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Abstract	One of the challenges in a kidney exchange program (KEP) is to choose policies that ensure an effective and fair management of all participating patients. In order to understand the implications of different policies of patient allocation and pool management, decision makers should be supported by a simulation tool capable of tackling realistic exchange pools and modeling their dynamic behavior. In this paper, we propose a KEP simulator that takes into consideration the wide typology of actors found in practice (incompatible pairs, altruistic donors, and compatible pairs) and handles different matching policies. Additionally, it includes the possibility of evaluating the impact of positive crossmatch of a selected transplant, and of dropouts, in a dynamic environment. Results are compared to those obtained with a complete information model, with knowledge of future events, which provides an upper bound to the objective values. Final results show that shorter time intervals between matches lead to higher number of effective transplants and to shorter waiting times for patients. Furthermore, the inclusion of compatible pairs is essential to match pairs of specific patient–donor blood type. In particular, O-blood type patients benefit greatly from this inclusion.

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Kidney exchange simulation and optimization

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One of the challenges in a kidney exchange program (KEP) is to choose policies that ensure an effective and fair management of all participating patients. In order to understand the implications of different policies of patient allocation and pool management, decision makers should be supported by a simulation tool capable of tackling realistic exchange pools and modeling their dynamic behavior. In this paper, we propose a KEP simulator that takes into consideration the wide typology of actors found in practice (incompatible pairs, altruistic donors, and compatible pairs) and handles different matching policies. Additionally, it includes the possibility of evaluating the impact of positive crossmatch of a selected transplant, and of dropouts, in a dynamic environment. Results are compared to those obtained with a complete information model, with knowledge of future events, which provides an upper bound to the objective values. Final results show that shorter time intervals between matches lead to higher number of effective transplants and to shorter waiting times for patients. Furthermore, the inclusion of compatible pairs is essential to match pairs of specific patient–donor blood type. In particular, O-blood type patients benefit greatly from this inclusion.

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1. Introduction

Kidney transplant is the best option of renal replacement therapy for patients with end-stage renal disease—a growing public health problem affecting many persons worldwide. In most countries, patients have the possibility to enter a waiting list where they hope to get a compatible organ from a deceased donor. An alternative is living donor transplantation, when a patient has a donor that volunteers to donate one of her or his healthy kidneys. But even in this situation the transplant cannot proceed unless patient and potential donor are blood and tissue type compatible. This hinders patients with an available organ from benefiting. To overcome this deadlock, some countries extended the living donor donation concept and developed programs that allow the exchange of kidneys between incompatible patient–donor pairs if the patient in one pair is compatible with the donor in another. The program is managed by a central or local health authority that conducts a matching periodically choosing the pairs to proceed to transplant. The process of matching patients and donors in a pool is known as *kidney exchange program* (KEP) (Roth *et al*, 2005). A common objective is to select the pairs that will lead to the maximum number of transplants, taking into consideration blood and tissue type incompatibilities (Klerk *et al*, 2005). After being matched, selected pairs are subject to additional tissue compatibility tests, which confirm whether the transplant is viable or not. This has an impact in the actual number of transplants that does not necessarily correspond to the number of selected pairs. Other reasons for planned and actual number of transplants to differ are, e.g., a pair leaving the pool due to patient or donor illness, or resignation.

The events discussed above introduce a particular dynamics in the pool and lead to the division of the problem into two main versions: the static variant, where transplants are decided for a pool as it is at a given instant, and the dynamic variant, which studies successive iterations of the static problem. Other variants relate to the type of pairs that participate in a KEP. Initial kidney exchange programs were composed exclusively of incompatible pairs, but there was a significant evolution and nowadays may include patients with multiple donors, altruistic donors (who are willing to donate a kidney for no return), and patients that have a compatible donor, but enter the exchange program hoping to find a more suitable organ. The increasing complexity of the pool led to the development of various matching algorithms (Abraham *et al*, 2007). Simulators have also been developed to study the efficiency of matching algorithms and of different policies, as well as their impact in the evolving kidney exchange pool.

In this work, we present a simulation framework that models dynamic KEPs. The tool is extremely flexible,

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allowing the simulation of the dynamics of populations with diverse characteristics and the selection of different pool management policies. It has six main components: a configuration module, a data characterization module, a PRA estimator, a pool generator, a discrete event simulator, and an optimization module. With the PRA estimator, we obtain approximations for values characterizing the general population. The obtained information allows the pool generator to produce more realistic data and improve on the current standard. This module's output includes information about the pairs, such as arrival times, possible departure times, and crossmatch data. It is possible to generate pools with incompatible pairs only, but also to include compatible pairs, patients with multiple donors and altruistic donors. The discrete event simulator controls the evolution of the simulation and manages the succession of events. Its structure is highly modular, allowing the implementation of arbitrarily complex matching algorithms and policies. Finally, the optimization module calculates the matching of pairs with a predefined frequency.

For the purposes of benchmark and comparison, we also provide an integer programming model that makes use of all the relevant information, including future events. This allows the comparison of simulated models with an upper bound that could be reached in the hypothetical scenario of complete information.

Before proceeding, and for the sake of clarity, the following definitions used in the remaining of this document are introduced:

- Virtual crossmatch—an examination that detects the presence or absence of donor's Human Leukocyte Antigen (HLA)-specific antibodies in a patient by comparing the patients' HLA antibody specificity profile to the HLA antigens of a potential donor.[1] If a patient has antibodies to the donors antigens, donor and patient are considered to be tissue incompatible. If a pair patient–donor is considered compatible, based on virtual crossmatch, and if later the pair is selected for an exchange, a more elaborated examination—serological crossmatch—will be performed prior to the actual transplant. Based on virtual crossmatch, a donor may be wrongly considered compatible with a patient. Serological crossmatch is the ultimate examination to confirm compatibility.
- Serological crossmatch—an examination where a portion of donor blood is combined with patient plasma or serum and is checked for agglutination, which would signify incompatibility between patient and donor. If not otherwise stated, this is the test meant by "crossmatch" in the remain of this document.
- Panel-reactive antibody (PRA)[2] provides an estimate of the percentage of donors that will be crossmatch incompatible for a candidate. The higher the PRA value, the lower the probability of a patient finding a compatible donor.

In the proposed simulator, the PRA of each patient is used to construct the initial compatibility graph, i.e., to represent results of virtual crossmatch. Based on this, an optimal matching is determined. After this step, an additional test is done, again based on the patient's PRA, to simulate the serological crossmatch.

This paper is organized as follows: Section 2 presents a summary of the relevant literature. The simulation–optimization approach proposed in this work is detailed in Section 3. An experimental analysis of its capabilities is provided in Section 4, and conclusions and directions for future research are drawn in Section 5.

2. Dynamic kidney exchange: state-of-the-art

In their simplest format, kidney exchange programs evolve as a sequence of static problems. When a patient in need of a transplant finds a potential living donor who, although willing to donate one kidney, is blood type and/or tissue incompatible with the patient, that pair can join a pool composed of similarly incompatible pairs. At pre-specified moments during a year, a matching algorithm will select for transplant pairs in the pool, such that compatible donors are assigned to patients. The selection is done in such a way that a given criterion—usually the number of transplants is maximized—is optimized. Other criteria such as maximizing the number of blood identical type transplants have also been addressed (Glorie *et al*, 2014).

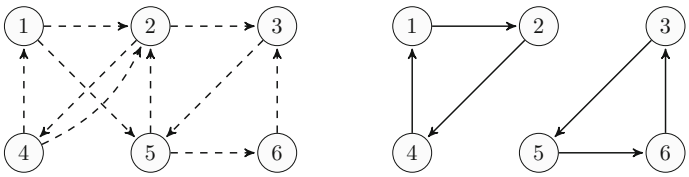
A KEP pool can be represented by a directed graph $G = (V, A)$ as the one shown in Figure 1a, where the set of vertices V consists of all incompatible patient–donor pairs in the pool, and A is the set of arcs (i, j) connecting vertices $i, j \in V$ iff the patient in pair j is presumed to be compatible with the donor in pair i. To each arc $(i, j) \in A$ is associated a (typically unitary) weight w_{ij}. A feasible exchange in a KEP is represented by a set of disjoint cycles of length at most k. For example, the optimal solution for the graph in Figure 1a for $k = 3$ is displayed in Figure 1b.

For $k = 2$ or unbounded, the problem is solvable in polynomial time using, respectively, Edmonds algorithm (Edmonds 1965) and an assignment algorithm. However, for $k \geq 3$ and bounded, the problem was proven to be NP-complete (Abraham *et al*, 2007).

Integer programming (IP) formulations have been proposed by Abraham *et al* (2007), Roth *et al* (2007), Constantino *et al* (2013), Dickerson *et al* (2016). In Abraham *et al* (2007) and Roth *et al* (2007), the authors proposed an *edge* formulation,

[1] This examination is done without carrying out a serologic crossmatch such as a Complement Dependent Cytotoxic (CDC) or flowcytometric crossmatch.

[2] https://www.unos.org/wp-content/uploads/unos/CPRA_Patients?e4f722.



(a) Compatibility graph **(b)** Solution to implement

Figure 1 Static KEP: an example.

with exponential number of constraints, and a *cycle* formulation, with exponential number of variables. Later, in Constantino *et al* (2013) the authors proposed and analyzed the performance of alternative, compact edge formulations. The formulations can be adapted to incorporate problem variants such as the possibility of a patient having multiple donors, or of a donor having no patient associated (a so-called *altruistic donor*). In the latter case, the altruistic donor initiates a *chain*, where the donor of the last pair in the chain either donates to a patient in the deceased donors' waiting list, or acts as a "bridge" donor for future matches. Usually chains are also assigned a maximum size, k'. More recently, Dickerson *et al* (2016) presented two new compact IP formulations. Furthermore, they showed that one of those formulations has a linear programming relaxation that is exactly as tight as the previous tightest formulation known—the *cycle* formulation.

All the above-mentioned works consider a static modeling of KEPs and cannot address questions such as:

- *What is the best interval between matches?* This has implications in, e.g., reducing waiting times and dropouts.
- *Which policies should be used to protect O-blood type patients, and how do they affect the other patients?*
- *What is the impact of including different types of pairs (compatible, multiple donors,* etc.*) in the overall performance of the KEP?*

To provide an answer to such questions, the evolution of a KEP pool over time must be studied.

Several dynamic approaches based on simulation techniques have been developed for this. Existing simulators can be classified according to the characteristics of the pool they are modeling and to the performance indicators addressed. Patients' and donors' blood type compatibility is taken into consideration in Ünver (2010) and Beccuti *et al* (2011). Both papers consider pools with incompatible pairs only. The first one proposes efficient dynamic matching mechanisms for two-way and multi-way exchanges, and aims at maximizing the discounted exchange surplus. The latter considers only two-way exchanges and tries to maximize the overall number of transplants by adjusting the time interval between matches.

An improvement in terms of pool representation can be found in two papers that take into consideration virtual tissue type incompatibility between patients and donors. In Segev *et al* (2005), the authors consider two-way exchanges and the maximization of the number of transplants, weighted by the quality of the transplant and the waiting time. The method suggests when a patient should enter a kidney paired donation program or, alternatively, choose a desensitization treatment, i.e., a treatment for depletion of donor-specific anti-HLA antibodies that, if successful, will allow the patient to be transplanted with a kidney from his related donor. In Awasthi and Sandholm (2009), the potential of three-way cycles is studied. The aim is to maximize the overall number of transplants.

Another important characteristic is the way patients are matched upon pool arrival. Typically, the matching is conducted with a static KEP algorithm and the operation is conducted periodically, with an interval of, usually, from one to a few months. However, it is also possible to match a given pair as soon as it arrives in the pool. This is described as *online matching* and is studied in Ünver (2010), Awasthi and Sandholm (2009) and Ashlagi *et al* (2013).

The probability of transplant failure due to patients' withdrawal or other viability issues is taken into consideration in Li *et al* (2011), Klimentova *et al* (2016). In Li *et al* (2011), three-way exchanges are analyzed by incorporating fall-back options, which can be implemented when the primary choice does not lead to the planned set of exchanges. The proposed approach tries to maximize the total utility, which is related to transplant quality and to logistic issues (e.g., having donor and candidate in the same transplant center). In Klimentova *et al* (2016), the authors propose new schemes for matching rearrangement in case of failure, along with a new tree search algorithm that is used for the computation of optimal expected values.

Although initial kidney exchange programs were composed exclusively of incompatible pairs, programs have been evolving and nowadays may include donors without an associated patient, who are willing to donate a kidney for no return. The impact of allowing altruistic donor chains in a KEP is studied in Chen *et al* (2011), Dickerson *et al* (2012a, b). The first of these articles evaluates the impact of chains of length equal to three at most and aims at maximizing the expected utility. The two others aim instead at maximizing the number of transplants, in weighted (considering vertex potentials) and standard versions. An evolution of this approach can be found in Dickerson *et al* (2013), where a branch-and-price approach is proposed to solve large-scale problems. Altruistic donor chain transplants may be done simultaneously or not. As for cycles, in the first case a limit on chain length must be defined.

Table 1 Comparison of features found in existing simulators

Article	*Pool*	*Extra*	*Objective*
Segev *et al* (2005)	s BT 2	w	Maximize weighted number of transplants
Awasthi and Sandholm (2009)	o BT 3		Maximize number of transplants
Ünver (2010)	o B n		Minimize discounted surplus
Beccuti *et al* (2011)	s B 2		Maximize number of transplants
Li *et al* (2011)	s BT 3	eu fb	Maximize expected utility
Chen *et al* (2011)	s BT 3	eufbch^3	Maximize expected utility
Dickerson *et al* (2012a)	s BT 3	wch$^\infty$	Maximize weighted number of transplants
Dickerson *et al* (2012b)	s BT 3	ch^5	Maximize number of transplants
Dickerson *et al* (2013)	s BT 3	euch$^\infty$	Maximize expected utility
Ashlagi *et al* (2013)	o/s T 3	ch$^\infty$	Maximize number of transplants

The latter is related to Never Ending Altruistic Donor (NEAD) chains (Rees *et al*, 2009) with no limit imposed to the length of the chain.

For the sake of comparison, we summarize in Table 1 the modeling characteristics of several simulators for the dynamic variant of the KEP.

The first column *(article)* contains the reference to the paper.

The second column *(pool)* contains three fields describing the pool management system: the first field is o if matches are conducted online, or s if a static algorithm is used periodically; capital letters indicate that for generating the compatibility graph the model considers blood compatibility (B), tissue compatibility (T), or both (BT); and the third field indicates the maximum cycle size allowed (n stands for no restrictions in the cycle size).

Column *extra* describes particular simulator features that are not common across all implementations. The following acronyms are used: w for weighted versions of the problem; eu when an expected utility function is used to express weights and probabilities between donors and patients; fb indicates that the simulator includes a fall-back mechanism to minimize the impact of dropouts; and ch^n if the simulator considers altruistic donor chains (the exponent n being their maximum chain length).

The objective is stated in the last column.

Even though simulation in KEPs has been studied before, some issues have not been addressed yet. To the best of our knowledge, multiple donors and the inclusion of compatible pairs have only been addressed in static approaches (Saidman *et al*, 2006; Gentry *et al*, 2007). As a consequence, an unexplored aspect in the current literature is to consider all possible actors in the simulation software (i.e., evaluate the performance of all potential pool combinations of incompatible pairs, compatible pairs, and altruistic donors). Another innovative element of the approach we propose is the way that post-matching serological crossmatch tests are modeled, and the study of its effect in pool evolution. None of the papers reported in Table 1 explores this relevant practical aspect. Our contribution is a holistic simulation–optimization tool capable of handling all these issues simultaneously.

3. Kidney exchange programs simulator

The simulator proposed in this paper was developed in a modular way. Its main components, as well as the interactions between the different modules, are shown in Figure 2. The main features of each module are the following:

1. Configuration module: allows the user to select general parameters for running the simulation;
2. Population data input module: allows the user to specify data characterizing the population;
3. PRA estimator module: uses population's target PRA values to calibrate PRA parameters, and hence to determine tissue type incompatibilities in the simulated pool;
4. Pool generation module: responsible for generating pools according to the population data and the desired configuration;
5. Pool management module: discrete event simulator which controls the evolution of the population and manages the succession of events;
6. Optimization module: determines the actual matches in the pool at the requested moments.

Next, we detail the capabilities of each of the modules.

3.1. Configuration module

The configuration module allows the user to set up the characteristics of the scenario to be tested. At the top level, the user is able to define the matching policy to be tested, e.g., the matching frequency, the simulation duration, and the maximum cycle/chain size allowed.

At a second level, the user is able to select the characteristics of the simulated pool. It is possible to select if only incompatible patient–donor pairs compose the pool, or if compatible pairs and/or altruistic donors should be included in the scenario. When considering incompatible pairs, the user can decide if patients can have multiple incompatible donors. When considering altruistic donors, the user is also able to determine what happens to the donor at the end of a chain. More precisely, whether his transplant is performed with a patient in the deceased list (and hence this donor is discarded in the simulation) or if it will be

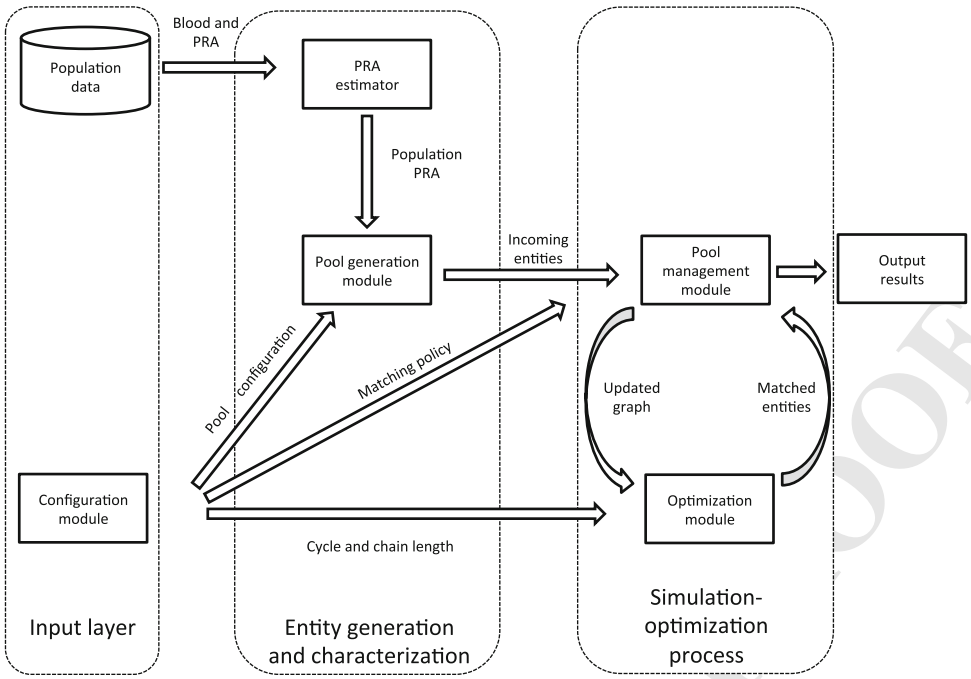


Figure 2 Component interaction in the proposed simulation–optimization tool.

used in the future. It is also possible to configure the maximum time a compatible pair will wait in the pool before proceeding with its own transplant and the maximum time an altruistic donor will wait before dropping out.

At a third level, the user can decide whether to consider only (before matching) virtual crossmatch, or to simulate also the serological crossmatch test, implying that possible incompatibilities are found out after matching. Finally, the user can choose either to maximize the number of transplants (unitary weights) or other weights [e.g., a measure of the benefit of potential transplants, as in Manlove and OMalley (2012)]. Hence, the configuration module is a tuning tool for both simulation and optimization components.

3.2. *Population characterization module*

The population characteristics can be specified through an input module. Data required for characterizing donors are their blood type and age; for patients, there is additional data concerning their PRA level. In this module, we input the probabilities to be used in the generator for each of the blood types (assumed to be identical for patients and donors).

PRA is usually divided into three levels: low (0–20%), medium (20–80%), and high (80–100%). Low PRA indicates a small or no previous exposure to external cells, while high PRA signals that a patient will reject an organ with high probability.[3] In this module, we input the probability of patients having low, medium, or high PRA levels; these values are used for initializing the procedure described in the next section.

Other characteristics specified in this module are the arrival rate for the different elements of the simulation, the patient and donor age distributions, the percentage of pairs expected to drop out of the pool, and the probability of a patient having more than one donor.

3.3. *PRA estimation module*

Typically the input parameters used in KEP simulators to describe a population's PRA are defined as the probabilities of belonging to each PRA level observed in real-world KEP pools. However, in a preliminary computational analysis, we observed that the average PRA percentages observed in the generated pools, after discarding compatible pairs, were substantially different from the desired ones. In particular, when compared with the original data, the generated pools exhibited a smaller number of low-PRA patients and a higher number of medium- and high-PRA patients.

In order to obtain a better approximation in the simulator pools, it is necessary to adapt PRA probabilities used in the generator by solving the following problem. Let $\bar{P}$ be a vector with the percentages of patients with low, medium, and high PRA levels in a real KEP pool. Let P^i be the vector or PRA levels used in the generator, and P be the PRA level observed in pairs in the pool (after removing compatible pairs). We then adapt P^i so that the mean squared error between $\bar{P}$ and P is minimum; these P^i values are used afterward to generate

[3] A high PRA level is explained by a patient having been submitted to blood transfusions or transplants in the past.

patient's PRA in the simulation. We verified that a simple algorithm doing a grid search was enough for obtaining an error close to zero.

3.4. Pool generation module

The pool generator creates realistic KEP pools based on parameters specified in the above-described modules. Given the desired total simulation time and the arrival rate for incompatible pairs, compatible pairs and altruistic donors, arrival times of patients and donors are generated through a Poisson process. The next step is to characterize pool elements. We first sample the number of donors for each incompatible pair, based on estimated probabilities. Afterward, we generate the KEP pool. The following steps are used for generating pairs:

1. Draw patient and donor blood types following the percentages observed in the country's population.
2. Draw patient PRA level (low, medium, or high) and corresponding value as a uniformly distributed random number between the levels' lower and upper values.
3. Determine patient–donor compatibility: If their blood type is incompatible, they are immediately considered incompatible. Otherwise, we consider the generated PRA, which is assumed to be the probability of any donor being tissue incompatible with the patient. We generate a uniformly distributed random number r, with $0 \leq r < 100$. If $r <$ PRA, we also assume that the pair is incompatible.
4. Complete the pair information, and generate age and probability of positive crossmatch, c, for the given PRA values. Age is sampled from a specified distribution, while c is obtained from the expression $c = \Phi(-1.5007 + 0.0170 \times \text{PRA})$, as suggested in Glorie (2012), where Φ is the cumulative distribution function of the standard normal distribution.

To generate an altruistic donor, we only need to draw his/her blood type and age.

After all the elements of the population have been generated, their arrival time and the maximum time they remain in the pool are drawn based on a Poisson distribution. If the dropout time (i.e., the arrival time plus the maximum remaining time) precedes the total simulation time considered, when the simulation reaches that moment the element is removed from the pool.

At this point, we have generated arrival time, dropout time, blood type, PRA, and age information for each element. We now need to generate information to represent the compatibility of elements in the pool in the virtual crossmatch. Traditionally, this is done by generating a compatibility graph. Besides doing this, we also store a list of arcs that will fail in the crossmatch test, so that all the information for completely describing the instance is prepared. This information, as well as dropout times, is used entirely in the complete information model, but is discovered progressively, as the simulator clock advances, in the other models.

3.5. Pool management module

The simulation pool evolution and management process take course once the system is configured and the generated data are loaded. At each step, the engine checks if there are new pairs to include in the pool, and if any of the current pairs exceeded the maximum allowed time. At the defined matching times, the tool builds: (1) a compatibility graph based on the characteristics of the pairs that currently compose the pool; (2) the subset of arcs in the graph that will fail if the crossmatch test is applied; and (3) a table with relevant information concerning current elements in the pool, to be sent to the optimization module. In return, the module obtains the subset of pairs that were selected for transplant, and excludes those that fail when crossmatch tests are performed after the matching.

Pool information is updated, and relevant statistics are stored for posterior analysis. The module then advances to the next time step, and the process is repeated until the desired simulation time is reached.

3.6. Optimization module

The optimization module is the main decision unit in the simulation. It gets all the relevant information from the simulator's main loop and decides which patients will be selected for transplant.

Let $\mathcal{P}$ be the set of all patients in the pool, and $\mathcal{D}(p)$ be the set of donors of patient p. For each patient–donor combination (p, d) with $p \in \mathcal{P}, d \in \mathcal{D}(p)$, we consider a different vertex in the graph. Let k denote the maximum cycle size, and k' denote the maximum chain length allowed. Let $\mathcal{C}(k, k')$ be the set of all cycles and chains up to sizes k and k', respectively. We define a variable z_c for each element $c \in \mathcal{C}(k, k')$ such that:

$$z_c = \begin{cases} 1 & \text{if } c \text{ is selected for the exchange,} \\ 0 & \text{otherwise.} \end{cases}$$

Taking $V(c) \subseteq V$ as the set of vertices of c, and letting $w_c = \sum_{(i,j)\in c} w_{ij}$ be the weight of each cycle/chain given by the sum of the weights of its arcs, the integer optimization model to consider is the following:

$$\text{maximize} \sum_{c \in \mathcal{C}(k,k')} w_c z_c \qquad (1a)$$

$$\text{subject to} \sum_{k \in \mathcal{D}(p)} \sum_{c : k \in V(c)} z_c \leq 1, \qquad \forall p \in \mathcal{P}, \qquad (1b)$$

$$z_c \in \{0, 1\}, \quad \forall c \in \mathcal{C}(k, k'). \qquad (1c)$$

Objective (1a) maximizes the weighted number of transplants, and constraints (1b) ensure that a vertex is in at most one selected cycle/chain, even if the vertex is associated with a multiple donor.

After the matching is determined, we check if any of the arcs selected for transplant in the obtained solution is in the set of arcs for which the serological crossmatch fails. If so, we consider that every transplant in the corresponding cycle fails. Finally, the information of pairs matched in the current solution and of the incompatibilities discovered in crossmatch arcs is sent back to the pool management module, and the state of the pool is updated.

4. Computational results

An extensive computational experiment has been prepared for evaluating the flexibility of the tool, as well as the impact of different policies on the overall performance in terms of number of transplants, average waiting times, and non-matched patients. For different intervals between matches, and different cycle and chain sizes we considered the possibility of inclusion of altruistic donors and compatible pairs in the pool. Next we describe the data used in the experiment. Afterward, we present results for the percentage of transplants, waiting times, and characterization of patients in the pool at the end of the simulation. Finally, we compare the results with the ones of a complete information model.

All the results in this section have been obtained with the cycle formulation (Abraham *et al*, 2007), considering the extensions proposed in Constantino *et al* (2013) to include both incompatible and compatible pairs, altruistic donors, and patients with multiple donors.

4.1. Input data

In a first stage, to validate the quality of data generated by our simulator, we used information from the Dutch program, which has the most comprehensive accessible data sources. Blood type distribution is based on Beckman *et al* (1959): 45% of the population is blood type O, 43% type A, 9% type B, and 3% type AB. As for PRA, we have used the corrected values provided in Glorie (2012). In that work, the author observes that PRA values provided by transplant centers do not reflect the true probability of matching of a given patient. Because of that, they provide corrected PRA values based on virtual crossmatch between each patient and all possible donors that had participated in the program. We use these corrected values to estimate the general population PRA and generate instances with the obtained values.

Table 2 summarizes the original PRA reported by Dutch centers based on the general population, the corrected values by Glorie (2012) that were computed only for the KEP population using virtual crossmatches between each patient and all donors in the data set, our estimated population PRA, and the average PRA of the data that we generated. The latter closely follows the corrected values provided in Glorie (2012), validating our proposed PRA estimation procedure.

Table 2 Characterization of PRA

Source	*PRA*		
	Low	*Medium*	*High*
Center reported	78	17	5
Corrected	48	35	17
Population estimate	64	27	9
Generated data	48.1	34.9	17.0

Information on pair arrival rate, altruistic donors, dropouts and patient–donor age was retrieved from Klerk *et al* (2008). Age of patients and donors varies uniformly between 18 and 73 years old. The number of compatible pairs was determined analyzing Dutch transplantation reports publicly available,[4] and is about 5 times the number of incompatible pairs for the studied years. Pair arrivals are modeled with a Poisson distribution, and the arrival rates (in days) are: 6.0 for incompatible pairs, 1.2 for compatible pairs, and 75. for altruistic donors.

Most of the incompatible candidates remain in the simulation until the end. However, to simulate patients dropping out of the pool, we fixed an average permanence time such that about 12% of the candidates drop out in the 5 years simulated As for compatible pairs, we assume they only remain in the pool for 90 days after arrival. If unmatched after that limit, they proceed to make the transplant with the initial donor.

With this information, we generated 1000 instances for KEP with a duration of 5 years. Each instance has been studied under different configurations of the following factors: cycle size, time between matches, possibility of inclusion of compatible pairs and possibility of inclusion of altruistic donors. The values considered are the following:

CYC, maximum cycle size: 2 or 3;

TBM, time between matches: 30, 90, and 180 days;

COM, inclusion of compatible pairs:

(0) no compatible pairs;
(1) inclusion of all compatible pairs;
(2) inclusion of the pairs that will benefit from a younger donor;
(3) inclusion of some pairs which will participate in an altruistic manner (we had no data for this parameter; results are based on an experimental, small value of 10%);

ALT, inclusion of altruistic donors:

(0) no inclusion;

[4]Obtained from http://www.transplantatiestichting.nl/.

(2) altruistic chains of size 2;
(3) altruistic chains of size 3.

This resulted in 72 different configurations for each instance. Tests were performed in a computer with an Intel Xeon W3520 processor at 2.67GHz, with 16GB of RAM. The simulator was developed in Python/C++, and MIP models were solved with CPLEX version 12.6. The running times for each complete simulation vary from 0.37 s, for instances containing incompatible pairs only, to 49 s for instances that additionally include compatible pairs and altruistic donors.

For the sake of parsimony, we present the total number of transplants and percentages with respect to incompatible pairs only. Several key performance indicators have been analyzed for evaluating the impact of each KEP configuration: percentage of incompatible pairs transplanted, waiting time of matched pairs, sensitization of non-matched pairs, and, finally, a comparison with the complete information model.

4.2. Percentage of incompatible pairs transplanted

While some focus has been given to the matching of high PRA and blood type O patients, the most commonly used objective in a KEP is to maximize the total number of transplants. In this section, we study the percentage of transplants of incompatible pairs with respect to the total number of incompatible pairs, for the different KEP configurations considered.

4.2.1. Pool of incompatible pairs When considering a pool composed uniquely of incompatible pairs, the percentage of transplants increases with the maximum cycle size and decreases with the time between matches. However, the percentage of positive crossmatches (in average 23.1%) does not change much with the parameters. This suggests that with a smaller TBM the program able to recover faster from failure due to a positive crossmatch, and therefore to perform more transplants. In Table 3, we present the average number of crossmatch tests performed, the percentage of positive tests observed, and the percentage of transplants. Standard deviations are presented in parenthesis. In these combinations, the best results are 48.8% of transplants, obtained with cycle size 3 and TBM = 30.

Due to the consistent superior number of transplants obtained with CYC = 3, we will consider only this value in the remaining of this section. We will also denote by "baseline case" a pool having only incompatible pairs and maximum cycle size of 3.

4.2.2. Pool including compatible pairs In this section, we study the impact of allowing the participation of compatible pairs in the pool. As shown in Table 4, configurations with the compatible pair parameter COM = 1 (all pairs) and COM = 2 (only if the patient benefits) lead to an enormous increase in the percentage of matches: as much as 96.9% of the pairs can now be matched, for TBM = 30 and COM = 1. As in the previous case, smaller TBM leads to more transplants.

The greater number of compatible pairs that is available compensates for the lack of under-demanded pairs such as O-A. Transplants for COM = 2 are only accepted when donors' age is favorable for the patient of the compatible pair. This explains why the number of transplants in that case is slightly smaller than for COM = 1. Nevertheless, as much as 93.5% of incompatible pairs are transplanted for TBM = 30.

For COM = 3 (part of the compatible pairs), the results are more modest, as the number of compatible pairs that were considered for entering the pool is, in this case, quite small. Nevertheless, the number of transplants improves up to about 10% with respect to the baseline case for TBM = 30 and 90, and 4% for TBM = 180.

Allowing compatible pairs in the pool leads to an increase in the number of crossmatch tests, but we observe a smaller percentage of positive cases. This is due to the fact that patients from compatible pairs tend to have a smaller PRA and thus a smaller probability of failure.

4.2.3. Pools including altruistic donors The inclusion of altruistic donor chains also increases the percentage of transplants, with respect to the baseline case. Considering a maximum chain size of 2, we obtain a stable increase of 5/6% over the different time intervals, even though altruistic donors'

Table 3 Average results for a pool with incompatible pairs only

Configuration		*Number of crossmatches*	*Positive crossmatches (%)*	*Performed transplants (%)*
CYC	*TBM*			
2	30	216.2 (28.8)	22.9 (3)	41.9 (3.9)
3	30	305 (43.6)	22.8 (2.5)	48.8 (4.3)
2	90	211.7 (27.7)	22.9 (3)	41 (3.9)
3	90	304.1 (44.5)	23.3 (2.7)	47.5 (4.3)
2	180	205.2 (26.4)	22.9 (3.1)	39.8 (3.9)
3	180	296.5 (41.7)	23.8 (2.6)	45.3 (4.4)

Standard deviations are presented in parenthesis.

Table 4 Average results for the different variants of compatible pairs (COM)

Configuration		*Number of crossmatches*	*Positive crossmatches (%)*	*Performed transplants (%)*
COM	*TBM*			
0	30	305 (43.6)	22.8 (2.5)	48.8 (4.3)
1	30	1422.9 (99.6)	14.5 (1)	96.9 (1)
2	30	1267.2 (87.7)	14.7 (1.1)	93.5 (1.5)
3	30	455.2 (45.8)	19.7 (2)	59.7 (4.1)
0	90	304.1 (44.5)	23.3 (2.7)	47.5 (4.3)
1	90	1383.6 (96)	14.8 (1.1)	93.3 (1.5)
2	90	1227.3 (84)	15.2 (1.2)	90.4 (1.8)
3	90	408.1 (42.7)	21 (2.3)	55.2 (4.3)
0	180	296.5 (41.7)	23.8 (2.6)	45.3 (4.4)
1	180	1180.5 (57.3)	15.7 (1.3)	87 (2.3)
2	180	1048.1 (63)	15.9 (1.3)	84.1 (2.7)
3	180	347.9 (40.5)	22.3 (2.4)	49.3 (4.3)

Standard deviations are presented in parenthesis.

Table 5 Average results considering different possibilities for the inclusion of altruistic donors (ALT)

Configuration		*Number of crossmatches*	*Positive crossmatches (%)*	*Performed transplants (%)*
ALT	*TBM*			
0	30	305 (43.6)	22.8 (2.5)	48.8 (4.3)
2	30	319.2 (43.7)	22.7 (2.5)	53.5 (4.2)
3	30	329.3 (43.4)	22.6 (2.4)	55.5 (4.3)
0	90	304.1 (44.5)	23.3 (2.7)	47.5 (4.3)
2	90	318.9 (43.3)	23 (2.6)	52.8 (4.4)
3	90	332 (43.8)	23.1 (2.6)	54.7 (4.4)
0	180	296.5 (41.7)	23.8 (2.6)	45.3 (4.4)
2	180	314.2 (41.4)	23.5 (2.6)	50.8 (4.4)
3	180	321.6 (39.4)	23.5 (2.5)	52.4 (4.3)

Standard deviations are presented in parenthesis.

arrival is rather rare in our instances. If the chain size increases to 3, we observe a further improvement of 2% in the percentage of transplants. Detailed results are presented in Table 5.

4.2.4. Pools including compatible pairs and altruistic donors Finally, we consider the simultaneous inclusion of compatible pairs and altruistic donors in the pool. As bringing compatible pairs to the pool has a very high impact in the percentage of transplants, the benefits of additionally including altruistic donors, though observable, are rather limited. Detailed results are presented in Table 6.

4.3. Waiting times of matched pairs

One main concern in a KEP is the time patients have to wait until being matched. The anxiety and uncertainty of waiting may lead a pair to drop out of the pool. In more extreme cases, patients may become too ill to be submitted to surgery. For these reasons, policies that lead to smaller waiting times are preferable.

In Table 7, we present the average total waiting time (in months) per blood type and overall, and the average number of patients dropping out of the pool for different combinations of COM and TBM, when CYC = 3 and ALT = 0. Results for simultaneous inclusion of compatible pairs and altruistic donors are not presented as they are very similar to the inclusion of compatible pairs only. As expected, we can observe that longer TBM leads to longer total waiting times; as also expected, lower average dropouts are associated with lower values of total waiting time and TBM. Analyzing the waiting times per blood type, we conclude that type O patients benefit greatly from including compatible pairs in the pool. In general, lower TBMs correspond to lower waiting times. Patients with blood type O have longer waiting times than the others. For other types, waiting times are roughly equivalent. We also observe a higher standard deviation for COM = 0 and COM = 3.

4.4. Remaining patients and their PRA

In this section, we characterize the pool at the end of the simulation through the number of the patients that have not

Table 6 Average results for the inclusion of both compatible pairs and altruistic donors

Configuration			*Number of crossmatches*	*Positive crossmatches (%)*	*Performed transplants (%)*
COM	*ALT*	*TBM*			
0	0	30	305 (43.6)	22.8 (2.5)	48.8 (4.3)
1	2	30	1450.9 (100.6)	14.4 (1)	96.9 (1)
2	2	30	1285.9 (87.6)	14.6 (1.1)	93.8 (1.5)
3	2	30	468.3 (46.1)	19.6 (2)	63.7 (4.4)
1	3	30	1481.4 (100.3)	14.3 (1)	96.8 (1)
2	3	30	1308.4 (87.1)	14.6 (1)	94.1 (1.4)
3	3	30	475.7 (45.1)	19.6 (2)	65.4 (4.3)
0	0	90	304.1 (44.5)	23.3 (2.7)	47.5 (4.3)
1	2	90	1408.7 (94.5)	14.7 (1)	93.4 (1.4)
2	2	90	1245.8 (84.1)	15.2 (1.2)	91.2 (1.8)
3	2	90	423.5 (42)	20.8 (2.3)	60.2 (4.5)
1	3	90	1442.7 (93.4)	14.7 (1)	93.4 (1.4)
2	3	90	1272.4 (84.1)	15.1 (1.1)	91.3 (1.8)
3	3	90	431.7 (42.8)	20.9 (2.3)	61.5 (4.4)
0	0	180	296.5 (41.7)	23.8 (2.6)	45.3 (4.4)
1	2	180	1190.6 (54.5)	15.7 (1.3)	87.8 (2.1)
2	2	180	1064.4 (61.4)	15.9 (1.3)	86 (2.5)
3	2	180	365.5 (39.6)	22.1 (2.4)	54.6 (4.4)
1	3	180	1198.1 (52.2)	15.7 (1.2)	88.1 (2)
2	3	180	1083.5 (61.2)	15.9 (1.3)	86.5 (2.3)
3	3	180	372.3 (38.8)	22.2 (2.4)	55.9 (4.4)

Standard deviations are presented in parenthesis.

Table 7 Average waiting time and dropouts for different configurations

Configuration		*Average waiting time (months)*					*Number of dropouts*
COM	*TBM*	*Type O*	*Type A*	*Type B*	*Type AB*	*Overall*	
0	30	12.4 (13)	4.5 (6.9)	4 (6.5)	3.1 (5.6)	7 (10.1)	21.9 (3.2)
1	30	1.1 (1.6)	1.4 (1.8)	1.2 (1.7)	1.5 (2.1)	1.2 (1.7)	3.6 (1.9)
2	30	2 (3.8)	2.2 (3.8)	1.7 (3.3)	2.1 (3.7)	2 (3.7)	5.5 (2.2)
3	30	10.4 (11.1)	3.9 (6.2)	3.5 (5.9)	2.8 (4.9)	6.6 (9.2)	18.6 (3.2)
0	90	12.3 (12)	6.4 (7.3)	5.5 (6.6)	5.3 (6.2)	8.2 (9.5)	23.1 (3.2)
1	90	3.2 (3.5)	3.8 (4.1)	3.3 (3.6)	4.2 (4.7)	3.4 (3.7)	7.8 (2.7)
2	90	3.9 (4.7)	4.4 (5.1)	3.7 (4.4)	4.7 (5.4)	4 (4.8)	9.2 (2.8)
3	90	11.6 (11.4)	5.8 (6.7)	5 (6.2)	5.1 (5.9)	8 (9.3)	20.9 (3.3)
0	180	14.5 (12.6)	9.2 (8.7)	8.1 (7.9)	8.4 (8.2)	10.7 (10.4)	25.1 (3.1)
1	180	6.4 (6.3)	7.2 (7.1)	6.3 (6.1)	7.5 (7.2)	6.6 (6.5)	13 (3.1)
2	180	6.8 (6.9)	7.5 (7.4)	6.6 (6.6)	8.1 (7.9)	7 (7)	14 (3.2)
3	180	14.3 (12.4)	8.8 (8.4)	7.7 (7.6)	8.1 (8.1)	10.6 (10.4)	24.1 (3.2)

Standard deviations are presented in parenthesis.

been matched and their associated PRA. Table 8 shows the average size of the final pool in the last column, and its percentage of low-, medium-, and high-PRA patients.

For COM = 0 and COM = 3, PRA in the final pool does not seem to depend on TBM and does not change much with respect to the initial population; for those configurations, the average number of patients in the final pool increases with TBM.

For COM=1 and COM=2, the percentage of patients with high PRA level in the final pool tends to be higher than the corresponding percentage in the initial populations that follow the estimated values presented in Table 2. That percentage tends to decrease for larger TBM (notice, however, that for low values of TBM the size of the final pool is very small).

4.5. Comparison to the complete information model

In this section, we evaluate how many transplants would be achieved in the previous instances with the complete information model. This exercise, although theoretical, provides an upper bound to the results reported before.

The IP model used is the one presented in Section 3.6 with an additional index associated to time. The model is aware not only of the arrival and departure times of each element in the

Table 8 Percentage of patients in each PRA level (low, medium, and high) and average number of pairs in the pool at the end of the simulation

Configuration		*Patients in PRA level (%)*			*Number of pairs*
COM	*TBM*	*Low*	*Medium*	*High*	
0	30	75.9 (3.6)	15.5 (3)	8.6 (2.4)	154.9 (15.1)
1	30	37.9 (16.9)	18.9 (13.3)	43.2 (17)	9.5 (3.1)
2	30	44.3 (12.4)	22.3 (9.9)	33.4 (11.4)	19.6 (4.7)
3	30	74.1 (4.4)	16.1 (3.5)	9.8 (2.9)	121.8 (14.8)
0	90	76.2 (3.5)	15.5 (3)	8.4 (2.3)	158.6 (15.4)
1	90	48.9 (12.2)	24.3 (10.1)	26.8 (10.5)	20.1 (4.6)
2	90	50.8 (9.6)	24.1 (8.2)	25 (8.4)	29.2 (5.8)
3	90	75.4 (3.9)	15.7 (3.2)	8.9 (2.6)	135.6 (15.3)
0	180	76.4 (3.4)	15.6 (3)	7.9 (2.2)	165.5 (15.8)
1	180	55.4 (8.2)	25.6 (7.1)	19.1 (6.5)	39.5 (7.3)
2	180	57 (7.5)	24.4 (6.3)	18.6 (5.9)	48 (8.9)
3	180	76 (3.6)	15.8 (3.1)	8.2 (2.3)	153.2 (15.8)

Standard deviations are presented in parenthesis.

Table 9 Comparison of simulation results with full information model for the different time and cycle combinations

Configuration		*Simulation model*	*Complete information*	*Gap (%)*
TBM	*CYC*			
30	2	126.8 (14.2)	140.6 (16)	9.7 (3.2)
30	3	147.5 (15.9)	168.3 (16.4)	12.4 (3.3)
90	2	124.1 (14.2)	139.2 (15.9)	10.7 (3.4)
90	3	143.8 (15.6)	166.7 (16.4)	13.8 (3.7)
180	2	120.4 (14)	137.5 (15.8)	12.3 (3.6)
180	3	136.9 (15.6)	164.9 (16.3)	17 (4.3)

pool, but also of the arcs that will eventually fail. The result is optimal, though unlikely to be reachable, for the maximum cycle/chain size considered.

Results for a pool of incompatible pairs only, for different configurations of CYC and TBM, are shown in Table 9: Average number of transplants obtained with the simulation model and with the complete information model, and percentage of transplants lost in the simulation model relatively to complete information are reported. As before, more transplants are obtained when considering larger cycles sizes and shorter time between matches. Larger cycle sizes allow more matching options, and smaller times between matches allows better recovery from positive crossmatch tests. Interestingly, in some cases there are more transplants in the simulation model with cycle size 3 than in the complete information model with cycle size 2.

5. Conclusions

In this work, we present a simulation–optimization approach for kidney exchange programs (KEPs). The proposed tool gives policy makers the possibility to assess a KEPs' performance and study its dynamics under different configurations. Performance, in this context, concerns the overall number of transplants that can be made, rather than computational time. KEP dynamics can be described through the arrival and departure of new patient–donors pairs into a pool. Departure may be due to having been successfully matched or to dropping out.

Patient–donor generation and matching rules can be easily adapted in order to provide an accurate decision support tool which allows key performance indicators to be studied under different settings. Concerning patient–donor arrival, currently supported possibilities include considering incompatible pairs, patients with multiple incompatible donors, compatible pairs, and altruistic donors. These possibilities have been analyzed and compared under realistic scenarios. Two types of crossmatch tests are implemented: a virtual test, before matching, and a post-matching test simulating the last-minute compatibility confirmation.

For determining matchings, the simulator invokes an optimization subroutine that, given the characteristics of the compatibility graph as input, returns an optimal assignment. The optimization code can be tuned to reflect different objectives and policies.

Our tool can be used to test KEP policies for different regional and national settings. We have collected real data in order to calibrate our model and refined it through a parameter estimator. This allowed us to provide an analysis using very realistic instances. Our results include the solution of a complete information model, making use of knowledge of future events. The main conclusion is that policies should encourage compatible pairs to enter the KEP pool, as this leads to remarkable improvements on the number of transplants. Furthermore, policies should consider the impact that different times between matches have on the KEP performance.

We expect that our work provides a baseline for KEP analysis with simulation–optimization. A challenge for future research in this field concerns adapting the tool so that it can simultaneously model multiple national exchange programs and evaluate their integration in an international matching pool.

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