we lack any kind of intuition in predicting the relation between the number of bypassed patients and the cumulative number of standard offers extended. On the one

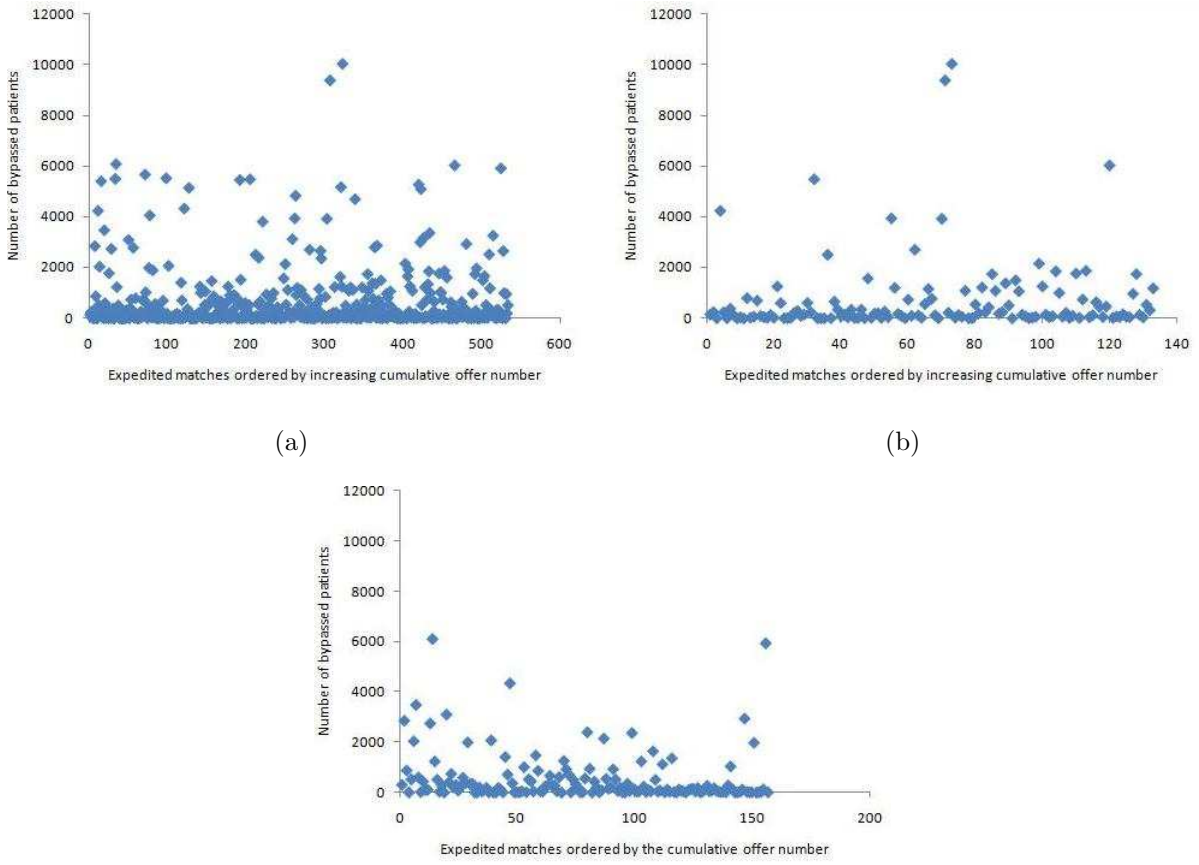


Figure 3.11: Scatter plot of cumulative standard offer numbers and bypassed patient numbers for expedited matches nationally (a), in Region 3 (b) and Region 11 (c)

hand, we would expect that an increasing number of patients will be bypassed as the number of cumulative offers increases. That is, the organ is then older and the OPO coordinator would be less concerned about bypassing a large number of patients as long as the organ is not wasted. On the other hand, as time goes on and standard offers are extended, the number of candidates which remain on the match list and can be potentially bypassed decreases. That means the bound on the maximum number of patients which can be bypassed gets tighter and therefore, smaller numbers of bypassed patients can be observed.

Next we question whether the mean and variance of the number of bypassed patients change by region. Therefore, we first conduct an F-test at a 5% level of significance to test the equality of variances of the number of bypassed patients in Region 3 and 11. The observed F-value of the test is 2.33 while the critical F-value is 1.32, and therefore we reject the null hypothesis that the variance of the number of bypassed patients in Regions 3 and 11 are the same. Next, we conduct a t-test to test the equality of means of the number of bypassed patients assuming unequal variances. The observed t-value is 1.14 while the critical t-value is 1.97, and therefore we cannot reject the null hypothesis that the mean number of bypassed patients in Regions 3 and 11 are the same.

3.5 OFFER RESPONSE CHARACTERISTICS

In previous sections we investigated the liver allocation practice from the OPO perspective. In this section we take individual transplant center/patient perspective and explore questions regarding the decision making of transplant centers/patients, e.g., how quickly they respond to offers and how likely they are to accept a standard or an expedited offer.

3.5.1 Standard Offer Response Times

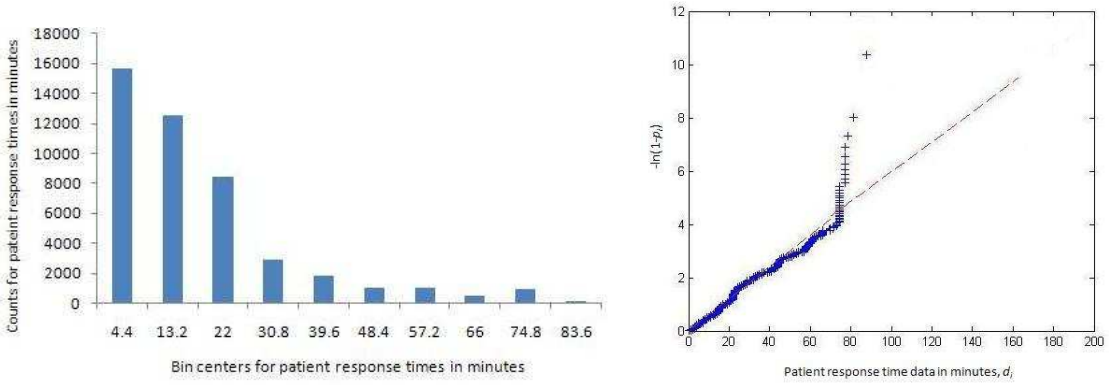
As we mentioned earlier in Chapter 1, once the electronic offer notification is sent, the surgeon in charge of the candidate receiving the offer has one hour to acknowledge the notification by accessing DonorNet for the match results of the organ offer and to start the evaluation process. According to UNOS, the median time from center notification to start of center evaluation for electronic offers is 1.2 minutes which suggests that the evaluation process starts almost immediately after the receipt of a notification [22]. After the initiation of the evaluation process, he has an additional hour to respond by either accepting or rejecting the offer. In this section, we define the response time as the

time between the receipt of an electronic offer by a transplant center and the submission of the final response to the offer, and investigate the distribution of patient response times.

Our analysis is based on the first 1500 match runs including over 45000 electronic offers. Because Donornet data indicate that the one hour evaluation time is exceeded with probability 0.032 [34], we view the response times exceeding 90 minutes as outliers and eliminate them from consideration.

First, we examine the histogram of the patient response times, illustrated in Figure 3.12 (a), which strongly suggests an exponential fit for the patient response time distribution. To test the hypothesis that the patient response times are exponentially distributed with mean $\frac{1}{\lambda}$, we first examine the corresponding probability plot. A probability plot, also known as a quantile-quantile plot, involves computing the empirical cumulative distribution function of the data which is simply a step function with a jump in cumulative probability, p_i, at each given data point, d_i, i.e., patient response times in minutes. We use these probabilities to compute the inverse of the cumulative exponential function, i.e., compute and plot $-\ln(1-p_i)$ for each d_i. Then, we use least squares to fit a straight line through the origin to data which represents the exponential distribution that is "closest" to the data. A linear relation between the plotted points and the fitted line confirms the hypothesis. Figure 3.12 (b) displays the resulting plot which illustrates an almost linear relation between the plotted data points and the fitted exponential distribution. We only observe a small number of significant deviations in the upper tail. Given the size of data manipulated and the good fit for the rest of the plot, we conclude that we cannot reject our hypothesis of exponentially distributed response times via a probability plot.

To confirm the hypothesis of exponentially distributed patient response times analytically, we conduct a chi-square goodness-of-fit test on the patient response times data. To facilitate this analysis, we calculate the mean response time using the maximum likelihood estimation (MLE) as 17.5 minutes. We test the hypothesis of exponentially distributed pa-



(a) (b)

Figure 3.12: The histogram (a) and the probability plotting (b) of patient response times

tient response times with rate $\lambda = \frac{1}{17.5}$ per minute, at a 5% level of significance and using 10 bins. As a result, we obtain a p-value of 0.129. Therefore, we fail to reject the null hypothesis at the 5% level of significance.

As a result of this analysis consisting of two visual testing tools and one analytical testing tool, we conclude that patient response times can be assumed to be exponentially distributed with a mean response time of 17.5 minutes. Figure 3.13 displays the corresponding cumulative distribution function.

3.5.2 Range Refusals

To identify range refusals from individual refusals, we use the first data set where an offer has a batch identification number only if it is extended via an electronic offer. A blank batch identification number for a specific candidate can imply that the offer is either made via a manual offer or the candidate is part of a range refusal.

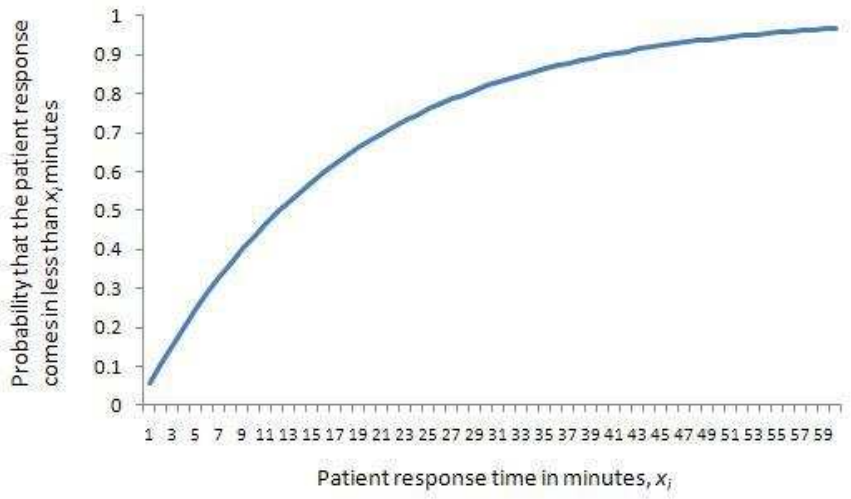


Figure 3.13: The cumulative distribution of the hypothesized exponential patient response times with mean response time 17.5 minutes

To distinguish range refusals from manual offers, we utilize the transplant center response batch numbers. In the case of a manual offer, the cell corresponding to the transplant center response batch number is blank while for range refusals, the same transplant center response batch number is recorded as in the individual refusal to the electronic offer.

Table 3.5 illustrates that a significant number of responses fall into the category of range refusals. Specifically, the fraction of responses that are range refusals is 67.25%. We conclude from these findings that if a transplant center is going to refuse an individual offer, it is very likely to refuse it for some subset of the waiting patients under its care.

Table 3.5: Range refusal statistics

Total Number of Records:	2,152,432
Number of Manual Offers:	276,783
Number of Range Refusals:	1,447,394
Range Refusal Rate:	0.6725

3.5.3 Acceptance Probabilities of Standard Liver Offers

In this section we investigate the probability of a standard offer acceptance as a function of offer number. We consider each region individually and use offer numbers up to 300. In Section 3.3.2 of this chapter we find that the average number of batches per match is 4.18 and the average number of offers per batch is 5.64. Therefore, the data get sparser with increasing offer number. To mitigate the sparsity of data for greater offer numbers, we use a binning scheme which uses a coarser aggregation with increasing offer number, presented in Table 3.6.

Table 3.6: Binning of standard offer numbers

Bin numbers for standard offers	1-14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Offer number range	No Aggregation	15-20	21-25	26-30	31-35	36-40	41-50	51-60	61-70	71-80	81-90	91-100	101-125	126-150	151-175	176-200	201-300

To estimate the acceptance probabilities of standard offers in each bin, we calculate the ratio of the number of acceptances and the total number of standard offers in a bin. Figure 3.14 illustrates the estimated acceptance probabilities of standard offers for all regions.

We observe that the probabilities first increase up to approximately 5^{th} offer number. This behavior is intuitive because the first few offers are made to Status 1 patients who are very likely to receive another offer soon if they reject the current offer. For offer numbers greater than 5, we observe that the acceptance probabilities decrease with increasing offer

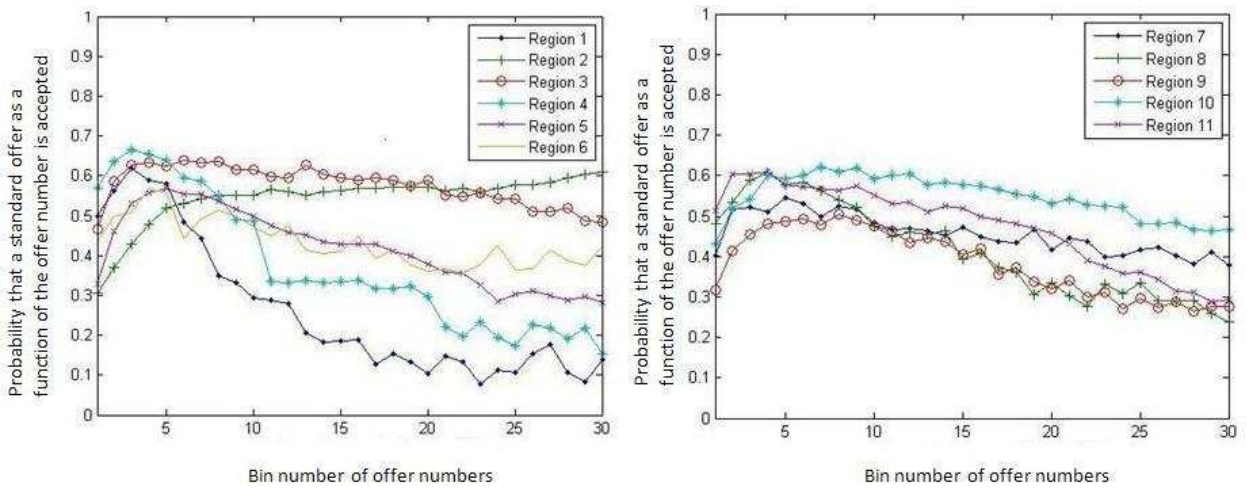


Figure 3.14: Standard offer acceptance probabilities as a function of offer number

number. The intuition behind this finding is based on the positive correlation between offer number and time elapsed because the start of a match, i.e., the greater is the offer number, the more has the donated organ depreciated in organ quality. The rate of this decrease varies by region and we observe that the probabilities either decrease slightly (e.g., Region 2, 3 and 7) or the slope of the decrease is steeper (e.g., Region 1).

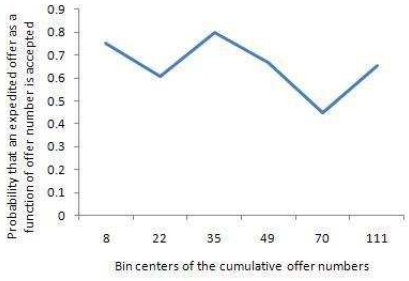
3.5.4 Acceptance Probabilities of Expedited Liver Offers

Among 534 expedited placement attempts nationwide, the number of attempts resulting in a successful allocation is 334 which implies that 63% of all expedited placement livers are transplanted. O'Connor et al. [31] report that 61.3% of all expedited placement livers were transplanted in 2005 and we observe a slight increase in the utilization of expedited placement livers between May 1, 2007 and February 28, 2009.

Next, we consider the acceptance probability to an expedited offer by region and as a function of the cumulative standard offer number extended until the initiation of expedited placement. As we illustrated earlier in Figure 3.8, the number of expedited placements decreases significantly as the number of cumulative offers increases and the data become sparse after especially offer number 100. Therefore, we manually readjust the bins of offer numbers so that the bin frequencies do not differ from each other significantly which can lead to misleading probabilities. To estimate the acceptance probability of expedited offers in each bin, we calculate the ratio of the number of expedited offer acceptances to the total number of expedited offers in that bin. Figure 3.15 (a) illustrates the readjusted binning scheme and Figure 3.15 (b) the calculated probabilities for Region 3.

	Bin centers of offer numbers					
Manually adjusted bins	8	22	35	49	70	111
Number of expedited offers	24	33	15	18	20	23
Number of acceptances	18	20	12	12	9	15
Number of refusals	6	13	3	6	11	8
Probability of acceptance of an expedited offer	0.75	0.61	0.80	0.67	0.45	0.65

(a)



(b)

Figure 3.15: Manually readjusted bins for cumulative standard offer number at the time of the expedited placement (a), expedited offer acceptance probabilities as a function of cumulative offer number (b) for Region 3

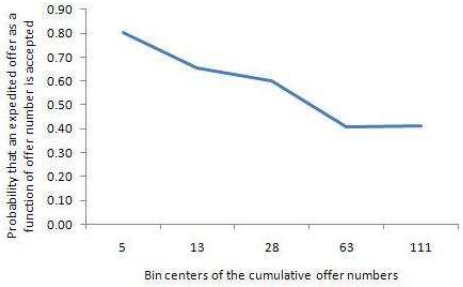
We observe that the probability that an expedited offer is accepted is approximately 0.75 for small numbers of cumulative offers and there is a decreasing trend with increasing offer number. The jumpiness of the plot is due to the limited number of match runs culminating in an expedited placement attempt.

We repeat the same steps of analysis for Region 11. Figure 3.16 (a) illustrates the readjusted binning scheme and Figure 3.16 (b) illustrates that the acceptance probabilities corresponding to small offer numbers are approximately 0.8 which is almost the same value

as in Region 3. However, the rate of decrease is steeper in Region 11 than that observed in Region 3. This finding is intuitive because Region 3 directs a greater portion of its expedited offers to Region 9 than Region 11 does, and Region 9 is very likely to accept an expedited offer as we earlier illustrated in Section 3.4.1.

	Bin centers of offer numbers				
Manually adjusted bins	5	13	28	63	111
Number of expedited offers	41	32	35	32	17
Number of acceptances	33	21	21	13	7
Number of refusals	8	11	14	19	10
Probability of acceptance of an expedited offer	0.80	0.66	0.60	0.406	0.412

(a)



(b)

Figure 3.16: Manually readjusted bins for cumulative standard offer number at the time of the expedited placement (a), expedited offer acceptance probabilities as a function of cumulative offer number (b) for Region 11

We conclude that the main trend shaping the response behavior to expedited offers in Region 3 and 11 is similar, i.e., acceptance probabilities for expedited offers initiated after a small number of standard offers are in the higher end of the range 0.7-0.8, and the probabilities decrease with increasing standard offer number. Therefore we hypothesize that the acceptance probabilities as a function of the number of offers made do not significantly change by regions. We test this hypothesis via a Kolmogorov-Smirnov test at a 5% level of significance using Region 3 and 11 data. We obtain a p-value of 0.11, and accept the null hypothesis that the expedited offer acceptance probabilities do not significantly change across regions.

3.6 CONCLUSIONS

In this chapter we examine various aspects of the current liver allocation practice. Specifically, we provide insight about the match list process of extending standard offers, the practice of expedited placements, as well as the response mechanism of the offer recipients.

Regarding the match list process, we find that the average match run length is less than 5 hours, and the probability that a match run takes more than 10 hours is 0.1. During the match list process, the batches of offers are extended frequently. Also, the total number of batches in a match is relatively small and so is the number of electronic offers included in a batch. These findings are intuitive given the time constrained nature of the allocation process and because the majority of donated livers are allocated locally. We anticipate an increase in the average batch size at the non-local level and therefore, we suggest that the current limit on the number of non-local simultaneous offers in a batch, 10 can be possibly increased.

Regarding the response mechanism for standard electronic offers, we find that refusals in the form of range refusals represent a significant fraction of all responses. Therefore, range refusals should be taken into account when analytically modeling the match list process of liver allocation. Additionally, we find that the patient response times are exponentially distributed with a mean response time less than 20 minutes. Thus, we suggest that the current one-hour limit to evaluate a standard offer can be further decreased to speed up the match list process and possibly decrease the rate of organ waste. Also, we establish a relation between the probability that a standard offer is accepted and the corresponding offer number. More specifically, the acceptance probabilities are decreasing in offer number and the rate of the decrease changes by region.

Regarding the practice of expedited placements, our findings imply that expedited offers are predominantly initiated by OPOs in Regions 3 and 11. The majority of expedited offers are either directed to transplant centers within the harvesting region or to Region 9, which alone accepts more than 30% of all expedited offers. We establish an intuitive relationship

between a region's donor density and the likelihood to initiate and to accept an expedited offer and show that the higher is the organ availability (shortage) in a region, the greater is the tendency to initiate (accept) an expedited offer. According to this relationship, we conclude that regions with low donor density values besides Region 9 can possibly benefit from receiving more expedited offers. Therefore, we suggest that the OPOs initiating an expedited placement should factor a region's donor density in their decision regarding the recipient of an expedited offer. Furthermore, we consider the timing of the expedited placement initiation in terms of clock time and the number of extended standard offers where the averages are 6.65 hours and 48 offers, respectively. Also, we find that the average number of bypassed patients due to an expedited placement is fairly constant in offer number and stable across regions. The acceptance probabilities for expedited offers are decreasing in the cumulative standard offer number and the rate of the decrease changes by region.

Given the lack of knowledge, especially regarding the practice of expedited offer placement, we believe that our findings are insightful for scientists who consider analytical modeling of some aspects of the current allocation, as well as for UNOS policy makers who continuously strive to improve the liver allocation policies.

4.0 OPTIMAL TIMING OF EXPEDITED LIVER PLACEMENT

In Chapter 3, we conducted a statistical analysis of liver data to assess various aspects of the current liver allocation practice. In this chapter, we focus our attention to the OPO's perspective and build a Markov Decision Process (MDP) model to provide optimal decision making strategies for managing the match list process. Our objective is the maximization of the benefit gained as the result of a successful organ allocation. This benefit reflects the OPO coordinator's adherence to the prioritized match list and is expressed via rewards of placement which are functions of number of offers extended. We experiment with a set of reward/cost structures and solve for the corresponding optimal policies. Also, we conduct a sensitivity analysis with respect to various model parameters to weigh in their impacts on the model outcomes.

The rest of this chapter is organized as follows. In Section 4.1 we present model assumptions and formulation. In Section 4.2 we present and explain our computational findings. We conclude this chapter with the model validation and conclusions in Section 4.3.

4.1 MARKOV DECISION PROCESS MODEL

We formulate the match list process, which can possibly terminate with organ allocation via a standard or an expedited offer, or with the discard of the organ due to exceeding the CIT, as an optimal stopping problem. We use a finite-horizon, discrete time MDP model and from the OPO coordinator's perspective we examine the optimal time to depart from the

match list process, i.e., initiate an expedited placement, and the number of standard offers to be included in a batch during the match list process. In Section 4.1.1 we present the assumptions which facilitate the modeling of this complex optimal stopping problem, and in Section 4.1.2 we provide the model formulation.

4.1.1 Assumptions

In Chapter 1 we explained the drawbacks of the current prioritization algorithm in detail and highlighted that this algorithm may not be serving the best interests of all liver transplantation candidates with respect to maximizing their life expectancy. In this chapter, we assume that the current candidate prioritization is fair. This implies a higher patient rank reflects a better match. However, because of the frequent occurrence range refusals noted in Chapter 3, the ranks of patients become intractable during the match list process. That is every time a range refusal occurs, blocks of candidates anywhere on the match list are possibly eliminated from further consideration to receive standard offers, i.e., the ranks of the candidates still eligible for standard offers get shifted and become intractable during the match list process. Our model accounts for the possibility of a range refusal implicitly by valuing organ placement according to the corresponding "offer number" rather than the match list rank of the recipient. More specifically, our model parameters are functions of chronologically ordered offer numbers as opposed to the match list ranks of the recipients and organ allocation via a standard offer of smaller number is more favorable.

As we defined in Chapter 1, the inequity induced by the initiation of an expedited placement is mainly due to the number of bypassed patients as a result of the expedited placement. However, we found in Chapter 3 that the number of bypassed patients due to an expedited liver offer does not significantly change by the harvesting region or the number of cumulative offers until the expedited offer initiation. Therefore, we assume that the expected number of bypassed patients is constant in the number of standard offers already extended. However, bypassing the same absolute number of patients should be valued differently depending on the time of the expedited placement initiation, which our model captures by the number

of standard offers extended before the the expedited offer initiation, i.e., the sooner an expedited placement is initiated, the more is the cost of bypassing some number of patients because the patients bypassed in an early initiation are likely to be higher on the list. Therefore, we express the reward of organ placement via an expedited placement as a function of the number of standard offers extended until the expedited placement initiation.

Because the livers have a limited CIT and their allocation must be realized within the limits of the CIT, our model has a finite set of decision epochs. Within each time period, we assume that the decision to extend a new batch of (possibly zero) electronic standard offers (i.e., continue) or to initiate expedited placement (i.e., quit) is made at the beginning. We assume that an OPO can initiate an expedited placement at any time unless there are some outstanding responses to earlier offers. This assumption is realistic because we expect an OPO to expedite an organ which is highly unlikely to be placed via a standard offer. Also, we assume an average organ quality, do not distinguish between local and nonlocal offers, and exclude manual offers from our analysis because electronic offers are more prevalent in the match list process. For model tractability, we assume that there exist limits on the number of concurrently outstanding offers which is consistent with the current practice of extending local offers.

It was pointed out in Chapter 1 that the initiation of the evaluation process after offer receipt is almost immediate. Therefore, we assume that any patient/transplant center to whom an offer notification is sent instantaneously receives the notification and begins the evaluation process. We found in Chapter 3 that response times to offers are exponentially distributed with a mean response time of 17.5 minutes. Hence, we calculate the probability that a response to an offer outstanding at the beginning of a time period arrives at the end of the time period by using the exponential distribution function corresponding to patient response times. Also, we assume that the likelihood a response time exceeds the one hour evaluation threshold is negligible [22]. Responses to offers arrive at the end of each period where multiple responses, or possibly no response, can be received within a time period. The number of the arriving responses is binomially distributed with the success probability

of a response arriving by the end of a time period. We assume that once the OPO receives the first acceptance response, the process terminates and the outstanding responses to the earlier offer numbers, if there are any, are received instantaneously.

4.1.2 Notation and Optimality Equations

We use the following notation to build the MDP model:

$t \in \{1, 2, \ldots, T\}$: The finite set of decision epochs

η: The maximum allowable number of simultaneously outstanding offers

n: The number of outstanding offers at the beginning of a period, $0 \leq n \leq \eta$

w: The cumulative number of standard offers already extended, i.e., $w+1$ is the offer number corresponding to the next individual standard offer to be extended

κ: An array of size η containing the offer numbers corresponding to currently outstanding offers. If there aren't any outstanding offers, $\kappa = \cdot$

κ_i: The i^{th} component of κ. If $n < \eta$, $\kappa_i = \cdot$ for $n + 1 \leq i \leq \eta$.

$S = \{(\kappa, n, w)\} \cup \{\Delta\}$: The state space of the process where Δ denotes the state in which the organ is refused in response to an expedited offer, e.g., for $\eta = 5$, the state $([2, 6, 7, \cdot, \cdot], 3, 10)$ implies that a total of 10 offers are so far extended, out of which 7 are declined and the 2^{nd}, 6^{th} and 7^{th} offers are still outstanding.

$\mathcal{A}_{(\kappa,n,w)} = \{0, 1, \ldots, \eta - n\}$: The set of possible actions in state (κ, n, w) where action $a \in \mathcal{A}_{(\kappa,n,w)}$ denotes extending a additional standard offers.

$\mathcal{A}_{(\cdot,0,w)} = \{0, 1, \ldots, \eta\} \cup \{Q\}$: The set of possible actions when there are no outstanding offers. Action Q implies quitting the process via initiating an expedited placement.

p: The probability that a response to a standard offer outstanding at the beginning of a time period arrives by the end of the time period.

$\delta_i(j)$: The probability that i responses arrive by the end of a time period when there are j standard offers outstanding at the beginning of the time period. The number of arriving responses is binomially distributed with mean jp.

$\phi^j(h,i)$: Given $i, i \geq 0$ out of $h, h > 0$ outstanding responses arrive at the end of a time period, there are $\binom{h}{i}$ possible combinations of responses which are all equally likely to be observed. The array $\phi^j(h,i), 1 \leq j \leq \binom{h}{i}$ contains the increasingly ordered offer numbers of the arriving responses in the j^{th} set of combinations where the sets are ordered lexicographically. Note that $\phi^1(h,0) = \cdot$ when there are no responses in a given time period.

$\phi^j_k(h,i)$: The k^{th} component of set $\phi^j(h,i)$, e.g., consider the previous example where the state at the beginning of a time period is $((2,6,7,\cdot,\cdot),3,10)$. Assume that the OPO extends one new offer and the number of responses arriving by the end of the time period is 2. Then the total number of possible sets of responses is $\binom{4}{2} = 6$ which are denoted by $\phi^1(4,2) = [2,6], \phi^2(4,2) = [2,7], \phi^3(4,2) = [2,11], \phi^4(4,2) = [6,7], \phi^5(4,2) = [6,11], \phi^6(4,2) = [7,11]$. Consider $\phi^1(4,2)$ whose components are denoted by $\phi^1_1(4,2) = 2$ and $\phi^1_2(4,2) = 6$.

$\alpha(i)$: The acceptance probability of the i^{th} standard offer

$\beta(i)$: The acceptance probability of an expedited offer initiated after i standard offers have been extended and declined.

$\rho(i)$: The probability that all outstanding offers which are made prior to the i^{th} offer and have smaller offer numbers are declined, i.e., $\rho(i) = \prod_{j=1}^{i-1}(1-\alpha(j))$. Note that $\rho(1) = 1$.

c: The disutility cost incurred for a standard or an expedited offer which represents the time and effort required by the patient to consider the offer.

$r(i)$: The reward which the OPO accrues for successfully allocating the organ via the i^{th} standard offer.

$r^Q(i)$: The reward which the OPO coordinator accrues for successfully allocating the organ via an expedited offer initiated after i standard offers.

Let $v_t(\kappa,n,w)$ be the maximum total expected reward-to-go starting in (κ,n,w) at time t,

$$v_t(\kappa,n,w) = \max_{a \in A(\kappa,n,w)} \{C^a_t(\kappa,n,w)\}, \text{for } n > 0, \tag{4.1}$$

$$v_t(\cdot,0,w) = \max_{a \in A(\cdot,0,w)} \{C^a_t(\cdot,0,w), Q_t(\cdot,0,w)\}, \tag{4.2}$$

where $C_t^a(\kappa, n, w)$ and $Q_t(\cdot, 0, w)$ are the total expected reward of extending a additional offers in state (κ, n, w) and the total expected reward of initiating expedited placement in state $(\cdot, 0, w)$, respectively, at time t. The total expected reward of extending a additional offers in state (κ, n, w) is

$$
\begin{aligned}
&C_t^a(\kappa, n, w) = -c \cdot a \qquad (4.3)\\
&+\delta_0(n+a)\phi^1(n+a,0)v_{t+1}(\kappa(\phi^1(n+a,0)), n+a, w+a)\\
&+\sum_{i=1}^{n+a} \frac{\delta_i(n+a)}{\binom{n+a}{i}} \sum_{j=1}^{\binom{n+a}{i}} \sum_{k=1}^{i} \Big[\alpha(\phi_k^j(n+a,i))\rho(\phi_k^j(n+a,i))r(\phi_k^j(n+a,i)) +\\
&+(1-\alpha(\phi_k^j(n+a,i)))v_{t+1}(\kappa(\phi^j(n+a,i)), n+a-i, w+a)\Big]
\end{aligned}
$$

where $\kappa(\phi^j(n+a,i)), i \geq 0, j > 0$ is the updated array of outstanding offer numbers when i responses arrive which are all refusals. Recall that κ is the array of outstanding responses at the beginning of a time period before a additional offers are extended. Then $\kappa(\phi^j(n+a,i))$ is the array of size η which contains the combined set of increasingly ordered offers after the elimination of refusals within κ and the newly extended a offers, e.g., consider the previous example where at the beginning of the time period the state is $([2,6,7,\cdot,\cdot],3,10)$ and one new offer is extended. If $\phi^1(4,2) = [2,6]$ is the set of arriving responses, then the updated array of outstanding responses is $\kappa(\phi^1(4,2)) = (7,11,\cdot,\cdot,\cdot)$. If there are no responses by the end of the time period, then $\kappa(\phi^1(4,0)) = (2,6,7,11,\cdot)$.

The total expected reward of initiating expedited placement in state $(\cdot, 0, w)$ at time t is

$$
\begin{aligned}
Q_t(\cdot, 0, w) &= \beta(w)r^Q(w) + (1-\beta_t(w))v_{t+1}(\Delta)\\
&= \beta(w)r^Q(w) \qquad (4.4)
\end{aligned}
$$

because $v_t(\Delta) = 0, \forall t$. Also note that $v_T(\kappa, n, w) = 0, \forall \kappa, n$ and w.

4.2 COMPUTATIONAL RESULTS

In this section we present numerical results driven by clinical data. First, we explain the details of our experimental design in Section 4.2.1. Then we present an example optimal policy in Section 4.2.2. Finally, Section 4.2.3 displays the results of the sensitivity analysis on the model parameters.

4.2.1 Experimental Design

Our findings from Chapter 3 indicate that the average match run length is less than 5 hours and the probability that a match run lasts longer than 10 hours is negligible. Also, 50% of all sequential batches are extended in less than 16 minutes apart from each other. Therefore we assume a 10-hour time horizon where each time period is 15 minutes long.

We found in Chapter 3 that the average batch size over all regions is 6. However, the number of possible combinations of outstanding responses increases exponentially in η, and so does the size of the state space in our model formulation, e.g., the size of the state space for a problem instance corresponding to a 10 hour match run with $\eta = 6$ is

$$\begin{aligned} |S| &= \sum_{t=1}^{T} \sum_{w=0}^{\eta * t} \sum_{n=0}^{\min(w,\eta)} \binom{w}{n} \\ &= \sum_{t=1}^{40} \sum_{w=0}^{6t} \sum_{n=0}^{\min(w,6)} \frac{w!}{(w-n)!n!} \\ &\approx 5 \times 10^{13}. \end{aligned} \tag{4.5}$$

Because of this computational burden, we limit the number of simultaneously outstanding offers in a batch, η to 3.

That implies that the probability that an outstanding response arrives at the end of a 15-minute time period is calculated using the cumulative distribution function of the exponentially distributed patient response times, $F_{exp}(t)$ with a mean response time of 17.5 minutes:

$$p = F_{exp}(15 \text{ minutes}) = 1 - e^{-15 \cdot \frac{1}{17.5}} = 0.5756. \tag{4.6}$$

We noted in Chapter 3 that the acceptance probabilities for standard offers, as well as for expedited offers, change by region. Additionally, the reward and cost parameters of our model, i.e., the OPO's reward of organ placement via a standard offer or an expedited offer and the recipient's disutility cost of processing an offer, cannot be quantified by the use of data by their definition. Therefore we experiment with different sets of values for these parameters.

4.2.1.1 Acceptance Probabilities

We already provided estimates of standard and expedited offer acceptance probabilities in Chapter 3 where we stated that the probability distributions do not significantly change by region. Here we use the estimations for Region 3 and 11 where the majority of donations are obtained and where expedited offers are made most aggressively. However, because of data scarcity and inaccuracies, the estimations as illustrated in Figures 3.14, 3.15 and 3.16 display jumps and non-monotone behavior. For our numerical results, we apply linear smoothing via simple linear regression to the portions of the curves where violations of monotonicity are observed. Figure 4.1 illustrates the original estimations of the standard and expedited offer acceptance probabilities as well as the smoothed versions used in our numerical experiments for Region 3 and 11 respectively. The jumpiness in the standard offer probabilities is less significant than the jumpiness in the expedited offer probabilities because of the greater volume of data available for the standard offer estimations. No smoothing is applied to the expedited offer acceptance probabilities in Region 11 because the original estimation itself is already monotone.

Figure 4.2 illustrates the sets of probabilities used for Region 3 and 11 respectively. We observe that both sets of probabilities start at close values, 0.5 for standard offers and between 0.7-0.8 for expedited offers. However the slope of the decrease for both types of probabilities is steeper in Region 11 than it is in Region 3. To assess the impact of this change, we conduct a one-way sensitivity analysis with respect to the probabilities in Section 4.2.3.

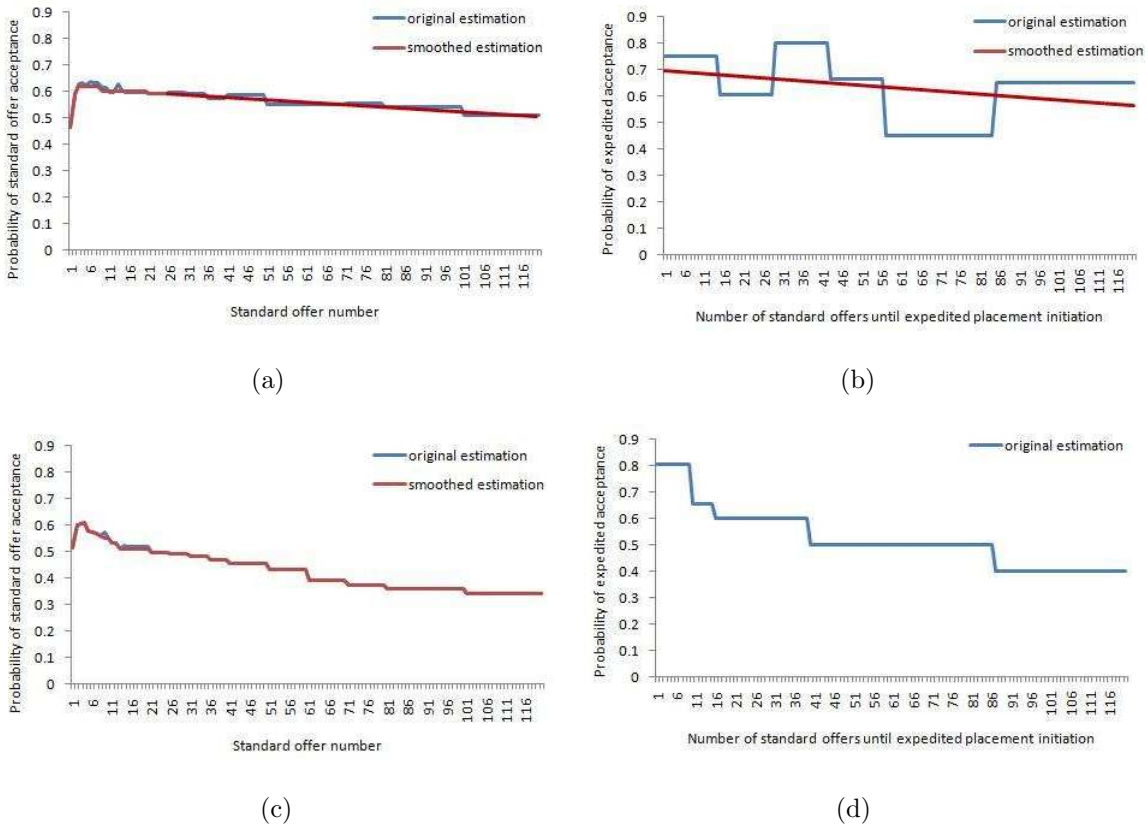


Figure 4.1: Standard offer acceptance probabilities in Region 3 (a) and Region 11 (c), expedited offer acceptance probabilities in Region 3 (b) and in Region 11 (d)

4.2.1.2 Rewards of Placement

The model inputs we have considered so far are based on our analysis of clinical data from the Chapter 3. However the reward of a standard or an expedited organ placement which expresses the OPO's adherence to the match list process cannot be quantified by the use of clinical data due to their definition.

Although the structure of the rewards of placement are ambiguous, some traits of these rewards are identifiable. We mention in Section 4.1.1 that the rewards of placement capture the OPO coordinator's adherence to the match list by offer number. Therefore, an

(a) (b)

Figure 4.2: Standard and expedited offer acceptance probabilities for Region 3 (a) and for Region 11 (b)

allocation after a smaller number of offers corresponds to a greater reward and we assume that the rewards of both types of placement should be monotone decreasing in offer number.

Also, for the same offer number the reward of placing an organ via a standard offer is always greater than or equal to the reward of placing the organ via an expedited placement because the placement of an expedited offer violates the adherence to the match list by bypassing some subset of candidates eligible to receive a standard offer. In the most optimistic scenario, the number of bypassed patients can be zero, but this case is less likely to be observed.

For the rewards of placement via a standard offer, we believe that a linear structure is the most fitting which we explain as follows. Our rewards capture the value of organ placement measured by the OPO's adherence to the match list which is prioritized to minimize pre-transplant mortality rate, risk of graft failure and inequity among candidates. The relation between risk of graft failure and donor quality is measured by the Donor Risk Index (DRI) which incorporates the CIT, i.e., the longer CIT, the higher DRI, and the higher the risk of graft failure. More specifically, the risk of graft failure is linearly increasing in CIT [45] which

is positively correlated to offer number. Because our rewards are functions of offer number, it is intuitive that the rewards for standard placements display a similar structure. However, in addition to linearly decreasing standard rewards structure, we consider decreasing decreasingly and decreasing increasingly structures as well.

For the rewards of placement via an expedited offer, we believe that a decreasing decreasingly structure is the most representative. As we explain earlier in Section 4.1.1, we assume that the expected number of bypassed patients due to an expedited placement is constant in number of offers extended and the reward of placement via an expedited offer is a function of only the number extended offers. Then, the sooner an expedited placement is initiated, i.e., the smaller is the number of offers extended until expedited placement initiation, the more is the cost of bypassing some number of patients because the patients bypassed in an early initiation are likely to be higher on the list. However, at later stages of the match run when the odds of placing the organ via a standard offer decreases significantly, an expedited placement is a valuable opportunity to prevent organ waste and thus can be encouraged, i.e., the OPO coordinator is "penalized" less for departing from the match list process. Therefore, we assume that the rewards for expedited offers decrease decreasingly with cumulative standard offer number after which they are initiated.

Next we question which functional forms to use to obtain the specific reward structures proposed above. For the rewards of an expedited placement which are decreasing decreasingly, we use the exponential function: $r^Q(i) = c_q \cdot \lambda_q \cdot e^{-\lambda_q \cdot i}$ where c_q is a constant and λ_q is the rate of decay. To determine the values of c_q and λ_q we take the following approach: For our results to be consistent and comparable throughout our numerical experiments, we need to determine a baseline point to put the changes in the reward structures into perspective. We use the smallest possible reward of all offers, i.e., the reward corresponding to an expedited offer initiated after the greatest possible offer number, $r^Q(120)$ as the baseline point and without loss of generality, we set the value of $r^Q(120)$ to 100. We choose λ_q by trial and error so that the resulting curve does not display any extreme behavior. Then we calculate the corresponding c_q so that we obtain the predetermined base value for offer number 120.

For the rewards of standard offers, we have three functional forms corresponding to linearly decreasing, decreasing decreasingly and decreasing increasingly trend. For the linearly decreasing trend, we simply use the functional form $r(i) = c_1 - c_2 \cdot i$ where c_1 and c_2 are constants and i is the standard offer number. For a decreasing decreasingly trend, we employ the exponential function $r(i) = c_3 \cdot \lambda_1 \cdot e^{-\lambda_1 \cdot i}$ where c_3 is a constant and λ_1 is the rate of decay. Lastly, for a decreasing increasingly trend, we make use of the square root function $r(i) = \sqrt{c_4 - c_5 \cdot i}$ where c_4 and c_5 are constants.

The remaining question is how to determine the values of the constants which will locate the standard offer structures relative to the reward structure of expedited offers. There are two main factors which affect the relative position of the rewards: the difference between the rewards of a standard offer and an expedited offer corresponding to the same offer number, i.e., the absolute difference between the rewards, and the ratio of the absolute difference between the rewards for an offer number to the reward values. These factors need to be considered simultaneously and therefore we develop the following metric which expresses the magnitude of the absolute difference between the rewards for an offer number as a percent of the standard reward value for the same offer number:

$$\gamma_i = \frac{r(i) - r^Q(i)}{r(i)} \cdot 100\%,$$

where $0\% \leq \gamma_i \leq 100\%$. We utilize the first and the last offer numbers to obtain γ_1 and γ_{120}, respectively. The combinations of the values of γ_1 and γ_{120} we consider in our numerical experiments are presented in Table 4.1. Then, the values of the constant parameters in the functional forms of the standard reward structures are determined so that the specified pairs of γ_1 and γ_{120} are met with respect to the expedited reward structure.

Figure 4.3 illustrates the expedited reward structure and the linearly, decreasing decreasingly and decreasing increasingly standard reward structures for $\gamma_1 = 25\%, 50\%, 75\%$ and for $\gamma_{120} = 5\%$. Figure 4.4 illustrates the different values of γ_{120} when $\gamma_1 = 75\%$ for linearly decreasing standard rewards.

Table 4.1: Levels of γ_1 and γ_{120} used in the numerical experiments

γ_1	γ_{120}
25%	5%
50%	5%
50%	10%
75%	5%
75%	10%
75%	25%

4.2.1.3 Cost of Disutility

Once a standard or expedited organ offer is obtained by the transplant surgeon, she logs in to DonorNet, examines the donor characteristics, possibly discusses the potential transplant outcomes with the rest of the transplant team and the patient to eventually arrive at a accept/reject decision. All this effort and time is accounted in the fixed cost of disutility which is assumed to be the same for both kinds of offers.

The value of this cost is ambiguous as in the case of rewards of placement. However considering the lifesaving benefits of a transplant, intuitively this cost should be comparably smaller than the rewards of any possible offer number. Therefore we assume that the cost of disutility is less than the smallest reward of placement, i.e., the reward of an expedited placement for the greatest cumulative offer number which also serves as the baseline value to level the rewards for standard offers. We use three different disutility costs: $c = \{1, 3, 10\}$.

4.2.2 A Numerical Example

We solve our problem optimally using backward induction [35] implemented in Matlab R2009a. After obtaining the optimal solution for a specific set of model parameters, we eliminate the states which are unreachable under the optimal policy, e.g., if it is optimal to extend 3 standard offers at the first time period, the cumulative number of offers in the following time period cannot be less than 3 and it cannot exceed 3 under any optimal policy.

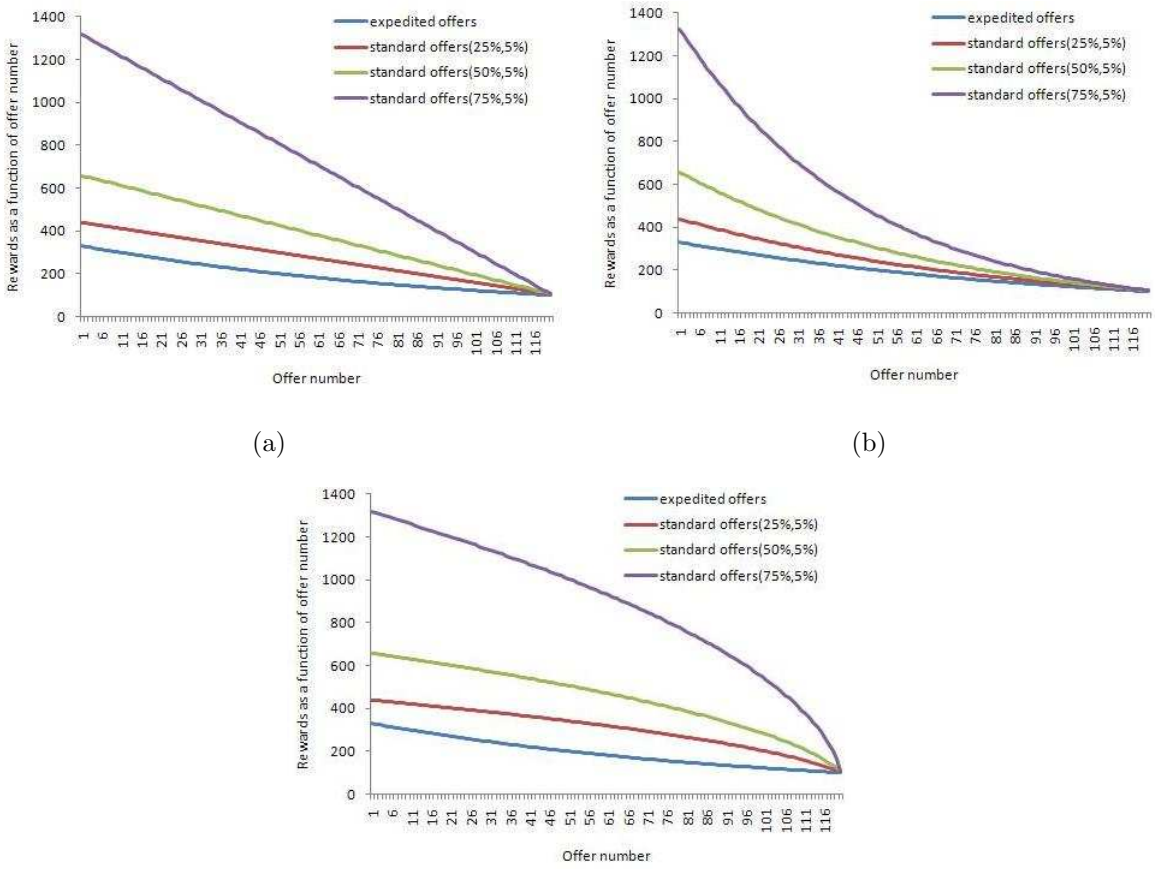


Figure 4.3: Linearly decreasing (a), decreasing decreasingly (b), and decreasing increasingly (c) standard rewards for different γ_1 values when $\gamma_{120} = 5\%$

Therefore, for each time period we identify the smallest and greatest w values which are reachable under an optimal policy, $w_l(t)$ and $w_u(t)$, respectively. We focus our attention to states which have w values in the range specified by $w_l(t)$ and $w_u(t)$.

Figure 4.5 represents the optimal policies for the problem instance with Region 11 acceptance probabilities, linearly decreasing standard rewards with $\gamma_1 = 50\%$ and $\gamma_{120} = 5\%$, and a fixed disutility cost of 3. For this instance, the smallest time period when the optimal

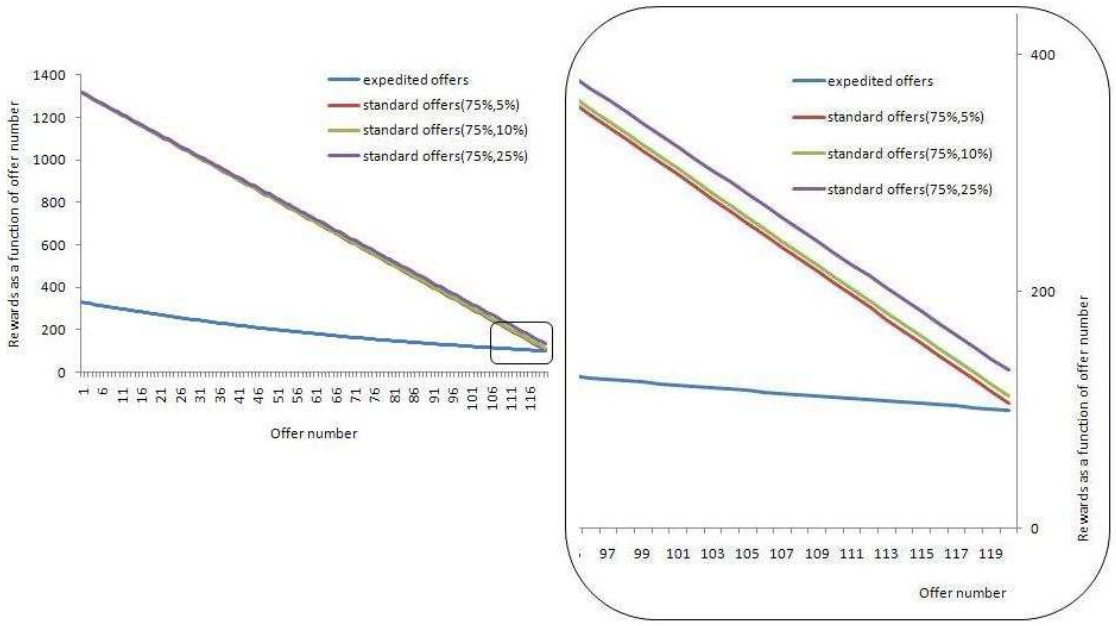


Figure 4.4: Linearly decreasing rewards for different γ_{120} values when $\gamma_1 = 75\%$

initiation of an expedited placement is observed, is 36, i.e., 9 hours after the start of the match run. The optimal policy for time periods smaller than 36 illustrated in Figure 4.5 (a) displays a monotone control limit structure in the number of outstanding offers. That is, the optimal number of standard offers to extend decreases with the increasing number of outstanding offers so that the total number of offers at the beginning of each time period is equal to 3, i.e., the maximum possible number for simultaneously outstanding offers. This structure is analogous to the so called base stock, or (s, S), policy from the inventory management literature [36] and is intuitive because it reflects the OPO coordinators tendency to extend as many offers as possible in the early stages of the match list process.

This optimal structure is not preserved for time periods which incorporate an optimal expediting action for some subset of states. However, for these time periods there is an optimal policy structure of control limit type changing with the number of time periods for

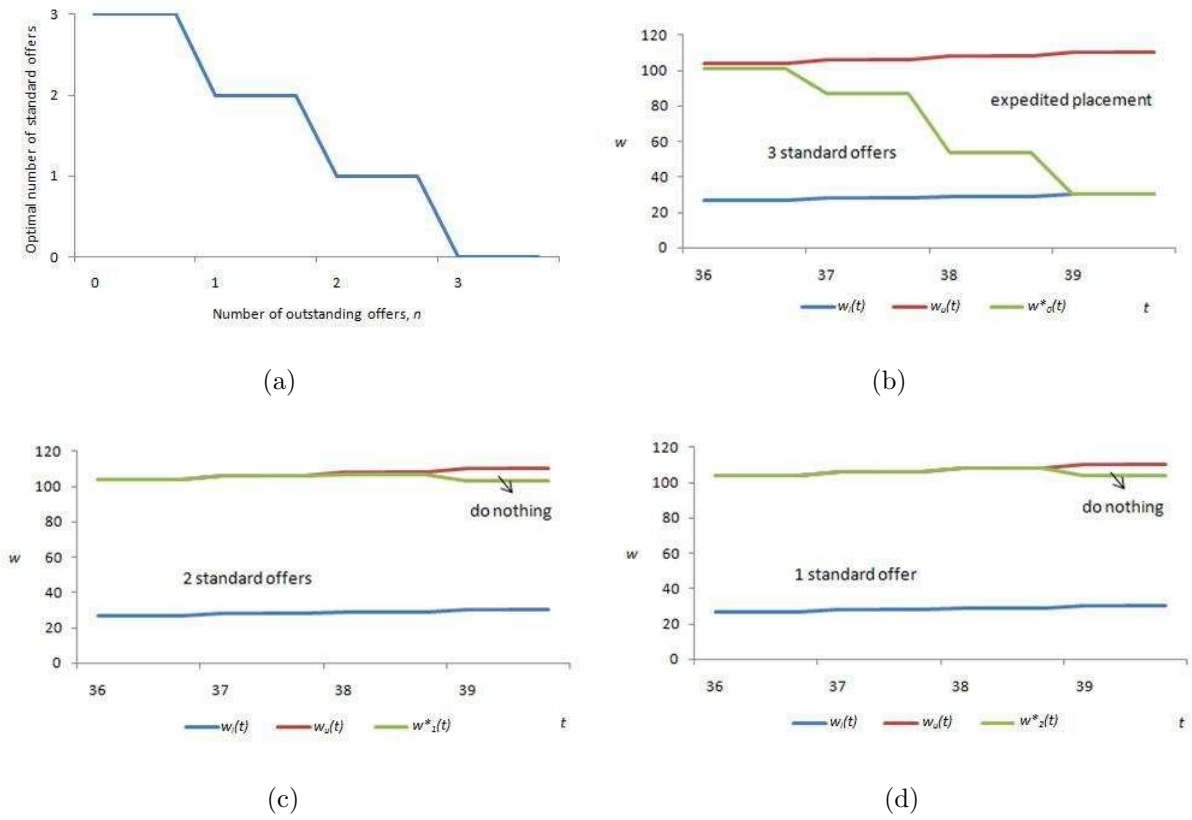


Figure 4.5: Optimal policy for $t < 36$ (a), for $t \geq 36$ and $n = 0$ (b), $n = 1$ (c) and $n = 2$ (d)

each number of outstanding offers. More specifically, for a given value of n, there exists a control limit in time, $w_n^*(t), t \geq 36$, $n = 0, 1, 2$ such that for $w < w_n^*(t)$ it is optimal to extend $\eta - n$ standard offers and for $w \geq w_n^*(t)$ it is optimal to expedited for $n = 0$ and to do nothing for $n > 0$. Figure 4.5 (b) illustrates this structure when no standard offer is outstanding, i.e., $n = 0$. In this case, we observe that the optimal action at time periods $t \geq 36$ for $w < w_0^*(t)$ is extending 3 standard offers and initiating an expedited offer otherwise. The values of $w_0^*(t)$ are decreasing in t, i.e., the more time has elapsed since the start of the match run, the smaller is the cumulative offer number to optimally initiate an expedited offer. We note that for the last time period initiating an expedited offer is optimal for all possible values of w. Figure 4.5 (c) and Figure 4.5 (d) illustrate the optimal policies

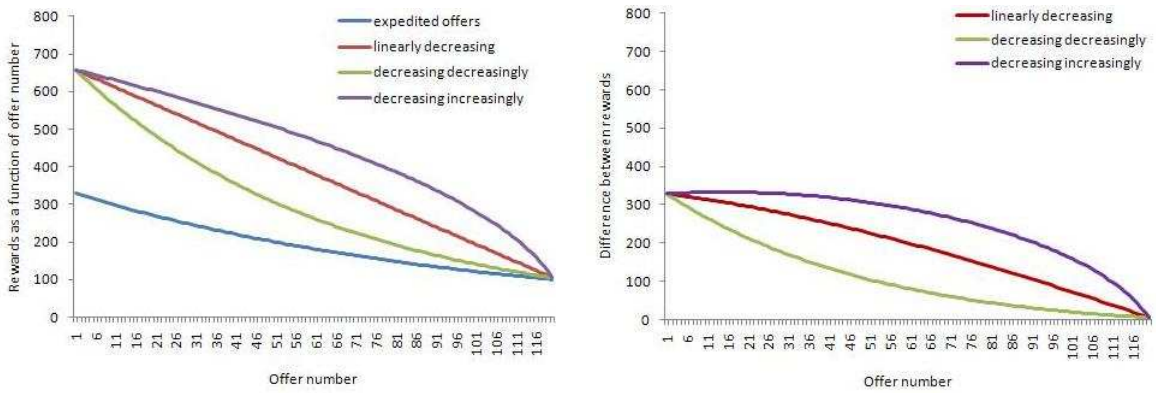
for $n = 1$ and $n = 2$, respectively. Recall that for $n = 3$, the only possible action is doing nothing because $n = \eta$. We observe this optimal policy structure consistently for all of our numerical experiments.

4.2.3 Sensitivity Analysis

We conduct one-way sensitivity analyses with respect to the structures and values of standard rewards in Section 4.2.3.1, the acceptance probabilities for both offer types in Section 4.2.3.2 and the cost of disutility in Section 4.2.3.3 to assess the impact of the change in the values of these model inputs.

4.2.3.1 Rewards of Placement

To examine the sensitivity of model outcomes with respect to rewards of placement, we consider problem instances with different reward structures for all possible combinations of γ_1 and γ_{120} using Region 11 probabilities and $c = 3$. Table 4.2 represents the model outcomes, i.e., the smallest time periods and the corresponding cumulative standard offer number where expediting becomes optimal. First, we consider how the changes in the reward structure affect the outcomes when γ_1 and γ_{120} are fixed. Figure 4.6 illustrates the different reward structures where γ_1 and γ_{120} are set to 50% and 5%, respectively and we observe that the greater the average difference between the rewards of expedited and standard offers is, the later becomes the expedited offer initiation optimal. This pattern is observed across all rows of Table 4.2, i.e., for all combinations of γ_1 and γ_{120}. Also, with greater difference between the rewards, the smallest offer number to optimally expedite increases. Both results are intuitive because a greater difference between the rewards implies that organ placement via a standard offer is relatively more valuable which delays the initiation of an expedited offer.



(a) (b)

Figure 4.6: Different reward structures when $\gamma_1 = 50\%$ and $\gamma_{120} = 5\%$ (a) and the corresponding absolute differences (b)

Table 4.2: Results using different structures for standard offers for all combinations of γ_1 and γ_{120}

γ_1	γ_{120}	Trends of decrease					
		decreasingly		linearly		increasingly	
		smallest time period to optimally expedite	smallest offer number to optimally expedite	smallest time period to optimally expedite	smallest offer number to optimally expedite	smallest time period to optimally expedite	smallest offer number to optimally expedite
25%	5%	34	88	35	89	36	89
50%	5%	34	89	36	101	37	107
50%	10%	35	88	36	103	37	107
75%	5%	35	89	37	106	39	88
75%	10%	36	88	37	107	39	88
75%	25%	36	89	38	89	39	88

Next we analyze the sensitivity with respect to γ_1 for a fixed γ_{120} value and reward structure. Consider a linear reward structure with $\gamma_{120} = 5\%$. The corresponding rewards are illustrated in Figure 4.3 (a). Table 4.2 illustrates that the greater the value of γ_1, the later becomes the expedited offer initiation optimal which is intuitive because a greater γ_1 value implies relatively more valuable standard rewards for all offer numbers.

Finally we examine the changes in outcomes with respect to γ_{120} for a fixed γ_1 value and reward structure. Figure 4.4 illustrates the rewards for possible γ_{120} values for a linearly decreasing reward structure with $\gamma_1 = 75$. Table 4.2 displays that the results behave intuitively, that is, the greater the value of γ_{120} is, the later is the first time period to optimally expedite.

To assess the robustness of model outcomes with respect to changes in reward structures, we use the maximum observed deviation of the smallest time period and the cumulative number of offers for an optimal expediting action among all structures and all combinations of γ_1 and γ_{120}. In Table 4.2 the smallest time period to initiate expedited placement ranges between 34 and 39, i.e., the maximum deviation for the smallest time period to initiate expedited placement is 5 time periods which implies 1.25 hours. This deviation corresponds to 12.5% of the total time horizon, i.e., 10 hours. Similarly, we calculate the robustness in the cumulative offer number to initiate an expedited placement which ranges vetween 88 and 107, i.e., the maximum deviation in the offer numbers is 19. This deviation corresponds to 15.8% of the total number of possible standards offer, i.e., 120.

4.2.3.2 Acceptance Probabilities

In this section we illustrate the results of the sensitivity analysis with respect to the acceptance probabilities where we use linearly decreasing standard rewards and $c = 3$. Table 4.3 illustrates the impact of acceptance probabilities (Figure 4.2) on the model outcomes. We observe that the initiation of an optimal expedited placement occurs sooner for organs obtained in Region 11 than in Region 3. This result is compatible with our findings from the previous chapter. That is, the average difference by which the expedited offer acceptance probabilities are greater than the standard offer acceptance probabilities, is greater in Region 11 than in Region 3 which makes the expedited offer a relatively more favorable approach. This structure holds for all combinations of γ_1 and γ_{120}.

Table 4.3: Results using different sets of expedited and standard offer acceptance probabilities for linearly decreasing standard rewards for $\gamma_1 = 50\%$ and $\gamma_{120} = 5\%$

γ_1	γ_{120}	Region 3		Region 11	
		smallest time period to optimally expedite	smallest offer number to optimally expedite	smallest time period to optimally expedite	smallest offer number to optimally expedite
25%	5%	38	41	35	89
50%	5%	38	99	36	101
50%	10%	38	100	36	103
75%	5%	39	91	37	106
75%	10%	39	91	37	107
75%	25%	39	93	38	89

4.2.3.3 Cost of Disutility

Lastly, we conduct a one-way sensitivity analysis with respect to the cost of disutility where we use Region 11 acceptance probabilities and linearly decreasing standard rewards with $\gamma_1 = 50\%$ and $\gamma_{120} = 5\%$. Table 4.4 illustrates that the optimal time to initiate an expedited offer is observed sooner with increasing cost of disutility. This result is intuitive given the structure of the optimal policy highlighted in Section 4.2.2. As Figure 4.5 (b) illustrates the optimal action for $n = 0, t \geq 36$ is either extending 3 offers or initiating an expedited offer. Then as the cost of disutility increases, the total cost of optimally extending standard offers experiences a greater increase than the initiation of an expedited offer. Therefore the optimal time to initiate an expedited placement is observed sooner.

Table 4.4: Results using different disutility costs for linearly decreasing standard rewards with $\gamma_1 = 50\%$ and $\gamma_{120} = 5\%$

γ_1	γ_{120}	Cost of utility					
		1		3		10	
		smallest time period to optimally expedite	smallest offer number to optimally expedite	smallest time period to optimally expedite	smallest offer number to optimally expedite	smallest time period to optimally expedite	smallest offer number to optimally expedite
50%	5%	37	88	36	101	35	88

4.3 MODEL VALIDATION AND CONCLUSIONS

To validate our model, we use the historical data described and analyzed in Chapter 3. That is, the current practice provides a baseline for the validation of our results, and our aim is to confirm that our findings are compatible with current practice. However, there is no indication that current policies are optimal.

To this end, we compare model outcomes, i.e., the smallest time period and the cumulative offer number to optimally initiate an expedited placement between the computed results and clinically observed results. In our numerical results, the minimum and average time period to initiate an expedited offer is 34 and 36.4, which correspond to 8.5 and 9.1 hours after the start of a match run, respectively. Our analysis of clinical data in Chapter 3 indicates that the majority of expedited offers is initiated within 10 hours, which confirms our findings. However, the average time to initiate an expedited placement in the current practice is 6.65 hours after the initiation of a match run, which seems to be fairly sooner than the average time indicated by our computational results, 9.1 hours. Similarly, we compare the cumulative offer number to optimally initiate an expedited placement. In our numerical results, the minimum and average offer numbers to initiate an expedited offer is 88 and 94, respectively. In the current practice, the majority of expedited offers is initiated after 100 standard offers which confirms that our findings are in an acceptable range. However, the average offer number after which an expedited offer is initiated is 48 which falls short of the average indicated by our computational results, 94. These comparisons indicate that our model produces results which are compatible with the current clinical practice. Furthermore, our findings indicate that the initiation of expedited offers may be too soon and a greater benefit can be obtained by delaying initiation of expedited placement attempts.

As we illustrated in Section 4.2.1.2, the rewards of placement in our model are intended to approximate the valuation of organ allocation in real practice as closely as possible. To this end, we impose intuitive assumptions on the rewards, e.g., monotonicity in offer number, and we experiment with as many feasible structures and combinations of γ_1, γ_{120}

values as possible. In addition, the sensitivity and robustness analysis from Section 4.2.3.1 show that model outcomes behave intuitively. In the complete set of numerical experiments with different reward structures and combinations of γ_1, γ_{120} values, the observed maximum deviation in the smallest time period is 12.5% of the total time horizon, and the observed maximum deviation in the number of offers extended is 15.8% of the total possible number of offers. These findings suggest that although the reward structures are highly ambiguous, the model outcomes are fairly robust to changes in the reward structures. This observation increases the reliability of our results despite arbitrary model rewards. More specifically, independent of the structure of the rewards the model outcomes behave intuitively and are in harmony with the results indicated by clinical historical data.

Also, we illustrate an intuitive optimal policy structure which is consistently observed throughout the numerical experiments. This optimal control limit policy dictates that the process of extending standard offers for time periods when the initiation of an expedited offer is not yet optimal for any state, is analogous to a base stock policy, i.e., it is optimal to extend $\eta - n$ standard offers. For time periods which involve the optimal initiation of an expedited offer for some subset of states, we observe a monotone control limit structure in time, i.e., for offer numbers below the threshold value corresponding to the specific time period, the optimal policy is again analogous to base stock policy. However, for offer numbers above the threshold value, the optimal action is the initiation of an expedited offer or doing nothing, for $n = 0$ and $n > 0$ respectively.

Related future research directions are discussed in Chapter 5.

5.0 CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Given the complex and sensitive nature of organ allocation, inequity questions raised by ethical concerns and allocation system guidelines are likely to persist and the controversies triggered by inequity sources are not easily resolved. Therefore, a liver allocation system ideal for all liver patients seems to be rather unrealistic, but still the allocation system is continuously refined to ensure higher equity levels. In this dissertation, we resolve to improve the equity in liver allocation by targeting two sources of inequity; the first stemming from the patients' flexibility regarding health status updates, and the second stemming from the OPO coordinator's premature departure from the match list process via an expedited placement. We examine the decision problems incorporating these two sources of inequity via MDP models and providing guidelines to attain higher levels of equity among patients, as well as optimal policies for patient level decision making to maximize patients' life expectancies. As opposed to existing literature which suggest significant infrastructure changes to improve the level of equity in liver allocation [2], [19] our findings are practical to implement and thus strengthens our contribution.

5.1 MITIGATING INEQUITIES IN LIVER ALLOCATION VIA REVISED HEALTH REPORTING FREQUENCIES

Existing literature about the organ accept/decline decision of an individual patient implicitly assumes that UNOS knows the patient's current health at all times. In Chapter 2 we relax this assumption by explicitly incorporating a "do nothing" action in the MDP formulation of the patient's accept/decline decision. From an individual patient's perspective, we provide optimal accept/update/do nothing policies to maximize the patient's life expectancy and examine the degree to which an individual patient can benefit from the updating flexibility. Our findings suggest that by exploiting the updating flexibility, a typical patient can increase his life expectancy by up to 1% and her updating burden can decrease by up to 40%, as compared to daily updates. From society's perspective, we analyze how the resulting inequities may be mitigated by revising the updating frequencies without significantly adding to the data processing burden. We construct a menu of 15 updating schemes that render the current updating scheme inefficient with respect to an increase in system inequity versus a decrease in the data processing burden. This menu suggests that requiring the sicker (healthier) patients to update more (less) frequently than they must under the current policy can improve both metrics. This menu appears to be robust with respect to patient characteristics.

In future work, one can relax the assumption that patients always know their current MELD score which could be modeled as a partially observable Markov Decision Process (POMDP). Additionally, a more rigorous approach can be taken to approximate the efficient frontier of updating policies [8]. Also, a similar model can be used to investigate the accept/update/do nothing problem faced by lung transplantation candidates who are required to update their lung allocation scores at least once every six months [22].

5.2 ASSESSMENT OF THE CURRENT PRACTICE OF EXTENDING OFFERS AND RESPONDING TO OFFERS

In Chapter 3, we analyze various aspects of the current allocation practice using clinical OPTN data. To facilitate the interpretation of our findings, we introduce the definition of donor density as a measure of organ availability. First, we focus on the performance measures of the current practice of extending standard electronic offers during the match list process and examine the length of match runs, patterns in offer batching, and the time between sequential batches of offers. We find that the average match run length is 4.36 minutes which indicates that match runs terminate fairly quickly. The average batch size is 5.94 and there might be a possible increase in the batch size for non-local offers. Also, we observe that the OPO coordinators tend to extend sequential batches of offers frequently, i.e., median time between extending two sequential batches is 16 minutes. Because the web-based environment which enables the extension of electronic offers was fully implemented in 2007, many aspects we analyze within the framework of this dissertation are novel to the literature, e.g., the distribution of batch sizes, time between sequential batches of offers. Therefore, we believe that our findings may be utilized to improve the current guidelines of organ allocation.

Second, we examine the current mechanics of the expedited offer placement practice. The literature regarding the expedited placement of livers is very limited and we provide insight of the aspects of expedited placement practice, which has not been investigated before. Specifically, we investigate the prevalence of expedited placement livers where we evaluate and assess the magnitude of the expedited liver placement practice. We find that expedited offers are predominantly initiated by OPOs in Regions 3 and 11, and the majority of expedited offers are either directed to transplant centers within the harvesting region or to Region 9. We establish an intuitive relationship between a region's donor density and the likelihood to initiate and to accept an expedited offer which can serve as a guideline to formulate a transparent process for expedited liver placement. We also consider

the timing of the expedited placement initiation in terms of clock time and the number of extended standard offers where the averages are 6.65 hours and 48 offers, respectively. Regarding the number of bypassed patients, we conclude that the expected number of patients bypassed due to an expedited offer initiation is constant in the number of offers extended.

Finally, we turn our attention to patients' response characteristics. We examine the prevalence of range refusals and find that range refusals represent a significant fraction of all responses. We analyze the patient response time distribution and find that patient response times are exponentially distributed with mean 17.5 minutes. Based on our analysis of patient response times, we suggest that the current one-hour limit to evaluate a standard offer can be reduced to accelarate the match list process and possibly decrease the rate of organ waste. Also, we establish a relationship between the probability that a standard or an expedited offer is accepted and the corresponding offer number.

As an extension of the analyzes presented in this chapter, time of day dependencies for expedited placements can be investigated. More specifically, one can question whether there is a relationship between the time of day when an organ is harvested and the initiation of an expedited placement either as a function of clock time or number of offers extended. Another possible extension is a closer investigation of range refusals where the distribution of the number of patients involved in a range refusal can be analyzed.

5.3 OPTIMAL TIMING OF EXPEDITED LIVER PLACEMENT

In Chapter 4 we formulate the OPO coordinator's progression through the match list process, which can possibly culminate in an expedited offer. We use an MDP model with an objective of maximizing the benefit gained by successful organ allocation. In our numerical experiments, we evaluate problem instances with a variety of feasible reward structures and

illustrate a structured optimal policy which is observed consistently throughout the numerical experimentation. Also, our results are robust to changes in rewards, and model outcomes are compatible with real world observations. Furthermore, we suggest that expedited liver placement may be exercised too early in the current practice.

The major setback within our modeling framework is the definition of rewards and costs. These model inputs cannot be expressed in quantifiable measures like the patients' life expectancy because the prioritization algorithm is not monotone in patients' health status due to the geographical considerations. Therefore, we experimented with different feasible reward structures at various levels to determine the model inputs for these parameters and show that our findings are compatible with the measures provided by the current practice. Another way to estimate the rewards of placement is interviewing the OPO coordinators regarding how they valuate the trade-off between departing from the match list process to prevent waste of organ and continuing the match list process to maintain fairness among patients. To quantify this valuation, a conjoint analysis can be conducted where the OPO coordinators are asked to rate their preference between an expedited placement and a placement via a standard offer at different points in the match run and for different organ qualities, e.g., based on your previous interactions with transplant surgeons and/or UNOS members, how do you rate the value of organ placement via an expedited placement (or a standard offer) at the $x^{th}, 1 \leq x \leq 18$ hour during the match run on a scale of 1(poor) to 10(good)? The answers to these questions can then be utilized to elicit the relative values of rewards corresponding to standard offers and to expedited placements.

As we pointed out earlier, the current practice provides a baseline for the validation for our results, however there is no indication that current policies are optimal. Therefore, a quantifiable way to assess how our model performs next to the current practice, would be using the rate of organ waste. That is, the organ waste rate within the current practice can be computed using the historical data. Then, a simulation study of the current liver allocation system can be conducted to evaluate the optimal policies suggested by our

model outcomes. Finally, the rate of waste resulting from the simulation study can be compared with the clinical rate, and if the simulation outcome performs better than the one in the current practice, we can conclude that the current practice behaves suboptimally.

Despite the curse of dimensionality arising from the size of the state space, we solve problem instances which present the current practice, i.e., we consider a 10-hour time horizon with 15-minute time periods. However, shorter time periods would present a better approximation of the real world liver allocation problem. Also, we assume that the limit on the number of concurrently outstanding offers, η is known and is equal to 3 in our numerical results. However, the value of η is another optimization problem on its own and may be further considered for future research.

We assume an average organ quality and conduct our numerical results at a regional level. However, the organ quality is highly likely to have an impact on the initiation of an expedited offer and different OPO's may pursue different systematic ways of initiating expedited offers. Therefore, a new mathematical model considering organ quality may be built which then can be solved using input parameters at the OPO level.

Another modeling assumption is that an expedited liver placement can only be initiated when there are no outstanding standard offers. Although this assumption is realistic, as we discuss in Section 4.1.1, it can be relaxed so that an expedited offer can be initiated anytime during the match list. Optimal policies for the model with this relaxed assumption can be obtained and compared with the policies of the present model.

APPENDIX A

EXPERIMENTATION WITH DIFFERENT SETS OF BREAKPOINTS FOR MELD UPDATING FREQUENCIES

We conducted numerical experiments with updating schemes where the updating frequencies change according to a different set of breakpoints than those currently used by UNOS. Table A1 displays a sample of such updating schemes and Figure A1 depicts the evaluation of these schemes for a 60-year old male from Disease Group 1. We conclude that different sets of breakpoints are unlikely to result in significant performance improvements.

Table A1: List of the updating schemes using a different set of breakpoints than currently used by UNOS

	MELD Score						
Updating Scheme	6-10	11-14	15-18	19-20	21-24	25-32	33-40
UNOS	365	90	90	30	30	7	7
1	180	180	60	60	14	7	7
2	365	90	60	60	14	7	7
3	365	90	60	60	30	7	7
4	365	180	180	14	14	7	1
5	365	180	180	30	30	7	1

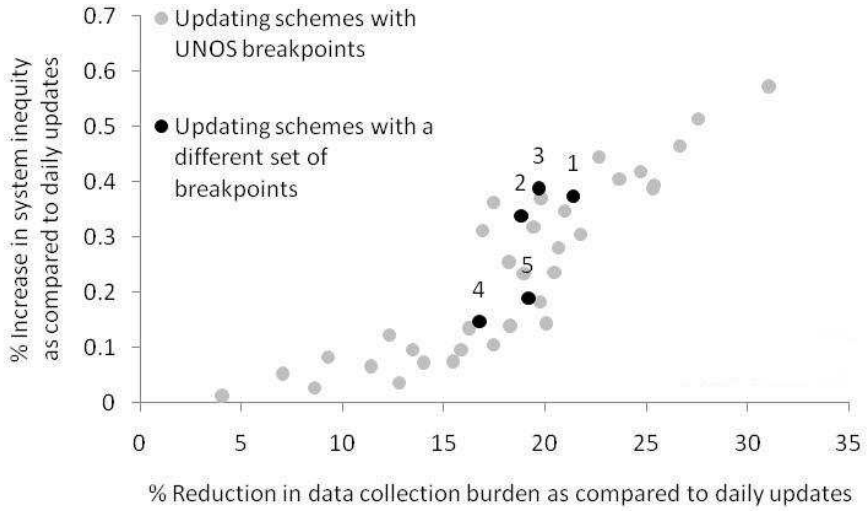


Figure A1: The performance of the updating schemes in Table A1 for a 60-year old male from Disease Group 1

APPENDIX B

PROOFS OF STRUCTURAL RESULTS

Proof of Lemma 1. We proceed by induction on the steps of the value iteration algorithm. Let $v_n(h, m, \tau, l)$ be the value function in the n^{th} step of the value iteration algorithm. Without loss of generality, let $v_0(h, 6, \tau, l) = 0$ for $h \in S^H$, $\tau \in S^{\bar{\tau}(m)}$ and $l \in S^L$, and assume that $v_n(h, 6, \tau, l)$ is independent of τ for $n = 1, \ldots, k, h \in S^H$ and $l \in S^L$. Note that $v^T_{k+1}(h, l)$ and $v^U_{k+1}(h)$ are by definition constant in τ. Hence, showing that $v^W_{k+1}(h, 6, \tau)$ is constant in τ for all $h \in S^H$ and $l \in S^L$ will establish the result.

Consider $v^{DN}_{k+1}(h, 6, 0)$:

$$\begin{aligned} v^{DN}_{k+1}(h, 6, 0) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v_k(h', 6, \bar{\tau}(6) - 1, l') \right) \\ &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v_k(h', 6, \tau - 1, l') \right), \tau > 0 \quad \text{(B.1)} \\ &= v^{DN}_{k+1}(h, 6, \tau) \end{aligned}$$

where Inequality (B.1) follows by the induction assumption.

Proof of Proposition 1.

(a) Observe that $v^U(h)$ and $v^{DN}(h, m, \tau)$ are independent of l whereas $v^T(h, l)$ is decreasing in l by As1.

(b) We proceed by induction on the steps of the value iteration algorithm. Without loss of generality, let $v_0(h,m,\tau,l)=0$, for $h\in S^H$, $m\in S^M$, $\tau\in S^{\bar{\tau}(m)}$ and $l\in S^L$, and assume that $v_n(h,m,\tau,l)$ is increasing in m for $n=1,\ldots,k$, $h\in S^H$, $\tau\in S^{\bar{\tau}(m)}$ and $l\in S^L$. Observe that $v^U_{k+1}(h)$, $v^T_{k+1}(h,l)$ and $v^{DN}_{k+1}(h,m,0)$ are independent of m, and consider $v^{DN}_{k+1}(h,m,\tau)$ for $\tau\geq 1$:

$$\begin{aligned}
v^{DN}_{k+1}(h,m,\tau) &= r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m)v_k(h',m,\tau-1,l')\right)\\
&\leq r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m+1)v_k(h',m,\tau-1,l')\right) \qquad \text{(B.2)}\\
&\leq r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m+1)v_k(h',m+1,\tau-1,l')\right) \qquad \text{(B.3)}\\
&= v^{DN}_{k+1}(h,m+1,\tau).
\end{aligned}$$

Inequality (B.2) follows by As3, part (a) of Proposition 1 and Lemma 4.7.2 of [35]. Inequality (B.3) follows by the induction assumption.

(c) We proceed by induction on the steps of the value iteration algorithm. Without loss of generality, let $v_0(h,m,\tau,l)=0$ for $h\in S^H$, $m\in S^M$, $\tau\in S^{\bar{\tau}(m)}$ and $l\in S^L$, and assume that $v_n(h,m,\tau,l)$ is increasing in τ for $n=1,\ldots,k$, $h\in S^H$, $m\in S^M$ and $l\in S^L$. Observe that $v^U_{k+1}(h)$, $v^T_{k+1}(h,l)$ are independent of τ, and consider $v^{DN}_{k+1}(h,m,\tau)$. First, consider $v^{DN}_{k+1}(h,m,0)$,

$$\begin{aligned}
v^{DN}_{k+1}(h,m,0) &= r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|6)v_k(h',6,\bar{\tau}(6)-1,l')\right)\\
&\leq r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m)v_k(h',6,\bar{\tau}(6)-1,l')\right), \qquad \text{(B.4)}\\
&= r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m)v_k(h',6,0,l')\right) \qquad \text{(B.5)}\\
&\leq r_h+\beta\sum_{h'\in S^H}\mathcal{H}(h'|h)\left(\sum_{l'\in S^L}\mathcal{L}(l'|m)v_k(h',m,0,l')\right) \qquad \text{(B.6)}\\
&= v^{DN}_{k+1}(h,m,1),
\end{aligned}$$

where Inequality (B.4) follows by As3, part (a) of Proposition 1 and Lemma 4.7.2 of [35]. Inequality (B.5) follows by Lemma 1 and Inequality (B.6) follows by part (b) of Proposition 1.

Now consider $v_{k+1}^{DN}(h,m,\tau)$ for $\tau > 0$:

$$\begin{aligned} v_{k+1}^{DN}(h,m,\tau) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\ &\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v_k(h', m, \tau, l') \right) \qquad \text{(B.7)} \\ &= v_{k+1}^{DN}(h,m,\tau+1), \end{aligned}$$

where Inequality (B.7) follows by the induction assumption.

Proof of Corollary 1.

(a) By definition,

$$\begin{aligned} v^{DN}(h,m,0) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(6) - 1, l') \right) \\ &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.8)} \\ &\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v(h', 6, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.9)} \\ &\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v(h', h, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.10)} \\ &= v^U(h), \qquad \text{(B.11)} \end{aligned}$$

where Inequality (B.8) follows by Lemma 1, Inequality (B.9) by As3, part (a) of Proposition 1 and Lemma 4.7.2 of [35], Inequality (B.10) by part (b) of Proposition 1, and Inequality (B.11) follows since $v^U(h)$ is independent of τ.

(b) Observe that the result holds for $\tau = 0$ by part (a) of Corollary 1. For $\tau > 0$,

$$\begin{aligned} v^{DN}(h,6,\tau) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \tau - 1, l') \right) \\ &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.12)} \\ &\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v(h', 6, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.13)} \\ &\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v(h', h, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.14)} \\ &= v^U(h) \end{aligned}$$

where Inequality (B.12) follows by Lemma 1, Inequality (B.13) by As3, part (a) of Proposition 1 and Lemma 4.7.2 of [35], and Inequality (B.14) by part (b) of Proposition 1.

(c) First consider the case where $\tau = 0$:

$$\begin{aligned} v^{DN}(6,m,0) &= r_6 + \beta \sum_{h' \in S^H} \mathcal{H}(h'|6) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(6) - 1, l') \right) \\ &= v^U(6) \end{aligned}$$

for all $m \in S^H$, $l \in S^L$, and $\tau \in S^{\bar{\tau}(6)}$ and thus the claim holds for $\tau = 0$.

Now consider the case where $\tau > 0$ and for all $m \in S^H$, $l \in S^L$, $\tau \in S^{\bar{\tau}(6)}$:

$$\begin{aligned} v^{DN}(6,m,\tau) &= r_6 + \beta \sum_{h' \in S^H} \mathcal{H}(h'|6) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v(h', m, \tau - 1, l') \right) \\ &\geq r_6 + \beta \sum_{h' \in S^H} \mathcal{H}(h'|6) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', m, \tau - 1, l') \right) \qquad \text{(B.15)} \end{aligned}$$

$$
\begin{aligned}
&\geq r_6 + \beta \sum_{h' \in S^H} \mathcal{H}(h'|6) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \tau - 1, l') \right) && \text{(B.16)} \\
&= r_6 + \beta \sum_{h' \in S^H} \mathcal{H}(h'|6) \left(\sum_{l' \in S^L} \mathcal{L}(l'|6) v(h', 6, \bar{\tau}(6) - 1, l') \right) && \text{(B.17)} \\
&= v^U(6)
\end{aligned}
$$

where Inequality (B.15) holds by As3, part (a) of Proposition 1, Inequality (B.16) holds by part (b) of Proposition 1 and Inequality (B.17) holds by Lemma 1.

(d) If $h = m$,

$$
\begin{aligned}
v^{DN}(m, m, \tau) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|m) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v(h', m, \tau - 1, l') \right), \\
&\leq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|m) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v(h', m, \bar{\tau}(m) - 1, l') \right), \\
&= v^U(m)
\end{aligned}
$$

by part (c) of Proposition 1.

Proof of Proposition 2. We proceed by induction on the steps of the value iteration algorithm. Without loss of generality, let $v_0(h, m, \tau, l) = 0$, for $h \in S^H$, $m \in S^M$, $\tau \in S^{\bar{\tau}(m)}$ and $l \in S^L$ and observe that the claim holds. Now we assume that for $n = 1, \ldots, k$, $v_n^U(h) \geq v_n^{DN}(h, m, \tau)$ for all $l \in S^L$, $\tau \in S^{\bar{\tau}(m)}$ and $h > m$ and show that $v_{k+1}^U(h) \geq v_{k+1}^{DN}(h, m, \tau)$ for all $l \in S^L$, $\tau \in S^{\bar{\tau}(m)}$ and $h > m$.

By As3, parts (a), (b) and (c) of Proposition 1, Lemma 4.7.2 of [35], and the fact that $\bar{\tau}(h) \geq \tau$ we obtain

$$
\begin{aligned}
v_{k+1}^U(h) &= r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&\geq r_h + \beta \sum_{h' \in S^H} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\
&= v_{k+1}^{DN}(h, m, \tau).
\end{aligned}
$$

Proof of Proposition 3. We proceed by induction on the steps of the value iteration algorithm. Let $v_0(h, m, \tau, l) = 0$ for all h, m, τ, l and observe that the claim holds. Now we assume that for $n = 1, \ldots, k$, $v_n^U(h) \geq v_n^{DN}(h, m, \tau)$ for all l, τ and $h > m$ and show that $v_{k+1}^U(h) \geq v_{k+1}^{DN}(h, m, \tau)$ for all l, τ and $h > m$.

We show that $v^U(h) \geq v^{DN}(h, m, \tau)$ for $\bar{\tau}(h) \geq \tau$ in Proposition 2. Now consider $\bar{\tau}(h) < \tau$ in the following three cases: $h' \in \{6, \ldots, h-2\}, h' \in \{h-1\}, h' \in \{h, \ldots, 41\}$. First consider the interval $6 \leq h' \leq h-2$ for which we obtain

$$\begin{aligned}
&\lambda \sum_{h'=6}^{h-2} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&= \lambda \sum_{h'=6}^{h-2} \mathcal{H}(h'|h) \left(\sum_{l' \in S^L} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\
&= 0
\end{aligned}$$

by Definition 1.

Now consider the case when $h' = h - 1$:

$$\begin{aligned}
&\lambda \mathcal{H}(h-1|h) \sum_{l' \in S^L} \mathcal{L}(l'|h) v_k(h-1, h, \bar{\tau}(h) - 1, l') \\
&\geq \lambda \mathcal{H}(h-1|h) \sum_{l' \in S^L} \mathcal{L}(l'|m) v_k(h-1, h, \bar{\tau}(h) - 1, l') && \text{(B.18)} \\
&\geq \lambda \mathcal{H}(h-1|h) \sum_{l'} \mathcal{L}(l'|m) v_k(h-1, m, \bar{\tau}(h) - 1, l' && \text{(B.19)} \\
&= \lambda \mathcal{H}(h-1|h) \sum_{l'} \mathcal{L}(l'|m) v_k(h-1, m, \tau - 1, l'), && \text{(B.20)}
\end{aligned}$$

where (B.18) follows by As3, part (a) of Proposition 1 and Lemma 4.7.2 of [35]; (B.19) follows by part (b) of Proposition 1; and (B.20) follows by the induction assumption and since $h - 1 \geq m$, i.e., in state $(h-1, m, \bar{\tau}(h) - 1, l')$, the optimal decision can not be "do nothing" and the values of transplanting and updating are independent of the current τ.

Finally, consider the interval $h \leq h' \leq 41$:

$$\begin{aligned}
&\lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&\geq \lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', m, \bar{\tau}(h) - 1, l') \right) \qquad \text{(B.21)} \\
&\geq \lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', m, \tau - 1, l') \right) \qquad \text{(B.22)} \\
&\geq \lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right), \qquad \text{(B.23)}
\end{aligned}$$

where (B.21) follows by part (b) of Proposition 1; (B.22) by the induction assumption (since $h' \geq h$); and (B.23) follows by As3, part (a) of Proposition 1, and Lemma 4.7.2 of [35].

As a result we obtain

$$\begin{aligned}
v_{k+1}^U(h) &= r_h + \lambda \sum_{h'=6}^{m-1} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&\quad + \lambda \sum_{h'=m}^{h-1} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&\quad + \lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|h) v_k(h', h, \bar{\tau}(h) - 1, l') \right) \\
&\geq r_h + \lambda \sum_{h'=6}^{m-1} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\
&\quad + \lambda \sum_{h'=m}^{h-1} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\
&\quad + \lambda \sum_{h'=h}^{41} \mathcal{H}(h'|h) \left(\sum_{l'} \mathcal{L}(l'|m) v_k(h', m, \tau - 1, l') \right) \\
&= v_{k+1}^{DN}(h, m, \tau).
\end{aligned}$$

Proof of Proposition 4. (a) This result follows from Proposition 1 part (a), since $v^{DN}(h, m, \tau)$ and $v^U(h)$ are constant in l while $v^T(h, l)$ is decreasing in l.

(b) This result follows from Proposition 1 part (b), since $v^T(h, l)$ and $v^U(h)$ are constant in τ while $v^{DN}(h, m, \tau)$ is increasing in τ.

(c) This result follows from Proposition 1 part (c), since $v^T(h,l)$ and $v^U(h)$ are constant in m while $v^{DN}(h,m,\tau)$ is increasing in m.

Proof of Proposition 5. Assume that for updating scheme A, transplanting is not optimal in state $(h,m,1,l)$. This assumption implies that updating is optimal because doing nothing is not an option and the state after updating is $(h,h,1,l) \equiv (h,l)$. Now showing that for updating scheme B transplanting is not optimal in state (h,m,τ,l) establishes $l_B^*(h,m,\tau) \leq l_A^*(h)$. To show this result, we make use of a sample path approach. Consider updating scheme A. Starting in state (h,l), let η be the number of periods until transplanting becomes the optimal action or death occurs, and p_T be the probability that transplanting becomes the optimal action after η periods. Then,

$$\begin{aligned} R(h,l) &< E[\eta] + \beta^\eta \left[p_T \cdot E_{h_\eta}[E_{l_\eta}[R(h_\eta,l_\eta)]] + (1-p_T)\cdot v(H+1,l_\eta)\right] && \text{(B.24)} \\ &= E[\eta] + \beta^\eta \left[p_T \cdot E_{h_\eta}[E_{l_\eta}[R(h_\eta,l_\eta)]]\right] && \text{(B.25)} \end{aligned}$$

where $(h,l),(h_1,l_1),\ldots,(h_\eta,l_\eta)$ is the sequence of states visited during these η time periods. Observe that the next health transition and the next liver quality only depend on the current MELD score because scheme A requires an update in every period. Now consider updating scheme B. Starting in state (h,m,τ,l), assume we apply the same sequence of actions for η time periods as the one we obtained under updating scheme A starting in state (h,l), i.e., update for the following η periods, and then transplant unless death occurs. Observe that under this policy, which is not necessarily optimal for updating scheme B, we obtain the same sample path of (h,l) pairs. Then,

$$E[\eta] + \beta^\eta \left[p_T \cdot E_{h_\eta}[E_{l_\eta}[R(h_\eta,l_\eta)]]\right] \tag{B.26}$$

is the expected value corresponding to this possibly suboptimal sequence of actions, and by (B.25) we obtain $R(h,l) < E[\eta] + \beta^\eta \left[p_T \cdot E_{h_\eta}[E_{l_\eta}[R(h_\eta,l_\eta)]]\right] < v(h,m,\tau,l)$ which completes the proof.

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