

Optimizing Liver Allocation System Incorporating Disease Evolution

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Abstract

We propose an efficient liver allocation system for allocating donated organs to patients waiting for transplantation, the only viable treatment for End-Stage Liver Disease. We optimize two metrics which are used to measure the efficiency: total quality adjusted life years and the number of organs wasted due to patients rejecting some organ offers. Our model incorporates the possibility that the patients may turn down the organ offers. Given the scarcity of available organs relative to the number patients waiting for transplantation, we model the system as a multiclass fluid model of overloaded queues. The fluid model we advance captures the disease evolution over time by allowing the patients to switch between classes over time, e.g. patients waiting for transplantation may get sicker/better, or may die. We characterize the optimal solution to the fluid model using the duality framework for optimal control problems developed by Rockafellar (1970a). The optimal solution for assigning livers to patients is an intuitive dynamic index policy, where the indices depend on patients' acceptance probabilities of the organ offer, immediate rewards, and the shadow prices calculated from the dual dynamical system. Finally, we perform a detailed simulation study to demonstrate the effectiveness of the proposed policy using data from the United Network for Organ Sharing System (UNOS).

1 Introduction

Donated organs for liver transplantation, the only viable therapy for patients with end-stage liver diseases (ESLD), are scarce resources. Because of the huge imbalance between the number of ESLD patients awaiting for a liver and the number of available organs for transplantation, these

patients are placed on a liver waiting list, managed by the United Network for Organ Sharing System (UNOS). Currently, there are approximately 16,000 patients on the waiting list, 10,546 of them were added in 2007 alone UNOS (2008*b*). Although 6,939 cadaveric organs were donated in 2007, the median waiting time for transplantation is over 300 days UNOS (2008*b*). As a result of insufficient supply of organs, more than 18,000 patients died while waiting for a liver between 1998 and 2007 UNOS (2008*b*). On the other hand, each year approximately 6% of all donated livers are wasted and 15% of all patients who receive an organ die within the first year UNOS (2008*b*).

The economic impact of organ transplantation is also huge. Alter & Moyer (1998) report that a liver transplant costs approximately \$300,000 in 1996 dollars. A liver transplant for a patient with hepatitis C would cost over 1 million dollars when factoring together the surgery and lifelong immunosuppressant medication, cf. Naito (2005). Business Communications Company BCC (2006) estimates that tissue and organ transplantation in the U.S. was a \$20.5 billion market in 2007. These data suggest that there is a need to improve the allocation of available organs to patients and any improvement on the efficient usage of organs for transplantation would lead to significant savings in terms of both dollars and life years.

When an organ is harvested, UNOS offers this organ to the patients on the waiting list sequentially, where patients are prioritized based on geographic location, medical urgency, waiting time and blood type. Patients and/or their transplant surgeons, who are acting as agents of the patients, have the right to decline an organ offer without penalty. Transplant surgeons have limited time, namely, one hour to make their decision due to the acceptable range of the cold-ischemia time, the time that the organ spends outside of the body. It is estimated that the acceptable range for the cold-ischemia time for livers is between 12 and 18 hours, cf. SRTR (2004). Surprisingly, although there is a significant shortage of organs, a recent analysis of liver transplant data shows that 45% of all cadaveric liver offers are declined by the first transplant surgeon and/or patient to whom they are offered, cf. Howard (2002).

This paper focuses on the design of a new organ allocation policy that will improve the efficiency of the liver allocation system, which is measured by the total number of organs wasted, total expected quality-adjusted life years, total number of patient deaths while waiting for transplantation, and 1-year post-transplant survival rate. The current liver allocation policy (see Section 2) focuses primarily on medical urgency. We recognize that focusing solely on current medical urgency may lead to ignoring other important criteria such as the impact of current decisions on the future well-being of the patients as a whole. Our main contribution is to model this trade-off quantitatively

using an analytically sound approach. To the best of our knowledge, this study is the first one to consider an analytical model for optimizing the liver allocation system. To be specific, we develop a dynamic fluid model to represent the liver allocation system and use a novel duality approach for solving that. The dual optimal control problem associated with the fluid model gives rise to optimal shadow prices, which in turn are used to solve the fluid model optimally (see Theorems 1 and 2). Moreover, we develop a discrete-event simulation model of the liver allocation system to test our results. Using real clinical data, we show in Sections 6 and 7 that our policy leads to significant improvements over the current allocation policy.

There are many interesting and controversial policy questions associated with the design of a new liver allocation system. What should be the primary criterion for prioritizing patients, medical urgency of the patients or the marginal benefit of transplanting an organ, cf. Gazelle et al. (2003), Neuberger (2003)? Should we penalize patients if they decline an organ offer, cf. Su & Zenios (2005)? What would be the potential benefits of requiring patients to specify their organ acceptance preferences in advance? Although the answers to some of these questions require the consideration of other issues such as ethical and political issues, a quantitative analysis is essential to identify and evaluate alternative policies.

Several researchers investigate the problem of accepting/declining an organ offer for transplantation while optimizing a particular patient's welfare Ahn & Hornberger (1996), Alagoz et al. (2004), Alagoz et al. (2007*b*), Alagoz et al. (2007*a*), David & Yechiali (1985), Hornberger & Ahn (1997) and Howard (2002). Several others use simulation models to evaluate the effects of various organ allocation policies on the allocation system's performance Corporation (1995), Kreke et al. (2002), Pritsker et al. (1995), Shechter et al. (2005) and Zenios et al. (1999). Much of the research on the optimal allocation of organs (particularly kidneys) focuses on designing an optimal allocation system that maximizes society's welfare. In particular, the researchers seek to provide an optimal match between organs and patients that maximizes objectives such as mean expected quality-adjusted life years, average one-year graft survival probability, and quality of the prospective matches, cf. David (1995), David & Yechiali (1990), David & Yechiali (1995), Richter (1989), Su & Zenios (2005) and Zenios et al. (2000).

In a series of papers, Su and Zenios study the impact of patient choice on kidney allocation mechanisms. Su & Zenios (2005) adopts a sequential stochastic assignment model and proves the asymptotic optimality of a simple partition policy as both the number of patients and the number of kidneys available tend to infinity under the simplifying assumption that the patients

accept all organ offers. The authors then incorporate the patient choice and characterize the best partition policy, which ensures that accepting the kidney offer is in the best interest of each patient when the numbers of patients and available organs are sufficiently large. Finally, using the data from US transplantation system, the authors show that patient choice may introduce substantial inefficiencies, but their policy recovers the losses by minimizing the variability in the type of offers expected by each patient. Su & Zenios (2006) considers the impact of information asymmetry and use a mechanism design approach to propose an organ allocation system by having patients declare which types of kidneys they would be willing to accept when they join the waiting list. The authors consider two alternative social welfare functions: one emphasizing the efficiency while the other emphasizing equity. They derive an assortative partition policy as the solution to their problem formulation, which corresponds to an outcome in the middle of the efficiency-equity spectrum. Finally, Su & Zenios (2004) explores the role of queuing discipline as an instrument for maximizing the social welfare when patients choose whether or not to accept a kidney offer. The authors show that first-come-first-serve queuing discipline amplifies patients' desire to refuse offers of marginal quality, which in turn generates excessive organ wastage. On the contrary, using the extreme opposite priority rule of last-come-first-serve ensures that patients internalize the externalities of their own actions, leading to a socially optimal outcome.

Another related paper Zenios et al. (2000) uses a fluid model to study the problem of finding the best kidney allocation policy with three criteria of maximizing total quality-adjusted life years (QALYs) and minimizing two measures of inequity. Zenios et al. (2000) uses various approximations to develop a heuristic dynamic index policy for the problem since their fluid model does not seem to admit an obvious analytic solution.

This paper differs significantly from the previous optimization studies on organ allocation problem. First, this research addresses livers, rather than kidneys. ESLD are different from the end-stage renal diseases (ESRD) because the only viable therapy for ESLD patients is organ transplantation whereas there are alternative therapies such as dialysis for ESRD patients. Moreover, the dynamic health characteristics (i.e. laboratory values in the blood) of the patient at the time of transplantation significantly affect the outcome of the transplantation for the ESLD patients whereas these are of secondary importance to the static health characteristics (i.e. antigen type) to determine the outcome of kidney transplantation, cf. Roberts et al. (2004). Therefore, the optimization model should consider the dynamic evolution of patient health, which is typically assumed to be static in previous research. Furthermore, while previous research also seeks to provide an optimal match

between organs and patients by considering factors such as expected quality-adjusted life years to find an optimal allocation of organs, they often assume that the patient does not have the right to refuse the organ offer. However, Alagoz (2004) reports that 60% of all liver offers are declined by the ESLD patients to whom they are offered therefore patient preferences should be incorporated into any realistic model that considers the problem of optimizing the liver allocation system.

As mentioned above, the analysis of Su and Zenios focus primarily on the patient choice, while our analysis focuses more on the supply side of the organ allocation problem. Our analysis advances a detailed, yet tractable, model of the patient waiting lists as well as the organ allocation decisions, thereby allowing a framework for exploring dynamic liver allocation decisions. Our model also allows us to incorporate the evolution of ESLD in decision making, which is of key importance for liver transplants contrary to kidney transplants. Moreover, although we do not model the patient choice endogenously, our model *does* incorporate the possibility of patients turning down the organ offers.

Fluid models are commonly used to approximate linear dynamical systems. Indeed, in operations research literature, fluid models are most commonly used as tractable approximations to queueing systems. We also use a fluid model to study liver allocation system as done for the kidney allocation system in Zenios et al. (2000). In particular, we model the liver allocation system as a multiclass fluid model of overloaded queues. However, we follow a different solution approach, which enables us to solve the problem optimally. In particular, we use duality theory developed by Rockafellar (1970a) for convex (non-smooth) optimal control problems, and arrive at an optimal dynamic index policy which uses the optimal dual state variables, cf. Theorems 1 and 2. Moreover, in contrast to Zenios et al. (2000), we model the evolution of the disease over time, allowing the possibility of patients rejecting organ offers, and show that the optimal policy should take into account three factors: Immediate rewards resulting from transplantation, impact of disease evolution on future rewards (as captured by the dual variables) and acceptance probabilities associated with organ offers.

The remainder of the paper is organized as follows. Section 2 describes the current liver allocation system. We present the fluid model that can be used to develop an alternative liver allocation policy in Section 3. Section 4 presents the dual control problems, the duality results and the proposed policies. In Section 5, we establish various structural results. Sections 6 and 7 describe the simulation model that is used to test our proposed policies and our computational results, respectively. Finally, Section 8 summarizes our conclusions and provides future research directions.

Proofs are relegated to Appendices A and B throughout the paper. Appendix A consists of the proofs of the results in Section 4; and Appendix B provides the proofs for Section 5.

2 Liver Allocation System

This section describes the current liver allocation system. Basic knowledge of this system is necessary to understand the liver allocation problem. UNOS is responsible for managing the national organ donation and allocation system. The UNOS Board of Directors approved for implementation the new liver allocation procedure as of February 28, 2002 UNOS (2008*a*). According to the General Accounting Office, the organ allocation policy has been changed at least four times in the last six years, cf. Office (2003). These changes in policy over a short time span is indicative of the ever-changing opinions surrounding the optimal allocation of livers. Although the new policy is anticipated to “better identify urgent patients and reduce deaths among patients awaiting liver transplants” UNOS (2008*a*), there is strong evidence that the transplant community disagrees that the new allocation rules are satisfactory, cf. Garber (2002), Lladó et al. (2002) and Trotter & Osgood (2004).

UNOS manages the organ donation and procurement via Organ Procurement Organizations (OPOs) which are non-profit agencies responsible for coordinating the recovery, preservation, and transportation of organs donated for transplantation. There are currently 59 OPOs that operate in designated service areas, which may cover multiple states, a single state, or just parts of a state UNOS (2008*a*). The national UNOS membership is also divided into 11 geographic regions, each consisting of several OPOs. UNOS maintains a patient waiting list to determine the transplant candidates among the patients. Under the current policy, when a liver becomes available, the following factors are considered for its allocation: liver and patient OPO, liver and patient region, medical urgency of the patient, patient points, and patient waiting time.

The medical urgency of the adult liver patients is represented by UNOS Status 1 and scores assigned by UNOS. According to the new UNOS policy, a patient listed as Status 1 “has fulminant liver failure with a life expectancy without a liver transplant of less than 7 days” UNOS (2008*a*). Patients who do not qualify for classification as Status 1 do not receive a status level. Rather, these patients are assigned a “probability of pre-transplant death derived from a mortality risk score” calculated by the MELD scoring system, cf. UNOS (2008*a*). The MELD score is a continuous function of total bilirubin, creatinine and prothrombin time. It indicates the status of the liver

disease, cf. Malinchoc et al. (2000), and Wiesner et al. (2001). Wiesner et al. (2001) develop the following formula for computing MELD scores:

$$\text{MELD Score} = 9.57 \times \ln(\text{creatinine mg/DL}) + 3.78 \times \ln(\text{bilirubin mg/DL}) + 11.20 \times \ln(\text{INR}) + 6.43 \times I_c$$

where INR, international normalized ratio, is computed by dividing prothrombin time (PT) of the patient by a normal PT value, and I_c is an indicator variable that shows the cause of cirrhosis, i.e., it is equal to 1 if the disease is alcohol or cholestatic related and it is equal to zero if the disease is related to other etiologies. As Wiesner et al. (2001) note, the etiology (cause) of disease is removed from the formula by UNOS, which makes several other modifications to the formula such as any lab value less than 1 mg/DL is set to 1 mg/DL, any creatinine level above 4 mg/DL is set to 4 mg/DL and the resulting MELD score is rounded to the closest integer, cf. UNOS (2008a). By introducing these changes, UNOS restricts the range of MELD scores to be between 6 and 40, where a value of 6 corresponds to the best possible patient health and 40 to the worst.

Patients in the waiting list are further stratified within Status 1 and each MELD score using patient "points" and waiting time. Patient points are assigned based on the compatibility of their blood type with the donor's blood type. For Status 1 patients, candidates with an exact blood type match receive 10 points; candidates with a compatible, but not identical, blood type receive 5 points; and a candidate whose blood type is incompatible receives zero points. For non-Status 1 patients with the same MELD score, a liver is offered to patients with an exact blood type match first, compatible patients next, and incompatible patients last. If there are several patients having the same blood type compatibility and MELD scores, the ties are broken using patient waiting time. The waiting time for a Status 1 patient is calculated only from the date when that patient was listed as Status 1. Points are assigned to each patient based on the following strategy: "Ten points will be accrued by the patient waiting for the longest period for a liver transplant and proportionately fewer points will be accrued by those patients with shorter tenure", cf. UNOS (2008a). Similarly, for the MELD patients, waiting time for a particular MELD score is calculated as the time accrued by the patient at or above his current score level.

In summary, the current liver allocation system operates as follows: each liver available for transplant is first offered to Status 1 patients located within the harvesting OPO. If more than one Status 1 patient exists, then the liver is offered to those patients according to the points they received where the patient with the most points receives the highest priority. If there are no suitable Status 1 matches within the harvesting OPO, the liver is then offered to Status 1 patients within

the harvesting region. If a match has not yet been found at this point, then the liver is offered to all non-Status 1 patients with MELD scores greater than or equal to 15 in the harvesting OPO in descending order of MELD score. If this search for a suitable match fails, then the search is again broadened to the patients with MELD scores greater than or equal to 15 in the harvesting region. If no suitable match exists in the harvesting region, then the liver is offered to patients with MELD scores less than 15 in the harvesting OPO, and then to patients with MELD scores less than 15 in the harvesting region. Finally, if a match has not yet been found, then the liver is offered nationally to Status 1 patients followed by all other patients in descending order of MELD scores.

UNOS maintains that the final decision to accept or decline a liver “will remain the prerogative of the transplant surgeon or physician responsible for the care of that patient”, cf. IOM (1999). The surgeon or the physician have very limited time, namely one hour, to make his decision UNOS (2008*a*), because the acceptable range for cold ischemia time is short. The Scientific Registry of Transplant Recipients states that the acceptable cold ischemia time limit for a liver is 12 to 18 hours, cf. SRTR (2004). In the event that a liver is declined, it is then offered to another patient in accordance with the UNOS policy described immediately above. The patient who declines the organ will not be penalized and will have access to future livers. In current practice, organs are frequently declined. Indeed, Alagoz (2004) reports that 60% of all liver offers are declined.

3 The Fluid Model

This section provides a detailed yet analytically tractable model of the dynamics of ESLD population to study the liver allocation system. Our model divides the ESLD population waiting for transplant into different classes along two dimensions: static patient characteristics such as blood type, cytomegalovirus (CMVGR), etc. and dynamic patient characteristics representing the health status, that is, MELD score. The former dimension will also be referred as the static patient type and is indexed by $i = 1, \dots, I$, while the latter is indexed by $j = 1, \dots, J$. Health status of a patient may change over time, which corresponds to the patient changing classes in our model. Thus, our definition of patient classes allows us to model the evolution of the patient’s health status over time. The class structure used in our model is depicted in Figure 1.

Patients of class ij arrive to the system at rate $\lambda_{ij}(t)$ for $t \geq 0$, and the number of class ij patients waiting for transplantation at time t is denoted by $x_{ij}(t)$; there are $x_{ij}(0)$ patients in class ij initially. As mentioned in the opening paragraph of this section, while ESLD patients are

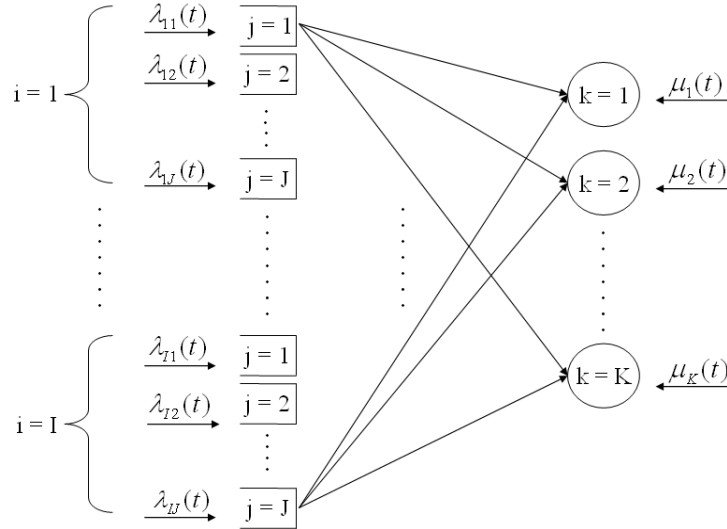


Figure 1: The class structure of the model.

waiting for transplantation their health status may change. To be specific, we let α_j denote the rate at which patients of health status j become patients of health status $j + 1$ for $j = 1, \dots, J - 1$, that is, α_j is the rate at which their health deteriorates. Let β_j denote the rate at which patients of health status j become patients of health status $j - 1$ for $j = 2, \dots, J$, that is, the rate at which their health status improves. Although it may seem counter intuitive, the MELD scores of ESLD patients, particularly the ones with chronic liver diseases such as primary biliary cirrhosis, might improve temporarily over time. We assume that $\alpha_j > \beta_j$ for $j = 2, \dots, J - 1$. (We set $\alpha_J = \beta_1 = 0$ for notational convenience.) The rate at which a patient of health status j dies is denoted by d_j for $j = 1, \dots, J$. We assume that sicker patients (patients with higher MELD scores) are more likely to die, that is, $d_J > \dots > d_1$, which is a reasonable assumption supported by the studies by Malinchoc et al. (2000) and Wiesner et al. (2001).

There are K liver types, and type k livers arrive at the system at rate $\mu_k(t)$ for $t \geq 0$. The type of a liver is defined by various donor attributes that describe the quality of liver such as donor age, donor blood type, etc. The UNOS must decide what fraction of the incoming livers of each type to allocate to patients of various classes waiting for transplantation dynamically over time. Equivalently, for each liver type $k = 1, \dots, K$, the UNOS wants to choose the rate $u_{ijk}(t)$ of organs to be allocated to class ij patients dynamically over time for $t \geq 0$, $i = 1, \dots, I$, and $j = 1, \dots, J$. Patients may reject the organs offered. Let p_{ijk} denote the probability that a class ij patient will accept an organ offer of type k . We define p_{ijk} as a function of static patient characteristics such as

blood type, patient MELD score and liver type since Howard (2002) and Alagoz (2004) report that the probability of organ acceptance depends highly on these factors. In our model, an organ can be offered to multiple patients. To be specific, if the organ is offered to n patients of class ij , then the probability that nobody accepts the organ (that is, the organ is wasted) is given by $(1 - p_{ijk})^n$. Then letting π_{ijk}^n denote the probability that the organ is transplanted when it is offered to n patients of type ij , we have that

$$\pi_{ijk}^n = 1 - (1 - p_{ijk})^n.$$

We denote the system state by $x(t) = (x_{11}(t), \dots, x_{1J}(t), \dots, x_{I1}(t), \dots, x_{IJ}(t))'$ for $t \geq 0$, where $x_{ij}(t)$ represents the number of class ij patients on the waiting list at time t . Similarly, letting

$$u^k(t) = (u_{11k}(t), \dots, u_{1Jk}(t), \dots, u_{I1k}(t), \dots, u_{IJk}(t))'$$

for $t \geq 0$ and $k = 1, \dots, K$, we denote our control by $u = \{u^k(t) : k = 1, \dots, K, t \geq 0\}$. Then a feasible control u must satisfy the following restrictions for $t \geq 0$ and $k = 1, \dots, K$:

$$u^k(t) \geq 0, \tag{1}$$

$$e \cdot u^k(t) \leq \mu_k(t), \tag{2}$$

where e is an IJ -dimensional column vector of ones. Equation (1) imposes the non-negativity constraint on the allocation rates, while equation (2) states that the total rate of livers assigned to each patient type should be less than or equal to the arrival rate of livers.

Given a feasible control u the system state evolves as follows:

$$\dot{x}(t) = \lambda(t) - \sum_{k=1}^K P^k u^k(t) - (d + \alpha - \beta)x(t), \quad t \geq 0, \tag{3}$$

where P^k is an $IJ \times IJ$ dimensional diagonal matrix with entries $\{\pi_{ijk} : i = 1, \dots, I \text{ and } j = 1, \dots, J\}$ for $k = 1, \dots, K$. The arrival rate of the patients is modeled by the vector process $\lambda(t)$ whose ij^{th} entry at time t is $\lambda_{ij}(t)$. The square matrices d, α and β represent the death, deterioration and recovery of the patients' health status. More precisely, d is a diagonal matrix such that ij^{th} diagonal entry is d_{ij} . In matrix β , for all $i = 1, \dots, I$, in row $i1$, only the $i2^{nd}$ entry is nonnegative and is equal to β_2 , in row ij for $j = 2, \dots, J-1$, ij^{th} column is equal to $-\beta_j$ and $(ij+1)^{st}$ column is equal to β_{j+1} and all other entries are zero. Finally, in row iJ , only iJ^{th} column is equal to $-\beta_J$ and the rest are zero. Similarly, in matrix α , for all $i = 1, \dots, I$, in row $i1$, only the $i1^{st}$ entry is nonnegative and is equal to α_1 , in row ij for $j = 2, \dots, J-1$, ij^{th} column is equal to α_j and $(ij-1)^{st}$ column

is equal to $-\alpha_{j-1}$ and all other entries are zero. Finally, in row iJ , only $(iJ - 1)^{st}$ column is equal to $-\alpha_{J-1}$ and the rest are zero. We also require that the number of patients in each class is always non-negative, that is,

$$x(t) \geq 0 \text{ for } t \geq 0. \quad (4)$$

The objective is to maximize the total quality adjusted life years (QALY) of the patients, which clearly requires us to take into account how long a patient who is transplanted a liver will live in the future. To capture this, let h_{ijk} denote the expected QALY of a patient of class ij who is transplanted a liver of type k . Note that h_{ijk} accounts for mortality during the transplant operations as well as morbidity associated with post-transplant complications. The h_{ijk} variables consider QALYs instead of life-years because it is known that liver transplant recipients may experience a lower quality of life of than people with no medical problems due to the use of immunosuppressive drugs that minimize the risk of bodily rejection of the transplanted organ, cf. Trotter et al. (2002).

To capture the reward accrued by the patients while waiting for transplantation, let q_{ij} denote the quality-of-life scores of class ij patients waiting for transplantation. Similar to the h_{ijk} , q_{ij} also depends on patient type. The dependence on MELD score is reasonable because MELD scores provide a good proxy for the quality of life experienced by patients with ESLD. For instance, a patient with a MELD score over 30 will very likely stay in the hospital, or in the intensive care unit and experience a lower quality of life than a patient with MELD score less than 10. Finally, let ϑ_{ij} denote the expected future QALY of a patient of class ij who is still waiting for transplantation at the end of the planning horizon. Using the terminology that is standard in control theory, $x(T) \cdot \vartheta$ denotes the terminal reward associated with the patients who are still in the waiting list at the end of the planning horizon, where $\vartheta = (\vartheta_{11}, \dots, \vartheta_{1J}, \dots, \vartheta_{I1}, \dots, \vartheta_{IJ})'$. Then the problem of the UNOS is to choose an organ allocation policy u so as to

$$\text{maximize } \sum_{k=1}^K \int_0^T h^k \cdot P^k u^k(t) dt + \int_0^T q \cdot x(t) dt + x(T) \cdot \vartheta \text{ subject to (1)-(4),} \quad (P)$$

where $q = (q_{11}, \dots, q_{1J}, \dots, q_{I1}, \dots, q_{IJ})'$ and $h^k = (h_{11k}, \dots, h_{1Jk}, \dots, h_{I1k}, \dots, h_{IJk})'$ for $k = 1, \dots, K$.

An alternative objective is to minimize the total organ wastage, which is equivalent to maximizing the total number of organs transplanted. We formulate this problem as follows: Choose the organ allocation policy u so as to

$$\text{maximize } \sum_{k=1}^K \int_0^T e \cdot P^k u^k(t) dt \text{ subject to (1)-(4).} \quad (PW)$$

One can also consider other objectives such as minimizing the total number of patient deaths while waiting, maximizing the mean graft and patient survival times, or maximizing the total number of successful transplants, etc. The optimal control problems considering other objectives would similarly be constructed and are not presented here for purposes of brevity. In the next section, we will present the dual problem formulations and the coextremality results between the primal and dual formulations as well as the proposed policies motivated by these results.

4 Dual problem formulation and the proposed policies

In this section, we first present the dual problem formulation (D) of the problem of maximizing QALY, and the coextremality results between the two formulations. The dual problem is obtained using the general methods of convex analysis introduced by Rockafellar (1968), Rockafellar (1969), Rockafellar (1970a) and Rockafellar (1970b). Following Rockafellar (1970a), the dual problem of control associated with the problem (P) of maximizing QALY can be stated as follows (see Appendix for its derivation): Choose an IJ dimensional process $\{y(t) : 0 \leq t \leq T\}$ so as to

$$\begin{aligned} & \text{minimize } \int_0^T [y(t)\lambda(t) + f(t, y(t))] dt + x(0) \cdot y(0) \\ & \text{subject to} \\ & y(t) = y(0) + \int_0^t \dot{y}(s) ds, \\ & \dot{y}(t) \leq (d + \alpha - \beta) y(t) - q, \\ & y(T) = \vartheta, \end{aligned} \tag{D}$$

where

$$f(t, y) = \sum_{k=1}^K \sup \left\{ \left(h^k - y \right) \cdot P^k u^k : u^k \geq 0, e \cdot u^k \leq \mu_k(t) \right\} \quad \text{for } y \in \mathbb{R}^{IJ}.$$

In the dual problem formulation (D), y denotes the dual state variables. The value of the state variable y at time T is given by ϑ . The dual state vector $y(t)$ can be interpreted as the shadow price for (or the value assigned to) the patients waiting for transplantation at time t . If the number of patients in class ij increases by 1 at time t , then the total QALY that can be achieved in the system increases by $y_{ij}(t)$, which is the ij^{th} component of $y(t)$. That is, $y_{ij}(t)$ provides a proxy for the total expected QALYs of a class ij patient while he waits. Although $y(t)$ represents the dual system state, we will also view it as the dual control.

The dual problem (D) and the primal problem (P) are closely linked to each other. Above all, the objective function values of (P) and (D) are equal. Moreover, any optimal primal solution and any optimal dual solution satisfy a set of coextremality conditions, which are necessary and sufficient conditions for optimality. The following theorem summarizes the duality results between the two formulations that are relevant for our purposes; its proof is given in Appendix A.

Theorem 1 *The primal problem (P) of maximizing QALY, and the dual problem (D) have the same optimal objective value. Moreover, letting u be a feasible organ allocation policy for (P) with the corresponding state trajectory x , and y be a feasible control for (D), the controls u and y are optimal for (P) and (D), respectively, if and only if they satisfy the coextremality conditions (5) and (6) given below: For i, j and $t \in [0, T]$,*

$$\dot{y}_{ij}(t) = -q_{ij} + [y(t)(d + \alpha - \beta)]_{ij} \quad \text{if } x_{ij}(t) > 0 \quad \text{for } t \in [0, T], \quad (5)$$

$$u^k(t) \in \arg \max_{z \geq 0, e \cdot z \leq \mu_k(t)} \left\{ (h^k - y(t)) \cdot P^k z \right\} \quad \text{for } k = 1, \dots, K. \quad (6)$$

Motivated by Theorem 1, we next propose our policy to maximize the total quality adjusted life years of all patients with ESLD, the ultimate goal of the liver allocation system. The policy is named the marginal benefit of transplant policy for maximizing QALY, because it considers not only the immediate benefits of transplantation but also the future rewards. Hence, it truly captures the marginal benefit of transplantation for each possible allocation decision.

Marginal Benefit of Transplant Policy for Maximizing QALY (MBTP-Q). Given the number of parallel offers n , when a liver of type k arrives, say at time t , the system manager ranks various patient classes ij (for $i = 1, \dots, I$ and $j = 1, \dots, J$) with respect to the effective reward $(h_{ijk} - y_{ij}(t))\pi_{ijk}^n$. Recall that h_{ijk} represents total expected QALYs of a patient in class ij when he is transplanted with a type k liver and $y_{ij}(t)$ represents the total expected QALYs of a class ij patient waiting for transplantation; therefore the difference $(h_{ijk} - y_{ij}(t))$ represents the potential benefit of transplanting a class ij patient with a liver of type k .

The patients in the same class are ordered with respect to their waiting time in that class. More specifically, the patient who has been in a class for the longest time has the highest priority in that class. Given this ordering, the system manager offers the organ to the first n patients in class ij for which $(h_{ijk} - y_{ij}(t))\pi_{ijk}^n$ is highest. In the case that there are fewer than n patients in that class, the system manager offers the organ to the patients in the lower ranked classes as well until the organ is offered to n patients. The organ is then transplanted to the patient with the highest

index, who accepts the organ offer. Intuitively, this policy implies that when a new liver arrives, it will be offered to the patient who would benefit most from receiving that organ.

The dual problem of control associated with the problem (P_W) of minimizing the organ wastage can be stated as follows (see Appendix for its derivation): Choose an IJ dimensional process $\{y(t) : 0 \leq t \leq T\}$ so as to

$$\begin{aligned} & \text{minimize } \int_0^T [y(t)\lambda(t) + g(t, y(t))] dt + x(0) \cdot y(0) \\ & \text{subject to} \\ & y(t) = y(0) + \int_0^t \dot{y}(s) ds, \\ & \dot{y}(t) \leq y(t)(d + \alpha - \beta), \\ & y(T) = 0, \end{aligned} \tag{D_W}$$

where

$$g(t, y) = \sum_{k=1}^K \sup \left\{ (e - y) \cdot P^k u^k : u^k \geq 0, e \cdot u^k \leq \mu_k(t) \right\} \quad \text{for } y \in \mathbb{R}^{IJ}.$$

In the definition of the function $g(t, y)$, the term $\sum_{k=1}^K e \cdot P^k u^k$ denotes the immediate organ usage, whereas $\sum_{k=1}^K y \cdot P^k u^k$ captures the effect of the current transplants on the objective through the evolution of the system. Note that at time T , we have $y(T) = 0$ and it is optimal to allocate the livers so as to maximize the total acceptance rate. However, for $t < T$, the evolution of the system, in particular, the evolution of the disease for all patients in the system, should be taken into account to achieve the optimal allocation of the livers.

The next result summarizes the duality results between (P_W) and (D_W) and its proof is similar to the proof of Theorem 1, and hence, is skipped.

Theorem 2 *The primal problem (P_W) of minimizing organ wastage, and the dual problem (D_W) have the same optimal objective value. Moreover, letting u be a feasible organ allocation for (P_W) with the corresponding state trajectory x , and y be a feasible control for (D) , the controls u and y are optimal for (P_W) and (D_W) , respectively, if and only if they satisfy the coextremality conditions (7) and (8) given below: For i, j and $t \in [0, T]$,*

$$\dot{y}_{ij}(t) = [y(t)(d + \alpha - \beta)]_{ij} \quad \text{if } x_{ij}(t) > 0 \quad \text{for } t \in [0, T], \tag{7}$$

$$u^k(t) \in \arg \max_{z \geq 0, e \cdot z \leq \mu_k(t)} \left\{ (e - y(t)) \cdot P^k z \right\} \quad \text{for } k = 1, \dots, K. \tag{8}$$

Motivated by Theorem 2, we next propose our policy to minimize the organ wastage, which is called the marginal benefit of transplant policy for minimizing organ wastage.

Marginal Benefit of Transplant Policy for Minimizing Organ Wastage (MBTP-W). Given the number of parallel offers n , when a liver of type k arrives, say at time t , the system manager ranks various patient classes ij (for $i = 1, \dots, I$ and $j = 1, \dots, J$) with respect to $(1 - y_{ij}(t))\pi_{ijk}^n$. The patients in the same class are ordered with respect to their waiting time in that class. More specifically, the patient who has been in a class for the longest time has the highest priority in that class. Given this ordering, the system manager offers the organ to the first n patients in class ij for which $(1 - y_{ij}(t))\pi_{ijk}^n$ is highest. In the case that there are fewer than n patients in that class, the system manager offers the organ to the patients in the lower ranked classes as well until the organ is offered to n patients. The organ is then transplanted to the patient with the highest rank, who accepts the liver.

5 Structural Results

In this section, we provide structural results regarding the characterization of the optimal allocation policy under reasonable conditions, and the derivation of structured optimal policies such as static index policies. We first study the effect of the number of parallel organ offers and acceptance probabilities on the objective function value of both problems.

Proposition 1 *As the number of parallel organ offers n increases, the optimal objective function values of both (P) and (P_W) improve.*

Proposition 1 shows that as the number of parallel offers increases, the system performance improves. The following proposition shows the positive impact of motivating patients to accept organ offers.

Proposition 2 *As acceptance probabilities increase, the optimal objective function values of both (P) and (P_W) improve.*

Proposition 2 shows that as the probabilities of acceptance increase, the system performance improves. This also implies that if the patients are not permitted to decline organ offers, then the allocation system will perform better. This result would lead to alternative designs for the organ allocation system. For instance, UNOS may assign extra points (MELD scores) to the patients on

the waiting list with the condition that they will not decline any organ offers. Such an incentive would reduce the number of wasted organs by offering the organs to the patients on the "cannot decline" list. This would lead to the following heuristic policy, called B-bonus policy.

B-bonus heuristic. *Assign B bonus points (MELD scores) to patients who agreed to accept any organ that will be offered by UNOS and apply the current UNOS policy.*

Although artificially increasing the MELD scores seems counter intuitive, UNOS is already making similar adjustments in MELD scores. For instance, according to the current UNOS policy, because patients with hepatocellular carcinoma (HCC) are known to have lower MELD scores than other ESLD patients, a patient with an HCC tumor that is greater than or equal to 2 cm and less than 5 cm or no more than 3 lesions receives additional MELD scores, cf. UNOS (2008b)

For the problem (P_W) of minimizing the organ wastage, the coextremality condition (8) suggests that the optimal policy for minimizing the number of wasted organs is to offer the organs to the patients with highest acceptance rate under some conditions. The next proposition formalizes this idea and its proof is provided in Appendix B.

Proposition 3 *In the problem of minimizing the organ wastage, for each liver type $k = 1, \dots, K$, it is optimal to assign the arriving livers to the patient class $i'j' \in \arg \max_{i,j} \pi_{ij}^n$ provided that $x_{ij}(t) > 0$ for all i, j and $t \in [0, T]$.*

Proposition 3 simply suggests that organs be assigned to the patients who are most likely to accept it and, hence, effectively results in a prioritization of the patient types for a given organ type. Moreover, if the probability of accepting a given organ increases as the patient's health status deteriorates, then Proposition 3 suggest that sickest person on the waiting list should be prioritized to minimize the number of wasted organs.

The next proposition studies the effect of the match between organ and patient types for the problem of maximizing QALY.

Proposition 4 *Suppose that the terminal rewards and the quality-of-life scores of patients waiting for transplantation are the same across static types, that is, if $\vartheta_{ij} = \vartheta_{i'j}$ and $q_{ij} = q_{i'j}$ for all i, i' and $j = 1, \dots, J$. Suppose also that for each liver type k , static patient types are ordered with respect to acceptance probabilities and expected QALYs after transplantation. That is, for each liver type k , there exists a permutation $r_k(\cdot)$ of $\{1, \dots, I\}$ such that*

$$h_{r_k(1)jk} > h_{r_k(2)jk} > \dots > h_{r_k(I)jk} \quad \text{and} \quad p_{r_k(1)jk} > p_{r_k(2)jk} > \dots > p_{r_k(I)jk}, \quad j = 1, \dots, J.$$

Then, livers of type k are only assigned to static patient type $r_k(1) = \arg \max_i \{h_{ijk}\}$ provided that $x_{ij}(t) > 0$ for all i, j and $t \in [0, T]$.

Proposition 4 shows that the problem (P) can be decomposed across organs and static patient types. In other words, there exists a partition K_1, \dots, K_I of liver types $\{1, \dots, K\}$ such that liver types in K_i are only assigned to patients of static type i . Thus, the decision to allocate organs to patients can be achieved in a hierarchical way: For a liver of type k , only consider the static types i such that $k \in K_i$. Then, allocate a type k liver among the static types $\{i : k \in K_i\}$ depending on their health status.

This partition policy resembles the partition policy of Su & Zenios (2005) where kidneys are divided into different domains (each corresponding to a different patient type) and each kidney is allocated to the patient type corresponding to its domain. Similarly, livers are assigned to static patient classes a priori in the setting of Proposition 4. However, when a liver for a particular static patient class arrives, our policy also takes health status of the patients within that static class into account as the health status of the patients change over time and is a key factor in determining the success of the liver transplantation.

Finally, we identify a setting where patients are prioritized based on their health status only. Note that the condition $d_{j+1} - d_j - \beta_j > 0$ for all j of Proposition 5 is readily satisfied when $\beta_j = 0$ or is small for all j since we already assume that $d_{j+1} > d_j$.

Proposition 5 *Without loss of generality assume that $I = 1$ (single static patient class). If $h_j = h_{j'}$, $q_j = q_{j'}$ and $\vartheta_j = \vartheta_{j'} > 0$ for all $j, j' = 1, \dots, J$ and $p_{J,k} \geq p_{J-1,k} \geq \dots \geq p_{1,k}$ for all $k = 1, \dots, K$, then an optimal solution to (P) allocates organs to patients in the order of their health status, giving the priority to the sickest patients provided that $x_j(t) > 0$ for all j and $t \in [0, T]$ and $d_{j+1} - d_j - \beta_j > 0$ for all $j = 1, \dots, J - 1$.*

6 Simulating the National Liver Allocation System

We build a simulation model of the national liver allocation system, and use it to compare the performance of our proposed liver allocation policies to that of the current UNOS policy. In this section, we present a brief description of the simulation model. A more detailed description of the model as well as its validation are provided in Erenay et al. (2008). As noted before, the current organ allocation system consists of 11 regions and 59 OPOs. Our simulation model assumes that

each region consists of a single OPO. There are two types of entities: donated livers and patients who are waiting for a liver transplant. The state of the model is represented by a vector that includes information about the number and the characteristics of the patients on the waiting list and the quality of the available liver. Following Alagoz et al. (2007b)'s liver classification scheme, we use 14 discrete categories of liver types.

The system state is updated whenever a new patient joins the waiting list; or a liver is donated and is offered to the patients on the waiting list; or a patient's health state changes; or when a patient leaves the system due to other reasons. The sequence of these events is illustrated in Figure 2. The simulation model consists of six core modules that manage these four events: patient generator, organ generator, pre-transplant health transition, matching algorithm, patient preferences, and post-transplant survival.

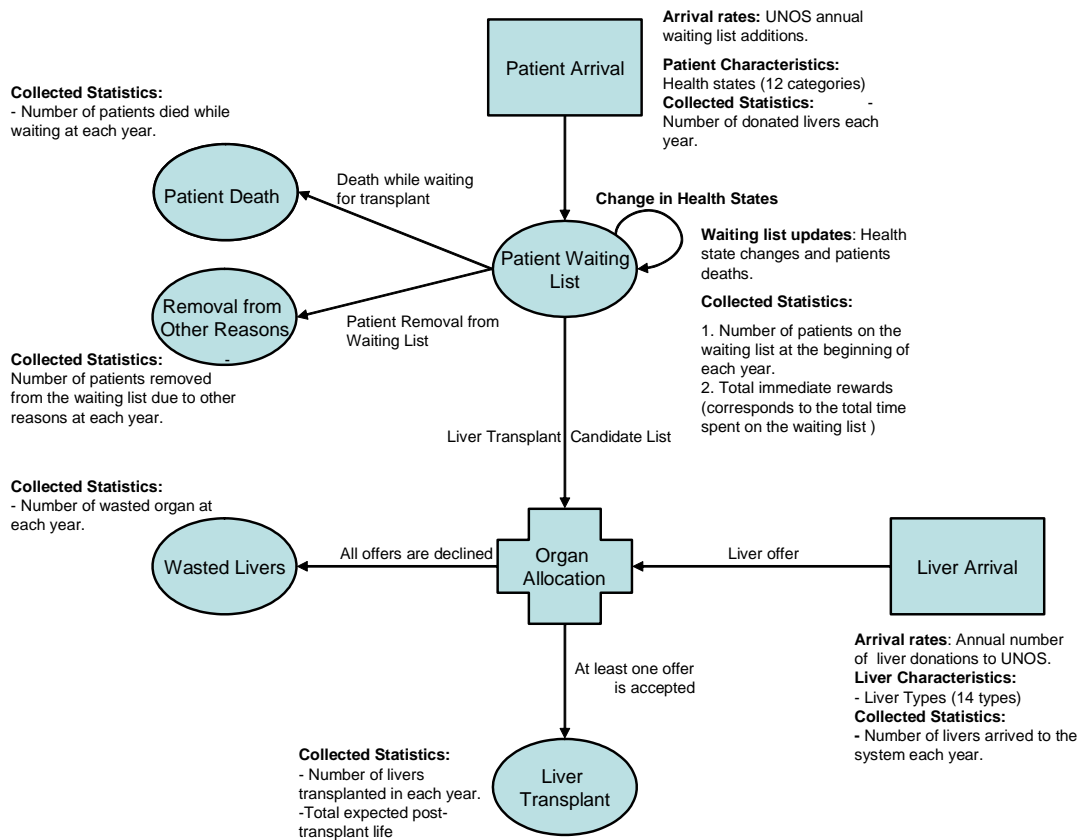


Figure 2: Simulation Flow Chart.

The patient generator creates the interarrival time and assigns the static type as well as the initial health status to the new patients. We use UNOS data to estimate patient arrival rates, cf.

UNOS (2008*b*). Likewise, the organ generator creates the interarrival times of the donated livers and assigns a quality level to each liver. We consider both living and cadaveric liver donors in our simulation model. Data for liver arrival rates are also estimated from UNOS Data, cf. UNOS (2008*b*). The distribution of liver types is estimated from a private UNOS data that was collected between February 27, 2002 and May 31, 2003. The matching algorithm module determines the list of patients to whom the donated liver should be offered sequentially according to the pre-defined allocation policy. The patient preferences module determines how each patient responds to the liver offers and who accepts the offer first. The patient preferences, i.e. organ acceptance probabilities under the current UNOS policy are estimated by Alagoz (2004) using the private UNOS database.

Pre-transplant health transition module determines the timing of each patient's health status change as well as his new health status. These transitions are estimated by the Natural History Model of Alagoz et al. (2005), which uses data from the The Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center (UPMC), one of the largest liver transplant centers in the world. Patients are removed from the waiting list mostly when they undergo a liver transplant or when they die while waiting for a transplant. Patients can be also removed from the waiting list due to other reasons such as being medically unsuitable for transplantation. The post-transplant survival module determines the post-transplant life-expectancy for a patient when he accepts a liver for transplantation. Post-transplant life expectancy for a given patient and liver is estimated by the Cox model provided by Roberts et al. (2004), which also uses UPMC data.

Our model is modular so that we can incorporate possible changes to the natural history, post-transplant survival, patient prioritization, patient preferences and the allocation policy. The inputs of the simulation model are the liver transplant waiting list in 2002, patient arrival rates, liver arrival rates, acceptance probabilities, patient health transition rates, death rates, expected post-transplant QALYs, quality-of-life scores while waiting and the terminal rewards. The output variables include the number of patients on the waiting list at the end of each year, the annual number of new patient arrivals, the number of donated liver arrivals, the number of transplants, the number of wasted livers, the number of patients died while waiting, 1-year post-transplant survival rate and the total QALYs of the patients.

We validate the simulation model by comparing the simulation results to the actual UNOS data statistically. The details of the validation are provided in Erenay et al. (2008). The simulation model is used to evaluate different allocation policies obtained from the fluid model as well as to evaluate the B-Bonus heuristic.

7 Computational Results

We use the simulation model described in the previous section to test our proposed policies. For this purpose, we simulate the national liver allocation system from 2002 until 2015 and compare the performance of our policies to the current UNOS policy across four measures: total expected QALYs for all patients, total number of wasted livers, total number of patients died while waiting, and total number of patients died within one year after transplantation. We use data from UNOS for the period between 2002-2007, whereas a projection of data between 2002 and 2007 is used for simulating the period 2008-2015.

Our proposed liver allocation policies are based on shadow prices for the fluid models that are presented in Section 4. We discretize the fluid models on a daily basis. That is, the decision horizon $[0, T]$ is replaced with $\{0, 1, 2, 3, \dots, T\}$. We then solve the discretized linear program (LP) and extract the dual variables from the solution. We solve an LP for each region and use 10 replications to calculate the system performance. The variation within the replications is very small (i.e. the standard deviation is less than 5% of the mean for most cases), therefore we report only the mean values throughout this section for brevity.

Because the input parameters of the LPs would change over time, we use a rolling-horizon strategy to evaluate our policies and compare our results to the current UNOS policy. Our rolling horizon strategy solves the discretized model periodically for a fixed duration and interacts with the simulation model. For example, if the rolling-horizon solution frequency (rf) is 1 year and rolling-horizon length (rh) is 10 years, the first LP is solved at the beginning of 2002 for years 2002-2011. Then using the dual variables of the solution for 2002, the simulation model is run for 1 year and the system state for 2003 is obtained. The process is repeated until the end of decision horizon. If the simulation is run between 2002 and 2015, then a total of 14 LPs are solved for each replication.

Table 1 shows how our Marginal Benefit of Transplant Policy for Maximizing QALY (MBTP-Q) performs with different rolling horizon settings between 2002 and 2015. As presented in the table, our policies outperform the current UNOS policy in total expected QALYs for all patients (TQALY), total number of wasted livers (NWL), and total number of patients died within one year after transplantation (NPTD) criteria whereas the UNOS policy outperforms our policy in the number of patient deaths while waiting for transplantation (NPDWT) criterion. Our policies result in a 4.09% to 6.2% improvement in total expected QALYs for years 2002-2015. The relatively

MBTP-Q Policy	% Improvement over current UNOS policy			
	TQALY	NWL	NPDWT	NPTD
(rh = 2 yrs), (rf = 1 yr)	5.35	9.19	-23.11	26.53
(rh = 5 yrs), (rf = 1 yr)	4.44	8.98	-15.39	19.16
(rh =10 yrs), (rf = 1 yr)	4.09	8.49	-12.48	16.49
(rh = 2 yrs), (rf = 2 yrs)	6.23	4.92	-48.44	41.07
(rh = 5 yrs), (rf = 2 yrs)	4.73	9.27	-17.65	21.14
(rh = 10 yrs), (rf = 2 yrs)	4.16	8.45	-13.98	17.95

Table 1: Performance of MBTP-Q policy for years 2002-2015 for various rolling horizons (rh) and LP solution frequencies (rf).

worse performance in the number of patient deaths while waiting for transplantation is due to the fact that UNOS policy assigns organs to the sickest patients who are most likely to die in the near future. Therefore, the current policy does not cause many patient deaths while waiting for transplantation. On the other hand, this does not necessarily imply that more ESLD patients will die if our policies are implemented since sickest patients who receive a transplant typically have shorter post-transplant survival times. Indeed, the significant improvement in 1-year post-transplant survival rates under our policy (presented in the last column of the table) suggests that it reduces the number of deaths after transplantation dramatically. The total expected QALYs criterion is the most comprehensive measure for various criteria including the number of deaths. Indeed, it accounts for deaths at various time points, for which our policy offers a significant improvement.

Table 1 also reveals relations between various criteria. In particular, improvements in the TQALY are positively correlated with those in the NPTD and negatively correlated with those in the NPDWT. We also observe that as the rolling-horizon length and the rolling-horizon solution frequency increase the performance of our policies do not change significantly (except for rh=2, rf=2), which may indicate that our models are robust to parameter changes. In the remainder of this paper, we use rh=5 and rf=1 unless stated otherwise.

Note that it is not clear how to estimate the terminal rewards. Ideally, one would simulate the optimal policy to estimate them, which does not seem viable because deriving the optimal policy requires knowledge of the terminal rewards. A naïve approach is to do this estimation using the

	% Improvement Over Current UNOS Policy			
TRM Value	TQALY	NWL	NPDWT	NPTD
TRM=0	5.70	9.93	-36.52	36.16
TRM=0.1	5.50	9.94	-30.81	32.72
TRM=0.2	5.27	10.46	-25.75	28.46
TRM=0.3	4.91	9.91	-19.77	23.96
TRM=0.4	4.78	9.61	-17.80	22.41
TRM=0.5	4.44	8.98	-15.39	19.16
TRM=0.6	3.80	8.00	-11.71	15.61
TRM=0.7	3.56	7.05	-9.76	13.22
TRM=0.8	3.41	6.40	-8.04	12.08
TRM=0.9	3.07	5.85	-7.53	10.94
TRM=1.0	2.80	4.66	-6.64	9.65
TRM=1.5	1.79	0.76	-3.51	5.60

Table 2: Performance of MBTP-Q policy in comparison to UNOS’s policy for years 2002-2015 for various TRM values and $\rho=5$, $r=1$.

current UNOS policy, which clearly yields terminal rewards different from the true ones. At the other extreme, one may ignore terminal rewards altogether. We choose a middle ground and use half of the estimate based on the UNOS policy in Table 1. However, recognizing the potential issues with this approach, we do perform a sensitivity analysis varying the terminal rewards. For this purpose, we multiply the terminal rewards estimated from the simulation using UNOS policy with a constant (Terminal Reward Multiplier (TRM)) and use the new value as the terminal rewards. Table 2 presents the results of our sensitivity analysis, which shows that our policy yields good results across possible parameter values. As the TRM increases, the value assigned to patients remained in the system at the end of the planning horizon increases, our policy results in fewer transplantations and keeps more patients at the end of the planning horizon in the system, and the performance of our policy gets closer to that of the current UNOS policy. As a result, as TRM value increases, the improvements in the TQALY, NWL, and NPTD reduce whereas the improvement in the NPDWT increases. In the remainder of this paper, we use $\text{TRM}=0.5$.

As for the MBTP-W policy, Table 3 shows how it performs for different rolling horizon settings

MBTP-W Policy	% Improvement over current UNOS policy			
	TQALY	NWL	NPDWT	NPTD
(rh = 2 yrs), (rf = 1 yr)	4.35	11.20	-29.58	30.11
(rh = 5 yrs), (rf = 1 yr)	4.32	12.05	-26.94	27.51
(rh = 10 yrs), (rf = 1 yr)	4.24	11.56	-25.53	26.25
(rh = 2 yrs), (rf = 2 yrs)	5.14	9.15	-33.66	32.59
(rh = 5 yrs), (rf = 2 yrs)	4.47	11.19	-29.20	29.65
(rh = 10 yrs), (rf = 2 yrs)	4.38	12.21	-27.81	27.77

Table 3: Performance of MBTP-W policy between 2002 and 2015 for various rolling horizons (rh) and LP solution frequencies (rf).

between 2002 and 2015. It outperforms the current UNOS policy in TQALY, NWL, and NPTD criteria whereas underperforms in NPDWT criterion. The improvement in the total number of wasted livers under our policy range between 9.15% and 12.21%. Table 3 maintains similar trends observed in Table 1.

Next, we test how the total number of parallel liver offers affect the system performance. An analysis of the private UNOS data shows that on average a liver is offered to 23 patients, which is used in our base cases. Table 4 shows how the system performance would change if the number of parallel offers increases. As presented in Table 4 and proven by Proposition 1, as n increases, the system performance also improves in all dimensions except NPTD criterion. The reduction in the post-transplant survival rates appears to be counterintuitive. However, increasing the number of parallel offers may lead patients to accept offers which may not necessarily optimize their expected QALYs. That is, patients may benefit more from declining low-quality organ offers and continuing to wait, which is also noted by Alagoz et al. (2004), Alagoz et al. (2007b), and Alagoz et al. (2007a). This experiment suggests that UNOS would improve the system significantly if they increase their efforts to make more parallel offers such as encouraging quicker response from the transplant centers and/or patients regarding organ acceptance/declination decisions, requesting advance organ acceptance/declination decisions from the patients, informing a larger number of patients when a donated liver becomes available, etc.

Finally, we test the performance of our B-bonus policy. Because the performance of B-bonus depends highly on the number of patients who agree to switch to this policy and the number of

Number of parallel offers (n)	% Improvement			
	TQALY	NWL	NPDWT	NPTD
25	1.01	13.07	2.45	-0.70
30	2.89	35.97	8.07	-1.87
40	4.94	62.27	13.63	-3.25
50	5.97	75.33	15.80	-4.15
100	7.37	92.22	19.70	-5.07

Table 4: The Effect of number of parallel offers on the liver statistics between 2002 and 2015 under the current UNOS policy.

bonus MELD scores assigned to these patients, we vary the number of bonus MELD scores and B-bonus policy compliance rates (the percentage of patients who agree to accept all liver offers in exchange for extra MELD scores). Table 5 shows that B-bonus policy outperforms the current policy in all criteria except in NPTD criterion. In general, as expected, the performance of B-bonus policy improves as the B-bonus policy compliance rates increase. These results suggest that UNOS may consider the use of B-bonus policy to improve the performance of the liver allocation system.

8 Concluding Remarks

This study uses a fluid model and duality theory for optimal control problems to optimize the liver allocation system maximizing society’s welfare, while accounting for disease evolution and patient preferences. Our models provide an alternative prioritization scheme among ESLD patients that uses the shadow prices from the dual optimal control problem associated with our fluid model, which suggests prioritizing patients based on their immediate rewards (i.e. medical urgency of the patients), post-transplant life expectancy when transplanted with an organ, and the probability of accepting the particular organ offer. Our computational experiments using real clinical data show that such an alternative system have the potential of improving the current system.

To repeat, recognizing the need to balance the trade-off between the medical urgency and the impact of current decisions on the future well-being of the patients on the waiting list, we developed a dynamic fluid model of the liver allocation system. Indeed, our main contribution is to capture this trade-off quantitatively. Using a novel duality approach, we solve the fluid model analytically,

	% Improvement over current UNOS policy			
Bonus MELD Scores	TQALY	NWL	NPDWT	NPTD
	5% B-bonus Policy Compliance Rate			
2 MELD Scores	0.67	7.87	1.78	-0.60
5 MELD Scores	0.81	9.61	2.24	-0.46
10 MELD Scores	0.82	11.81	2.58	-0.37
20 MELD Scores	0.95	13.11	1.98	-0.25
	10% B-bonus Policy Compliance Rate			
2 MELD Scores	1.16	15.04	3.21	-0.80
5 MELD Scores	1.44	17.75	3.82	-0.92
10 MELD Scores	1.67	22.64	4.09	-0.99
20 MELD Scores	1.65	25.02	4.16	-0.37
	25% B-bonus Policy Compliance Rate			
2 MELD Scores	3.59	44.06	8.95	-2.60
5 MELD Scores	3.66	47.62	8.68	-2.33
10 MELD Scores	3.80	53.14	10.94	-1.99
20 MELD Scores	3.66	55.11	8.03	-0.64
	50% B-bonus Policy Compliance Rate			
2 MELD Scores	6.71	86.06	18.00	-5.35
5 MELD Scores	6.71	87.10	17.78	-4.87
10 MELD Scores	6.65	84.95	15.73	-3.04
20 MELD Scores	6.17	79.26	8.57	1.77

Table 5: Performance of B-Incentive policy compared to UNOS’s policy for years 2002-2015 for various bonus MELD score amounts and B-Incentive policy compliance rates.

hence, optimally balance the trade-off between the two effects. Moreover, we verify the effectiveness of the proposed policy using real clinical data in our simulation study.

Our proposed policy can be interpreted as follows: when an organ is donated, rank patients based on their marginal benefit when transplanted with that organ, i.e. the difference between their post-transplant life expectancy and pre-transplant life-expectancy, and offer that organ to these patients sequentially. We prove the optimality of this alternative policy using analytical models under simplifying assumptions. We also perform computational tests using real clinical data which show that our model's potential savings could be significant. For instance, our policies generate approximately 5% more QALYs per patient on average, and 9% fewer number of wasted livers than the current UNOS policy.

We also develop and test another heuristic policy called B-Bonus heuristic, in which patients are given the choice of giving up their autonomy in return of extra priority in access to liver offers. That is, patients either follow the current policy or are assigned extra MELD scores with the condition that they will accept every organ. We test various scenarios by changing the fraction of patients who would be willing to accept all offers, which generated a range of 0.67% to 6.71% more QALYs per patient on average and reduced the number of wasted organs in a range of 1.78% and 18% on average.

There are several policy implications of our models. The current UNOS policy uses medical urgency as the primary criterion for allocating organs to ESLD patients whereas we suggest a prioritization scheme depending on both the medical urgency and the potential future savings of transplanting with a particular organ. UNOS uses only blood type compatibility as a second factor in determining the priority, which can be an important factor indicating potential savings of transplanting with a particular organ, however blood type compatibility is only one of the many clinical factors that affect the outcome of the transplantation, cf. Roberts et al. (2004). UNOS uses MELD scores for determining the medical urgency of patients, which might still be used for determining the medical urgency of patients in a new liver allocation system or might be extended with more dynamic clinical characteristics that indicate the status of the liver disease such as encephalopathy, blood albumine level, history of variceal bleeding, spontaneous bacterial peritonitis, ascites Roberts et al. (2004). There exist many models in the literature that estimate the expected transplant outcomes for given patient and organ characteristics such as Roberts et al. (2004), Ghobrial et al. (2002), Olthoff et al. (2005), Jain et al. (2000). We use the model by Roberts et al. (2004) in this study. However, any post-transplant survival model can be used to implement

our proposed policy.

An important issue in any public policy design problem such as organ transplant problem is equity among various patient groups. That is, the organ allocation system should not put any part of the society in a disadvantageous position for having access to available organs. Some of the optimization studies in the organ transplant area including Su & Zenios (2006) and Zenios et al. (2000) explicitly address the equity issue. In this paper, we did not explicitly consider the equity issue and one might argue that our proposed policy is disfavoring some classes of patients over others which might violate the equity among various patient types. For instance, the post-transplant survival model of Roberts et al. (2004) suggest that the post-transplant life-expectancy of a young patient is significantly higher than that of an identical older patient when transplanted with the same organ, which might reduce the access of older patients to organs. Note that our analytical model is able to explicitly model the equity issue by simply adding a new term to the objective function or an additional constraint. On the other hand, instead of explicitly modeling the equity issue in this paper, we suggest the following to implement our proposed policy: Calculate the post-transplant and pre-transplant life expectancy for each patient class by removing factors that might violate the equity among patients such as age, gender, and race while keeping clinical factors that do not cause an inequity issue such as blood type compatibility with the donor, cytomegalovirus (CMVGR), encephalopathy and/or disease type. The determination of which factors should be included in such an alternative prioritization scheme requires a comprehensive study by a multi-disciplinary team consisting of expertise on many areas including but not limited to public policy, ethical studies, and transplantation. Such a study is beyond the scope of this research.

Our policy considers the acceptance probability of ESLD patients in allocating a liver, however, implementing a policy based on the probability of acceptance by individual patients may not be practical due to potential ethical issues. On the other hand, transplant community has been long debating whether to penalize transplant centers who decline organs more frequently than others, cf. Howard (2002). Despite the controversy, the European transplant system implemented a variant of this penalizing policy where the number of offers per organ declined from 3.5 to 2.3 within 18 months, cf. Jost et al. (1993). To the best of our knowledge, designing a mechanism for implementing a policy that penalizes transplant centers for declining more organ offers is an open research question. Our proposed policy provides an analytical model for considering organ refusal rates in allocating organs to patients and hence may help UNOS to implement such a policy.

Admittedly, our study has several limitations. Our study does not address all of the policy

questions regarding liver allocation system such as geography. That is, what should be the role of location in prioritizing patients? Moreover, we do not consider the effects of changing the allocation policy on patient preferences in accepting/declining liver offers. Such an analysis requires a dynamic mechanism design approach, which is left for future research.

Our study may not only improve the current liver allocation system, but also provides insights for designing a better allocation system for other organs used for transplantation such as hearts, lungs, kidneys, etc. Although there are more kidney transplantations than liver transplantations, livers are more suitable for the organ allocation study due to the additional controversy. When Congress instructed the Institute of Medicine (IOM) to assess the impacts of the changes in the organ allocation procedures, it focused on liver transplantation because "much of the current debate has centered on the procurement and allocation of livers" IOM (1999).

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A Proofs of the Results in Section 4

Derivation of the dual problem (D). We will follow the road map provided by Rockafellar (1970a) to derive the dual problem of control associated with (P). In particular, we first append the penalty expressions corresponding to the organ availability restrictions on allocations in the objective function by defining the convex, extended real valued integrand L and the convex functional l . We also formulate the problem towards minimization. Next, we compute the conjugate convex functions associated with L and l so as to define the dual integrand M and the dual functional m . The dual problem of control is defined using M and m .

To facilitate the analysis to follow, define the indicator function $\chi_F(\cdot)$ for a given set F by

$$\chi_F(x) = \begin{cases} 0 & \text{if } x \in F, \\ \infty & \text{otherwise.} \end{cases}$$

We express (P) in terms of the convex integrand L and the convex lower semi-continuous functional l which are defined as follows. Define L on $[0, T] \times \mathbb{R}^{IJ} \times \mathbb{R}^{IJ}$ as follows:

$$L(t, x, \dot{x}) = - \sum_{k=1}^K h^k \cdot P^k u^k - q \cdot x + \chi_{\mathbb{R}_+^{IJ}}(x) + \sum_{k=1}^K \chi_{\mathbb{R}_+^{IJ}}(u^k) + \sum_{k=1}^K \chi_{\mathbb{R}_-}(e \cdot u^k - \mu_k(t)) \quad (9)$$

if $\dot{x} = \lambda(t) - (d + \alpha - \beta)x - \sum_{k=1}^K P^k u^k$ and $L(t, x, \dot{x}) = \infty$ otherwise. The integrand L eliminates the hard constraints of (P) by appending them to the objective function as penalty expressions. In this sense, the penalty expression $\sum_{k=1}^K \chi_{\mathbb{R}_-}(e \cdot u^k - \mu_k(t))$ is the organ restriction on allocations and replaces the constraint (2). In the same vein, the penalty expressions $\sum_{k=1}^K \chi_{\mathbb{R}_+^{IJ}}(u^k)$ and $\chi_{\mathbb{R}_+^{IJ}}(x)$ replace the constraints (1) and (4), respectively and ensure the nonnegativity of the control u and the state x . Notice also that we have reformulated the problem towards minimization and $-\sum_{k=1}^K h^k \cdot P^k u^k$ is the negative of the rate at which QALY of the patients transplanted with livers changes. The system dynamics equation (3) is incorporated in L by the fact that we require \dot{x} to be equal to $\lambda(t) - (d + \alpha - \beta)x - \sum_{k=1}^K P^k u^k$.

Next step is to define the functional l on $\mathbb{R}^{IJ} \times \mathbb{R}^{IJ}$ with values on $\mathbb{R} \cup \{\infty\}$ so as to initiate the problem with $x_{ij}(0)$ patients in class ij and account for the fact that ϑ_{ij} denote the expected QALY of a patient of type ij who is still waiting for transplantation at time T . The functional l is defined as

$$l(x_0, x_T) = l_0(x_0) + l_T(x_T), \quad (10)$$

where the convex, lower semi-continuous functionals l_0 and l_T are given by

$$l_0(x_0) = \chi_{\{x(0)\}}(x_0), \quad l_T(x_T) = -\vartheta \cdot x_T. \quad (11)$$

The functional l_0 dictates that initially there are $x_{ij}(0)$ patients in class ij and l_T makes sure that the total QALY of the patients still not transplanted with a liver is given by $\vartheta \cdot x(T)$. Then, the primal problem (P) can equivalently be stated as a problem of minimizing

$$\int_0^T L(t, x(t), \dot{x}(t)) dt + l(x(0), x(T)).$$

As our second step, we compute the conjugates to the functions L and l . Let L^* denote the conjugate to L . To be specific,

$$L^*(t, s, p) = \sup_{z \in \mathbb{R}^{IJ}, y \in \mathbb{R}^{IJ}} \{z \cdot s + y \cdot p - L(t, z, y)\} \quad \text{for } s, p \in \mathbb{R}^{IJ}. \quad (12)$$

We can express L^* more explicitly as follows. Note that $L(t, z, y) < \infty$ only if $z \geq 0$ and there exists some $u^k \in \mathbb{R}_+^{IJ}$ such that $y = \lambda(t) - (d + \alpha - \beta)z - \sum_{k=1}^K P^k u^k$ and $e \cdot u^k \leq \mu_k(t)$ and $u^k \geq 0$

for all $k = 1, \dots, K$. Then, for $s, p \in \mathbb{R}^{IJ}$, we can write L^* as

$$\begin{aligned}
& L^*(t, s, p) \\
&= \sup_{z \in \mathbb{R}_+^{IJ}, e \cdot u^k \leq \mu_k(t), u^k \geq 0} \left\{ z \cdot s + p \cdot \left(\lambda(t) - (d + \alpha - \beta)z - \sum_{k=1}^K P^k u^k \right) + \sum_{k=1}^K h^k \cdot P^k u^k + q \cdot z \right\}, \\
&= \sup_{z \in \mathbb{R}_+^{IJ}} \{z \cdot (s + q - p(d + \alpha - \beta))\} + p \cdot \lambda(t) + \sum_{k=1}^K \sup_{e \cdot u^k \leq \mu_k(t), u^k \geq 0} \{h^k \cdot P^k u^k - p \cdot P^k u^k\}, \\
&= \chi_{\mathbb{R}_-^{IJ}} \{s + q - p(d + \alpha - \beta)\} + p \cdot \lambda(t) + \sum_{k=1}^K \sup_{e \cdot u^k \leq \mu_k(t), u^k \geq 0} \left\{ (h^k - p) \cdot P^k u^k \right\},
\end{aligned}$$

The first line is obtained by replacing y with $\lambda(t) - (d + \alpha - \beta)z - \sum_{k=1}^K P^k u^k$ for $e \cdot u^k \leq \mu_k(t)$ and $u^k \geq 0$ for all $k = 1, \dots, K$ and noting that $L(t, z, y) = -\sum_{k=1}^K h^k \cdot P^k u^k - q \cdot z$. The second line follows from the observation that we can take the supremum in the first line separately for z and u^k for each k . To get the third line, note that we have

$$\sup_{z \in \mathbb{R}_+^{IJ}} \{z \cdot (s + q - p(d + \alpha - \beta))\} = \chi_{\mathbb{R}_-^{IJ}} \{s + q - p(d + \alpha - \beta)\},$$

since $\sup_{z \in \mathbb{R}_+^{IJ}} \{z \cdot (s + q - p(d + \alpha - \beta))\}$ takes the value ∞ if $(s + q - p(d + \alpha - \beta))_{ij} > 0$ for $i = 1, \dots, I$ and $j = 1, \dots, J$.

Using the conjugate L^* of the primal integrand L , we calculate the dual integrand M . For $t \in [0, T]$ and $s, p \in \mathbb{R}^{IJ}$, the dual integrand M is given by

$$M(t, p, s) = L^*(t, s, p).$$

That is, for $t \in [0, T]$ we have

$$\begin{aligned}
M(t, y(t), \dot{y}(t)) &= L^*(t, \dot{y}(t), y(t)), \\
&= \chi_{\mathbb{R}_-^{IJ}} \{\dot{y}(t) + q - y(t)(d + \alpha - \beta)\} + y(t) \cdot \lambda(t) \\
&\quad + \sum_{k=1}^K \sup_{e \cdot u^k \leq \mu_k(t), u^k \geq 0} \left\{ (h^k - y(t)) \cdot P^k u^k \right\}, \\
&= \chi_{\mathbb{R}_-^{IJ}} \{\dot{y}(t) + q - y(t)(d + \alpha - \beta)\} + y(t) \cdot \lambda(t) + f(t, y(t)),
\end{aligned}$$

where the expression $\chi_{\mathbb{R}_-^{IJ}} \{\dot{y}(t) + q - y(t)(d + \alpha - \beta)\}$ in the third line forces $\dot{y}(t) \leq y(t)(d + \alpha - \beta) - q$ for $t \in [0, T]$.

What remains is to derive the terminal conditions associated with the dual problem. To that end, define the functional m on $\mathbb{R}^{IJ} \times \mathbb{R}^{IJ}$ as follows:

$$m(y_0, y_T) = l_0^*(y_0) + l_T^*(-y_T),$$

where l_0^* and l_T^* are the conjugates of l_0 and l_T . We calculate l_0^* as follows:

$$l_0^*(y) = \sup_x \{y \cdot x - l_0(x)\} = \sup_{x \in \{x(0)\}} \{y \cdot x\} = x(0) \cdot y.$$

Similarly,

$$l_T^*(y) = \sup_x \{y \cdot x + \vartheta \cdot x\} = \sup_x \{(y + \vartheta) \cdot x\} = \chi_{\{0\}}(y + \vartheta).$$

From Rockafellar (1970a), the functional m for the dual problem is given by

$$\begin{aligned} m(y_0, y_T) &= l_0^*(y_0) + l_T^*(-y_T), \\ &= x(0) \cdot y_0 + \chi_{\{0\}}(\vartheta - y_T), \\ &= x(0) \cdot y_0 + \chi_{\{\vartheta\}}(y_T), \end{aligned} \tag{13}$$

where the expression $\chi_{\{\vartheta\}}(y_T)$ imposes that $y(T) = \vartheta$.

The dual problem of control is then to minimize

$$\int_0^T M(t, y(t), \dot{y}(t)) dt + m(y_0, y_T),$$

which is equivalent to minimizing

$$\int_0^T [y(t)\lambda(t) + f(t, y(t))] dt + x(0) \cdot y(0)$$

subject to

$$y(t) = y(0) + \int_0^t \dot{y}(s) ds, \tag{D}$$

$$\dot{y}(t) \leq y(t)(d + \alpha - \beta) - q,$$

$$y(T) = \vartheta.$$

Since the primal problem (P) is trivially feasible (simply let $u^k(t) = 0$ for $k = 1, \dots, K$ and $t \in [0, T]$) and bounded, the objective function values of (P) and (D) are equal to each other, cf.

Theorem 4 of Rockafellar (1970a). ■

Proof of Theorem 1. The primal problem (P) and its dual (D) have the same optimal objective value by Theorem 4 of Rockafellar (1970a). Moreover, by Theorem 5 of Rockafellar (1970a), letting u be a feasible organ allocation for (P) with the corresponding state trajectory x , and letting y be a feasible control for (D), the controls u and y are optimal for (P) and (D),

respectively, if and only if they satisfy the following coextremality conditions:

$$(y(0), -y(T)) \in \partial l(x(0), x(T)) \text{ and } (\dot{y}(t), y(t)) \in \partial L(t, x(t), \dot{x}(t)) \text{ for almost every } t \in (0, T), \quad (14)$$

where ∂L and ∂l denote the subgradients of the convex integrand L and the the functional l , defined as in (9) and (10).

To be more specific about the coextremality conditions, we derive the subgradients of L , l_0 and l_T , where L is a convex integrand and l_0 and l_T are convex functionals as in the derivation of the dual problem (D). The theory of subgradients of convex functions on \mathbb{R}^n is presented at length in Section 9 of Rockafellar & Wets (1997). This theory includes formulas to calculate subgradients in various situations.

First, we calculate the subgradient of L from its epigraphical normals. To that end, we use Theorem 8.9 of Rockafellar & Wets (1997) which proves that for $h : \mathbb{R}^n \rightarrow [-\infty, +\infty]$ and any point \bar{x} at which h is finite, one has

$$\partial h(\bar{x}) = \{v : (v, -1) \in N_{\text{epi } h}(\bar{x}, h(\bar{x}))\},$$

where, $\text{epi } h$ denotes the epigraph of h defined as

$$\text{epi } h := \{(x, \gamma) \in \mathbb{R}^n \times \mathbb{R} : \gamma \geq h(x)\},$$

and $N_{\text{epi } h}(\bar{x}, h(\bar{x}))$ is the set of vectors normal to the set $\text{epi } h$ at $(\bar{x}, h(\bar{x}))$ in the general sense as in Definition 6.3 of Rockafellar & Wets (1997).

For $t \in [0, T]$, the epigraph of the integrand L is defined as follows: $\text{epi } L(t)$ consists of points $(x, \dot{x}, \gamma) \in \mathbb{R}^{2IJ+1}$ such that

$$\dot{x} = \lambda(t) - (d + \alpha - \beta)x - \sum_{k=1}^K P^k u^k, \quad x \geq 0, \quad \gamma \geq - \sum_{k=1}^K h^k \cdot P^k u^k - q \cdot x \quad \text{and} \quad e \cdot u^k \leq \mu_k(t), \quad u^k \geq 0 \quad \forall k,$$

since the points $(x, \dot{x}) \in \mathbb{R}^{2IJ}$ where $L(t, x, \dot{x}) = \infty$ are such that the vertical line $(x, \dot{x}) \times \mathbb{R}$ misses $\text{epi } L(t)$. Then, we can write

$$\partial L(t, \bar{x}, \bar{\dot{x}}) = \left\{ (v^1, v^2) \in \mathbb{R}^{2IJ} : (v^1, v^2, -1) \in N_{\text{epi } L(t)} \left(\bar{x}, \bar{\dot{x}}, L \left(t, \bar{x}, \bar{\dot{x}} \right) \right) \right\}. \quad (15)$$

First, note that for $t \in [0, T]$, $\text{epi } L(t)$ is a convex set and the point $(\bar{x}, \bar{\dot{x}}, L(t, \bar{x}, \bar{\dot{x}}))$ is an element of $\text{epi } L(t)$ for $(\bar{x}, \bar{\dot{x}}) \in \mathbb{R}^{2IJ}$. Let \mathbf{v} denote an arbitrary element of \mathbb{R}^{2IJ+1} , where the first IJ components of \mathbf{v} is denoted as v^1 , the subsequent IJ components by v^2 and the last component by

v^γ . That is, $\mathbf{v} = [v^1, v^2, v^\gamma]'$, where $v^1, v^2 \in \mathbb{R}^{IJ}$ and $v^\gamma \in \mathbb{R}$. Then, Theorem 6.9 of Rockafellar & Wets (1997), gives

$$\begin{aligned} & N_{\text{epi } L(t)} \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right) \\ &= \left\{ \mathbf{v} \in \mathbb{R}^{2IJ+1} : \left[\left(x, \dot{x}, \alpha \right) - \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right) \right] \cdot \mathbf{v} \leq 0, \forall (x, \dot{x}, \gamma) \in \text{epi } L(t) \right\}. \end{aligned} \quad (16)$$

We next establish the following properties of $N_{\text{epi } L(t)} \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right)$ for $t \in [0, T]$, which will assist us in finding the subgradients of L .

Property 1 For $t \in [0, T]$, if $\mathbf{v} = (v^1, v^2, v^\gamma)' \in N_{\text{epi } L(t)} \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right)$, then $v^1 \leq v^2 (d + \alpha - \beta) + v^\gamma q$. Moreover, $v_{ij}^1 = v^\gamma q_{ij} + [v^2 (d + \alpha - \beta)]_{ij}$ when $\bar{x}_{ij} > 0$.

To verify Property 1, we first show that any $\mathbf{v} = (v^1, v^2, v^\gamma)'$ such that $v_{ij}^1 > v^\gamma q_{ij} + [v^2 (d + \alpha - \beta)]_{ij}$ for some ij cannot be in $N_{\text{epi } L(t)} \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right)$. Suppose not. Then, we could find an element $\left(\tilde{x}, \tilde{\dot{x}}, \tilde{\gamma} \right)$ of $\text{epi } L(t)$ such that it is equal to $\left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) - q_{ij} (\tilde{x}_{ij} - \bar{x}_{ij}) \right)$ except the difference that $\tilde{x}_{ij} > \bar{x}_{ij}$ and $\tilde{\dot{x}} = \lambda(t) - (d + \alpha - \beta) \tilde{x} - \sum_{k=1}^K P^k u^k$. However, in that case, we obtain

$$\begin{aligned} & \left[\left(\tilde{x}, \tilde{\dot{x}}, \tilde{\gamma} \right) - \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right) \right] \cdot \mathbf{v} = v_{ij}^1 (\tilde{x}_{ij} - \bar{x}_{ij}) + v^2 \cdot (\tilde{\dot{x}} - \bar{\dot{x}}) - v^\gamma q_{ij} (\tilde{x}_{ij} - \bar{x}_{ij}), \\ &= (\tilde{x}_{ij} - \bar{x}_{ij}) (v_{ij}^1 - v^\gamma q_{ij}) + v^2 (d + \alpha - \beta) (\tilde{x} - \bar{x}), \\ &= \left(v_{ij}^1 - v^\gamma q_{ij} - [v^2 (d + \alpha - \beta)]_{ij} \right) (\tilde{x}_{ij} - \bar{x}_{ij}), \\ &> 0, \end{aligned}$$

contradicting the fact that $(v^1, v^2, v^\gamma) \in N_{\text{epi } L(t)}(\bar{x}, \bar{x}, L(t, \bar{x}, \bar{x}))$, cf. (16). Similarly, we can show that if $\bar{x}_{ij} > 0$, then any $\mathbf{v} = (v^1, v^2, v^\gamma)'$ such that $v_{ij}^1 \neq v^\gamma q_{ij} + [v^2 (d + \alpha - \beta)]_{ij}$ for some ij cannot be in $N_{\text{epi } L(t)}(\bar{x}, \bar{x}, L(t, \bar{x}, \bar{x}))$. Coupled with (15) and (14), Property 1 proves the coextremality conditions in (5), that is, for $t \in [0, T]$, $\dot{y}(t) \leq -q + y(t) (d + \alpha - \beta)$ and whenever $x_{ij}(t) > 0$, it must be that $\dot{y}_{ij}(t) = -q_{ij} + [y(t) (d + \alpha - \beta)]_{ij}$.

Property 2 For $t \in [0, T]$ and $k = 1, \dots, K$, if $\bar{x} = \lambda(t) - (d + \alpha - \beta) \bar{x} - \sum_{k=1}^K P^k \bar{u}^k$ for \bar{u}^k such that $\bar{u}^k \geq 0$, $e \cdot \bar{u}^k \leq \mu_k(t)$ and $\mathbf{v} = (v^1, v^2, v^\gamma) \in N_{\text{epi } L} \left(\bar{x}, \bar{x}, L \left(t, \bar{x}, \bar{x} \right) \right)$, then, $\bar{u}^k \in \arg \max_{z \geq 0, e \cdot z \leq \mu_k(t)} \{ [h^k - v^2] \cdot P^k z \}$.

To establish Property 2, first recall that for any $(x, \dot{x}, \gamma) \in \text{epi } L(t)$, there exists some $u^k \in \mathbb{R}^{I^J}$ for $k = 1, \dots, L$ such that

$$\dot{x} = \lambda(t) - (d + \alpha - \beta)x - \sum_{k=1}^K P^k u^k, u^k \geq 0, e \cdot u^k \leq \mu_k(t) \text{ and } \gamma \geq - \sum_{k=1}^K h^k \cdot P^k u^k.$$

For an arbitrary $k' \in \{1, \dots, K\}$, consider now an element

$$\left(\bar{x}, \dot{\bar{x}}, - \sum_{k \neq k'}^K h^k \cdot P^k \bar{u}^k - h^{k'} \cdot P^{k'} u^{k'} \right) \in \text{epi } L(t),$$

where $\dot{\bar{x}} = \lambda(t) - (d + \alpha - \beta)\bar{x} - \sum_{k \neq k'}^K P^k \bar{u}^k - P^{k'} u^{k'}$. Then, the following holds for $\mathbf{v} = (v^1, v^2, v^\gamma) \in N_{\text{epi } L} \left(\bar{x}, \dot{\bar{x}}, L \left(t, \bar{x}, \dot{\bar{x}} \right) \right)$:

$$\begin{aligned} & \left[\left(\bar{x}, \dot{\bar{x}}, - \sum_{k \neq k'}^K h^k \cdot P^k \bar{u}^k - h^{k'} \cdot P^{k'} u^{k'} \right) - \left(\bar{x}, \dot{\bar{x}}, L \left(t, \bar{x}, \dot{\bar{x}} \right) \right) \right] \cdot \mathbf{v} \\ &= v^1 \cdot (\bar{x} - \bar{x}) + v^2 \cdot (\dot{\bar{x}} - \dot{\bar{x}}) + v^\gamma \left(-h^{k'} \cdot P^{k'} u^{k'} + h^{k'} \cdot P^{k'} \bar{u}^{k'} \right), \\ &= v^2 \cdot (-P^{k'} u^{k'} + P^{k'} \bar{u}^{k'}) + v^\gamma h^{k'} \cdot P^{k'} (\bar{u}^{k'} - u^{k'}), \\ &= (v^2 + v^\gamma h^{k'}) \cdot P^{k'} (\bar{u}^{k'} - u^{k'}), \end{aligned}$$

Then, we have $(v^2 + v^\gamma h^{k'}) \cdot P^{k'} (\bar{u}^{k'} - u^{k'}) \leq 0$, only if

$$(-v^2 - v^\gamma h^{k'}) \cdot P^{k'} u^{k'} \geq (-v^2 - v^\gamma h^{k'}) \cdot P^{k'} \bar{u}^{k'}.$$

>From (16), since $\left(\bar{x}, \dot{\bar{x}}, - \sum_{k \neq k'}^K h^k \cdot P^k \bar{u}^k - h^{k'} \cdot P^{k'} u^{k'} \right)$ is an element of $\text{epi } L(t)$, this proves Property 2.

Recall that the subgradient of L is related to the normal cone of its epigraph as follows:

$$\partial L(t, \bar{x}, \dot{\bar{x}}) = \left\{ (v^1, v^2) : (v^1, v^2, -1) \in N_{\text{epi } L} \left(\bar{x}, \dot{\bar{x}}, L \left(t, \bar{x}, \dot{\bar{x}} \right) \right) \right\}.$$

The coextremality conditions (14) state that for all $t \in [0, T]$, $(\dot{y}(t), y(t)) \in \partial L(t, x(t), \dot{x}(t))$. That is, for $t \in [0, T]$,

$$(\dot{y}(t), y(t), -1) \in N_{\text{epi } L}(x(t), \dot{x}(t), L(t, x(t), \dot{x}(t))).$$

This implies that $u^k(t) \in \arg \max_{z \geq 0, e \cdot z \leq \mu_k(t)} \{ [h^k - y(t)] \cdot P^k z \}$, which establishes the coextremality conditions stated in (6). This concludes the proof of Theorem 1. ■

B Proofs of the Results in Section 5

Proof of Proposition 1. We will prove the result for (P) and the argument for proving the result for (P_W) is similar. Let u^n denote an optimal organ allocation policy for (P) with n patients being offered a harvested liver simultaneously. For $n' > n$, since $\pi_{ijk}^{n'} > \pi_{ijk}^n$, using u^n , we construct \bar{u}^n as follows:

$$\bar{u}_{ijk}^n(t) = u_{ijk}^n(t) \frac{\pi_{ijk}^n}{\pi_{ijk}^{n'}} < u_{ijk}^n(t) \text{ for } i, j, k \text{ and } t \in [0, T].$$

Then, \bar{u}^n is a feasible organ allocation policy for the problem (P) with n' patients being offered a liver simultaneously and the objective function value of \bar{u}^n for the problem with n' simultaneous offers is the same as the objective function value of u^n for the problem with n simultaneous offers. Since the objective function value of \bar{u}^n for the problem with n' offers is less than or equal to the optimal objective function value, the objective function value of (P) improves. ■

Proof of Proposition 2. We will prove the result for (P) and the proof for (P_W) is similar. The proof is along the same lines as the proof of Proposition 1. Let u denote an optimal organ allocation policy for (P). Suppose for some patient type ij the probability of accepting a liver of type k increases. That is, letting \tilde{P}^k denote the new acceptance probability matrix for liver k , we have $\tilde{\pi}_{i'j'k}^n = \pi_{i'j'k}^n$ for all $i' \neq i, j' \neq j$ and $\tilde{\pi}_{ijk}^n > \pi_{ijk}^n$. Let (\tilde{P}) denote the new problem of maximizing QALY using the acceptance probability matrix \tilde{P}^k for liver type k . Then, given u , we can construct a feasible organ allocation \tilde{u} for the new problem (\tilde{P}) as follows: Let $\tilde{u}_{i'j'k'}(t) = u_{i'j'k'}(t)$ for all $i' \neq i, j' \neq j, k' \neq k$ and $\tilde{u}_{ijk}(t) = u_{ijk}(t) \left(\frac{\pi_{ijk}^n}{\tilde{\pi}_{ijk}^n} \right)$ for $t \in [0, T]$. Since the optimal objective function value of the new problem (\tilde{P}) is greater than or equal to the objective function value of \tilde{u} for (\tilde{P}) , the objective function value of (P) improves. ■

Proof of Proposition 3. Note that for $k = 1, \dots, K$, the primal control u^k such that $u^k(t) \in \arg \max_{z \geq 0, e \cdot z \leq \mu_k(t)} \{e \cdot P^k z\}$ and $x_{ij}(t) > 0$ for $i = 1, \dots, I$ and $j = 1, \dots, J$ and $t \in [0, T]$ and the dual control $y = 0$ satisfy the coextremality conditions of Proposition 3. Hence, u and y constitute an optimal primal-dual solution pair. ■

Proof of Proposition 4. Since the terminal rewards and the quality-of-life scores of patients waiting for transplantation are the same across static types and $x_{ij}(t) > 0$ for all i, j and $t \in [0, T]$, we have from the coextremality condition (5), cf. Theorem 1, that $y_{ij}(t) = y_{i'j}(t)$ for all i, i', j and $t \in [0, T]$. That is, for all feasible solutions y to (D), for any given health status j , the dual variables $y_{ij}(t)$ do not vary with the static patient type i for all $t \in [0, T]$. Then, since there exists

a permutation $r_k(\cdot)$ of $\{1, \dots, I\}$ such that

$$h_{r_k(1)jk} > h_{r_k(2)jk} > \dots > h_{r_k(I)jk} \quad \text{and} \quad p_{r_k(1)jk} > p_{r_k(2)jk} > \dots > p_{r_k(I)jk}, \quad j = 1, \dots, J,$$

we conclude that

$$h_{r_k(1)jk} > h_{r_k(2)jk} > \dots > h_{r_k(I)jk} \quad \text{and} \quad \pi_{r_k(1)jk}^n > \pi_{r_k(2)jk}^n > \dots > \pi_{r_k(I)jk}^n, \quad j = 1, \dots, J.$$

Then the result follows from the coextremality condition (6), cf. Theorem 1. ■

Proof of Proposition 5. Consider the dual problem formulation (D). Since $\vartheta_j = \vartheta_{j'}$ for all j, j' , for all optimal solutions y to (D), we have $y_j(T) = y_{j'}(T)$ for all j, j' . Moreover, as $x_j(t) > 0$ for all j and $t \in [0, T]$, by the coextremality condition (5), cf. Theorem 1, the dual system dynamics is given by $\dot{y}_j(t) = -q_j + [y(t)(d + \alpha - \beta)]_j$ for $t \in [0, T]$. In addition, notice that $y_j(t) > 0$ for all j and $t \in [0, T]$. To see this, recall that we can interpret the dual variable $y_j(t)$ as the contribution to the objective function of an additional patient to class j at time t . This contribution is strictly positive for all j and time t since $\vartheta_j > 0$ for all j and every additional patient has a strictly positive probability of still being in the waiting list at the end of the horizon regardless of his health status even if we do not allocate any organs to him. Thus, $y_j(t) > 0$ for all j and $t \in [0, T]$. Finally, notice that if $p_{J,k} \geq p_{J-1,k} \geq \dots \geq p_{1,k}$ then for any positive integer n , we obtain $\pi_{J,k}^n \geq \pi_{J-1,k}^n \geq \dots \geq \pi_{1,k}^n$.

We will first prove that $y_j(t) < y_{j'}(t)$ for all $t < T$ if $j > j'$. We argue by induction. That is, we will prove that for all $J - n \leq j < j' \leq J$, $y_j(t) < y_{j'}(t)$ for all $t < T$. The result is trivial if $n = 0$. Suppose that for some $n \in \{1, 2, \dots, J - 1\}$ and for all $J - n \leq j < j' \leq J$, we have $y_j(t) < y_{j'}(t)$ for all $t < T$. If $y_{J-n-1}(t) = y_{J-n}(t)$ for some t , then

$$\begin{aligned} \dot{y}_{J-n}(t) &= -q_{J-n} + [y(t)(d + \alpha - \beta)]_{J-n}, \\ &= -q_{J-n} + y_{J-n}(t)(d_{J-n} + \alpha_{J-n} + \beta_{J-n}) - \alpha_{J-n}y_{J-n+1}(t) - \beta_{J-n}y_{J-n-1}(t), \\ &= -q_{J-n} + y_{J-n}(t)(d_{J-n} + \alpha_{J-n}) - \alpha_{J-n}y_{J-n+1}(t), \end{aligned}$$

where the last line is true since $y_{J-n-1}(t) = y_{J-n}(t)$. Similarly, if $y_{J-n-1}(t) = y_{J-n}(t)$ for some t , then

$$\begin{aligned} \dot{y}_{J-n-1}(t) &= -q_{J-n-1} + y_{J-n-1}(t)(d_{J-n-1} + \alpha_{J-n-1} + \beta_{J-n-1}) - \alpha_{J-n-1}y_{J-n}(t) \\ &\quad - \beta_{J-n-1}y_{J-n-2}(t), \\ &= -q_{J-n-1} + y_{J-n-1}(t)(d_{J-n-1} + \beta_{J-n-1}) - \beta_{J-n-1}y_{J-n-2}(t), \end{aligned}$$

where the last equality is again true since $y_{J-n-1}(t) = y_{J-n}(t)$. Subtracting, we obtain

$$\begin{aligned}
\dot{y}_{J-n}(t) - \dot{y}_{J-n-1}(t) &= y_{J-n}(t)(d_{J-n} + \alpha_{J-n}) - \alpha_{J-n}y_{J-n+1}(t) - y_{J-n-1}(t)(d_{J-n-1} + \beta_{J-n-1}) \\
&\quad + \beta_{J-n-1}y_{J-n-2}(t), \\
&= y_{J-n}(t)(d_{J-n} + \alpha_{J-n} - d_{J-n-1} - \beta_{J-n-1}) - \alpha_{J-n}y_{J-n+1}(t) \\
&\quad + \beta_{J-n-1}y_{J-n-2}(t), \\
&> y_{J-n}(t)(d_{J-n} - d_{J-n-1} - \beta_{J-n-1}), \\
&> 0
\end{aligned}$$

where the first inequality follows from the induction hypothesis that $y_{J-n}(t) > y_{J-n+1}(t)$ for all $t < T$ and the fact that $y_j(t) > 0$ for all t . The second inequality is true since $d_{J-n} - d_{J-n-1} - \beta_{J-n-1} > 0$ by assumption and $y_j(t) > 0$ for all t . Then, this proves that if $y_{J-n-1}(t) = y_{J-n}(t)$ for some $t < T$, we have $y_{J-n-1}(t - \varepsilon) > y_{J-n}(t - \varepsilon)$ for $\varepsilon > 0$ small enough. In other words, if the paths of the functions $y_{J-n-1}(\cdot)$ and $y_{J-n}(\cdot)$ intersect at some point t , then it must be that $y_{J-n}(\cdot)$ is arriving at the intersection from below. Notice that this eliminates the possibility of more than one intersection for the functions $y_{J-n-1}(\cdot)$ and $y_{J-n}(\cdot)$ on the interval $[0, T]$. To see this, recall that the functions $y_{J-n-1}(\cdot)$ and $y_{J-n}(\cdot)$ are continuous and if there had been more than one intersection, then in at least one of them $y_{J-n}(\cdot)$ should be arriving at the intersection from above. This contradicts the fact that $y_{J-n-1}(t - \varepsilon) > y_{J-n}(t - \varepsilon)$ for $\varepsilon > 0$ small enough whenever $y_{J-n-1}(t) = y_{J-n}(t)$ for some $t < T$. Finally, as $y_{J-n-1}(T) = y_{J-n}(T)$, the functions $y_{J-n-1}(\cdot)$ and $y_{J-n}(\cdot)$ cannot intersect for any $t < T$, i.e., one of them should strictly dominate the other for all $t < T$. Since $\dot{y}_{J-n}(T) > \dot{y}_{J-n-1}(T)$, this proves that $y_{J-n-1}(t) > y_{J-n}(t)$ for all $t < T$. Thus, the induction hypothesis is true and we have $y_j(t) < y_{j'}(t)$ for all $t < T$ if $j > j'$. Then, Proposition 5 follows from the coextremality condition (6), cf. Theorem 1 and the fact that $h_j = h_{j'}$ for all j, j' . ■

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