

Optimizing the Kidney Exchange Problem with a Budget for Simultaneous Crossmatch Tests

Valeria Romanciuc[1] and Filipe Alvelos[2(✉)]

[1] Centro Algoritmi, Universidade do Minho, 4710-057 Braga, Portugal
pg33724@uminho.pt
[2] Centro Algoritmi/Departamento de Produção e Sistemas, Universidade do Minho, 4710-057 Braga, Portugal
falvelos@dps.uminho.pt

Abstract. Many people in the world suffer from end stage renal disease, which has transplantation as the most effective form of treatment. However, kidneys obtained from deceased donors are not nearly enough to meet demand and willing living donors may display incompatibilities with their intended recipient. Kidney Exchange Programs have emerged as an attempt to answer the transplant shortage and bypass these incompatibility issues between donor-patient pairs. The process of selecting the pairs participating in the transplantation plan requires optimization models, one of which is presented in the current paper. We focus on maximizing the expected number of transplants taking into account that only a given number of actual incompatibility (crossmatch) tests can be made. We present an integer programming model to address this problem when recourse is feasible and we compare computationally its outcomes with other two approaches in 150 instances.

Keywords: Kidney exchange program · Integer programming · Optimization

1 Introduction

End stage renal disease (ESRD) affects about one in a thousand people in Europe [5]. Two options are available for treatment: dialysis and transplantation [4]. The latter has proved to be the preferred alternative, as it usually provides higher quality of life and higher chances of patient survival, while also being less costly than the former [14,19].

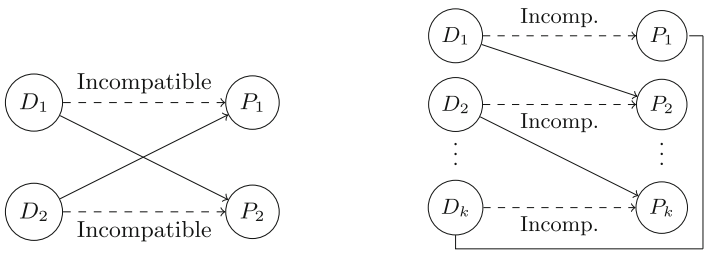
Kidneys for a transplant may be obtained both from deceased and living donors. In the first case, patients are placed on a waiting list, hoping to find a compatible donor. Despite being the standard practice for a long time, it failed to keep up with the fast growth of the number of patients suffering from ESRD, which significantly increased waiting times for transplantation [19]. As such, in order to bridge the gap between this shortage of kidneys and their ever-growing

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demand, new transplantation strategies emerged, one of them being the inclusion of living donors in the donor pool [7,8]. This not only increased the number of transplants taking place, but also improved the outcomes of transplantation when compared to using deceased-donor kidneys [8]. However, in order for transplantation to be carried out, the willing donor must be physiologically compatible with their intended recipient, which fails to happen in over 30% of the cases [18].

Evidence has shown very similar results in graft survival considering transplants conducted with kidneys obtained from genetically unrelated donors when compared to kidneys transplanted from siblings or other histocompatible donors [8,10]. As a result, alternative approaches have been adopted, including kidney exchange programs (KEPs).

KEPs provide an alternative solution for patients with willing yet incompatible donors. First proposed by Rapaport in 1986 [16], their simplest form consists in the following: given a patient P_1 with a willing but incompatible donor D_1, and another such donor-patient pair, D_2 and P_2, respectively, let us suppose that D_1 is compatible with P_2 and D_2 is compatible with P_1 (Fig. 1a). Therefore, by swapping donors, we could proceed with both transplants, as opposed to conducting none in the original scenario. This exchange can be generalized to include k incompatible pairs, as depicted in Fig. 1b. For logistic reasons, since the transplants in an exchange must be done simultaneously, usually a certain limit is imposed on the number of pairs taking part in an exchange.



(a) 2-way exchange (b) k-way exchange

Fig. 1. Representation of a 2-way kidney exchange and a k-way kidney exchange. The dashed arrows represent incompatibility and the full arrows represent compatibility between donor (D_i) and patient (P_i).

Additional variations were studied, including the non-directed donors (people willing to donate a kidney without having an associated recipient) as well as patient desensitization [12]. However, we will be focusing only on 2-way and 3-way exchanges within a network.

Compatibility between pairs is determined based on blood type and human leukocyte antigen (HLAs) matching. In the latter case, a preliminary test is performed (called "virtual" crossmatch): the pair is considered to be compatible if the virtual crossmatch is negative and incompatible otherwise [5]. Based on

this information, a transplantation plan is defined. Afterwards, a more accurate test is applied (the "actual" crossmatch, henceforth referred to as crossmatch), possibly revealing new incompatibilities between pairs and thus cancelling programmed exchanges. Given the number of combinations, testing every two pairs for compatibility is only feasible in very small pools.

As for the definition of transplantation plans, KEPs have been addressed mostly with integer programming based approaches [1,7,13]. Different criteria can be maximized in order to determine the best transplantation plan, such as the number of transplants, the number of 2-way exchanges [6] or the expected number of transplants [13]. In order to take into account the uncertainty of the results of the crossmatch tests, we assume the probability of match failure for each transplant is known.

We address the problem of selecting which possible transplants should be tested, taking into account that each test has a cost, there is a budget, and all tests must be conducted simultaneously. A potential reason for simultaneity comes from the lack of time to wait for the result of a (set of) crossmatch test(s) to decide the next (ones) to conduct. The budget constraint allows modelling the case where there is a limit on the number of tests that can be performed. In this case, each arc has a unitary cost and the budget corresponds to the maximum number of tests. The budget constraint is also relevant in multi-agent (i.e., when several agents participate in a joint donor pool) kidney exchange programs, where tests may have different costs as a consequence, for example, of different logistic costs, as it happens in multi-country KEPs.

We will study two approaches. In the first, we do not consider the possibility of recourse once a certain solution is determined, so it is final and can not be modified. In the second approach, we consider the possibility of rearranging the transplants in a transplantation plan in case new incompatibilities arise and part of the exchange is cancelled. Such recourse approaches have been considered in [13,15].

As the tests are conducted simultaneously, the decision on which tests to conduct must be made before any results are known. We derive an integer programming model that takes into account this uncertainty and the budget constraint and perform a computational study.

Related work on deciding which arcs to test assume several runs of the KEP. In that case, after knowing the results of a set of tests, a new set of tests to conduct is decided. Different policies and approaches for that problem were proposed in [2,3,9].

The paper is structured as follows. In Sect. 2, we present the problem without recourse and an integer programming model. In Sect. 3, we extend the model for when recourse is allowed. In Sect. 4, results from computational tests are presented and compared for each approach. Finally, in Sect. 5 we provide some conclusions.

2 Problem Description and Model

KEPs are typically represented via graph theory. Let us consider a directed graph $G = (N, A)$, where N is the set of nodes representing incompatible pairs

of donor-patient, and A is the set of arcs representing compatibility between pairs. Thus, given two pairs $i, j \in N$, the arc (i, j) is in A if the donor in pair i is compatible with the patient in pair j. Furthermore, associated to each arc is a weight p_{ij}, which represents the probability of match failure of arc (i, j).

Each feasible exchange between two or more pairs will be represented by a cycle in the aforementioned graph and we will only consider cycles of lengths 2 and 3 (2-cycles and 3-cycles, respectively), as they are the most common in actual KEPs.

In this section, we consider the problem of deciding which arcs to select such that they form a set of disjoint cycles corresponding to a maximum value of the expected number of transplants. The main difference to the well-known cycle formulation is the additional budget constraint. Transplants will be conducted only with tested arcs.

Let C be the set of all cycles in G (with at most 3 arcs). Given a 2-cycle $c \in C$ with arcs (i, j), $(j, i) \in A$, the expected number of transplants is given by

$$E(c) = 2(1 - p_{ij})(1 - p_{ji}), \tag{1}$$

where p_{ij} is the probability of failure associated with arc $(i, j) \in A$. Similarly for a 3-cycle $c \in C$ with arcs (i, j), (j, k), $(k, i) \in A$, the expected number of transplants is given by

$$E(c) = 3(1 - p_{ij})(1 - p_{jk})(1 - p_{ki}), \tag{2}$$

where p_{ij}, p_{jk} and p_{ki} are the probabilities of failure associated with arcs $(i, j), (j, k)$, and (k, i), respectively.

The following parameters are defined.

$$a_{ij}^c = \begin{cases} 1, & \text{if arc } (i,j) \in A \text{ is in cycle } c \\ 0, & \text{otherwise} \end{cases} \qquad \forall c \in C$$

p_{ij} – probability of match failure of arc $(i, j) \in A$, $\quad \forall (i, j) \in A$
b_{ij} – cost of a test conducted on arc $(i, j) \in A$, $\quad \forall (i, j) \in A$
B – total budget available

The decision variables are defined as follows

$$w_c = \begin{cases} 1, & \text{if cycle } c \in C \text{ is selected for the plan} \\ 0, & \text{otherwise} \end{cases} \qquad \forall c \in C$$

$$y_{ij} = \begin{cases} 1, & \text{if arc } (i,j) \in A \text{ is tested} \\ 0, & \text{otherwise} \end{cases} \qquad \forall (i, j) \in A$$

The integer programming model is

$$\text{Maximize} \qquad z = \sum_{c \in C} E(c) w_c \tag{3}$$

$$\text{Subject to:} \qquad \sum_{c \in C} \sum_{(i,j) \in A} a_{ij}^c w_c \leq 1, \quad \forall i \in N \tag{4}$$

$$w_c - a_{ij}^c y_{ij} \leq 0, \quad \forall (i,j) \in A, \forall c \in C \tag{5}$$

$$\sum_{(i,j)\in A} b_{ij} y_{ij} \leq B \tag{6}$$

$$w_c, y_{ij} \in \{0,1\}, \forall c \in C, \forall (i,j) \in A \tag{7}$$

The objective function (3) maximizes the expected number of transplants. Constraints (4) ensure that each node (that is, each pair donor-patient) is in at most one selected cycle for the exchange. This is necessary because each pair can only donate (and consequently receive) one kidney. Constraints (5) make sure only cycles where every arc is tested are selected. Finally, constraints (6) ensure that the total available budget is not exceeded.

To illustrate this model, let us consider an example of a KEP network, which can be seen in Fig. 2.

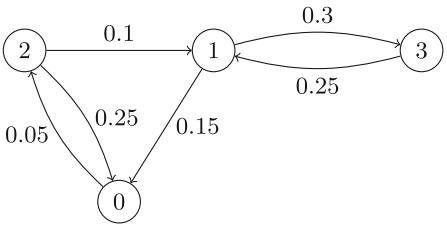


Fig. 2. Example of a KEP instance with four incompatible pairs and probabilities of failure.

In this instance we have four incompatible donor-patient pairs, represented by the nodes 0, 1, 2 and 3. We assume performing a test on each arc costs 1. The cycles in this network are $c_0 = \{02, 20\}$, $c_1 = \{13, 31\}$ and $c_2 = \{02, 21, 10\}$, with expected values of 1.425, 1.05 (both calculated with the formula in (1)) and 2.180 (calculated with the formula in (2)), respectively.

Assuming we only have two available crossmatch tests, the optimal solution would be to test the arcs of cycle c_0. If the number of tests increases by one, the optimal solution would be the cycle c_2, as it has the highest expected number of transplants and all its arcs can be tested.

However, if the number of available crossmatch tests is four, the optimal solution is no longer c_2 but rather the cycles c_0 and c_1 combined, as the expected number of transplants is equal to 2.475, which is higher than the expected value of cycle c_2.

We may also consider a particular case of the above model, when $p_{ij} = 0$, for every $(i,j) \in A$. In this situation, the expected value for each cycle is simply its length, which means we are maximizing the number of transplants. We have mentioned previously that it is the most studied variant (neglecting uncertainty), so in Sect. 4 we will also compare the expected value approach with the deterministic approach.

3 Dealing with Recourse

In this section, we will address the problem from the perspective where recourse is allowed. As mentioned, crossmatch tests may reveal new incompatibilities, cancelling some of the planned transplants. In such cases, we may try to rearrange the remaining arcs so that the rest of the planned transplants are salvaged and the crossmatch tests performed on them are not wasted. This is achieved by making use of backarcs in 3-cycles: arcs that form 2-cycles with other arcs in the current 3-cycle.

Let us consider again the example in Fig. 2. For two and three crossmatch tests, we would obtain the same solution as with the previous model. However, assuming we have available four tests, cycle c_2 with one backarc has an expected number of transplants of 2.515 (calculated with the expressions given in [15]), which is the maximum expected number of transplants for this number of tests (higher than cycles c_0 and c_1 combined). This illustrates how recourse may provide better results for a determined number of crossmatch tests.

The main difference in the recourse integer programming model with respect to the model (3–7) is the definition of the decision variables. In the recourse approach, these are associated not only with 2- and 3-cycles, but also sets of arcs made of 3-cycles and additional arcs (backarcs). In order to achieve this, we use the concept of "configurations": a set of arcs forming a 2-cycle, a 3-cycle or a 3-cycle with up to three backarcs (including none). A more detailed explanation of configurations of 3-cycles can be found in the appendix.

This allows us to define the following sets: C_3^0 as the set of all 3-cycle configurations with no backarcs, C_3^1 as the set of all configurations with one backarc, C_3^2 as the set of all configurations with two backarcs and finally C_3^3 as the set of all configurations with three backarcs. In this approach, by defining C as the union of these four sets along with the set of 2-cycles (C_2), $C = C_2 \cup C_3^0 \cup C_3^1 \cup C_3^2 \cup C_3^3$, the model (3–7) applies to the recourse approach.

4 Computational Tests

Computational tests were conducted in order to evaluate the variation of the expected number of transplants, given an increase in the number of possible crossmatch tests. This model was implemented in C++ and CPLEX. Tests were carried out with 50 instances of 30, 40 and 50 pairs generated by the instances' generator described in [17] which takes into account the probabilities of blood type and tissue incompatibility. The probabilities of a positive crossmatch were obtained according to [11].

We assume conducting a test on each arc costs 1, with the total budget being equal to the number of nodes of a given instance. We defined this as such since, for an instance of n nodes, the maximum possible number of transplants in a solution is precisely n (that is, at most n transplants are planned), which also means that no more than n tests are needed.

In Table 1 some averages are presented, where we consider the three models previously discussed: optimization of the expected number of transplants with no

recourse, optimization of the expected number of transplants with recourse and optimization of the number of transplants assuming no failures. It is important to note that the latter must be seen as an *upper bound* to the actual number of transplants and not an *expected* value as in the other two approaches. We name the approaches "No recourse", "Recourse", "Upper bound".

We consider the following for each set of instances with the same size (30, 40 and 50) and each approach:

- Average number of arcs;
- Average expected number of transplants for an unlimited number of tests;
- Average number of tests needed to achieve the maximum expected number of transplants;
- Convergence: the number of tests necessary so that all instances converge to their respective maximum expected number of transplants;
- Average execution time.

Table 1. Average results for 50 instances of 30, 40 and 50 nodes each.

Number of pairs	30	40	50
Avg. no. of arcs	217	377	594
No recourse			
Avg. expected no. transplants	8.244	10.996	14.940
Avg. no. tests	11.7	16.2	21.8
Convergence	17	25	34
Avg. time (sec)	0.939	1.5264	2.801
Recourse			
Avg. expected no. transplants	9.024	12.184	16.56
Avg. no. tests	14.796	20.94	28.531
Convergence	24	33	48
Avg. time (sec)	1.188	2.2554	4.4386
Upper bound			
Avg. no. of transplants	12.27	17.3	23.4
Avg. no. tests	12.27	17.3	23.4
Convergence	19	27	36
Avg. time (sec)	0.808	1.516	2.712

Instances of 30 pairs registered, on average, 217 arcs and 8.244 expected transplants. An average of 11.7 tests were necessary for each instance, but convergence was attained in all instances after 17 tests. Comparing to the recourse results, we have an average of 9.024 expected transplants, which is equal to an increase of about 10% of transplants. However, more tests are needed on average. If we consider the third model where an upper bound for the number of

transplants is obtained, we obtain 12.3 transplants on average, which means an increase of about 49% when considering the "best case scenario". In this case, all instances converge after 19 tests.

A similar analysis can be done for instances of 40 nodes, where we registered an average of 377 arcs per instance. The average expected number of transplants with no recourse is 10.996, compared to 12.184 average expected transplants when allowing recourse, which is an increase of about 11%. As for the third model, we have an average for the upper bound on the number of transplants of 17.3.

Finally, for instances of 50 pairs, we have an average of 594 arcs per instance. On average, the first model has 14.94 expected transplants whereas the second model has 16.56, representing again an increase of approximately 11%. The final model gives us about 23.4 transplants, which is about 57% higher than the first approach considered.

A couple of conclusions can be drawn from these results. The expected number of transplants with recourse is around 10% higher than the expected number of transplants without recourse, regardless of the pool size, but requires more tests. The expected number of transplants with recourse is between 25% and 30% less than the upper bound given by neglecting potential failures. This is an optimistic empirical estimate on the proportion of cancelled transplants due to not taking into account the uncertainty associated with the crossmatch tests after the transplantation plan is set.

Computational times are negligible, as usually decisions must be taken in much more than a few seconds. Being fast allows models to be incorporated as submodels in other problems that address larger instances.

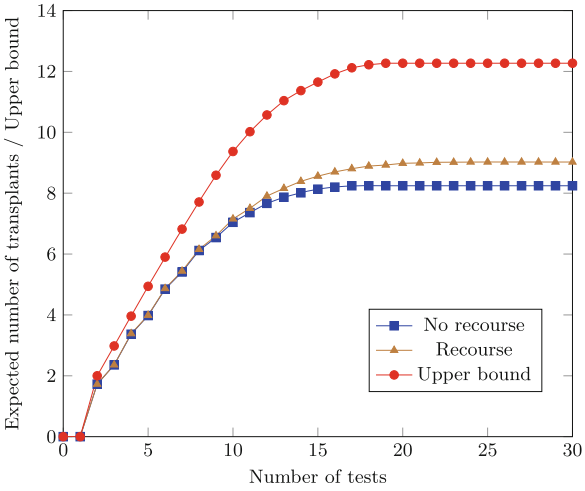


Fig. 3. Comparison of three approaches for instances of 30 pairs: expected number of transplants without recourse vs. expected number of transplants with recourse vs. upper bound on the number of transplants.

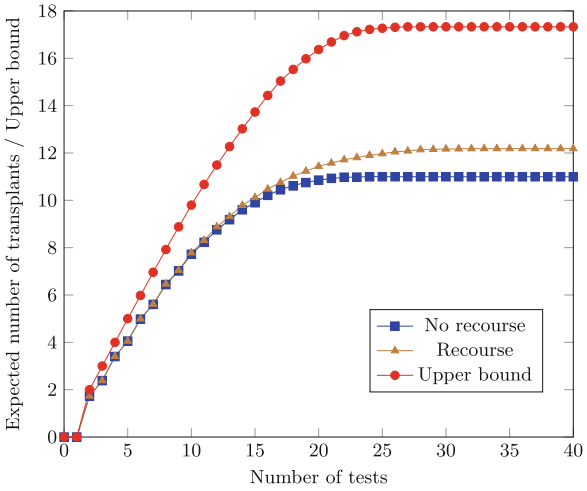


Fig. 4. Comparison of three approaches for instances of 40 pairs: expected number of transplants without recourse vs. expected number of transplants with internal recourse vs. upper bound on the number of transplants.

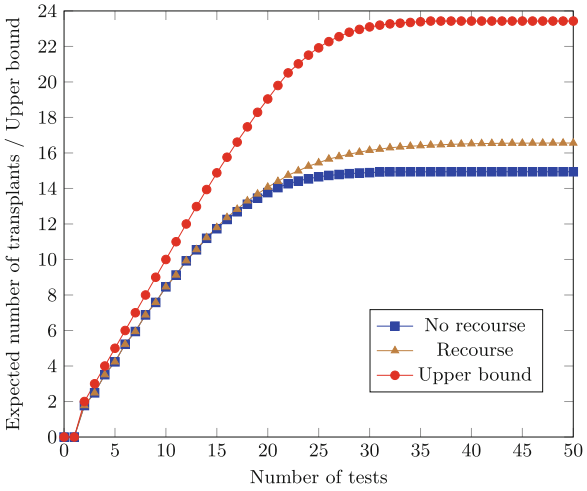


Fig. 5. Comparison of three models for instances of 50 pairs: expected number of transplants without recourse vs. expected number of transplants with internal recourse vs. upper bound on the number of transplants.

In addition, from Figs. 3, 4 and 5, we were able to not only take the same conclusions, but we can also observe that the expected number of transplants displays approximate linear growth until close to the convergence value. For instances of 30 pairs and considering the first 10 crossmatch tests, we see an average increase of around 0.7 expected transplants per test with no recourse

and 0.8 with recourse. Instances of 40 and 50 nodes behave similarly, as can be seen in the mentioned figures. These slopes represent how many transplants we can expect by performing an additional crossmatch test.

5 Conclusions/Discussion

In this paper we presented optimization approaches for kidney exchange programs that aim to maximize the expected number of transplants considering constraints on the number of tests which can be carried out, or more generally, a budget constraint.

Two approaches were considered: one where there is no possibility of recourse, and the other where recourse is available. On top of this, we also established a comparison with the model that maximizes the number of transplants assuming no failures.

Computational tests were conducted and showed that both approaches have similar results when the number of tests is small, but a turning point is reached where recourse provides a significant higher expected number of transplants (around 10%).

For a small number of tests, it may be said that the expected number of transplants grows linearly with respect to the number of tests. For each additional test, there is an slightly less than one increase in the maximum number of transplants.

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Appendix A Enumerating Configurations and Calculating Their Expected Values

The concept of configuration that we used is based on the definition in [13]. Let us then consider a cycle of length 3. This cycle may contain zero, one, two or three backarcs. In the first case, it has one possible configuration (itself). In the second case, the backarc can be associated to three different arcs (Fig. 6), but all these graphs are isomorphic, belonging to the same equivalence class. In the third case, we also have three different combinations of each two backarcs, but again, they are isomorphic to one another (Fig. 7). In the last case, there is one possible configuration of three backarcs. This gives us four equivalence classes total, which can be observed in Fig. 8.

In order to use the formulas for the expected number of transplants in [15], we must then rearrange each configuration into what we may call “standard form”. This means we will identify which equivalence class this configuration belongs to

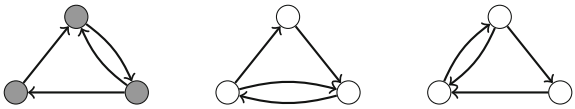


Fig. 6. The three possible configurations of a 3-cycle with one backarc (one equivalence class) and the representative on the left.

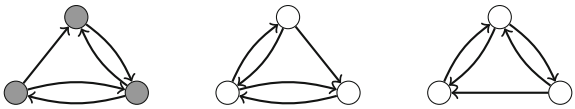


Fig. 7. The three possible configurations of a 3-cycle with two backarcs (one equivalence class) and the representative on the left.

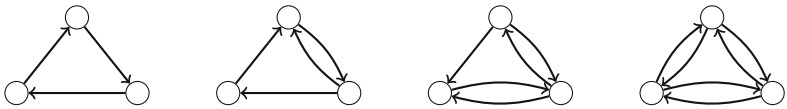


Fig. 8. All four possible configurations (representatives of each equivalence class) of a 3-cycle.

and consider its representative, calculating the expected number of transplants for this object. Considering the representative of the class each time means the disposition of the arcs in the configuration is always the same, which allows us to use the mentioned formulas regardless of the position of the backarcs (as we can always reduce them to the same four cases).

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