Models and algorithms for fair exchange of kidneys

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1 Introduction

End-stage renal disease, also known as kidney failure, affects about one in thousand of the European population. There are only two treatments for patients suffering from kidney failure: dialysis, and kidney transplant. In the case of dialysis, patients have to spend hours every day in the hospital, hooked to a blood filtering machine. This kind of treatment severely affects the quality of life of the patient, and statistics show the life expectancy of patients under dialysis is shorter than the life expectancy of transplanted patients.

A kidney transplant can come from two possible different sources: a recently deceased donor, or a living donor. However, the demand in kidney transplantations far exceeds the number of deceased kidney donors; the waiting time for a transplantation can be several years. In the United States, there are currently 95 thousand patients on the waiting lists for kidney transplantation, and about 50000 patients are added to that list every year; by contrast, there were only 10000 deceased kidney donors in the United States in 2018 [Department of Health, 2019].

Some patients can find a willing living donor among their relatives. However, about 40% of willing donors are incompatible with their intended recipient. Kidney incompatibility can result from different blood types, or different antigen types. Incompatibility between a specific donor and recipient can be tested for by a crossmatch; a blood test that determines how the recipient will react to the transplant.

Deceased donors result in immediate transplants, since the time of ischemia of a kidney, *i.e.*, the time between the removal of the kidney from a donor, and the time of its implantation in a recipient, severely affects the success of the transplantation. By contrast, transplantations involving willing living donors can be carefully planned for and optimised on a large scale.

In order to reduce the number of deaths due to kidney failure, there has been an organised effort in the past few years to find cycles of paired donor-and-patient. The willing donor of a patient A_1 can give a kidney to patient A_2, whose willing donor will in turn give a kidney to patient A_3, etc., until the cycle completes and patient A_1 receives a kidney from the willing donor of patient A_k.

In addition to donor cycles, there can also be donor chains. A chain is initiated by an altruistic donor; a donor with no intended recipient. If the kidney of an altruistic donor is donated to a patient who had an incompatible willing donor, this donor could decide to become an altruistic donor themselves. The result is called a non-simultaneous altruistic donor chain, by contrast with donor cycles, which for ethical and practical reasons are constrained to be short (often involving at most three patients) and simultaneous.

In 2012, the Nobel prize in Economic Sciences was given to Lloyd Shapley and Alvin Roth "for the theory of stable allocations and the practice of market design", which includes their theoretical work on algorithms assigning organ donors to patients, most notably Gale-Shapley's algorithm for top-trading cycles [Shapley and Scarf, 1974], as well as their efforts to apply those algorithms in the United States by the foundation of the New England Program for Kidney Exchange [Roth et al., 2005].

2 The model

Although kidney compatibility between a specific donor and patient must be tested by a crossmatch before a transplantation is carried out, it is possible to individually test all patients and donors for blood type and antigen types, and use the result to build a directed graph $G = (V, E)$, where:

1. each vertex $v \in V$ represents an incompatible donor-patient pair;
2. for two vertices u and $v \in V$, there is a directed edge (u, v) if and only if the donor of u is believed to be kidney-compatible with the patient of v;
3. alternatively, each directed edge $(u, v) \in E$ is equipped with a weight $w(u, v)$ such that a high weight represents a high probability that donor u and patient v are kidney-compatible.

The *clearinghouse problem* consists in finding a collection of disjoint cycles that maximises the sum of lengths of the cycles; in other words, a collection of disjoint cycles that maximises the number of transplanted patients.

The *weighted clearinghouse problem* consists in finding a collection of disjoint cycles that maximises the sum of weights of the cycles, where the weight of a cycle is defined as the sum of weights of the edges making the cycle.

The weight of an edge (u, v) represent the utility of a transplantation from the donor of u to the patient of v. In particular, this accounts for the probability that a donor and patient are compatible; indeed, although it is possible to get a pretty good idea of kidney compatibility by comparing the blood types and antigen types, a crossmatch test must always be performed between the donor and the patient prior to a transplant to deny or confirm the compatibility. If the result of the crossmatch is positive, *i.e.*, if the patient reacts to the donor's tissue, the donor and patient are judged incompatible. The transplant between this patient and donor cannot be carried out, and if the donor and patient were part of a cycle, all transplantations in the cycle must be canceled. For this reason, it is better to keep the length of each cycle small.

For incentive and ethical reasons, all transplants in a donor cycle must be carried out simultaneously; indeed, an organ donor can always change their mind at the last minute and refuse to donate their kidney, effectively breaking the cycle. In any other bartering economy, this issue could be solved by writing down a contract binding all donor-patient pairs in the circle. In the case of organ donation, however, it is not possible to write a contract, as a living donor can never be forced to donate. In fact, contract for organ donations are explicitly forbidden by law in most countries. This is a second argument in favour of small cycles, because hospitals typically cannot perform more than three kidney transplantations simultaneously; indeed, each transplantation requires an operating room, as well as a number of doctors, anaesthetists, and nurses.

The clearinghouse problem can easily be represented as an integer linear program, with a binary decision variable for every edge in E. With such a representation, it is easi to modify the problem by adding constraints or modifying the objective function; for instance, it is possible to add a penalty for larger cycles, since smaller cycles might be preferable.

The constraint of small cycles can be added explicitly to the clearinghouse problem by requiring that all cycles in the collection have length at most k, where k is a given parameter, usually 2 or 3. If $k = 2$, the clearinghouse problem is exactly the problem of finding a maximum matching. It is shown in [Abraham et al., 2007] that the clearinghouse problem becomes NP-complete as soon as $k \geq 3$.

An altruistic donor can be added to the model in the form of a vertex $v \in V$ representing the altruistic donor paired with a dummy patient compatible with all other donors [Manlove and O?Malley, 2012]. Similarly, a patient who does not have an incompatible willing donor can be added to the model in the form of a vertex $u \in V$ representing the patient and a dummy donor compatible only with dummy patients.

Finally, a word should be said about the utility of a transplantation. The weight of an edge (u, v) does not only represent the probability that the donor and patient involved will be compatible. It also accounts for the benefit gained from this transplantation, in particular the life expectancy of the patient after the transplantation. In the case of a dummy patient, this utility is of course zero. In the case of a real patient, a score is calculated by a government organism, for instance the United Network for Organ Sharing in the United States [UNOS, 2019], based on several criteria, among which their age (favouring younger patients) and their alcohol consumption prior to the transplantation. This score is usually the same used to rank patients on the waiting list for deceased donors. Determining the weights is a heavy ethical question, which can have strong repercussions on the optimal solution to the problem.

3 Other related problems

In this section, two other problems encountered in kidney exchange programs are briefly exposed. They have been studied and addressed with artificial intelligence methods.

3.1 Attributing weights to edges

In the weighted version of the clearinghouse problem, the weights are first decided by a committee following a set of rules, then fed into the clearinghouse algorithm. Those weights are also used when ranking patients in the waiting list for deceased donors or altruistic living donors. The impact of the weights might be very important: patients with low weights are more likely to be left out of the optimal solution, and not receive a kidney transplant. Last year, the impact of weights on the clearinghouse problem was measured with some precision and it was proposed to automatically calculate weights for all patients by generalising from human judgment on a small set of patients [Freedman et al., 2018]. They use the Bradley-Terry model [Bradley, 1984] and its implementation in the language R [Turner et al., 2012] to aggregate relative judgments between pairs of patients: the judges were only asked to state which patient they favoured out of two patients. This kind of automated moral decision making could also have applications in other domains, such as self-driving cars.

3.2 Individual rationality of hospitals

If a nationwide kidney exchange program is deployed, hospitals are faced with a decision: should they report their donor-patient pairs in the program, and let a central algorithm decide the donor cycles, or should the hospital try to find internal cycles involving only their own patients?

An hospital forming internal cycles can be seen as an extra constraint on the clearinghouse problem; those extra constraints have a high cost on the objective function, *i.e.*, on the number of transplantations in an optimal solution (or on the total weight of the optimal solution in the weighted version of the problem).

There are several reasons why a hospital might not want to report all of their patient-donor pairs to the central program. If two donor-patient pairs u and v from the same hospital can form a cycle of length 2, it is possible that an optimal solution to the clearinghouse problem would include pair u in a cycle with pairs from other hospitals, while leaving pair v outside of all cycles. In that case, the number of transplanted patients from this hospital would be higher by keeping the two pairs u and v out of the program and matching them internally.

In addition, because of the way blood types compatibility works, some patient-donor pairs are more difficult to match than others. For instance, an AB-type donor paired with an O-type patient might be much more difficult to include in a cycle than an O-type donor paired with an AB-type patient. It would make sense for a hospital to report its difficult pairs to the program, but keep its easier pairs for internal cycles. Such behaviour from hospitals might have a strong impact on the overall quality of the solution.

Other reasons why a hospital would not report all of its patients to the program include the difficulties of bureaucracy, such as a lack of standardisation of the compatibility test, the inability for a hospital to collect the medical data required by the program, or the financial cost for a hospital of performing tests on a donor who will end donating their organ to another hospital.

A number of papers in the literature of kidney exchange model the problem as a game in which the hospitals are players who must decide which of their donor-patient pairs to report to the central program [Ashlagi and Roth, 2014, Ashlagi and Roth, 2011, Toulis and Parkes, 2011]. They study the impact of the individual rationality of hospitals on the objective function, comparing it to the optimal value of the objective if hospitals reported all their patients and donors, as well as incentive mechanisms and their impact on the objective function.

3.3 Uncertainty and robustness

Although the weights in the clearinghouse problem result from the uncertainty of the outcome of transplantations, the weighted clearinghouse problem itself does not reflect this uncertainty. A classic approach to optimisation under uncertainty is robust optimisation [Bertsimas et al., 2011].

There are several sources of uncertainty on the weights. The first one is kidney compatibility; the blood-type and antigen-types test results from donor D and patient P are not sufficient to determine whether patient P and donor D would get a negative or positive crossmatch; and eventually, whether patient P would reject a kidney from donor D. Additionally, a donor my retract from the exchange at the last moment. Another source of uncertainty is the social utility of transplanting a patient; for instance, some policymakers prioritise younger patients, while other policymakers might prioritise sicker patients above all healthier patients.

The Position-Index Traveling Salesman Problem [McElfresh et al., 2018] is a robust approach to the kidney exchange problem.

4 Solutions

4.1 Two classic formulations as an integer linear program

The clearinghouse problem was most often written as the following integer linear program [Constantino et al., 2013]:

$$\text{maximise} \sum_{(i,j)\in E} w_{ij} x_{ij} \tag{1}$$

$$\text{subject to } \forall i \in V, \sum_{j:(i,j)\in E} x_{ij} = \sum_{j:(i,j)\in E} x_{ji} \tag{2}$$

$$\forall i \in V, \sum_{j:(i,j)\in E} x_{ij} \leq 1 \tag{3}$$

$$\forall \text{path } i_1, i_2, ..., i_{k+1}, \sum x_{i_p i_{p+1}} \leq k-1 \tag{4}$$

$$\forall (i,j) \in E, x_{ij} \in \{0,1\} \tag{5}$$

There is a binary decision variable x_{ij} for every edge (i, j) in the graph. The objective function (1) corresponds to the weighted version; the nonweighted version is obtained by setting $w_{ij} = 1$ for all edges (i, j).

Constraint 2 ensures that each patient receives as many kidneys as their incompatible willing donor donated.

Constraint 3 ensures that at most one kidney is donated by each donor.

Constraint 4 depends on the parameter k and ensures that no cycle has length $> k$. However, this constraint explicitly lists all paths of length $k+1$. The number of such paths can be exponential in k. Practically speaking, even with $k = 3$, a complete graph with 1000 vertices has over 400 million 3-paths.

Another possible formulation of the clearinghouse problem as an integer linear program is to use a decision variable for each cycle instead of a decision variable for each edge. However, the number of cycles can itself be exponential in k.

4.2 Solving the two classic formulations

The edge-formulation has too many constraints; this can be tackled with constraint-generation methods, such as cutting-plane.

The cycle-formulation has too many variables. A solution is column-generation. The principle is to consider initially only a small subset of possible cycles; then add cycles to the problem if they have positive reduced cost.

Those methods have been compared and tested experimentally on randomly-generated kidney exchange markets [Abraham et al., 2007]. The process to randomly generate patients and donors is described in [Saidman et al., 2006] and is based on real data from [Data, 2004].

4.3 Polynomial formulation as an integer linear program

The following, more recent, formulation of the clearinghouse problem only uses a polynomial number of decision variables and constraints [Constantino et al., 2013].

Because the number of cycles in the solution cannot exceed the number of patients, it is possible to index all cycles by a number between 1 and $|V|$. Then, we can have extra binary variables y_i^l deciding whether the donor-patient pair i belongs to cycle l. Using these variables, the constraints on cycle length can be rewritten using only a polynomial number of constraints:

$$\text{maximise} \sum_{(i,j)\in E} w_{ij}x_{ij} \tag{6}$$

$$\text{subject to } \forall i \in V, \sum_{j:(i,j)\in E} x_{ij} = \sum_{j:(i,j)\in E} x_{ji} \tag{7}$$

$$\forall i \in V, \sum_{j:(i,j)\in E} x_{ij} \leq 1 \tag{8}$$

$$\forall 1 \leq l \leq |V|, \sum_{i\in V} y_i^l \leq k \tag{9}$$

$$\forall i \in V, \sum_{1\leq l\leq |V|} y_i^l = \sum_{j:(i,j)\in E} x_{ij} \tag{10}$$

$$\forall 1 \leq l \leq |V|, \forall (i,j) \in E, y_i^l + x_{ij} \leq 1 + y_j^l \tag{11}$$

$$\forall (i,j) \in E, x_{ij} \in \{0,1\} \tag{12}$$

Constraint 9 ensures cycles have length less than k.

Constraint 10 ensures that a donor-patient pair is part of exactly one cycle if and only if it is donating one kidney, and is not in any cycle if and only if it is donating no kidney.

Constraint 11 ensures that if pair i is in cycle l and donating to patient j, then pair j is also in cycle l.

It can be seen that the number of constraints in this formulation is at most cubic in the number of patients, and the number of decision variables is quadratic. Thus, the problem can be solved by classic integer linear programming methods, such as branch-and-bound.

5 Conclusion

Although kidney paired donation was first suggested in 1986, and the first paired exchange transplants happened in 1991 in South Korea, it took decades for national paired donation programs to develop. A national kidney exchange program is a large barter market; in the USA for instance, the number of patients waiting for a kidney is as large as 10^5 and the annual number of deaths due to kidney failure is counted in thousands. Hence, it is vital to develop algorithms to optimise the market.

In this paper, I exposed several optimisation problems encountered in nationwide kidney donation, as well as algorithms used to solve those problems.

Kidney exchange remains an open area of research. Kidney exchange programs still suffer from many practical or financial deficiencies, and are subject to ongoing discussions about ethics. Kidney exchange programs are expected to grow in size in the future year, as a result of the increasing number of kidney failures, as well as barriers to enter the system diminish; international cooperation could also result in an even larger market. As the practical and medical constraints on donor cycle length and donor chain length evolve, the algorithms must evolve to adapt to the reality of the situation.

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