Practitioner's Commentary: The Outstanding Kidney Exchange Papers

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Mathematical Models Can Influence Public Policy on the Organ Shortage

The topic of kidney allocation and the shortage of kidneys for transplantation was a timely choice for the Interdisciplinary Contest in Modeling. In the past few years, public policy on organ donation and allocation has been changing rapidly, often in response to conclusions drawn from increasingly sophisticated mathematical models. Already in 2007, numerical projections of the significant impact of kidney paired donation in this country have prompted federal legislative and judicial action, which was necessary to clarify the indeterminate legality of paired donation. Bills passed in the House and Senate, and a Department of Justice memorandum, state that paired donation does not violate the National Organ Transplantation Act's prohibition on giving organs for valuable consideration.

The United Network for Organ Sharing (UNOS) is charged with oversight of all transplantation in the United States, including the allocation of organs from deceased donors to recipients. UNOS provides voluminous and easily accessible data on transplants at its Website http://www.unos.org. Within the past five years, UNOS has completely redrawn allocation procedures for liver and lung transplants. Recently, after statistical evidence showed that recipients with a liver allocation score of 15 or lower had shorter expected lifespans if they received a transplant than if they did not, liver allocation policy was revised to ensure that liver transplants went only to recipients who receive a survival benefit. The Department of Health and Human Services has also urged the

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transplant community to eliminate geographical disparities in allocation of organs.

Organ allocation makes an appealing target for interdisciplinary research, and not just because of the very real influence that mathematical modeling can have in shaping public policy. An application that can improve health care using mathematics also has tremendous motivational value for students, and makes a compelling advertisement of the contributions of operations research and interdisciplinary approaches to the lay public.

The Outstanding Papers

The problem statement asks students to address a range of questions about public policy and individual decisions in organ transplantation. A strong paper, then, should clearly state what changes to national policy are being advocated, and should use well-documented and correct analytical models to substantiate its conclusions.

Both Outstanding papers begin with dynamical models of the deceased donor kidney waiting list. There are more than 70,000 people on the waiting list to receive a kidney transplant from a deceased donor, and every year more people are added to the list than are removed. The team from Princeton University used a Markov-chain birth-and-death process to represent the size of the queue. The team used actual UNOS data to calculate fixed probabilities of each transition event: a new waitlist arrival increments the size of the queue, while transplantation, recovery of kidney function, or death all decrement the size of the queue. They validated their model's predictions against real data for net waiting-list additions in 2006. Importantly, the team used this model to evaluate two policies numerically: presumed consent for organ donation, and restricting the population that could join the waiting list. The team estimated annual list growth under perturbed versions of their model with increased transplantation rates or decreased waitlist arrival rates, and focused on zero waiting-list growth as the outcome of interest.

The Duke University team created a detailed discrete-event simulation in C++ to track the size of the queue as these events unfolded. By making the likelihood of death in each time period depend on the length of time that each individual had been waiting, this team captured the likely increase in deaths on the waiting list as the list grows longer. This latter property suggests that the size of the queue will stabilize when deaths on the waiting list occur at a rate that balances new additions, but the team did not explore this possibility. Because this detailed model of the waiting list contains recipient-specific information, this group was able to implement the UNOS point system for allocating kidneys and compare it to the Eurotransplant point system. Unfortunately, the results of the comparison were hard to interpret, because some figures that the team provided lacked axis labels, had cryptic captions, and were not cited in the text.

This team ran into a familiar dilemma for operations researchers working in organ transplantation, namely, that the objective of organ allocation is ill-specified by the transplant community and has myriad reasonable formulations. In particular, should allocation try to maximize the expected number of life-years gained from transplants? If so, then African-Americans and people older than 40 will be effectively denied any opportunity for transplantation, because these groups have lower expected lifetimes after transplant. This issue is being debated because the Kidney Allocation Review Subcommittee of UNOS proposes to increase the weight given to net lifetime survival benefit in allocation decisions. Historically, fairness to disadvantaged subgroups has been included in UNOS kidney allocation objectives. As another example, because kidney recipients can wait indefinitely on dialysis before receiving their transplants, but no life-prolonging therapies are available for liver or heart recipients, liver and heart allocation favors severely ill patients who are most at risk of death without a transplant rather than those who will receive the largest survival benefit after transplant.

Some members of the transplant community view deceased-donor organs as a local resource because local residents are the donors and local professionals counsel families about donation. These stakeholders feel that allocating organs recovered in one geographical area to recipients in a different area is unfair. However, the "Final Rule" legislation of 1999 requires that UNOS allocate organs in a way that minimizes the geographically-dependent variance in waiting times, outcomes, or other performance measures [Organ Procurement and Transplantation Network 1999]. This goal not yet been achieved, because waiting times for deceased-donor kidneys can vary by a factor of three or four between regions. The disparity is such that some hopeful recipients register in multiple regions to decrease waiting time.

Geographical aspects of transplantation were addressed well in both Outstanding papers. The models explored a tradeoff between

- achieving a high HLA (human leukocyte antigen) match, to ensure better outcomes for recipients; and
- decreasing transport distances, to reduce in-transit cold ischemic time and the associated risk of injury to the kidney.

Both teams made a crucial observation that the total cold ischemic time could be reduced even for kidneys shipped long distances, simply by speeding up the pretransit allocation process. Thus, the teams recommended that time to placement for each organ should be reduced if possible. Stefanos Zenios has published an excellent analysis of a system that could effectively reduce placement time by offering lower-quality deceased donor organs only to those recipients who are likely to accept them, which could mean using broader geographic sharing.

Finally, both teams discussed in detail the practical aspects of transplantation that they chose to simplify in each model, and in what way the messy details might alter their results and conclusions. For instance, the Princeton University team reported that its model of donor decision making does not account for factors such as the recipient's blood type and geographic location that would affect the person's estimated lifetime if the person remains on the deceased-donor kidney waiting list. The Duke University team correctly pointed out a lack of consensus in the literature about whether HLA matching affects survival of the transplanted organ, a question that has caused difficulties in my own research.

Optimization and Kidney Paired Donation

The problem statement set out an array of different tasks for the teams, so the teams did well to address some topics in more detail than other topics. As it happened, neither of the Outstanding papers proposed optimization models for kidney paired donation.

About one-third of recipients who have a loved one willing to be a live donor will find that the donor is incompatible. Without paired donation, these available donors do not give an organ and the recipient is added to the waiting list. In kidney paired donation, a match is made between two such incompatible pairs, so that the donor of the first pair can give to the recipient of the second pair, and vice versa. More generally, paired donation can include an exchange of kidneys among more than two incompatible pairs. There have been more living kidney donors than deceased kidney donors in recent years, and so kidney paired donation represents one of the most promising avenues for increasing the number of kidneys available.

Embedded within paired donation is a fascinating combinatorial optimization problem with a rich history: Among a set of incompatible pairs, how can the largest number of transplants overall be arranged? This is a graph-theory problem known as *maximum matching*, and it was first solved by Jack Edmonds about 50 years ago. A paired donation graph has a vertex to represent each recipient and his incompatible donor, with edges connecting two vertices iff they are mutually compatible. For example, in **Figure 1** many pairs could exchange with pair E, but the only pair which could exchange with pair C is pair A.

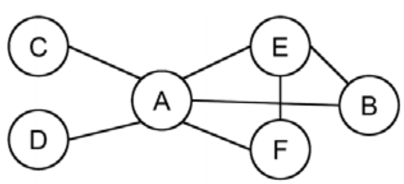

Figure 1. A kidney paired donation graph. Each vertex represents a recipient and the recipient's incompatible donor, and each edge indicates a mutually compatible exchange.

A *matching* is any subset of edges which does not contain any two edges incident on a single vertex. Some of the matchings on the graph of **Figure 1** are {AC, BE}, {AB, EF}, and {AB}. However, {AB, AC} is not a matching. To use maximum matching algorithms in practice, a paired donation system must allow a number of pairs to arrive before deciding which transplants should occur. If instead paired donations were performed as soon as possible, and if pair A and pair B arrived first, then only two transplants would occur for this group instead of the four that would otherwise be possible. Kim and Doyle [2006; 2007] have designed two interactive puzzles that allow students to solve tricky maximum matching problems and test out their favorite heuristics for the problem.

The team from Princeton University reported on a simulation of paired donation, but they did not comment on their matching algorithm. Their paper alluded to running a program every time a new pair arrives, which suggests that their method may not achieve the maximum number of transplants. Their results showed about 90% of incompatible pairs finding another pair with a complementary incompatibility. The best available results have match rates lower than 50%, but there was not sufficient detail provided to determine which modeling assumptions needed revision. Possibly the simulated blood types were not appropriately skewed towards the blood types likely to wind up in incompatible pairs.

List paired donation is a somewhat different approach whereby the living donor gives to a person on the deceased donor waiting list in return for moving the donor's intended recipient to the top of the waiting list. The team from Duke University made a strong claim that list paired donation alone might stabilize the queue size. However, deceased donor kidneys survive only half as long on average as live donor kidneys, so living paired donation is always preferable to list paired. Our own simulations show that list paired donation would not be an important contributor to transplantation rates if living paired donation were widely available [Gentry et al. 2005].

Mathematical simulations have been indispensable in demonstrating the impact of paired donation, because UNOS does not collect any data about the incompatible donors who come forward with recipients. The missing data can be reconstructed from known statistics using discrete event simulation. An interdisciplinary approach can be very successful in influencing public debate on these issues by offering detailed projections of the impact of new policies, as exemplified by some of the teams active in paired donation research. Extensive work in this arena has come from the team of Alvin Roth, Tayfun Sönmez, and Utku Ünver in cooperation with transplant surgeon Francis Delmonico; and I have enjoyed a very productive collaboration with my husband Dorry Segev, a transplant surgeon at Johns Hopkins.

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About the Author

Sommer Gentry studied applied mathematics and operations research at Stanford University and the Massachusetts Institute of Technology, receiving her Ph.D. in 2005. She was a Department of Energy Computational Science Graduate Fellow from 2001 to 2005. She is an Assistant Professor of Mathematics at the United States Naval Academy and a Research Associate in the Division of Transplantation at Johns Hopkins. Her research on maximizing paired donation to help ease the organ shortage has been profiled in *Time* and *Reader's Digest* and featured on the Discovery Channel. She serves as an adviser to both the United States and Canada in their efforts to create national paired donation registries.