HANDBOOK OF OPTIMIZATION IN MEDICINE
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Aims and Scope
Optimization has been expanding in all directions at an astonishing rate during the last few decades. New algorithmic and theoretical techniques have been developed, the diffusion into other disciplines has proceeded at a rapid pace, and our knowledge of all aspects of the field has grown even more profound. At the same time, one of the most striking trends in optimization is the constantly increasing emphasis on the interdisciplinary nature of the field. Optimization has been a basic tool in all areas of applied mathematics, engineering, medicine, economics and other sciences.

The Springer Series in Optimization and Its Applications publishes undergraduate and graduate textbooks, monographs and state-of-the-art expository works that focus on algorithms for solving optimization problems and also study applications involving such problems. Some of the topics covered include nonlinear optimization (convex and nonconvex), network flow problems, stochastic optimization, optimal control, discrete optimization, multi-objective programming, description of software packages, approximation techniques and heuristic approaches.
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There are in fact two things, science and opinion; the former begets knowledge, the later ignorance.

— Hippocrates (460–377 BC), Greek physician
Preface

In recent years, there has been a dramatic increase in the application of optimization techniques to the delivery of health care. This is in large part due to contributions in three fields: the development of more and more efficient and effective methods for solving large-scale optimization problems (operations research), the increase in computing power (computer science), and the development of more and more sophisticated treatment methods (medicine). The contributions of the three fields come together because the full potential of the new treatment methods often cannot be realized without the help of quantitative models and ways to solve them. As a result, every year new opportunities unfold for obtaining better solutions to medical problems and improving health care systems.

This handbook of optimization in medicine is composed of carefully refereed chapters written by experts in the fields of modeling and optimization in medicine and focuses on models and algorithms that allow for improved treatment of patients. Examples of topics that are covered in the handbook include:

- Optimal timing of organ transplants;
- treatment selection for breast cancer based on new classification schemes;
- treatment of head-and-neck, prostate, and other cancers; using conventional conformal and intensity modulated radiation therapy as well as proton therapy;
- optimization in medical imaging;
- classification and data mining with medical applications;
- treatment of epilepsy and other brain disorders;
- optimization for the genome project.

We believe that this handbook will be a valuable scientific source of information to graduate students and academic researchers in engineering, computer science, operations research, and medicine, as well as to practitioners who can tailor the approaches described in the handbook to their specific needs and applications.
We would like to take the opportunity to express our thanks to the authors of the chapters, the anonymous referees, and Springer for making the publication of this volume possible.

Gainesville, Florida
March 2008

Panos M. Pardalos
H. Edwin Romeijn
Contents

Preface ........................................................ vii

List of Contributors ........................................... xi

1 Optimizing Organ Allocation and Acceptance
Oguzhan Alagoz, Andrew J. Schaefer, and Mark S. Roberts ............ 1

2 Can We Do Better? Optimization Models for Breast Cancer
Screening
Julie Simmons Ivy ............................................ 25

3 Optimization Models and Computational Approaches
for Three-dimensional Conformal Radiation Treatment
Planning
Gino J. Lim .................................................... 53

4 Continuous Optimization of Beamlet Intensities
for Intensity Modulated Photon
and Proton Radiotherapy
Rembert Reemtsen and Markus Alber .................................... 83

5 Multicriteria Optimization in Intensity Modulated
Radiotherapy Planning
Karl-Heinz Küfer, Michael Monz, Alexander Scherrer, Philipp Süß,
Fernando Alonso, Ahmad Saher Azizi Sultan, Thomas Bortfeld,
and Christian Thieke ............................................ 123

6 Algorithms for Sequencing Multileaf Collimators
Srijit Kamath, Sartaj Sahni, Jatinder Palta, Sanjay Ranka,
and Jonathan Li ............................................. 169
7 Image Registration and Segmentation Based on Energy Minimization
   Michael Hintermüller and Stephen L. Keeling....................... 213

8 Optimization Techniques for Data Representations with Biomedical Applications
   Pando G. Georgiev and Fabian J. Theis.............................. 253

9 Algorithms for Genomics Analysis
   Eva K. Lee and Kapil Gupta ...................................... 291

10 Optimization and Data Mining in Epilepsy Research: A Review and Prospective
    W. Art Chaovalitwongse ....................................... 325

11 Mathematical Programming Approaches for the Analysis of Microarray Data
    Ioannis P. Androulakis ......................................... 357

12 Classification and Disease Prediction via Mathematical Programming
    Eva K. Lee and Tsung-Lin Wu .................................. 381

Index ................................................................. 431
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1

Optimizing Organ Allocation and Acceptance

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1.1 Introduction

Since the first successful kidney transplant in 1954, organ transplantation has been an important therapy for many diseases. Organs that can safely be transplanted include kidneys, livers, intestines, hearts, pancreata, lungs, and heart-lung combinations. The vast majority of transplanted organs are kidneys and livers, which are the focus of this chapter. Organ transplantation is the only viable therapy for patients with end-stage liver diseases (ESLDs) and the preferred treatment for patients with end-stage renal diseases (ESRDs). As a result of the urgent need for transplantations, donated organs are very scarce. The demand for organs has greatly outstripped the supply. Thus organ allocation is a natural application area for optimization. In fact, organ allocation is one of the first applications of medical optimization, with the first paper appearing 20 years ago.

The United Network for Organ Sharing (UNOS) is responsible for managing the national organ donation and allocation system. The organ allocation system is rapidly changing. For instance, according to the General Accounting Office, the liver allocation policy, the most controversial allocation system \cite{14}, has been changed four times in the past six years \cite{17, 28}. The multiple changes in policy over a short time period is evidence of the ever-changing opinions surrounding the optimal allocation of organs. For example, although the new liver allocation policy is anticipated to “better identify urgent patients and reduce deaths among patients awaiting liver transplants” \cite{28}, anecdotal
evidence suggests that there is some question among the transplant community as to whether the new allocation rules are satisfactory [10, 26].

UNOS manages organ donation and procurement via Organ Procurement Organizations (OPOs), which are non-profit agencies responsible for approaching families about donation, evaluating the medical suitability of potential donors, coordinating the recovery, preservation, and transportation of organs donated for transplantation, and educating the public about the critical need for organ donation. There are currently 59 OPOs that operate in designated service areas; these service areas may cover multiple states, a single state, or just parts of a state [28]. The national UNOS membership is also divided into 11 geographic regions, each consisting of several OPOs. This regional structure was developed to facilitate organ allocation and to provide individuals with the opportunity to identify concerns regarding organ procurement, allocation, and transplantation that are unique to their particular geographic area [28].

Organs lose viability rapidly once they are harvested, but the rate is organ-specific. The time lag between when an organ is harvested and when it is transplanted is called the cold ischemia time (CIT). During this time, organs are bathed in storage solutions. The limits of CIT range from a few hours for heart-lung combinations to nearly three days for kidneys. Stahl et al. [24] estimated the relationship between CIT and liver viability. The Scientific Registry of Transplant Recipients states that the acceptable cold ischemia time limit for a liver is 12 to 18 hours [22], whereas the Center for Organ Recovery and Education gives the maximum limit as 18 to 24 hours [5].

There are two major classes of decision makers in organ allocation. The first class of decision makers is the individual patient, or the patient and his or her physician. Typically, the objective for such a perspective is to maximize some measure of that patient’s benefit, typically life expectancy. The second class may be described as “society,” and its goal is to design an organ allocation system so as to maximize some given criteria. Some examples of these criteria include total clinical benefit and some measure of equity. Equity is a critical issue in the societal perspective on organ allocation as there is considerable evidence that certain racial, geographic, and socioeconomic groups have greater access to organs than do others [27].

We limit our discussion to the U.S. organ allocation system. The remainder of this chapter is organized as follows. In Section 1.2, we describe the kidney allocation system, and in Section 1.3, we detail the liver allocation system. These two organs comprise the vast majority of organ transplantations; the details for other organs are described on the UNOS webpage [28]. Previous research on the patient’s perspective is discussed in Section 1.4, and the societal perspective is described in Section 1.5. We provide conclusions and directions for future work in Section 1.6.
1.2 Kidney Allocation System

More than 60,000 patients are on the nationwide kidney waiting list. In 2003, 15,000 patients received a kidney transplant, of which more than 40% were from living donors [29]. The kidney waiting list and number of transplants are larger than those of all other organs combined. However, this need is somewhat mitigated by the fact that an alternate kidney replacement therapy (dialysis) is widely available. We describe the kidney allocation system as of late 2004 below. This allocation system is subject to frequent revision; readers are referred to the UNOS webpage [28] for updates to these and other allocation policies.

Kidneys are typically offered singly; however, there are certain cases when a high risk of graft failure requires the transplant of both kidneys simultaneously. UNOS defines two classes of cadaveric kidneys: standard and expanded. Kidneys in both classes have similar allocation mechanisms, as described below. Expanded-criteria kidneys have a higher probability of graft failure and are distinguished by the following factors:

1. Age: kidneys from some donors between 50 and 59 years and kidneys from every donor older than 60 years are expanded-criteria kidneys.
2. Level of creatinine in the donor’s blood, which is a measure of the adequacy of kidney function: kidneys from donors with higher creatinine levels may be considered expanded-criteria kidneys.
3. Kidneys from donors who died of cardiovascular disease may be considered expanded-criteria.
4. Kidneys from donors with high hypertension may be considered expanded-criteria.

Patients who are willing to accept expanded-criteria kidneys do not have their eligibility for regular kidneys affected.

The panel-reactive antibody (PRA) level is a measure of how hard a patient is to match. It is defined as the percentage of cells from a panel of donors with which a given patient’s blood serum reacts. This estimates the probability that the patient will have a negative reaction to a donor; the higher the PRA level, the harder the patient is to match.

A zero-antigen mismatch between a patient and a cadaveric kidney occurs when the patient and donor have compatible blood types and have all six of the same HLA-A, B, and DR antigens. There is mandatory sharing of zero-antigen-mismatched kidneys. When there are multiple zero-antigen-mismatched kidneys, there is an elaborate tie-breaking procedure that considers factors including the recipient’s OPO, whether the patient is younger than 18, and certain ranges of PRA level. One interesting concept is that of debts among OPOs. Except in a few cases, when a kidney is shared between two OPOs, the receiving OPO must then share the next standard kidney it harvests in that particular blood type category. This is called a payback debt.
An OPO may not accumulate more than nine payback debts at any time. Priority for matching zero-antigen-mismatched kidneys is given to patients from OPOs that are owed payback kidneys. The full description of the tie-breaking procedure is available from the UNOS webpage [28].

If a kidney has no zero-antigen mismatches, kidneys with blood type O or B must be transplanted into patients with the same blood type. In general, kidneys are first offered within the harvesting OPO, then the harvesting region, and finally nationally. Within each of these three categories, patients who have an ABO match with the kidney are assigned points, and each kidney is offered to patients in decreasing order of points. A patient has the opportunity to refuse a kidney for any reason without affecting his or her subsequent access to kidneys.

Once minimum criteria are met, patients begin to acquire waiting time. One point is given to the patient who has been on the waiting list the longest amount of time. All other patients are accorded a fractional point equal to their waiting time divided by that of the longest-waiting patient. A patient receives four points if she has PRA level 80% or greater. Patients younger than 11 years old are given four points, and patients between 11 and 18 years of age are given three points. A patient is given four points if he or she has donated a vital organ or segment of a vital organ for transplantation within the United States. For the purposes of determining the priority within the harvesting OPO, a patient’s physician may allocate “medical priority points.” However, such points are not considered at the regional or national levels.

It is interesting to note that, excluding medical priority points, points based on waiting time can only be used to break ties among patients with the same number of points from other factors. In other words, kidneys are allocated lexicographically: the first factors are PRA level, age, and so on. Only among tied patients in the first factors is waiting time considered.

1.3 Liver Allocation System

This section describes the current liver allocation system. Basic knowledge of this system is necessary to understand the decision problem faced by the ESLD patients and the development of the decision models. The UNOS Board of Directors approved the new liver allocation procedure for implementation as of February 28, 2002 [28].

UNOS has different procedures for adult and for pediatric patients. Because researchers consider only the adult patients, we describe only the adult liver allocation procedure. UNOS maintains a patient waiting list that is used to determine the priority among the candidates. 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 Model for End Stage Liver Disease (MELD) scores. 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 seven days” [28]. Patients who do not qualify for classification as Status 1 do not receive a status level. Rather, these patients will be assigned a “probability of pre-transplant death derived from a mortality risk score” calculated by the MELD scoring system [28]. The MELD score, which is a continuous function of total bilirubin, creatinine, and prothrombin time, indicates the status of the liver disease and is a risk-prediction model first introduced by Malinchoc et al. [16] to assess the short-term prognosis of patients with liver cirrhosis [30]. Wiesner et al. [30] developed the following formula for computing MELD scores:

\[
\text{MELD Score} = 10 \times [0.957 \times \ln(\text{creatinine mg/dl}) + 0.378 \times \ln(\text{bilirubin mg/dl}) + 1.120 \times \ln(\text{INR}) + 0.643 \times I_c]
\]

where INR, international normalized ratio, is computed by dividing prothrombin time (PT) of the patient by a normal PT value, mg/dl represents the milligrams per deciliter of blood, 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 0 if the disease is related to other etiologies (causes). As Wiesner et al. [30] note, the etiology of disease is removed from the formula by UNOS. In addition to this, UNOS makes several modifications to the formula: 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 [28]. By introducing these changes, UNOS restricts the range of MELD scores to be between 6 and 40, where a value of 6 corresponds with the best possible patient health and 40 with the worst.

Kamath et al. [15] developed the MELD system to more accurately measure the liver disease severity and to better predict which patients are at risk of dying. However, there are concerns about the accuracy of the MELD system. First, there were some biases in the data used to develop the model. For instance, the data available to the researchers were mostly based on patients with advanced liver disease [16]. Furthermore, the MELD system was validated on the patients suffering from cirrhosis [30], therefore it is possible that the MELD system does not accurately measure the disease progression for other diseases, e.g., acute liver diseases. Moreover, as stated, although they presented data to indicate that the consideration of patient age, sex, and body mass is unlikely to be clinically significant, it is possible that other factors, including a more direct measurement of renal function (iothalamate clearance), may improve the accuracy of the model [15]. Additionally, the MELD system was validated on only three laboratory values: creatinine and bilirubin levels and prothrombin time. Thus, it is possible that the MELD system does
not accurately consider patients with liver cancer because they would score as if they were healthy [10]. Consequently, relying mainly on laboratory results may not be the best solution for all patients [9].

Patients are 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, though not identical, blood type receive 5 points; and a candidate whose blood type is incompatible receives 0 points. As an exception, though type O and type A_2 (a less common variant of blood type A) are incompatible, patients of type O receive 5 points for being willing to accept a type A_2 liver. 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 second, and incompatible patients last. If there are several patients having the same blood type compatibility and MELD scores, the ties are broken with 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” [28]. For MELD patients, waiting time is calculated as the time accrued by the patient at or above his or her current score level from the date that he or she was listed as a candidate for liver transplantation.

Figure 1.1 shows a schematic representation of the liver allocation system. In summary, the current liver allocation system works as follows: every liver available for transplant is first offered to those Status 1 patients located within the harvesting OPO. When more than one Status 1 patient exists, the liver is offered to those patients in descending point order where the patient with the highest number of 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 still has not been found, the liver is offered to all non–Status 1 patients in the harvesting OPO in descending order of MELD score. The search is again broadened to the harvesting region if no suitable match has been found. If no suitable match exists in the harvesting region, 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 and/or physician responsible for the care of that patient” [14]. The surgeon and/or the physician have very limited time, namely one hour, to make their decision [28] because the acceptable range for cold ischemia time is very limited. Furthermore, as the Institute of Medicine points out, there is evidence that the quality of the organ decreases as cold ischemia time increases [14]. In the event that a liver is declined, it is then offered to another patient in accordance with the above-described policy. The patient who declines the organ will not be penalized.
1.4 Optimization from the Patient’s Perspective

This section describes the studies on the optimal use of cadaveric organs for transplantation that maximizes the patient’s welfare. Section 1.4.1 summarizes studies that consider the kidney transplantation problem. Section 1.4.2 describes studies that consider the liver transplantation problem.

1.4.1 Optimizing kidney transplantation

David and Yechiali [6] consider when a patient should accept or reject an organ for transplantation. They formulate this problem as an optimal stopping problem in which the decision maker accepts or reject offers \( \{X_j\}_0^\infty \) that are available at random times \( \{t_j\}_0^\infty \), where \( \{X_j\}_0^\infty \) is a sequence of independent and identically distributed positive bounded random variables with distribution function \( F(x) = P(X \leq x) \). If the patient accepts the offer at time \( t_j \), the patient quits the process and receives a reward \( \beta(t_j)X_j \), where \( \beta(t) \) is a continuous nonincreasing discount function with \( \beta(0) = 1 \). If the patient does not accept the offer, then the process continues until the next offer, or patient
death. The probability that the decision maker dies before the new offer arrives at time $t_j + 1$ is given by the variable $1 - \alpha_{j+1} = P(T \leq t_{j+1} | T > t_j)$ defined by $T$, the lifetime of the underlying process. Their objective is to find a stopping rule that maximizes the total expected discounted reward from any time $t$ onward.

They first consider the case in which the offers arrive at fixed time points and there are a finite number of offers ($n$) available. In this case, they observe that the optimal strategy is a control-limit policy with a set of controls $\{\lambda^j_n\}_{j=0}^n$, and an offer $X_j$ at time $t_j$ is accepted if and only if $\beta_j X_j > \lambda^j_n$, where $\lambda^j_n$ is the maximum expected discounted reward if an offer at time $t_j$ is rejected. Because for each $j \leq n$, $\{\lambda^j_n\}_{n=0}^\infty$ is a nondecreasing bounded sequence of $n$, it has a limit $l_j$.

They extend their model to the infinite-horizon problem in which the offers arrive randomly. They prove that if the lifetime distribution of the decision maker is increasing failure rate (IFR) [4], then the optimal policy takes the form of a continuous nonincreasing real function $\lambda(t)$ on $[0, \infty)$, such that an offer $x$ at time $t$ is accepted if and only if $\beta(t)x \geq \lambda(t)$. $\lambda(t)$ is equal to the future expected discounted reward if the offer is rejected at time $t$, and an optimal policy is applied thereafter. They show that the IFR assumption is a necessary assumption in this setting.

David and Yechiali also consider the case where the arrivals follow a nonhomogeneous Poisson process. They consider several special cases of this model such as the organ arrival is nonhomogeneous Poisson with nonincreasing intensity and the lifetime distribution is IFR. In this case, they prove that the control limit function $\lambda(t)$ is nonincreasing, so that a patient becomes more willing to accept lower quality organs as time progresses. They obtain a bound for the $\lambda(t)$ for this special case.

They provide an explicit closed form solution of the problem when the lifetime distribution is Gamma with homogenous Poisson arrivals. They present a numerical example for this special case using data related to the kidney transplant problem.

Ahn and Hornberger [1] and Hornberger and Ahn [11] develop a discrete-time infinite horizon discounted Markov decision process (MDP) model for deciding which kidneys would maximize a patient’s total expected (quality-adjusted) life. In their model, the patient is involved in the process of determining a threshold kidney quality value for transplantation. They use expected one-year graft survival rate as the criterion for determining the acceptability of a kidney. The state space consists of the patient state and includes five states: alive on dialysis and waiting for transplantation ($S_1$); not eligible for transplantation ($S_2$); received a functioning renal transplant ($S_3$); failed transplant ($S_4$); and death ($S_5$). They assume that the patient assigns a quality-of-life score to each state. They use months as their decision epochs because of the sparsity of their data. The patient makes the decision only when he or she is in state ($S_1$). The quality-adjusted life expectancy (QALE) of the patient in
state \((S_1)\) is a function of (1) QALE if a donor kidney satisfying eligibility requirements becomes available and the patient has the transplantation, (2) QALE if an ineligible donor kidney becomes available and the patient is not transplanted, and (3) the quality of life with dialysis in that month. Because of the small number of states, they provide an exact analytical solution for threshold kidney quality.

They use real data to estimate the parameters and solve the model for four representative patients. The minimum one-year graft survival rate, \(d^*\), differs significantly among the four patients. They compare their results with what might be expected by using the UNOS point system for four representative donor kidneys. They also perform a one-way sensitivity analysis to measure the effects of the changes in the parameters. Their results show that the important variables that affect the minimum eligibility criterion are quality of life assessment after transplant, immunosuppressive side effect, probability of death while undergoing dialysis, probability of death after failed transplant, time preference, and the probability of being eligible for retransplantation.

### 1.4.2 Optimizing liver transplantation

Howard [12] presents a decision model in which a surgeon decides to accept or reject a cadaveric organ based on the patient’s health. He frames the organ acceptance decision as an optimal stopping problem. According to his model, a surgeon decides whether or not to accept an organ of quality \(q \in (0, \bar{q}]\) for a patient in health state \(h \in (0, \bar{h}]\), where the state \(q = 0\) describes a period in which there is no organ offer and the state \(h = 0\) corresponds with death. The organ offers arrive with distribution function \(f(q)\). If the surgeon rejects the organ, the patient’s health evolves according to a Markov process described by \(f(h' | h)\), where \(f(h' | h)\) is IFR. If the surgeon accepts an organ offer, then the probability that the operation is successful in period \(t + 1\) is a function of current patient health \(h\) and organ offer \(q\) and is denoted by \(p(h, q)\). If the patient’s single period utility when alive is \(u\) and the immediate reward of a successful operation is \(B\), the total expected reward from accepting an organ at time \(t\), \(EV^{TX}(h, q)\) and from rejecting an organ at time \(t\), \(EV^W(h)\) are as follows:

\[
EV^{TX}(h, q) = p(h, q)B,
\]

and

\[
EV^W(h) = \int_q \int_h V^W(h', q')f(h' | h)f(q')dh'dq',
\]

where \(V^W(h, q)\) is defined by the following set of equations:

\[
V^W(h, q) = u + \delta \max \{EV^{TX}(h, q), EV^W(h)\},
\]

where \(\delta\) is the discount factor.
Howard estimates the parameters in his decision model using liver transplantation data in the United States. However, he does not provide any structural insights or numerical solutions to this decision model. Instead, he provides statistical evidence that explains why a transplant surgeon may reject a cadaveric liver offer. His statistical studies show that as the waiting list has grown over time, the surgeons have faced stronger incentives to use lower quality organs. Similarly, the number of organ transplantations has increased dramatically in years when the number of traumatic deaths decreased.

Howard also discusses the trends in organ procurement in light of his findings and describes some options to the policy makers who believe that too many organs are discarded. One option is to use the results of a decision that calculates the optimal quality cutoff and enforce it via regulations. Another option is to penalize hospitals that reject organs that are subsequently transplanted successfully by other transplant centers. It is also possible to implement a dual list system in which the region maintains two waiting lists, one for patients whose surgeons are willing to accept low-quality organs and one for patients whose surgeons will accept only high-quality organs.

Alagoz et al. \cite{2} consider the problem of optimally timing a living-donor liver transplant in order to maximize a patient’s total reward, for example, life expectancy. Living donors are a significant and increasing source of livers for transplantation, mainly due to the insufficient supply of cadaveric organs. Living-donor liver transplantation is accomplished by removing an entire lobe of the donor’s liver and implanting it into the recipient. The non-diseased liver has a unique regenerative ability so that a donor’s liver regains its previous size within two weeks. They assume that the patient does not receive cadaveric organ offers.

In their decision model, the decision maker can take one of two actions at state $h \in \{1, \ldots, H\}$, namely, “Transplant” or “Wait for one more decision epoch,” where 1 is the perfect health state and $H$ is the sickest health state. If the patient chooses “Transplant” in health state $h$, he or she receives a reward of $r(h, T)$, quits the process, and moves to absorbing state “Transplant” with probability 1. If the patient chooses to “Wait” in health state $h$, he or she receives an intermediate reward of $r(h, W)$ and moves to health state $h' \in S = \{1, \ldots, H + 1\}$ with probability $P(h'|h)$, where $H + 1$ represents death. The optimal solution to this problem can be obtained by solving the following set of recursive equations:

$$V(h) = \max \left\{ r(h, T), r(h, W) + \lambda \sum_{h' \in S} P(h'|h)V(h') \right\}, \ h = 1, \ldots, H,$$

where $\lambda$ is the discount factor, and $V(h)$ is the maximum total expected discounted reward that the patient can attain when his or her current health is $h$. 
They derive some structural properties of this MDP model including a set of intuitive sufficient conditions that ensure the existence of a control-limit policy. They prove that the optimal value function is monotonic when the transition probability matrix is IFR and the functions $r(h, T)$ and $r(h, W)$ are nonincreasing in $h$. They show that if one disease causes a faster deterioration in patient health than does another and yet results in identical post-transplant life-expectancy, then the control limit for this disease is less than or equal to that for the other. They solve this problem using clinical data. In all of their computational tests, the optimal policy is of control-limit type. In some of the examples, when the liver quality is very low, it is optimal for the patient to choose never to have the transplant.

Alagoz et al. [3] consider the decision problem faced by liver patients on the waiting list: should an offered organ of a given quality be accepted or declined? They formulate a discrete-time, infinite-horizon, discounted MDP model of this problem in which the state of the process is described by patient state and organ quality. They consider the effects of the waiting list implicitly by defining the organ arrival probabilities as a function of patient state.

They assume that the probability of receiving a liver of type $\ell$ at time $t + 1$ depends only on the patient state at time $t$ and is independent of the type of liver offered at time $t$. According to their MDP model, the decision maker can take one of two actions in state $(h, \ell)$, where $h \in \{1, \ldots, H + 1\}$ represents patient health and $\ell \in S_L$ represents current liver offer. Namely, “Accept” the liver $\ell$ or “Wait for one more decision epoch.” If the patient chooses “Accept” in state $(h, \ell)$, he or she receives a reward of $r(h, \ell, T)$, quits the process, and moves to absorbing state “Transplant” with probability 1. If the patient chooses to “Wait” in state $(h, \ell)$, then he or she receives an intermediate reward of $r(h, W)$ and moves to state $(h', \ell') \in S$ with probability $P(h', \ell'|h, \ell)$. The optimal solution to this problem is obtained by solving the following set of recursive equations [18]:

$$V(h, \ell) = \max \left\{ r(h, \ell, T), r(h, W) + \lambda \sum_{(h', \ell') \in S} P(h', \ell'|h, \ell) V(h', \ell') \right\},$$

where $\lambda$ is the discount factor, and $V(h, \ell)$ is the maximum total expected discounted reward that the patient can attain when his or her current state is $h$ and the current liver offered is $\ell$.

Alagoz et al. derive structural properties of the model, including conditions that guarantee the existence of a liver-based and a patient-based control-limit optimal policy. A liver-based control-limit policy is of the following form: for a given patient state $h$, choose the “Transplant” action and “Accept” the liver if and only if the offered liver is of type $1, 2, \ldots, i(h)$ for some liver state $i(h)$ called the liver-based control limit. Similarly, a patient-based control-limit policy is of the simple form: for a given liver state $\ell$, choose the “Transplant”
action and “Accept” the liver if and only if the patient state is one of the states $j(\ell), j(\ell) + 1, \ldots, H$, for some patient state $j(\ell)$ called the patient-based control limit.

The conditions that ensure the existence of a patient-based control-limit policy are stronger than those that guarantee the existence of a liver-based control-limit policy. They compare the optimal control limits for the same patient listed in two different regions. They show that if the patient is listed in region A where he or she receives more frequent and higher quality liver offers than in region B, then the optimal liver-based control limits obtained when he or she is listed in region A are lower than those obtained when he or she is listed in region B.

They use clinical data to solve this problem, and in their experiments the optimal policy is always of liver-based control-limit type. However, some optimal policies are not of patient-based control-limit type. In some regions, as the patient gets sicker, the probability of receiving a better liver increases significantly. In such cases, it is optimal to decline a liver offer in some patient states even if it is optimal to accept that particular liver offer in better patient states. Their computational tests also show that the location of the patient has a significant effect on liver offer probabilities and optimal control limits.

1.5 Optimization from the Societal Perspective

This section describes the studies on optimal design of an allocation system that maximizes the society’s welfare. Section 1.5.1 summarizes studies that consider the general organ allocation problem. Section 1.5.2 describes studies that consider the kidney allocation problem.

1.5.1 Optimizing general organ allocation system

Righter [19] considers a resource allocation problem in which there are $n$ activities each of which requires a resource, where resources arrive according to a Poisson process with rate $\lambda$. Her model can be applied to the kidney allocation problem, where resources represent the organs and activities represent the patients. When a resource arrives, its value $X$, a nonnegative random variable with distribution $F(\cdot)$, becomes known, and it can either be rejected or assigned to one of the activities. Once a resource is assigned to an activity, that activity is no longer available for further assignments. Activities are ordered such that $r_1 \geq r_2 \geq \cdots \geq r_n \geq 0$, where $r_i$ represents the activity value. Each activity has its own deadline that is exponentially distributed with rate $\alpha_i$ and is independent of other deadlines. When the deadline occurs, the activity terminates. The reward of assigning a resource to an activity is the product of the resource value and the activity value. The objective is to assign arriving resources to the activities such that the total expected return is maximized. If all activity deadlines are the same, i.e., $\alpha_i = \alpha$ for all $i$, then
the optimal policy has the following form: assign a resource unit of value $x$ to activity $i$ if $v_i(\alpha) < x \leq v_{i-1}(\alpha)$, where each threshold $v_i(\alpha)$ represents the total expected discounted resource value when it is assigned to activity $i$ under the optimal policy. She defines $v_0(\alpha) = \infty$ and $v_{n+1}(\alpha) = 0$. Furthermore, $v_0(\alpha) > v_1(\alpha) > \cdots > v_n(\alpha) > v_{n+1}(\alpha)$, where $v_i(\alpha)$ does not depend on $n$ for $n \geq i$, and $v_i(\alpha)$ does not depend on $r_j$ for any $j$.

Righter analyzes the effects of allowing the parameters to change according to a continuous time Markov chain on the structural properties of the optimal value function. She first assumes that the arrival rate of resources change according to a continuous Markov chain whereas all other model parameters are fixed and proves that the optimal policy still has the same structure, where the thresholds do not depend on the $r_j$ but depend on the current system state (environmental state). She then considers the case in which the activity values and deadline rates change according to a random environment and proves that the thresholds and the total returns are monotonic in the parameters of the model. In this case, the thresholds depend on the $r_j$’s as well as the environmental state. She also provides conditions under which model parameters change as functions of the environmental state that ensure the monotonicity of the total returns.

David and Yechiali [7] consider allocating multiple organs to multiple patients where organs and patients arrive simultaneously. That is, an infinite random sequence of pairs (patient and organ) arrive sequentially, where each organ and patient is either of Type I with probability $p$ or of Type II with probability $q = 1 - p$. When an organ is assigned to the candidate, it yields a reward $R > 0$ if they match in type or a smaller reward $0 < r \leq R$ if there is a mismatch. If an organ is not assigned, it is unavailable for future assignments, however, an unassigned patient stays in the system until he or she is assigned an organ. The objective is to find assignment policies that maximize various optimality criteria.

David and Yechiali first consider the average reward criterion. A policy $\pi$ is average-reward optimal if it maximizes the following equation:

$$\phi_\pi(s) = \liminf_{t \to \infty} \frac{E\left[\sum_{n=0}^{t-1} r_\pi(n) | \text{initial state} = s\right]}{t},$$

where $r_\pi(n)$ is the average reward earned in day $n$, and states are represented by pairs $(i, j)$ denoting $i$ Type I and $j$ Type II candidates waiting in the system $(0 \leq i, j < \infty)$. They prove that when there are infinitely many organs and patients, the optimal policy is to assign only perfect matches for any $0 \leq p \leq 1$ and $0 \leq r \leq R$, and the optimal gain is the perfect-match reward, $R$. If there exist at most $k$ patients, then the reasonable policy of order $k$ is the optimal policy, where a reasonable policy of order $k$ is defined as follows. A policy is a reasonable policy of order $k$ if it satisfies the following conditions: (i) assign a match whenever possible and (ii) assign a mismatch when $n_1$ candidates are present prior to the arrival, with $k$ being the smallest number $n_1$ specified in (ii).
David and Yechiali then consider the finite- and infinite-horizon discounted models. They show that for a finite-horizon model, the optimal policy has the following form: assign a perfect match when available, and assign a mismatch if and only if \( r > r_{n,N}^* \), where \( r_{n,N}^* \) is a control limit that changes with the optimal reward-to-go function when there are \( n \) Type I candidates and \( N \) periods to go. Unfortunately, they could not find a closed-form solution for \( r_{n,N}^* \). They also show that the infinite-horizon discounted-reward optimal policy is of the following form: assign a perfect match when available, and assign a mismatch according to a set of controls

\[
r_1^* \geq r_2^* \geq \cdots \geq r_{k-1}^* \geq r_k^* \geq \cdots
\]
on \( r \) and according to \( k \), where \( k \) represents the number of mismatching candidates in the system and \( r_k \) are a set of control limits on \( r \).

David and Yechiali [8] consider allocating multiple \( (M) \) organs to multiple \( (N) \) patients. Assignments are made one at a time, and once an organ is assigned (or rejected), it is unavailable for future assignments. Each organ and patient is characterized by a fixed-length attribute vector \( X = (X_1, X_2, \ldots, X_p) \), where each patient’s attributes are known in advance, and each organ’s attributes are revealed only upon arrival. When an offer is assigned to a patient, the two vectors are matched, and the reward is determined by the total number of matching attributes. There are at most \( p + 1 \) possible match levels. The objective is to find an assignment policy that maximizes the total expected return for both discounted and undiscounted cases. They assume that \( p \) equals 1, so that each assignment of an offer to a candidate yields a reward of \( R \) if there is a match and a smaller reward \( r \leq R \) if there is a mismatch.

They first consider the special case in which \( M \geq N \), each patient must be assigned an organ, and a fixed discount rate \( (\alpha) \) exists. They assume that \( f_1 \leq f_2 \leq \cdots \leq f_N \), where \( f_1, \ldots, f_N \) are the respective frequencies \( P\{X = a_1\}, \ldots, P\{X = a_N\} \), the \( N \) realizations of the attribute vector. Using the notation \( (f) \) for \( (f_1, \ldots, f_{N+1}) \) and \( (f_-) \) for \( (f_1, \ldots, f_{i-1}, f_{i+1}, \ldots, f_{N+1}) \), the optimality equations are

\[
V_{N+1,M+1}(f)|X_1 = \max \begin{cases} R + \alpha V_{N,M}(f_-)|\{X_1 = a_1\} & (\text{match}) \\ r + \alpha \max_k V_{N,M}(f_-k) & (\text{a mismatch}) \\ \alpha V_{N+1,M}(f) & (\text{rejection}) \end{cases}
\]

where \( V_{N,M}(f) \) is the maximal expected discounted total reward when there are \( N \) waiting patients with \( N \) attribute realizations \( (a_1, \ldots, a_N) \) and \( M \) offers available. They prove that if \( N < M \) and \( a_1, \ldots, a_N \) are distinct, the optimal policy is to assign a match whenever possible and to reject a mismatch or assign it to \( a_1 \) depending on whether \( \alpha \xi_1 \geq r \) or \( \alpha \xi_1 < r \), where \( \xi_1 = f_1 R + (1 - f_1)r \).

David and Yechiali then consider the case where \( M = N \) and no rejections are possible. In this case, the optimal policy is as follows: if an offer matches
one or more of the candidates, it is assigned to one of them. Otherwise it is assigned to a candidate with the rarest attribute.

Finally, they relax the assumption that all candidates must be assigned and $M \geq N$. In this case, they prove that the optimal policy is to assign the organs to one of the candidates if a match exists and to assign to $a_1$ when $f_1 < \varphi$, where $\varphi$ is a function of $f_i$’s and can be computed explicitly for some special cases.

Stahl et al. [23] use an integer programming model to formulate and solve the problem of the optimal sizing and configuration of transplant regions and OPOs in which the objective is to find a set of regions that optimizes transplant allocation efficiency and geographic equity. They measure efficiency by the total number of intra-regional transplants and geographic equity by the minimum OPO intra-regional transplant rate, which is defined as the number of intra-regional transplants in an OPO divided by the number of patients on the OPO waiting list.

They model the country as a simple network in which each node represents an OPO, and arcs connecting OPOs indicate that they are contiguous. They assume that a region can consist of at most nine contiguous OPOs, an OPO supplies its livers only to the region that contains it, and both transplant allocation efficiency and geographic equity could be represented as factors in a function linking CIT and liver transport distance. They also assume that the probability of declining a liver offer, which is measured by the liver’s viability, is solely dependent on its CIT. Primary nonfunction occurs when a liver fails to work properly in the recipient at the time of transplant. They use two functional relationships between primary nonfunction and CIT: linear and polynomial.

Stahl et al. solve an integer program to find the optimal set of regions such that the total number of intra-regional transplants are maximized. They define the binary variable $x_j$ for every possible region $j$ such that it is equal to 1 if region $j$ is chosen and is equal to 0 if region $j$ is not chosen. Then, the integer program is as follows:

$$\max \left\{ \sum_{j \in J} c_j x_j : \sum_{j \in J} a_{ij} x_j = 1, i \in I; x_j \in \{0, 1\}, j \in J \right\},$$  \hspace{1cm} (1.2)

where $I$ is the set of all OPOs; $J$ is the set of all regions; $a_{ij} = 1$ if region $j$ contains OPO $i$, and 0 otherwise; and $c_j$ represents the total number of intra-regional transplants for region $j$. They provide a closed-form estimate of $c_j$. If the number of regions is constrained to be equal to 11, then the constraint $\sum_{j \in J} x_j = 1$ is added. The integer program defined in (1.2) does not consider the geographic equity. Let $f_{ij}$ and $\lambda_{min}$ represent the intra-regional transplant rate in OPO $i$ contained in region $j$ and the minimal local transplant rate, respectively. Then, the integer program considering the geographic equity can be reformulated as follows:
max \left\{ \sum_{j \in J} c_j x_j + \rho \lambda_{\min} : \sum_{j \in J} a_{ij} x_j = 1, i \in I; \right. \\
\left. \sum_{j \in J} f_{ij} x_j - \lambda_{\min} \geq 0, i \in I; x_j \in \{0, 1\}, j \in J \right\}, \quad (1.3)

where $\rho$ is a constant that indicates the importance the decision makers place on the minimum transplant rate across OPOs versus intra-regional transplants. Hence, changing $\rho$ will provide a means for balancing the two conflicting factors, transplant allocation efficiency and geographic equity.

Stahl et al. conduct computational experiments using real data to compare the regional configuration obtained from their model to the current configuration. The optimal sets of regions tend to group densely populated areas. Their results show that the proposed configuration resulted in more intra-regional transplants. Furthermore, for all values of $\rho$, the minimum intra-regional transplant rate across OPOs is significantly higher than that in the current regional configuration. However, as $\rho$ increases, the increase over the current configuration diminishes. They also perform sensitivity analyses, which show that the outcome is not sensitive to the relationship between CIT and primary nonfunction.

### 1.5.2 Optimizing the kidney allocation system

Zenios et al. [31] consider the problem of finding the best kidney allocation policy with the three-criteria objective of maximizing total quality-adjusted life years (QALYs) and minimizing two measures of inequity. The first measures equity across various groups in terms of access to kidneys, and the second measures equity in waiting times. They formulate this problem using a continuous-time, continuous-space deterministic fluid model but do not provide a closed-form solution.

In their model, there are $K$ patient and $J$ donor classes. They assume that patients of class $k = 1, \ldots, K_W$ are registered on the waiting list and patients of class $k = K_W + 1, \ldots, K$ have a functioning graft. The state of the system at time $t$ is described by the $K$-dimensional column vector $x(t) = (x_1(t), \ldots, x_K(t))^T$, which represents the number of patients in each class. Transplant candidates of class $k \in \{1, \ldots, K_W\}$ join the waiting list at rate $\lambda_k^+$ and leave the waiting list with rate $\mu_k$ due to death or due to organ transplantation. Organs of class $j \in \{1, \ldots, J\}$ arrive at rate $\lambda_j^-$, from which a fraction $v_{jk}(t)$ is allocated to transplant candidates $k$. Note that $v_{jk}(t)$ is a control variable and $u_{jk}(t) = \lambda_j^- v_{jk}(t)$ is the transplantation rate of class $j$ kidneys into class $k$ candidates. When a class $j$ kidney is transplanted into a class $k \in \{1, \ldots, K_W\}$ patient, the class $k$ patient leaves the waiting list and becomes a patient of class $c(k, j) \in \{K_W + 1, \ldots, K\}$. Furthermore, $c(k, j)$ patients depart this class at rate $\mu_{c(k, j)}$ per unit time; a fraction $q_{c(k, j)} \in [0, 1]$
of these patients are relisted as patients of class $k$ as a result of graft failure, whereas a fraction $1 - q_{c(k,j)}$ of them exit the system due to death.

The system state equations are given by the following linear differential equations:

$$\frac{d}{dt} x_k(t) = \lambda_k^+ - \mu_k x_k(t) - \sum_{j=1}^{J} u_{jk}(t) + \sum_{j=1}^{J} q_{c(k,j)} \mu_{c(k,j)} x_{c(k,j)}(t);$$

$$k = 1, \ldots, K_W,$$ (1.4)

$$\frac{d}{dt} x_k(t) = \sum_{j=1}^{K_W} \sum_{i=1}^{K} u_{ji}(t) 1_{\{c(i,j) = k\}} - \mu_k x_k(t); \quad k = K_W + 1, \ldots, K,$$ (1.5)

and are subject to the state constraints

$$x_k(t) \geq 0; \quad k = 1, \ldots, K.$$ (1.6)

The organ allocation rates $u(t)$ must satisfy the following constraints:

$$\sum_{k=1}^{K_W} u_{jk}(t) \leq \lambda_j^-; \quad j = 1, \ldots, J,$$ (1.7)

$$u_{jk}(t) \geq 0; \quad k = 1, \ldots, K_W \quad \text{and} \quad j = 1, \ldots, J.$$ (1.8)

Zenios et al. note that this model ignores the three important aspects of the kidney allocation problem: crossmatching between donor and recipient, unavailability of recipients, and organ sharing between OPOs. The model assumes that the system evolution is deterministic. They use the QALY to measure the efficiency of the model. Namely, they assume that UNOS assigns a quality of life (QOL) score $h_k$ to each patient class $k = 1, \ldots, K$, and the total QALY over a finite time horizon $T$ is found using

$$\int_0^T \sum_{k=1}^{K} h_k x_k(t) dt.$$

For a given allocation policy $u(t) = (u_1(t))^T, \ldots, u_J(t))^T$, where $u_j(t) = (u_{j1}(t), \ldots, u_{jK_W}(t))^T$, their first measure of equity, waiting time inequity, is calculated by

$$\frac{1}{2} \int_0^T \sum_{k=1}^{K_W} \sum_{i=1}^{K} \lambda_k(t, u(t)) \lambda_i(t, u(t)) \left( \frac{x_k(t)}{\lambda_k(t, u(t))} - \frac{x_i(t)}{\lambda_i(t, u(t))} \right)^2 dt,$$

where $\lambda(t, u(t)) = (\lambda_1(t, u(t)), \ldots, \lambda_{K_W}(t, u(t)))$ represents the instantaneous arrival rate into class $k$ under allocation policy $u(t)$.

The second measure of equity considers the likelihood of transplantation. They observe that
\[
\lim_{T \to \infty} \frac{\int_0^T \sum_{j=1}^J u_{jk}(t) \, dt}{\lambda_k^+ T}
\]
gives the percentage of class \( k \) patients who receive transplantation. Then the vector of likelihoods of transplantation is given by
\[
\int_0^T \tilde{D}u(t) \, dt \quad \lambda^+ T,
\]
where \( \tilde{D} \in \mathbb{R}^{K_W \times K_W \times J} \) is a matrix with components
\[
\tilde{D}_{ki} = \begin{cases} 1 & \text{if } i \mod K_W = k; \\
0 & \text{otherwise.} \end{cases}
\]
Because this form is not analytically tractable, they insert the Lagrange multipliers \( \gamma = (\gamma_1, \ldots, \gamma_{K_W})^T \) into the objective function using the following expression in the objective function:
\[
\int_0^T \gamma^T \tilde{D}u(t) \, dt.
\]
They combine the three objectives and the fluid model to obtain the following control problem: choose the allocation rates \( u(t) \) to maximize the tri-criteria objective of
\[
\int_0^T \left( \beta \sum_{k=1}^K h_k x_k(t) - (1 - \beta) \sum_{k=1}^{K_W} \sum_{i=1}^{K_W} \lambda_k(t, u(t)) \lambda_i(t, u(t)) \cdot \left( \frac{x_k(t)}{\lambda_k(t, u(t))} - \frac{x_i(t)}{\lambda_i(t, u(t))} \right)^2 + \gamma^T \tilde{D}u(t) \right) \, dt,
\]
subject to (1.4)–(1.8), where \( \beta \in [0, 1] \).

Because there does not appear to be a closed-form solution to this problem, they employ three approximations to this model and provide a heuristic dynamic index policy. At time \( t \), the dynamic index policy allocates all organs of class \( j \) to the transplant candidate class \( k \) with the highest index \( G_{jk}(t) \), which is defined by
\[
G_{jk} = \pi_{c(k, j)}(x(t)) - \pi_k(x(t)) + \gamma_k,
\]
where \( \pi_{c(k, j)}(x(t)) \) represents the increase in
\[
\beta \sum_{k=1}^K h_k x_k(t) - (1 - \beta) \sum_{k=1}^{K_W} \sum_{i=1}^{K_W} \lambda_k(t, u(t)) \lambda_i(t, u(t)) \cdot \left( \frac{x_k(t)}{\lambda_k(t, u(t))} - \frac{x_i(t)}{\lambda_i(t, u(t))} \right)^2
\]
if an organ of class \( j \) is transplanted into a candidate of class \( k \) at time \( t \).