Optimizing the Effectiveness of Organ Allocation

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Introduction

The first successful organ transplant occurred in 1954, a kidney transplant between twin brothers in Boston [Woodford 2004]. Since then, although the number of transplants per year has steadily risen, the number of organ donors has not kept up with demand [Childress and Liverman 2006] (**Figure 1**).

To ensure equitable distribution of available organs, Congress passed the National Organ Transplant Act in 1984. The act established the Organ Procurement and Transplantation Network (OPTN), a regionalized network for organ distribution [Conover and Zeitler 2006]. In 2000, the U.S. Department of Health and Human Services (HHS) implemented a additional policy called the *Final Rule*, which ensured that states could not interfere with OPTN policies that require organ sharing across state lines [Organ Procurement . . . 1999].

The organ matching process involves many factors, whose relative importance depends on the type of organ involved. These include compatibility, region, age, urgency of patient, and waitlist time [Organ Procurement . . . 2006]. Although most countries use the same basic matching processes, systems vary in their emphasis on particular parameters [Transplantation Society . . . 2002; UK Transplant 2007; Doxiadis et al. 2004; De Meester et al. 1998].

In 2006, kidneys comprised 59% of all organs transplanted [Organ Procurement . . . 2007]. In determining compatibility in kidney transplants, doctors look at:

- **ABO blood type:** The ABO blood type indicates the presence of two types of antigens, A and B, present in the patient's body. Antigens are foreign molecules or substances that trigger an immune response. People with blood
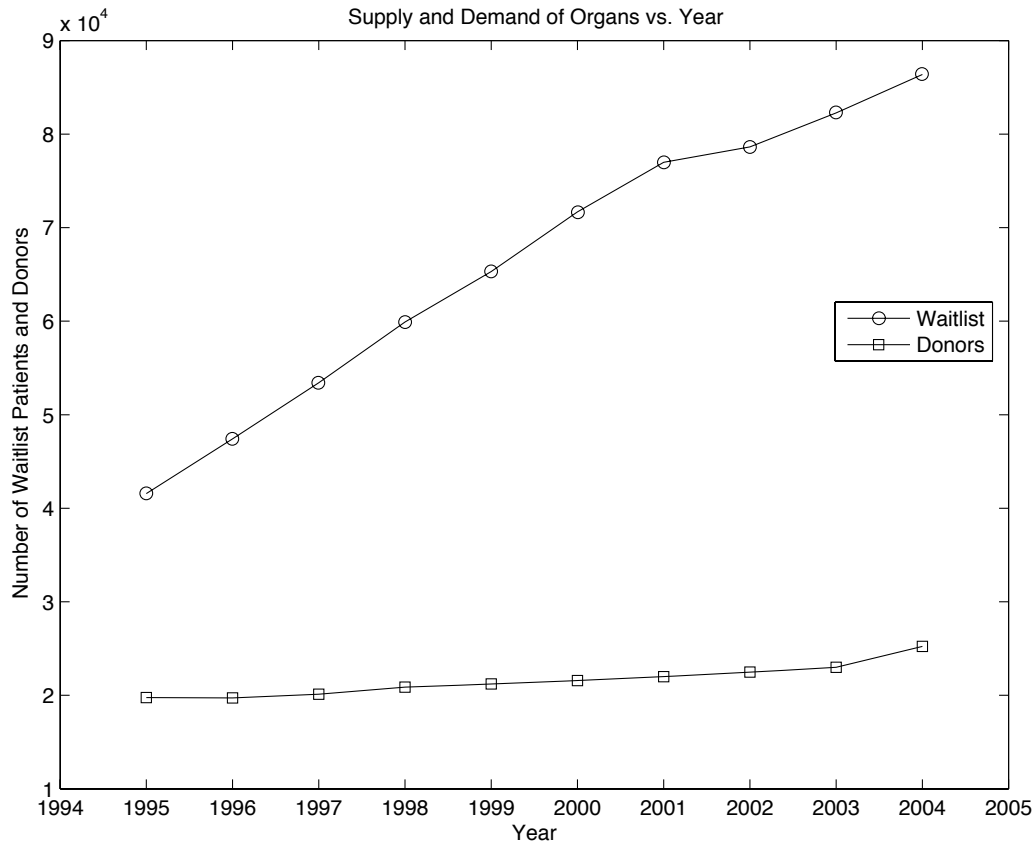
Figure 1. Number of transplants and cadaveric organ donors. Source: OPTN Annual Report 2005 [U.S. Organ Procurement . . . 2005].

type A have antigen A in their body, people with blood type B have antigen B, people with blood type AB have both, and people with blood type O have neither. A person with blood type AB can receive an organ from anyone, a person with blood type A or B can receive an organ from a person of blood type O or the same blood type, and a person with blood type O can receive an organ only from someone with type O blood.

- **Human Leukocyte Antigens (HLA):** HLA indicates a person's tissue type, whose most important components are the A, B, and DR antigens. Each antigen consists of two alleles, and matching all six components results in a significantly increased success rate for kidney transplants. Patients with mismatched components, however, can still survive for many years [U.S. Organ Procurement . . . 2005].

- **Panel Reactive Antibody (PRA):** PRA is a blood test, measuring the percentage of the U.S. population that blood samples are likely to react with. It tests for the presence of antibodies, proteins that bind to foreign molecules [University of Maryland . . . 2004a]. Blood can become more sensitive due to previous transplants, blood transfusions, or pregnancies [Duquesnoy 2005].

Kidney transplants are common partly because kidneys, unlike most other organs, can be safely obtained from live donors. In fact, live-donor kidneys are more effective than cadaveric kidneys, with longer half-lives and lower rejection rates [Gentry et al. 2005]. Over 75% of living donors in 2004 were related (parents, siblings, spouses) to the transplant recipients [Childress and Liverman 2006]. However, some people willing to donate to an intended recipient cannot because of blood type or HLA incompatibility, leaving over 30% of patients without a suitable kidney transplant [Segev et al. 2005]. One solution is kidney paired donation (KPD), which matches two incompatible donor-recipient pairs where the donor of each pair is compatible with the recipient of the other, satisfying both parties [Ross et al. . Another is list paired donation (LPD), where a recipient receives higher priority on the waitlist if an associated donor gives to another compatible recipient on the waitlist [Gentry et al. 2005].

We incorporate all these factors in modeling the various aspects of transplantation. First, we focus on the U.S. network and produce a generic model of the processes that impact the number of people on the waitlist, the number of transplants, and the length of wait time. To illustrate our model, we use data specific to kidney transplants, and also examine the policy of Eurotransplant for ideas on improving the current U.S. system. We then construct a model of list paired donation to determine how to maximize the number of exchanges while maintaining compatibility. Finally, we analyze the implications of our model for patient and donor decisions, taking note of important ethical and political issues.

Generic U.S. Transplant Network

Overview

We model the generic U.S. transplant network as a rooted tree (growing downward). The root represents the entire network, and its immediate children represent the regions. Each node represents some kind of organization, whether an Organ Procurement Center, a state organization, or a interstate region. At each node, there is a patient wait list, the concatenation of the wait list of the node's children.

We approximate the network's functioning as a discrete-time process, in which each time step is one day with four phases:

- In phase I, patients are added to the leaf nodes. We approximate the rate of wait list addition by a Poisson process; doing so is valid because we can reasonably assume that the arrivals are independent, identically distributed, and approximately constant from year to year. Suppose that this number of candidates added to the wait list at time t is addition$_t$, then we model

$$Pr(\text{addition}_{t+1} - \text{addition}_t = k) = \frac{e^{-\lambda}\lambda^k}{k!}.$$

For the rate constant λ, we use the number of organ applicants in a given year, $\lambda \approx$ (number of new applicants)$/365.25$.

- In phase II, we add cadaver organs to the leaf nodes. As with patients, we model cadaver arrivals as a Poisson process, with rate the average number of cadaver organs added in a given year.

- In phase III, we allocate organs based on *bottom-up priority rules*. A bottom-up priority rule is a recursive allocation process propagated up from the bottom of the tree, which requires any organ-patient match to meet some minimum priority standard. For example, for kidney allocation, the first priority rule is to allocate kidneys to patients who match the blood type and HLA profile exactly. Within this restriction, OPTN dictates that kidneys be allocated locally first, then regionally, then nationally. In our model, this corresponds to moving from the leaves up the tree. Matched organ-patient pairs undergo transplantation, which has a success rate dependent on the quality of the match. (In later sections, we explore the success rate as also a function of the experience of the doctors at the center and the quality of the kidney.)

- In phase IV, we simulate the death of patients on the waiting list. We treat the death rate k of a patient as a linear function $aT + b$ of the person's wait time T. Hence, calculating from time 0, a person's chance of survival to time T is $e^{-kT} = e^{-(aT+b)T}$.

Under this mathematical model, our problem becomes finding a good tree structure and an appropriate set of bottom-up priority rules.

Simulation

To study this model, we average results over many simulations of the kidney transplant network. Our simulation works as follows: At every time round, in phase I, we generate a number according to the Poisson distribution of the number of new candidates. For each new patient added, we randomly generate the person's race and age according to data on race and age distributions. Using the person's race, we generate the person's blood type and HLA makeup, according to known distributions, and the patient's PRA, based on probabilities published by the OPTN.

Similarly, in Phase II, we generate a list of donor organs according to known distributions of blood type and HLA makeup. Moreover, we record where the organ was generated, so we can study the effect of having to move the organ before transplantation, the time for which lowers its quality.

In Phase III, we implement recursive routines that traverse the tree from the bottom up, following the OPTN system for kidneys. To model the success rate of an operation, we use the statistics published by the OPTN; our main method of determining whether an operation is successful is the number of

HLA mismatches. Success is affected by the sensitivity of the person, measured by the person's PRA, which we model by adding a linear term to the success rate. Moreover, we reduce the success rate by 5 percentage points if the organ is not procured from the same center as the patient; 5% is the average effect on the success rate of increasing the delay by 10–20 hrs, according to OPTN data.

In Phase IV, we regress the coefficients a and b of the previous section, and use this formula to calculate the probability of death.

To adjust the parameters for this model, we use the OPTN national data for the national active wait list for cadaver kidneys from 1995 to 2004 and feed into our model the number of donations for each year.

Results of the Basic Model

To quantify the quality of a network, we use a set of objective functions, which represent various ideas about the desirability of policy outcomes. For these functions, let

x be the number of "healthy" patients to receive a successful transplant each year,

y be the corresponding number of "sick" patients (those with some terminal illness or serious medical condition) to receive a successful transplant,

a be the average age of the transplant recipients, and

m be the maximum wait time in the queue.

We examine the following objective functions:

$x + y$: This is simply the number of successful transplants per year.

$(100 - a) \times (x + y)$: This considers the premise that transplants are more valuable when given to young recipients.

$x + 0.5y$: This is a stylized adoption of the idea that transplants given to terminally ill recipients are less valuable.

$(x + y)/\max(9, m)$: This incorporates queue wait time.

We also include a proposed tradeoff between big and small centers:

- In a big center, the doctors are more experienced. We simulate this by decreasing the success rate of operations at centers that do not perform a threshold number of operations per year.

- With small centers, kidneys are allocated on a more local basis, which minimizes deterioration of organs in transportation. We simulate this by applying a penalty when kidneys are moved to larger regional centers, and also when kidneys are moved between centers.
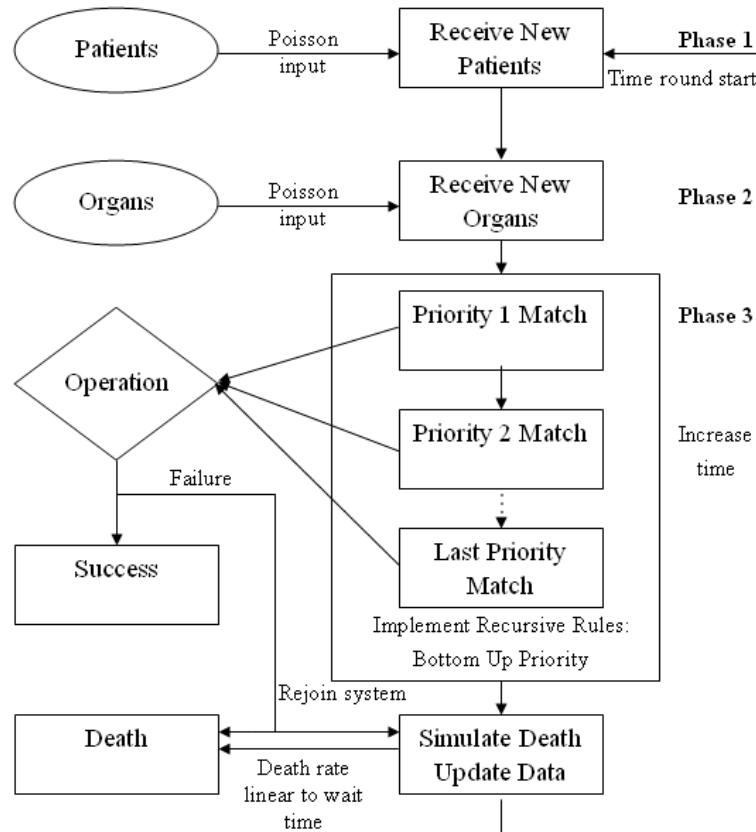
Figure 2. Flowchart for simulation.

Summary of Assumptions

- Arrivals in the waiting queue, both of cadaver donors and needy patients, are independent and randomly distributed

- The generic U.S. transplant network can be simulated as a rooted tree

- Death rate can be approximated as a linear function of time on the waiting list.

Other Countries' Transplantation Policies

We researched the policies of other countries, such as China, Australia, and the United Kingdom; they differ little from the U.S. policy. China uses organs from executed prisoners, which we do not believe to be ethical. We decided that the policies of Eurotransplant have the best groundwork: People analyze their policy each year, tweaking the waiting-time point system.

The Eurotransplant policy does not emphasize regions as much, with the maximum number of points for distance being 300. In contrast, the number

of points received for zero HLA mismatch is 400. The Eurotransplant policy also has greater emphasis on providing young children with a kidney match, giving children younger than 6 years an additional 1095 waiting-time points.

We implemented the Eurotransplant policy in our model to see if that policy could also benefit the U.S., but we found little difference.

Utilizing Kidney Exchanges

A promising approach for kidney paired exchange is to run the maximal matching algorithm over the graph defined by the set of possible exchanges. However, this approach takes away from the autonomy of patients, because it requires them to wait for enough possible pairs to show up before performing the matching, and sometimes it may require them to take a less than perfect matching.

We sought to improve this supposedly "optimal solution" by implementing list paired donation in our model.

According to each patient's phenotypes, we calculate the expected blood types of the person's parents and siblings, and make that the person's contribution to the "donor pool." In other words, the person brings to the transplant network an expected number r of potential donors. We then make the patient perform list paired donation with the topmost person in the current queue who is compatible in blood type to the donor accompanying the new patient. According to our research, kidneys from live donors are about 21% better than cadaver kidneys in terms of success rate. Thus, it is in the cadaver-list person's best interest to undergo this exchange.

We find that for any value of r from 0.2 to 2, list paired donation drastically decreases the length of the waitlist, by factors as large as 3, and makes the queue size stabilize (**Figure 3**).

Patient Choices

What should a patient do when presented with the opportunity for a kidney? The decision is not clear-cut; for instance, if the patient is offered a poorly matched kidney now, but a well-matched kidney is likely to arrive in a reasonable time, the patient should perhaps wait. We examine the this tradeoff.

We assume that a patient who has already received a kidney transplant may not receive another in the future. While this is not always true, it suffices for the purposes of our model, since we posit a choice between accepting a "lesser" kidney today and a better kidney later. (When a patient receives a second kidney transplant after the first organ's failure, there is no reason to expect a better organ, since the patient cannot immediately return to the top of the cadaver kidney queue, and live donors are likely to be more reluctant after a previous failure.)
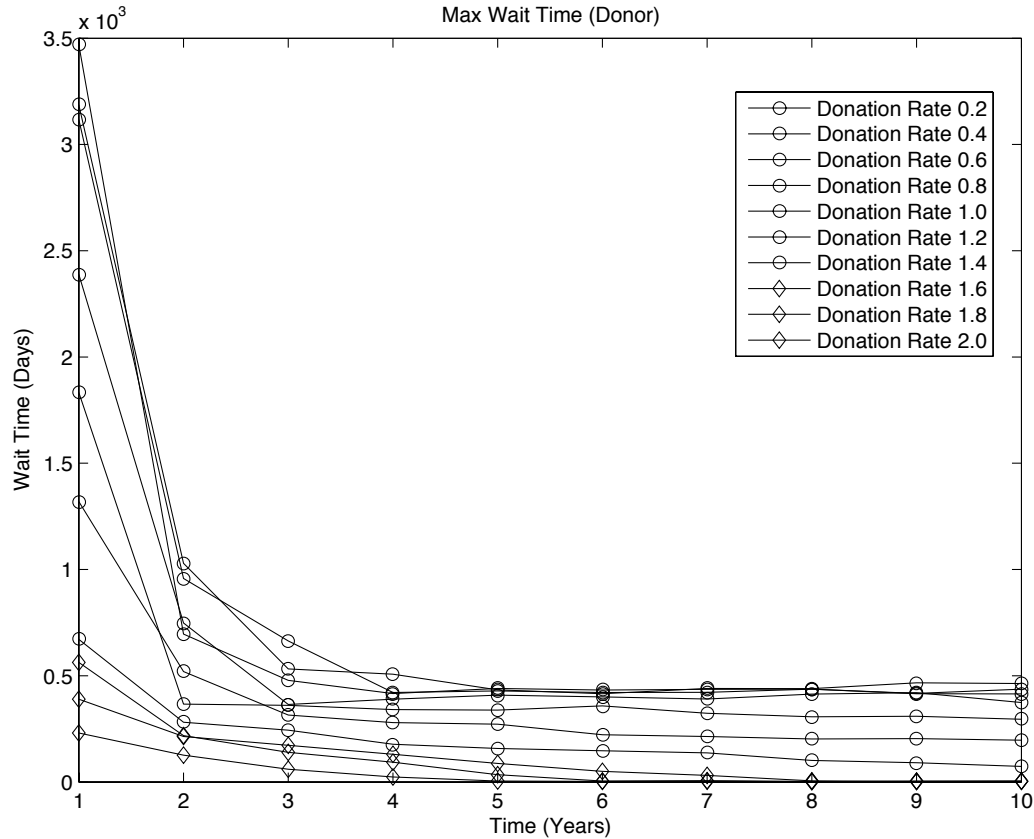
Figure 3. Wait time (in days) for various values of donation rate r, with list paired donation, applied over time to the current waitlist.

We assume that patients want to maximize expected years of life.

Let there be a current transplant available to the patient; we call this the *immediate alternative* and denote it by $\mathcal{A}_0$. The patient and doctor have some estimate of how this transplant will affect survival; we assume that they have a *survival function* $s_0(0, t)$ that describes chance of being alive at time t after the transplant. We further assume that this survival function is continuous and has limit zero at infinity: In other words, the patient is neither strangely prone to die in some infinitesimal instant nor capable of living forever.

The patient also has a set of possible future transplants, which we call *future alternatives* and write as $(\mathcal{A}_1, \mathcal{A}_2, \dots, \mathcal{A}_n)$. Each future alternative $\mathcal{A}_i$ also has a corresponding survival function $s_i(t_0, t)$, where t_0 is the starting time of transplant and t is the current time. We assume that there is a constant probability p_i that alternative $\mathcal{A}_i$ will become available at any time. While this is not completely true, we include it to make the problem manageable: More complicated derivations would incorporate outside factors whose complexity would overwhelm our current framework. Finally, if the patient opts for a future alternative and delays transplant, survival is governed by a *default survival function* s_d.

Summary of Assumptions

- The patient can choose either a transplant now (the immediate alternative $\mathcal{A}_0$), or from a finite set of transplants $(\mathcal{A}_1, \mathcal{A}_2, \ldots, \mathcal{A}_n)$ in the hypothetical future (the future alternatives).

- Each alternative has a corresponding survival function $s_i(t_0, t)$, which describes the chance of survival until time t as a function of t and transplant starting time t_0. Survival functions have value 1 at time 0, are continuous, and have limit zero at infinity.

- Each future alternative $\mathcal{A}_i$ has a corresponding constant probability p_i of becoming available at any given time. Hence, the probability at time t of the alternative not yet having become available is $e^{-p_i t}$.

- A default survival function $s_d(t)$ defines the chance of survival when there has not yet been a transplant. To maintain continuity, $s_d(t_0) = s_i(t_0, t)$.

- The patient can have only one transplant.

- The patient attempts to maximize expected lifespan; in case of a tie in expected values, the patient chooses an option that provides a kidney more quickly.

The survival functions must behave consistently; they cannot become wildly better or worse-performing relative to each other. We propose a formal definition to capture this concept.

A **separable** *survival function $s_i(t_0, t)$ is one that can be expressed as the product of two functions, one a function of only t_0 and the other a function of only $t - t_0$:*

$$s_i(t_0, t) = a_i(t_0)b_i(t - t_0).$$

We stipulate that $b(0) = 1$. In a **separable set** *of survival functions, all functions are individually separable with the same function $a(t_0)$.*

Is it be reasonable to assume that for any patient, the set of survival functions is separable? It is not an entirely natural condition, and indeed there are cases where it does not seem quite right—for instance, when some t_0 is high, so that higher values of t approach extreme old age, where survival decreases rapidly and the patient is less likely to survive than the product of a and b predicts. But in this case, the absolute error is small anyway: $a(t_0)$ accounts for the probability of survival that stems from waiting for a kidney until time t_0, and thus if t_0 is large, $a(t_0)b(t - t_0)$ is likely to be quite tiny as well.

Moreover, separability is intuitively reasonable for modeling the effects of a delayed kidney donation. The function $a(t_0)$ measures the decrease in survival rate that results from waiting for an organ transplant. This *should* be consistent across all survival functions for a given patient; we express this notion in the

concept of a separable set. Meanwhile, the factor $b(t - t_0)$ accounts for the decrease in survival during the time $(t - t_0)$ spent with the new kidney.

Consequently, we assume that our survival functions are separable. This will lead us to an explicit heuristic for lifespan-maximizing decisions, which is the goal of this section.

For $\mathcal{A}_i$ and $\mathcal{A}_j$ two future alternatives in a separable set, we assign an order according to:

$$\int_0^\infty b_i(t)\, dt \le \int_0^\infty b_j(t)\, dt \;\longleftrightarrow\; \mathcal{A}_i \le \mathcal{A}_j$$

We turn to the derivation of an lifespan-maximizing strategy. Such a strategy, when presented with alternative $\mathcal{A}_i$ at time t_0, will either accept or wait for other alternatives. In fact:

Theorem. *If a patient's alternatives form a separable set, then the optimal strategy is either to accept an alternative $\mathcal{A}_i$ at all times t_0 or to decline it at all times t_0. If the patient declines $\mathcal{A}_i$, then the patient must decline all alternatives less than or equal to $\mathcal{A}_i$ in the order relation defined above. Similarly, if the patient accepts $\mathcal{A}_j$, then the patient must accept all alternatives greater than or equal to $\mathcal{A}_i$.*

Proof: The patient will accept the alternative or probabilistic bundle of alternatives that the patient's survival functions indicate gives the greatest lifespan. For alternative $\mathcal{A}_i$, the expected lifespan beyond time t_0 is

$$\int_0^\infty s_i(t_0, t)\, dt.$$

Suppose that a patient at time 0 declines this alternative in favor of some optimal set of future alternatives. Furthermore, suppose that this set includes some alternative $\mathcal{A}_k$ such that $\mathcal{A}_k \le \mathcal{A}_i$. Then the expected lifespan from this set is

$$\left(\textstyle\sum_j p_j + p_k\right) \int_0^\infty \exp\left[-\left(\textstyle\sum_j p_j + p_k\right) t_0\right] a(t_0) \int_0^\infty \frac{\left(\sum_j p_j b_j(t) + p_k b_k(t)\right)}{\sum_j p_j + p_k}\, dt\, dt_0,$$

where j ranges over all alternatives $\mathcal{A}_j$ in the optimal set except $\mathcal{A}_k$. This double integral does not mix integration variables and is therefore equal to a product of two integrals:

$$\left(\textstyle\sum_j p_j + p_k\right) \int_0^\infty \exp\left[-\left(\textstyle\sum_j p_j + p_k\right) t_0\right] a(t_0)\, dt_0 \int_0^\infty \frac{\sum_j p_j b_j(t) + p_k b_k(t)}{\sum_j p_j + p_k}\, dt.$$

Since $\mathcal{A}_k$ is less than or equal to $\mathcal{A}_i$, and $\mathcal{A}_i$ was declined in favor of the set of alternatives that we are examining, the presence of the k term in the weighted average under the right integrand lowers the value of the average. The previous expression is thus less than

$$\left(\textstyle\sum_j p_j + p_k\right) \int_0^\infty \exp\left[-\left(\textstyle\sum_j p_j + p_k\right) t_0\right] a(t_0)\, dt_0 \int_0^\infty \frac{\sum_j p_j b_j(t) + p_k b_k(t)}{\sum_j p_j}\, dt.$$

Using integration by parts on the left, we finally get:

$$\left[1 + \int_0^\infty \exp\left[-\left(\textstyle\sum_j p_j + p_k\right) t_0\right] a(t_0)\, dt_0\right] \left[\int_0^\infty \frac{\sum_j p_j b_j(t) + p_k b_k(t)}{\sum_j p_j}\, dt\right]$$

$$< \left[1 + \int_0^\infty \exp\left[\left(-\textstyle\sum_j p_j\right) t_0\right] a(t_0)\, dt_0\right] \left[\int_0^\infty \frac{\sum_j p_j b_j(t)}{\sum_j p_j}\, dt\right].$$

The expression on the right is strictly larger than our starting expression, but it is is also equal (as inverse integration by parts shows) to the expected lifespan for the same optimal set of alternatives except *without* $\mathcal{A}_k$. This is a contradiction: By removing $\mathcal{A}_k$ from our "optimal" set, we have found a bundle with longer expected lifespan, indicating that the original set was not truly optimal. Our assumption that $\mathcal{A}_k$ is part of the optimal set is therefore false; in general, this means that when alternative $\mathcal{A}_i$ is declined for an optimized set of future alternatives, no alternative less than or equal to $\mathcal{A}_i$ can be in that set.

An analogous argument proves the opposite result: When alternative $\mathcal{A}_i$ is taken, all alternatives greater than or equal to $\mathcal{A}_i$ must also be taken when possible.

That the choice to accept or decline a given alternative is independent of the time of decision now follows immediately. With separable survival functions, the only difference between the expected lifetimes of alternatives and optimal sets over a time interval from t_1 to t_2 is the constant ratio $a(t_2)/a(t_1)$, which does not alter the direction of the inequality sign.   □

This theorem immediately implies a heuristic for an optimal strategy:

Heuristic for Finding an Optimal Strategy over Separable Survival Functions:

1. Determine the set of possible alternatives and the separable survival functions accompanying each.

2. Use the order relation given earlier to put the alternatives in order from $\mathcal{A}_1$ to $\mathcal{A}_n$, with $\mathcal{A}_1$ lowest and $\mathcal{A}_n$ highest.

3. Start with alternative $\mathcal{A}_n$.

4. Label the current alternative $\mathcal{A}_k$. Determine whether the expected value for a set including all alternatives $\mathcal{A}_{k-1}$ and greater is higher than the expected value for the set of alternatives at and above $\mathcal{A}_k$.

5. If yes, move down to $\mathcal{A}_{k-1}$ and repeat the previous step, unless you are already at $\mathcal{A}_0$. In that case, it is optimal to take all alternatives available, in particular, the immediate alternative.

6. If no, the optimal strategy is to take all alternatives from $\mathcal{A}_k$ to $\mathcal{A}_n$, but none smaller.

Ethical and Political Ramifications

It is reasonable to question kidney assignment to a patient who is less likely, for whatever reason, to benefit fully from the transplant's impact on lifespan.

We incorporate these situations into our model by altering the objective function for a particular class of patients. We simply alter the "returns" that determine how we measure success in the first place. This is a clean and efficient way to incorporate both practical (diseased people are not likely to benefit much from organ transplants) and moral ("save the kids!") judgments into our model.
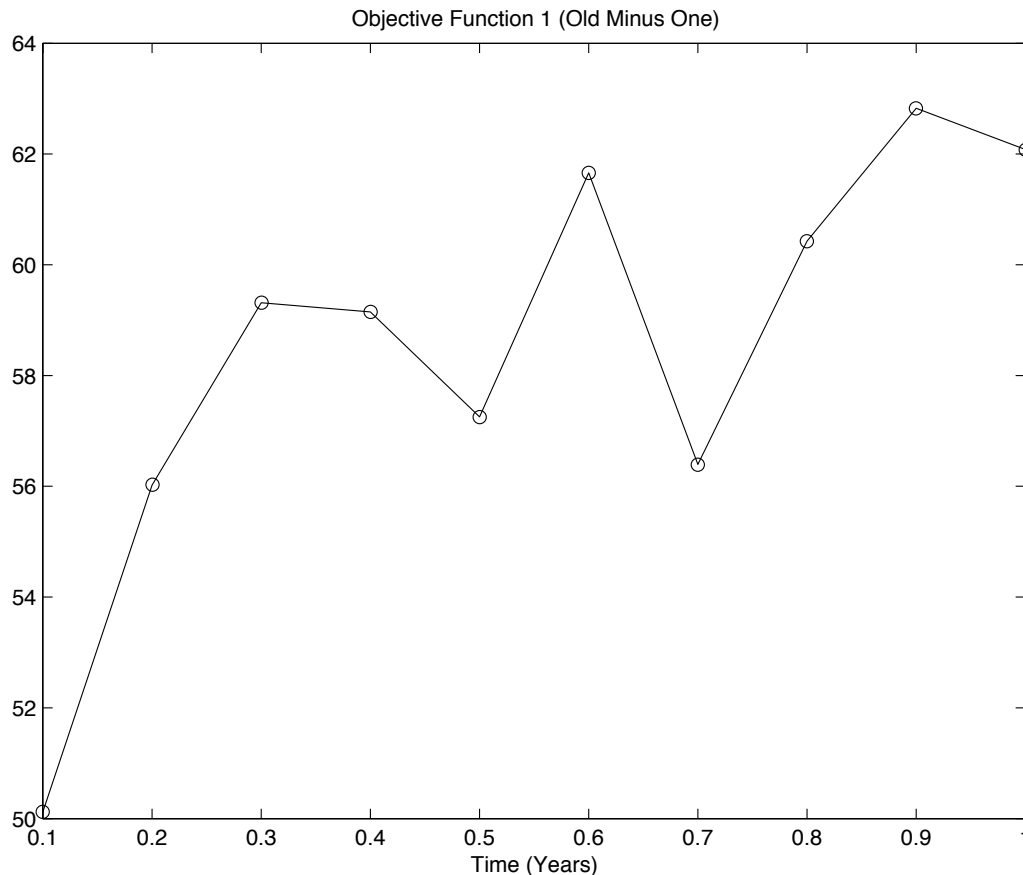

Figure 4. Results of policy of subtracting one point from the objective function of those above 60.

That transplantation is an enormously complex medical procedure, demanding dedicated facilities and experienced doctors, raises questions about the location of the surgery. Should we always ship kidneys to large, well-established medical centers, which may be more consistent in performing the operation? Or should we make transplants mostly local, so that all facilities become more experienced and maintain proficiency?

To reflect these concerns, we add two new and important wrinkles to our model.

- First, we introduce a "doctor experience function," which maps greater experience in transplant surgery to greater success and consistency in performing the procedure. Although it is impossible to pinpoint a precise analytical relationship between the number of transplants performed and success in performing them, we use regression on an OPTN data set to identify a rough linear function, and examine the effect of several other functions as well.

- Currently in the United States, fewer than half of cadavers with the potential to provide kidneys are used as donors. This is due to a system that relies heavily on *family wishes*: In most situations, doctors will defer to family members on the decision not to donate organs, even when there is preexisting affirmation of desire to donate from the deceased individual.

  One dramatic improvement, already implemented in some countries and since early this year in the State of Illinois, is *presumed consent*. Under presumed consent, every individual (possibly with limited restrictions) is assumed to have given consent for postmortem organ donation. An individual opposed to the prospect must explicitly "opt out." In many other countries, such a system has dramatically increased the pool of cadaveric kidneys available for transplant; in Austria, for instance, availability is nearly equal to demand. The result in the U.S. would not be quite so favorable; the Austrian system "benefits" from a high rate of traumatic road deaths.

In our model of living kidney donation, donors are limited to individuals with a substantial relationship to the patient: spouse, siblings, parents, children, and close friends. Excluding the black market in commercial kidneys, this setup accurately reflects the situation in the U.S. today, and in an ideal world it would be enough to provide high-quality living organs to those in need. But while list paired donation dramatically improves the usefulness of this system, its dependence on a limited pool of kidneys prevents full distribution. Moreover, some related donors decide against donation, further narrowing the supply for matching schemes.

Multiple studies identify financial disincentives as some of the main barriers to donation. Surprisingly, donors are sometimes liable for a portion of the medical costs of their procedure (and its consequences). Meanwhile, they often lose income, as they generally cannot work for some period of time during and after the transplant. And although exact figures on the number of potential donors dissuaded by these costs are difficult to obtain, sources suggest possible percentages as high as 30%.

What are the solutions? First, an authority (most likely the government) could provide for the full medical expenses of the operation, along with insurance for any future health consequences.

Some observers have proposed an even more radical reform: legalizing trade in human organs and creating "kidney markets" to ensure supply. A worldwide black market already exists in live-donor kidneys, offering some insights into how a legal system might work. The verdict is unclear; researchers

have been both surprised by the quality of black-market transplants and appalled by them. Arguably, however, concerns about quality and safety in an legal organ-trading system are misplaced, since there is little reason to believe that a regulated market (with transplants conducted by well-established centers) would be any worse than the general kidney transplant system.

More controversial is the *ethical* propriety of compensation from organs. By banning all "valuable considerations" in exchange for organs, the National Organ Transplant Act of 1984 expressed a widespread sense that any trade in organs is ethically appalling. Many commentators assert that it would inevitably lead to exploitation and coercion of the poor. At the same time, others claim that markets in organs are morally *obligatory*: If these markets are the only way to save lives, they must be implemented. We do not take a firm position on the ethics of this question but recommend studies of it.

Donor Decision

When considering donating a kidney, a potential donor takes into account many factors: the risk to self, the risk of future health issues, personal issues, and the chance of transplantation success.

Immediate Risk to Donor

Especially when the recipient of the kidney has no relation to the donor, the risk to the donor is of greatest importance. After all, they are putting their lives at risk when they are not otherwise in any danger of dying themselves. Of course, steps are taken to ensure that the donor is healthy enough to undergo a successful operation. At many institutions, the criteria for exclusion of potential living kidney donors include kidney abnormalities, a history of urinary tract infection or malignancy, extremely young or old age, and obesity. In addition, the mortality rate around the time of the operation is only about 0.03% [Jones et al. 1993].

Future Health Concerns

There have been suggestions that the early changes that result from the removal of the kidney, increase in glomerular filtration rate and renal blood flow, may lead to insufficiency of kidney function later on. However, a study of 232 kidney transplant patients, with a mean follow-up time of 23 years, demonstrated that if the remaining kidney was normal, survival was identical to that in the overall population [Jones et al. 1993]. In fact, another study suggests that kidney donors live longer than the age-matched general population, most likely due to the bias that occurs in the selection process [Ramcharan and Matas

2002]. Therefore, there is not a higher risk for development of kidney failure in the long run for kidney transplant donors.

Psychological Issues

There may, however, be future psychological issues stemming from depression. According to donor reports from a follow-up conducted by the University of Minnesota, 4% were dissatisfied from their donation experience, with non-first-degree relatives and donors whose recipient died within a year of transplant more likely to say that they regretted their decision and wish that they had not donated [Johnson et al. 1999]. To reduce this percentage, a more careful selection based on a rigorous psychosocial evaluation should be conducted.

Personal Issues

Some potential donors believe that they would incur the costs for the operation, discouraging them from following through with donating [United Network . . . 2007]. This is simply not true. Also, a survey of 99 health insurance organizations found that kidney donation would not affect an insured person's coverage and a healthy donor would be offered health insurance, so money is not a problem [Spital and Kokmen 1996]. However, money is lost from time away from work, and time away from home is also another significant contributor to the decision of a potential donor. Another personal issue that might deter potential donors is their attitude towards surgery in general, which may be affected by irrational fears or previous experiences. Such potential donors would be unable to cope psychologically with surgery, in spite of knowledge of the high probability of success.

Relationship

The relationship between the potential donor and the intended recipient is also a key factor. Close family members and the spouses of the recipients are three times as willing to participate in paired donation compared to other potential donors [Waterman et al. 2006]. Although it is hard to quantify, there also appears to be a significant number of altruistic donors. Most potential donors would not want to participate in nondirected donation, since it would not benefit their intended recipients, but 12% of potential donors were extremely willing to donate to someone they did not know [Waterman et al. 2006]. Since the risk/benefit ratio is much lower for living anonymous donors (LAD), there are concerns that such donors are ! psychologically unstable. However, studies conducted by the British Columbia Transplant Society indicate otherwise. About half of the potential LADs who contacted their center and completed extensive assessments that looked at psychopathology and personality disorder met rigorous criteria to be donors [Henderson et al 2003].

Across the different donor-exchange programs, there is a association between the willingness of potential donors to participate and how likely they thought their intended recipient would receive a kidney. With kidney paired donation, willingness to participate is 64% [Waterman et al. 2006]. For a compatible donor-recipient pair, the willingness for a direct transplant would be arguably closer to 100%. So we hypothesize that as the size n of a kidney exchange increases, potential donors become less willing to participate, because of the increasing chance for error in one of the swaps and the increasing difficulty of coordination. Potential donors would not wish to go through so much trouble without certainty of acquiring a kidney for their recipient, especially since they are giving up one of their own kidneys. For list paired donation, the data are inconclusive; in our model, we hypothesized that a random percentage of a predefined donor base would become actual organ donors.

There are essentially four basic models of systems that deal with incentives for live donors:

- **Market compensation model**, which is based on a free-market system in which the laws of supply and demand regulate the monetary price for donating a kidney.

- **Fixed compensation model**, where all donors are paid a fixed amount regardless of market value, for any trouble caused by the donation.

- **Expense reimbursement model**, which covers only the expenses incurred by the donor, such as travel and childcare costs, that are related to the transplant process.

- **No-compensation model**, the current system in the U.S., which forces an altruistic donor to cover his or her own expenses [Israni et al. 2005].

The market compensation model guarantees that the demand for kidneys will be met, as seen from Iran's organ market [President's Council on Bioethics 2006]. But it discourages altruistic donors, since they gain only monetary and no altruistic benefit. Also, the large demand for kidneys would likely drive the price up, causing ethical concerns about kidneys becoming a commodity available only to the rich. To encourage more altruistic donors, we argue that the expense reimbursement model is the best approach. This model allows altruistic donors to volunteer for the transplantation procedure without worrying about financial costs, and, unlike the fixed compensation model, prevents donors from making a profit from their donation. When there is an opportunity for profit, there is a risk of developing a market for organs, which many would argue is unethical. Still, we believe that given the enormous potential for increase in the kidney donor pool, it is important to investigate the possible results from compensation and incentive-based systems.

Conclusion

We believe in the absolute necessity of implementing a list paired donation system. Its dramatic positive effect on outcomes for kidney patients in need of replacement organs is remarkable and cannot be ignored.

We have also found several other less striking results.

- The basic importance of **geography**. High transportation time leads to deterioration of the organs being transferred; in poorly designed systems, this occurs even when there are plausible and equally valuable local routes for transmission.

- We recognize the importance of **age and disease stage** in allocating kidneys. When these factors are incorporated into our objective function, altering the point system for allocation decisions becomes important.

- It is critical to reflect the **objectives** of the transplant system. Without a well-verified and established relationship between what we include in our allocation decisions and our moral and ethical bases for judgment, we will always be dissatisfied.

Evaluation of Solutions

Strengths

Our main model's strength is its enormous flexibility. For instance, the distribution network can acquire many different structures, from a single nationally-run queue to a heavily localized and hierarchical system. Individuals, represented as objects in C++ code, are made to possess a full range of important attributes, including blood type, HLA type, PRA level, age, and disease. Including all these factors into a single, robust framework, our model enables realistic simulation of kidney allocation but remains receptive to almost any modification.

This strength allows us to make substantive conclusions about policy issues, even without extensive data sets. By varying parameters, allocation rules, and our program's objective function—all quite feasible within the structure—we can examine the guts of policymaking: the ethical principles underlying a policy, the implementation rules designed to fulfill them, and the sometimes nebulous numbers that govern the results.

Weaknesses

Although we list the model's comprehensive, discrete simulation as a strength, it is (paradoxically) also the most notable weakness. Our results lack clear illustrative power; data manipulated through a computer program cannot achieve

the same "aha" effect as an elegant theorem. Indeed, there is a fundamental tradeoff here between realism and elegance, and our model arguably veers toward overrealism.

Second, our model demands greater attention to numbers. While its general structure and methodology are valid, the specific figures embedded in its code are not airtight. For instance, the existing literature lacks consensus on the importance of HLA matching, possibly because developments in immunogenic drugs are changing the playing field too rapidly. Our use of parameters derived from OPTN data cannot guarantee numerical accuracy.

Third, and perhaps most fundamentally, the bulk of our simulation-based analysis hinges on the "objective functions" that we use to evaluate the results. This raises a basic question: What "good" *should* the kidney allocation system maximize? We attempt to remedy this problem by including multiple objective functions.

Appendices

Appendix I: Letter to Congress

We have undertaken an extensive examination of organ procurement and distribution networks, evaluating the results of differences in network structure on the overall success of the transplant system. In particular, we took a close look at the impact of two representative schemes for kidney allocation. First, we evaluated a simple model consisting of one nationally-based queue, where kidney allocation decisions are made without regard for individual region. Second, we looked at a more diffuse system with twenty regionally-based queues. We simulated the trade-off in effectiveness between the two systems by including a "distance penalty," which cut success rates for organs that were transported between different regions. This was implemented to recognize the role that cold ischemia, which is necessary for long-distance transportation of organs, plays in hurting transplant outcomes.

Higher levels of this parameter hurt the single-queue system, which transports its kidneys a noticeably greater average distance. Indeed, we found that for essentially all values of the distance penalty parameter, the multiple-queue system was superior. This is because the regionalized system in our simulation, modeled directly on the American system, uses geography to allocate organs when there is a "tie": when the organ has many similarly optimal potential destinations. This approach has no apparent downside, while minimizing inefficiency tied to unnecessary organ transportation. We recommend that you preserve the current regionally-based allocation system. Additionally, if you desire to allocate additional funds to improve the organ distribution system, we suggest that you support the streamlining of organ transportation.

We also compared the American OPTN organ allocation system to the analogous Eurotransplant system. Both use rubrics that assign "points" for various

characteristics important to their matching goals. They differ, however, in their scheme of point assignment; while the contrasts are largely technical, they have real impacts on the overall welfare of transplant patients. Although the systems were relatively close in effectiveness overall, our simulations identified the American point system as slightly superior. Therefore, we recommend you preserve the main points underlying the OPTN point allocation scheme.

Appendix II: Letter to the Director of the U.S. HRSA

We write having undertaken an extensive simulation-based review of the various political and ethical questions underlying decisions about organ allocation, and of policies for increasing live and cadaveric organ donation. First, we implemented a portion of code that represents the value of transplant center and doctor experience in improving donation outcomes. When we input a sizable experience effect, which does not appear to exist from the empirical data at this point, we found that a centrally based allocation and treatment system became substantially more effective than a more diffuse, multiple-queue based model. Given the lack of evidence that there is actually such an "experience" effect–the main available data, which comes from the Organ Procurement and Transportation Network, does not appear to indicate one–we advise caution before changing the system to reflect this theoretical result.

We also examined the usefulness of including heavy weights for age and terminal illness in the kidney allocation system. In general, we concluded that such measures are both justified and effective. Although blood type, HLA match, and PRA are still the most fundamental factors to consider, we believe that the extreme difference in effectiveness of helping people of different ages and health status justifies substantial inclusion of those factors in the allocation process.

Finally, we examined literature and existing research as they relate to the possibility of changing our system of consent and compensation for donation. We recommend implementing a "presumed consent" system for cadaveric organs, which will automatically tally deceased individuals as donors unless they have specifically opted out of the system. We also recommend exploring, but not necessary implementing, the possibility of some sort of compensation for live kidney donation. While we are mindful of widespread ethical concerns about the practice, we believe that the extreme demand for kidneys should prompt us to consider all alternatives. Specifically, we suggest a pilot program of light to moderate compensation for live kidney donors, and a thorough review of the outcome and change in incentives for those involved.

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Duke ICM 2007 team members Matt Rognlie, Amy Wen, and Peng Shi, wearing T-shirts with "nice numbers," and advisor David Kraines.