UNIVERSIDADE DE LISBOA
FACULDADE DE CIÊNCIAS
DEPARTAMENTO DE ESTATÍSTICA E INVESTIGAÇÃO OPERACIONAL

Joint Management Models of Kidney Exchange Program and Deceased Donor Waiting List

Carolina Teles de Carvalho Caldas Xavier

Mestrado em Estatística e Investigação Operacional
Especialização Investigação Operacional

Dissertação orientada por:
Prof. Doutor Miguel Constantino
Prof.ª Doutora Conceição Fonseca

2019

“PURE MATHEMATICS IS, IN ITS WAY, THE POETRY OF LOGICAL IDEAS”

Albert Einstein

Esta dissertação foi financiada por fundos nacionais da FCT - Fundação para a Ciência e a Tecnologia, âmbito do projeto/instituição de I&D “mKEP – Modelos e algoritmos de otimização em programas internacionais de doação renal cruzada”, “PTDC/IIMGES/2830/2014”.

RESUMO

Pacientes com problemas renais que levem a insuficiência renal têm de se submeter a hemodiálise, um tratamento que substitui a função do rim e filtra as substâncias tóxicas do sangue. É um tratamento que envolve bastante tempo e que tem de ser repetido várias vezes por semana e como tal, dá uma qualidade de vida baixa aos pacientes. Como alternativa a este tratamento os doentes podem fazer um transplante renal e para isso podem ser transplantados através de um dador vivo ou cadáver. Um dador vivo é alguém que geralmente conhece o paciente e quer doar um dos seus dois rins saudáveis enquanto o dador cadáver é alguém que quando falece pode ser considerado um potencial dador de órgãos, dependendo das circunstancias da sua morte. A lista de espera para transplantação através de dadores cadáver normalmente é bastante longa e demorada, por isso aconselha-se sempre o paciente a tentar arranjar um dador vivo compatível. Como por vezes é bastante difícil arranjar alguém compatível, criou-se o programa de doação renal cruzada.

Este programa permite criar trocas entre pares de pacientes-dadores incompatíveis de forma a arranjar compatibilidades. Assim, o dador de um par pode doar um rim a um paciente de outro, desde que o seu paciente receba um transplante de um dador de outro par. Desta forma criam-se ciclos onde se pretendem maximizar o número de transplantes.

Ao longo dos anos foram-se criando várias variantes deste programa de doação renal e foram efetuados diversos estudos que pretendem aumentar o número de transplantes e ao mesmo tempo reduzir o tempo de espera dos pacientes, reduzindo assim o tamanho da lista de espera, mas este trabalho foca-se nos modelos propostos por Haynes et al. (2017).

Estes três modelos misturam o conceito de troca entre pares incompatíveis e transplantes de dadores cadáveres. Desta forma podem-se criar cadeias iniciadas por dadores cadáveres onde o rim destes é transplantado para um paciente que se encontrava no programa com o seu dador incompatível. De seguida o seu dador doa para o paciente de outro par e assim sucessivamente até que o dador do último par doa de volta para a lista de espera, para um paciente que não tinha um dador vivo e que portanto não estava no programa. Os modelos diferem principalmente quanto à prioridade que se dá aos pacientes e pela ordem com que se efetuam os transplantes.

O simulador criado por Santos et al. (2018) foi adaptado para simular a utilização destes modelos numa população também criada pelo simulador e foram analisados e comparados de acordo com a percentagem de transplantes feita e com o tempo de espera médio e máximo para pacientes de acordo com o seu tipo de sangue e PRA (*Panel-active antibody*). As maiores conclusões que se retiraram são que existe um benefício enorme em ter um dador vivo disponível para doar um rim e que, na maior parte dos casos, estes três modelos são mais vantajosos do que usar um modelo que separa a gestão do programa de doação renal cruzada e a lista de espera de dadores cadáveres.

Palavras- Chave: Transplante; KEP; Otimização; Lista de Espera; Rim; Maximização

ABSTRACT

Patients with kidney diseases leading to kidney failure have to undergo hemodialysis, a treatment that replaces kidney function and filters out toxic blood substances. It is a treatment that involves a lot of time and that must be repeated several times a week and as such, gives a low quality of life to patients. As an alternative to this treatment, patients can have a kidney transplant and can be transplanted through a living donor or a deceased one. A living donor is someone who usually knows the patient and wants to donate one of his two healthy kidneys while a deceased donor is someone who, when dies, can be considered a potential organ donor, depending on the circumstances of his/her death. The waitlist for transplantation by deceased donors can usually be quite long in terms of patients and waiting time, so it is always advisable for the patient to try to find a compatible living donor. As it is sometimes quite difficult to find a match, a kidney exchange program (KEP) was created.

This program allows to create exchanges between incompatible patient-donor pairs in order to achieve compatibilities. Thus, the donor of one pair can donate a kidney to a patient of another, as long as his/her patient receives a transplant from a donor of another pair. This creates cycles where the number of transplants aims to be maximized.

Over the years, several variants of the KEP have been created and several studies have been conducted to increase the number of transplants and at the same time reduce the patients' waiting time, thus reducing the size of the waiting list, but this work focuses on the models proposed by Haynes et al. (2017).

These three models mix the concepts of incompatible pair exchange and deceased donor transplantation. Therefore, chains initiated by deceased donors can be created where the kidney is transplanted to a patient who was in the program with the incompatible donor. Then the incompatible donor donates to the patient of another pair and so on until the donor of the last pair donates back to the waitlist, to a patient who did not have a living donor and consequently was not in the program. The models differ mainly in the priority given to the patients and in the order in which the transplants are performed.

The simulator created by Santos et al. (2018) was adapted to simulate the use of these models in a population also created by the simulator, being analyzed and compared according to the percentage of transplants performed and the mean and maximum waiting time for patients according to their blood type and PRA (Panel-active antibody). The main conclusions drawn were that there is an enormous benefit in having a living donor available to donate a kidney and that, in most cases, these three models are more advantageous than using a model that separates the management of the KEP and the deceased donors waitlist.

Keywords: Transplantation; KEP; Optimization; Waitlist; Kidney; Maximization

CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1. INTRODUCTION

1.1. INTRODUCTION

Kidney failure patients must submit to dialysis, a treatment that plays the role of the kidney through an external machine, which is to filter waste from blood. The life quality of patients that must go through this process several times a week is very low. Therefore "many patients opt to withdraw from dialysis, leading to a natural death" (Abraham, Blum, & Sandholm, 2007) and still, only 12% of these patients survives 10 years.

Instead, the best option is to do a kidney transplant, thus many patients that need one are added to a waiting list (or waitlist) where they wait to eventually receive a compatible kidney from a deceased donor. Patients are given kidneys depending on their priority on the list, which is established according to their urgency on being transplanted and some other factors such as "time on dialysis, age (children and young people have priority), histocompatibility criteria (donor-recipient tissue similarity), donor-recipient age differences" (Nunes, 2010). So, when there is an available kidney it is transplanted to the patient of all possible receivers that had the higher number of factors in his favor.

Another way of patients to be transplanted is through living donor transplantation, which consists on a healthy living person donating one of his two healthy kidneys to a patient. Although many people might have someone willing to donate them, they may not be a match due to blood or tissue type compatibility. Two persons are blood compatible if their blood type matches accordingly to Table 1.1 and are tissue compatible if there is not a positive crossmatch. This positive crossmatch test mixes blood samples from both the patient and the potential donor and has a positive result if the patient's antibodies attack the donor's, which means that they are not suitable for transplant (Johns Hopkins Medicine, n.d.).

Table 1.1 - Blood Compatibilities

Patient's blood type	Compatible donor's blood types
O	O
A	O, A
B	O, B
AB	O, A, B, AB

Rapaport (1986) suggested the concept of kidney exchange program (KEP), a sort of barter-exchange market in which patients swipe their incompatible donors with each other. Basically, the KEP manages a pool of incompatible donor-patient pairs where one pair's patient is being transplanted with another pair's donor whose kidney is a match. In the other hand the first pair's donor is donating to another pair's patient, who is also compatible, this way forming various cycles and making the

maximum number of matches possible, using optimization models. For example, a 2-way cycle consists of having two patient/donor pairs in which the first donor donates a kidney to the second patient and the second donor donates to the first patient, if they're both compatible, forming a cycle that ensures that if one donor donates a kidney, then his patient is receiving one (Figure 1.1).

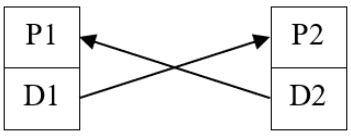

Figure 1.1 - A 2-way exchange (donor 1 donates to patient 2 and donor 2 to patient 1)

These exchanges are usually simultaneous in order to avoid donor's withdrawal, this way ensuring that all procedures are successfully concluded. As a result, this creates logistical constraints such as available number of operating rooms and number of doctors, limiting the number of pairs on each exchange to two or three at most. A 2-way cycle, for example, requires four operating rooms and four surgical teams (one for each donor to remove the kidney, and one to transplant to each patient) (Anderson, et al., 2015), illustrating how difficult it would be to perform exchanges between a higher number of pairs since it will always be necessary the double of rooms and medical staff.

Since "demanding for kidneys far exceeds supply" (Haynes & Leishman, 2017) and the number of patients on the waitlist and the transplant waiting times are in general very long, another type of exchange was considered. Kidney paired exchange chains consist of having a non-directed donor (NDD), such as an altruistic donor or a deceased donor (DD), that initiates a chain donating a kidney to a patient of a pair in the KEP pool and starting the incompatible pairs exchange described previously. The chain could be ended by an incompatible pair donor, whose patient had already received a transplant, donating to the deceased donor waitlist, if it's not possible to perform more KEP transplants (Melcher, Roberts, Lechtman, Roth, & Ress, 2016).

Melcher et al. (2016) and Haynes & Leishman (2017), suggested the utilization of deceased donor kidneys to start KEP chains, which they believe, could increase the number of transplants, since a deceased-donor, by donating both kidneys, has the potential of initiating two chains. For that, the concept paper by Haynes & Leishman, proposes three models that may characterize these chains, in which the waitlist is composed by single patients (patients without a living donor) and incompatible pair's patients from the KEP (only in two models) that consent on receiving a DD kidney for exchange of their pair's donation. This donation starts a chain through the KEP and always finishes on a single patient from the waitlist. The agreement the pair makes is not binding and so the donor can decline the donation at any time.

1. **Candidate-Driven KEP Model**: a pair on the KEP consents and the patient is given high priority on the waitlist, and after receiving a DD kidney, his/her pair donates and initiates the chain;

2. **List Exchange Chains**: Contrary to the previous model, in this one only after the pair's donor initiates a chain (like a NDD chain) the patient receives high-priority on the waitlist and awaits to be transplanted by a deceased donor;
3. **Donor-Driven KEP Model**: In this case a DD kidney doesn't go to the waitlist, instead it goes directly to the KEP and a chain may be identified after running a match on the program. So, it's identical to a NDD chain and differs from the first model because pair's patients are not given priorities and so the DD kidney allocation doesn't take that into consideration.

The main objective in this work is to compare these three models in terms of several performance measures such as the number of transplants and patients' waiting times, especially of particular groups such as O blood-type patients and highly sensitive patients (with bigger risk of positive crossmatch), who tend to wait a long time.

This work is structured as follows: in first chapter an introduction to this problem and past studies are described; second chapter defines the kidney exchange program and the models in study; the implementation methods, including assumptions made to perform the computational test, are mentioned in chapter 3; chapter 4 analyses the results of tests performed in chapter 3; and finally, chapter 5 overviews the conclusions of this work.

1.2. LITERATURE REVIEW

The first concept of a paired kidney exchange programme was proposed by Rapaport (2006), being the first two transplants of this program, in the Unites States, performed in 2000 (Anderson, et al., 2015). The first models of KEP conceived 2 and 3-way cycles but since then a lot of new models and exchange policies were developed to keep improving kidney failure patients' quality of life.

Several simulation studies were performed in order to learn the advantages of these systems. These studies results' analysis covered numerous topics, such as patients' waiting times, dynamic/static scenarios and different formulations, models, types of participants or policies.

The waiting time for different blood types and racial groups studied by Segev et al. (2005) allowed to conclude, through a simulation of 3 years, that there is an accumulation of pairs of type AB and O patients in the pool over time. It was also perceived that the waiting time per race improves when there is no distinction between them, that is, when the exchanges are organized between all types of race. Another conclusion was that easier pairs groups (have more blood compatibilities and less PRA [panel-active antibody]) have an average waiting time of less than 1 year differing from the most difficult groups, that have an average waiting time of 2 or more years. Beccuti et al.(n.d.) also came to the same conclusions, through the observation of difficult pairs (highly sensitive patients, type O patients, etc.) accumulation in their dynamic (and so, more adapted to a real-life scenario) simulation. Moreover, Segev argues that there is a great advantage in integrating a national crossed kidney donation system and therefore with a larger pool.

Saidman et al. (2006) focused the study on the number of transplants using 2 and 3-way exchanges. They simulate a static case with 45 patients and 68 donors, generated through the distribution of patient characteristics on OPTN / SRTR (Organ Procurement and Transplant Network / Scientific Registry of Transplant Recipients) data. As said, models with maximum size cycles 2 and 3 were used, resulting in 8 exchanges in the first case and 11 in the second. It also demonstrates that the second case is always

beneficial because it brings an increase in transplants regardless of the pool size, as defended by Segev et al. (2005).

The first algorithm capable of "cleaning" the highly populated markets that are the pool of kidney failure patients, is proposed by Abraham et al. (2007). The algorithm came up as an alternative to Edmond's algorithm, used in (Segev D. L., Gentry, Warren, Reeb, & Montgomery, 2005) study, which the author considers conservative. Thus, proposes the edge and cycle formulations, explaining the first models of maximum weight, using an incremental formulation as a response to the memory problem. Later Constantino et al. (2013) proposed two compact and reduced formulations from the previous ones, solving the exponential number of variables and constraints created by Abraham et al. (2007). Through the same pair generation that Saidman et al. (2006) used and another generator created by the authors, the kidney exchange program was simulated and adapted the altruistic donors, compatible pairs and multiple donors' cases. The conclusion was that the non-compact edge formulation has poor performance, the non-compact cycle performance is efficient for low density and small cycle limited graphs, and compact formulations yield better results, especially edge assignment formulation.

A more complete simulation, where the dynamic scenario is also included along with the different types of participants in the exchanges (incompatible and compatible pairs and altruistic donors) and different kidney assignment policies is also explored in (Santos, Tubertini, Viana, & Pedroso, 2018).

The implementation of NEAD chains (nonsimultaneous extended altruistic donor) was developed by APD (Alliance for Paired Donation) and it has been proven that the number of transplants increases and the percentage of very sensitive patients who usually have a very long waiting time increases by 50% (Anderson, et al., 2015). At the same time, it also reduces the competition of patients on the waiting list for deceased donors (Melcher, Roberts, Lechtman, Roth, & Ress, 2016). The relaxation of the restriction that required simultaneous transplantation of the cycles allowed longer chains to be implemented. Despite several obstacles to this initiative, described by Anderson, the studies of these two articles allowed to conclude on the broad advantage that these chains have over the initial kidney donation programs, and it is necessary to define rules for the priorities and decide the management of such chains.

Thus, a conceptual article by Haybes et al. (2017) proposes the review of three models where deceased donors initiate crossed kidney donation chains (DD KPD chains), in which case deceased donors are treated as non-direct living donors, as Melcher et al. (2016) describes. These three models, described in the previous chapter, will be the basis for the study of this article, with a comparison of the issues and benefits that each one brings, being that two of these models have already been discussed by Melcher et al. (2016) and Delmonico et al. (2004).

CHAPTER 2. MODELS' DESCRIPTION

Kidney transplants can be done from either a deceased donor (DD) or a living donor (LD). In the first case when someone dies, they can or cannot be eligible for organ donation and when they are, a kidney donation is made to a kidney transplant waitlist. In this list there are kidney failure patients who need a kidney transplant, ordered by their priorities. So, when a DD kidney is allocated to the waitlist, it is transplanted to the highest priority compatible patient. In the second case, a transplant from a LD is made either through an altruistic donor (a donor that as no association with the patients) or by someone who knows the patient and is willing to donate the kidney. This donor may or may not be compatible with the patient and when it is not, the donor/patient pair can enter a program that basically "switches" donors between these incompatible pairs in order to find compatibilities and create cycles of kidney transplants.

2.1. WAITLIST

The kidney transplant waitlist is a list that holds every patient who needs a kidney transplant and is waiting to get a compatible organ from a deceased donor. Each patient is given a priority according to the rules of the kidney transplant waitlist, which may vary according to each country.

Since this list tends to be long in terms of patients and their waiting times (in Portugal there are, approximately, about 2000 people on the list and their waiting times can reach five and a half years (S.K./Lusa, 2017)) a program between pairs of patients and living donors was explored in order to get shorter waiting times.

2.2. KIDNEY EXCHANGE PROGRAM (KEP)

When a patient of the waitlist has someone willing to donate him/her one of his healthy kidneys and the patient-donor pair is compatible, a donation can be made, increasing the patient's life expectancy and quality. But when the pair is not physiologically compatible, i.e. is not blood and tissue type compatible, they can choose to enter a kidney exchange program (KEP) and, in some countries, also choose to continue to be on the waitlist waiting for a DD kidney, increasing the chances to be transplanted as soon as possible.

The program was developed by some countries to upgrade the LD donation concept making exchanges between incompatible pairs possible, in which one pair's donor donates to another pair's patient, whom he is compatible with, creating cycles between a certain number of pairs as illustrated in Figure 2.1. In this figure nodes represent pairs and an arrow from pair i to j means that a donor from pair i donates a kidney the patient in pair j.

Figure 2.1 - 2-way cycle (left) and 3-way cycle (right) exchanges

The main objective of this program consists in maximizing the number of transplants made in a given pool of incompatible pairs. The recommendation for practical solutions is to limit the size of the cycles to 2-cycle and 3-cycle exchanges due to logistic problems. Since the exchanges are preferably made simultaneously, to avoid dropouts, a k-cycle needs 2k doctor teams and the same amount of operation rooms, because in a single exchange it is necessary an operation to remove the LD kidney and another to transplant it to the patient. Moreover, last minute tests between a donor and patient can show new incompatibilities, cancelling this way all the exchanges in the cycle, making shorts cycles preferable.

2.2.1. Optimization Model

To calculate the maximum number of exchanges in the pool several Integer Programming (IP) models were developed using graph theory. Let G = (V,A) be a direct graph with V = {1,2,…,|V|} (a set of vertices representing all incompatible pairs) and A the set of arcs representing the compatibilities between all donors and patients, meaning that the arc (i,j) exists if the donor of the vertex (pair) i is compatible with the patient from vertex (pair) j. A weight w_{ij} is associated with every arc (i, j) ∈ A, that is equal to 1 if the objective is to maximize the number of transplants (as it is this case). In these terms Constantino et al. define the Kidney Exchange Program as: "find a maximum weight set of vertex-disjoint cycles having length at most k".

Although there is more than one formulation for these problems the one we consider in this work is the Cycle Formulation. We define C(k) as the set of all cycles in G with length at most k and the variable $z_{c,}$ for each cycle c ∈ C(k) as:

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

Denoting V(c) ⊆ V as the set of vertices which belong to cycle c, and $w_c = \sum_{(i,j)\in c} w_{ij}$ the model can be written as follows:

Maximize

$$\sum_{c \in C(k)} w_c z_c \qquad (2.1)$$

Subject to:

$$\sum_{c: i \in V(c)} z_c \leq 1, \qquad \forall\, i \in V \qquad (2.2)$$

$$z_c \in \{0, 1\}\, \forall c \in C(k) \qquad (2.3)$$

Since we want to maximize the number of transplants (2.1), the weights are unitary and w_c is the number of transplants in cycle c. Constraints (2.2) guarantee that each vertex (pair) does not belong to more than one cycle, ensuring disjoint cycles and (2.3) is the binary constraint making sure that each cycle is either selected or not.

2.2.2. EXAMPLE

Figure 2.2 shows an example of compatibilities between five incompatible pairs. If the maximum cycle length was k = 2 the possible cycles were 2-4-2 and 3-5-3, two sets of disjoint cycles with four transplants. In the case k = 3 we have the possibilities of the k = 2 case plus 1-4-2-1, with k = 4, all the previous possibilities and the case 2-4-5-3-2 and finally, with k = 5 the adding the 1-4-5-3-2-1 case. Evaluating all these cases we can conclude that the solutions that maximize the number of transplants would be one 5-cycle exchange (1-4-5-3-2-1) or a 3-cycle and a 2-cycle (1-4-2-1 and 3-5-3). As explained before, due to logistic complications, the last case would be preferable, so the optimal solution consist in donor 1 donating to patient 4, donor 4 to patient 2, donor 2 to patient 1, donor 5 to patient 3 and donor 3 to patient 5.

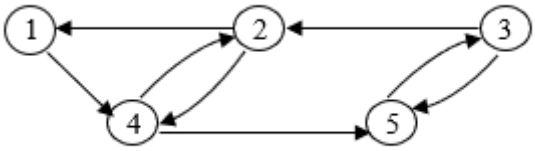

Figure 2.2 - KEP Graph

2.2.3. KEP VARIATIONS

As the kidney exchange program was implemented, some variations were developed, such as different types of donors. One of these cases is compatible pairs, that may enter kidney exchange programs if it is expected that the patient of the pair would be transplanted with a more beneficial kidney than its original compatible donor (Gentry, Segev, Simmerling, & Montgomery, 2007). Another one is

the multiple donors case, in which some KEP participants have more than one donor. In this case only the donor that will lead to the maximum benefit is selected.

Altruistic donors are people willing to donate a kidney to someone in need, without being associated with any of those patients and without expecting anything in return. Through these nondirected donors (NDDs) KEP chains (Figure 2.3) can be initiated, since the altruistic donor donates to a patient in the KEP and its donor donates to the waitlist or to another incompatible pair, adding them to the chain which as a maximum size, according to national or regional programs (Constantino, Klimentova, Viana, & Rais, 2013).

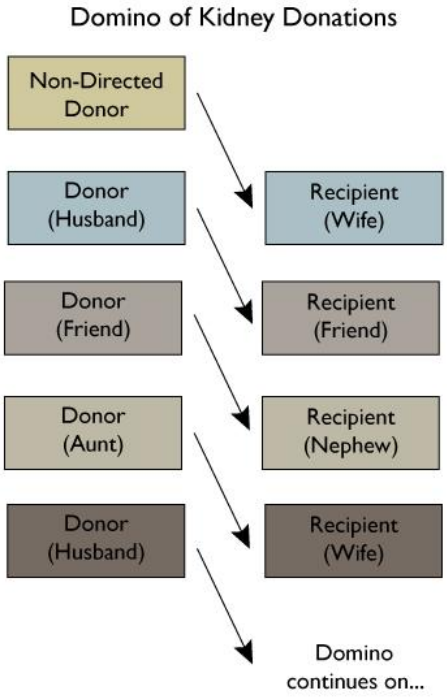

Figure 2.3 - NDD chain

The previous problems were considered simultaneous (hence the maximum length restriction we had to impose) but with non-simultaneous extended altruistic donor (NEAD) chains initiated by a non-directed living donor (NDLD), the maximum length constraint is relaxed. The advantage of this type of chain is its potentiality in numbers of transplants, because the non-simultaneous transplant characteristic permits the chain to have no limit. In that way, a NEAD chain is only interrupted when a LD associated to a KEP pair donates to the waitlist or, after its patient is transplanted, drops the program.

In all these cases we can declare the problem as static or dynamic, the latter case stating that the problem's participants arrive and leave over time.

2.3. MODELS' DESCRIPTION

The next models were proposed by Haynes & Leishman (2017) and intend to study the advantages and disadvantages of combining the KEP and the waitlist, using deceased donor-initiated chains, a variant of NDD chains. Such model aims to know if the potential of KEP donors and DD is improved, resulting in an increase in the overall number of transplants.

The optimization model described in chapter 2.2.1 is also valid considering chains. The only modifications consist on changing C(k), the set of all cycles, to C(k, k'), the set of all cycles and chains, and considering V being the set of all entities (incompatible pairs, deceased donors or patients in the waitlist without donors) but the variable z_c remains the same. Therefore, the model is defined as follows:

Let G = (V,A) be a direct graph with V = {1,2,…,|V|} (a set of vertices representing all involved entities and A the set of arcs representing the compatibilities between all donors and patients, meaning that the arc (i,j) exists if the donor of the vertex i is compatible with the patient from vertex j. For vertices representing deceased donors only arcs of type (*a*, *x*) could exist, where *a* represents a deceased donor and *x* does not, as for vertices representing patients without donors only arcs of type (*x*, *b*) could exist, where *b* represents a patient with no donor and *x* does not. The weights w_{ij} are defined as in the previous model, but in this case $w_{xb} = 0$ meaning the weight or arcs that go to single patients is 0. This is because the affectation of kidneys to single patients is performed at the end of the KEP exchanges and so it is only counted there, as it is going to be explained in chapter 3.2. C(k, k') is as explained in above paragraph and variable z_c, for each cycle c ∈ C(k) as:

$$z_c = \begin{cases} 1, if\ cycle/chain\ c\ is\ selected\ for\ the\ exchange \\ 0, otherwise \end{cases}$$

Once again, V(c) ⊆ V is the set of vertices which belong to cycle or chain c, and $w_c = \sum_{(i,j)\in c} w_{ij}$ the weight of each cycle/chain. So, model can be written as follows:

Maximize

$$\sum_{c \in C(k,k\prime)} w_c z_c \qquad (2.4)$$

Subject to:

$$\sum_{c: i \in V(c)} z_c \leq 1, \qquad \forall\, i \in V \qquad (2.5)$$

$$z_c \in \{0,1\}\ \forall c \in C(k,k') \qquad (2.6)$$

Where the objective function (2.4) and restrictions (2.5) and (2.6) have the same meaning but now applying to chains as well.

The object being considered in the model is c and it does not really matter whether it is a chain or a cycle, as long as the vertices considered do not belong to more than one cycle/chain. That way a chain can begin with a deceased donor or an incompatible pair donor and end with a patient with or without donor, as it's going to be explained below.

2.3.1. MODEL 1 - CANDIDATE-DRIVEN KEP MODEL

In this system a patient/donor incompatible pair, enrolled in the KEP, consents to receive a DD kidney transplant in exchange for the pair's donor kidney. Because of this consent, the paired patient is given high priority on the DD waitlist (1st) and after being transplanted (2nd) its donor donates to the KEP (3rd), initiating a chain (4th) that ends on the waitlist (5th) (Figure 2.4).

Given the pair consent on the exchange mentioned above, its patient is given a waitlist priority higher than all SP but still lower than paired patients who had been given high priority previously, so a DD can donate a kidney to either a SP or a pair's patient, depending on their priorities on the waitlist.

When the DD kidney is transplanted to a paired patient, the donor is available to donate and then KEP chains can only begin with a living donor whose patient has already received a kidney. After possible exchanges through incompatible pairs in the pool, every chain ends in the waitlist when, in the last chain pair of the KEP, the patient is transplanted, and the donor is able to donate to two types of patients on the waitlist, a SP or a pair's patient, again according to their priority. If the person with the highest priority among those compatible with the donor is a patient with an incompatible donor, it means that the chain reached its maximum size, otherwise the patient's pair would have been considered inside the pool, allowing another transplant to be made to the waitlist. Since the chain reached its maximum size the patient receives the kidney without their donor immediate donation, that can be made later, initiating another waitlist ending chain, giving the donor the choice of leaving the KEP (even without donating) whenever they want. On the other hand, if the last donor on the chain does not find a match in the waitlist, his donation remains on hold until he is able to initiate another chain or decides to leave the program.

Through this process KEP cycles are conducted at the same time, the same way as they were before, with only incompatible pairs (whose patients could be on the waitlist too, if they want to).

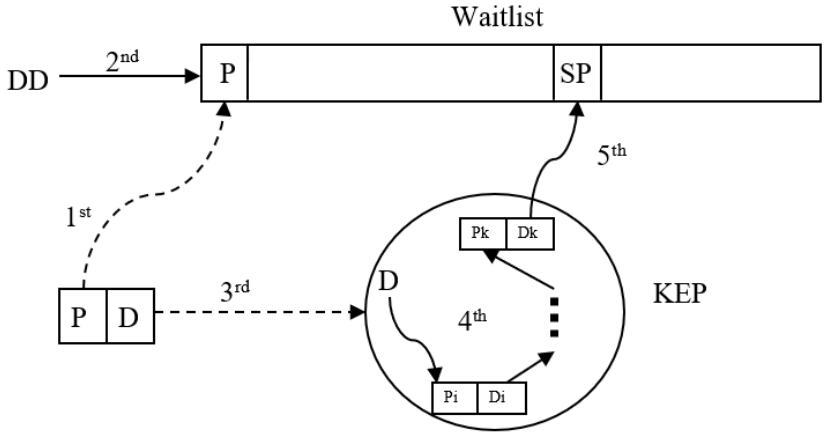

Figure 2.4 - Candidate Driven Model

2.3.2. MODEL 2 - LIST EXCHANGE CHAINS

In similarity to the previous model, a KEP pair gives the same consent but this time the pair's candidate only receives elevated priority after its donor's donation. Therefore, Figure 2.5 exemplifies that after the living donor's transplant (1st), he is matched with another paired candidate, initiating a chain, like a NDD chain, (2nd), that will end on the waitlist (3rd) and resulting on the pair's patient increased priority (4th) that, hopefully, will get him transplanted faster (5th).

When some patients from the KEP pool, who are also on the waitlist in the same circumstances as SP (before their pairs initiate a chain and their priority being elevated), are transplanted by a DD or a LD of a KEP chain, their donor leaves the pool and so the pair's living donor never initiates a chain. The reason why the donor leaves is because the agreement the pair makes in the beginning ensures that the patient receives high priority after his incompatible donor donates, but since he received a kidney transplant before the donor donation, his priority was never increased and so the pair leaves the system. Contrarily, in the previous model, the donor does not leave the KEP immediately because the agreement was to donate after his pair received a transplant, and when the patient is transplanted his priority was already increased.

The last configurations of the previous model, referring to DD donations and KEP cycles still apply here, except the KEP chains, which are now initiated by living donors without their patients having to be transplanted first.

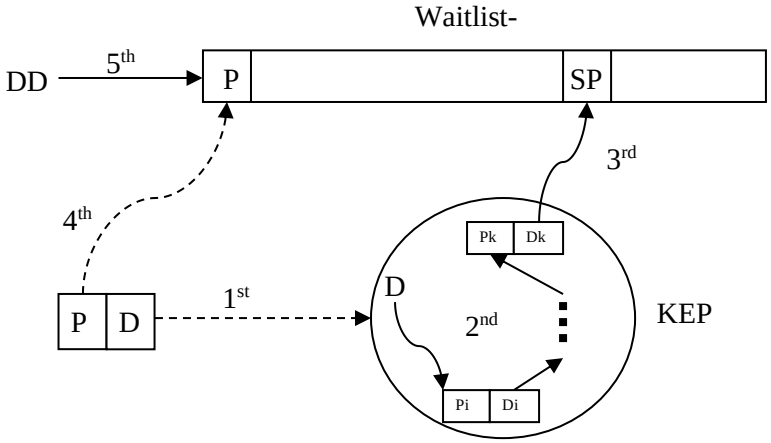

Figure 2.5 - List Exchange Chains

2.3.3. MODEL 3 - DONOR-DRIVEN KPD MODEL

The main differences between this model and the Candidate-Driven Model are that, the consent the pair makes on receiving a DD kidney in exchange for their donor's donation, does not elevate the patient's priority on the list and some DD kidneys go directly to the KEP pool, according to some criteria previously set.

Basically, pairs enter the KEP pool consenting the exchanges described above (1st) and the DD kidneys are redirected from the waitlist to the KEP (2nd), identically to an NDD chain. Next, chains would be identified (3rd) after running a match on the program, choosing chains based only on the number of transplants that may be performed and not by the priorities of the first patients. As expected, the last pair of the chain will donate to the waitlist (4th) (Figure 2.6). As explained before, some paired patients are also on the waitlist and KEP chains end in them or in a SP, depending on the priorities already set on the waitlist.

If a DD kidney is not compatible with any of the pair's patients then goes to the waitlist and is transplanted according to the priorities explained before. In similarity to the previous model, if a paired patient is transplanted in the waitlist, through a DD or a LD from a chain (this indicates that the chain reached its maximum size), his donor does not donate, and the pair leaves the system.

Like the other models, KEP cycles are conducted at the same time and in the same way.

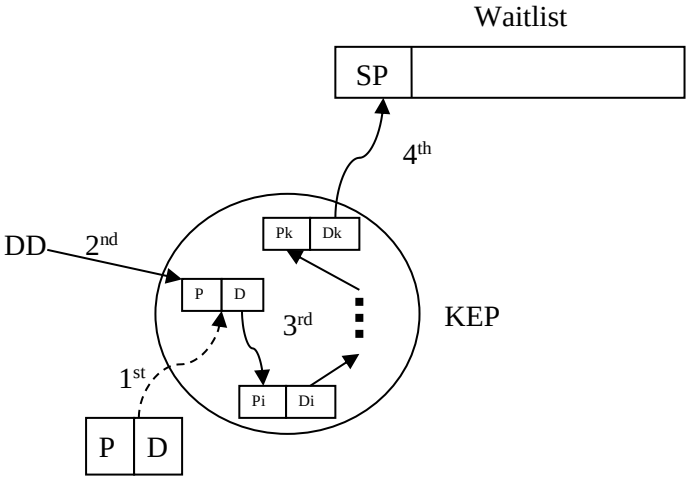

Figure 2.6 - Donor-Driven KPD Model

CHAPTER 3. IMPLEMENTATION METHODS

The simulator created by Santos et al. (2018) was used to implement the policies of the models described in the previous chapter. This simulator has the capacity of implementing different policies for the KEP, regarding several types of people considered in the exchanges (incompatible pairs, altruistic donors, multiple donors and compatible donors), the evaluation of positive crossmatch and the possibility of a person dropping out of the pool.

In this case, only incompatible pairs were considered, and changes had to be made to add single patients and the deceased donors (who behave in a similar way to altruistic donors).

In addition, a basic model (Model 0) was constructed to compare the results of the previously described models to the policy that is currently used in Portugal, that is the KEP and the waitlist working independently.

3.1. COMPUTATIONAL TESTS

For the implementation of the models proposed by Haynes & Leishman, 2017, and to be able to study and compare them, a few assumptions had to be made.

Regarding the incompatible pairs, it was assumed that all of them who are enrolled in the kidney exchange program consent on eventually receiving a deceased donor kidney, for transplantation for the pair's patient, in exchange for their living donor's donation to another paired patient or single patient, thus initiating a chain or donating directly to the waitlist. Also, all patients from an incompatible pair are in the KEP pool with their donor and in the waitlist at the same time and so, can enter a KEP cycle or a chain initiated by either a deceased donor or a living donor. Furthermore, it has been set that no patient or donor would leave the system (KEP or waitlist), except in the list exchange model and the donor-driven model, where donors do not make a kidney donation when their pair is transplanted before receiving a waitlist priority increase (in the first case) or being transplanted in the waitlist (in the second case). Although in the candidate-driven KEP model the agreement is not binding and the donor can refuse to donate any time, it was assumed that this would not happen, and these living donors never decline donations.

The waitlist priorities are managed through various rules that vary from country to country, but for implementation reasons the priorities of all patients were attributed according to their arrival time. In the models that the patients only receive higher priorities when their donor makes a donation (List Exchange Chains and Donor-Driven KPD Model), it was implemented that their priority is increased in the same day, influencing the order of the donations made to the waitlist on that day.

Finally, to compare two different time between matches (tbm) policies, the program could be run every three months (90 days) or daily. When the program was run every three months, deceased donor donations to the waitlist were still made (or tried) every day, and only after 90 days did the available living donors initiate chains that ended in any kind of patient of the waitlist and the incompatible pairs

formed circles in the KEP. These two types of policies were implemented in the first two models, but only daily matches were implemented in the third one, because in this Donor-Driven KPD model chains are always started with deceased donors' kidneys, that cannot wait longer than a day to be transplanted.

3.1.1. MODEL 0 - BASIC MODEL

The model shown in the Figure 3.1 was used as a base model to compare the policies described in the previous models with the currently used in Portugal.

This last one states that the KEP and the waitlist function independently, meaning that deceased donors only donate to the waitlist and only cycles are formed in the KEP, since there are no donors (deceased or living) initiating a chain that would end in the waitlist.

The same conditions described above still apply here, in particular the waitlist has single patients and patients from incompatible pairs, which are enrolled in the KEP too. A deceased donor kidney transplantation is made to the highest priority patient with whom it is compatible, on the waitlist. These matches occur (or tried to be made) every day and KEP cycles can be formed running the program every three months or daily.

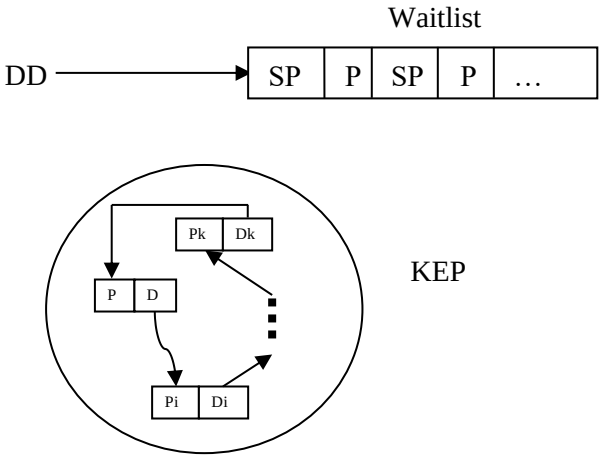

Figure 3.1 – Basic Model

3.2. Assignment Problem

As mentioned before, KEP cycles and chains are obtained through an optimization model that maximizes the number of transplants, i.e. the length of the cycles/chains restricted to their maximum size. Beside these matches made between incompatible pairs there are also the donations made by deceased donors and living donors from the end of the chains, to the waitlist. It was described that when a donor donates to the waitlist, the kidney is transplanted to the first compatible patient with highest priority. But what about the case when there are several deceased donor kidneys and living donors at the end of the chain willing to donate in the same day? Since they are not all compatible with the same patients a decision must be taken regarding to whom gets transplanted by who, as exemplified in Figure 3.2. This figure represents the compatibilities between two donors and three patients on the waitlist, who are sorted by their priority (P1 has the highest priority followed by P2 and P3), and so donor 1 is compatible with patients 1 and 2 and donor 2 is compatible with patient 1 and 3. The objective here is to make the biggest number of matches, respecting the waitlist priorities, meaning that one patient cannot be transplanted if a patient with higher priority is not and was compatible with a previously available donor.

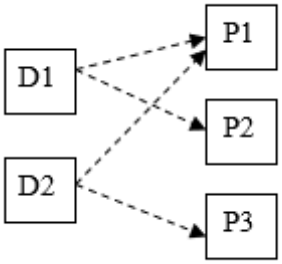

Figure 3.2 – Assignment Problem

Suppose that D1 donates to P1 and D2 to P3. This does not respect the waitlist priorities because there was a way of a higher priority patient than P3 (P2) to be transplanted, if D1 donated to P2 and D2 to P1. In this way P3 is not transplanted but the greatest number of matches was made, and the priorities were respected.

In order to resolve the problem described above an assignment problem must be formulated. Given $D = \{1, \ldots, d\}$ the set of available donors and $P = \{1, \ldots, p\}$ the set of available patients with priority $j \in P$, where 1 is the highest priority and p the lowest. It is intended to assign donors to transplant their kidneys to patients to make the maximum number of matches and at the same time respect the waitlist priorities. So, the assignment problem can be formulated as follows:

Variables:

$$x_{ij} = \begin{cases} 1, if\ donor\ i\ transplants\ to\ a\ patient\ with\ priority\ j \\ 0, otherwise \end{cases}$$

Constants:

$$a_{ij} = \begin{cases} 1, if\ donor\ i\ and\ patient\ j\ are\ compatible \\ 0, otherwise \end{cases}$$

$c_{ij} = 2^{p-j}$, the utility of donor i transplanting to patient with priority j or the weight of arc (i,j).

This represents the gain of having $x_{ij} = 1$. If patient has priority p, the lowest, then $c_{ip} = 1$ and if it has priority 1, the highest, then $c_{i1} = 2^{p-1}$. This means that the higher the priority of a patient then the higher the utility of donating to that patient. This guarantees that a transplant to a patient of higher priority will always be favoured if it is possible due to the following expression:

$$2^n > \sum_{i=0}^{n-1} 2^i \quad (3.1)$$

Since $\sum_{i=0}^{n-1} 2^i = 2^n - 1$, a geometric series, expression (3.1) assures that the utility of transplanting to a patient with a certain priority is greater than the sum of utilities of transplanting to all patients with lower priority.

Objective function:

$$Max\ z = \sum_{i \in D} \sum_{j \in P} c_{ij} x_{ij} \quad (3.2)$$

Subject to:

$$\sum_{i} a_{ij} x_{ij} \leq 1, \quad j = 1, \ldots, p \quad (3.3)$$

$$\sum_{j} a_{ij} x_{ij} \leq 1, \quad i = 1, \ldots, d \quad (3.4)$$

$$x_{ij} \in \{0, 1\}, \quad i = 1, \ldots, d;\ j = 1, \ldots, p \quad (3.5)$$

The objective function in (3.2) intends to maximize the utility value of the transplants made. This way the optimal solution will make the maximum number of transplants, while respecting the priorities.

Restrictions (3.3) and (3.4) guarantee that each patient and donor can only be involved in a transplant at most once, respectively. Last restriction, (3.5) states that the variable x_{ij} is binary and so, only takes the value 0 or 1.

The utility of a patient grows exponentially the more available patients are and so, implementing this formulation on a computer raises an issue of memory and very long time. Caron et al. (1999) and Volgenant (2004) studied an approach to solve a similar problem but in this work, the solution found was a constructive heuristic that does not guarantee optimality but guarantees the waitlist priorities are respected. Basically, every time this affectation must be made, the program goes through each patient from the waitlist, starting from the one with highest priority and tries to make a match with the first donor available, and so on until it reaches the end of the waitlist, there are no more available donors or no more compatible donors with the rest of the patients.

In model 0 this affectation is made each day with the available deceased donors' kidneys to the waitlist. The same is done in the first model (Candidate-Driven KEP Model), but since all patients from incompatible pairs were given a higher priority than single patients, the affectation is made to only paired patients, and so their living donors can make donations that may start chains. In the end of the day, the remaining DD and the living donors from the last incompatible pairs of the chains donate to the waitlist. Since in the second model (List Exchange Chains) patients only receive higher priority after their living donor donates, the affectation is made after the cycles and chains generation, from the last living donors from the chains and DD kidneys to all patients of the waitlist, given that if incompatible patients are transplanted before they had an increase in priority, their LD leave the system. Finally, in the third model (Donor-Driven KPD Model), only one affectation is made and again is from LD in the end of chains and the DD that could not initiate a chain, because there were no compatible patients in the KEP. So, it is natural that DD only donate to SP in the waitlist while the last LD from the chains can donate to any type of patients, since they were unable to donate to another pair in the chain due to the length extension restriction.

CHAPTER 4. TESTS RESULTS

As mentioned before, the main objective of this work is to compare the models in study in terms of their efficiency. This efficiency is measured through the percentage of transplants performed and patients' waiting time to be transplanted, this considering the types of blood and PRA and different time between matches policies.

In this chapter the results of the computational tests based on the implementation of the models described in chapter 2 will be analysed. First, an explanation of the generation of instances used to simulate each one of the three models will be given. These tests were run on a computer with an *Intel® Core™ i7-6500U CPU @ 2.50GHz 2.60GHz*, using the *Geany* text editor to run the simulator written with the programming language *Python* version 2.7 and to run the optimization model in the solver *Gurobi*. The average runtime of each simulation is about 5 minutes.

4.1. INSTANCE GENERATION

To run and test each of the models in study, it is necessary to create an instance with all the entities involved on the models such as deceased donors, incompatible pairs and single patients, as well as their compatibilities. In order to better replicate the state of an actual waitlist and KEP pool, a warm-up of four years was made, along which the entities were created and in the last year (fourth) the models' policies were run. Single patients were generated through the whole warm-up time, whilst incompatible pairs were generated only in the last two years and deceased donors only in the last year, when the policies are actually implemented. This is due to the fact that deceased donors' kidneys last a very short time since they are available until they are transplanted (one or two days), and if they were created before the implementation time, they would never be allocated to any patient.

Each instance consists of a characterization file, where each one of the entities created are described, as shown in Table 4.1, and an arcs file, where the arcs correspond to compatibilities between every donor (deceased or from incompatible pair) and every patient (single patient or from an incompatible pair) possible. Therefore, each arc has the form (donor, patient, 1), where 1 is the weight of the arc and indicates that the donor and patient are compatible.

Table 4.1 – Entities Characteristics

Entities Characteristics	
Entity ID	Each entity has its own ID, being that the ID numbers are attributed first to incompatible pairs, then deceased donors and ending in single patients, within each arrival time.
Donor ID	This ID correspond to the entity ID and since it is only applicable in the incompatible pairs and deceased donors, it has the value -1 on the single patients' case.
Donor Blood	It is the donor blood type, that can vary between A, B, AB or O, according to their probabilities. These probabilities were given according to the distribution of blood types in Italy (O = 46%, A = 42%, B = 9%, AB = 3%). As in the last case, single patients have the value -1 in this characteristic.
Donor Age	It is the donor's age, that takes a random integer value between 18 and 73. It has the value -1 on single patient entities.
Patient ID	The same case as the donor ID (they are equal in the incompatible pairs case). Again, this parameter has the value -1 in the deceased donor entities.
Patient Blood	It can also range within the same four options with the same probabilities as the donor blood and has the value -1 in the deceased donors case.
Patient PRA	The panel-active antibody (PRA) is an antibody that indicates the proportion of people the person will react against and ranges between 0% and 100%, so the bigger the percentage the higher the risk of organ rejection. It can be divided into three categories that in this generation were defined as follows: • Low PRA: a random integer value between 0% and 9%, with a probability of 0.64 of being in this category; • Medium PRA: a random integer value between 10% and 79%, with a probability of 0.27 of being in this category; • High PRA: a random integer value between 80% and 99%, with a probability of 0.09 of being in this category; This characteristic is -1 in the deceased donor parameters.
Patient Crossmatch	A positive crossmatch determines that two people are not tissue compatible, so this parameter is a probability dependent on the PRA calculated by $\Phi(-1.5007 + 0.017 \times \text{PRA})$, the cumulative distribution function for the standard normal distribution. Once again, the value is -1 on deceased donor entities.
Patient Age	It is the patient's age, that takes a random integer value between 18 and 73, except in the deceased donor's case, whose value is -1.
Arrival	The arrival of each entity is generated randomly using an exponential function whose mean is a rate that represents the average number of days between the arrival of an entity and varies according to the type of entity. For each type of entity, the first arrives on the day generated by the function plus the beginning time and the next one by adding the previous arrival to another value generated by the function, until the last day of the simulation (after four years) is reached. For incompatible pairs the rate is 5 and the beginning time is in the second year, for deceased donors the rate is 2 and begin to arrive in the third year and for single patients the rate is 1 and begin the arrivals at the beginning of the simulation.

Departure	The departure time of each entity depends on the entity type. Deceased donors have a departure time 1 day after their arrival time, because the kidneys cannot hold much time without being transplanted into a living body. As for incompatible pairs and single patients, it was assumed that they never drop out of the program or waitlist for any reason, so their departure always exceeds the maximum simulation time.
Description	This parameter can either be "incompatible, if the entity is a donor/patient incompatible pair, "deceased", if is a deceased donor, or "singlePatient", if is a patient without donor.
Country	In this case, the country data used is from Italy.
Priority	This is the priority of every patient in the waitlist, so it has the value -1 for deceased donors. When the instance is generated all patients (incompatible pairs entities and single patients) receive a priority based on their arrival time, so the first patient to arrive has priority 1 (highest), the second priority 2, and so on and so forth. It is only when the models are implemented that their priorities may change.
Deceased Kidneys	This parameter is only applicable to deceased donors and determines whether they donate one or two kidneys, with a probability of 0.8 of donating two.

An example of an instance can be:

- **Characterization**: (1, 0, B, 24, 0, O, 77, 0.4239886214034858, 60, 720, 2910, incompatible, IT, 680), meaning that this entity has an ID 1, the donor has ID 0, blood type B, 24 years old, the patient has ID 0, blood type O, 77% PRA (medium PRA), approximately 0.42 probability of crossmatch, 60 years old, the entity arrived in day 720 (beginning of the 3rd year), will leave the system on day 2910 (after the four years of simulation), represents an incompatible patient, from Italy, with a patient priority of 680 (this means that the patient is behind 679 patients in the waitlist).

- **Arcs**: (0, 24, 1), meaning that the donor whose donor ID is 0 is compatible with the patient with ID 24.

Fifty different instances were randomly generated, with the parameters previously described to have a better coverage of possible cases. The next table describes the average constitution of these 50 instances, regarding their types of entities.

Table 4.2 – Entities Distribution

SP	1442.1
incompatible pairs	139.4
deceased donors	321.9

Table 4.2 shows that 1442.1 single patients, 139.4 incompatible pairs and 321.9 deceased donors were generated, on average for one instance. To see more details on the distribution of the patients (SP and incompatible pairs) regarding types of blood and PRA consult Appendix A.

4.2. Simulation Results

The simulator was run with the four models for each of the 50 instances. For models 0, 1 and 2 there were two policies regarding the time between matches (tbm), i.e., the number of days between a KEP run, where the program tries to create cycles and chains with incompatible pairs. The two policies are doing KEP matches every day or every 90 days (3 months), so there are 7 different types of models to compare: models 0, 1 and 2 with tbm of 1 or 90 each one (lets denote them by Model 0-1, Model 0-90, Model 1-1, Model 1-90, Model 2-1 and Model 2-90), and model 3, which has a daily KEP run policy. For each of these models and for every instance, the percentage of transplants, the average waiting time and the maximum waiting time were recorded for each type of patient (SP or from incompatible pairs) and for each blood type and PRA. The results shown below represent the average value of the 50 instances created initially.

4.2.1. Percentage of Transplants

The first model comparison method used was through the analysis of the percentage of transplants made. This measure was calculated for the twelve combinations of types of blood and PRA for each type of patient, as the average waiting time and maximum waiting time were, and by dividing the number of transplants of one combination made in a model by the number of this particular type of patient existing in the instance. Meaning that if this value was equal to 1, then all patients on that instance (for SPs or incompatible pairs' patients) with that particular combination of blood and PRA were transplanted. So, contrary to the other two measures, the bigger the percentage of transplants is, the better.

Results taken from Figure 4.1 indicate a higher efficiency in incompatible pairs' patients than single ones as it would be expected since the first type of patients can be in the waitlist and in the KEP at the same time, generating more possible compatibilities and so a bigger chance of transplantation. In SPs case, it can be perceived that the results do not change almost anything between models, being that the difference between the maximum (obtained in all Models 0 and 1) and the minimum (in Model 2-1) is only of 0.56%. But for incompatible pair' patients, there is a clear increase of the percentage of transplants between Models 0 and the rest of them, which almost have the total possible number of transplants made, wherein the minimum percentage is at Model 0-1 day and the maximum at Model 1-90 days.

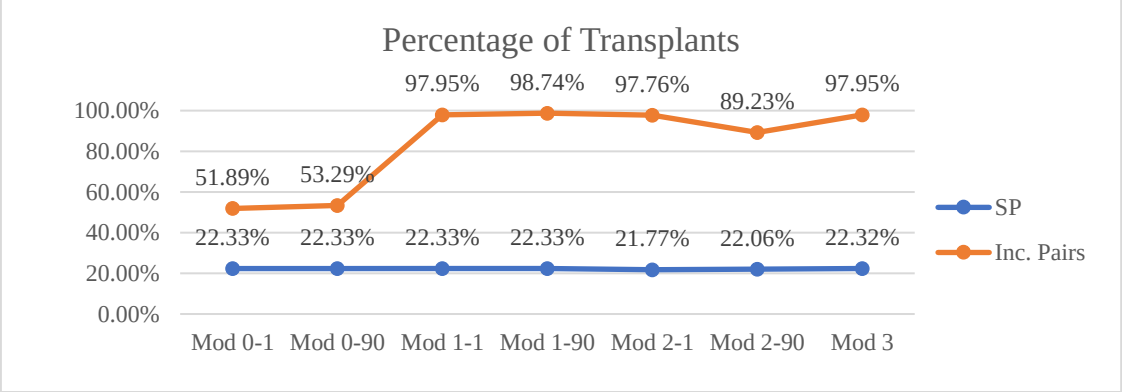

Figure 4.1 – Percentage of Transplants

Figure 4.2 illustrates the percentage of transplants made in the models, by the blood types. As it would be expected, due to the types of blood compatibilities, patients with blood type AB have higher percentage of transplants, than A, B and O types, being that the last one has the smallest values and A and B type, very similar results. This behaviour is clearer within SPs, since in the incompatible pairs case this only happens in Model 0 because in the rest of them, they all have almost the same results. So, for SPs with blood type A, B and AB, Model 0 has smaller values compared to the other models, so the minimum percentage is found on that model and the maximum is in Model 1-90 days for blood types B and AB and Model 2-90 for type A. As for blood type O, the results are almost opposite: Models 0 have the maximum value and Model 2-1 day has the maximum. In the incompatible pairs case, as it was mentioned, Models 0 show smaller results, with the one with tbm of 1 having the minimum value for blood types O (in this case, a significant lower value), A and B, and the one with tbm of 90 days the minimum for blood type AB. Additionally Model 2-90 days also shows a smaller percentage of transplants compared to the rest of the models. All other models show similar values and almost the total number of possible transplants made, being the maximum value at Model 1-90 days for all blood types.

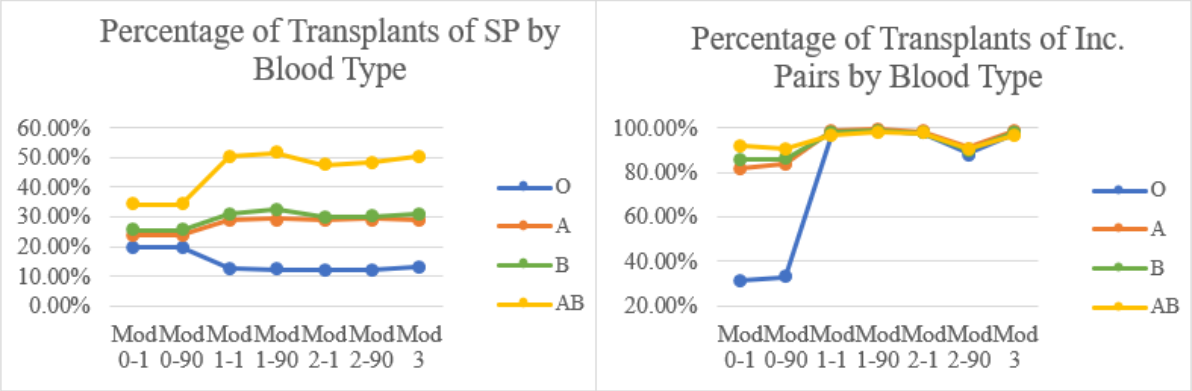

Figure 4.2 – Percentage of Transplants by Blood Type

Considering PRA types, for single patients, the behaviour seen in Figure 4.3 is as expected: patients with low PRA have the highest percentage of transplants, the ones with medium PRA have the intermediate values, but practically the same ones as the low PRA patients have, and those with high PRA have the smallest percentage of transplants made, with a visible difference between the other two. The values between models do not seem to vary much, and their minimum values are in Model 2-1 day for all PRA types, while the maximum is in both Models 0 for PRA high and medium and Model 1-1 day also, for the low type. For incompatible pairs' patients the behaviour explained above is also observed, except in Models 0. In these models all PRA types show considerable smaller values and also, low PRA patients show smaller percentage of transplants compared to the others. Additionally, in these models the percentual value range between near 40% and 60%, opposing to the other models who show almost perfect results raging between almost 80% and 100%. Here the maximum number of transplants is always observed in Model 1-90 days and the minimum at Model 0-1.

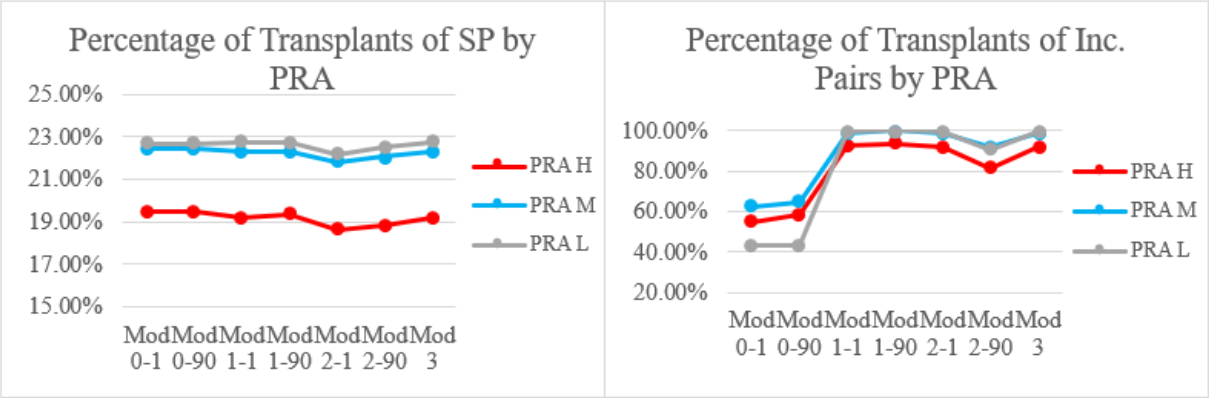

Figure 4.3 – Percentage of Transplants by PRA type

4.2.2. Average Waiting Time (AWT)

The waiting time of a patient is calculated by subtracting the arrival day (the arrival parameter of the entity) to the day the patient gets transplanted. This factor was calculated for every transplanted patient and the mean was stored for each type of patient, blood and PRA (type O and PRA high, type O and PRA medium, etc.), so 12 different means for SPs and other 12 for incompatible pairs were calculated. Since the number of transplants for these types was also recorded, the average waiting time for the four blood types, the three PRA types and in general was calculated by a weighted arithmetic mean, again for each type of patient.

The average waiting time of patients was compared among all the four models and their variations regarding the tbm. Figure 4.4 shows a comparison between the AWT of patient's types, and it can be observed that SPs have a much higher average waiting time than incompatible pairs' patients, in every model (approximately 1100 days comparing to roughly 150 days). Comparing the models, both types of patient have very homogeneous values in all of them, although SPs show smaller variance. Model 2-90 days shows the minimum AWT value for SPs but a maximum for incompatible pairs' patients, while Model 0 shows the maximum value for SP's, no matter which type of tbm, and Model 3 the minimum for the other kind of patients. The big discrepancy between the two types of patients AWT can be explained not only for the benefit incompatible pairs' patients get in their waitlist priority, but mostly due to the warm-up made in the instance generation. Since SPs were being created from the beginning of the four years and the other patients were not, most of SPs arrival day is very small, influencing their waiting time to be bigger. For this, it is best to separate the AWT results by type of patient.

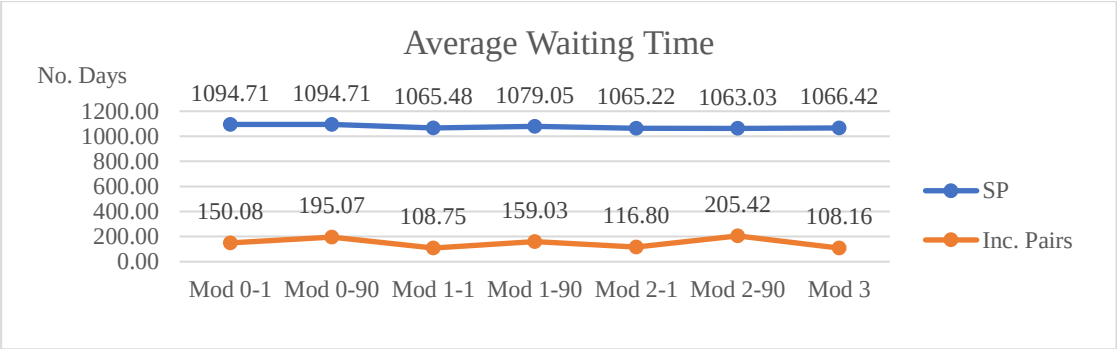

Figure 4.4 – Average Waiting Time

Within each type of patients, the results were separated by blood type and by PRA type, as shown if Figure 4.5. Concerning the blood type, in both types of patients the AWT shows the same behaviour regardless of the model: type O has the higher average waiting time, followed by type A and B, that have very similar values to each other, and type AB shows the lower AWT. These results were expected, since type O patients can only have one type of donor, A and B two types, and AB four types, as explained in the blood compatibilities in Table 1.1. Single patients with blood type O show a significant lower AWT in Model 0 unlike the other models (a difference of about 100 days), that have very similar values within each other, contrarily to the other blood types, which have higher values in Model 0 comparing to the others (about 100 days of difference with type A and B and almost 200 days for type AB), that are also similar with each other. As for incompatible pairs' patients, their AWT has a bigger value variance between models. The lowest values are found in Models 1-1, 2-1 and 3, for all blood types, except for Model 0-1, where this affirmation is only valid for A, B and AB types, being that Model 3 has minimum values for all blood types. Considering higher values, Model 0-1 for type O patients and Models 0-90, 1-90 and 2-90, for all blood types, stand-out, especially Model 2-90 that has the maximum values for blood types A, B and AB, and Model 0-1, for blood type O.

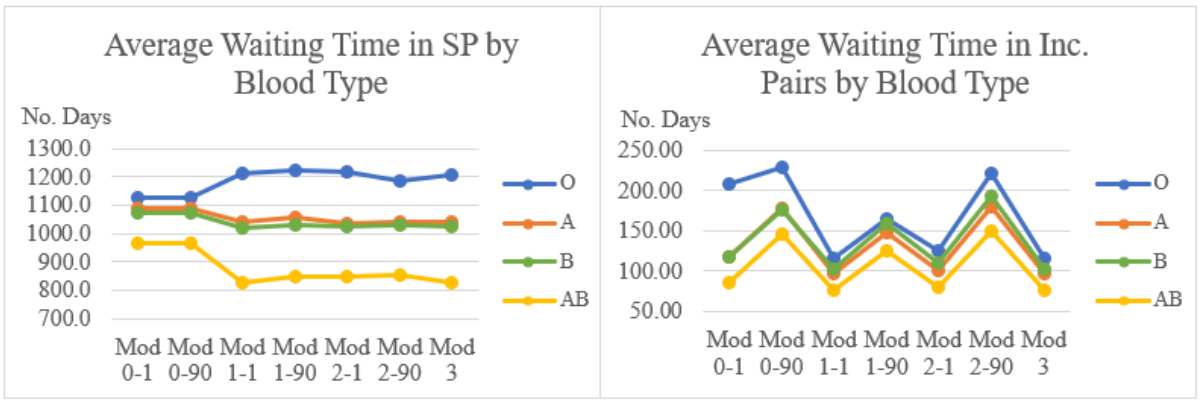

Figure 4.5 – Average Waiting Time by Blood Type

After analysing the AWT results for the three types of PRA shown in Figure 4.6, it can be concluded that their behaviour is not as similar has in the blood types case. For single patients, the ones with PRA high have a bigger AWT value, followed by patients with PRA medium and finally the ones

with PRA low, as it should be expected, because the higher the PRA the more difficult it is to get a compatible donor. But on the other hand, on incompatible pairs' patients that expected behaviour does not occur, since patients with PRA medium and low have almost the same values, except in Model 0, where the AWT of patients with PRA low exceeds the other two types. Evaluating the performance of the models, in SPs, for all PRA types, Model 0-1, both Models 2 and Model 3 have similar values and the lowest, and both Models 0-90 and Model 1-90 exhibit more high values, being that the maximum and minimum values are always observed in Models 0, with both tbm types, and 2-90, respectively, with a difference of approximately 30 days. For the other patients, local minimum values are observed in Models 0-1, 1-1 and 2-1, and Model 3, and local maximum values in the other models. More specifically the minimum value is always observed in Model 3 and the maximum in Model 0-90, for PRA low and Model 2-90 for the other two types, similar to the blood type case and with a difference of roughly 100 days.

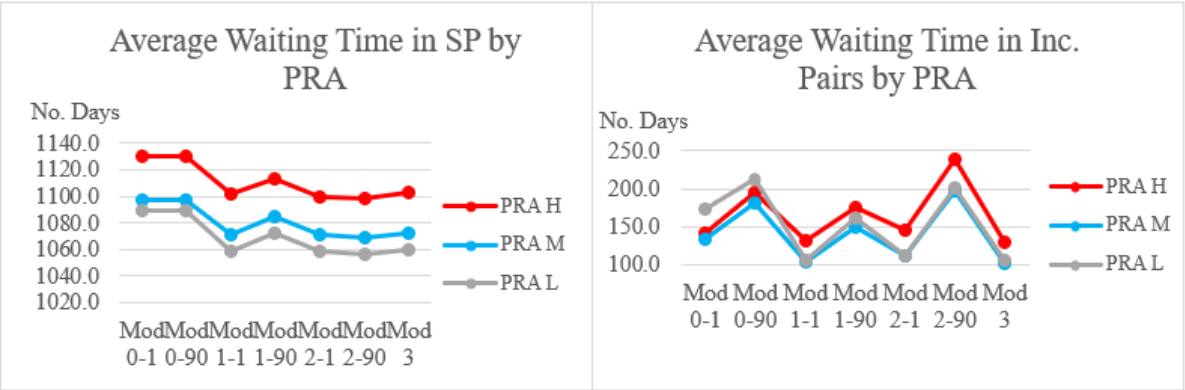

Figure 4.6 - Average Waiting Time by PRA Type

4.2.3. MAXIMUM WAITING TIME (MWT)

Another model's evaluation measure was the maximum waiting time (MWT) that, as the average waiting time, was calculated for each combination of patient, blood type and PRA type. This factor is also important to contemplate because even though an AWT seems to have a decent value, i.e. not very large, it can be masked by several high values that are compensated by several low values. And although having many patients with low waiting time values is good, the fact that also many patients have very high values is very undesirable and so it is better to have more constant values between the patients.

The behavior observed in Figure 4.7 is very similar to the previous case. There is a very large difference between the two types of patient concerning the maximum waiting times (about 1300 days for SPs compared to 500 days for the others) and it can still be verified that those values do not suffer a very large variation between the models, especially for SPs. Furthermore Model 2-90 has de maximum value for SPs and Models 0 the minimum, while in the other patients' case, Model 0-90 records the maximum value and Model 1-1 the minimum. Moreover, it can be observed that SPs' AWT range between 1063 and 1194 days and the MWT between 1265 and 1320, meaning that there is an increase of about 200 days compared to an usual patient AWT. For incompatible pairs' patients the AWT ranges

between 108 and 205 days as the MWT between 419 and 597, indicating an increase of about 350 days compared to the average case, which is greater than the SPs case. This suggests that there are more constant values for the models for SPs than for incompatible pairs, which is a good thing, although SPs waiting time values are still much bigger than the other ones.

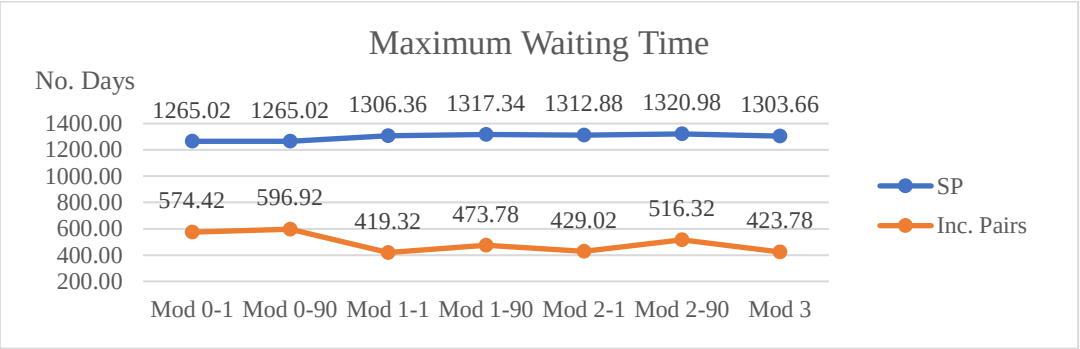

Figure 4.7 – Maximum Waiting Time

For a more meticulous investigation, the types of patients' results were, once again, separated by blood and PRA type. Considering the blood type, results in Figure 4.8 show that the MWT is larger in type O, followed by type A, type B (although these last two have very similar values in SPs) and type AB, similar to the AWT case. For single patients with blood types A and B the values between models do not vary much and the minimum and maximum are obtained in Model 2-1 and Model 1-90, correspondingly. As for blood type AB, the variation is slightly bigger and the minimum and maximum are found in Model 2-1 day and both Models 0, respectively. Finally, for the blood type O both Models 0 record the minimum value and the rest of them are very similar within each other and with a larger value, while Model 1-90 holds the maximum value. As for incompatible pairs' patients, their MWT is always bigger with blood type O, followed by A, B and AB. All blood types, except blood type O, display lower values in Models 0, 1 and 2, all with tbm of 1 day, and Model 3, and higher values in the rest. In blood type O, similar to the others, the lower values are in Models 1-1 and 2-1and Model 3 but Model 0 has the highest values. The minimum values observed here are in Model 1-1 for blood types O and AB, and Model 3 for blood types A, B and again, AB, and the maximum values in Model 0-90 for all blood types except B, that as its maximum in Model 2-90 days.

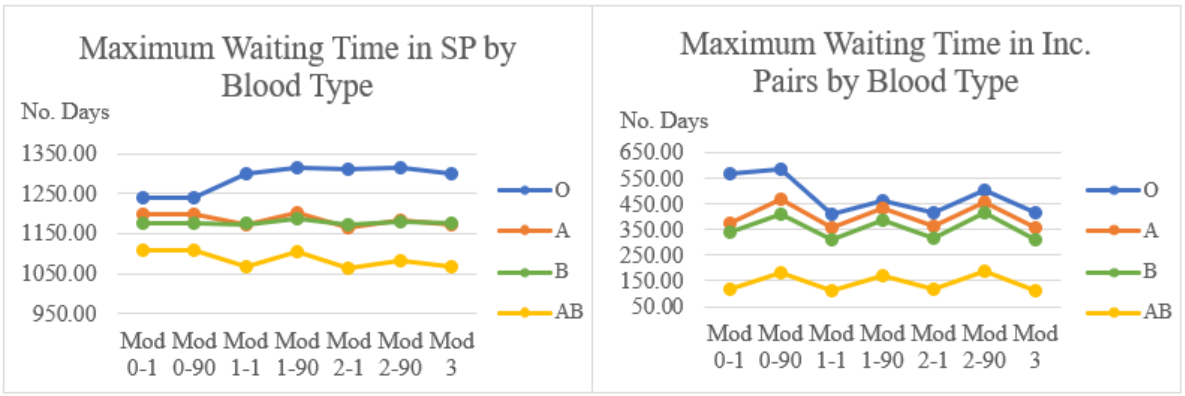

Figure 4.8 – Maximum Waiting Time by Blood Type

By observation of the PRA results in Figure 4.9 it can be concluded that, single patients with medium and low PRA have almost the same results throughout the models, showing smaller values in both Models 0 and similar within the rest. As for the ones with high PRA they show higher values in all models, especially in both Models 0, exhibiting a similar behaviour within the models, but not such a big difference between the first two models and the rest. Additionally, all PRA types for SPs record their maximum and minimum value in the same models: Model 2-90 days for the maximum and both Models 0 for the minimum. Now, for the incompatible pairs' patients MWT analysis, it is visible that the values suffer a great variation between models and PRA types. For patients with high PRA the highest values are in Models 0-90, 1-90 and 2-90, being that the last one holds the maximum, and the rest of the models have lower values, in particular Model 0-1, that has the minimum. Regarding the medium PRA type of patients, higher values are in both Models 0, and Models 1-90 and 2-90, as in the previous case, and smaller values in the other ones, where the maximum is in Model 0-90 and the minimum in Models 1-1 and 2-1. Lastly, the low PRA case is very similar to the medium PRA one, except that the minimum, in this case, is only found in Model 1-1. Comparing the PRA types within each other, in both Models 0 low PRA patients have the higher MWT, followed by medium PRA and high PRA, wherein the other models high PRA patients always have higher values (except in Model 1-90, that is similar to the medium and low PRA values) and the other two types have almost the same MWT.

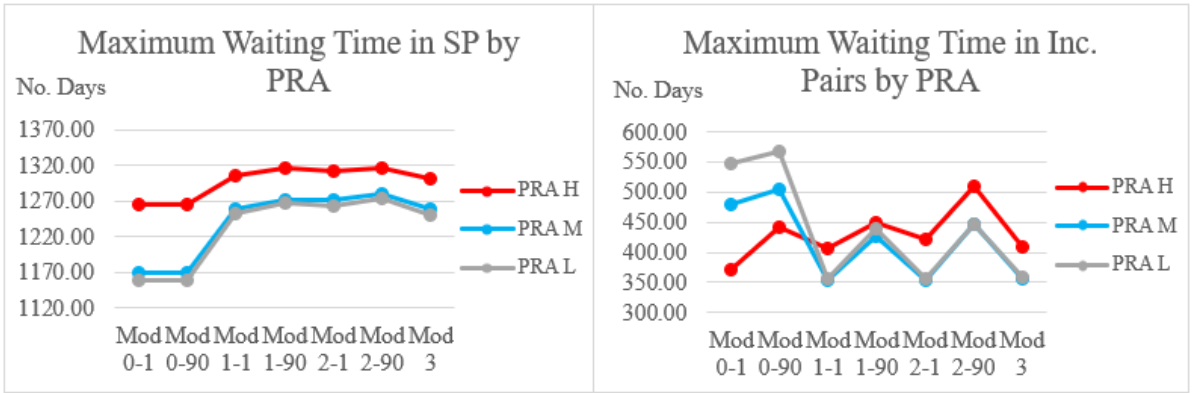

Figure 4.9 – Maximum Waiting Time by PRA Type

4.3. RESULTS' ANALYSIS

In a general way, it is visible that patients from incompatible pairs have a quite superior percentage of transplants than single patients, being this difference clearly more accented on Models 1, 2 and 3. On SPs, the percentage of transplants does not seem to vary much between models, specially between the several PRA types. But considering the type of blood, it shows an advantage on types A, B and AB on using Models 1, 2 and 3, over blood type O, being that for this type it is the opposite behavior. It is natural to conclude that type O patients have the lower percentage of transplants, followed by types A and B (practically the same values) and finally type AB. SPs with PRA H have the lowest values comparing to types M and L, whose values are very similar, although patients with PRA L with slightly higher values, as expected. Regarding patients from incompatible pairs the advantage of Models 1, 2 and 3 comparing to Model 0 is obvious, particularly analyzing between PRA types or on blood type O. Moreover, the remaining values are similar and the order of percentage of transplants stays the same as in SPs' case, except on Model 0 regarding PRA types, where PRA L patients' values lower significantly.

In average waiting time case, once again, it is visible a much-accented difference between a single patient's waiting time and one from an incompatible pair, where the last case has an average of 950 days less than the first case. They also present very homogeneous values throughout models for the same type of patient, being that for incompatible pairs the variance is of 100 days between the model yielding the maximum value (Model 2-90) and the minimum (Model 3). As in the percentage of transplants case, blood type O single patients, have higher waiting times than A, B and AB type patients, being that A and B types show similar values and even higher than AB type, and patients with PRA H greater than PRA M, followed by PRA L. Once again Model 0 shows disadvantages comparing to the other models, booth in blood and PRA types, except in blood type O where the situation is reversed. Still, regarding PRA type, Model 1-90 displays an increase of value compared with the new models proposed in this work. As far as patients from incompatible pairs, the case is not as static as before. It is clear an increase within each model when the tbm of 90 days policy is implemented. Models 0 and 2 show higher values than Models 1 and 3 and there's a particularly visible increase on Model 0 regarding blood type O patients. The order from highest to lowest values is maintained for blood and PRA type as in SPs' case, except on Model 0 where patients with PRA L type have the highest values, similar to what was reported in the percentage of transplants analysis.

Lastly, the behavior observed in the maximum waiting time analysis is very similar to the average waiting time. Values for single patients are much higher than for patients from incompatible pairs and do not seem to vary much between models. As for the results by blood type there is not a great difference between the models' performance observing types A, B and AB, but regarding type O, the lower values in Model 0 behavior repeats. Regarding PRA type is notorious the similarity between PRA M and L maximum waiting times, being that these times are still lower than for patients with PRA H type, as expected, and still all types have lower values on Model 0, contrary to expected. On incompatible pairs' patients the peaks of higher values on models with tbm of 90 days repeats and is even higher on model 0, when concerning PRA L, M and blood type O.

The biggest conclusion to be made from this analysis is the clear advantage that patients coming from incompatible pairs have over patients with no living donor. As it would be expected patients from

blood type O always have disadvantages compared to A, B (which present very similar values) and still AB, as PRA H type patients comparing to M followed by PRA L type, except for some cases.

Concerning the models in study it can also be perceived the benefit of using a joint management policy of KEP and deceased donors waitlist, comparing to the separate use of these two transplant assignment methods, represented by Model 0. This benefit is more evident for incompatible patients, since single patients with blood type O are harmed by the use of these models.

Yet so, it is still very difficult to choose an ideal model for all cases but, as it was verified several times, models with a policy of 1 day between matches showed more positive results. In Appendix B it can be verified which model had the minimum or maximum values for each described case. The reader could tend to end up favoring the model that most often appears as maximum, in the percentage of transplants case, and minimum on other cases, but many times the variations between values of the models are very tenuous, therefore is not possible to establish a linear connection for an idyllic model.

CHAPTER 5. CONCLUSION

Patients who suffer from a kidney disease and must submit to dialysis often are waiting from a compatible donor to be available so that they can be transplanted with a new kidney. This option increases their life quality and obviously their life span. This transplant can be performed via two ways: a deceased donor or a living donor. Transplants from deceased donors follow the rules from a priority waitlist, so when a kidney is available it is transplanted to the compatible patient who as the highest priority. Since the waiting time for a transplant from a deceased donor is very long, due to the shortage of donors compared to the number of patients, and the fact that it may not be easy to find a compatible person willing to donate, a new policy was created.

The kidney exchange program (KEP) calculates the best way to exchange kidney transplants between pairs composed by a patient and a person who was willing to donate them a kidney but is incompatible. Thereby pairs swap their donors and a donor from one pair gives his kidney to a patient from another pair, if the patient he originally intended to donate receives a kidney from another living donor.

In order to further improve this transplantation process three new models were proposed by Haynes & Leishman (2017) and were studied in this work. These models combine the KEP with the DD waitlist, creating chains that are initiated by deceased donors to a patient from the KEP pool, whose priority is increased, and finish with a donation from a donor from KEP to a patient on the waitlist. The variation between models is essentially in the order the affectations are made and the time between matches policy.

The simulator created by Santos et al. (2018) was modified to adapt to these models, so they were implemented and compared with each other and the regular case model (where KEP and waitlist are managed independently). Fifty instances simulating a pool of deceased donors, incompatible pairs and single patients were created and used to run the simulator for each model, being that the outputs from that simulation were the percentage of transplants, the maximum waiting time and average waiting time. Each of these values was calculated for the average fifty instances and discriminated by blood and PRA type.

As far as conclusions made by the simulation, it is clear that the benefit gained from using the new models, specially for incompatible pairs and except in the O blood type single patients' case, and the advantage to have a living donor willing to donate and to enrol the KEP. It is also perceptible that most of the time models run with 1 day between matches have better results and, as expected because they are more difficult to find a match, groups like blood type O and high PRA patients show worst values than the others.

Comparing the new models there is not one ideal that had better results in every case. For some cases one has the greatest advantage but, in most cases, the values between these three models, when they have the same tbm policy, are very similar.

REFERENCES

Abraham, D. J., Blum, A., & Sandholm, T. (2007). Clearing Algorithms for Barter Exchange Markets: Enabling Nationwide Kidney Exchanges. *Proceedings of the 8th ACM conference on Electronic commerce* (pp. 295-304). San Diego: ACM.

Anderson, R., Ashlagi, I., Gamarnik, D., Rees, M., Roth, A. E., Sönmez, T., & Ünver, M. U. (2015). Kidney Exchange and the Alliance for Paired Donation: Operations Research Changes the Way Kidneys Are Transplanted. *Interfaces*, 26-42.

Caron, G., Hansen, P., & Jaumard, B. (1999). The Assignment Problem with Seniority and Job Priority Constraints. *Operations Research*, 449-453.

Constantino, M., Klimentova, X., Viana, A., & Rais, A. (2013, May 15). New insights on integer-programming models for the kidney exchange problem. *European Journal of Operational Research*, pp. 57-68.

Delmonico, F. L., Morrissey, P. E., Lipkowitz, G. S., Stoff, J. S., Himmelfarb, J., Harmon, W., . . . Rohrer, R. J. (2004). Donor Kidney Exchanges. *American Journal of Transplantation, 4*, 1628-1634.

Gentry, S., Segev, D., Simmerling, M., & Montgomery, R. (2007, August 31). Expanding Kidney Paired Donation Through Participation by Compatible Pairs. *American Journal of Transplantation*, pp. 2361-2370.

Haynes, C. R., & Leishman, R. (2017). Allowing Deceased Donor-Initiated Kidney Paired Donation (KPD) Chains.

Johns Hopkins Medicine. (n.d.). *Positive Crossmatch and Sensitized Patients*. Retrieved September 22, 2019, from Johns Hopkins Medicine: https://www.hopkinsmedicine.org/transplant/programs/kidney/incompatible/positive_crossmatch.html

Melcher, M. L., Roberts, J. P., Lechtman, A. B., Roth, A. E., & Ress, M. A. (2016). Utilization of Deceased Donor Kidneys to Initiate Living Donor Chains. *Am J Transplant*, 1367-1370.

National Kidney Foundation. (2017, February 10). *The Kidney Transplant Waitlist – What You Need to Know*. Retrieved April 19, 2018, from National Kidney Foundation: https://www.kidney.org/atoz/content/transplant-waitlist

Nunes, P. T. (2010, January). *Transplante Renal*. Retrieved September 21, 2019, from Associação Portuguesa de Urulogia: https://www.apurologia.pt/publico/frameset.htm?https://www.apurologia.pt/publico/transplante_renal.htm

Rapaport, F. T. (1986). The Case for a Living Emotionally Related International Kidney Donor Registry. *Transplantation proceedings*, 5-9.

S.K./Lusa. (2017, July 20). *PORTUGAL TEM UMA LISTA DE ESPERA PARA TRANSPLANTE RENAL DE DUAS MIL PESSOAS*. Retrieved September 22, 2019, from Sapo Lifestsyle: https://lifestyle.sapo.pt/saude/noticias-saude/artigos/portugal-tem-uma-lista-de-espera-para-transplante-renal-de-duas-mil-pessoas

Saidman, S. L., Roth, A. E., Sönmez, T., Ünver, M. U., & Delmonico, F. L. (2006). Increasing the Opportunity of Live Kidney Exchange Donation by Matching for Two- and Three-Way Exchanges. *Transplantation 81*, 773-782.

Santos, N., Tubertini, P., Viana, A., & Pedroso, J. P. (2018, February 15). Kidney exchange simulation and optimization. *Jornal of the Operational Research Society*, pp. 1521-1532.

Segev, D. L., Gentry, S. E., Melancon, J. K., & Montgomery, R. A. (2005). Characterization of Waiting Times in a Simulation of Kidney Paired Donation. *American Journal of Transplantation 5*, 2448-2455.

Segev, D. L., Gentry, S. E., Warren, D. S., Reeb, B., & Montgomery, R. A. (2005). Kidney paired donation and optimizing the use of live donor organs. *Journal of the AMA, 293*, 1883-1890.

Volgenant, A. (2004). A note on the assignment problem with seniority and job priority constraints. *European Journal of Operational Research 154*, 330-335.

APPENDIX

Appendix A – Patients distribution regarding types of blood and PRA

SP	general	1442.1
	type O	661.8
	type A	605.1
	type B	131.6
	type AB	43.6
	PRA H	129.1
	PRA M	386.1
	PRA L	926.9
	type O and PRA H	59.4
	type O and PRA M	177.8
	type O and PRA L	424.6
	type A and PRA H	52.7
	type A and PRA M	161.6
	type A and PRA L	390.8
	type B and PRA H	12.8
	type B and PRA M	35.9
	type B and PRA L	83.0
	type AB and PRA H	4.2
	type AB and PRA M	10.9
	type AB and PRA L	28.5
Incompatible pairs	general	139.4
	type O	83.5
	type A	38.8
	type B	15.2
	type AB	2.0
	PRA H	22.4
	PRA M	48.5
	PRA L	66.6
	type O and PRA H	10.8
	type O and PRA M	26.0
	type O and PRA L	46.7
	type A and PRA H	8.9
	type A and PRA M	17.7
	type A and PRA L	12.2
	type B and PRA H	2.7
	type B and PRA M	4.8
	type B and PRA L	7.7
	type AB and PRA H	0.6
	type AB and PRA M	1.1
	type AB and PRA L	0.3

Appendix B – Maximum and minimum values

Percentage of Transplants

SP	Min	Max
general	Mod 2-1	Mod 0, 1
O	Mod 2-1	Mod 0
A	Mod 0	Mod 2-90
B	Mod 0	Mod 1-90
AB	Mod 0	Mod 1-90
PRA H	Mod 2-1	Mod 0
PRA M	Mod 2-1	Mod 0
PRA L	Mod 2-1	Mod 1-1

Inc. Pairs	Min	Max
general	Mod 0-1	Mod 1-90
O	Mod 0-1	Mod 1-90
A	Mod 0-1	Mod 1-90
B	Mod 0-1	Mod 1-90
AB	Mod 0-90	Mod 1-90
PRA H	Mod 0-1	Mod 1-90
PRA M	Mod 0-1	Mod 1-90
PRA L	Mod 0-1	Mod 1-90

Average Waiting Time

SP	Min	Max
general	Mod 2-90	Mod 0
O	Mod 0	Mod 1-90
A	Mod 2-1	Mod 0
B	Mod 1-1	Mod 0
AB	Mod 3	Mod 0
PRA H	Mod 2-90	Mod 0
PRA M	Mod 2-90	Mod 0
PRA L	Mod 2-90	Mod 0

Inc. Pairs	Min	Max
general	Mod 3	Mod 2-90
O	Mod 3	Mod 0-90
A	Mod 3	Mod 2-90
B	Mod 3	Mod 2-90
AB	Mod 3	Mod 2-90
PRA H	Mod 3	Mod 2-90
PRA M	Mod 3	Mod 2-90
PRA L	Mod 3	Mod 0-90

Maximum Waiting Time

SP	Min	Max
general	Mod 0	Mod 2-90
O	Mod 0	Mod 1-90
A	Mod 2-1	Mod 1-90
B	Mod 2-1	Mod 1-90
AB	Mod 2-1	Mod 0
PRA H	Mod 0	Mod 2-90
PRA M	Mod 0	Mod 2-90
PRA L	Mod 0	Mod 2-90

Inc. Pairs	Min	Max
general	Mod 1-1	Mod 0-90
O	Mod 1-1	Mod 0-90
A	Mod 3	Mod 0-90
B	Mod 3	Mod 2-90
AB	Mod 1-1	Mod 2-90
PRA H	Mod 0-1	Mod 2-90
PRA M	Mod 1-1	Mod 0-90
PRA L	Mod 1-1	Mod 0-90