UNIVERSIDAD AUTÓNOMA DE NUEVO LEÓN

FACULTAD DE INGENIERÍA MECÁNICA Y ELÉCTRICA

ASSESSING THE IMPACT OF KIDNEY PAIRED DONATION IN MEXICO

POR

MICHEL ABRAHAM HERRERA MEDRANO

COMO REQUISITO PARCIAL PARA OBTENER EL GRADO DE MAESTRÍA EN CIENCIAS EN INGENIERÍA DE SISTEMAS

SEPTIEMBRE, 2017

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Los miembros del Comité de Tesis recomendamos que la Tesis "Assessing the Impact of Kidney Paired Donation in Mexico", realizada por el alumno Michel Abraham Herrera Medrano, con número de matrícula 1359867, sea aceptada para su defensa como requisito parcial para obtener el grado de Maestría en Ciencias en Ingeniería de Sistemas .

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A mi Mutter

La persona más maravillosa del universo

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Abstract

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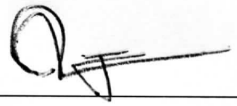
The application of Operations Research in the medical field has been the key to save more lives in a variety of decision-making problems. With the aid of mathematical models and algorithms developed for specific problems, we can now develop plans and polices, and take decisions that can lead to optimal or near optimal solutions. This is the case of the Kidney Exchange Problem addressed in this thesis. Recently, a new idea has arisen for those patients with renal disease in need of a transplant and have a willing but incompatible donor. Let us suppose we have two incompatible patient-donor pairs (PDPs), that is, in each pair, the donor is not compatible (blood type or crossmatch) with the recipient; however, the donor of pair A is compatible with the recipient of pair B, and the donor of pair B is compatible with the recipient of pair A. Then they can swap kidneys and both pairs would benefit from this exchange. This exchange is called a cycle and has cardinality 2. This may

sound easy at a first glance; however, when we have a pool of hundreds of PDPs, we need a way to decide the largest number of matches, this can be achieved with the aid of a mathematical model and specific algorithms to solve it. Additionally, allowing for cycles of larger cardinality or the introduction of donation chains (which arise when altruistic donors come into play) lead to different problems with more complex and challenging models to be solved.

Most patients with renal disease in Mexico who undergo through transplant, receive a kidney from a living donor, and this is because most of the families refuse to consent to organ donation from their deceased relative. Therefore many patients on the waiting list lose the chance of receiving a kidney passing away during the process. A viable alternative to the waiting list for patients with renal disease who need a transplant is a kidney exchange program. In this type of program, also referred to as kidney barter exchange market, PDPs would enroll and form a big pool of potential pairs. Once we have a pool, an appropriate solution algorithm for solving a related mathematical model for the kidney exchange problem is applied. Typically, these models seek to maximize the maximum number of PDPs that can be paired or a weighted function of these. The main contribution of this thesis is to implement a simulator based on data taken from Mexican databases that can be used to assess and estimate the effect a potential kidney exchange program may have in the Mexican population.

Firma del director: 

Dr. Roger Z. Ríos Mercado

Chapter 1

Introduction

1.1 Barter exchange markets

Barter exchange is one of the oldest and most straight forward forms of economic activity [32]. It concerns the direct trading of one product or service for another, in other words, agents seek to swap their items with one another, in order to improve their own utilities. We can consider various examples of barter exchange [20].

1. House exchange, where participants seek to swap homes.
2. Room exchange, where college students trade up for better roommates.
3. Car exchange, where participants seek to obtain better cars.
4. Book exchange, where readers seek to trade for new books for reading.
5. General barter exchange, where agents swap different goods or services.

There is many people outside wanting things who others may posses and probably are willing to exchange for some other item. However, it is sometimes hard to find such good match that fulfills the need of both persons. It also may be the case that you enroll a barter exchange market (e.g., house swapping) and you find and

swap a house, then after swapping you find another more suitable house which if you had made a bigger effort in seeking, you could have obtained more gain.

Digital market places may overcome these kind of complexities of finding such coincidences of wants [32], where people sign up and post their needs and their possessions, so some other users me be interested in that item and therefore proceed with the swapping goods. Some examples of these digital marketplaces may include: www.mercadolibre.com, www.ebay.com, www.amazon.com, www.besthouseswap.com.

1.2 Kidney exchange and the clearing problem

1.2.1 Kidney disease

Kidney failure, also called end-stage renal disease (ESRD), is the last stage of chronic kidney disease (CKD). When your kidneys fail, it means they have stopped working well enough for you to survive without dialysis or a kidney transplant [3]. Leading causes of kidney failure include diabetes in first place and high blood pressure in second place.

After the diagnosis of ESRD is determined, a decision concerning the most appropriate mode of renal replacement for the patient must be made. Options for renal replacement therapy for ESRD may include kidney transplantation, peritoneal dialysis and hemodialysis [15]. Kidney transplantation is the most desired and cost-effective modality of renal replacement therapy for patients with irreversible chronic kidney failure (end-stage renal disease, stage 5 chronic kidney disease) [1].

However, it is not that easy to find a good donor. There are certain constrains that may make a willing donor incompatible with the recipient. Such constraints are mainly the blood type compatibility and the crossmatch test. This last test determines if the recipient has antobodies against the donor cells. If they do, they

are crossmatch positive and the transplant is not carried out even if they are ABO compatible (see Appendix A).

In the past, due to these complications, recipients did not have another choice than signing up in the waiting list, where many of them died before receiving the kidney. Later on, another alternative was proposed, which was to develop a kidney barter exchange market, where recipients with willing but incompatible donors had the posibility of enrolling such market creating a large pool of incompatible pairs.

The way the kidney exchange works is simple. Suppose we have an incompatible pair, let us call it pair A, whose donor is compatible with recipient of pair B, and the donor of pair B is compatible with recipient of pair A. Then they can "swap" kidneys and both pairs would benefit from this exchange. This is called a cycle of size two. Chains are also possible. These are explained in the next chapter.

1.2.2 Clearing problem

Given a set of agents, the objects they brought to the market, and the agent's reported preferences over objects, the clearing problem in barter exchange markets is to determine an allocation of objects to agents so as to maximize the gains of trade. In general, there may be side payments to compensate for unequal exchanges. Every agent may for instance have an asking price for the good he brought to the market and a maximum buying price for every good he is interested in [32].

Having stated the clearing problem, we can now implement this methodology in the kidney barter exchange market, where we seek to obtain the maximum weight matching or, in other words, the maximum number of transplants, all depending on the approach or the algorithms implemented. Sometimes we seek for different objectives. We will review other approaches besides the maximum weight matching in the following chapters.

1.3 Motivation and objective

Kidney barter exchange markets are nothing new. In the United States there are distinct organizations that offer kidney exchange programs. The most important organizations in the United States are [38]:

1. **OPTN/UNOS Kidney Paired Donation Program.** The vision of the OPTN/UNOS Kidney Paired Donation Program is that every kidney transplant candidate with an incompatible but willing and approved living donor receives a living donor kidney transplant. The mission is to develop a successful Kidney Paired Donation (KPD) program with universal access to all UNOS/OPTN members that prioritizes the medical and psychosocial safety of living donors and candidates.
2. **Alliance for Paired Donation.** The mission of the Alliance for Paired Donation™ is to save lives by significantly reducing the wait time for a kidney transplant through kidney paired donation.
3. **National Kidney Registry.** The mission of the National Kidney Registry is to save and improve the lives of people facing kidney failure by increasing the quality, speed, and number of living donor transplants in the world.

In the United States, the following statistics are known [38, 39]:

1. Over 3,000 new patients are added to the kidney waiting list each month.
2. 13 people die each day while waiting for a life-saving kidney transplant.
3. Every 14 minutes someone is added to the kidney transplant list.
4. In 2014, 4,761 patients died while waiting for a kidney transplant. Another, 3,668 people became too sick to receive a kidney transplant.

Meanwhile in Mexico it is not much different. There are currently 21,510 registered individuals who need a transplant, from which more than half of them, 13,313 need a kidney transplant [12]. There are around 9.6 million individuals who suffer from CKD in the early stages, while there are 140,000 with ESRD [28].

Chronic kidney disease is among the top ten of mortality in Mexico (according to the IMSS) [36] and unlike the United States and other countries, Mexico does not have a kidney barter exchange market. Currently, ESRD patients who do not have a compatible donor, do not have another choice than sticking to the waiting list, where many of them die before receiving a kidney. With the introduction of a kidney barter exchange program, we would give another alternative and chance of living to those patients.

The objective of this thesis is to motivate the implementation of a kidney exchange program in Mexico, in order to give patients another opportunity to live. We will assess the potential impact of a kidney exchange program for the next years with the aid of a simulator.

1.4 Contribution

A kidney barter exchange market sounds like a great idea. Unfortunately, to the best of our knowledge, no database regarding incompatible pairs exists in Mexico. There is certainly information of the individual patients waiting for a kidney; however, a successful kidney exchange program would require patients bringing living donors and compatibility information among pairs. In this thesis a computer program that simulates the effects of kidney exchange programs is developed. The underlying model includes data gathered from different sources from the Mexican population such as blood type distribution, gender distribution, age distribution, and PRA distribution (see Appendix B). This approach is based on a previous study carried out by Gentry et al. [31] in the United States.

A brief description of the simulator is as follows: Basically we simulate potential donors a patient might have, these potential donors include the whole family and other not directly related or unrelated donors. Once we have the potential donors (2 potential donors are considered for each recipient), we proceed with the ABO test, the medical work-up (this is to determine if donor's kidney is healthy enough and if the donor passes the psychological test) and the crossmatch test.

The possible outcomes for a patient are:

1. Patient goes to the waiting list (does not have a healthy willing donor)
2. Pair goes to exchange program (has an incompatible willing and healthy donor)
3. Pair goes to direct donation (has a willing, healthy, and compatible donor)

The simulator generates pairs until the stopping condition is met. This condition is to reach a certain number of direct donations. A total of 30 repetitions are carried out for statistical testing. Once the number of incompatible pairs is estimated, we create a pool of incompatible pairs and optimize it with a clearing

algorithm. This is to estimate an average of incompatible pairs that could be served from a kidney exchange program. We also estimate the number of current incompatible pairs in the waiting list and, based on certain model assumptions, estimate the behaviour of the waiting list for the following 10 years.

Chapter 2

Kidney Transplant Overview

2.1 History and legislation

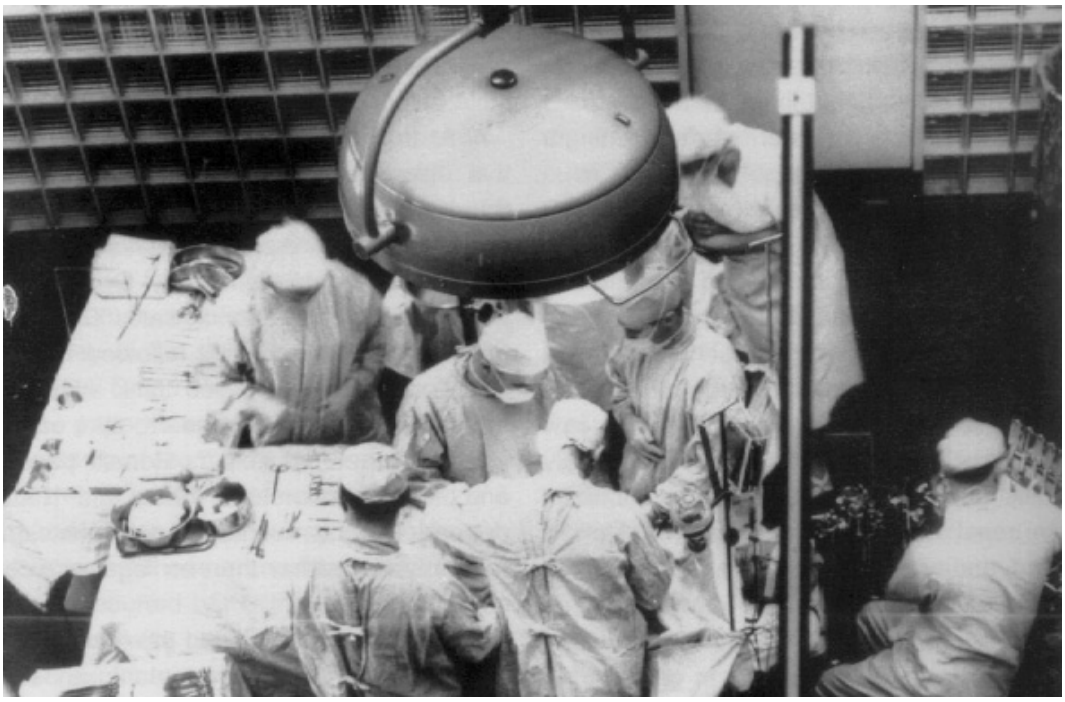


Figure 2.1: First successful transplant from twins in 1954.

2.1.1 History around the world

Transplantation is a recent phenomena. Many of the big developments in this discipline have taken place within the past 40 years. Much of the story of transplantation is a story of barriers and how modern scientific medicine overcame those barriers. Here we present a time line that gives a brief outline of how transplantation progressed through this century [41].

Early experiments

1902 - The first sucessful experimental kidney transplants were performed at the Vienna Medical School in Austria with animals.

1909 - The first kidney transplant experiments were performed in humans in France using animal kidneys.

A surgeon inserted slices of rabit kidney into a child suffering from kidney failure. Although "the immediate results were excellent" the child died about two weeks later. While such transplants did sucessfully produce urine, they lasted only for about an hour before ceasing to function. Scientists of the time believed kidney transplants were possible, but their success was limited by unknown "biochemical barriers," which prevented long-term kidney survival.

1933 - The first human-to-human kidney transplant was performed

Unknown to doctors at the time, there were mismatches in donor and recipient blood groups and the donor kidney never functioned

1940s - Sir Peter Medawar at the University of London experimented with the immunologic basis of organ rejection.

Early 1950s - Cortisone-like medications were used to suppress the human body's self-defense system (immune system), resulting in some kidney transplant success.

The perfect match

1954 - Joseph Murray and his colleagues at Peter Bent Brigham Hospital in Boston performed the first truly successful kidney transplant from one twin to another. This was done without any immunosuppressive medication. A photograph of this procedure is seen in Figure 2.1.

Scientists predicted that immune system reactions should be minimal between identical twins (because their organs were indistinguishable to each other's immune systems). More kidney transplants between identical twins were successfully performed, and some of those kidney recipients are still alive today.

Rejection perfection

Late 1950s - New approaches were needed to prevent the body from fighting off a "foreign" donor kidney when an identical twin donor was not available.

1960s - *Tissue typing advancements* - Better techniques for matching donor and recipient blood and tissue types, as well as improvements in preserving cadaveric (from recently deceased donors) kidneys, were developed.

1961 - *Immunosuppression advancements* - Powerful immunosuppressives became available and, in combination, helped decrease the chance for kidney rejection

1980s and 1990s - New tecniques, new medications and new patient information have helped make kidney transplants a safer, more effective and more routine procedure

Barriers

In order for sucessful kidney transplants to become a reality, science needed to outwit the human body's own defense systems.

The procedure

First, surgeons had to develop a surgical procedure that would not only place a new kidney in the patient, but connect all the necessary tubes and blood vessels. This was largely done by surgeons such as Dr. Thomas Starzl.

Dialysis

Throughout all of this experimentation, there were other developments being perfected that helped keep renal failure patients alive. This was called kidney dialysis and it kept patients alive by using an artificial kidney to purify human blood, which is what normal functioning kidneys do every day. In 1948 Dr. Willem Kolff first used his Kolff-Brigham "artificial kidney" on human patients and set the stage for innovative new approaches to controling renal disease.

Rejection

Scientists needed to learn why organs in our bodies rejected new organs. The pioneering work in this field of immunology was largely done during the 1950s by researchers such as Dr. Joseph Murray.

Immunosuppression

After scientists more accurately understood why our bodies fight off foreign organs, they experimented with ways to combat these defences. Surgeons used X-ray, bone marrow infusion, immunoparalysis, donor-recipient matching, and drugs to stop rejection.

Organ preservation

Another crucial part of kidney transplantation is proper organ preservation. Although today's solutions and cooling methods can safely preserve kidneys for up to 48 hours, there were times when surgeons rush organs from decapitated prisoners!

2.1.2 History and legislation in Mexico

In Mexico, the first organ transplant was performed in 1963 with no pre-existing legislation. However, in 1973, a regulation of transplants was formulated for the first time in the Sanitary Code of the United States of Mexico.

For the aim of regulating the disposal of organs, tissues and cadavers of human beings for medical applications, scientific research and teaching purposes, the Federal Regulation for the Disposal of Organs, Tissues and Cadavers of Human Beings was published in 1976 [6] .

In The General Health Law published in 1984, a title on the sanitary control of the disposal of organs, tissues and bodies of human beings was included. In this title, the characteristics of procurement, selection, and transplantation of organs and tissues were specified, in order to regulate such activities throughout the national territory.

With the purpose of establishing mechanisms for concerted actions to promote and facilitate the procurement of organs, tissues, and human bodies, a collaboration agreement between the Secretariat of Health, the National Institute of Nutrition "Salvador Zubirán," and the Mexican Red Cross "Guillermo Barroso" was signed in 1990. Also, between 1991 and 1994, collaboration agreements were established between the Secretariat of Health and the State Governments, in order to carry out, at the state level, the National Program of Transplants.

In 1999, the National Transplant Council (CONATRA) began operations as an intersecretarial commission of the federal public administration, with the objective of promoting, supporting, and coordinating actions with regard to transplants carried out by the healthcare institutions of the public, social, and private sectors. In 2000, the Federal Government established the National Center for Transplantation (CENATRA), which was assigned the sanitary control of donations and transplants of organs, tissues, and cells of human beings.

In the reform of the General Health Law in 2000, it was established that CENATRA would have the faculty to decide and monitor the allocation of organs, tissues, and cells, and promote the culture of donation.

On June 2003, the attributions of sanitary monitoring and controlling of transplant activities were transferred to the Federal Commission for the Protection against Sanitary Risks (COFEPRIS), such that CENATRA would concentrate its efforts in the design and coordination of the National Transplant System and its program of action.

In 2008, the General Health Law was reformed with regard to the disposal of organs, tissues, and human cadavers, such that the attribution of regulation on cadavers regarding general health remain in charge of the governments of each federative entity, as well as local authorities and within their respective territorial jurisdictions.

Furthermore, in 2009, the Federal Government acknowledged that the demand for organs and tissues exceeded the available amount, such that it was therefore necessary to implement mechanisms to ensure that the allocation became transparent. Therefore, an agreement was published, establishing the guidelines for the allocation and distribution of organs and tissues of cadavers of human beings for transplantation, which defined specific criteria of urgency by type of organ and tissue.

In the modification of the General Health Law of 2011, it was stated that the governments of the federative entities would establish State Transplant Centers (CETRA), in order to Collaborate with CENATRA in the elaboration of transplant programs, and integrating and updating the information of the National Registry of Transplants.

In order to update the regulations governing the disposal of organs, tissues, and cells, the Regulation of the General Law on Health with regard to Transplants was issued in 2014. In this regulation, the attributions of CENATRA, the aspects of the donation for the purpose of transplants, and transplants were defined.

2.2 Kidney failure

Kidneys filter waste and extra fluids out of the blood to make urine. When kidneys do not work the way they should, they allow waste and water to flow back into the blood stream instead of sending them out through the urine. This causes waste and water to build up in the body, which can cause problems with heart, lungs, blood, and bones.

In most cases, kidney disease is preventable, but not curable. The most common causes of kidney disease are diabetes and high blood pressure. If a person has chronic kidney disease, meaning her or his kidneys are damaged and can not work as well as they should, she or he may still be able to prevent kidney failure, which is when her or his kidneys do not work at all. Kidney failure is the last (most severe) stage of chronic kidney disease. This is why kidney failure is also called end-stage renal disease, or ESRD for short [3].

2.2.1 Treatments

If a person has ESRD, she/he will need dialysis or a kidney transplant to survive. It is important to know that dialysis cannot do everything that healthy kidneys do. Therefore, even when a patient is on dialysis, she/he may experience some of the complications of kidney failure.

There are options for treating kidney failure, including:

Hemodialysis - One treatment for kidney failure is called hemodialysis, or "hemo" for short. This type of treatment uses a machine to clean the patient's blood, and it can be done at a dialysis center or at home.

Peritoneal dialysis - A treatment that uses the lining of the patient's abdomen (belly area), called your peritoneum, and a cleaning solution called dialysate to clean

her/his blood. Peritoneal dialysis may be done at home or even at work if the patient has a suitable area.

Kidney transplant - It is a surgery to give the patient a healthy kidney from someone else's body. A kidney transplant may come from a live donor (usually someone the patient knows) or from a deceased donor. The healthy kidney can do the job that the kidneys did when they were healthy [3].

As previously mentioned, kidney transplantation is the most desired and cost-effective modality of renal replacement therapy for patients with irreversible chronic kidney failure (end-stage renal disease, stage 5 chronic kidney disease) [1].

2.2.2 Source of donor kidneys

A donated kidney may come from someone who died and donated a healthy kidney. A person who has died and donated a kidney is called a deceased donor. When we mention deceased donors, we refer to two kinds: brain death donors and cardiac death donors [38].

Brain death donors can donate most organs including the kidney because even though they have suffered complete loss of all brain function and are clinically and legally dead, mechanical ventilation and medications keep their heart beating and blood flowing to their organs, meanwhile for the cardiac death donors, vital organs quickly become unusable for transplantation, but their tissues such as bone, skin, heart valves and corneas can be donated within 24 hours.

Donated kidneys may also come from a living donor. This person may be a blood relative (such as a brother or sister) or non-blood relative (such as a husband or wife). They may also come from a friend or even a stranger.

When a kidney is donated by a living person, the surgeries may be done on the same day and can be scheduled at a convenient time for both the patient and

the donor. A healthy person who donates a kidney can live a normal life with the remaining healthy kidney. Since the operation is a major surgery for both the donor and the recipient, as in any operation, there are some associated risks [38].

2.2.3 Benefits of living donor kidney transplantation

Living Donor Kidney Transplantation (LDKT) has become the preferred treatment for those with ESRD. Organ replacement from either a live or a deceased donor is preferable to dialysis therapy because transplantation provides a better quality of life and improved survival rates. The advantages of live versus deceased donor transplantation now are readily apparent as it allows for earlier transplantation and renders best long-term survival [16].

Next we summarize LDKT benefits for patients and donors [47]:

Potential benefits to recipients

- Greater long-term survival of the transplanted kidney
- Shorter wait time for transplant, with reduction in pretransplant dialysis duration
- Planned surgery
- Shorter hospital stay
- Greater likelihood of preemptive transplantation
- Less likelihood of delayed graft function
- Better quality of life
- Ability to undergo preoperative desensitization in the case of blood types ABO or HLA incompatibility (see Appendix B)

- Ability to assure optimal medical status with a known transplant date

Potential benefits to living donors

- Satisfaction in providing an organ that has the potential to yield the recipient the benefits listed above
- Less time assisting with dialysis care (in cases where donors provide social support for recipients)
- Less caregiver burden (if donor is recipient's caregiver)
- Less financial burden (if recipient is supported by donor)
- Emotional benefit from seeing family/friend regain health

2.3 Statistics and facts

2.3.1 Increasing of the waiting list

According to CENATRA, patients that are currently waiting for a kidney transplant, conform more than the half of the total number of patients waiting for an organ (see Table 2.1). The kidney has been the most demanded organ over the years, and this is not a surprise, since CKD is one of the most catasthrofic diseases due to the increasing number of cases. The main reason for such increase are the high investment costs, limited infrastructure and human resources, late detection and high morbidity and mortality rates [36].

Table 2.1: Number of transplants required by July 13, 2017 [12].

Organ	Number of patients
Kidney	13,313
Cornea	7,731
Liver	360
Heart	46
Pancreas	10
Kidney-Pancreas	6
Kidney-Liver	2
Lung	1
Heart-Lung	1

The kidney waiting list has presented a considerable increase in the past 10 years (see Figure 2.2), this only means that there are not enough kidneys to meet the demand and each time more people aquire CKD.

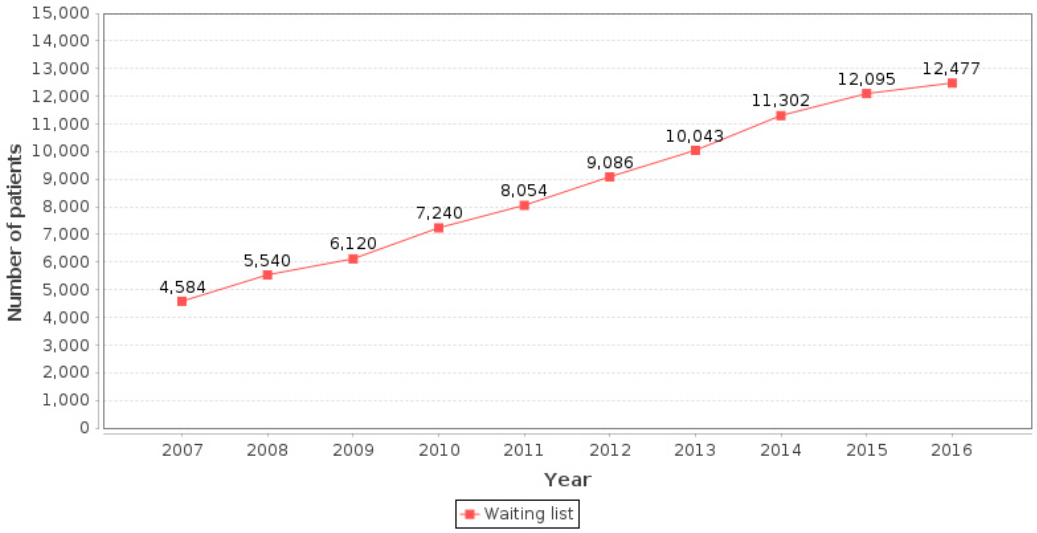


Figure 2.2: Kidney waiting list increase in the past 10 years.

In 2016, only 23.8% of the patients in the waiting list received a transplant. This was devastating as many patients died in the wait. Also, in the past year, 2,977 kidney transplants were reported, from which 2,126 came from living donors, whereas only 852 from deceased donors (see Figure 2.3). This is bad, in developed countries, 80% of transplants come from deceased donors. In Mexico, it is the other way around, from each 10 transplants, only 2 come from deceased donors [43].

2.3.2 An estimate of the expected brain deceased donors in Mexico

In the United States of America, in 2016, there was a total of 19,060 kidney transplants, from which 13,431 came from deceased donors and 5,629 from living donors [39]. This means that the number of brain death donors in Mexico is very low.

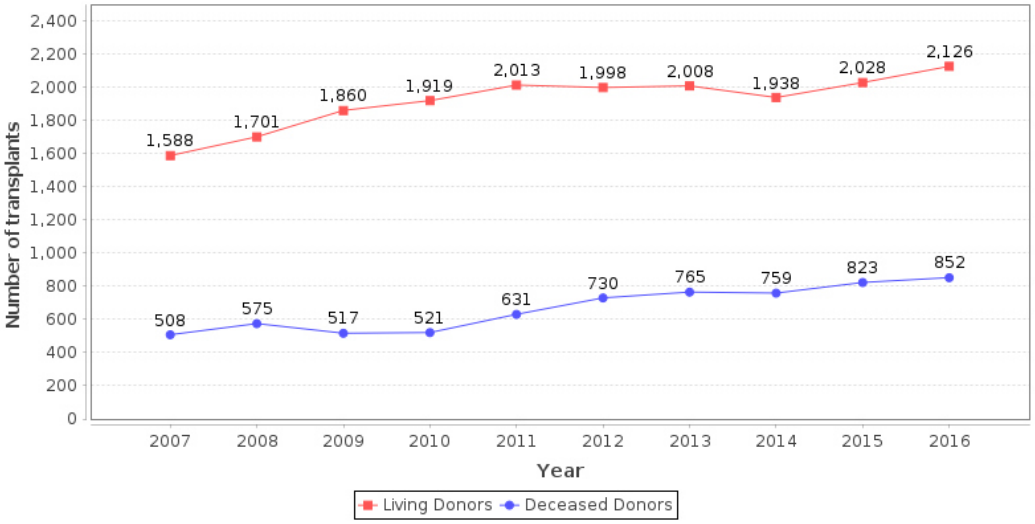


Figure 2.3: Kidney transplantations in the past 10 years.

Worldwide, there should be between 50 to 80 brain death donors per million inhabitants. From 100% of brain deaths, around 25% of them are potential donors, the rest go to the trash due to medical contraindications, family refusal, or having a heart attack during the process [29]. By now there is a population of 127 million inhabitants in Mexico, therefore we should have at least $50 \times 127 = 6,350$ brain death donors per year, from them, approximately $6,350 \times 0.25 = 1,587$ should be potential donors, where each donor can donate 2 kidneys, then there should be 3,175 kidney transplants per year, however we are still too far from that number.

In the United States, in 2016, there were 31.78 deceased donors per million inhabitants, while in Mexico, there were only 3.99 deceased donors per million inhabitants (considering the population of United States: 321.4 millions of inhabitants, and the population of Mexico: 127 millions of inhabitants, the number of deceased donors in the United States in 2016: 9,971, and in Mexico: 507 [39, 11]). The rate of brain death donors has slighty increased in Mexico, in 2000, the rate was 2.05 deceased donors per million inhabitants [19], however, we are still too far from the rates in developed countries.

2.3.3 Reasons for the low rate of deceased donations

There are several reasons for the low rate of deceased donations in Mexico, one of them is the family refusal rate to consent for organ donation of their deceased relative. Around 40 to 60% of families refuse to consent for organ donation, some factors for refusal include: religion, culture, socioeconomic status and education level. The main reasons for refusal, according to recent studies [43, 34], where 35 families who refused were interviewed, are shown in Figure 2.4.

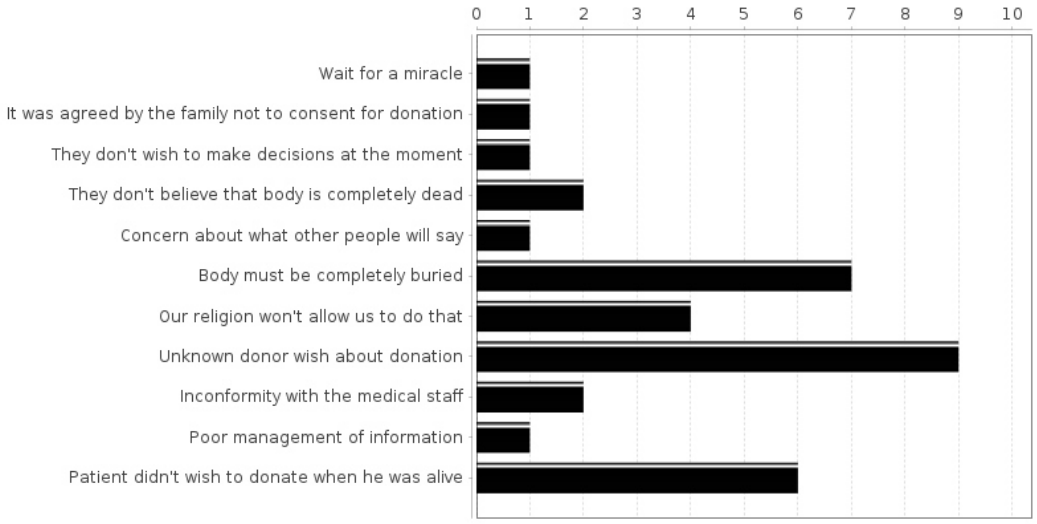


Figure 2.4: Causes of family refusals from recent study [43].

The family refusal rate is very important, but if we look carefully, when we calculate how many deceased donors there would have been last year, in the case all families consent for donation, considering a 60% refusal rate, we would obtain $507/0.6 = 845$ total donors, which is still far from the 1,587 donors previously calculated. There must be something else aditionally to the family refusal.

Another important reason for the low rate of deceased donations in Mexico is the identification of potencial donors in Brain Deceased individuals. Identification of potencial donors represents a current challenge in developing countries for two main

barriers, first, we do not have the essencial insfrastructure neither material resources, and second, many of the physicians in this area are not well trained. Without a doubt, the identification and diagnosis of brain death in a timely manner, improves the chances of obtaining organic donations [50, 45].

2.3.4 Other important facts

Next, we mention important facts regarding kidney transplantation in Mexico [10]:

- In 2015, a computer based system for the National Transplantation Registry (SIRNT) was created. The project features 15 main modules, where many functions are carried out, such as the registry of authorized centers and authorized medical staff, the registry of patients waiting for an organ or tissue, the registry of donation and transplantation activity at a National level, the tracking of each donated organ or tissue, the follow-up of transplantation results, and the Nation Registry of Volunteer Donors.
- According to the SIRNT, the number of authorized centers for procurement, transplantation and bank increased to 5.5%, from 477 in 2015 to 503 in 2016, where 176 of them procure organs and 225 transplant organs and tissues.
- It was reported that 96% of patients involved in Living Donor Kidney Transplantation, were still alive after 1 year post-transplantation, whereas only 89% was alive regarding Deceased Donor Kidney Transplantation.
- In 2016, the rate of brain death donors in Nuevo León, Mexico, was 7.9 deceased donors per million inhabitants, which doubles the national rate.
- At the end of the year 2016, 12,477 patients were registered in the waiting list for kidney transplant and only 23.8% of them proceeded to transplantation.
- The average waiting time for a patient to receive a kidney is 30 months since registration.

- Regarding Living Donors Kidney Transplants, we are doing a good job, in 2016, there was 2,126 (see Figure 2.3). This means that there is $2,126/127 = 16.74$ LDKT per million inhabitants. In the United States in 2016 there was 5,629 LDKT, this means that there was $5,629/321.4 = 17.5$ LDKT per million inhabitants. We are not too far from this number, if we had a Kidney Exchange Market, we could increase this number.

- The first paired donation transplant in Mexico was carried out in Juarez Hospital, Mexico in January 2016, where 2 incompatible pairs and 32 medical staff were involved. The kidney exchange was carried out simultaneously in four surgical rooms.

- A paired donation transplant was carried out in the National Institute of Medical Sciences and Nutrition, in Mexico in April, 2016, where 4 incompatible pairs and 60 medical staff were involved. One kidney exchange was performed one day, and the other the next day.

- The most common causes of ESRD are high blood pressure, and diabetes mellitus [28].

- In 1966, the second kidney transplant in Mexico was performed in the "Dr. José Eleuterio González" University Hospital of the Universidad Autónoma de Nuevo León [40].

- The average annual cost per patient undergoing hemodialysis in public units is $158,964.00 MX. The estimated cost for the care of all population estimated in need of renal replacement therapy (via hemodialysis) was estimated to be $10,921,788,072.00 MX [25].

- In 2014, a kidney exchange market was proposed by Professor Alvin Roth, Nobel Prize laureate, during the master lecture entitled: "Market design for the kidney exchange" carried out in Hospital ABC. He stated that Mexico has more living donor kidney transplants than the United States, and that they might exchange kidneys in the future [37].

Chapter 3

The Kidney Exchange Problem

3.1 Problem statement

As previously mentioned, kidney transplant is the best treatment option for patients with kidney failure. These patients may have a donor willing to donate, however kidneys may not be compatible due to blood type incompatibility or positive cross-match. We call a pair of patient and his/her incompatible donor an Incompatible Patient-Donor Pair (PDP). A pool of these PDPs is called a Kidney Exchange Pool [35].

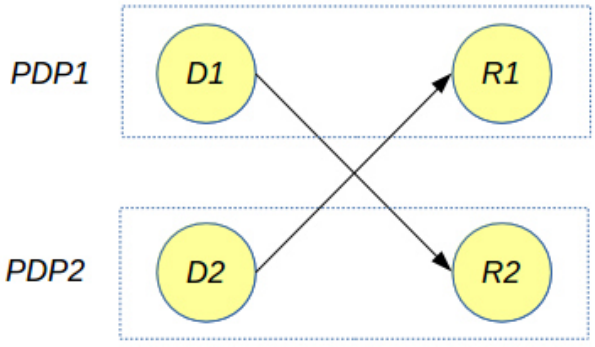


Figure 3.1: 2-cycle kidney exchange.

The idea of kidney exchange provided new hope for kidney failure patients. Suppose we have two pairs of incompatible patient-donors: PDP-1 and PDP-2 (shown in Figure 3.1, where Dx and Rx denote the donor and the recipient of PDP-x, respectively). If the kidney of Donor 1 is compatible with Patient 2, and that of Donor 2 is compatible with Patient 1, then the two PDPs can exchange kidneys. We call this a 2-way exchange (or, mathematically, a 2-cycle, see Figure 3.1) [35].

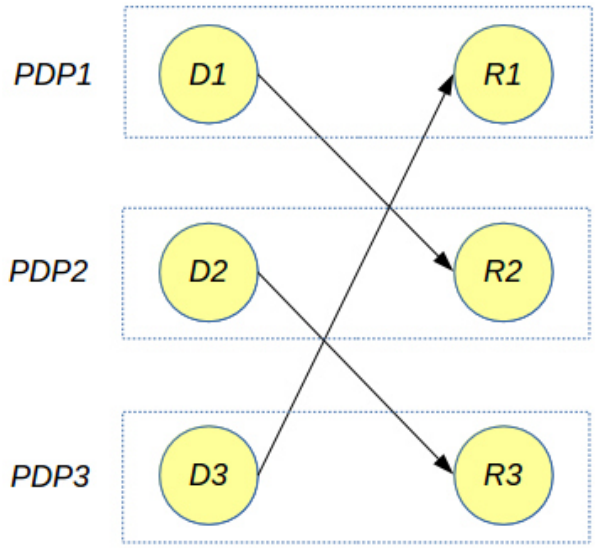


Figure 3.2: 3-cycle kidney exchange.

Cycles may have cardinality 2, 3 (see Figure 3.2), or more. With the introduction of altruistic donors (donors who do not have patients associated with them), chains may be formed (see Figure 3.3). Mathematically, the Kidney Exchange Problem (KEP) is a combinatorial optimization problem that can be defined on a directed graph, and typically concerns solutions with either just cycles, or cycles and chains.

The way the KEP works is as follows. Let us suppose we have a pool of PDPs, we seek to optimize this pool as to find the maximum number of kidney exchanges. There are different approches for the KEP. For example, in some approaches, the objective is to maximize the arc weights defined by a solution, while in others, failure probabilities are considered [23].

As we previously mentioned, cycles may have any size; however, some considerations and restrictions need to be taken. A donor, as soon as the partner patient has received a kidney, can technically exit the program without donating one, as he/she is not legally bound to do so. To avoid this from happening, usually exchanges are carried out simultaneously. As each transplant involves two surgeries, there is a limit as to how many exchanges can be performed at once, due to human resource and logistic reasons. We use k to represent the maximum number of transplants that can be carried out concurrently (i.e., a k-way exchange).

The standard model for kidney exchange encodes a kidney exchange pool as a directed compatibility graph $G = (V, E)$ by associating one vertex $v \in V$ to each PDP. A directed arc $e = (v_i, v_j) \in E$ from v_i to v_j is added if the donor of PDP v_j is compatible (and may donate) with the patient of PDP v_j. A donor is willing to give her kidney if and only if the corresponding patient in the same vertex v_i receives a kidney. The weight w_e of an edge e represents the utility to v_j of obtaining v_i's donor kidney. The criteria used to assign weights to edges is determined by a committee of medical professionals, and takes into account such factors as donor and patient location, health, CPRA score, etc. [23]. A cycle c in the graph G represents a possible kidney swap, with each vertex in the cycle obtaining the kidney from the previous vertex. If cycle c includes k PDPs, we refer to it as a k-cycle [23].

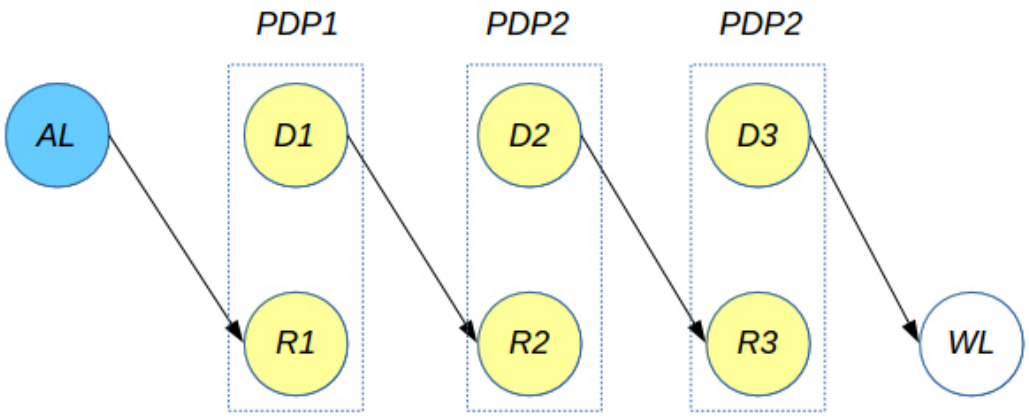


Figure 3.3: An example of a chain.

With altruistic donors, the KEP digraph becomes more complex. A sequence of kidney exchanges that begins from an altruistic donor and terminates at the "wait-list" (which usually refers to the deceased donor waiting list) forms a chain [35] (see Figure 3.3 where WL denotes the waiting list). Chains can be (and typically are) longer than cycles in practice because it is not necessary to carry out all the transplants in a chain simultaneously [23].

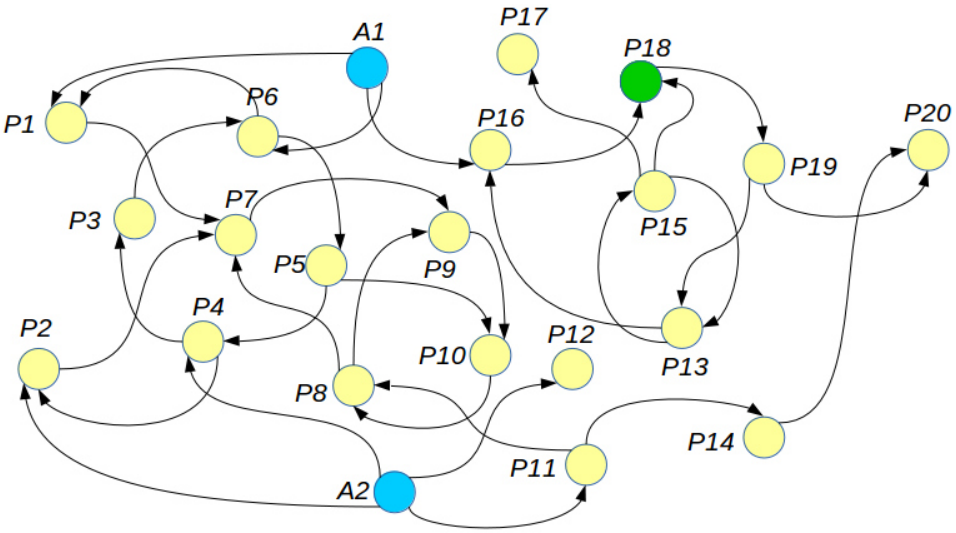


Figure 3.4: An example of a kidney exchange pool.

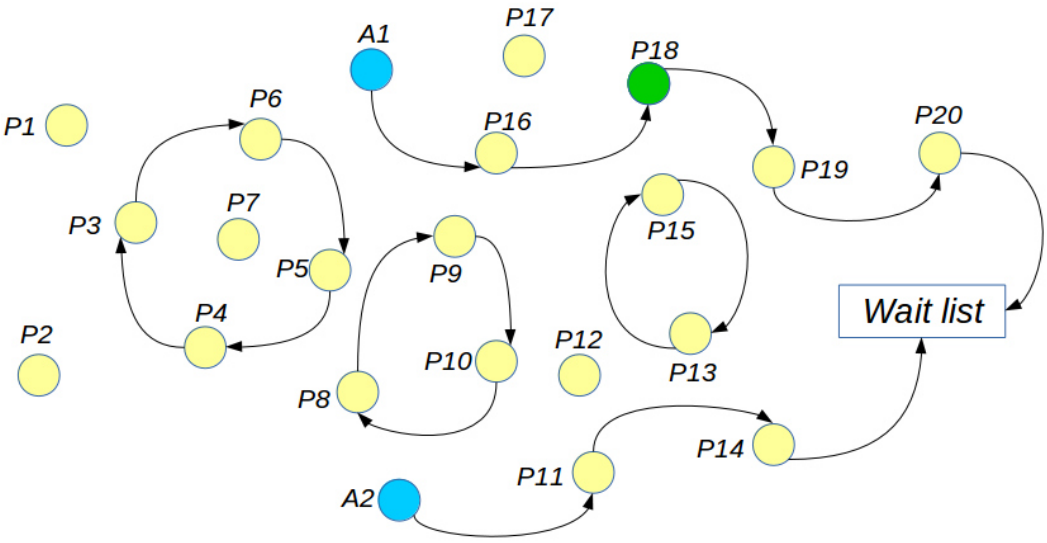


Figure 3.5: An example of a solution associated to the pool from Figure 3.4

In Figure 3.5 we can see the solution obtained after optimizing the problem in Figure 3.4 (solving the KEP) taking a pool of incompatible pairs (denoted by the yellow and green circles) and altruistic donors (denoted by the blue circles). We can see in Figure 3.5 that a 2-way cycle ($P13 - P15$), a 3-way cycle ($P8 - P9 - P10$), and a 4-way cycle ($P3 - P4 - P5 - P6$) were found. Also 2 chains were found, where altruistic donor $A1$ triggers a chain ($A1 - P16 - P18 - P19 - P20 - WL$) ending in the waiting list. This chain was not simultaneous, as donor in $P18$ (often called bridge donor) has to wait to donate, after his associated recipient receives a kidney. Also altruistic donor $A2$, triggers another chain ($A2 - P11 - P14 - WL$). We can also see that PDP's $P1, P2, P7, P12$ and $P17$, did not find a match.

3.2 Clearing algorithms

The KEP concerning cycle and chains, and cycles only, are interesting combinatorial optimization problems in their own rights. In the literature we can find different operations research approaches to KEP variations.

Among integer programming formulations concerning cycles only we can mention the well known Cycle Formulation and the Edge Formulation. They were proposed independently by Abraham, Blum and Sandholm [2] and Roth, Sönmez and Ünver [44], respectively. The Cycle Formulation considers one variable for each cycle and uses an exponential number of variables (one per each cycle). The Edge Formulation considers a variable for each edge and uses an exponential number of constraints. Both formulations allow cycles to have length at most 3.

Among integer programming formulations concerning cycles and chains, we can mention two models proposed by Anderson et al. [4]. The first model is an arc-based formulation, in which a binary variable represents chains as well as cycles. The second model is inspired by the Prize Collecting Traveling Salesman Problem (PC-TSP) [8, 33]. The substantial difference with the TSP is that now, we are

allowed to form a cycle excluding some cities by paying a penalty [42]. In these formulations, the length of chains is unbounded while only cycles of length at most 3 are allowed.

There are of course operations research techniques other than integer programming (e.g., game theory or heuristic methods) that have been studied in the literature for various aspects/forms of the KEP [35]. Among these we can cite the works of Biró et al. [9], Zenios et al. [48], Chen et al. [13], Dickerson et al. [22], Ashlagi et al. [5], and Gentry et al. [30]. Most recently, there have been studies considering situations where failure probabilities are taken into account and fairness issues are considered for patients hard to match [23, 24]. Next, we present the Cycle Formulation by Dickerson et al. [21] , which is the one we use for solving the KEP in this thesis.

3.2.1 Cycle formulation

An alternative IP model for the edge formulation is the so called Cycle Formulation [14]. Let $C(k)$ be the set of all cycles in G with length at most k. We assume that a cycle is an ordered set of arcs. Define a variable z_c for each cycle $c \in C(k)$:

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

Denote by $V(c) \subseteq V$ the set of vertices which belong to cycle c. The model can be written as follows (where $w_c = \sum_{(i,j)\in c} w_{ij}$):

$$\text{Maximize} \sum_{c \in C(k)} w_c z_c \tag{3.1}$$

$$\text{subject to} \sum_{c: i \in V(c)} z_c \leqslant 1 \quad \forall i \in V \tag{3.2}$$

$$z_c \in \{0, 1\} \quad \forall c \in C(k). \tag{3.3}$$

In the case of unitary weights, w_c equals the number of edges in c, i.e., the number of transplants associated with cycle c. The objective function (3.1) maximizes the weighted number of transplants. Constraints (3.2) ensure that every vertex is in at most one of the selected cycles (i.e., each donor may donate, and each patient may receive only one kidney). Compared to the Edge Formulation [14], the difficulty with this formulation is induced by the exponential number of variables. Indeed, the number of cycles can grow exponentially with k.

The KEP under these conditions is not easy to solve, it takes a lot of computational effort and sophisticated algorithms to solve. When we consider cycles of cardinality $k > 2$, the problem is NP complete. Only for the cases when $k = 2$ and not chains are allowed, or $k = \infty$ the problem can be solved in polynomial time. However significantly better (i.e., higher cardinality) results are found with $k = 3$ over $k = 2$, so solving the NP-complete version of the problem is necessary in practice [20].

Chapter 4

Description of the Simulation Framework

4.1 Introduction

Having stated all statistics to date regarding kidney transplantation in Mexico, we can see that the number of living donor transplants is much higher than the number of deceased donor transplants. We can also see that the waiting list has been increasing over the years and although the number of transplants has also been increasing, it is still not enough to satisfactorily deal with the waiting list.

A kidney exchange market would help alleviate the waiting list as those who aquire CKD or ESRD, and have a willing but incompatible donor, could join this kidney exchange market instead of the waiting list. Also those who already are in he waiting list and have an incompatible donor, may join the kidney exchange market.

But, how can we be certain that a kidney exchange market would be a suitable alternative? how many incompatible pairs would emerge during a year? how many incompatible pairs would be served by kydney exchange?

The first question is not hard to answer. The kidney exchange market is not

new, many countries including the United States, United Kingdom, Spain, etc. have a kidney exchange market implemented and has been working during several years. Also in Mexico last year, 2- and 4-way kidney exchanges were successfully performed without a kidney exchange market [10].

The second and third questions are harder to answer, as there is not any data regarding incompatible pairs. In this chapter we try to answer these questions and prove that a kidney exchange market would benefit a large amount of patients.

4.2 Methods

To simulate the number of incompatible pairs that would emerge during a year, we need to go deep inside and think as in real life. In real life, individuals diagnosticated with CKD or ESDR, are recommended to have a kidney transplant. If that is the case, and they have someone willing to donate, they go to the hospital, both patient and donor, where they are subject to a blood test. If the result turns out to be compatible, the first filter is passed; however, they are not ready yet to proceed to transplant.

The donor needs to be examined to verify that he is healthy enough to donate, also he needs to take a psychological test to check weather he is not being forced to donate and warn him about possible risks during transplantation and post-transplantation. After these barriers, there is an additional one, the crossmatch test (see Appendix B). If a donor passes all these barriers, then donor and recipient may proceed to a direct donation transplant. If donor fails in any step, patient have 2 options, he goes to the waiting list to wait for a deceased donor, or he can bring another donor willing to donate and have him through all procedure of transplantation.

Basically, that is what we do in this simulation. We simulate families, begining with the intended patient and his two parents [31]. Possible candidates to donate included in this simulation are parents, siblings of recipient, spouse, children and

others (friends, unrelated family, etc.). We assign an age to the patient in order to select potential donors from the donor pool. We consider 3 age groups: Youngs (17 or less), Adults (18-49) and Olds (50 or more). Each age group is assigned a donor-patient relationship distribution, for example, a young patient has more probability of having a parent as a donor, than an old patient, also, an old patient has more probability of having a child as donor, than a young patient.

Now that we have assigned an age to the patient, we randomly select 2 donors from the donor candidate pool (in the simulation, we always consider 2 donors for each patient) according to the donor-patient relationship distribution previously described.

Then we assign a blood type to the patient and to each donor candidate. First, parents, spouse and others, are randomly assigned blood type according to Mexican population blood type distribution. Then, patient and siblings inherit bloodtype according to parents blood types and some inheritance rules. Now having the blood types of the patient and spouse, children inherit a blood type from them.

All information gathered is based on OPTN [39], Lorenzo [18], Gentry [31], Fehrman [27], and Zenios [49].

4.2.1 Decision tree

So now that we have selected 2 donors from the candidate pool and we have assigned blood types to the patient and donors, we proceed to the decision tree model of Zenios [49] (see Figure 4.1).

We have the first step of the decision tree now completed, which is to specify the number of willing donors and their relationship to the recipient. The second step is to select blood type compatible donors (blood types had been previously assigned to donors and patient), what we do here is to take a blood test for each donor and

the patient, and check compatibility. So now that we know if donor 1 and donor 2 are compatible or not, we proceed to step 3. Here in the medical work-up we determine weather the donor is healthy enough and willing to donate.

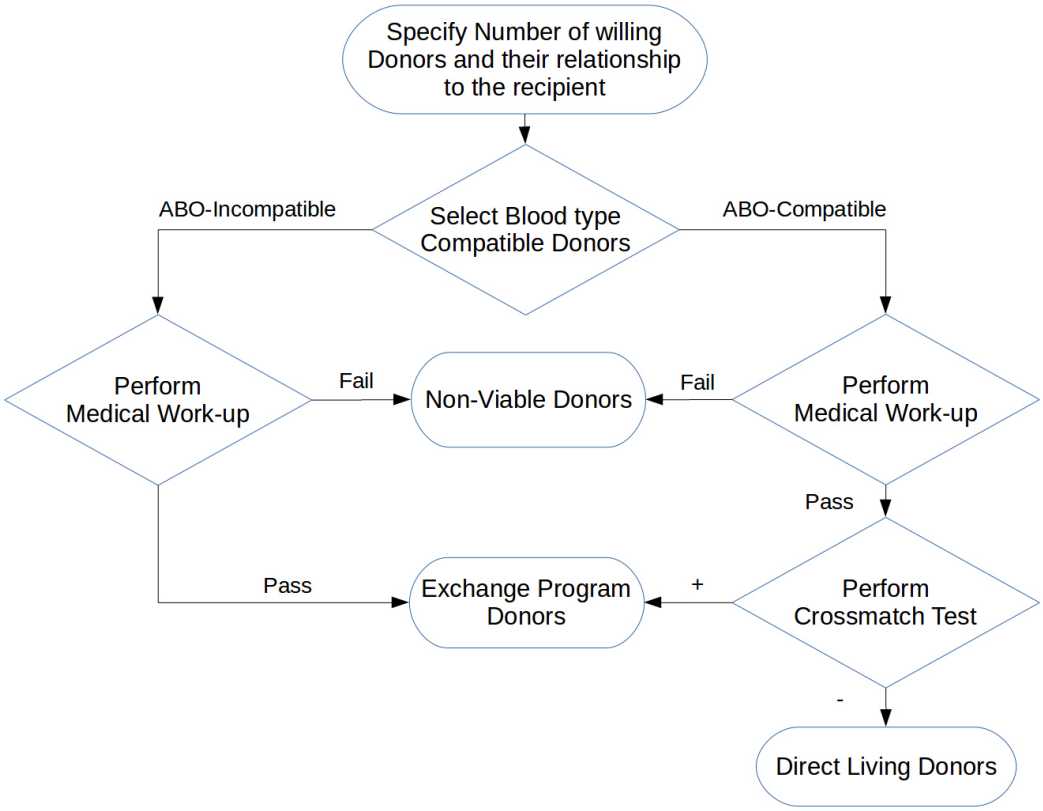


Figure 4.1: Decision tree model.

For ABO compatible donors who pass the medical work-up, there is still one more barrier, that is the crossmatch test. Following we list the possible outcomes for the decision tree:

- Donor fails the medical work-up and becomes non-viable donor.
- ABO incompatible donor passes medical work-up and joins exchange program.
- ABO compatible donor passes medical work-up but fails crossmatch test and joins exchange program.

- ABO compatible donor passes medical work-up and crossmatch test and goes through direct donation.

Next, we describe each step in detail, and provide distributions and probabilities used in this simulation.

4.2.2 Age assignment and donor selection

Table 4.1: U.S. Transplants performed: January 1, 1988 - May 31, 2017, based on OPTN data as of june 19, 2017.

Patient age / Donor relation	Youngs <17	Adults 18-49	Olds 50+	Total
Parent	7,064	11,317	102	18,483
%	(75.16%)	(15.68%)	(0.2%)	(14%)
Child	0	3,251	18,936	22,187
%	(0%)	(4.5%)	(37.57%)	(16.81%)
Sibling	668	31,970	9,704	42,342
%	(7.11%)	(44.29%)	(19.25%)	(32.08%)
Spouse	0	7,784	7,426	15,210
%	(0%)	(10.78%)	(14.73%)	(11.52%)
Other	1,666	17,854	14,239	33,759
%	(17.73%)	(24.74%)	(28.25%)	(25.58%)
Total	9,398	7,276	50,407	131,981
%	(100%)	(100%)	(100%)	(100%)
Age distribution	7.12%	54.69%	38.19%	100%

As previously described, we assign an age to patients based on age distribution. This data has been obtained from OPTN [39] and corresponds to a data set reported from January 1, 1988 to May 31, 2017 which includes a total of 141,492

pairs who have been through living donor transplantation. In this report, there are 16 categories for the donor relation, and 8 categories for patient age. I summarized everything into a table of 6 categories for the donor relation and 3 categories for the age of the patient (see Table 4.1).

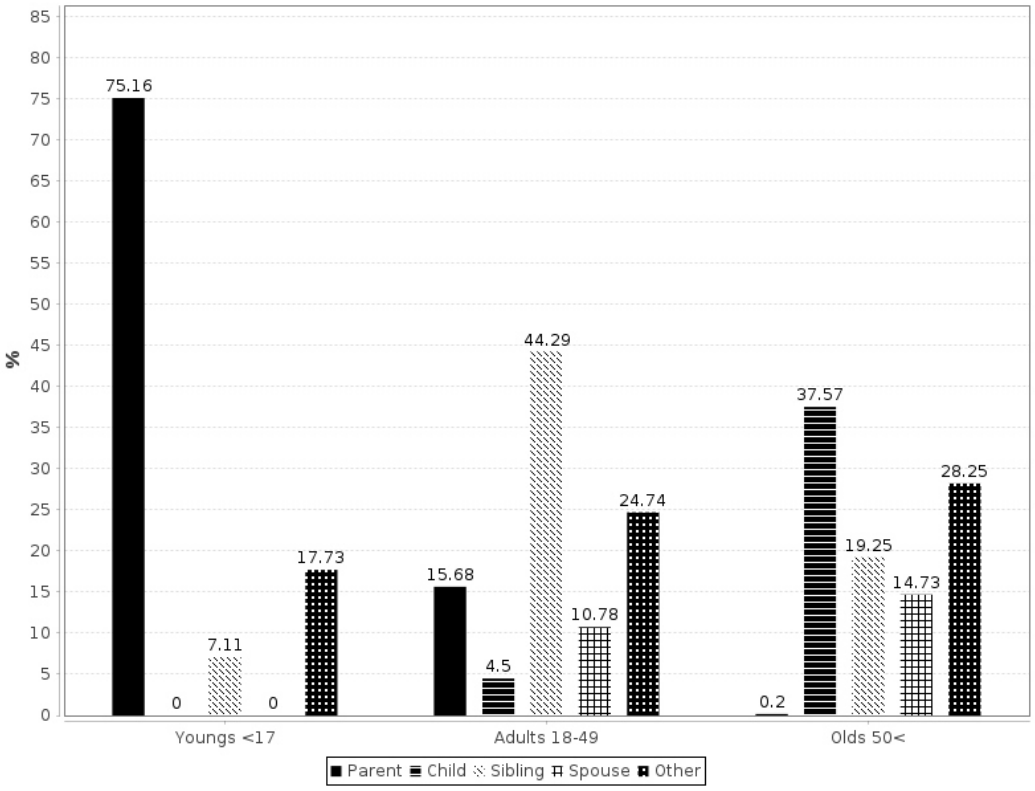


Figure 4.2: Donor-patient relationship distribution.

In the OPTN report, I ignored the "Not reported" and the "Unknown" categories for the donor relation. I combined the "Biological, related identical twin", "Biological, blood related Full Sibling" and "Biological, blood related Half Sibling" into the Sibling category. Also combined the "Biological, blood related Other Relative", "Non-Biological, Life Partner" and "Non-Biological, Other Unrelated Directed" into the Other category. I also summarized the 8 age categories into 3 categories which I called: Youngs, Adults and Olds. In Figure 4.2 we have a better visualization of donor-patient relationship distribution upon patient age group.

Once an age group has been assigned to the patient, and having these distributions according to each age group, we can now randomly select 2 donors from the donor candidate pool and proceed with the blood type assignment.

4.2.3 Blood type assignment

After having assigned an age to the patient and selected the two donors, the next step is to assign them a blood type.

It was challenging to find data regarding Mexican population blood type distribution, since there are not any online databases available. However, a calculated average of blood type distribution for Mexican population is obtained from particular studies on 19 states in Mexico [18] see Table 4.2.

Table 4.2: Blood type distribution of Mexican population.

ABO group	%
A	25.0
B	8.6
AB	1.4
O	65.0

However, as in this simulation we consider inheritance probabilities to determine children blood types, having the blood type distribution would not suffice to determine children blood types. We need to know parents genotypes in order to know such inheritance probabilities. A child randomly inherits one allele from each parent, meaning that child genotype will be a combination of these two alleles (see Appendix A).

4.2.3.1 Genotypes

In order to obtain genotype frequencies, we first need to obtain allele frequencies. We can determine that using the Hardy-Weinberg principle (see Appendix C), obtaining the following results (see Table 4.3 and 4.4):

Table 4.3: Allele frequencies of Mexican population.

Allele	Frequency
A	0.14
B	0.05
O	0.81

Table 4.4: Genotype frequencies of Mexican population.

Genotype	%
AA	2.03
AO	22.97
BB	0.26
BO	8.27
AB	1.46
OO	65

4.2.3.2 Assignment

We first assign a random genotype to the parents, spouse, and others according to the genotype distribution in Table 4.4. Having now the genotypes of the parents, patient, and siblings randomly inherit an allele from each parent. Then having now assigned genotypes to the patient and spouse, children inherit genotype from them. In Figure 4.3 there is an example of genotype drawing of the whole pool of donor candidates. Nodes highlighted in yellow represent candidates whose genotype is

randomly assigned, whereas non-highlighted nodes represent candidates who inherit their genotypes from their respective parents.

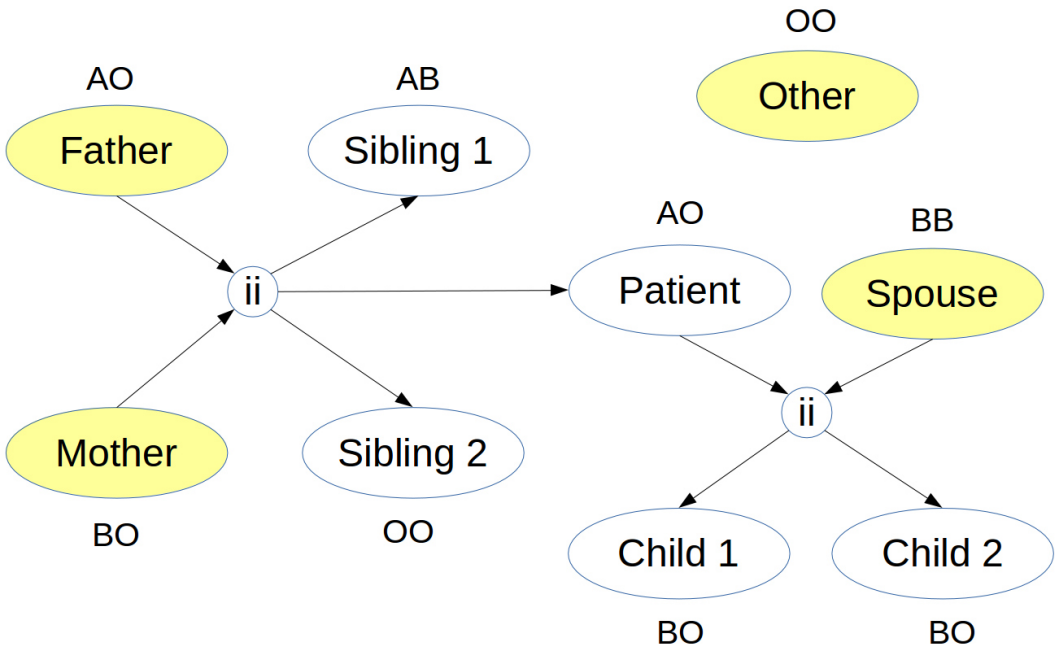


Figure 4.3: Genotype assignment example.

4.2.4 Blood test

Now that we have selected the 2 donors and having assigned blood types to patient and donors, we can certainly know weather donors are ABO compatible or incompatible to the patient according to the ABO compatibility Table 4.5.

Table 4.5: Blood type compatibility table.

Blood type	Can receive from	Can give to
O	O	ALL
A	A, O	A, AB
B	B, O	B, AB
AB	ALL	AB

4.2.5 Medical work-up

Regardless blood test results, both patients have a medical work-up. This is to determine medical ineligibility or donor unwillingness to donate. We discard 25% of spousal donors and 56.7% of other donors [31, 49], according to a published paper [27] where reasons for not accepting living kidney donors were studied.

If donor is ABO incompatible and passes the medical work-up, he joins the exchange program pool. If donor is ABO compatible and passes the medical work-up, she/he still has to take the crossmatch test. However if any donor fail the medical work-up, they become a non-viable donor, then they disappear from the simulation.

4.2.6 Crossmatch test

Table 4.6: PRA distribution and simulated crossmatch likelihood based on PRA group

PRA group	Distribution (%)	Rate of positive XM (%)	Rate of positive XM for wife/mother (%)
0-9	72.4	5	25
10-79	17.1	45	65
80+	10.5	90	95

Those ABO compatible donors who pass the medical work-up, still need to take the crossmatch test. We first assign the patient with a gender. This is important because if patient is female, patient has more probability of failing the crossmatch test. Gender is assinged randomly according to gender distribution where 40% patients are female [39] according to OPTN data from kidney transplants performed from 1988 to 2017.

After assigning gender to the recipient, we assign them with a PRA group. For

each PRA group, there is a different positive crossmatch rate, which differs when a patient is a wife or a mother. This is mainly because wives become sensitized to their husbands and mothers to their children. All this data is reflected in Table 4.6 (XM denotes crossmatch) [31].

If the crossmatch result turns out to be positive, donor becomes incompatible and joins the exchange program pool. If result is negative, this means that the donor has passed all steps and a direct transplant can be performed.

4.3 Considerations

Next, we mention some considerations about the simulation:

- Except for the spouse, other candidates (sibling, child, parent, other) may be selected twice, this is, for example, a patient may have 2 siblings as donors.
- Patient is considered to be a mother when patient is randomly assigned a female gender and has a child as a donor.
- Patient is considered to be a wife when patient is randomly assigned a female gender and has a spouse as a donor.
- When neither of the two selected donors pass the medical work-up, patient is considered to have no donors, thus patient joins the waiting list.
- When both selected donors pass the medical work-up, and both pass the crossmatch test, only one donor is randomly selected to undergo through direct transplant.
- When both selected donors pass the medical work-up, but both donors are incompatible with the patient (i.e. fail the blood test or crossmatch), only one of them is randomly selected to join the exchange program.

- When both selected donors pass the medical work-up, and one of them is compatible with the donor (pass the blood test and crossmatch test) and the other is incompatible, incompatible donor dissapears from simulation and compatible donor undergoes through direct transplant.

Chapter 5

Experimental Work

5.1 Estimation of incompatible pairs

In the previous chapter, we have reviewed the methodology for the generation of patients and donors, the assignment of blood types, and the possible outcomes of the simulator after several tests, which include exchange program, direct transplant and non-viable donor. In order to estimate the number of incompatible pairs in a year, we simulate patients and donors, until 2,126 direct transplants are realized, which is the number of living donor kidney transplants performed last year. Once that number is reached, we can estimate the number of expected incompatible pairs in a year, that is, the number of pairs that would eventually joined the hypothetical kidney exchange program [31].

Table 5.1: Predicted number of incompatible pairs in Mexico in a year.

Total number of patients generated	3,121	100.0%
Pairs who undergo through direct transplant	2,126	68.1%
Pairs who join the exchange program	995	31.9%
Pairs who join exchange program due ABO	500	50.2%
Pairs who join exchange program due crossmatch	495	49.8%

Since this number may change with each execution, we take averages from a sample of 30 replicates. Average results are displayed in Table 5.1.

The simulation estimated an average of 995 incompatible pairs in Mexico in a year, which is 31.9% of the total number of generated pairs. We can also tell by the results that from incompatible pairs, a mean of 50.2% joined the exchange program due to blood test failure, and the rest due to crossmatch test failure.

Table 5.2: Genotype distribution on USA population.

Genotype	%
AA	6.40
AO	34.80
BB	0.46
BO	9.20
AB	3.43
OO	46.14

For the purpose of comparison, we run the same experiment (simulate patients and donors, until 2,126 direct transplants are realized) using USA blood type distribution (shown in Table 5.2) obtained from Zenios [49] obtaining the following results in Table 5.3 (from now on, we will use this blood type distribution when running experiments regarding USA population).

Table 5.3: Estimated number of incompatible pairs in USA in a year.

Total number of patients generated	3,336	100.0%
Pairs who undergo through direct transplant	2,126	63.7%
Pairs who join the exchange program	1,210	36.3%
Pairs who join exchange program due ABO	709	58.6%
Pairs who join exchange program due crossmatch	501	41.4%

As we can see in Table 5.2, genotype OO percentage in USA blood type distribution is much lower than it is in the Mexican blood type distribution, meaning that in the USA, there is a lower percentage of donors having genotype OO. According to blood type compatibility (Table 4.5), donors with blood type O can donate to anyone, then a Mexican pair has more chance of passing the blood test than an American pair.

These results are consistent with our previous experiment where it was found an average of 1,210 and 995 incompatible pairs in USA and Mexico, respectively. As we can see from Table 5.3, 58.6% of incompatible pairs are due to blood test failure.

5.2 Pool characteristics

Once we have predicted the number of incompatible pairs that would arise in a year in Mexico, we proceed to create a pool of the predicted 995 incompatible pairs.

5.2.1 Age distribution

Analyzing the age distribution in both pools in Table 5.4, we can see that there is not much difference. In both cases, most patients in the pools fall into Adult and Old category. Also only around 7% of them fall into the Young category.

Table 5.4: Patient age distribution in Mexican and USA pool respectively.

Young count	66	6.6%	70	7.0%
Adult count	499	50.2%	516	51.9%
Old count	430	43.2%	409	41.1%
Total	995	100.0%	995	100.0%

5.2.2 Blood type distribution

In Tables 5.5, 5.6 and further tables, dX denotes donor blood type and rX denotes recipient blood type.

Table 5.5: Blood type distribution of donor/recipient pairs in Mexican pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	297	320	108	12	737	29.8%	32.2%	10.9%	1.2%	74.1%
rA	66	63	32	10	171	6.6%	6.3%	3.2%	1.0%	17.2%
rB	28	26	17	8	79	2.8%	2.6%	1.7%	0.8%	7.9%
rAB	2	4	1	1	8	0.2%	0.4%	0.1%	0.1%	0.8%
Total	393	413	158	31	995	39.5%	41.5%	15.9%	3.1%	100.0%

Table 5.6: Blood type distribution of donor/recipient pairs in USA pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	154	337	94	18	603	15.5%	33.9%	9.4%	1.8%	60.6%
rA	70	121	56	30	277	7.0%	12.2%	5.6%	3.0%	27.8%
rB	4	51	18	26	99	0.4%	5.1%	1.8%	2.6%	9.9%
rAB	3	7	3	3	16	0.3%	0.7%	0.3%	0.3%	1.6%
Total	231	516	171	77	995	23.2%	51.9%	17.2%	7.7%	100.0%

Analyzing the blood type distribution in both pools we can find some interesting information.

- Most recipients in both pools are blood type O, in Mexico 74.1% (see Table 5.5) while in USA 60.6% (see Table 5.6. This is because recipients with blood type O can only receive blood from a donor with blood type O (see blood type compatibility Table 4.5), so most of them have an incompatible pair.

- In the Mexican pool there is a greater percentage of recipients with blood type O than the USA pool, that's because as previously said, there is a greater percentage of OO genotype in Mexican genotype distribution than in the USA.
- In both pools, there are a very few recipients and donors with blood type AB. Also the amount of recipients and donors with blood type A, is greater in the USA pool than in Mexico.

5.3 Optimizing predicted incompatible pairs

Now that we have generated the pool of the predicted incompatible pairs, we proceed to optimize it to find the maximum number of matches. For this, we used the clearing algorithm for the Cycle Formulation (described in Chapter 3) allowing only length-2 cycles and no chains (as altruist donors are not considered). The solution algorithm for this model was made available by John Dickerson [20]. Running one instance, the algorithm found an objective of 624, this means that 624 pairs found a compatible pair (in real life, not all recommended matches proceed to transplant [23]). Also, when optimizing a pool of 995 incompatible pairs using USA blood type distribution, the algorithm found an objective of 562. As we can see, using Mexican blood type distribution leads to more matches due greater amount of donors with blood type O. We verify that in the next results where we will study the characteristics of the previous generated pools for USA and Mexico.

5.3.1 Matched pairs

Regarding matched pairs in the Mexican pool, it is not surprising that almost half (47%) of matched pairs, are pairs where both recipient and donor are blood type O (see Table 5.7). In the USA, matched pairs are more balanced between pairs where patient and donor have either blood type A or blood type O (see Table 5.8).

Table 5.7: Matched pairs in Mexican pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	296	67	28	0	391	47.4%	10.7%	4.5%	0.0%	62.7%
rA	66	62	30	1	159	10.6%	9.9%	4.8%	0.2%	25.5%
rB	28	26	12	1	67	4.5%	4.2%	1.9%	0.2%	10.7%
rAB	2	4	1	0	7	0.3%	0.6%	0.2%	0.0%	1.1%
Total	392	159	71	2	624	62.8%	25.5%	11.4%	0.3%	100.0%

Table 5.8: Matched pairs in USA pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	154	71	5	1	231	27.4%	12.6%	0.9%	0.2%	41.1%
rA	70	120	53	4	247	12.5%	21.4%	9.4%	0.7%	44.0%
rB	4	51	13	1	69	0.7%	9.1%	2.3%	0.2%	12.3%
rAB	3	7	3	2	15	0.5%	1.2%	0.5%	0.4%	2.7%
Total	231	249	74	8	562	41.1%	44.3%	13.2%	1.4%	100.0%

5.3.2 Unmatched pairs

In the Mexican pool, most of the unmatched pairs have a recipient with blood type O (93.3%, see Table 5.9). This is obvious since they can only receive blood from a donor with blood type O. In the other hand, there is only 1 unmatched pair, where the donor is blood type O (as previously mentioned, donors with blood type O can donate to anyone).

Table 5.9: Unmatched pairs in Mexican pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	1	253	80	12	346	0.3%	68.2%	21.6%	3.2%	93.3%
rA	0	1	2	9	12	0.0%	0.3%	0.5%	2.4%	3.2%
rB	0	0	5	7	12	0.0%	0.0%	1.3%	1.9%	3.2%
rAB	0	0	0	1	1	0.0%	0.0%	0.0%	0.3%	0.3%
Total	1	254	87	29	371	0.3%	68.5%	23.5%	7.8%	100.0%

Table 5.10: Unmatched pairs in USA pool.

Pairs	dO	dA	dB	dAB	Total	dO	dA	dB	dAB	Total
rO	0	266	89	17	372	0.0%	61.4%	20.6%	3.9%	85.9%
rA	0	1	3	26	30	0.0%	0.2%	0.7%	6.0%	6.9%
rB	0	0	5	25	30	0.0%	0.0%	1.2%	5.8%	6.9%
rAB	0	0	0	1	1	0.0%	0.0%	0.0%	0.2%	0.2%
Total	0	267	97	69	433	0.0%	61.7%	22.4%	15.9%	100.0%

In the USA pool there is not any unmatched pair where donor is blood type O. Also, as well as the Mexican pool, most of the unmatched pairs have a recipient with blood type O (85.9%, see Table 5.10).

5.3.3 Matching rates

The matching rates are calculated by dividing the total number of matched pairs by the total number of pairs. This is to have an idea of the likelihood of finding a match for each combination of blood type of patients and donors.

Table 5.11: Matching rate in Mexican pool.

Pairs	dO	dA	dB	dAB	Total
rO	99.7%	20.9%	25.9%	0.0%	53.1%
rA	100.0%	98.4%	93.8%	10.0%	93.0%
rB	100.0%	100.0%	70.6%	12.5%	84.8%
rAB	100.0%	100.0%	100.0%	0.0%	87.5%
Total	99.7%	38.5%	44.9%	6.5%	

Table 5.12: Matching rate in USA pool.

Pairs	dO	dA	dB	dAB	Total
rO	100.0%	21.1%	5.3%	5.6%	38.3%
rA	100.0%	99.2%	94.6%	13.3%	89.2%
rB	100.0%	100.0%	72.2%	3.8%	69.7%
rAB	100.0%	100.0%	100.0%	66.7%	93.8%
Total	100.0%	48.3%	43.3%	10.4%	

We can see in Tables 5.11 and 5.12 that when donor is blood type O, the pair has almost 100% probability of finding a match. The same situation happens when recipient is blood type AB. In the other hand, the lowest probability of finding a match is when donor is blood type AB.

5.4 Incompatible pairs in the waiting list

Certainly, many patients are in the waiting list because they do not have any willing donor. Also, there are patients waiting for a kidney who might have a willing but incompatible donor, that would be candidates for joining a kidney exchange program. However, the amount of these is not known.

We can estimate how many patients have an incompatible donor in the waiting list using the simulator. In order to do this, we simulate patients until the sum of pairs who join the exchange program and the patients without donor, equals the number of patients in the waiting list (13,313 as of July, 2017 [12]).

As previously done, averages were taken over a sample of 30 replicates. Results are displayed in Table 5.13.

Table 5.13: Estimated number of incompatible pairs in Mexico in the waiting list.

Total number of patients in the waiting list	13,313	100.0%
Patients without donor	7,351.5	55.2%
Pairs who join the exchange program	5,961.5	44.8%
Pairs who join exchange program due ABO	2,996	50.3%
Pairs who join exchange program due crossmatch	2,965.5	49.7%

As we can see in previous results, there is a large value of estimated amount of patients in the waiting list with an incompatible donor (44.8%). However, since there is not any kidney exchange market implemented, they do not have another alternative but wait for a kidney in the waiting list.

5.5 Impact of a kidney exchange market

We have estimated the number of incompatible pairs that would arise in Mexico during a year, and the number of patients with an incompatible donor in the waiting list. However, in real life, not all patients with an incompatible donor will join the kidney exchange program [46]. Neither all recommended matches will proceed to transplant [23]. In order to estimate the potential future impact of a hypothetical kidney exchange market in Mexico, we carry out a simulation under the assumptions shown in Table 5.14.

Table 5.14: Assumptions for the estimation of the impact of a kidney exchange program.

Year	Amount of pairs who join the kidney exchange program
2018	10% of patients with incompatible donor in the waiting list
	50% of new patients with incompatible donor
2019	20% of patients with incompatible donor in the waiting list
	60% of new patients with incompatible donor
2020	40% of patients with incompatible donor in the waiting list
	70% of new patients with incompatible donor
2021	60% of patients with incompatible donor in the waiting list
	80% of new patients with incompatible donor
2022+	80% of patients with incompatible donor in the waiting list
	80% of new patients with incompatible donor

These assumptions are under the consideration that a kidney exchange program would be implemented in Mexico starting in the year 2018. They are made thinking that a fewer amount of incompatible pairs regarding the waiting list (compared to new incoming incompatible pairs) would join the kidney exchange program at the beginning, since they do not know about this new alternative. New incoming patients

may have more chance of knowing about the kidney exchange program since doctors may explain and offer these patients the alternative of kidney exchange at the time they find out their willing donor is incompatible. As time goes on, the amount of incompatible pairs joining the kidney exchange program would increase, as more people will know about this alternative.

Also, we assume the following:

- 20% of unmatched incompatible pairs leave the kidney exchange program every year.
- 60% of recommended matchings do not proceed to transplant.

In reality, not all of the recommended matches proceed to transplantation, due to varying levels of sensitization between candidates and donors in the pool, illness, uncertainty in medical knowledge, logistical problems, and patient receiving a kidney from the waiting list or another exchange [23].

We have data regarding the number of transplants carried out in Mexico each year until 2016 and also the size of the waiting list. The waiting list has been growing constantly each year as we have seen in previous chapters. A yearly average growth over the last 8 years has been calculated, obtaining an average growth of 877 patients in the waiting list. This means that, since in 2016 there was 12,477 patients in the waiting list [11], at the end of 2017 we expect 13,354 patients in the waiting list. Also using the same methodology, we expect 2,186 living donor kidney transplants at the end of 2017.

Starting with the data we have and considering the given assumptions, we simulate pools every year, and then optimize them to find the maximum number of matchings. Unmatched pairs will stay in the pool for the following years. We start with the predicted 995 incompatible pairs at the end of 2018 and the predicted 5,961 incompatible pairs in the waiting list. Each year, there will be 995 new incompatible pairs, however, only a precentage of them (depending on the year and the

assumptions from Table 5.14), would join the kidney exchange program. Regarding the waiting list, there will not be more incompatible pairs, only those predicted will stay in the pool until they find a match or leave the kidney exchange program. Next we present the results for each year in Tables 5.15 and 5.16.

Table 5.15: Calculation of incompatible pairs served by kidney exchange from 2018 to 2023.

Year	2018	2019	2020	2021	2022	2023
New IP	497	597	696	796	796	796
IP from WL	596	1,072	1,716	1,545	824	164
Total pairs	1,093	2,327	3,813	4,635	4,408	3,613
Matched	678	1,443	2,364	2,873	2,733	2,240
Transplanted	271	577	945	1,149	1,093	896
Remaining in pool	822	1,750	2,867	3,485	3,315	2,717
Remaining in WL	5,364	4,291	2,575	1,030	206	41

Table 5.16: Calculation of incompatible pairs served by kidney exchange from 2024 to 2028.

Year	2024	2025	2026	2027	2028
New IP	796	796	796	796	796
IP from WL	32	6	1	0	0
Total pairs	3,002	2,608	2,366	2,220	2,131
Matched	1861	1,617	1,467	1,376	1,321
Transplanted	744	647	586	550	528
Remaining in pool	2,257	1,961	1,779	1,669	1,603
Remaining in WL	8	1	0	0	0

We denote in Tables 5.15 and 5.16, incompatible pairs as “IP” and waiting list as “WL”. Total pairs each year is the sum of the new incompatible pairs and incompatible pairs from the waiting list that join the kidney exchange program

regarding that year. Also the addition of 80% of unmatched pairs for the last year (as 20% of them are supposed to leave the pool). Now having a pool of the total pairs each year, we optimize it and find the maximum number of matches, however only 40% of these matches proceed to transplant. The remaining unmatched pairs (pool of incompatible pairs) for each particular year equals the total number of pairs for that year minus the number of transplanted pairs. The remaining incompatible pairs in the waiting list for each year is equal to the remaining number of incompatible pairs of the past year minus the number of incompatible pairs in the waiting list that joined the kidney exchange program in that year.

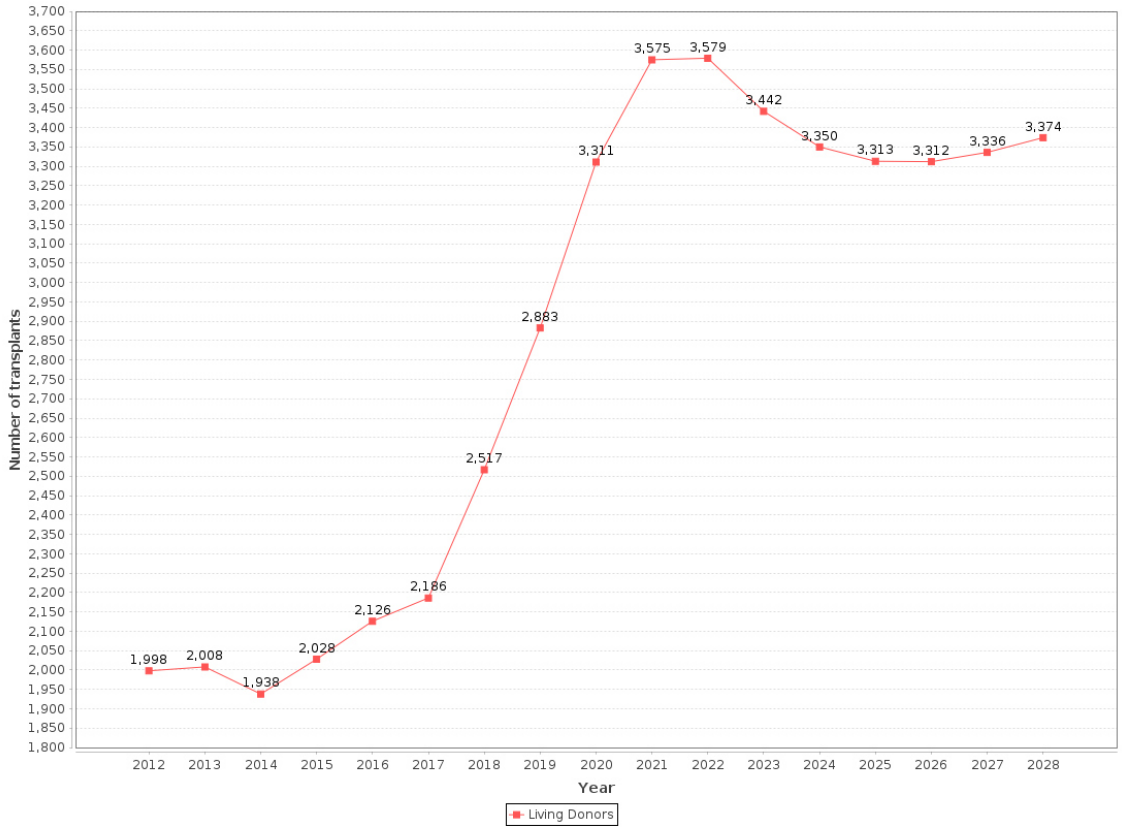


Figure 5.1: Estimation of LDKT in the next 10 years.

In Figure 5.1 we can see how the number of transplants regarding living donors increases dramatically compared to last years previous to 2018. Since the hypothetical implementation of the kidney exchange program in 2018, the number of

transplants keeps increasing until 2021, where it stabilizes. At this point, based on the simulation, we can confirm that a lot of patients would benefit from a kidney exchange program in the next years once it is implemented.

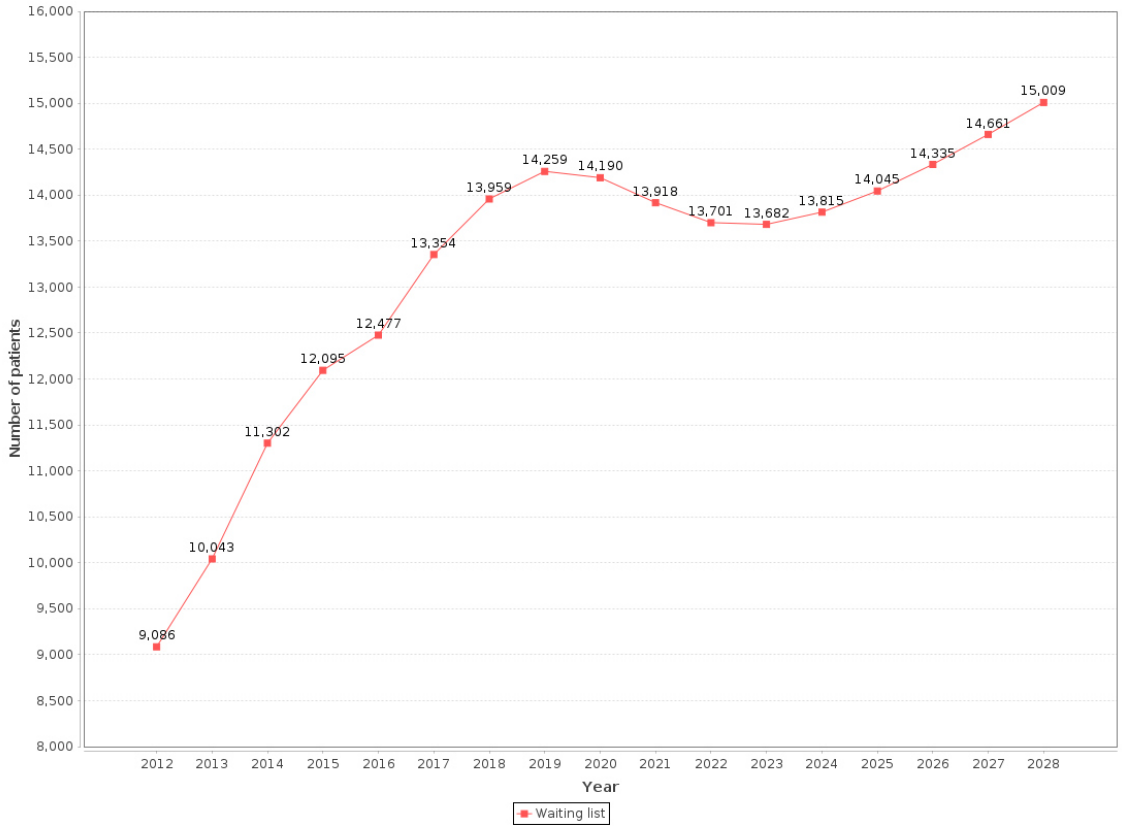


Figure 5.2: Estimation of patients in waiting list in the next 10 years.

In Figure 5.2 we can see how the waiting list, as seen in previous chapters, increases constantly. However with the implementation of the kidney exchange program in 2018, it will keep increasing until 2019. Then it will start decreasing until 2022. It decreases because initially, there is a large amount of incompatible pairs in the waiting list, and having a big pool of incompatible pairs, more patients find a match and get transplanted, overpassing the average growth in the waiting list. However, as patients get transplanted or leave the pool, pool becomes smaller, then the waiting list will start increasing again but at a lower rate (see Tables 5.15 and 5.16).

Chapter 6

Conclusions

6.1 Main findings and conclusions

The waiting list has been constantly increasing over the years, this is devastating, as many people with kidney failure die waiting for a transplant. According to the statistics studied, many organs go to trash due to families refusal to consent to organ donation from their deceased relative. Also the rate of deceased donors is very low in Mexico compared to other countries. Families need to be educated, they need to know more about transplantation, in my own experience, people prefer dyalisis than transplantation even if they have a willing donor, and that is because they are afraid to get transplanted or they just not consider transplantation as an option. Also, some physicians should be trained enough in order to detect potential deceased donors.

A kidney exchange program would also help to deal with the waiting list, and would decrease the growing rate each year. In this thesis we address the impact that a kidney exchange program would have in Mexico. As demonstrated in previous chapters with the simulation and some assumptions, if we implement a kidney exchange program in Mexico, a lot of patients would benefit from it. We could save many lives. Some succesful kidney exchanges were carried out in 2016 in Mexico

without a kidney exchange program. This means that a kidney exchange program would have a great impact in Mexico.

Based on the simulations, we have predicted a mean of 995 incompatible pairs that would arise in Mexico each year and about 5,961 (44.8% of the waiting list) patients in the waiting list that would have an incompatible donor. We would have a huge pool of incompatible pairs, and fortunately, according to the Mexican blood type distribution, it would be easier to find a match compared to other countries.

According to the results of the simulation, we could have a dramatic increase of living donor kidney transplants in the following years once the kidney exchange program is implemented. Also, the waiting list would start to decrease for the first time, which could be a great benefit, since it has been constantly increasing each year.

A transparent database should also be implemented online in Mexico, such as UNOS. Very important findings would arise to help patients in need of a transplant.

6.2 Future work

The simulation carried out in the present study always considers two donors per patient, as there is no current information about a distribution of how many donors patients may have. It would be a good idea to try to find out this distribution.

Medical work-up and crossmatch probabilities are taken from papers regarding USA population. It also would be a great idea to do some research about these probabilities pertaining to Mexican population.

The final part of the study was based on assumptions shown in Table 5.14. It would be very interesting to carry out a sensitivity analysis for different values of the parameters.

Another line of work worthwhile pursuing is to carry out a similar study but considering failure probabilities. This study was based on solving deterministic KEP models which is a common approach in the literature. However, with recent studies on developing mathematical problems for kidney exchange under uncertainty, it would be very interesting to study the possible sources of uncertainty from the Mexican population or eventual kidney exchange programs.

This thesis should provide a good starting point for these possible futures lines of work.

Appendix A

Blood Types

The material of the present appendix is taken from [7]. Our blood is composed of blood cells and an aqueous fluid known as plasma. Human blood type is determined by the presence or absence of certain identifiers on the surface of red blood cells. These identifiers, also called antigens, help the body's immune system to recognize it's own red blood cell type. There are four main ABO blood type groupings (also known as phenotypes): A, B, AB, and O. These blood groups are determined by the antigen on the blood cell surface and the antibodies present in the blood plasma (see Table A.1). Antibodies (also called immunoglobulins) are specialized proteins that identify and defend against foreign intruders to the body. Antibodies recognize and bind to specific antigens so that the foreign substance can be destroyed by other immune cells.

Table A.1: Antigens and antibodies according to ABO type.

ABO blood type	Antigen A	Antigen B	Antibody anti-A	Antibody anti-B
A	YES	NO	NO	YES
B	NO	YES	YES	NO
O	NO	NO	YES	YES
AB	YES	YES	NO	NO

Human blood type is determined by co-dominant alleles [17]. An allele is one of several different forms of genetic information that is present in our DNA at a specific location on a specific chromosome. There are three different alleles for human blood type (although there are three alleles possible, each person only has two genes for every trait), known as I^A, I^B, and i. For simplicity, we can call these alleles A (for I^A), B (for I^B), and O (for i).

Table A.2: Phenotypes and genotypes.

Genotype	Phenotype
AA	A
AO	A
BB	B
BO	B
AB	AB
OO	O

These DNA codings determine distinct traits that can be passed on from parents to offspring through sexual reproduction. These multiple alleles are passed from parent to offspring such that one allele is inherited from each parent (see Table A.3). A description of the pair of alleles in our DNA is called the genotype. Since there are three different alleles, there are a total of six different genotypes at the human ABO genetic locus (genetic makeup of inherited alleles) see Table A.2. The A and B alleles are dominant to the O allele. When both inherited alleles are O, the genotpye is homozygous recessive and the blood type is O. When one of the inherited alleles is A and the other is B, the genotype is heterozygous and the blood type is AB. AB blood type is an example of co-dominance since both traits are expressed equally.

Due to the fact that a person with one blood type may produce antibodies against another blood type, it is important that individuals be given compatible

Table A.3: Possible genotypes from inheritance of 1 allele from each parent.

Parent alleles	A	B	O
A	AA	AB	AO
B	AB	BB	BO
O	AO	BO	OO

blood types for transfusions. For example, a person with blood type B makes antibodies against blood type A. If this person is given blood of type A, his or her type A antibodies will bind to the antigens on the type A blood cells and initiate a cascade of events that will cause the blood to clump together. This can be deadly as the clumped cells can block blood vessels and prevent proper blood flow in the cardiovascular system. Since people with type AB blood have no A or B antibodies in their blood plasma, they can receive blood from persons with A, B, AB, or O type blood.

Appendix B

HLA, PRA, and Crossmatch

B.1 HLA

The material of the present appendix is taken from [39]. HLA stands for Human Leukocyte Antigen. HLA antigens are substances, usually a protein, found on the surface of our cells that stimulate the production of antibodies. These antigens are referred to with a letter and a number such as A2 or B23.

Each person's HLA make-up is unique. You inherit it from your parents. If something foreign is introduced into your body, your immune system recognizes the foreign intruder and mounts an antibody attack against it. In the case of an organ transplant, the body will recognize the HLA antigens on the transplanted organ as not being the same as its own, and form specific antibodies against those particular HLA antigens.

HLA is important in organ transplantation for two main reasons:

First, a body may reject any transplanted organ (eg, kidney, pancreas, heart, lung, liver, and intestine) because the recipient's immune system recognizes the organ as foreign and initiates a rejection response (this can be in the form of antibody production) which could eventually destroy the organ. Patients receive anti-rejection

drugs after a transplant to prevent antibodies from forming.

Second, because of previous medical events, some patients have already developed antibodies to specific HLA antigens. For example, if a candidate has developed a specific antibody to the HLA antigen A2, that person is said to be "sensitized" to the A2 antigen. If a donor organ that displayed the A2 antigen were placed in that candidate, there may be an immediate rejection response (a hyperacute response) which would lead to the rejection of the transplanted organ.

It is not easy to become sensitized to human HLA antigens. Most people waiting for a transplant (around 80%) are not sensitized. Patients can become sensitized to HLA antigens because of:

- Pregnancies. About 30-50% of women with three or more pregnancies will develop HLA antibodies. In some women the antibodies could be present for just a short time (weeks to months), while in others they may persist for many years.
- Blood transfusions. About 50% of patients who receive multiple transfusions will develop antibodies. Today, most patients who require blood transfusions receive filtered blood, which decreases the chances for a patient to become sensitized.
- Previous transplant. About 90% of patients develop HLA antibodies within two weeks of a failed graft. However, by the time the patient is relisted (some will have "lost" their antibodies.
- Viral/bacterial infections. There are some reports that patients with virus infections develop HLA antibodies, although this is relatively rare.

After HLA is determined, there is a second test which will indicate if there is specific immune reactivity between the donor and recipient. This test is the "crossmatch" [39].

B.2 PRA

PRA stands for Panel Reactive Antibodies. In order to determine whether or not a patient already has any specific HLA antibodies, a lab specialist will test a patient's blood (serum) against lymphocytes (white blood cells) obtained from a panel of about 100 blood donors. These 100 donors represent the potential HLA makeup for a donor from that area. Percent PRA (%PRA) is the number of reactions within that panel. If a candidate's serum does not react with any of the donor samples, the candidate is not sensitized and has a PRA of 0. If a candidate's serum reacts in 80 out of 100 samples, the patient has a PRA of 80%. Theoretically, that means that if a donor becomes available from that donor pool, the recipient would experience acute rejection 8 out of 10 times. That patient might have to wait a very long time until a compatible donor becomes available [39].

B.3 Crossmatch

The crossmatch is a test which determines if the recipient has antibody to the potential donor. The antibody will only injure the donor's cells if it is specific for the donor's particular HLA. Not everyone has antibody against HLA.

The crossmatch is performed by mixing a very small amount of the patient's serum with a very small amount of the potential donor's white cells [17]. Patient and donor will have a crossmatch test multiple times, including right before transplant surgery. If the patient has antibody to the donor's HLA, the donor's cells will be injured and this is referred to as a "positive crossmatch". A positive crossmatch is a strong indication against transplant, since it signifies that the patient has the ability to attack the donor's cells, and would, most likely attack the donor's implanted kidney. A negative crossmatch indicates that the patient does not have HLA antibody against that particular donor, and a transplant can be performed.

Appendix C

The Hardy-Weinberg Principle

C.1 Review of probability rules

We start by recalling a couple of rules for the computation of probabilities [26]. First, for the multiplicative rule for probabilities, if two events E_1 and E_2 are independent (that is, the occurrence of one event does not affect the probability of the other event occuring), $P(E_1) = p_1$, and $P(E_2) = p_2$, then the probability of both E_1 and E_2 is

$$P(E_1 \text{ and } E_2) = P(E_1) \times P(E_2)$$

Second, by the additive rule for probabilities, if events E_1 and E_2 are mutually exclusive (that is, both cannot occur together), then the probability of either E_1 or E_2 occuring is

$$P(E_1 \text{ or } E_2) = P(E_1) + P(E_2)$$

Let us now shift our attention to genetic models. We consider a one-locus/two-alleles model. Suppose the two alleles at this locus are denoted as A and a. The frequency of allele A is the percentage (expressed in decimal form) of alleles at the given locus which are the A allele. Denote this frequency as p. In our model, then, the frequency of the a allele is $q = 1 - p$. Suppose that a population has these frequencies of A and a. Let us now calculate the frequency of the genotypes in the

next generation. Here, we are assuming nonoverlapping, discrete generations. The only way for an offspring in the next generation to have genotype AA is to inherit an A allele from each parent. The father contributes an A allele with probability p and the mother contributes an A allele with the same probability. The probability of both of these events is, by the Multiplication Rule for Probability (since the two events are independent) is $p \times p = p^2$.

Similarly, the probability of both parents contributing the a allele to an offspring is $q \times q = q^2 = (1-p)^2$. It follows that the probability of a heterozygous offspring is as follows. The probability that the father contributes an A allele is p and the probability that the mother contributes an a allele is $q = (1-p)$. So the offspring can have genotype Aa in this way with probability pq. However, the offspring can have the same heterozygous genotype by getting the A allele from the mother and the a allele from the father—also an event with probability pq. So, again, the probability of an Aa offspring is $2pq$ by the addition rule of probabilities (since these are disjoint events).

This can be summarized in Table C.1.

Table C.1: Frequency of the genotypes in the next generation

Parent alleles	$A(p)$	$a(q)$
$A(p)$	$AA(p^2)$	$Aa(pq)$
$a(q)$	$Aa(pq)$	$aa(q^2)$

Alternatively, we can accomplish the same computation by squaring $p + q$: $(p+q)^2 = p^2 + 2pq + q^2$. The conclusion is that, regardless of the distribution of genotypes in the first generation, after one generation of random mating (and subsequently), the genotypes will be distributed according to the frequencies given above.

C.2 Statement of the Hardy-Weinberg Principle

We can summerize these observations in the Hardy-Weinberg Principle:

Hardy-Weinberg Principle. Consider a population which experiences no mutation, migration, drift, or selection with respect to a locus which contains two possible alleles, A and a. Also assume discrete (nonoverlapping) generations. If the frequency of allele A is p (in both sexes), then after one generation of random mating, the genotypes and frequencies will be AA with frequency p^2 , Aa with frequency $2pq$, and aa with frequency q^2.

C.3 ABO blood type

Blood type is determined by three alleles at a single locus. The alleles are commonly denoted A, B, O. These alleles combine to give the following phenotypic blood types: AA and AO (type A), BB and BO (type B), AB (type AB), and OO (type O). Denote the frequencies of alleles A, B, O as p, q, r respectively. Under the assumptions of the Hardy-Weinberg Principle, we would expect the genotypic frequencies: AA with frequency p^2, AB with frequency $2pq$, AO with frequency $2pr$, BB with frequency q^2 , BO with frequency $2qr$, and OO with frequency r^2 . Notice that, again, these frequencies can be calculated by squaring the appropriate multinomial. This time it is $(p+q+r)^2 = p^2 + 2pq + 2pr + q^2 + 2qr + r^2$ [26].

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Resumen autobiográfico

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