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MASTER THESIS

Racial Disparity in Deceased Donor Kidney Transplantation: Causes and Solutions

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Abstract

End Stage Renal Disease (ESRD) is the last stage of Chronic Kidney Disease and if not treated, will result in a certain death of the patient. Currently, transplantation of a new kidney is the treatment option with the highest life expectancy. Despite the goal to provide equity among patients, some ethnic minority groups have a lower probability to get a deceased donor kidney. This thesis analytically shows that two fundamental matching rules, which are used in matching procedures around the world, cause racial disparity. We examine the role of identical blood type matching and HLA type matching. We have used the average waiting time of an ethnic group as indicator of racial disparity and have used queuing models to calculate the average waiting times. We have shown, with the stochastic ordering theory, that different blood type distributions and different ESRD and donor rates among ethnic groups cause racial disparity if identical blood type matching is used. We have also shown, with a probabilistic service discipline in a queuing model, that HLA type matching leads to racial disparity. Every ethnicity has a different probability of finding a donor with a suitable HLA profile, which negatively affects the average waiting time of ethnic minorities. We have formulated an approach to solve the racial disparity that occurs when the identical blood type matching and HLA type matching is used. Reducing this disparity contains three parts: First, a number of (compatible) cross transplants between blood types must be allowed. Second, kidneys that are used for these cross transplants must have the right composition of ethnicities. Third, the selection probabilities of ethnic groups within blood types must be adjusted. It is, due to the high complexity of this model, not possible to find an analytical expression that calculates the values of these three parts within the scope of this research. We however give an extensive description of the modeling approach.

Keywords: Organ transplantation, Racial disparity, Blood type Matching, HLA type matching, Probabilistic service order

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Contents

1 Introduction

End-Stage Renal Disease (ESRD) is the last stage of chronic kidney disease and, if not treated, the kidneys stop working completely. This will results in a certain death of the patient (Evans and Taal, 2015). Kidney transplantation is the treatment option with the highest life expectancy for a patient diagnosed with ESRD (Albertus et al., 2016). Most kidneys used for transplantation come from deceased donors (Organ Procurement and Transplantation Network (OPTN), 2016*a*). Unfortunately, because availability of deceased donors is low, not everybody can get one in time. This makes matching kidney recipient candidates with a deceased donor kidney an extremely delicate task (Roth et al., 2004). To fulfill this task in the best way, various countries and regions have distinct sets of rules regarding kidney allocation. These matching rules can be formulated as algorithms. All algorithms currently in use are based on the same two principles to ensure an optimal and fair distribution of kidneys (Glorie et al., 2015): First, the kidney should have a significant chance of long-term survival in the recipient's body. This depends on the medical characteristics of both donor and recipient. Second, the algorithm should provide equity among patients: All should have a fair chance to get a kidney, adjusted for their medical needs and possibilities. Despite the goal to create equity among patients, several data sources and previous literature suggest that certain ethnic groups benefit more from the matching rules than others, leading to differences in ESRD survival between ethnic groups in Western countries (Sayeed et al., 2011; Callender et al., 2002; Cleary et al., 2000). This thesis will show analytically that this racial disparity in kidney transplantation is indeed inherent to parts of the current matching procedures. We will also propose adjusted matching rules to reduce the existing disparity, while respecting important medical constraints. The reason why we focus on the kidney is that it is the world's most frequently transplanted organ (World Health Organization (WHO), 2016). Our approach, however, could be applied to other solid organs.

Racial disparity in kidney allocation is evident when we examine the differences among ethnic groups in the probability of getting a kidney. In the USA, for example, (depending on the year and region) the probability to get a kidney is at least twice as low for ethnic minority groups compared to the majority group (Williams et al., 2015). This probability is calculated as the percentage of patients listed on the waiting list who actually get a kidney. Although chances have recently slightly increased for minority groups, the proportion of listed minority patients that received a transplant in 2016 is still a few percentage points behind, despite great efforts to reduce disparity (Organ Procurement and Transplantation Network (OPTN), 2016*a*).

In this research we are not primarily interested in the exact probability that a particular recipient candidate gets a kidney, as this is affected by specifics within matching procedures that differ per country. It would be impractical to construct a mathematical model that incorporates all these specifics and it would suit only a single country or region. As such, in this thesis we will focus on fundamental principles of the matching procedures used around the world. A causal relationship between these principles and racial disparity has been theorized (Takemoto et al., 2004; Williams et al., 2015), but never before has this been formally shown in an analytical way. We will model the probable causal factors in racial disparity separately in order to isolate their effects on racial disparity. To emphasize these effects, we will not incorporate any other matching components that are used in the real matching procedures. We will use differences in the average waiting time of a patient as the indicator of racial disparity. We elaborate further on this choice in Section 3.1.

This thesis tries to formally prove that some of the ethnic groups have a longer average waiting time by incorporating various racial aspects in a queuing model. We will show that the inequity is inherent to current matching procedures and propose a way to reduce this. Thus, these are our two main research questions:

How can we analytically explain racial disparity in waiting times for the transplantation of a deceased donor kidney?

Can we design and describe methods to reduce racial disparity in waiting times for the transplantation of a deceased donor kidney?

For solving the disparity, it is important to consider that the root of the matching problem lies in the fact that matching every potential candidate with a donor is impossible. Before a (good) match is possible, certain medical restrictions should be taken into account. Thus, proposed changes in the algorithm should not lead to worse matches and certainly not to less matches. Also, we underscore that the results from our approach concerning showing and solving the disparity should be handled with some care. We use a theoretical approach where we try to find an analytical solution, not a solution by means of a simulation. This means that we do not incorporate every aspect of real allocation algorithms and so it is not possible to use our results directly in the existing algorithms. The results will mainly serve as a guideline for further (medical) research regarding fair organ distribution. The model is not specifically designed for one country. We will use data from the USA, as it is the best documented.

In the remainder of this section we first elaborate further on the problem and possible causes. Later we will discuss the approach that we will use to show racial disparity and to come to our suggestions for reducing it.

1.1 Possible Causes

In most countries, people who choose a deceased donor kidney as treatment for ESRD are placed on a regional waiting list, overseen by an independent organization (Boer, 2013; Organ Procurement and Transplantation Network (OPTN), 2016*b*). Whenever a kidney becomes available, this organization makes an ordered list of all patients based on scores obtained from a matching algorithm. The patient with the highest score gets the kidney (Boer, 2013; Organ Procurement and Transplantation Network (OPTN), 2016*b*). The characteristics that determine the matching score are medical (health status) or genetic (blood type and HLA types) in nature, or they fall in a remainder category (region, age and waiting time) (Boer, 2013; Organ Procurement and Transplantation Network (OPTN), 2016*b*). By considering all these aspects, the algorithm should provide equity among patients and provide the best medical match for the available kidney. The logical consequence of this matching procedure is that the chances of getting a kidney differ between patients, according to their medical characteristics. In this thesis we will not look at these medically explainable differences but at the differences between two patients with the same health status, but with differing ethnicities.

Matching procedures do not have explicit racial criteria that forces matches among patients from certain ethnicities (Boer, 2013; Organ Procurement and Transplantation Network (OPTN), 2016*b*). But, some of the genetic aspects of the matching are strongly related to the ethnic background of the patient. This could cause racial disparity in combination with parts of the matching procedure. Two of the most important genetic parts, that will be extensively explored in this thesis, are the patient's blood type in combination with identical blood type matching (Williams et al., 2015) and the patient's HLA type in combination with HLA type matching (Pidala et al., 2013). In the remainder of this section we will first describe how ethnicity affects these characteristics, then how they are used in the matching and finally how they potentially lead to racial disparity.

1.1.1 Different Blood Type Distributions

For the case of blood types, the influence of ethnicity is relatively easy to show: The share of each blood type within an ethnic group differs between ethnic groups. For example, in the USA 19 % of the Afro-Americans have blood type B and 26 % of Asian Americans have blood type B whereas only 11% of the White American population has this blood type (American Red Cross, 2016). Figure 1 illustrates the blood type distribution for the four largest ethnic groups in the USA. We do not use other blood group systems such as Rh because these are not relevant for organ transplantation (Reddy et al., 2013).

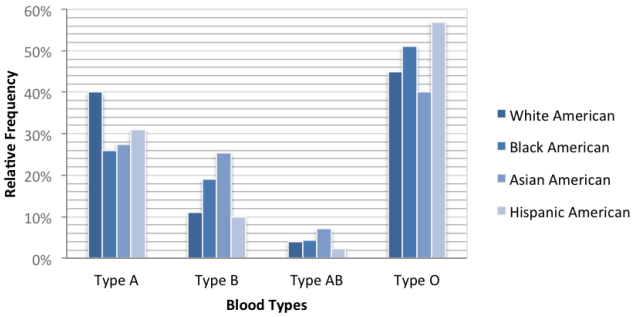

Figure 1: Relative frequency of blood types per ethnic group for the major ethnic groups in the USA.

With identical blood type matching, that is used in most Western matching procedures (Stanford et al., 2014), a patient with a certain blood type is only matched with a donor that has the same blood type. It is important to note that, from a medical perspective, this is not a strict requirement for a successful match (Reddy et al., 2013). Two problems can arise with this identical blood type matching in combination with the previously described genetic dependence of blood types. First, the relative frequency of blood types within ethnic groups differs from the relative frequency of blood types in the general population (Zachary and Maryland, 1995). So a blood type can be common within an ethnic group but rare within the general population. As the average waiting time of a patient depends on the proportion of that patient's blood type in the general population (Stanford et al., 2014), we can expect that an ethnic group with a large proportion of of relatively rare blood types will have a longer average waiting time. We will explain the work of Stanford et al. (2014) more extensively in Section 2.

This effect can even be strengthened by a second problem: The blood type distribution is not the same in the patient and donor group. This is true because of different donation rates (Morgan et al., 2006) and ESRD rates among ethnic groups (Zadshire et al., 2005). In the USA, the proportion of donors from an Afro American background is 12.8 %, which is equal to 1779 kidneys in 2015. The proportion of patients waiting for a kidney from an Afro American background is 33.6%, equaling 33600 patients (Organ Procurement and Transplantation Network (OPTN), 2016*a*). This discrepancy, combined with a different distribution of blood types, could lead to even more inequity when identical blood type matching is used.

1.1.2 Different HLA Types

Human Leukocyte Antigens (HLA) are antigens central to immune function (Takemoto et al., 2004). Therefore, compatibility between donor and recipient HLA types affects transplant rejection. The HLA genes are highly polymorphic which means that HLA types can consist of many different alleles (Takemoto et al., 2004). The amount of possible combinations of HLA alleles makes it difficult to express the relation between HLA types and ethnicity in numbers. However, large databases with HLA types of populations show that two people with the same ethnicity tend to have more HLA compatibility than two people from different ethnicities (Pidala et al., 2013).

For HLA types, the effect of the matching procedure is more complex. A person can develop antibodies against other HLA types during his life (Takemoto et al., 2004). This happens whenever a person is exposed to foreign cells that express a different HLA type, for example via pregnancy or an earlier transplantation (Triulzi et al., 2009). If the kidney recipient has developed antibodies against the HLA type of the donor, transplanting the kidney would result in immediate rejection (Valenzuela and Reed, 2013). Therefore the patient and donor will not be matched. The likelihood that patient and donor are incompatible (the CPRA value) is higher among ethnic minorities (Gebel et al., 2016). If the HLA type of the donor is not likely to lead to an immediate rejection, the patient gets a score based on the sim-

ilarity of his and the donor's HLA type. A perfect match is not necessary because these dissimilarities will not lead to the immediate rejection we see with previously developed antibodies. However, several HLA allele mismatches between the patient and the donor can lead to a lower graft survival probability on the longer term (Takemoto et al., 2004). As such, a more similar HLA match is more desirable and awarded with more points in the matching procedures (Boer, 2013; Organ Procurement and Transplantation Network (OPTN), 2016*b*). Because HLA types are ethnically determined, this leads to matches that are preferable within the same ethnic group. We expect that an inequitable situation can occur with the disproportionate distribution of ethnic groups in the patient and donor pool.

In this thesis we start by examining the effects of identical blood type matching on differences in the average waiting time among ethnic groups. The effects of the different HLA types will be less clear due to the large number of possible HLA type combinations that all have different medical implications. We show that HLA types affect racial disparity without discussing these medical details.

1.2 Research Approach

In Section 2 we start by discussing previous literature on the problem. We describe mathematical as well as practical literature that has previously explored causes of the disparity or similar problems.

In Section 3 we explain the methods that will be used in the remainder of the thesis. Special attention will be given to the choice of the average waiting time as metric to show racial disparity and the assumptions that enable us to use a queuing model to model the transplant process.

We start the quantitative analysis of racial disparity in Section 4 by examining the influence of identical blood type matching. We build a mathematical model which can help us to show racial disparity among ethnic groups when assuming identical blood type matching as the only matching criterion. We will consider two different cases of the model. The first one is an ideal situation in which every ethnic group has the same propensity to donate and the same probability to develop ESRD. The second scenario is more realistic and makes the donation and ESRD rates dependent on the ethnicity of a donor and patient. In both cases we show that racial disparity exists and we will relate the ethnic specific input parameters to the disparity. We will also discuss a numerical example at the end of the section. The model will be based on earlier work of Stanford et al. (2014) which leads to the following question that is answered in Section 4:

How can we extend the existing identical blood type model from Stanford et al. (2014) into a model that accommodates different ethnic groups to show racial disparity?

In Section 5 we extend the model with HLA types in order to show how HLA types affect racial disparity. Due to the complexity around HLA type matching we can not model the exact effect of HLA type matching in an analytical way but we use two approaches that enable us to approximate the effect closely. This leads to the following question:

How can we extend the identical blood type model with HLA type matching in order to show racial disparity caused by different HLA types among ethnic groups.

If we can proof that inequity is caused by the use of identical blood type matching and the HLA type matching, the next task is to find a way to mathematically restore equity in Section 6. In order to solve the disparity caused by identical blood type matching we construct a new model with adjusted matching rules. For the case of HLA type matching we do not build the required model but only discuss a possible approach. It leads to the following question:

Which changes in the allocation mechanism should we allow, and to what extent, in order to restore equity among ethnic groups?

In Section 7 we will evaluate our findings. We will discuss our recommendations and use the limitations of our work to formulate possibilities for further research.

2 Literature Review

The fact that in most Western countries certain ethnic groups have a lower probability to survive ESRD has been well documented by different sources (Callender et al., 2002; Rodrigue et al., 2012; Eckhoff et al., 2007; Williams et al., 2015) and by available data in the USA (Organ Procurement and Transplantation Network (OPTN), 2016*a*). The USA has extensive data regarding kidney transplants sorted on ethnicity and is therefore used as example in most of the literature regarding racial disparity. It should however be noted that, despite the lack of data from Europe, racial disparity in the matching of kidneys has been documented there as well (Tjaden et al., 2016). Earlier research has indicated some possible causes for racial disparity that distinguish between disparity in access to health care and disparity on the waiting list. (Sayeed et al., 2011; Callender et al., 2002). The latter will be the focus of this research.

The first aspect often mentioned in explaining racial disparity on the waiting list is the role of blood types (Williams et al., 2015). Because the blood type distribution differs among ethnic groups, donors that have certain blood types are more rare than others. It appears that blood type B candidates awaiting a donor have a significantly lower probability of getting a donor than other blood type candidates (Williams et al., 2015). Because blood type B is more common among ethnic minorities, they may have a lower chance of getting a kidney (Williams et al., 2015).

Stanford et al. (2014) underlined this thought by using queuing theory. They described the effects of identical blood type matching on the average waiting time of a patient. The proportion of a blood type in the donor group was shown to determine the average waiting time of a patient when identical blood type matching is used. Before identical blood type matching was introduced, a lot of regions used blood type compatible matching. However, this caused a problem for type O patients who tended to have a lower probability to get a kidney than people from the other blood types. Type O donors can give organs to all other patients, whereas a type O patient can only receive an organ from a type O donor, resulting in a below average probability to get a kidney for type O patients (Glorie et al., 2015). With identical blood type matching, the probability to get a kidney is the same for all blood types if the patient and donor group have the same relative frequencies of blood types and if a patient can wait indefinitely for the kidney. However, with a yearly mortality rate of 20% among patients waiting for a kidney, waiting time is crucial (Glorie, 2014). The difference in the average waiting time between two blood types is inversely proportional to the difference in prevalence (Stanford et al., 2014). This means that people with a rare blood type have a longer average waiting time and so a larger probability to die of ESRD. As such Stanford et al. (2014) showed that identical blood type matching leads to disparity among blood types.

Because both the non-identical as well as the identical blood type matching policies result in an inequitable situation, Stanford et al. (2014) argue that an ideal situation should be somewhere in between. They showed that by allowing some blood types to be matched with other (medically feasible) blood types, an equitable situation can exist. The number and nature of cross transplants depends on the average blood type distribution in the country. In Section 6 we use the same approach but now accommodated for ethnic groups to find a suitable solution for the racial disparity problem.

In this thesis we mainly focus on stable queues. That means that the number of new patients in the model is smaller than the number of new donors per time unit (Kleinrock, 1975). Glorie et al. (2015) have described analytically the effect of unstable transplant queues on disparity among blood types. They have shown that in unstable queues identical blood type matching leads to equity among blood types on the long term, whereas in stable queues identical blood type matching with some cross transplants between blood types is necessary to ensure equity. We will use this information to briefly discuss the consequences for our model when ethnic groups are incorporated in the identical blood type matching model.

The influence of HLA type matching has also been mentioned as a possible cause of racial disparity in earlier work (Gragert et al., 2014). Takemoto et al. (2004) describe extensively the role of HLA type matching in the matching procedure. The HLA types are strongly related to a person's ethnicity and matches with a more similar HLA type are preferred. If we combine this knowledge with the fact that in most populations ethnic minorities are over represented in the patient group and under represented in the donor group (Organ Procurement and Transplantation Network (OPTN), 2016*a*), we can expect that HLA types cause racial disparity. According to Pidala et al. (2013) the overall probability to get a suitable HLA match for African Americans is around 66% whereas 97 % of White Americans find a suitable donor based on a zero or one allele mismatch. Takemoto et al. (2004) mentioned that improving these ratios could negatively affect the graft survival rates because more allele mismatches lead to a higher probability of kidney rejection in the long term. Because of this reason we only use matches that have a zero allele mismatch when we incorporate HLA type matching.

The HLA problems do not only exist because matches within the ethnic group are preferred, it also seems that HLA genes of ethnic minorities in the USA are more polymorphic than the HLA in majority groups (Beatty et al., 1995). This means that the variety of HLA types is higher among minority groups which makes it more difficult to find a match for these patients, even within their own ethnic group.

Some research has suggested that ethnic minority patients have less access to health care or are referred less for a transplant, resulting in fewer patients from ethnic minorities applying for a kidney (Nilakantan et al., 2016). We will not discuss these entry barriers as we focus only on racial disparity that is caused by the matching procedure.

Last, we want to notice that some (recent) sources seek the cause of disparity in regional disparity, suggesting that certain regions in the USA have more racial disparity than others (Patzer et al., 2016). However, we expect that the reasons that racial disparity is larger in some regions, are likely to be found within one of the above stated points and as such we do not explicitly focus on the regional differences in this work.

3 Methodology

We use the average waiting time as an indicator to compare the outcome of the matching procedure between ethnic groups and to show that racial disparity exists . We start this section by explaining why we have chosen the average waiting time as indicator of disparity. Afterwards, we discuss the general layout and assumptions of the transplant queues that we use to calculate the average waiting time per ethnic group. We conclude this section with a general calculation of the average waiting time.

3.1 Average Waiting Time as Metric

The performance indicator that we use to compare the outcome of (parts of) the matching procedure for different ethnic groups must only depend on the relevant parts of the matching procedure as discussed in Section 1.1. For example, the health status of patients before joining the queue or lack of access to medical care are factors that should not influence the performance indicator. Also, the performance indicator should give a good approximation of the health status of the patients when they leave the transplant queue. The average waiting time of a patient in the transplant queue is an indicator to show disparity previously used by Glorie et al. (2015) and Stanford et al. (2014) to show disparity. With some assumptions we can make sure that the average waiting time depends only on the matching procedure and is able to reflect the health status of patients. We introduce three assumptions in order to meet these two requirements in our queuing model:

First of all, we assume that everyone joins the transplant queue at the same moment during their disease progression and as such everyone has the same health status as they enter the queue. Next, we assume that for everyone the disease progresses at the the same rate in time. With these two assumptions, two patients who have been on the waiting list for the same time have the same health status. As we explain more extensively in Section 3.2.1, we also need to assume that patients in our queuing model will not die while waiting on the waiting list, because the average waiting time will be affected by abandonments.

3.2 Transplant Queuing Model

Transplant queues are used to model the arrival and departure process of patients waiting for a transplant. For each genetic characteristic that we model, we use a different queuing model that consists of multiple individual transplant queues. Every transplant queue describes the arrival and service process of the patients who join that specific queue. The queuing model determines which patients join which transplant queue. In this section we describe the layout of a single transplant queue. The layout of the queuing models differs per included characteristic and will be discussed in their respective sections.

3.2.1 General Layout Transplant Queue

The transplant queue represents the list of people waiting for a kidney. The moment that someone in real life registers on the waiting list corresponds with the moment that the patient joins the transplant queue. When a patient gets a kidney in real life, the patient leaves the transplant queue.

Transplant queues typically use the time between two donors becoming available as the service time of the process (Stanford et al., 2014). The service process can be approximated by a Poisson process, which leads to inter arrival times that are exponentially distributed (Stanford et al., 2014). A Poisson process is typically used when you have a large population with a very small probability for a certain event (Feller, 1986). The time of the transplantation is assumed to be zero.

The arrival process of the queue is the process of patients registering on the waiting list which is also an event with a small probability in a large population. Some research used a Poisson process to model the arrivals, but other research indicates that a Poisson process does not fit the real data and used a general arrival process (Stanford et al., 2014). However, because the tractability of the the model is easier with a Poisson process and we try to prove all our results in an analytical way, we use the Poisson process. We assume that the placements of patients are independent of each other.

The transplant queue has one server because an available kidney can only serve one patient. We assume that the transplantation is always successful, so all kidneys that are donated are used whenever patients are waiting for a kidney. This means that the transplant queue is modeled as an M/M/1 queue. The M/M/1 queue has one server and both the arrival process and the service process are Poisson distributed with exponentially distributed inter arrival times (Kleinrock, 1975).

We assume that the arrival of patients in the queues has reached stationarity. The arrival rate does not grow or decline in time. This assumption is necessary for computational reasons but in reality the arrival rate of patients and donors is likely to change in time. However, because we look at the current situation and are not interested in the development of the disparity, we can assume a stationary process.

In all except one of the transplant queues the patients are treated “First Come First Serve”. In reality, as we have described in Section 1.1, whenever a donor becomes available, all patients get a matching score that results in a prioritization among patients based on their medical situation. We assume that in our transplant queues no such prioritization exists. The prioritization based on medical profiles is irrelevant given that we focus on average waiting time as the performance indicator of interest. In one queuing model, for the HLA type matching, we make a slight adjustment to this rule and use a probabilistic service discipline, the exact reason for this different discipline is discussed in Section 5.1.

We have to keep in mind that we use multiple transplant queues in one queuing model. The distribution of kidneys among the transplant queues is done according to the matching rules of the included part of the matching procedure. For example, such a rule can be an identical blood type or a HLA type match. The exact rules will be discussed when we introduce the layout of the queuing models belonging to the matching characteristics. It is clear that these rules are not according to the FCFS principle. Only whenever a kidney becomes available for one of the transplant queues in the queuing model, we assume there exists no prioritization in the queue.

In reality people can be removed from the waiting list. These patients have become too sick to get a transplant, have died while waiting on a kidney or have received a kidney from a living donor (Drekic et al., 2015). In our model we assume that it is not possible to leave the transplant queue, so everyone who joins the queue gets a kidney. You could argue that these abandonments should be included because in some ethnic groups significant more people abandon the queue than in others (Organ Procurement and Transplantation Network (OPTN), 2016*a*). We do not include these abandonments because we use the average waiting time as the sole indicator to show racial disparity. If we model abandonments in the transplant queue, it leads to lower average waiting times for queues with many abandonments. The reason for an abandonment is mostly because patients die or become too sick to get a transplant (Drekic et al., 2015). Thus, if we include abandonments, the average waiting time becomes lower in queues where the average health status is worse. By including the abandonments, the average waiting time would not reflect the health status of a patient anymore.

Lastly, we will especially focus on the stable version of the model. Waiting lists in some countries are unstable but because of the tractability of the model we show the disparity for the stable variant. We do give a short comment on racial disparity for the unstable version of the queue for the identical blood type matching models.

3.2.2 Calculation of the Average Waiting Time

The transplant queues in this thesis are modeled as M/M/1 queues and all but one use a FCFS service discipline. With all of these queues and our specific assumptions, we can use the average sojourn time of the transplant queue to calculate the average waiting time per patient in reality. The average sojourn time of a queue is equal to the service time plus the average waiting time of a client (Kleinrock, 1975). In our transplant queues the time of the transplantation is assumed to be zero. That means that the average sojourn time in our queues is equal to the average waiting time till someone is in front of the queue, plus the time till the next donor becomes available (the service time), which is exactly the same as the average waiting time in reality. Some notation is needed in order to introduce the equation for the average sojourn time.

λ = The arrival rate of the total population.
μ = The service rate of the total population.
W = The average sojourn time of a patient.
$\rho = \frac{\lambda}{\mu}$

The average sojourn time of a person in an M/M/1 queue with arrival rate λ and service rate μ is given by Equation (3.1) (Kleinrock, 1975):

$$W = \frac{1}{\mu \cdot (1 - \frac{\lambda}{\mu})} = \frac{1}{\mu - \lambda}. \tag{3.1}$$

The rates in Equation (3.1) are adjusted when we introduce the different ethnic characteristics. Equation (3.1) does not hold for the M/M/1 queue with the probabilistic priority service order. We elaborate further on the average waiting time calculation for this model in Section 5.2. Unless stated otherwise, if we use the average waiting time in the remainder of the thesis, we mean the average waiting time in real life as calculated by the average sojourn time in the models.

4 Showing Racial Disparity with Identical Blood Type Matching

In this section we want to show that identical blood type matching is a source of racial disparity. In Section 2 we have described the work from Stanford et al. (2014) who built a queuing model to show that the average waiting time for a kidney transplant is dependent on the blood type of the patient. The use of identical blood type matching was the main assumption on which they based their model. This same assumption is very important in this section and therefore we use their model and part of their assumptions as a start for our research. We answer the following question in this section:

How can we extend the existing identical blood type model from Stanford et al. (2014) into a model that accommodates different ethnic groups to show racial disparity?

We will show analytically how ethnic characteristics in combination with the identical blood type matching cause racial disparity. In consultation with experts on this area and after research in literature we have identified two racial aspects in Section 1.1 that are likely to cause racial disparity in combination with identical blood type matching. We repeat them shortly:

- Stanford et al. (2014) proved that the expected waiting time of a patient is high if the patient has a rare blood type. We expect that the use of identical blood type matching can lead to racial disparity because the blood types are differently distributed among ethnic groups (Zachary and Maryland, 1995).
- The prevalence rate of ESRD is higher among some ethnic minorities which is caused by social or genetic differences among ethnic groups (Zadshire et al., 2005). It also appears that some ethnic groups have a lower propensity to donate kidneys (Morgan et al., 2006). We expect that this can lead to disparity in the average waiting times among blood types and combined with the different blood type distributions, it can cause racial disparity.

In this section we show for both ethnic characteristics how they affect the average waiting time of the ethnic groups when identical blood type matching is used. For each characteristic we discuss the specific assumptions that we use, the way of calculating the average waiting time and the way in which the average waiting time of an ethnic group relates to the parameters that are used in the matching procedure. With this relation we can relate the differences in the average waiting times of two ethnic groups with the ethnic characteristics of both groups and the population. We illustrate the disparity with a numerical example in which the effect of each characteristic on racial disparity is visible.

4.1 Different Blood Type Distributions

The first model explains racial disparity by the different distribution of blood types among ethnic groups in combination with the use of identical blood type matching. We will review the following hypothesis in this section: If the blood type distribution of an ethnic minority is different from the average blood type distribution in the general population, it has a negative influence on the average waiting time of the ethnic minority.

In order to show that this hypothesis holds, we need one extra assumption compared with our standard transplant queue as discussed in section 3.2.1. We assume that people from all blood types have the same propensity to donate and the same need for organs. In reality this is not correct because ethnic groups have a different probability of developing ESRD and a different propensity to donate (Zadshire et al., 2005; Morgan et al., 2006). We examine this situation in Section 4.2. For now we assume that the probability to donate or to develop ESRD is equal among ethnic groups in order to isolate the effect of the different blood type distributions on racial disparity. We start the proof by calculating the average waiting time per ethnic group.

4.1.1 Average Waiting Time per Ethnic Group

As explained in Section 3.2.1 we use multiple transplant queues that cohere with each other in a queuing model to calculate the average waiting time. The model in this section is designed to relate the differences in the average waiting times between two ethnic groups to their different blood type distributions. For this reason, we assume that only identical blood types are necessary for the matching of two kidneys. All other medical requirements such as HLA matching, age and size will not be considered.

The queuing model consists of four transplant queues, one for each blood type $j \in B$, with the set B defined as the set of possible blood types: $B = \{j \mid j = A, B, AB, O\}$. With these queues, we can calculate the average waiting time for a patient with blood type $j \in B$. At this stage, we do not consider ethnic groups. The service and arrival rate depend on the size of the donor and the patient group with blood type $j \in B$. Figure 2 illustrates the queuing model with a separate queue for every blood type.

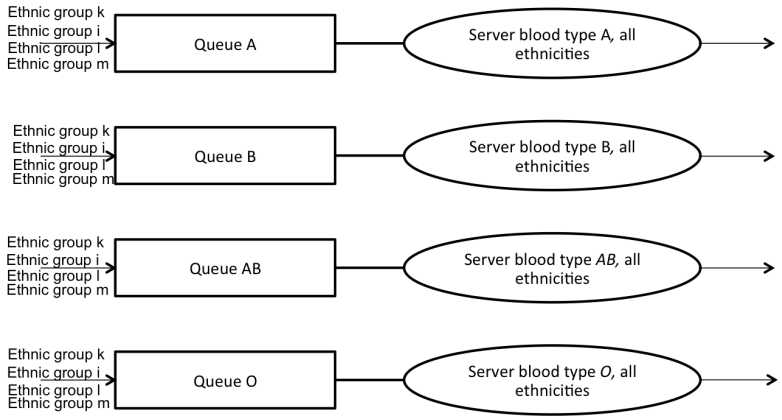

Figure 2: Layout of the queuing model for identical blood type matching with a separate queue and server for every blood type.

In the remainder of this subsection we explain the derivation of the equation that determines the average waiting time per ethnic group in the described queuing model. We start by introducing some notation. For all variables that we use in this thesis, the superscript is used to indicate an ethnic group, the subscript is used to indicate a blood type.

G = A set of ethnic groups: $G = \{i \mid i = 1, 2, \ldots, m\}$
p_j^i = The proportion of the entire population having blood type j and ethnicity i, for all $i \in G$ and $j \in B$ (where $\sum_{i \in G, j \in B} p_j^i = 1$).
p_j = The proportion of the entire population having blood type j for all $j \in B$ (where $\sum_{j \in B} p_j = 1$). It holds that $p_j = \sum_{i \in G} p_j^i$ for all $j \in B$.
p^i = The proportion of the entire population from ethnic group i for all $i \in G$ (where $\sum_{i \in G} p^i = 1$). It holds that $p^i = \sum_{j \in B} p_j^i$ for all $i \in G$.

The service rate and arrival rate per ethnic group and/or per blood type are indicated with a superscript and/or a subscript. The service rate per transplant queue (per blood type) in this model is calculated as $\mu_j = p_j \cdot \mu$ and the arrival rate per queue is equal to: $\lambda_j = p_j \cdot \lambda$. In which μ and λ are the service and arrival rate of the total population. By inserting these equations in Equation (3.1), the average waiting time of a blood type, W_j, is given by

$$W_j = \frac{1}{\mu_j - \lambda_j} = \frac{1}{p_j \cdot \mu - p_j \cdot \lambda} = \frac{1}{p_j \cdot (\mu - \lambda)}. \tag{4.1}$$

We use a weighted average of the four blood types to calculate the average waiting time per ethnic group. We multiply the average waiting time of a blood type by the relative frequency of the blood type in the ethnic group and sum over all blood types. The average waiting time of someone in ethnic group i is then given by

$$W^i = \sum_{j \in B} \frac{1}{p_j \cdot (\mu - \lambda)} \cdot \frac{p_j^i}{p_i} \tag{4.2}$$

This equation does not give a clear insight in racial disparity that is caused by the different blood type distributions. In the next subsection we use this equation to show how the average waiting time of one ethnic group relates to the average waiting time of an other ethnic group.

4.1.2 Relation between Two Ethnic Groups

In this subsection we try to establish a general relation between the average waiting times of two ethnic groups with different blood type distributions when identical blood type matching is used. The first task is to relate the average waiting time of an ethnic group to its input parameters. Some of these depend on the whole population and others on characteristics of the ethnic group. If we know how the average waiting time of an ethnic group is influenced by its input parameters, then we can relate the differences in average waiting time between two ethnic groups to the differences in their characteristics.

The average waiting time in Equation (4.2) depends on both the relative frequencies of the blood types in the population (p_j) as well as the relative frequencies of the blood types per ethnic group ($\frac{p_j^i}{p_i}$). By slightly rewriting Equation (4.2), we can isolate the two parameters that affect the average waiting time of an ethnic group:

$$W^i = \sum_{j \in B} \frac{1}{p_j \cdot \mu - p_j \cdot \lambda} \cdot \frac{p_j^i}{p_i} = \sum_{j \in B} \frac{1}{p_j} \cdot \frac{p_j^i}{p_i} \cdot \frac{1}{\mu - \lambda}. \tag{4.3}$$

If we relate the average waiting time of two ethnic groups the λ and the μ disappear because they are equal for all ethnic groups as they depend on the whole population. This holds if the service and arrival rate per queue solely depend on the relative frequencies of the blood types. The relation between two ethnic groups i and k is given by

$$W^i = \frac{\sum_{j \in B} \frac{1}{p_j} \cdot \frac{p_j^i}{p_i}}{\sum_{j \in B} \frac{1}{p_j} \cdot \frac{p_j^k}{p_k}} \cdot W^k. \tag{4.4}$$

We notice that Equation (4.4) is not so informative. It gives us the quantitative result for the racial disparity if we have all input information but it remains unclear which input parameters exactly cause racial disparity.

We elaborate further on the behavior of the average waiting time with Equation (4.3). The prevalence of one blood type per ethnic group ($\frac{p_j^i}{p_i}$) is divided by the prevalence of the same blood type in the whole population (p_j). So, if the fraction of a blood type in an ethnic group is large but in the whole population small (meaning that $\frac{1}{p_j} \cdot \frac{p_j^i}{p_i}$ is large), it leads to relatively long average waiting times for blood type j in ethnic group i. However, the average waiting time of ethnic group i can still be short if the other blood types compensate for the blood type with the long average waiting time. As such, it remains unclear what the relation is between the average waiting time of two ethnic groups and how this is affected by the relative frequencies of blood types. We will use an other technique called stochastic ordering that is better capable of formalizing the precise relation between two ethnic groups using the relative frequencies of blood types.

The most commonly used method in this theory is the usual stochastic ordering. With this theory we can state that one of two random variables is "bigger" than the other (Sordo, 2008). We know from Equation (4.1) that the relative frequency of a blood type in the population determines the average waiting time of the blood type. We will show that we can use the stochastic ordering theory to relate the differences in average waiting time between two ethnic groups. In order to use this theory, we will later introduce two random variables that can take values equal to the relative frequencies of blood types. We first discuss an example of the stochastic ordering theory.

Example. We start by introducing all relevant variables. We can calculate the relative frequencies of blood types in a population, notated by the value p_j. Imagine that we assign a value equal to p_j to everyone that has blood type j. For example, if the relative frequency of blood type B in the population is 0.15, a patient with blood type B is given the value 0.15. This is just a number that will be given to every patient. The relative frequencies of blood types in the population are given by Table 1.

Table 1: Relative frequencies of blood types in a population.

Relative frequency	**Type A**	**Type B**	**Type AB**	**Type O**
p_j	0.10	0.15	0.45	0.30

We know that the relative frequencies of blood types differ per ethnic group. So, the value p_j is assigned to every patient from ethnic group i with the probability that the patient from ethnic group i has blood type j. Table 2 shows the probability that a person from ethnic group i or k has a certain blood type in this example.

Table 2: Relative frequencies of blood types per ethnic group.

Relative frequency	**Type A**	**Type B**	**Type AB**	**Type O**
$\frac{p_j^i}{p^i}$	0.60	0.30	0.05	0.05
$\frac{p_j^k}{p^k}$	0.30	0.20	0.10	0.40

With Table 1 and Table 2 we can, for example, see that someone from ethnicity i is given the value 0.1 with a probability of 0.6. Furthermore, we introduce the random variables X^i and X^k for two ethnic groups that can take the values p_j from Table 1 with probabilities $\frac{p_j^i}{p^i}$ from Table 2 for all $j \in B$. Now we have formulated all input parameters and can apply the usual stochastic order theory, which states the following (Sordo, 2008): If

$$P(X^i \geq p_j) \leq P(X^k \geq p_j), \tag{4.5}$$

for all $j \in B$, then we can say that $X^i \preceq X^k$ or equivalently that the random variable X^i is smaller than the random variable X^k. Note that the value p_j is just a number that is assigned to every patient. The fact that this value is equal to p_j will appear useful when we apply the theory to the average waiting time problem. We check Equation (4.5) for the current example:

$P(X^i \geq 0.45) \leq P(X^k \geq 0.45)$ (indeed: 0.05 is smaller than 0.10).
$P(X^i \geq 0.30) \leq P(X^k \geq 0.30)$ (indeed: 0.10 is smaller than 0.50).
$P(X^i \geq 0.15) \leq P(X^k \geq 0.15)$ (indeed: 0.40 is smaller than 0.70).
$P(X^i \geq 0.10) \leq P(X^k \geq 0.10)$ (indeed: 1.00 is equal to 1.00).

We conclude this example by stating that the distribution of random variable X^k is larger than the distribution the random variable X^i according to the stochastic ordering theory.

If we know the stochastic order of the two random variables X^i and X^k that take the values p_j with probability $\frac{p_j^i}{p^i}$, then we can use the stochastic order theory to say something about the relation between the average waiting times of two ethnic groups in our model. We will do this with an other property of the stochastic order theory (Shaked and Shanthikumar, 1994). Slightly adjusted for our model this property is given by

$$X^i \preceq X^k \Leftrightarrow E(U(X^i)) \geq E(U(X^k)), \tag{4.6}$$

for all non-increasing functions U.

Equation (4.6) states the following: If the stochastic order indicates that X^k is larger than X^i, the expected value of any non-increasing function $U(X^k)$ is smaller than the expected value of $U(X^i)$. We can now apply this property to our model. If we can construct a non-increasing function $U(X^i)$ that determines the average waiting time of a random person with ethnicity i such that its expectation is the average waiting time of ethnic group i, for all $i \in G$, then we can use Equation (4.6). From Equation (4.1) we know that the average waiting time for a patient with known blood type j is equal to

$$W_j = \frac{1}{p_j \cdot (\mu - \lambda)}. \tag{4.7}$$

As we can see from Equation (4.7), the average waiting time of a blood type is smaller if the relative frequency of the blood type in the population is larger. Equation (4.7) is a non-increasing function in the relative frequency of the blood type. Let $U(X^i)$ be the function that determines the average waiting time of a random patient with unknown blood type. We can replace p_j by the random variable X^i or X^k because we have defined these random variables to take the value p_j with a certain probability. The average waiting time of a patient with a random blood type is then given by

$$U(X^i) = \frac{1}{X^i \cdot (\mu - \lambda)}, \tag{4.8}$$

for all $i \in G$.

We know that Equation (4.7) and as such also Equation (4.8) are non-increasing functions in the relative frequency of the blood type in the population. The expectation of $U(X^i)$ is the average waiting time of ethnic group i, for all $i \in G$.

So far, we have defined the random variables X^i and X^k and a non-increasing function $U(X^i)$ of which the expectation is the average waiting time of an ethnic group. Now we can use Equation (4.6) to draw a conclusion about the expected waiting time differences between two ethnic groups. We have formalized the results in theorem 1.

Theorem 1 Define X^i and X^k as the random variables that assign a value equal to p_j (the relative frequency of blood type j in the population) to every patient with a probability equal to the relative frequency of blood type j in the ethnic group i respectively k, for all $j \in B$. Furthermore, define $U(X^i)$ and $U(X^k)$ as the non-increasing functions that calculate the average waiting time of a patient with a random blood type and ethnicity i respectively k. If the random variables X^i and X^k satisfy the stochastic order relation, $P(X^i \geq p_j) \leq P(X^k \geq p_j)$, for all $j \in B$, then we know that the average waiting time of ethnicity i is larger than the average waiting time of ethnicity k.

Proof 1 If a stochastic order is known between the random variables of two ethnic groups that assign a value equal to the relative frequency of a blood type in the population to every patient, or equivalently if Equation (4.5) holds, we know from Equation (4.6) that the expected value of the non-increasing function $U(X^i)$ is larger for one of the two ethnicities. The non-increasing function $U(X^i)$ determines the average waiting time for a single patient with random blood type and the expected value of $U(X^i)$ is

equal to the average waiting time of an ethnicity, for all $i \in G$.

This mathematical result confirms our hypothesis. We expected that if the blood type distribution of an ethnic group i differs more from the average distribution in the population than the blood type distribution of ethnic group k, ethnic group i would have a longer average waiting time. If the random variable of group i is smaller than k according to the stochastic ordering, the deviation from the average blood type distribution is larger for i than for k. As such we know from theorem 1 that the average waiting time of ethnic group i is longer which confirms our hypothesis. We have to note that there are situations in which the stochastic order theory does not indicate that one of the two distributions is larger and in those cases we can not use theorem 1.

We know that all ethnic groups have different blood type distributions and as such it is more likely that the blood type distributions of minorities differ more from the average than the majority groups. Thus, we can conclude that in most cases different blood type distributions in combination with the identical blood type matching lead to racial disparity. In order to make racial disparity visible, we use a numerical example and show the effect of different blood type distributions on racial disparity.

4.1.3 Practical Example

For the examples in this thesis we use four ethnic groups in the USA: Black Americans, White Americans, Asian Americans and Hispanic Americans. Despite the fact that our demographic data is correct, the examples are not representative for reality. This is partly because we only examine the effect of different blood type distributions on racial disparity and do not include any other criteria from the real algorithm, and partly because we use a stable version of the queue whereas in reality the queues in the USA are unstable (Glorie et al., 2015).

The service rate in our example is equal to 1000, the arrival rate equal to 995. The ρ is almost equal to 1 which we need in order to have a stable waiting list and to reflect the real situation in which donors are scarce. In Table 3 we have listed the proportions of blood types per ethnic group as percentages from the total population (p_j^i) (American Red Cross, 2016):

Table 3: Relative frequencies of blood types per ethnic group as proportions of the whole population.

Ethnicity	**Type A**	**Type B**	**Type AB**	**Type O**
White Americans	24.4%	6.7%	2.4%	27.5%
Black Americans	3.4%	2.5%	0.6%	6.6%
Asian Americans	1.7%	1.5%	0.4%	2.4%
Hispanic Americans	5.6%	1.8%	0.4%	10.2%

By using Equation (4.2) and the given blood type distributions, we can calculate the average waiting times per ethnic group which we listed in Table 4. We have not assigned units to the waiting time as it is not possible to compare these results with empirical data.

Table 4: Average waiting time per ethnic group in the identical blood type matching model.

Ethnicity patient	**Model 1**
White Americans	0.791
Black Americans	0.877
Asian Americans	1.084
Hispanic Americans	0.681

We see in Table 4 that the average waiting time differs per ethnic group. The average waiting times of

the larger ethnic groups (White and Hispanic Americans) is lower than the average waiting times of the smaller ethnic groups (Asian and Black Americans). However, we notice that the the size of an ethnic group is not leading in determining which group has the shortest average waiting time. The Hispanic American group is a lot smaller than the White American group, but has a shorter average waiting time in this model. This can be explained by our theoretical results in which we stated that the deviation of an ethnic group's blood type distribution from the average blood type distribution in the population determines the average waiting time. A very large group is likely to differ less from the average blood type distribution because the blood type distribution of a large ethnic group will have a lot of influence on the average blood type distribution in the population. But despite their size, it is still possible that smaller groups differ even less from the average blood type distribution.

In Table 5 we have listed the racial disparity that arises because of the different blood type distributions and identical blood type matching. We have normalized the average waiting times of Table 4 and used the White American group (the majority group) as index.

Table 5: Racial disparity levels of the ethnic groups compared with the White American group in the identical blood type matching model.

Ethnicity patient	**Model 1**
White Americans	1.00
Black Americans	1.11
Asian Americans	1.37
Hispanic Americans	0.86

We know from Equation (4.4) that the general service and arrival rate do not affect the relation between the average waiting times of two ethnic groups. Therefore, changing the rates does not affect racial disparity in this model. The average yearly mortality rate is 20% (Glorie, 2014), and therefore, an 11% or 37% difference in average waiting time can have a substantial impact on the probability that a minority patient dies while he is on the waiting list.

4.1.4 Unstable Queues

The queues that we have discussed were stable, meaning that the number of arriving donors was larger than the number of arriving patients per time unit. Some queues, such as the transplant queue in the USA, are unstable (Glorie et al., 2015). We will not analyze this situation in all its detail but want to make a brief reference to earlier work of Glorie et al. (2015). For unstable queues we cannot derive the steady state equations because the input parameters change trough time. As such we cannot use the results of the stable queues to derive conclusions for the unstable queues. However, Glorie et al. (2015) showed that you can derive the expected waiting time for a patient who arrives at time t, given the current number of patients at the waiting list. Glorie et al. (2015) stated that identical blood type matching in an unstable queue with the same ESRD and donor rates among ethnic groups would not lead to blood type disparity. As such we expect that identical blood type matching will not lead to racial disparity on the long term in unstable queues. However, a formal proof will not be derived in this thesis.

4.1.5 Concluding Remarks on Different Blood Type Distributions

In this section we have examined the effect of different blood type distributions among ethnic groups in combination with identical blood type matching. We assumed that people from all ethnic groups had the same probability to become a patient and the same propensity to donate a kidney. We have shown that if the blood type distribution of an ethnic group i differs more from the average blood type distribution in the population than ethnic group k, the average waiting time of ethnic group i will be longer. We have proven this with theorem 1. Because ethnic minorities have less influence on the average blood type distribution, it is more likely that the difference with the average blood type distribution

is larger for ethnic minorities than for the majority group in the population. This results in racial disparity unfavorably for ethnic minorities.

In the next model we introduce different service and arrival rates per ethnic group which is a more realistic model of the real situation. The current model is nevertheless very useful because policy makers around the world are trying to improve donation rates of certain ethnic groups (Deedat et al., 2013). The current model shows us, that even if every ethnic group donates the same and has the same ESRD rates, racial disparity still exists when identical blood type matching is used.

4.2 Different ESRD and Donor Rates

In this model we extend the previous model by introducing different probabilities to develop ESRD among ethnic groups and by introducing different rates at which people from different ethnic groups donate. This will reflect the real situation better than equal rates among ethnic groups (Zadshire et al., 2005; Morgan et al., 2006). Our hypothesis is that higher/lower arrival rates and higher/lower donation rates in an ethnic group affect the average waiting times of the blood types that are common within that the ethnic group. This hypothesis is based on the assumptions that identical blood type matching is used and the distribution of blood types among ethnic groups is different.

It is no longer valid to assume that the service and arrival rate only depend on the relative frequency of the blood type. Both the service and the arrival rate still depend on the relative frequency of the blood type, but also on the ethnic groups that are part of the blood type. If a large share of the blood type comes from an ethnic group that donates a lot, the service rate of this blood type is higher. If a large share of the blood type comes from an ethnic group with a high ESRD rate, then the arrival rate of this blood type is higher.

Besides the different probabilities to develop ESRD and the different donation rates, we do not change any of the assumptions used in the previous model. We use the same approach as in Section 4.1: We first derive an equation for the average waiting time of a patient from an ethnic group and later we try to find a relation between the average waiting times of two ethnic groups.

4.2.1 Average Waiting Time per Ethnic Group

The queuing model that we use to calculate the average waiting time is similar to the previous model, we only adjust the service and arrival rates. The rates will now depend on the prevalence of ethnicities in the patient and donor group. We use again the queuing model in which every transplant queue represents one blood type (see Section 4.1.1 for a more detailed description of this model).

The service rate is given by μ_j and is calculated as a combination of all ethnic groups that form the blood type: $\mu_j = \sum_{i \in G} \frac{p_j^i}{p^i} \cdot \mu^i$. The variable μ^i depends both on the size and on the donation rate of ethnic group i. If we multiply μ^i with the relative frequency of blood type j within ethnic group i, it results in the number of donors that come from ethnic group i with blood type j, per time unit. The arrival rate looks similar: $\lambda_j = \sum_{i \in G} \frac{p_j^i}{p^i} \cdot \lambda^i$. The variable λ^i depends both on the size and on the prevalence rate of ESRD in ethnic group i. Again if we multiply λ^i with the relative frequency of blood type j within ethnic group i, it results in the number of patients that come from ethnic group i with blood type j, per time unit. In order to calculate both rates per blood type, we sum over all ethnic groups. The average waiting time of a blood type j is then given by

$$W_j = \frac{1}{\sum_{i \in G} \frac{p_j^i}{p^i} \cdot \mu^i - \sum_{i \in G} \frac{p_j^i}{p^i} \cdot \lambda^i} = \frac{1}{\sum_{i \in G} \frac{p_j^i}{p^i} \cdot (\mu^i - \lambda^i)}. \tag{4.9}$$

And by using a weighted average of the four blood types we can calculate the average waiting time of an ethnic group:

$$W^i = \sum_{j \in B} \frac{1}{\sum_{i \in G} \frac{p_j^i}{p^i} \cdot (\mu^i - \lambda^i)} \cdot \frac{p_j^i}{p^i}. \tag{4.10}$$

The average waiting time equation per ethnic group depends on more factors than in the previous model which makes it harder to find a relation between two ethnic groups.

4.2.2 Relation between Two Ethnic Groups

The analytical relation between the average waiting times of different ethnic groups is important in order to say something general about racial disparity caused by the different blood type distributions and different arrival and service rates. We use the same approach as in Section 4.1.2: we start by relating the average waiting time to its input parameters and then we use this relation to explain the differences between the average waiting times of two ethnic groups.

The average waiting time for a patient with blood type j depends on $\frac{p_j^i}{p^i}$ for all $i \in G$, and the service and donation rates of all ethnic groups. Given the average waiting time of the blood types, the average waiting time of an ethnic group i is determined by the relative prevalence of all blood types in ethnic group i ($\frac{p_j^i}{p^i}$), for all $j \in B$. A quantitative relation between the average waiting time of two ethnic groups looks similar to the one found in the first model and is given by

$$W^i = \frac{\sum_{j \in B} \frac{1}{\sum_{i \in G} \frac{p_j^i}{p^i} \cdot (\mu^i - \lambda^i)} \cdot \frac{p_j^i}{p^i}}{\sum_{j \in B} \frac{1}{\sum_{k \in G} \frac{p_j^k}{p^k} \cdot (\mu^k - \lambda^k)} \cdot \frac{p_j^k}{p^k}} \cdot W^k. \tag{4.11}$$

In contrast to the previous model, the relative frequency of a blood type is not the only factor that determines the arrival and service rates, making it more difficult to explain the relation between the input parameters and the average waiting time of an ethnic group. Whereas we could say in the previous model that the smallest blood type has the longest average waiting time, we can now only state that the blood type with the largest difference between the arriving number of donors and patients per time unit, has the longest waiting time. If an ethnic group has a large share of this blood type, it has a long waiting time. The difference between the number of arriving donors and patients per time unit can be caused by a few reasons: It can be that a blood type is large or small, it is possible that the blood type is made up of ethnic groups that develop ESRD a lot (or a little) or the blood type can be made up of ethnic groups that donate a lot (or a little). It is always a combination of these effects and it is impossible to isolate one of these effects as the cause of racial disparity.

We make this qualitative interpretation of Equation (4.11) more formal by using the stochastic ordering theory. Again we need random variables to use the stochastic ordering theory. These random variables must, in order to say something about the average waiting time of an ethnic group, take values that can determine the average waiting time of a blood type. In the previous model, the random variables X^i and X^k could take values equal to the relative frequencies of blood types in the population because we could relate the average waiting time of a blood type to its relative frequency in the population. In the current model we can relate the average waiting time of a blood type j to the difference in arriving donors and patients with blood type j, per time unit. As explained earlier, it is not possible to isolate one of the effects that cause this difference as source of different average waiting times. As such, we will assign values equal to the difference between the number of arriving donors and patients per blood type, per time unit to the random variables in this model.

To avoid any confusion, we notate these new random variables as Y^i and Y^k and the values that they can take as e_j. The variable e_j is calculated as $e_j = \sum_{i \in G} \frac{p_j^i}{p^i} \cdot (\mu^i - \lambda^i)$, which is the difference in arriving donors and patients per blood type, per time unit. The probability that Y^i or Y^k assigns the value e_j to a patient is still equal to the relative frequency of blood type j within ethnic group i or k. In order to use the stochastic ordering property (see Equation (4.6)), we need a non-increasing function that uses the random variables Y^i and Y^k and determines the average waiting time of a patient with a random blood type.

In Equation (4.9) we calculate the average waiting time of a patient with known blood type j. In this equation the difference between the number of arriving donors and patients per blood type, per time unit must be known. We have previously defined this difference as e_j and as such we change the average waiting time equation for a person with known blood type j into

$$W_j = \frac{1}{\sum_{i \in G} \frac{p_j^i}{p^i} \cdot (\mu^i - \lambda^i)} = \frac{1}{e_j}. \tag{4.12}$$

This is a non-increasing function in the difference between the number of arriving patients and donors per blood type, per time unit. If the difference between the arriving patients and donors per time unit gets bigger, the average waiting time of a blood type decreases. We will formulate a non-increasing function $V(Y^i)$ based on Equation (4.12) that determines the average waiting time of a patient with unknown blood type for every ethnic group $i \in G$. We have defined the random variable Y^i to take the values of e_j, and as such we can change equation (4.12) into

$$V(Y^i) = \frac{1}{Y^i}, \tag{4.13}$$

for all $i \in G$.

We have defined all necessary parameters and can formulate a theorem that relates the difference in arriving patients and donors per time unit to racial disparity, similar to the proof in Section 4.1.2.

Theorem 2 Define Y^i and Y^k as the random variables that assign a value equal to e_j (the difference between the arriving number of patients and donors per blood type, per time unit) to every patient with a probability equal to the relative frequency of blood type j in the ethnic group i respectively k, for all $j \in B$. Furthermore, define $V(Y^i)$ and $V(Y^k)$ as the non-increasing functions that calculate the average waiting time of a patient with a random blood type and ethnicity i respectively k. If the random variables Y^i and Y^k satisfy the stochastic order relation, $P(Y^i \geq e_j) \leq P(Y^k \geq e_j)$ for all $j \in B$, then we know that the average waiting time of ethnicity i is larger than the average waiting time of ethnicity k.

Proof 2 If a stochastic order is known between the random variables of two ethnic groups that assign a value equal to the difference in the number of arriving donors and patients of a blood type to every patient, or equivalently if Equation (4.5) holds. We know from Equation (4.6) that the expected value of the non-increasing function $V(Y^i)$ is larger for one of the two ethnicities. The non-increasing function $V(Y^i)$ determines the average waiting time for a single patient with random blood type and the expected value of $V(Y^i)$ is equal to the average waiting time of an ethnicity, for all $i \in G$.

We can conclude that different ESRD rates and donor rates are likely to contribute to the disparity. However, it remains analytically impossible to show by which of the effects in Equation (4.11) racial disparity is exactly caused. It is always a combination of donor rates, ESRD rates and distribution of blood types among ethnic groups. To clarify our results more, we have again made a numerical example based on the demographics of the USA.

4.2.3 Practical Example

We use the demographic data from the USA but again the results are not representative for the real disparity in the USA due to all assumptions. The sizes of ethnic groups and the blood type distributions per ethnic group are the same as used in the previous example. In Table 6 we have listed the proportions of the ESRD rates and donor rates per ethnic group. These are calculated as the real proportions of the total ESRD and donor rates in the USA (Organ Procurement and Transplantation Network (OPTN), 2016*a*):

Table 6: ESRD and Donor rates for the major ethnic groups in the USA.

Ethnicity patient	**% of population**	**% of ESRD patients**	**% of donors**
White Americans	62.24%	44.99%	69.27%
Black Americans	13.27%	29.75%	13.06%
Asian Americans	6.12%	7.20%	3.45%
Hispanic Americans	18.37%	17.98%	14.20%

As we can see from Table 6, White Americans donate on average more and develop ESRD less, whereas Black Americans develop a lot more ESRD and donate less. In Table 7 we present the results for the average waiting times of all ethnic groups calculated with Equation (4.10). We have used a total service rate of 1000 and a total arrival rate of patients of 865 in the population. The service rate of an ethnic group i is calculated as the percentage of donors from ethnic group i (see Table 6) multiplied with the total service rate in the population. The arrival rate of an ethnic group i is calculated as the percentage of patients from ethnic group i (see Table 6) multiplied with the total arrival rate in the population. We can not choose a higher arrival rate (which would result in a more realistic view) because then the model would become unstable for some of the transplant queues. We have also included the results of model 1 (with the same λ and μ as the new model) to compare the two models:

Table 7: Average waiting time per ethnic group for the identical blood type matching model with equal ESRD and donor rates (Model 1) and different ESRD and donor rates (Model 2).

Ethnicity patient	**Model 1**	**Model 2**
White Americans	0.165	0.293
Black Americans	0.268	0.325
Asian Americans	0.356	0.402
Hispanic Americans	0.149	0.252

All waiting times have increased compared with the first model. This can be explained by a shortage of type B donors, resulting in a long average waiting time for this blood type. Also type AB has a larger shortage but is less represented in the ethnic groups and as such, has less influence on the average waiting time of the ethnic groups. The groups with a relative large percentage of type B patients (Black and Asian Americans) experience the largest increase in average waiting times in the new model. Overall we see that this second model is showing more racial disparity than model 1. In Table 8 we have listed the racial disparity levels of all ethnic groups compared with the White American population for both models that use identical blood type matching.

Table 8: Racial disparity per ethnic group for the identical blood type matching model with equal ESRD and donor rates (Model 1) and different ESRD and donor rates (Model 2).

Ethnicity patient	**Model 1**	**Model 2**
White Americans	1.00	1.00
Black Americans	1.11	1.62
Asian Americans	1.37	2.15
Hispanic Americans	0.86	0.90

In the first model, Black Americans had an 11% longer average waiting time, whereas in the second model this has increased to a 62% longer average waiting time. Also the disparity for the Asian American population has increased a lot, from 37% to 115%. These differences might have a large impact on the probability to survive ESRD as we know that the mortality rate of patients waiting for a kidney is at least 20% (Glorie, 2014). As we can see in Equation (4.11), the mutually disparity is dependent on the average service and arrival rate. If we change the average service or arrival rate in the model, the disparity changes. Whenever we decrease the difference between the service and arrival rate (ensuring the ρ becomes closer to 1), the observed disparity increases. Figure 3 shows the relation between the disparity and the arrival rate of patients, assuming a constant service rate of 1000.

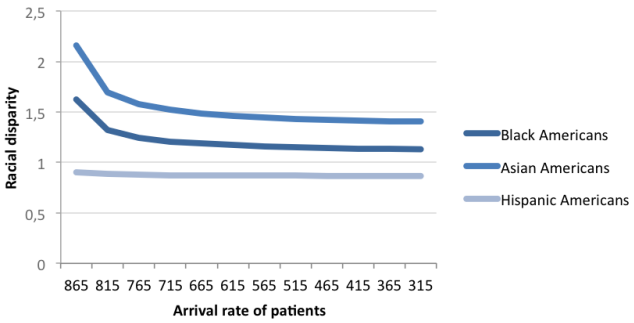

Figure 3: Relation between the racial disparity of the minority groups and the total arrival rate of patients in the population with equal service rate.

We clearly see that the disparity increases whenever the kidneys become more scarce. We can not model a higher arrival rate than 865 because some queues would become unstable. As we know that in reality kidneys are very scarce, we must treat our current results as a conservative estimate of racial disparity

4.2.4 Unstable Queues

Just as we did in the previous section, we briefly describe the effect of different ESRD and donor rates for unstable queues. For the situation in Section 4.1.4, identical blood type matching did not lead to blood type disparity on the long term according to Glorie et al. (2015). We expect that it leads to blood type disparity with the current assumptions because the ESRD and donor rates differ per blood type. As such, the queues grow at different rates. Different growth rates of the average waiting times per blood type cause blood type disparity and can potentially lead to racial disparity with the different blood type distributions. We will not derive a formal proof of this hypothesis in this thesis.

4.2.5 Concluding Remarks on Different ESRD and Donor Rates

In this section we have shown that racial disparity increased by including different ESRD and donor rates in combination with different blood type distributions and identical blood type matching. How-

ever, it is not possible to relate racial disparity between two ethnic groups exactly to the input parameters of the average waiting time equation. We can only state in general that when a certain ethnic group has a large share of a blood type with a long average waiting time, the ethnic group has a long average waiting time. It is impossible to say what exactly causes a blood type j to have a long average waiting time due to the number of possible reasons which all cohere with each other. This can be the relative frequency of the blood type j in the population, the donor rate or the ESRD rates of ethnic groups that are part of blood type j.

Based on our theoretical results and the example, we can conclude in general that the different ESRD and donor rates among ethnic groups combined with different blood type distributions among ethnic groups lead to racial disparity, if identical blood type matching is used.

5 Showing Racial Disparity with HLA Type Matching

In the first two models we considered identical blood types to be the only criterion that determined if a donor could be matched with a patient. In reality, several other criteria determine the success of a transplantation. One these other criteria, a compatible HLA type match, has been mentioned before as a potential cause of racial disparity (Takemoto et al., 2004). We incorporate HLA type matching in the queuing model of this section in order to show the relation between HLA types and racial disparity. We use the identical blood type model with different blood type distributions and different ESRD and donor rates, adjusted with the HLA type criterion. We answer the following question:

How can we extend the identical blood type model with HLA type matching in order to show racial disparity caused by different HLA types among ethnic groups?

This section especially focuses on finding a way of modeling HLA types analytically, and less on formalizing the relation between the input parameters and racial disparity. This is due the high complexity of the HLA type system which, as we shall see, makes it difficult to draw conclusions from the model in an analytical way.

An extensive description of the effect of HLA types on the matching of a donor and patient can be found in Section 2. Briefly stated HLA types have two functions in the matching of the patient and donor:

- First, the HLA types regulate the rejection of foreign body cells. A patient can develop antibodies against certain HLA types which causes the patient to reject a kidney that expresses these HLA types (Valenzuela and Reed, 2013). In the case of this immediate rejection, the patient is not considered at all for transplantation of the available donor.
- Besides this immediate rejection, it also appears that a better HLA match between the patient and donor increases the graft survival rates (Takemoto et al., 2004). Therefore, matches with less HLA allele mismatches are preferred, but not necessary. HLA types are largely determined by ethnicity and as such matches within the same ethnic group are more likely (Pidala et al., 2013).

As we introduce a suitable HLA type match as a criterion to match a donor with a patient we need to adjust our assumptions from the identical blood type model. We start this section with an overview of the ideal queuing model for the HLA type matching. We will see that this model is very complex and as such it is not possible to construct a queuing model for this ideal approach. Next, we we list our assumptions to overcome the difficulties of the ideal model. These assumptions are used in two approaches to calculate the average waiting time per ethnic group that both have their advantages and drawbacks. After the models have been constructed, we derive the average waiting time equations and relate the average waiting times of two ethnic groups to see which parameters affect racial disparity. This relation will not be so informative as the one we found for the identical blood type matching model because of the complexity and the assumptions of the two approaches. We end the section with a numerical example.

5.1 HLA Queuing Model

We still assume that an identical blood type is necessary in order to make a match between a patient and donor. With identical blood type matching we could easily exclude combinations that lead to rejection of the donor, whereas with HLA types a match can be suitable on the short term but lead to a negative impact on the graft survival rates on the long term (Takemoto et al., 2004). It is impossible to model all the different combinations of HLA types and their long term effects on racial disparity without using simulation. Therefore, we assume that all matches with a zero allele mismatch between the donor and patient can and will be made. We do not look at any long term performance issues of the kidney.

The probability that the HLA types of a patient and a donor are compatible depends on the ethnicity of both the donor and patient (Beatty et al., 1995). That means that we can calculate a probability that a suitable match is found for every patient and donor pair, based on their ethnicity. These probabilities have been derived by Beatty et al. (1995) in Table 9 for marrow bone transplants which also need a compatible HLA type match. The probabilities are calculated as the average probability that the patient and donor have a zero allele HLA mismatch and as such could potentially be a match in our model. These probabilities are based on an extensive simulation model with 500.000 instances.

Table 9: Average probabilities that a patient from an ethnic group can accept a donor of an (other) ethnic group based on a zero allele mismatch in the HLA types (Beatty et al., 1995).

Ethnicity patient	**White Americans**	**Black Americans**	**Asian Americans**	**Hispanic Americans**
White Americans	0.77	0.52	0.43	0.68
Black Americans	0.18	0.61	0.08	0.26
Asian Americans	0.29	0.15	0.78	0.30
Hispanic Americans	0.58	0.42	0.35	0.69

From Table 9 we can, for example, derive that White Americans accept 43% of the Asian American donors on average. The total service rate (donor rate) for a blood type per time unit is μ_j and is calculated just like in Section 4.2.1 as a combination of the donor rates of the ethnicities that are part of the blood type: $\mu_j = \sum_{i \in G} \frac{p_j^i}{p^i} \cdot \mu^i$. Given μ_j and the composition of ethnicities in the donor pool, we can calculate the average number of suitable donors per time unit for each ethnicity with Table 9. The fraction of the total donor rate, per blood type, that is suitable for a patient from ethnic group i with blood type j is notated as d_j^i. So, if a random donor arrives, the probability that it is suitable for a patient with ethnicity i and blood type j is equal to d_j^i.

In the next subsection we describe the ideal approach to model HLA types, that as we will see, is too complex to use in a queuing model.

5.1.1 Ideal HLA Model

The ideal model has one queue filled with patients of all ethnicities for every blood type j. We still use the identical blood type criterion so we split the donors and patients based on their blood type. Whenever a donor becomes available for the first patient in the queue of blood type j, the probability d_j^i determines if this patient gets the donor, in which i is the ethnicity of the patient in front of the queue. If the first patient does not get the donor, it should become available for the next patient in line for which again the probability d_j^i decides if the kidney is suitable. This continues until someone gets the kidney. When someone is rejected, the patients stays at the same place in the queue for the next kidney. This comes down to a model in which every patient in the queue has a certain probability to get the kidney, dependent on the people in front of him and the ethnicity of the donor. However, to the author's knowledge, no analytical expression is known for the average waiting times in queuing models where the service is offered to anyone in one queue with a certain probability. The different

probabilities in the queue as well as the fact that the kidney can be offered to anyone in the queue make the ideal approach very difficult to analyze. In the following we discuss the extra assumptions that are needed in order to construct a model that can serve as approximation of the ideal model.

5.1.2 Extra Assumptions

The first difficulty that the kidney is offered to anyone in the queue at the same time, can be solved by assuming that the kidney is offered only to the first patient in the queue as was normal in our transplant queues before. The second difficulty arises because the probability that a kidney is suitable for a patient differs per ethnic group. We know that a patient from ethnicity i with blood type j has a probability of d_j^i that the next available kidney is suitable. This probability depends on the blood type and the ethnicity of the patient. This means that we would have to use a different probability distribution for each ethnicity i in one queue. An analytical expression for the average waiting time per ethnic group in such a model does not exist to the author's knowledge. In order to solve this second difficulty we will use a different queue for every ethnicity i per blood type j. In this way, every person in a queue has the same probability to get the kidney if the patient arrives at the front of the queue. As we will see, it is easier to derive an analytical expression for the average waiting time in this model.

However, the next problem arises: in reality the kidneys are not mutually exclusive among patients from different ethnic groups. If both the donor and the patient have the same blood type, a donor which is suitable for ethnicity i may also be suitable for a patient with ethnicity k (Beatty et al., 1995; Pidala et al., 2013). It is unknown for how many ethnicities a single donor is suitable. In the previously discussed ideal model this was not a problem as a donor could be suitable for multiple ethnicities and was given to the first in line with a certain probability. If we use a separate queue for every ethnic group $i \in G$ per blood type j, for all $j \in B$, we have to find a way to divide the kidneys among the queues and take the exclusivity of kidneys into account. Notice that we have already used one extreme of exclusivity in the identical blood type matching model where we assumed that all kidneys could be used by anyone in the queue. We now introduce two new approaches that both treat the exclusivity of kidneys among ethnic groups differently.

The first approach is a queuing model with one server per blood type j but with a separate queue for every group of patients from ethnic group i with blood type j. A certain probability determines which queue is selected to receive the next available service. The second approach is a queuing model with multiple servers and queues per blood type j. One queue and server for the group of patients with ethnicity i and blood type j. The same probability as in the first approach is used as a fraction that determines how many donors are given to each server. We elaborate more extensively on these two different approaches and how they deal with the exclusivity of kidneys in Section 5.1.4. First we notice that for both approaches we have to define a probability or fraction that when a kidney becomes available, a certain queue (or ethnicity) is selected to get this kidney. Note that this is not the same as the suitability probability d_j^i as a kidney can be suitable for multiple ethnicities. We define this probability to be the selected for the next kidney as h_j^i.

5.1.3 Calculation of the Selection Probability

In this section we discuss the way in which we calculate h_j^i in this model. This is not an official way of calculating the probability to select an ethnic group but an approximation method in order to approach the ideal model.

The probability that a queue or ethnicity i is selected for the next kidney must depend on the arrival rate of patients with ethnicity i, as queues with a larger arrival rate need more donors. The probability must also depend on the percentage of donors that is suitable for ethnicity i (d_j^i), as queues that accept more donors should have a higher probability that they are selected for the next kidney. So, in order to calculate the selection probability, we have to use the sizes of the ethnic groups as well as the average

percentage of donors that is suitable for them. In the ideal model, the kidney could be refused by one person of ethnicity i but accepted by the next recipient candidate with the same ethnicity i. However, as will appear to be important for the calculation of h_j^i, we have assumed that every ethnicity only has one chance to get the kidney. If the kidney is refused by one person of ethnicity i, other persons in the queue with the same ethnicity i are not considered anymore for the available kidney. We have calculated h_j^i as follows:

Think of the selection process as drawing a ball out of box, in which every ethnic group has one ball when we start. Every ethnic group has a probability to be drawn out of the box determined by the relative size of the ball compared to the other balls (or equivalently the relative frequency of the ethnic group in the patient pool). If a ball is drawn, a number on the ball determines if the ball is correct (or equivalently if the donor is suitable for the ethnic group according to d_j^i). If the ball is not correct (or equivalently if the donor cannot be given to the ethnic group), the ball is thrown away and a new ball is chosen. This continues until an ethnic group is selected or if all ethnic groups have declined the kidney. We notice that according these rules an ethnic group can be selected to get the next kidney in a few different ways: an ethnic group i can be selected with the first ball, with the second ball (if the first ball is rejected by an other ethnic group), with the third ball (if the first two balls are rejected by two other ethnic groups) or with the fourth ball (if the first three balls are rejected by three other ethnic groups). The sum of the probabilities belonging to all these different ways is will be notated as q_j^i. The variable q_j^i is calculated with Equation (5.1). We use q_j^i in Equation (5.2) to get the final selection probability h_j^i. In order to avoid any confusion we notate the four different ethnic groups by a different letter, i,k,l,m in Equation (5.1).

The probabilities of all four possibilities are notated on separate lines in Equation (5.1) in order to avoid confusion. The first line represents the probability if ethnic group i is selected with the first ball, the second line for the second ball, etc.

$$\begin{aligned} q_j^i = & \frac{p_j^i}{\sum_{i\in G} p_j^i} \cdot d_j^i + \\ & \sum_{k\in G, k\neq i} \frac{p_j^k}{\sum_{k\in G} p_j^k} \cdot (1-d_j^k) \cdot \frac{p_j^i}{\sum_{i\in G, i\neq k} p_j^i} \cdot d_j^i + \\ & \sum_{k\in G, k\neq i} \sum_{l\in G, l\neq i,k} \frac{p_j^k}{\sum_{k\in G} p_j^k} \cdot (1-d_j^k) \cdot \frac{p_j^l}{\sum_{l\in G, l\neq k} p_j^l} \cdot (1-d_j^l) \cdot \frac{p_j^i}{\sum_{i\in G, i\neq k, i\neq l} p_j^i} \cdot d_j^i + \\ & \sum_{k\in G, k\neq i} \sum_{l\in G, l\neq i,k} \frac{p_j^k}{\sum_{k\in G} p_j^k} \cdot (1-d_j^k) \cdot \frac{p_j^l}{\sum_{l\in G, l\neq k} p_j^l} \cdot (1-d_j^l) \cdot \frac{p_j^m}{\sum_{m\in G, m\neq k, m\neq l} p_j^m} \cdot (1-d_j^m) \cdot d_j^i. \end{aligned} \tag{5.1}$$

In this approach, around 5% of the kidneys are rejected by all ethnic groups, whereas we have assumed in Section 3.2.1 that all offered kidneys are given to a recipient candidate. We will divide these rejected kidneys among the ethnic groups according to the relative share of all accepted kidneys per ethnic group. So, if an ethnic group, for example, has been given 60% of all accepted kidneys based on q_j^i, we assume they will be given 60% of the rejected kidneys. The calculation of h_j^i is then finally given by

$$h_j^i = q_j^i + \frac{q_j^i}{\sum_{i\in G} q_j^i} \cdot (1 - \sum_{i\in G} q_j^i). \tag{5.2}$$

We can now model every ethnic group as a separate queue of patients that all have a different probability to be selected for the next kidney. We use this information in two different queuing models that both have their advantages and drawbacks.

5.1.4 Two Approaches to Model HLA Types

In this section we discuss the layout of two approaches of the ideal model and the way in which the models treat exclusivity of kidneys among ethnic groups.

Approach 1: Probabilistic service order. In this queuing model we do not use the FCFS principle anymore but instead a probabilistic service order. Each blood type j has one server for all potential recipients with blood type j. Each patient with ethnicity i and blood type j is placed in a separate ethnicity queue, for all $i \in G$ (see Figure 4). The service rate is still exponentially distributed and different per blood type due to the different sizes and donation rates of the ethnic groups that are part of the blood type. The arrival rate is also exponentially distributed but different for all ethnic groups due do their different sizes and ESRD rates. Every time that the server becomes empty, the first person in the queue of ethnic group i is being served with probability h_j^i for all $i \in G$ if all queues are nonempty. This probability needs to be adjusted to include only the nonempty queues. If all queues, except the queue from ethnic group i, are empty, ethnic group i is served with probability 1. If, for example, only the two queues from ethnic group i and k are nonempty, the probability that ethnic group i is selected is equal to $\frac{h_j^i}{h_j^i+h_j^k}$. We will have to calculate the probability that queue i is selected for any composition of nonempty and empty queues. The exact calculation of this probability is given by Equation (5.4), which we will discuss later in more detail. Note that the suitability probability is used to calculate the selection probability h_j^i (see Section 5.1.3) and as such, we incorporate the HLA compatibility in the queuing model.

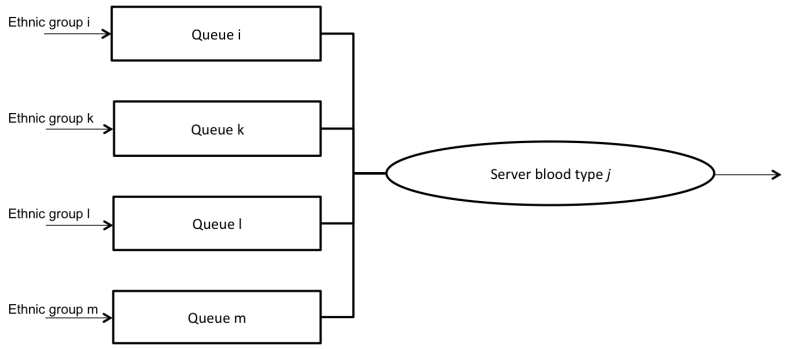

Figure 4: The layout of the probabilistic service model for one blood type in which every blood type has one server and every ethnic group has one queue per blood type.

The donors are now assumed to be only partly exclusive among ethnic groups. If a selected queue is empty, the kidney is given to one of the other queues based on their respective probabilities. This is not entirely correct because we used the suitability probabilities (d_j^i) to determine the selection probabilities (h_j^i). If a group i is selected for the kidney, we already took the suitability probabilities into account and in practice it would not always be possible to give the kidney to one of the other groups. However, it is also not entirely incorrect because it is not impossible that the kidney is suitable for the other group. We do not know how many donors are exclusive suitable for one ethnic group so we must treat the degree of exclusivity in this model as an approximation of the real situation.

Unfortunately, to the author's knowledge, so far nobody has developed an analytical way of calculating the exact average waiting time per queue in a probabilistic service model with above stated assumptions. However, we can use an estimation method that calculates the average waiting time per queue for the probabilistic priority service model which as we shall see is exactly the same as the probabilistic service model without priorities (Jiang et al., 2002).

Approach 2: Multiple M/M/1 queues. The second model uses the same selection probability (h_j^i) that a kidney becomes available for a certain ethnic group. We will not only use a different queue for all patients from ethnic group i with blood type j, but also a different server for all patients from ethnic group i with blood type j (see Figure 5). Within these queues we use a FCFS principle. The service rate per ethnic group i is equal to the share of donors with blood type j that according to h_j^i are selected for ethnic group i. This share is calculated as: $h_j^i \cdot \mu_j$. The arrival rates depend on the size and ESRD rates of the ethnic groups. All other assumptions stay the same as in the identical blood type model.

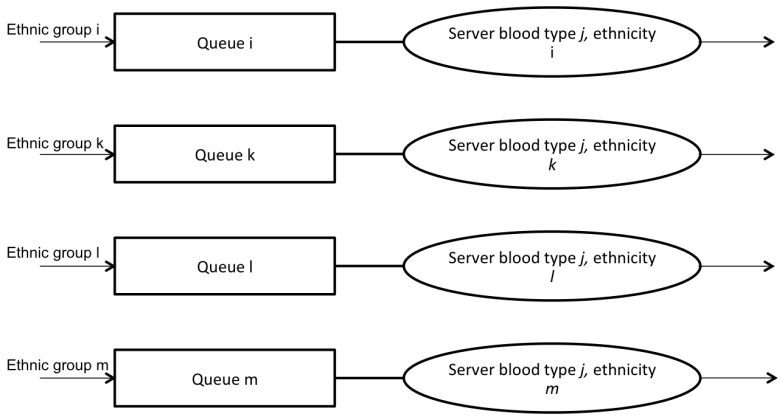

Figure 5: The layout of an identical ethnicity matching model for one blood type in which every ethnicity has one queue and server per blood type.

This approach is an other extreme case of the degree of exclusivity. All donors are now mutually exclusive among ethnic groups. In the previous approach a queue could get a kidney that in reality was sometimes not suitable (if the "selected" queue was empty), in this model we restrict the number of possible kidneys per queue beforehand which makes all donors mutually exclusive.

We notice that we now have three models of which two are extremes regarding the degree of exclusivity of donors: First, we have the identical blood type model in Section 4.2 in which all donors could be used by any ethnic group. The other extreme is the second HLA type approach in which all donors are mutually exclusive among ethnic groups. The first HLA type approach, with the probabilistic service discipline, has a degree of exclusivity somewhere in between the two extremes and will probably be the best approximation of the real situation.

5.2 Average Waiting Time per Ethnic Group

In the previous subsection we have introduced two queuing models that enable us to approximate the average waiting time per ethnic group with HLA type matching. For both models we derive an equation to calculate the average waiting time per model.

Approach 1: Probabilistic service order. We will calculate the average waiting time in the probabilistic service model by using a slightly different model with a probabilistic priority service order (Jiang et al., 2002). We will first prove that this model with priorities is the same as the probabilistic service model without priorities and afterwards we discuss the calculation of the average waiting time.

The probabilistic priority model has the same assumptions as the model that was described in Section 5.1.4 except that every time when a kidney becomes available, all nonempty queues are considered for the next kidney in a specified order. First, the queue i with the highest priority is considered and the

kidney is accepted with a certain probability a_j^i (this probability is defined as p in the work of Jiang et al. (2002)). The second nonempty queue k in the priority cycle is considered if the kidney is rejected by the first queue with a probability $1 - a_j^i$ and the kidney is accepted by this queue with a probability of a_j^k. The queue with the lowest priority is considered for the kidney if all other queues have rejected the kidney and it accepts the kidney with a probability of 1 in order to assure that the kidney is always given to an ethnic group. In this way, we can calculate for every nonempty queue a certain probability that it gets a kidney depending on it's priority level, it's acceptance probability a_j^i and the acceptances probabilities of all queues with a higher priority. This probability, called ω in the work of Jiang et al. (2002), is by definition equal to our previously defined probability to get a kidney h_j^i. So, by choosing the right acceptance probabilities a_j^i and the corresponding priority levels, we can get any distribution of probabilities h_j^i. Only the final probabilities to get a kidney (h_j^i) are relevant for the calculation of the average waiting time, so we do not need to use the probabilities a_j^i or the priority levels (Jiang et al., 2002). As such, we can conclude that we can use the probabilistic priority model to calculate the average waiting time in the probabilistic service model without priorities.

The probabilistic priority model is a highly complex system that has not been studied in all its detail yet and exact methods to determine the average waiting time per queue do not exist. However, an estimation method has been derived that has a small estimation error for the average waiting time (Jiang et al., 2002). We will first derive the average waiting time equation, and later discuss the estimation error. Jiang et al. (2002) have only derived the equation for approximating the average waiting time in the case of two different classes (ethnicities), however, we have extended their model to calculate the average waiting time for more ethnicities. The approximation of the average waiting time of an ethnic group i with blood type j, derived by Jiang et al. (2002), is given by

$$W_j^i \approx \frac{\frac{1}{\mu_j} \cdot (1 + \frac{1-B_j^i}{B_j^i})}{1 - \rho_j^i (1 + \frac{1-B_j^i}{B_j^i})} + \frac{1}{\mu_j}. \tag{5.3}$$

Equation (5.3) corresponds with Equation (16) in the work of Jiang et al. (2002), except that it is adjusted with the parameters as defined in this thesis. We explain all parameters of Equation (5.3) in more detail. The variable μ_j is the service rate of the blood type and is defined as a composition of the service rates that are part of the blood type. It is calculated as $\mu_j = \sum_{i \in G} \mu_j^i$. The variable μ_j^i depends on the size and donor rate of ethnic group i. The variable ρ_j^i is calculated as $\rho_j^i = \frac{\lambda_j^i}{\mu_j}$.

The variable B_j^i is the probability that, if the queue of ethnic group i is nonempty, it gets the kidney. This depends on the selection probability h_j^i of ethnic group i and the probability that other queues of ethnic groups are nonempty (Jiang et al., 2002). The probability that the queue of an ethnic group is nonempty is given by the variable M_j^i (see Equation (5.5)). The variable B_j^i for four ethnic groups is then given by Equation (5.4). To avoid any confusion we have split the equation over multiple lines. A more extensive explanation of Equation (5.4) is given below the equation. The probability that ethnic group i with blood type j gets a kidney, given that the queue of patients from ethnic group i with blood

type j is nonempty, is calculated as:

$$\begin{aligned} B_j^i = & \frac{h_j^i}{\sum_{r\in G} h_j^r} \cdot \prod_{r\in G, r\neq i} M_j^r + \\ & \sum_{k\in G, k\neq i} \frac{h_j^i}{\sum_{r\in G, r\neq k} h_j^r} \cdot \prod_{r\in G, r\neq i,k} M_j^r \cdot (1-M_j^k) + \\ & \sum_{k\in G, k\neq i} \sum_{l\in G, l\neq i, l>k} \frac{h_j^i}{\sum_{r\in G, r\neq k,l} h_j^r} \cdot \prod_{r\in G, r\neq i,k,l} M_j^r \cdot (1-M_j^k)\cdot(1-M_j^l) + \\ & (1-M_j^k)\cdot(1-M_j^l)\cdot(1-M_j^m). \end{aligned} \tag{5.4}$$

The first line represents the probability that the queue of ethnic group i is selected when all four queues are full which we calculate as the probability that the three other queues are full multiplied with the selection probability of ethnic group i. The second line is the sum of the probabilities that group i is selected when one other queue is empty. We calculate this as the probability that one queue is empty and the other two nonempty ($\prod_{r\in G, r\neq i,k} M_j^r \cdot (1-M_j^k)$), multiplied with the probability that ethnic group i is selected among the nonempty queues. The third line does the same for two empty queues and the fourth line for three empty queues (meaning that only the queue of ethnic group i is full). In the summation of the third line we have used the statement $l > k$ which assumes that the ethnic groups are numbered. This is true as we have defined the set of ethnic groups in Section 4.1 as: $G = \{i \mid i = 1, 2, \ldots, m\}$. We have incorporated this statement because otherwise certain combinations would be counted twice in the summation.

The variable M_j^i is defined as the probability that the queue of ethnic group i with blood type j is nonempty. This probability is calculated as a solution of Equations (11) and (12) in the work of Jiang et al. (2002). Only two queues are considered in their work, however we have adjusted the solution to accommodate more queues. For the calculation of M_j^i we treated all queues (except i) as one queue and aggregated the arrival rates and service probabilities. This is important for two expressions in their solution: first, we adjusted the probability that one of the other queues was selected (ω in their work) as $\sum_{k\in G, k\neq i} h_j^k$, and secondly we adjusted the corresponding ρ of all others queues as $\sum_{k\in G, k\neq i} \rho_j^k$. By inserting these two expressions in the equation from Jiang et al. (2002) we obtain the following expression for M_j^i with multiple queues:

$$M_j^i = \frac{(1 + h_j^i \cdot \rho_j^i - (\sum_{k\in G, k\neq i} h_j^k \cdot \sum_{k\in G, k\neq i} \rho_j^k)) \cdot \sqrt{(1 + h_j^i \cdot \rho_j^i - (\sum_{k\in G, k\neq i} h_j^k \cdot \sum_{k\in G, k\neq i} \rho_j^k))^2 - 4 \cdot h_j^i \cdot \rho_j^i}}{2 \cdot h_j^i}. \tag{5.5}$$

With Equation 5.3 we can approximate the average waiting time of class i in blood type j. The last step is to take the weighted average of all blood types of an ethnic group to calculate the average waiting time per ethnic group by

$$W^i \approx \sum_{j\in B} W_j^i \cdot \frac{p_j^i}{p_i}, \tag{5.6}$$

with W_j^i given by Equation (5.3).

Equation (5.3) is an approximation of the real average waiting time. Jiang et al. (2002) have shown that the estimation error is small under certain conditions. They have compared the average waiting times as obtained with Equation (5.3) with a simulation model that has 1.000.000 instances (patients) per class (ethnicity). Their main conclusion was that the approximation method performs well under light or medium load conditions (a low or medium ρ) and if holds that $M_j^i < \sum_{k\in G, k\neq i} M_j^i$ for all $i \in G$. They

showed that the estimation error in these circumstances is mostly somewhere between 2 - 5 %. Both conditions hold in our example with the demographic data in the USA (see Section 5.4) and as such we can use this approximation method to analyze the effect of HLA types on racial disparity.

Approach 2: Separate M/M/1 queues. In this second approach, the service rate and arrival rate differ per queue. The arrival rate is determined by the number of people from ethnicity i with blood type j. The service rate is determined by the average service rate of blood type j and the probability to have a suitable HLA match h_j^i and is calculated as $h_j^i \cdot \mu_j$. Because we still use an M/M/1 queue with a FCFS discipline, calculating the average waiting time per queue stays exactly the same as for the identical blood type matching model (see Equation (3.1)). The average waiting time per queue is then calculated by

$$W_j^i = \frac{1}{h_j^i \cdot \mu_j - \lambda_j^i}. \tag{5.7}$$

And again, using a weighted average of the four blood types we can calculate the average waiting time per ethnic group by

$$W^i = \sum_{j \in B} \frac{1}{h_j^i \cdot \mu_j - \lambda_j^i} \cdot \frac{p_j^i}{p^i}. \tag{5.8}$$

5.3 Relation between Two Ethnic Groups

Both approaches are too complex to show, in an analytical way, how racial disparity relates to one of the input parameters as we did in Section 4. In order to calculate the racial disparity we can simply divide the average waiting time equations for one ethnic group by the outcome for an other ethnic group. We explore the calculation of the average waiting time in both approaches a bit deeper:

Approach 1: Probabilistic service order: Racial disparity in the first approach is calculated by

$$W^i = \frac{(\frac{1}{\mu_j} \cdot (1 + \frac{1-B_j^i}{B_j^i})) \cdot (1 - \rho_j^i (1 + \frac{1-B_j^i}{B_j^i}))^{-1}}{(\frac{1}{\mu_j} \cdot (1 + \frac{1-B_j^k}{B_j^k})) \cdot (1 - \rho_j^k (1 + \frac{1-B_j^k}{B_j^k}))^{-1}} \cdot W^k. \tag{5.9}$$

It will be clear that analyzing this equation is a very complex task because some of the parameters cohere with each other. The most important parameter that affects Equation (5.9) via Equation (5.4) and Equation (5.5) is h_j^i; the probability of an ethnic group to be selected for a kidney. As previously explained, the variable h_j^i is determined by the size of the ethnic group and the suitability probability of the ethnic group (d_j^i). The suitability probability is therefore very important, a higher suitability probability leads in general to a lower average waiting time.

Approach 2: Separate M/M/1 queues In the second approach, racial disparity is calculated by

$$W^i = \frac{\sum_{j \in B} \frac{1}{h_j^i \cdot \mu_j - \lambda_j^i} \cdot \frac{p_j^i}{p^i}}{\sum_{j \in B} \frac{1}{h_j^k \cdot \mu_j - \lambda_j^k} \cdot \frac{p_j^k}{p^k}} \cdot W^k. \tag{5.10}$$

Again, h_j^i determines how many donors become available for a certain ethnicity. In this model these donors become exclusively available for one ethnic group. As we will show more extensively in Section 6.1, a model with an identical ethnicity criterion will lead to longer average waiting times for smaller ethnic groups. If we introduce HLA type matching, disadvantaging the minority groups, we expect that

racial disparity increases even more. It is therefore likely to expect that the second HLA approach results in huge racial disparity.

In the next subsection we use an example to show the racial disparity that our approaches predict due to HLA type matching.

5.4 Practical Example

The numerical example in this section is especially important because we could not derive analytical conclusions like in Section 4.1.2 and 4.2.2 that related input parameters of the average waiting time equations directly to racial disparity.

We have used the demographic data from the USA. The sizes of ethnic groups, the blood type distributions per ethnic group, the ESRD rates and donor rates are all the same as in Section 4. In Table 9 we have listed the probabilities that a patient with ethnicity i could be matched with a donor from ethnicity i, for all $i \in G$. Together with the sizes of ethnic groups and their blood type distributions, we can calculate the values for h_j^i in Table 10.

Table 10: The selection probability for all ethnic groups and blood types.

Ethnicity	**Type A**	**Type B**	**Type AB**	**Type O**
White Americans	0.66	0.57	0.63	0.60
Black Americans	0.06	0.11	0.08	0.08
Asian Americans	0.06	0.11	0.10	0.06
Hispanic Americans	0.23	0.21	0.19	0.26

For the first HLA approach we have used Table 10 to define the probabilistic priorities and for the second HLA approach we have used the values from table 10 to divide the kidneys between the different servers of the ethnic groups, per blood type. The general service rate in the population is equal to 1000 and the general arrival rate is 550. We need a low arrival rate to keep the models stable. This resulted in the following average waiting times per ethnic group.

Table 11: Average waiting times per ethnic group for both approaches of the HLA type matching.

Ethnicity	**Approach 1**	**Approach 2**
White Americans	0.0148	0.0145
Black Americans	0.0286	1.1458
Asian Americans	0.0300	0.1441
Hispanic Americans	0.0115	0.0249

And by using the average waiting time of White Americans as index, we have calculated the following racial disparity levels.

Table 12: Racial disparity levels per ethnic group for both approaches of the HLA type matching.

Ethnicity	**Disparity approach 1**	**Disparity approach 2**
White Americans	1.00	1.00
Black Americans	1.93	79.20
Asian Americans	2.02	9.96
Hispanic Americans	0.78	1.72

The results in Table 11 are as we expected. First of all, the average waiting is a lot longer for most ethnicities in the second HLA approach. This follows from the layout of the queuing model in which we divide the available donors among multiple servers per blood type, resulting in a lower service rate per server. If, in the first HLA approach an ethnic group i is selected for a kidney with probability h_j^i and the selected queue is empty, the kidney is given to one of the other groups. In the second HLA approach, this kidney is not given to one of the other groups, resulting in longer average waiting times.

In both approaches racial disparity exists. The disparity is a lot higher in the second HLA approach than in the first. The disparity levels in the second HLA approach are not realistic and therefore we can state that this model is too extreme to reflect the real situation. The disparity levels in the first HLA approach are more realistic. The drawback of the first HLA approach is that if the queue of an ethnic group is empty, the kidney can be given to a patient from any other ethnic group for which it may not be suitable in reality. The exclusivity degree in the first HLA approach was an approximation, and as such the kidneys can in reality be more exclusive than assumed in the first HLA approach. We know from the second HLA approach that if the kidneys become more exclusive, the disparity increases. If the degree of exclusivity in the first approach is too low, we must treat the result of the first HLA approach as a conservative approximation of racial disparity created by different HLA types.

In Table 13 we have again listed the average waiting times and racial disparity of the situation with the first HLA approach but now compared with the average waiting times and racial disparity of the situation without HLA (see Section 4.2). For both situations we have used the same input data as in the current example.

Table 13: Comparison of approach 1 of the HLA type model with the identical blood type matching model in which we did not consider different HLA types as a matching restriction.

Ethnicity	**Avg. waiting time with HLA**	**Avg. waiting time without HLA**	**Disparity with HLA**	**Disparity without HLA**
White Americans	0.0148	0.0092	1.00	1.00
Black Americans	0.0286	0.0106	1.93	1.16
Asian Americans	0.0300	0.0132	2.02	1.44
Hispanic Americans	0.0115	0.0080	0.78	0.86

In Table 13 we see that the average waiting time has increased by introducing a conservative HLA type model for most ethnic groups and especially for the minority groups. As a result, racial disparity has increased as well. Given the results of the second HLA approach, we expect that if the kidneys are more exclusive than in the first HLA approach, racial disparity increases even further.

5.5 Concluding Remarks on HLA Type Matching

We can conclude, with the two queuing models in this section and the practical example, that HLA types cause racial disparity. The ideal queuing model, to show racial disparity caused by HLA genes, has one queue and one server per blood type and a certain probability for everyone in the queue to be the next one in service. An analytical expression for the average waiting time in a queuing model with these properties does not exist to the author's knowledge. In this section we have shown two approaches that both approximate the average waiting time of the ideal model. In the first approach, the kidneys can be used by all ethnic groups but are firstly offered to one ethnic group according to h_j^i. The donors are partly exclusive in this approach. In the second approach, the kidneys are mutually exclusive among ethnic groups. As a result of the observed racial disparity levels we can conclude that the first HLA approach is the most realistic approximation. However, it can be a conservative approximation of racial disparity as we have seen from the second HLA approach that, if the kidneys are more exclusively divided among the ethnic groups than assumed in the first approach, disparity increases. All the average waiting times have increased by introducing HLA type matching in the queuing model compared to a

situation in which only identical blood type matching was necessary. Also racial disparity has increased with the new model.

6 Reducing Disparity

We have shown that racial disparity in the average waiting time of kidney transplantation is caused by the identical blood type matching and HLA type matching. In this section, we will show that the disparity can be reduced by using slightly adjusted matching rules. We answer the following question in this section:

Which changes in the allocation mechanism should we allow and to what extent in order to restore equity among ethnic groups?

We will construct a model to reduce racial disparity caused by identical blood type matching. We do not build a model to reduce disparity caused by HLA type matching as this would be too complex for the scope of this research. We will however give a guideline of a possible approach that could be used to reduce racial disparity caused by HLA type matching.

We consider two approaches to solve the disparity caused by identical blood type matching. First we introduce in Section 6.1 a matching method in which donors from all ethnic groups and blood types give their kidney to someone with the same ethnicity and blood type. We show that such a fragmented model lead to even more disparity. The other model which we introduce in Section 6.2 uses cross transplants between two blood types and is better capable of reducing disparity caused by identical blood type matching. In Section 6.3 we discuss the approach that could be used to solve the disparity caused by HLA types.

6.1 Equity by Identical Ethnicity Matching

The only criterion for a match, between a patient and donor in the identical blood type model, was an equal blood type. In the model in this subsection we introduce an other criterion: equal ethnicity. We want to explore this option to see whether it can reduce racial disparity caused by identical blood type matching. It would not be very informative to incorporate different ESRD and donor rates among ethnic groups because it gives a huge disparity for ethnic groups that donate less and get sick more often. We focus on the situation in which all ethnic groups have the same probability to become sick and same propensity to donate a kidney.

The queuing model looks similar to the second approach of the HLA type model and has a queue for every blood type within all ethnic groups. This means that the number of queues to be considered is equal to the number of ethnic groups multiplied by four. This queuing model can be represented by figure 6.

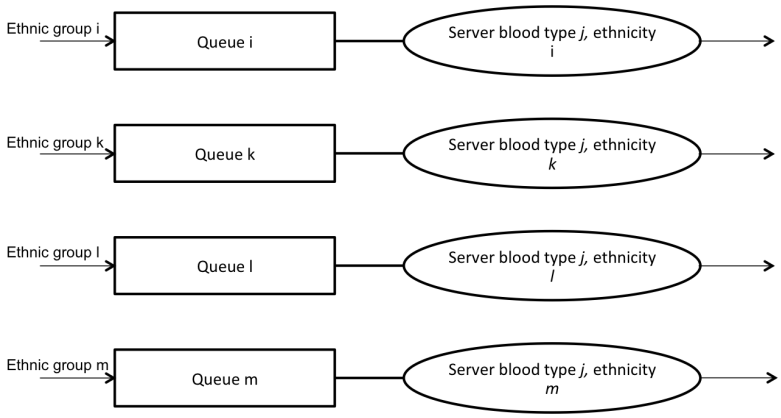

Figure 6: The layout of an identical ethnicity matching model for one blood type in which every ethnicity has one queue and one server per blood type.

We allocate the available organs among ethnic groups and blood types according to the prevalence of the ethnic groups and the blood types. The service rate is calculated as $\mu_j^i = p_j^i \cdot \mu$. The arrival rate of the queue is calculated as $\lambda_j^i = p_j^i \cdot \lambda$. By adjusting Equation (3.1), the average waiting time for a person from a certain ethnic group i with blood type j is given by

$$W_j^i = \frac{1}{\mu_j^i - \lambda_j^i} = \frac{1}{p_j^i \cdot (\mu - \lambda)}. \tag{6.1}$$

The average waiting time of the ethnic group can be calculated by a weighted average of the four different queues per ethnic group. This leads to the following equation for the average waiting time of an ethnic group:

$$W^i = \sum_{j \in B} \frac{1}{p_j^i \cdot (\mu - \lambda)} \cdot \frac{p_j^i}{p_i} = \sum_{j \in B} \frac{1}{p^i \cdot (\mu - \lambda)}. \tag{6.2}$$

We see, in Equation (6.2), that the average waiting time of an ethnic group depends on the relative size of the ethnic group compared to the total population (p^i) and does not depend on the blood type distribution of the ethnic groups. When group i is $\frac{p_i}{p_k}$ times as big as group k, we can define their relation as

$$W^i = W^k \cdot \frac{\sum_{j \in B} \frac{1}{p^i}}{\sum_{j \in B} \frac{1}{p^k}} = W^k \cdot \frac{p_k}{p_i}. \tag{6.3}$$

In Equation (6.3) the average waiting time of one ethnic group is expressed in terms of the average waiting time of an other ethnic group and their proportional size difference. The service and arrival rate of the population are important for the calculation of the average waiting time but they disappear when comparing the average waiting times of two ethnic groups. Equation (6.3) looks similar to the proof delivered by Stanford et al. (2014) regarding the dependency between the average waiting time and the relative frequency of blood types. According to Equation (6.3), small ethnic groups have a longer average waiting time than the large ethnic groups. As we know, in reality someone can not wait indefinitely for a kidney and therefore this model results in racial disparity.

We can conclude that such a fragmented model is not capable of reducing disparity and probably leads to more racial disparity. We have also shown in Section 4 that the model in which all cross transplants between ethnic groups were allowed results in disparity. Both extremes do not seem to work and this is probably because in both models identical blood type matching is used.

6.2 Equity by Compatible Blood Type Matching

In Section 4 we have shown that identical blood type matching leads to racial disparity because of the different blood type distributions among ethnic groups and different ESRD and donor rates. Given these two causes, we can use two ways of equalizing the average waiting time of ethnic groups. One way is to adjust the average waiting time of an ethnic group within a blood type. However, this approach will result in disparity among different blood types within an ethnic group, which would be just as bad as racial disparity. An other approach is to equalize the average waiting time of blood types. If all blood types have the same average waiting time (given the ESRD and donor rates of different ethnic groups), then all ethnic groups will automatically have the same average waiting time. Because it reduces all disparity, the latter approach has our preference and is explained in the remainder of this subsection.

To equalize the average waiting times of all blood types we follow the approach used by Stanford et al. (2014) and allow cross transplants between different blood types. Non-identical blood type matching is medically feasible for matches between compatible blood types (Reddy et al., 2013). The arrows in Figure 7 show the medically feasible and preferable matches between different blood types. Type O kidneys can be used for all other patients but it is medically less desirable to use type O donors for type AB patients (Stanford et al., 2014). Blood type A and blood type B can both donate to a type AB patient. Kidneys from a blood type with a short average waiting time are used for patients that have a blood type with a long average waiting time.

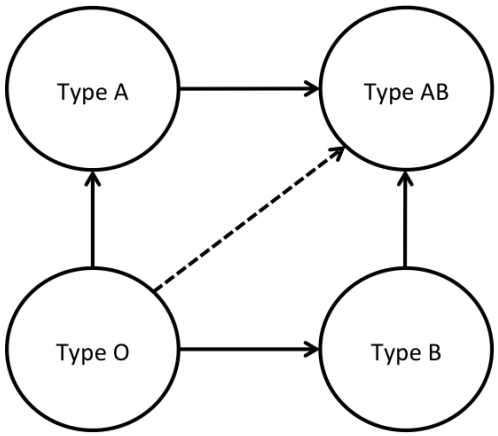

Figure 7: Possible cross transplants between compatible blood types.

The cross transplant approach for solving disparity will only work if blood type O is not the blood type with the longest average waiting time. The average waiting time of type O patients can not be reduced by other donors as only other type O kidneys are suitable for them. Blood type O is the most common blood type for the majority groups in most Western countries and as such blood type O has the shortest average waiting time (Stanford et al., 2014). So in most cases the type O patients will not be problematic and we can proceed with this approach.

We derive an equation that determines the number of cross transplants between two compatible blood types in order to equalize their average waiting times. In the derivation of the equation that calculates the necessary number of cross transplants, we allow a percentage of donor kidneys with blood type O to go to blood type B patients. This percentage is called R_{ob}. The approach for cross transplants between other (compatible) blood types is similar.

Part of the type O donors will go to type B patients and as such the service rate of type O changes into

$$\mu_o^{'} = \mu_o \cdot (1 - R_{ob}), \tag{6.4}$$

and for type B into

$$\mu_b^{'} = \mu_b + \mu_o \cdot R_{ob}. \tag{6.5}$$

When we allow cross transplants to blood type B, the average waiting time for blood type O patients is equal to

$$W_o = \frac{1}{\mu_o \cdot (1 - R_{ob}) \cdot (1 - \frac{\lambda_o}{\mu_o \cdot (1 - R_{ob})})} = \frac{1}{\mu_o \cdot (1 - R_{ob}) - \lambda_o}. \tag{6.6}$$

A similar way of reasoning can be followed in the case of blood type B. The service rate for blood type B changes to $\mu_b + \mu_o \cdot R_{ob}$ which gives us

$$W_b = \frac{1}{(\mu_b + \mu_o \cdot R_{ob}) \cdot (1 - \frac{\lambda_b}{\mu_b + \mu_o \cdot R_{ob}})} = \frac{1}{(\mu_b + \mu_o \cdot R_{ob}) - \lambda_b}. \tag{6.7}$$

In order to get equal average waiting times, we have to find the necessary percentage of cross transplants (R_{ob}). We start with equaling the average waiting time of both blood types to obtain

$$W_o = \frac{1}{\mu_o - \mu_o \cdot R_{ob} - \lambda_o} = W_b = \frac{1}{\mu_b + \mu_o \cdot R_{ob} - \lambda_b}. \tag{6.8}$$

Next, we get rid of the fraction and write all terms depending on R_{ob} on one side:

$$2 \cdot (\mu_o \cdot R_{ob}) = \mu_o - \lambda_o - \mu_b + \lambda_b. \tag{6.9}$$

Now we isolate R_{ob} by dividing trough $(2 \cdot \mu_o)$ on both sides in order to obtain the final equation for the cross transplant percentage from blood type O to blood type B. This percentage is calculated by

$$R_{ob} = \frac{\mu_o - \lambda_o - \mu_b + \lambda_b}{2 \cdot \mu_o} = \frac{(\mu_o - \lambda_o) - (\mu_b - \lambda_b)}{2 \cdot \mu_o}. \tag{6.10}$$

In Equation (6.10) the service rate is defined as $\mu_j = \sum_{i=1}^{m} \frac{p_j^i}{p^i} \cdot \mu^i$ and the arrival rate as $\lambda_j = \sum_{i=1}^{m} \frac{p_j^i}{p^i} \cdot \lambda^i$. The service and arrival rate per ethnic group depend on the size, the ESRD rate and the donor rate of the ethnic group. We will discuss a small example:

Example. We can calculate the percentage of cross transplants that is needed in order to equalize the average waiting times of two blood types with Equation (6.10). We use the same demographic data as in the example in Section 4.2.3. The service rate of the general population is 1000 and the arrival rate of the general population is 865. We can calculate μ^i and λ^i with the ESRD and donation probabilities per ethnic group in Table 6. In the example in Section 4.2.3, type O and type A patients had the shortest average waiting times whereas type B and type AB patients had the longest average waiting times. Therefore, we will use kidneys from type O donors for type B patients and kidneys from type A donors for type AB patients. With Equation (6.10) we calculate that 6.1 percent of the type O donors must go to type B patients in order to equalize the average waiting times of patients from both blood types. 10.5 percent of the type A donors need to go to type AB patients in order to equalize the average waiting times of type A and type AB patients. Using the new services rates in Equation (4.9) results in an average waiting time of 0.0315 units for patients from blood types O and B. This is almost a 10 times lower average waiting time for blood type B, whereas the average waiting time for blood type O becomes 50 percent higher. For type A and AB patients we find a new average waiting time of 0.0231 units. The average waiting times of the four major ethnic groups are summarized in Table 14:

Table 14: Racial disparity levels per ethnic group with identical blood type matching and compatible blood type matching.

Ethnicity	**Without cross transplants**	**With cross transplants**
White Americans	0.0855	0.0290
Black Americans	0.0581	0.0278
Asian Americans	0.1115	0.0286
Hispanic Americans	0.0519	0.0287

We have reduced the disparity almost completely among ethnic groups. Also we notice that the average waiting times of all ethnic groups have declined. This is a result of the lower average waiting times for type AB and type B patients. The increase of the average waiting time for type A and type O patients is relatively small compared to the decrease of average waiting time for type B and AB patients. We can see in Table 14 that the waiting times have not been equalized completely. The cross transplant approach that we use, equalizes the waiting time of two blood types, resulting in slightly different average waiting times between the two pairs of blood types. For some problem instances, like this example, it is not possible to use more cross transplants to reduce this effect. For others, however, more cross transplants can be used in order to reduce the differences in average waiting times further. If, for example, type A, type B and type AB all have long average waiting times, we need to make cross transplants from type O donors to type B patients and from type O donors to type A patients, but also from type A donors (or type B donors) to type AB patients. The percentages of all these cross transplants can be calculated with Equation (6.10).

6.3 Equity with HLA Types

Above derivation was done for the case in which all patients could match with all donors with compatible blood types. A HLA type match was not necessary. We will now incorporate the HLA types to solve the disparity caused by HLA type matching. The second HLA type approach, in which we split the ethnicities over multiple queues and servers, resulted in large, unrealistic disparities. In addition, we have shown in Section 6.1 that a model with equal ethnicities as a matching criterion is not capable of restoring equity. As such, we will not consider the second HLA approach for solving racial disparity. The probabilistic service model was better capable of showing realistic disparity levels. Unfortunately, due to the high complexity of this model we can not derive an analytical relation that shows us the necessary means to solve racial disparity. Therefore, we only discuss the steps that could be taken to equate the average waiting times among ethnic groups for the HLA model with a probabilistic service order.

Racial disparity in the HLA type model is caused by two different reasons: First, within blood types some ethnic groups have a much longer average waiting time than others. Secondly, between the blood types the average waiting time differs. This will negatively affect ethnic groups that have a large share of patients with the longer waiting blood type. This is clearly visible from Table 15 in which we listed the average waiting times per blood type and per ethnic group:

Table 15: Average waiting times per blood type, per ethnic group and the average waiting times per blood type with the HLA type matching model.

Ethnicity	**Type A**	**Type B**	**Type AB**	**Type O**
White Americans	0.0161	0.0563	0.1692	0.0128
Black Americans	0.0107	0.0290	0.0982	0.0076
Asian Americans	0.0147	0.0458	0.1309	0.0127
Hispanic Americans	0.0086	0.0297	0.0893	0.0070
Overall average	*0.011*	*0.036*	*0.1113*	*0.0084*

A method to solve the disparity between blood types has already been discussed in Section 6.2. We need to transfer transplants from donors with blood types that have a short average waiting time to patients with blood types that have a long average waiting time. In this case, we would need to transfer kidneys from donors with blood type O to blood type B patients, and kidneys from blood type A donors to blood type AB patients. Whereas in Section 6.2 the ethnicity of the transferred kidneys was not important, it now becomes very relevant as we know that a compatible HLA match depends on the ethnic background of both donor and patient (Pidala et al., 2013). The composition of ethnicities that are part of the cross transplants influence the probability to find a suitable HLA type match for the patients in both blood types.

The other source of disparity with HLA types is within blood types. Patients from some ethnic groups wait longer than patients with the same blood type from other groups. This is true because of the different probabilities of ethnic groups to be selected for a kidney. This probability must not be confused with the probability that someone from an ethnic group has a suitable HLA type match. The probability to be selected for a kidney is calculated not only by the percentage of suitable kidneys for the ethnic group, but also by its relative size and by the percentages of suitable donors of the other ethnic groups. This is more extensively explained in Section 5.1. However, theoretically, the probability that an ethnic group is selected for a kidney could be as high as its suitability percentage. For example, Black Americans with blood type A in the example of Section 5.4 were selected for a kidney in 6% of the donor options, whereas according to their suitability percentage they could accept up to 23% of the offered kidneys. In order to solve disparity within blood types, we can adjust the probabilities that the ethnic groups are selected for a kidney with a maximum probability that equals the percentage of suitable donors per ethnicity.

We can conclude that the approach to solve disparity among ethnic groups caused by HLA types, different ESRD rates, different donor rates and different blood type distributions contains three parts: We need to find the right amount of cross transplants between blood types, the right ethnic composition of kidneys that are part of these cross transplants and the right selection probabilities of ethnic groups within blood types. These three parts cohere with each other making it a very complex model to study analytically. We do not construct the model that provides the means to solve the racial disparity with HLA type matching in this thesis.

7 Conclusion and Discussion

In this thesis, we have examined the causal relation between racial disparity and two fundamental principles of the matching procedure for a patient and a deceased donor kidney. The two fundamentals are the use of identical blood type matching and the use of HLA type matching. These probable causes of racial disparity in kidney transplantation have been theorized before, but mostly based on empirical data. In the first part of this thesis the focus has been on an analytical explanation of the causality between the two parts of the matching procedure and racial disparity. This results in the first research question:

How can we analytically explain racial disparity in waiting times for the transplantation of a deceased donor kidney?

We have used differences in the average waiting time of a patient as the indicator of racial disparity between ethnic groups. To isolate the effect of the two fundamental principles of the matching procedure, no other rules that exist in the real algorithm were incorporated in our models. Consequently, the models cannot be used to predict disparity levels in a real population.

We have shown analytically that identical blood type matching causes racial disparity. We have distinguished two ethnic characteristics, that in combination with identical blood type matching, cause racial disparity: different blood type distributions among ethnic groups and different ESRD and donor rates

among ethnic groups. The effect of different blood type distributions on racial disparity can be proven with theorem 1. With theorem 1, we have proven that if the blood type distribution of an ethnic group i differs more from the average blood type distribution in the population than the blood type distribution of ethnic group k, ethnic group i will have a longer average waiting time. The blood type distribution of majority groups is more similar to the average blood type distribution in the population and as a result, identical blood type matching leads to racial disparity.

The different ESRD and donor rates also cause racial disparity. Donor rates in Western countries tend to be higher among ethnic majority groups as compared to ethnic minority groups, whereas ESRD rates on the contrary are high among minority groups and low among majority groups. This results in a bigger absolute difference in the number of arriving donors and patients per time unit for blood types that are common in the minority groups, whereas this difference decreases for blood types that are common in the majority groups. Patients from blood types that have a larger difference in the number of arriving patients and donors per time unit, will have a longer average waiting time. As proven with theorem 2, ethnic groups in which a large share of the group have these blood types, will on average have to wait longer for a transplant. Thus, the different ESRD and donor rates cause racial disparity.

Besides identical blood type matching we have also examined the effect of HLA type matching on racial disparity. We have used two approaches that approximate the way in which HLA types are used in the matching procedure. Previous research has shown that the ethnic background of both patient and donor determine the probability of a successful HLA match. However, the fact that some donors are suitable for patients from multiple ethnicities made it difficult to express the exact effect of HLA types on racial disparity. The two different HLA approaches and the previously used identical blood type model used all other degrees of exclusivity of the kidneys. In the identical blood type model all kidneys were suitable for anyone, in the first HLA approach we had some exclusivity and in the second HLA approach all kidneys were mutually exclusive. We have shown, based on our practical examples, that racial disparity increases if the kidneys become more exclusive among ethnic groups. We expect the first HLA approach, in which the kidneys were partially exclusive, to be a good approximation of the exclusivity degree in reality. As this model resulted in racial disparity, we can conclude that the different HLA types cause racial disparity. However, due to the high complexity of HLA type matching this has not been analytically proven.

Besides proving the presence of racial disparity, we were also interested in reducing the disparity. Therefore, the second research question of this thesis was set up:

Can we design and describe methods to reduce racial disparity in waiting times for the transplantation of a deceased donor kidney?

To reduce the disparity caused by identical blood type matching, we have shown that is necessary to let go of the identical blood type criterion and use cross transplants between different blood types. From a medical perspective, this is possible if the blood types are compatible. Kidneys from donors with blood types that have short average waiting times will be given to patients with blood types that have long average waiting times. In this way, we can equalize the average waiting times of two blood types. By choosing the right pairs of blood types we can reduce racial disparity almost completely. This will not only lead to equity among ethnic groups, but also to a decrease in average waiting times of all ethnic groups.

Racial disparity caused by HLA type matching can also be reduced. We have shown that racial disparity due to HLA types is caused by disparity between blood types and between ethnic groups within blood types. To remove the racial disparity, we need to reduce both causes. In order to reduce disparity between blood types, we can use blood type compatible cross transplants similar to those used for solving disparity due to identical blood type matching. The ethnicity of the donors, whose kidneys are used for the cross transplants, will become crucial as they affect the disparity levels between ethnic groups within blood types. Adjusting the selection probability of an ethnic group can solve the disparity within

blood types between ethnic groups. We can reduce racial disparity if we increase the selection probability for ethnic groups that have a long average waiting time in a blood type. The selection probability is not equal to the suitability probability as a kidney can be suitable for multiple ethnicities. We have shown that we can increase the selection probability of an ethnic group to a maximum equal to the suitability probability of the ethnic group.

We have researched racial disparity between ethnic groups caused by HLA types, different ESRD rates, different donor rates, different blood type distributions and the use of identical blood type matching. The approach to solve all the observed racial disparity contains three parts: a right number of cross transplants between blood types, the right ethnic composition of the donors whose kidneys are part of the cross transplants and the right selection probabilities of ethnic groups within blood types. It is, due to the high complexity of the model, not possible to find an analytical expression that calculates the values of these three parts within in the scope of this research.

We propose two possibilities for future work. We have shown that racial disparity is indeed caused by identical blood type matching and HLA types. However, the extent of racial disparity in real populations, caused by these factors, can be explored more extensively. Our first suggestion for future research would therefore be to further analyze the extent of racial disparity using a simulation approach as the real matching procedures consist of too many aspects to model in an analytical way.

A second interesting future study is to construct a model that calculates the necessary means to reduce disparity caused by HLA type matching and as such, also by identical blood type matching. We constructed a model that, based on the work of Stanford et al. (2014), can reduce racial disparity caused by identical blood type matching. However, when we incorporated HLA types, the model became too complex to find an analytical expression that determines the necessary means to solve racial disparity. The role of the ethnic composition of donors whose kidneys are part of the cross transplants between blood types, is particularly interesting to research. The use of (partially) compatible blood type matching to reduce racial disparity has been tried in reality (Williams et al., 2015), but the role of the ethnicities of donors whose kidneys are part of the cross transplants between blood types, has not been examined before.

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Appendices

A Overview of Variables

G	=	A set of ethnic groups: $G = \{i \mid i = 1,2,\ldots,m\}$. The ethnicity that belongs to a certain variable will always be indicated with the superscript.
B	=	A set of blood types: $B = \{j \mid j = A,B,AB,O\}$. The blood type that belongs to a certain variable will always be indicated with the subscript.
p^i_j	=	The proportion of the entire population having blood type j and ethnicity i, for all $i \in G$ and $j \in B$ (where $\sum_{i\in G, j\in B} p^i_j = 1$).
p_j	=	The proportion of the entire population having blood type j for all $j \in B$ (where $\sum_{j\in B} p_j = 1$). I.e. $p_j = \sum_{i\in G} p^i_j$ for all $j \in B$.
p^i	=	The proportion of the entire population from ethnic group i for all $i \in G$ (where $\sum_{i\in G} p_i = 1$). I.e., $p_i = \sum_{j\in B} p^i_j$ for all $i \in G$.
λ	=	The arrival rate of the total population.
μ	=	The service rate of the total population.
ρ	=	$\frac{\mu}{\lambda}$.
W	=	The average sojourn time of a patient.
e_j	=	The difference in the number of arriving donors and patients per time unit, per blood type j for all $j \in B$.
X^i	=	Random variable that takes values equal to the relative frequency of blood types for all $j \in B$ in the population with probabilities equal to the relative frequency of blood types in the ethnic group i for all $j \in B$.
Y^i	=	Random variable that takes values equal to the difference in the number of arriving donors and patients per time unit for all $j \in B$ in the population with probabilities equal to the relative frequency of blood types in the ethnic group i for all $j \in B$.
$U(X^i)$	=	The function that determines the average waiting time for a person with blood type i but unknown blood type, using the relative frequency of a blood type in the population.
$V(Y^i)$	=	The function that determines the average waiting time for a person with blood type i but unknown blood type, using the difference between arriving patients and donors.
h^i_j	=	The probability that someone is selected for the next available kidney from ethnicity $i \in G$ with blood type $j \in B$. (Selection probability)
d^i_j	=	The percentage of possible donors with HLA type matching for someone from ethnicity $i \in G$ with blood type $j \in B$. (Suitability probability
R_{jl}	=	Cross transplants from blood type $j \in B$ to blood type $l \in B$ (where $j \neq l$).
B^i_j	=	The probability, in the first HLA approach, that the queue with patients from ethnic group i with blood type j is selected.
M^i_j	=	The probability, in the first HLA approach, that the queue with patients from ethnic group i with blood type j is nonempty.