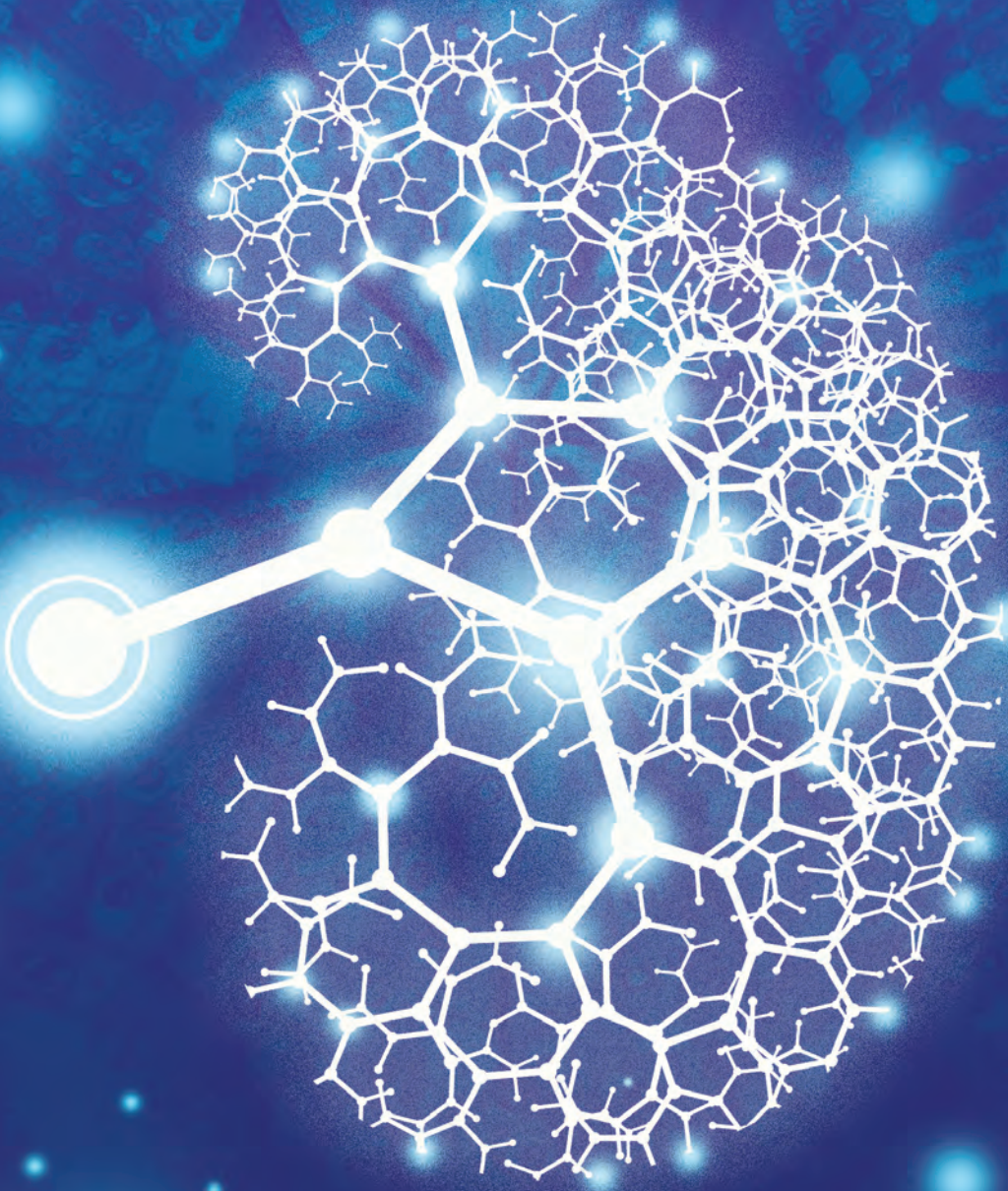
KRISTIAAN M. GLORIE

Clearing Barter Exchange Markets

Kidney Exchange and Beyond



CLEARING BARTER EXCHANGE MARKETS

Kidney Exchange and Beyond

Clearing Barter Exchange Markets: Kidney Exchange and Beyond

Allocatie in Ruilmarkten: Nieruitwisseling en Meer

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. H.A.P. Pols

and in accordance with the decision of the Doctorate Board

The public defense shall be held on

Thursday 27 November 2014 at 11:30 hrs

by

Kristiaan Michel Glorie
born in Gorinchem, the Netherlands.

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Erasmus Research Institute of Management - ERIM
The joint research institute of the Rotterdam School of Management (RSM)
and the Erasmus School of Economics (ESE) at the Erasmus University Rotterdam
Internet: http://www.erim.eur.nl

ERIM Electronic Series Portal: http://hdl.handle.net/1765/1

ERIM PhD Series in Research in Management, 329
ERIM reference number: EPS-2014-329-LIS
ISBN 978-90-5892-379-0

Design: B&T Ontwerp en advies www.b-en-t.nl

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Acknowledgments

Writing down the final words of this dissertation marks the end of a great journey. I would like to take this opportunity to thank the many people that have supported me throughout this journey and have made the last four years a very rewarding experience.

First of all, I would like to thank my promotors, Albert Wagelmans and Joris van der Klundert. Albert, thank you for encouraging me to become a PhD candidate. You have given me the freedom to pursue my own research path while providing useful guidance and advice whenever I needed it. I appreciate your thoroughness and punctuality and have really enjoyed working and socializing together. Whether it was for research or a general question, meetings with you have always been useful and have always left me with renewed energy. Joris, it was because of our initial conversations that I decided to study kidney exchanges. You have arranged meetings with important people in the field and you have taught me to become a better operations researcher. It has been a pleasure to work together. Thank you for all the ideas and advice you have given me.

Next, I would like to thank the members of my inner doctoral committee, Willem Weimar, David Manlove, and Ana Viana, for their valuable time to evaluate this dissertation. Willem, as a transplant surgeon and the chairman of the Dutch transplant foundation your support has been particularly valuable to me. Thank you for bringing me in touch with the transplant community and for working together on the papers that have led to Chapters 2 and 4. David, I am very happy to have met you during the Match-up workshop in Budapest. Your knowledge about matching algorithms has deeply impressed me. Thank you for your detailed comments on an early version of Chapter 3 and on this dissertation in general. Also, thank you for your hospitality when I visited you and Gregg O'Malley in Glasgow. Ana, it was very nice to have met you and your group in Porto. I am happy that it has led to a collaboration that has resulted in the paper that is the basis for Chapter 6. Thank you also for your feedback on this dissertation and for reaching out to me personally in difficult times. You are extraordinarily committed to the welfare of those around you and I am grateful to have been able to work with you.

I am also indebted to my co-authors Guanlian Xiao, Margarida Carvalho, Miguel Constantino, Paul Bouman, Marry de Klerk, Willij Zuidema, Frans Claas, and Bernadette Haase-Kromwijk. You all have strengthened my belief that the best research is performed by working together. Thank you for your valuable contributions, without which this dissertation could not have been the same.

I am thankful to Itai Ashlagi for hosting me while I visited him at MIT. Itai, although the research we performed during my visit did not end up in this dissertation, my experience in Cambridge has been very valuable and you have given me great advice. You have been a tremendous source of inspiration.

The data used for my research has been kindly provided by the Dutch transplant foundation, the Erasmus medical center and the national reference laboratory for histocompatibility testing in Leiden. I would like to thank Cynthia Konijn, Marry de Klerk, and Dave Roelen for their help in providing me with this data.

I would further like to express my gratitude to Wilco van den Heuvel, Erwin Hans and David Stanford for serving on my doctoral committee.

Remy Spliet and Harwin de Vries have been my office mates for the longest part of my PhD trajectory and I would like to thank them for all the fun times, interesting conversations and useful discussions. I am happy that they have agreed to be my paranymphs. Remy, you are one of the most social persons I know and a natural problem solver and organizer. I am happy that we have grown close as friends. Harwin, you are always able to come up with a fresh perspective on any topic we talk about. The legendary coffee breaks in our office became even better when you started bringing good coffee, and it has been great that we share many things beyond just research, especially because we both have become fathers.

I also would like to thank Anita Vlam for the period in which we shared an office during my first few months at the eleventh floor. Judith Mulder and Mathijn Retel-Helmrich, although not technically my office mates, often made me feel like they were. I am thankful to them for all the good laughs that we have had. Willem van Jaarsveld, while also not my office mate, often took the liberty of rearranging or relocating objects in my office. Fortunately, he made up for this by his priceless insights and delicious shrimp croquettes. Twan Dollevoet has been the master of analytical puzzles and always provided helpful advice. Lanah Evers brought up some of the most lively discussions. Evşen Korkmaz, Ilse Louwerse, Zahra Mobini Dehkordi and Evelot Duijzer often stopped by with a warm smile and helped create a joyous environment.

The staff and PhD candidates at the econometric institute are easily the best part of the Erasmus to me. I am grateful to Remy, Harwin, Judith, Mathijn, Twan, Willem,

Lanah, Ilse, Zahra, Charlie, Pieter, Evelot, Gertjan, Albert, Wilco, Adriana, Gönül, Jan, Martyn, Rommert, Dennis, Tommi, Alex, Tao-Ying, and all the others for the many interesting seminars, talks, coffee breaks, sports events, games, lunches, dinners, conferences, and other intellectual and social get-togethers. Of course, I should not forget to thank Carien, Marjon, Anneke, Ursula, and Marianne for their administrative support. We have also often been joined by Evşen, Başak, Paul, Luuk, Evelien, Joris, Jelmer, and others from the Rotterdam School of Management and I would like to thank them too for four memorable years.

Kevin Dalmeijer and Nico van der Windt have helped apply my research to housing markets and Jacob van der Weerd is helping me take it in yet other directions. It has been great to be able to work together with these inspirational people and I look forward to continuing our efforts.

I feel privileged to have met many great friends over the years. They make sure my life is about much more than research and I am very grateful for that. In particular I would like to thank Jurjen, Jacob, Evert, Hein, Remy, Priscilla, Michelle, Diederik, Yun-Feng, Hui-Fang, David, Ash and Najida for all the beautiful moments we have shared.

My final words of thanks go to my parents and brother for their unconditional love and support. Mom, although you are no longer with us, I hope this achievement makes you proud. My family in law has also always been there for me and I really appreciate their affection. My deepest thanks go to Vân. The last eight years have been the happiest years of my life and it has been because of you. You have given me the most precious thing in the world, our daughter Mali.

Kristiaan Glorie
Rotterdam, October 2014

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Chapter 1

Introduction

1.1 Smart barter exchange markets

Advanced computer assisted markets, otherwise known as smart markets, are becoming an important part of our modern society (Bichler et al., 2010). Smart markets rely on computers for operation, for ubiquitous access (e.g. through the internet), for trustworthy intermediation, and for determining market outcomes. Typically, all agents report their preferences to a centralized market operator or clearing house, and the operator or clearing house then provides an allocation and transfer prices so as to optimally match demand and supply (Roth, 2008). The problem of determining the optimal allocation and transfer prices is known as the market clearing problem. In this thesis we consider the clearing problem for barter exchange markets.

Barter exchange is one of the oldest and most straightforward forms of economic activity (Smith, 1937). It concerns the direct trading of one product or service for another. Nearly everyone will, over the course of their lives, have engaged in some form of barter or another. Trivial examples include trading collectibles such as marbles or sports pictures, trading books, or perhaps, trading a shift with a colleague. Typically, these forms of barter are bilateral and involve two agents whose disposable possessions mutually suit each other's wants. This reveals an important difficulty of barter exchange: there must be a coincidence of wants (Jevons, 1875). To quote Jevons:

> There may be many people wanting, and many possessing those things wanted; but to allow for an act of barter, there must be a double coincidence, which will rarely happen. ... The owner of a house may find it unsuitable, and may have his eye upon another house exactly fitted to his needs. But even if the owner of this second house wishes to part with it at all, it is exceedingly

> unlikely that he will exactly reciprocate the feeling of the first owner, and wish to barter houses.
>
> (Jevons, 1876, chapter 1)

Digital marketplaces can overcome the complexities of finding a coincidence of wants (Roth, 2008). Even opportunities for multilateral exchanges, involving many agents and many goods, can now be identified using computer algorithms. Examples of digital barter markets include house exchanges (in which agents seek to simultaneously buy each others houses, see for example www.besthouseswap.com), service exchanges (e.g., www.swapright.com), intra-organizational skilled worker exchanges (e.g., www.staffshare.co.uk), and book exchanges (see for example www.readitswapit.co.uk). Arguably, the most advanced barter exchange markets operated today are kidney exchange markets, which aim to enable transplants between incompatible patient-donor pairs (Rapaport, 1986; Roth et al., 2004; de Klerk et al., 2005).

1.2 Kidney exchange

In the United States alone, over 640,000 patients are presently suffering from end-stage renal disease (United States Renal Data System (USRDS), 2013). 430,000 of these patients are being treated with dialysis, which means their blood has to be filtered several times a week for multiple hours. The quality of life on dialysis is low and the annual mortality rate is over 20 % (United States Renal Data System (USRDS), 2013). Kidney transplantation has been established as the preferred alternative treatment (Wolfe et al., 1999). Compared to dialysis, it offers substantial advantages in terms of quality of life, patient survival, and costs (Port et al., 1993; Franke et al., 2003; Winkelmayer et al., 2002): on average, patients who receive a kidney transplant live 10 years longer than patients who remain on dialysis (Port et al., 1993), while the long term costs of transplantation are 4 to 5 times lower (Winkelmayer et al., 2002). Unfortunately, the number of kidneys available for transplantation is still largely insufficient to meet demand: only about 17,000 US patients can receive a transplant each year (SRTR, 2011).

Kidney transplants can come from both deceased and living donors. Deceased donor kidneys are allocated to patients by means of a waiting list, which in the US currently contains 108,571 patients and has an average waiting time of 4 years (SRTR, 2011). Living donors, such as a brother or sister of the patient, can provide a direct transplant. Grafts taken from living donors generally function twice as long as grafts taken from deceased

donors (SRTR, 2011). However, in over 30 % of the cases, a living donor and his or her intended recipient are medically incompatible (Segev et al., 2005b).

Kidney exchanges allow incompatible patient-donor pairs to swap donors in order to proceed with transplantation. If a patient's donor is compatible with some other patient, and the donor of the other patient is compatible with the first patient, the patients can swap donors so that both patients can obtain a transplant (de Klerk et al., 2005; Roth et al., 2004). Due to the large potential for increasing the number of transplants, many countries have developed kidney exchange programs. Leading examples are the Netherlands, the US, the UK, Australia, and South Korea (Keizer et al. (2005), Manlove and O'Malley (2012), Park et al. (1999), Delmonico et al. (2004)).

Compatibility in kidney exchange is determined by two factors: blood type compatibility and human leukocyte antigen (HLA) compatibility. In both cases, a patient and donor are incompatible if the patient has antibodies against an antigen contained in the donor's cells as then the patient's immune system will reject the donor's tissue. There are four blood types, A, B, AB, and O, corresponding to the presence of the antigens A and B. If the donor's blood contains an antigen that is not present in the patient's blood, the patient will have antibodies against the donor. The HLA system contains many antigens, and testing for antibodies against any of the donor's HLA is done by a so-called crossmatch test, which combines the patient's and donor's serum. If the crossmatch test is positive, the donor and patient are incompatible.

In kidney exchange, the trading preferences of agents are directly related to the compatibility structure. In most kidney exchange markets agents are assumed to be indifferent between compatible donors. However, because of the compatibility structure, some patients will have a disadvantaged position. These are in particular blood type O patients and highly sensitized patients, i.e. patients with antibodies against a large part of the donor population. Patient sensitization is measured by the percentage of panel reactive antibodies (PRA), which provides an estimate of the percentage of donors with whom the patient will have a positive crossmatch test. Patient's with a PRA of 80 % or more are considered to be highly sensitized.

1.3 The clearing problem

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

have an asking price for the good he brought to the market and a maximum buying price for every good he is interested in.

As barter exchange markets are a special case of matching markets in which one side (e.g. patients) is matched to another (e.g. donors) (Demange and Gale, 1985), the clearing problem in barter exchange markets is related to the maximum matching problem (Edmonds, 1965) which is a classic combinatorial optimization problem. The fundamental aspect in clearing barter exchange markets is that if an agent's object is allocated to another agent, the first agent should be allocated another object. Of course, there may be agents that provide goods without requiring goods in return and agents that want to obtain goods without providing any, but the actual barter takes place between agents that both provide and demand goods.

Barter exchange need not be limited to pairwise exchanges but may involve trading cycles in which each participant gives an object to the next participant in the cycle and receives an object from the previous participant (Shapley and Scarf, 1974; Roth et al., 2007). Alternatively, agents that only provide a good without requiring a good in return may initiate a trading chain which ends with an allocation to an agent that does not provide any good. In practice, there typically is a constraint on the number of participants in a trading cycle or chain. For example, to avoid reneging of donors, transplants in kidney exchange cycles are typically required to be performed simultaneously and the number of logistically feasible simultaneous transplants is limited. It is precisely this constraint that makes the clearing problem in barter exchange markets substantially more difficult to solve than the classical maximum matching problem (Abraham et al., 2007).

The clearing problem in barter exchange markets can also be related to the winner determination problem in combinatorial auctions (Cramton et al., 2006). The difference is that in barter exchange markets agents are not assumed to have preferences over combinatorial structures (i.e. packages) of objects, but the selected allocation must consist of combinatorial structures of agents (i.e. cycles and chains).

Solving the clearing problem for barter exchange markets in an acceptable amount of time requires the aid of sophisticated algorithms and significant computing power. This is particularly the case when the market contains hundreds or even thousands of agents and there are many complex constraints or objectives. In kidney exchange, for example, the primary objective is typically to maximize the number of transplants, but there can be many secondary objectives, such as minimizing waiting times or inequity (De Klerk et al., 2010). The most successful exact algorithms in the scientific literature to solve the clearing problem are so-called 'branch-and-price' algorithms (Abraham et al., 2007).

In practice, the clearing problem is typically considered in a *static* or offline context, in which exchanges are conducted at fixed time intervals and the assignment is optimized for the present state of the market. Of course, current agents and objects may disappear from the market and new agents may arrive. An alternative would therefore be to consider a *dynamic* or online context, in which the timing of exchanges is explicitly taken into account and the allocation is optimized with respect to the future evolution of the market. Such a dynamic context may have implications for what is considered an optimal allocation.

1.4 Incentives

In order to select an optimal allocation, accurate information regarding the agents, the objects, and the preferences is required. In case this information is self reported by the agents, there may be opportunities for agents to manipulate the information they reveal in order to try to achieve a better market outcome. Depending on the nature and severity of the manipulations, it may be necessary to implement incentive constraints that ensure that agents can never obtain a better outcome by providing false or incomplete information.

There are two main types of incentive constraints considered in the market design literature: individual rationality constraints (Roth, 1977) and incentive compatibility constraints (Myerson, 1979). Individual rationality constraints, which are alternatively known as participation constraints, guarantee that agents or groups of agents will not be worse off if they participate in the market than they would be if they did not participate in the market. Hence, under individual rationality constraints agents have no incentive to completely withhold themselves or their objects from the market. Incentive compatibility constraints, on the other hand, guarantee that no agent in the market can achieve a better market outcome by misrepresenting its information. Hence, under incentive compatibility constraints it is optimal for agents to truthfully report all their information.

Given a set of agents, objects and preferences, imposing incentive constraints on the clearing problem restricts the set of possible allocations. Solving the clearing problem with these constraints may therefore result in a lower objective value compared to solving the unrestricted clearing problem. However, when using the unrestricted clearing problem the set of agents, objects and preferences used in the optimization problem may not be the full or true set of agents, objects and preferences, and this may have even more negative consequences on the objective.

1.5 Market uncertainty

After an allocation has been selected, it may not always find continuation. In some barter exchange markets proposed transactions must be verified before they can proceed. Proposed transactions may fail to go forward if verification fails or if a participant withdraws. In housing markets, for example, it should be checked whether the participants in a transaction meet the financing requirements for side payments. In kidney exchange, proposed 'transactions' must be checked with a final crossmatch test (in addition to the initial virtual crossmatch test) to ensure the success of eventual transplants, and patients and donors may withdraw at the last moment due to medical, psychological or other reasons (Delmonico et al., 2004; de Klerk et al., 2005; Glorie et al., 2013).

In case one or more transactions fail, it may be possible to select a new allocation based on the updated information. Ideally, this new allocation is as close as possible to the initial allocation in order to minimize the material and emotional costs of the alteration. In kidney exchange markets, patients who are highly sensitized have an increased risk of match failure (besides having limited opportunities to be matched in the first place). Recovering solutions after failure may be particularly beneficial to these patients.

1.6 Contribution and thesis outline

This thesis considers the clearing problem in barter exchange markets. It focuses in particular on kidney exchange markets, but the findings are easily applicable to other types of barter exchange markets. The contributions made in this thesis are the following.

In Chapter 2 we first provide an extensive literature review of the state of the art in kidney exchange clearing. In particular, we discuss the underlying principles of matching and allocation approaches, the combination of kidney exchange with other strategies such as ABO incompatible transplantation, the organization of kidney exchange, and important future challenges.

Next, in Chapter 3, we consider solving the clearing problem with multiple objective criteria. We show that to achieve the best possible score on all criteria long trading cycles and chains are often needed, particularly when there are many hard-to-match patients. Long cycles and chains can be achieved by allowing some transactions to be non-simultaneous. We indicate why long cycles and chains may pose difficulties for existing approaches to clearing barter exchanges. We then present a generic iterative branch-and-price algorithm which can deal effectively with multiple criteria and side-constraints and

we show how the pricing problem may be solved in polynomial time in the cycle and chain length for a general class of criteria and constraints.

We also study multi-center coordination of unspecified living kidney donation and ABO incompatible transplantation in kidney exchange (Chapter 4). We address questions such as whether such coordination should utilize domino paired donation (DPD) or non-simultaneous extended altruistic donor (NEAD) chains, what the length of the segments in such chains should be, when they should be terminated, what can be done to convince transplant centers to participate, and what the time interval should be between clearing rounds. To this end we integrate our aforementioned clearing algorithm with a newly developed kidney exchange simulator based on actual data from the Dutch national kidney exchange program.

Chapter 5 considers the health outcomes of various allocation policies used in kidney exchange clearing. In order to analyze health outcomes, we introduce an individualized health value model for kidney exchange. This model is a Markov process with patient-donor specific transition probabilities. We also propose a new policy intended to maximize health value. This model links the individualized Markov model to the branch-and-price algorithm described in Chapter 3. We conduct long term simulations with kidney exchange data from the Netherlands. Policies are evaluated in terms of quality adjusted life years, equity, and number of transplants.

Chapter 6 considers the clearing of barter exchange markets in which proposed transactions must be verified before they can proceed. Proposed transactions may fail to go forward if verification fails or if a participant withdraws. In case one or more matches fail, a new allocation may be selected. The new allocation should be as close as possible to the initial set in order to minimize the material and emotional costs of the alteration. We present a robust optimization approach that intends to maximize the number of agents selected in both the first and second allocation in a worst case scenario. Our methodology allows in particular to protect the transactions for highly-sensitized kidney exchange patients, which unfortunately are often left without a transplant using the present algorithms employed to clear kidney exchanges. In addition to protecting against failure, we explicitly consider the option of flexible response to failures. We do this by allowing recourse actions. We consider three recourse policies that can be easily implemented in practice. Our clearing algorithm selects an optimal planned solution taking the possibility of recourse into account. If actual failures occur, our algorithm selects the optimal recourse action.

Finally, in Chapter 7 we summarize and discuss the main findings of this thesis and draw some general conclusions. A Dutch summary is also provided.

The chapters in this thesis can be read individually. Consequentially there is some overlap in the introduction to each of these chapters. The chapters are based on papers that were written with various coauthors and are either published in or are (to be) submitted to scientific journals. The references to these papers are given below.

Chapter 2 K. Glorie, B. Haase-Kromwijk, J. van de Klundert, A. Wagelmans, and W. Weimar, "Allocation and matching in kidney exchange programs". *Transplant International*, 27(4):333-43 (2014).

Chapter 3 K. Glorie, J. van de Klundert, and A. Wagelmans "Kidney exchange with long chains: an efficient pricing algorithm for clearing barter exchanges with branch-and-price". *Manufacturing & Service Operations Management*, 16(4):498-512 (2014).[1]

Chapter 4 K. Glorie, M. de Klerk, A. Wagelmans, J. van de Klundert, W. Zuidema, F. Claas, and W. Weimar, "Coordinating unspecified living kidney donation and transplantation across the blood-type barrier in kidney exchange". *Transplantation*, 96(9):814-20 (2013).

Chapter 5 K. Glorie, G. Xiao, and J. van de Klundert, "Health value analysis of allocation policies in kidney exchange". *Submitted to Operations Research* (2014).

Chapter 6 K. Glorie, M. Carvalho, M. Constantino, P. Bouman, and A. Viana, "Robust barter exchange". *Working Paper* (2014).

Appendix A K. Glorie, "Estimating the probability of positive crossmatch after negative virtual crossmatch". *Econometric Institute report*, 2012-25 (2012).

Summary in Dutch K. Glorie, A. Wagelmans, and J. van de Klundert, "Ethisch optimaliseren van het ruilen van nieren". *STAtOR*, 13(3-4) (2012).

[1] A previous version of this paper has appeared as (Glorie et al., 2012b).

Chapter 2

Literature review: clearing in kidney exchange[1]

2.1 Introduction

Living kidney donation is an obvious strategy to increase the number of kidney transplants (Spital, 1988; Wolfe et al., 1999; Port et al., 1993; Franke et al., 2003; Winkelmayer et al., 2002; Lopes et al., 2013). Moreover, grafts taken from living donors generally function twice as long as grafts taken from deceased donors (SRTR, 2011). Clinical advances such as laparoscopic nephrectomy and vaginal extraction have helped increase the number of living donor kidney transplants over recent years (Segev, 2012). In the Netherlands for instance, more than half of the transplants now involves a living donor (Nederlandse Transplantatie Stichting (NTS), 2012). Nevertheless, the number of kidneys available for transplantation is still largely insufficient to meet demand: in Europe and the United States together approximately 30 patients die each day while waiting for a kidney transplant (European Society for Organ Transplantation (ESOT), 2010; United States Organ Procurement and Transplantation Network (OPTN), 2011). A major part of the problem is that, even when a living donor is willing to donate, in over 30 percent of the cases, the donor is incompatible with his or her intended recipient due to blood type or crossmatch incompatibility (Segev et al., 2005b).

Several strategies have emerged to improve the utilization of living donors by mitigating or overcoming the causes of incompatibility. Kidney paired donation (KPD) (Rapaport, 1986), alternatively known as kidney exchange (Roth et al., 2004), is a strategy that allows incompatible patient-donor pairs to be matched with other incompatible pairs in

[1]This chapter is based on (Glorie et al., 2014b).

order to proceed with transplantation through an exchange procedure. Other strategies include patient desensitization, living donor-deceased donor list exchange, and altruistic (unspecified or non-directed) donation (Montgomery et al., 2005; den Hartogh, 2010; Montgomery et al., 2006a).

This review compares and discusses the various approaches to matching and allocation in kidney exchange as published in the international transplant community. In particular, it focuses on the underlying principles of market clearing and allocation approaches, the combination of KPD with other strategies such as ABO incompatible transplantation, the organization of kidney exchanges, and future challenges.

2.2 History of kidney exchange

The concept of kidney exchange was first proposed by Rapaport in 1986 (Rapaport, 1986). The initial idea was to facilitate exchange between pairs with reciprocal blood type incompatibilities (A-B and B-A), but this would later be expanded to other blood type combinations and crossmatch incompatible pairs. The first actual exchange procedure was performed in South Korea in 1991 (Kwak et al., 1999), followed by Europe in 1999 (Thiel et al., 2001), and then the US in 2000 (Zarsadias et al., 2010), the slow acceptance being mainly due to ethical and legal considerations (Ross and Woodle, 1998, 2000). After these first procedures, KPD has developed rapidly. In 2004, the Netherlands was first to launch a nationwide KPD program (de Klerk et al., 2005). Various countries have since then begun to develop national KPD programs, including the US (United Network for Organ Sharing Web Site, 2013), Australia (Ferrari et al., 2009), Canada (Canadian Blood Services Web Site, 2013), Romania (Lucan et al., 2003), and the UK (Johnson et al., 2008b,a). International exchanges, although on an ad hoc basis, have also been documented (Flanagan, 2013; La Vanguardia Ediciones, 2012).

2.3 Transplant modalities

2-Way KPD

Since the inception of KPD various transplant modalities have become available to incompatible pairs. The simplest modality is a pairwise exchange, or 2-way KPD, between two pairs with reciprocal incompatibilities (see Figure 2.1a). In this exchange the donor of the first pair donates to the patient of the second pair, and vice versa. Usually transplants take place simultaneously so as to prevent donors from withdrawing consent after their

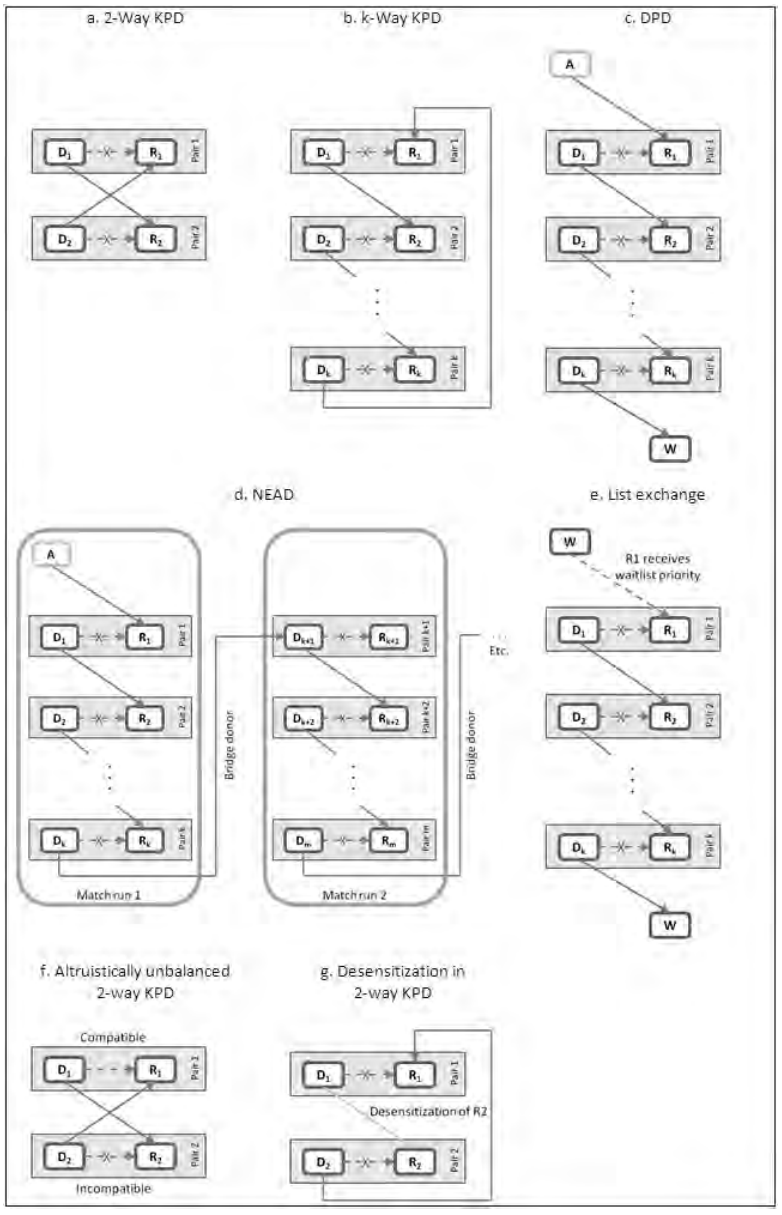

Figure 2.1: Transplant modalities. Solid arrows indicate matches between donors and recipients. D_i = donor i, R_i = recipient i, A = altruistic donor, W = waitlist.

intended recipient has received a transplant, but before they have donated themselves (Kwak et al., 1999; de Klerk et al., 2005).

k-Way KPD

Exchange can also take place between more than two pairs by generalizing the above concept to a so-called k-way KPD (Figure 2.1b). k-Way KPD which involves k pairs allows more benefits of trade to be captured as reciprocal matching is no longer required (Roth et al., 2007; De Klerk et al., 2010). In most cases, k is limited to 3 or 4 because of logistical reasons such as the simultaneous availability of operating rooms (Ferrari and de Klerk, 2009; Johnson et al., 2008b; Roth et al., 2007; De Klerk et al., 2010; Lee et al., 2009; Lucan, 2007; Montgomery et al., 2008). Although this limit is sufficient to provide full benefits of trade for blood type incompatible pairs in the pool (Roth et al., 2007), highly sensitized patients could benefit if k were allowed to be larger (Ashlagi et al., 2012).

Unspecified donor chains

As an alternative to the cyclic exchange procedures described above, transplants can be organized in chain procedures. One option is to initiate a chain with an unspecified donor. Instead of donating to a patient on the deceased donor waitlist, as has been common in many countries (Johnson et al., 2008b; Gilbert et al., 2005), an unspecified donor donates to a patient of an incompatible pair (Woodle et al., 2010; Dor et al., 2011). Subsequently, the donor of that pair donates to a patient of another pair, and so forth, until the donor of the last pair in the chain donates to a patient on the deceased donor waitlist. This modality is referred to as domino-paired donation (DPD)(Figure 2.1c)(Montgomery et al., 2006a). Since it is possible to arrange the transplants in a chain such that no donor-recipient pair needs to donate a kidney before having received one, donor withdrawal can do less harm in a chain than in a k-way KPD. Therefore, the requirement of simultaneous transplants could be relaxed in chains. Non-simultaneous extended altruistic donor (NEAD) chains (Figure 2.1d) do this by recruiting 'bridge donors who instead of donating to the deceased donor waitlist like the last donor in a DPD chain may continue the chain at a later moment in time (Rees et al., 2009). The relaxation of simultaneity allows chain procedures to involve more incompatible pairs than k-way KPD (if there is no donor withdrawal), potentially benefitting highly sensitized patients (Ashlagi et al., 2012). There has been an ongoing debate on whether it is best to use DPD or NEAD chains (Gentry et al., 2009; Ashlagi et al., 2011b; Gentry and Segev, 2011; Ireland, 2011). A recent study shows that the answer depends on the composition of the

KPD pool and that benefits of NEAD chains are limited in case of low numbers of highly sensitized patients and sufficient unspecified donors (Glorie et al., 2013).

List exchange

Another option is to initiate a chain with a list exchange (Figure 2.1e), in which the first patient in the chain does not directly receive a transplant, but instead receives priority on the deceased donor waitlist for a future deceased donor kidney, which is usually a blood type O kidney (Roth et al., 2004, 2006). The last donor of the chain again facilitates a transplant to a patient on the waitlist. However, the procedure is controversial because the latter transplant usually involves a non-blood type O kidney. Therefore list exchanges can produce disadvantages to blood type O patients on the deceased donor waitlist (den Hartogh, 2010). List exchanges have only been used in several regions in the US, where the procedure has been declared acceptable by the American Society of Transplantation (Ferrari and de Klerk, 2009).

Altruistically unbalanced exchange

All of the procedures described above can also take place with compatible pairs (Figure 2.1f). This is known as 'altruistically unbalanced exchange donation (Ross and Woodle, 2000; Kranenburg et al., 2006). It allows incompatible pairs a better chance of finding a match, while at the same time offering compatible pairs the opportunity of obtaining a better quality kidney (Gentry et al., 2007; Ratner et al., 2010; Roth et al., 2008). Studies suggest that 45 % of recipients in compatible pairs can obtain a kidney from a younger donor or a 0 mismatch kidney by participating in KPD (Gentry et al., 2007), and that approximately one third of compatible pairs would indeed be willing to do so (Kranenburg et al., 2006). Therefore altruistically unbalanced exchanges could result in both a higher number of transplants and a higher quality of transplants. Nevertheless, this form of exchange is ethically complicated as it involves asking otherwise suitable patient-donor pairs to exchange kidneys with strangers (Gentry et al., 2007).

Desensitization

Finally, there is the possibility of using desensitization techniques to overcome blood type or tissue type incompatibility. Although these techniques are costly and technically demanding, several programs have reported promising short-term and intermediate-term results and using such techniques has become an acceptable procedure in selected indi-

viduals (Montgomery et al., 2005; Montgomery, 2010; Montgomery et al., 2006b; Warren and Montgomery, 2010; Gloor et al., 2003; Jordan et al., 1998; Tanabe et al., 1998). In particular, desensitization for ABO incompatibility has been shown to provide good long-term graft survival, while still comparing favorably to dialysis in terms of costs (Wilpert et al., 2010; Gloor et al., 2010; Haririan et al., 2009). Combining desensitization with KPD can provide transplant opportunities to patients that would otherwise have been deemed contra-indicated and would have waited indefinitely for a suitable kidney (Claas and Doxiadis, 2009; Montgomery et al., 2011; Sharif et al., 2012; Crew and Ratner, 2010; Glorie et al., 2014b). This is particularly true if the modalities are not just offered separately to patients, but are coordinated such that hard-to-match patients can be desensitized after identifying a more favorable donor in a KPD (Glorie et al., 2013; Montgomery et al., 2011).

2.4 Imbalance

Not all incompatible patient-donor pairs have equal chances of success through KPD (Roth et al., 2007; de Klerk et al., 2011; Zenios et al., 2001; Gentry et al., 2005; Roodnat et al., 2012). This is primarily due to blood type imbalance. Because most blood type O donors can donate directly to their intended recipients, O donors will only need to enter a KPD pool if they have a positive crossmatch with their recipient. This leads to a scarcity of blood type O kidneys in KPD pools. At the same time, almost all patients are compatible with O donors. Consequentially, there will be higher demand for O kidneys than A or B kidneys, and, similarly, higher demand for A or B kidneys than AB kidneys. This leaves patient-donor pairs of types O-A, O-B, O-AB, A-AB and B-AB at a disadvantage since they need a kidney that is in higher demand than the kidney they offer (Roth et al., 2007). Table 1 provides a characterization of the pair types by blood type in terms of whether they are over-, under-, self-, or reciprocally-demanded (Roth et al., 2005b), and typical match results.

Another imbalance is due to patient sensitization. Highly sensitized patients are at a disadvantage since they can only accept a small fraction of kidneys, mostly from donors with few HLA types, which are in high demand. Patients who are both highly sensitized and have formed an under-demanded pair will be most difficult to match.

Success rates of KPD are further largely dependent on pool size and pool composition (Johnson et al., 2008b; Roth et al., 2007; Ferrari and de Klerk, 2009; Roodnat et al., 2012). The number of potential matches increases considerably with pool size. However, even in large pools typically only 50 % of pairs can be matched through KPD alone (de Klerk

et al., 2011) (see Table 1). In the Netherlands under-demanded pairs comprise 40 % of the national pool and they have a 19 % chance of finding a match. Other pairs, which comprise 60 % of the pool, have a 73 % chance of finding a match. Because compatible pairs, altruistic and deceased donors typically represent the blood type frequencies of the general population, allocating these donors to KPD programs permits better matching. Furthermore, because blood type and tissue type distributions may differ between countries, international exchanges may provide benefits for selected patient-donor pairs (Flanagan, 2013; La Vanguardia Ediciones, 2012). For instance, in the Dutch KPD program 17 % of the patients have a PRA > 80 with respect to the KPD donor population, whereas in the program of the Alliance for Paired Donation in the US over 50 % of the enrolled patients have a PRA > 80 (Ashlagi et al., 2012). Part of the reason for these differences may be the use of different techniques to detect unacceptable HLA specificities.

2.5 Allocation criteria

In KPD procedures, patient-donor pairs do not select the pairs with which they exchange kidneys. Instead, the allocation of donors to recipients is determined centrally. For this reason, the authority that oversees the KPD procedures must carefully consider the allocation criteria it will use. There can be many different perspectives as to what constitutes the best allocation.

European agreements governed in the convention on human rights and biomedicine (Council of Europe, 2002) prescribe that allocation of organs should be both ‘optimal and ‘fair, without stipulating precisely what is meant by those terms. Similarly, in the United States the National Organ Transplantation Act states that donated organs should be allocated ‘equitably among transplant patients (The National Organ Transplantation Act 42, 1984). The United Network for Organ Sharing (UNOS) defines ‘equitably as a balance between utility and justice (United Network for Organ Sharing (UNOS), 1992). While ‘optimality and maximum utility is generally interpreted as achieving the maximum number of transplants, defining ‘fairness and justice is less straightforward, particularly in light of the imbalance described earlier.

Although initial KPD programs have matched patient-donor pairs on an ad hoc basis taking in account the above principles, most programs have now formulated precise guidelines for the allocation process (Ashlagi et al., 2011b; Keizer et al., 2005; Glorie et al., 2014d; Ferrari et al., 2011; Böhmig et al., 2013; Kim et al., 2007; Manlove and O’Malley, 2012). In this regard it is important to make a distinction between allocation requirements that limit the number of feasible allocations, and thereby transplants, (e.g.

Patient blood type (% in population)	Donor blood type (% in population)			
	O (47 %)	A (42 %)	B (8 %)	AB (3 %)
O (47 %)	Self-demanded 16 % of pool 65 % success rate	Under-demanded 33 % of pool 20 % success rate	Under-demanded 6 % of pool 15 % success rate	Under-demanded 1 % of pool 0 % success rate
A (42 %)	Over-demanded 8 % of pool 84 % success rate	Self-demanded 13 % of pool 67 % success rate	Reciprocally-demanded 8 % of pool 89 % success rate	Under-demanded 1 % of pool 0 % success rate
B (8 %)	Over-demanded 4 % of pool 71 % success rate	Reciprocally-demanded 9 % of pool 74 % success rate	Self-demanded 1 % of pool 33 % success rate	Under-demanded 0 % of pool N.A. % success rate
AB (3 %)	Over-demanded 1 % of pool 100 % success rate	Over-demanded 1 % of pool 100 % success rate	Over-demanded 0 % of pool N.A. % success rate	Self-demanded 0 % of pool N.A. % success rate

Table 2.1: Characterization of the position of patient-donor types in KPD pools by blood type and their historical match results in the Dutch KPD program

requiring donors to be in the same age category or have the same CMV-EBV serology as their recipients) and actual allocation criteria that determine the selection of an allocation from the set of feasible allocations (e.g. maximum number of transplants between donors and recipients of the same blood type).

Traditionally, deceased donor organs have been allocated to recipients in priority order. Several KPD programs have also specified a priority order for KPD allocation criteria. These include the programs operated in the Netherlands, the UK, Australia, Austria, and Korea (Keizer et al., 2005; Glorie et al., 2014d; Ferrari et al., 2011; Böhmig et al., 2013; Kim et al., 2007; Manlove and O'Malley, 2012). Here the criteria are hierarchical and include such factors as: maximizing the number of matched recipients, maximizing the number of blood type identical matches (to maximize the likelihood of O patients receiving a kidney and to help overcome their disadvantage), prioritizing allocations based on the number of involved recipients with a low match probability, minimizing the length of the cycles and chains, and prioritizing allocations based on waiting time of the involved recipients. Simulations show that thanks to the inclusion of the above secondary criteria, the number of highly sensitized patients matched may increase by 10% (Glorie et al., 2014d).

Alternatively, criteria could also be weighted as is for example done in the UNOS KPD pilot program and the program of the Alliance for Paired Donation in the US (Ashlagi et al., 2011b; United Network for Organ Sharing (UNOS), 2012). These programs have specified weights for factors as waiting time, HLA match, PRA, prior crossmatch history, pediatric status and preferences of the incompatible pairs and their transplant centers (e.g. the distance the pair is willing to travel and whether the transplant center would accept a shipped kidney) and select the allocation that has the largest total weight (Ashlagi et al., 2011b; United Network for Organ Sharing (UNOS), 2012).

Other programs have formulated requirements and criteria with regard to age, travel distance, etc. (Lucan, 2007; Kim et al., 2007; Kute et al., 2013; Ycetin et al., 2013). Two unconventional possibilities are worth mentioning. The first is the use of quality adjusted life years from transplant. Use of quality adjusted life years is commonly accepted as a prime decision criteria for many medical interventions, following the framework of Health Technology Assessment (Hutton et al., 2006; Guindo et al., 2012). However, it may conflict with commonly accepted criteria such as maximizing the number of transplants (Wolfe et al., 2008; Zenios, 2002). Another possibility is to consider long term instead of short term criteria (Ünver, 2009; Awasthi and Sandholm, 2009; Dickerson et al., 2012). These two do not necessarily coincide. For example, to maximize the long term number of matched patients it may be necessary to allow for some match runs in which matches

are postponed (e.g. to allow for a future 3-way KPD to take place instead of a current 2-way KPD).

After an allocation has been selected, it may not always find continuation. Proposed matches may fail due to positive crossmatch tests or patient or donor illness. In such cases a new allocation can be determined based on the updated information, as is for instance done in the Netherlands, but this requires appropriate organization of crossmatching (see Section 2.8). An alternative solution is to maintain the initial allocation as much as possible and only reallocate pairs that are part of procedures that are discontinued. For instance, a discontinued k-way KPD could still result in multiple 2-way KPDs going forward (see Figure 2.2). The KPD program in the UK utilizes a set of hierarchical allocation criteria that aims to maximize the number of transplants that can take place after such a discontinuation (Manlove and O'Malley, 2012), by first maximizing the number of potential 2-way KPDs (including 'back-up 2-way KPDs), and as a secondary priority maximizing the total number of transplants (Manlove and O'Malley, 2012).

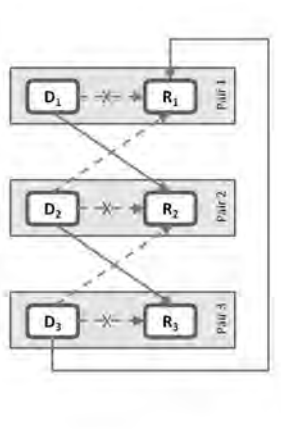

Figure 2.2: Match failure. Initially a 3-way KPD is selected. If the match between donor 3 and recipient 1 fails, it is still possible to perform a 2-way KPD, either between pair 1 and pair 2, or between pair 2 and pair 3.

It can happen that different allocations rank the same on all of the selected allocation criteria. In order to select an allocation then, most programs use a deterministic tie-breaking rule (Keizer et al., 2005; Manlove and O'Malley, 2012). However, an interesting alternative for such cases is to use a stochastic rule, i.e. a lottery which selects an allocation

randomly (Roth et al., 2005b). A stochastic rule can provide several fairness properties, in particular because the probability of selecting a recipient need not be the same for all recipients and can be set in a way that alleviates the imbalance due to blood type and tissue type distributions (Roth et al., 2005b).

2.6 Participation constraints

KPD programs benefit from the participation of as many centers as possible to create a large pool. However, multi-center cooperation has brought about several difficulties. Firstly, it requires consensus between participating transplant centers on the allocation requirements and criteria. Secondly, centers may judge that it is not in the interest of (some of their) patients to participate, and hence may prefer to not cooperate (fully). Thirdly, financial, scientific, or other incentives may exist, which cause cooperation to be potentially suboptimal. Thus, transplant centers may prefer to match some donors and patients locally instead of submitting them to the national pool (Glorie et al., 2013; Ashlagi and Roth, 2011a) (see Figure 2.3). One way to overcome such incentive issues is by implementing participation constraints which ensure that each transplant center can perform at least the same number of transplants in a national pool as that it can achieve on its own. Although such constraints limit the set of feasible allocations, it has been shown that they do not negatively affect the long-term benefits of KPD programs (Glorie et al., 2013; Ashlagi and Roth, 2011a).

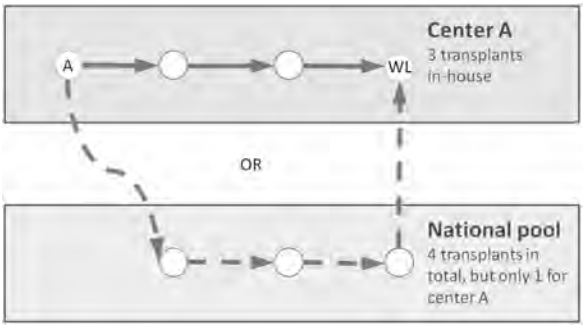

Figure 2.3: Potential participation problems. An unspecified donor (A) is registered at center A, which can generate 3 in-house transplants. In a nationally optimized program, 4 transplants are generated, but only 1 of those transplants is performed by center A.

2.7 Clearing algorithms

Initially most KPD programs manually selected the allocation that best fit their criteria. However, given that the number of possible allocations grows exponentially with the size of the KPD pool, manually evaluating all possible allocations is only feasible for very small pools. In the US, the process of finding a match therefore originally followed a 'first-accept scheme, which involves matching an incompatible patient-donor pair to the first pair that meets the acceptance requirements, even though matching with another pair might yield a better outcome (Segev et al., 2005a).

Most KPD programs today use computer software to identify the best allocation with respect to their criteria (Ashlagi et al., 2011b; Keizer et al., 2005; Ferrari et al., 2011; Böhmig et al., 2013; Kim et al., 2007; Manlove and O'Malley, 2012; Kaplan et al., 2005; Hanto et al., 2008). Such software typically compares all possible allocations and can perform virtual crossmatching based on known donor HLA types and patient unacceptable HLA mismatches. However, as KPD programs expand and start to be combined with other transplant modalities, the number of possible allocations becomes so large, that even for computer programs, it becomes intractable to enumerate all feasible allocations. In these situations mathematical optimization algorithms are required to guarantee the selection of the best possible allocation (Glorie et al., 2014d; Manlove and O'Malley, 2012; Abraham et al., 2007; Constantino et al., 2013). The best current algorithms use a technique known as 'branch-and-price' which enables them to select an optimal allocation within minutes because they only need to consider a small subset of all possible allocations (Glorie et al., 2014d; Abraham et al., 2007).

There are several aspects which provide challenges for the future. The first is that as KPD programs continue to evolve, highly sensitized and hard-to-match patients are likely to accumulate in the pool (Ashlagi et al., 2012). In such pools, the use of long chain procedures becomes essential to achieve the full benefits of exchange (Ashlagi et al., 2012). However, this renders the process of computing an optimal allocation substantially more difficult. Fortunately, recently developed algorithms have been shown to perform well even when pools are large and long chains are required (see Chapter 3).

Another aspect is that taking into account the probability of match failure by maximizing the expected number of transplants (which is different from maximizing the number of matches) may become more important as this will eventually lead to more transplants going forward (Pedroso, 2013; Dickerson et al., 2014; Glorie et al., 2014a). Although this still poses computational challenges, it may be an opportunity to significantly increase the success rates of KPD programs (Dickerson et al., 2013; Glorie et al., 2014a).

Similarly, considering online or *dynamic* instead of static optimization of kidney exchanges, takes into account the timing of exchanges and the fact that patients and donors enter and leave the KPD pool over time, to optimize the desired allocation criteria in the long run (Ünver, 2009; Awasthi and Sandholm, 2009; Dickerson et al., 2012; Ashlagi et al., 2013). Essentially, this better represents the real decision problem underlying KPD. As of yet, because of computational complexity, it is only possible to find approximate solutions to the dynamic problem, but even these are often significantly better than solutions achieved through static optimization. Figure 2.4 illustrates how dynamic optimization can provide benefits. Shifting focus from static to dynamic optimization and thereby from short term to long term goals raises questions as to what defines optimality and what is equity in a dynamic setting. Full answers to these questions await further research.

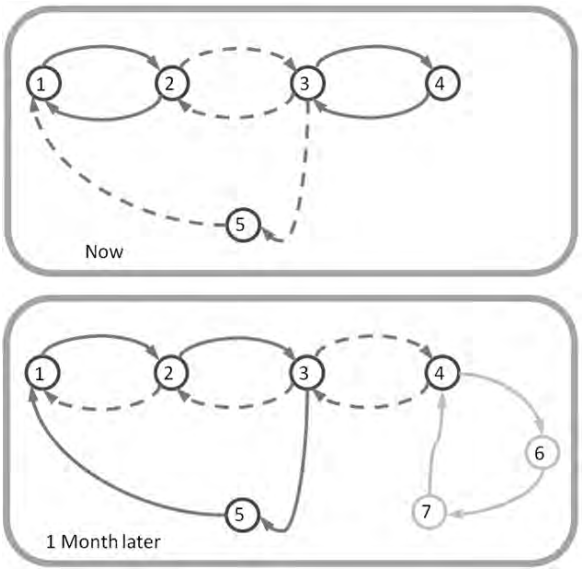

Figure 2.4: Dynamic optimization. There are 5 pairs in the current KPD pool. Two 2-way KPDs are performed involving pairs 1 and 2, and pairs 3 and 4. One month later pairs 6 and 7 enter the pool. In hindsight it would now have been better to perform one 4-way KPD between pairs 1, 2, 3, and 5, and one 3-way KPD between pairs 4, 6, and 7. Dynamic optimization anticipates such situations and maximizes the expected number of transplants.

2.8 Organization

Several countries have now implemented or pursue a national KPD program. However, there are several differences in how these programs are organized. Primarily this is because of geographical differences: for example, the US has 244 kidney transplant centers spread out over a large area (United Network for Organ Sharing (UNOS), 2012), while the Netherlands has 8 kidney transplant centers which are relatively close together (de Klerk et al., 2005). This has immediate implications for the coordination between transplant centers and donor travel. In the Netherlands, it is feasible to move donors to the center where the matched recipient will receive the transplant. This is preferable as the recipient's home institution can provide the recipient with continuity of care and follow-up, and avoids long cold ischemic times. In the US, the retrieval surgery typically takes place at the donor center and the kidneys are shipped to the recipient's center for transplantation. Even though this requires longer cold ischemic times and risks transportation delays, recent studies show comparable graft survival rates of shipped kidneys and non-shipped kidneys (Montgomery et al., 2008; Rees et al., 2009; Butt et al., 2009; Simpkins et al., 2007; Segev et al., 2011).

A major contributor to the success of the Dutch program in establishing consistent high match rates, is its use of a national centralized tissues typing laboratory (Ferrari and de Klerk, 2009; de Klerk et al., 2008). In this laboratory potential donors and recipients are tested for HLA crossmatch. Having a centralized laboratory substantially enhances coordination between centers as it removes dispute about crossmatch outcomes by setting a uniform crossmatch standard.

Finally, the frequency of match runs and thereby the timing of exchanges also is a differentiating element between KPD programs. Some programs perform match runs on demand such as Korea whereas others perform them once per month, or once per three months as in the Netherlands (Glorie et al., 2013; Ferrari and de Klerk, 2009; Kim et al., 2007). Although frequent performance of match runs may result in shorter waiting time for matched recipients, it risks removing only easy-to-match pairs as the pool may not always be saturated enough for the procedures involving hard-to-match pairs to take place. Deciding when to match is therefore an important decision for KPD programs (Glorie et al., 2013). New matching software is able to advice on the optimal timing based on the composition of the pool (Ünver, 2009; Awasthi and Sandholm, 2009; Dickerson et al., 2012; Ashlagi et al., 2013).

2.9 Outlook

Since its inception in 1986, KPD has greatly expanded and has become an accepted method of transplantation at transplant centers throughout the world. Many advances have been made in terms of surgical technique, shipping donor kidneys and international exchanges. Nevertheless, many blood type O and highly sensitized patients still remain without a transplant. Important factors that have limited the success of KPD programs are logistical issues, basic trust between the various participants, and match failures. Innovative transplant modalities as altruistic donor chains and desensitization can help ameliorate the problem for critical patient groups. However, to achieve the best possible outcomes, these modalities should be coordinated jointly with KPD (Glorie et al., 2013). In this regard, this review has summarized different allocation and matching strategies. While there are many other issues that could be explored in the evolving field of KPD, matching is a key element in KPD, and by selecting the right matching strategy many patients can benefit. Future opportunities and challenges include making full use of the various modalities that are now available through integrated and optimized matching software, encouragement of transplant centers to fully participate, improving transplant rates by focusing on the expected long run number of transplants, and selecting uniform allocation criteria to facilitate international pools.

Chapter 3

An efficient pricing algorithm for clearing barter exchanges with branch-and-price: enabling large-scale kidney exchange with long cycles and chains[1]

3.1 Introduction

Barter exchange markets are markets in which agents seek to directly trade their goods with each other. The trades in such markets consist of cycles in which each agent gives a good to the next agent in the cycle. Alternatively, the trades may consist of chains which are started by an agent that provides a good without requiring a good in return and end with an agent that receives a good without providing one. There are numerous examples of barter exchange markets: house exchanges (in which agents seek to simultaneously buy each others houses, see for example www.besthouseswap.com), shift exchanges (e.g., between nurses in hospitals), intra-organizational skilled worker exchanges (e.g., between projects or departments), and book exchanges (see for example www.readitswapit.co.uk). In the present paper we focus specifically on so-called kidney exchanges but our findings are easily applicable to other types of barter exchange markets.

[1]This chapter is based on (Glorie et al., 2014d). A previous version of it has appeared as (Glorie et al., 2012b).

Kidney exchanges aim to help end-stage renal disease patients with a living and willing, but medically incompatible donor to obtain a kidney transplant, which is the preferred treatment for these patients. In particular, kidney exchanges enable patients to exchange their donor with another patient: if a patient's donor is compatible with some other patient, and the donor of the other patient is compatible with the first patient, the patients can switch donors so that both patients can obtain a transplant (see e.g. Roth et al. (2004), de Klerk et al. (2011) and Glorie et al. (2014b)). Due to the large potential for increasing the number of transplants, many countries have developed kidney exchange programs. Leading examples are the Netherlands, the US, the UK, Australia, and South Korea (Keizer et al. (2005), Manlove and O'Malley (2012), Park et al. (1999), Delmonico et al. (2004)).

Kidney exchange need not be limited to two patient-donor pairs but may involve cycles in which the donor of each pair donates, simultaneously, a kidney to the patient of the next pair in the cycle. The simultaneity is required to prevent donors from reneging after their intended recipient has received a transplant from another donor. Because of simultaneity, the length of cycles is limited to the number of logistically feasible simultaneous transplants. Alternative to cycles, unspecified donors - i.e. donors without a specified recipient - may initiate a chain of transplants in which the last donor is allocated to the deceased donor wait list or is preserved for a future exchange. Because in a chain no patient-donor pair needs to donate before the patient in the pair has received a kidney, donor reneging in a chain would be less harmful than in a cycle. For this reason it is sometimes allowed to have one or more non-simultaneous transplants in a chain, allowing chains to be longer than cycles. Chains are increasingly common and important in clinical practice (e.g. Ashlagi et al. (2012), Glorie et al. (2013)).

Presently, over 30 percent of living donors are incompatible with their intended recipient (Segev et al., 2005b). A patient and donor are incompatible if the donor's blood contains an antigen that is not present in the patient's blood, because the patient will have antibodies against such an antigen. Two cases of incompatibility can be distinguished. The first case, known as blood type incompatibility, revolves around two major antigens: A and B (blood types are denoted as AB, A, B, and O, representing the presence of these antigens). The second case, known as crossmatch incompatibility, revolves around all other antigens against which the patient may have preformed antibodies.

The clearing problem in kidney exchange is to determine an assignment of donors to recipients that is feasible with respect to the medical compatibilities and maximizes one or more criteria such as the number of transplants. In practice, this problem is typically considered in a *static* or offline context, in which exchanges are conducted at

fixed time intervals and the assignment is optimized for the present population, as opposed to a *dynamic* or online context, in which exchanges are conducted continuously and the assignment is optimized with respect to the future evolution of the population. The difficulty of the clearing problem arises from the requirement that all transplants in a cycle must be performed simultaneously and that therefore cycles are limited in length. Whenever this limit is finite and larger than 2, the static clearing problem is NP-hard (Abraham et al., 2007).

Abraham et al. (2007) present a mixed integer programming formulation for the clearing problem with the objective of maximizing a weighted sum of transplants. They solve this formulation by a branch-and-price algorithm (see Barnhart et al., 1998), in which they identify positive price variables by depth-first search. Abraham et al. (2007) show that when each transplant has equal weight in the objective function and when exchanges are limited to cycles or chains involving at most 3 patients and 3 donors, this approach works well even when the instance size is large. The main argument for limiting cycles and chains to length 3 is that initially in many pools the maximum possible number of transplants can be achieved using only cycles and chains up to length 3 (Roth et al., 2007). As we will show, however, when kidney exchange programs continue to evolve, cycles and chains up to length 3 are often not enough to attain the maximum possible number of transplants (see also Ashlagi et al. (2011b)). Moreover, when heterogenous objective weights are used or when an objective other than maximizing the sum of transplants is desired, allowing longer cycles and chains may improve the objective function. Unfortunately, with long cycles and chains depth-first pricing becomes a major bottleneck. In this paper we will show how this problem can be overcome.

In practice, maximizing the (weighted) sum of transplants is not the only relevant objective criterion (see e.g. de Klerk et al. (2011)). Instead of a single weighted objective criterion, several existing kidney exchange programs use a hierarchically ordered set of criteria (e.g., De Klerk et al. (2010), Manlove and O'Malley (2012), and Kim et al. (2007)). The Dutch national kidney exchange program, in particular, uses the following hierarchical set:

Definition 3.1. *Hierarchical criteria used in the Dutch kidney exchange program:*

(i) Maximize the number of transplants;

(ii) Maximize the number of blood type identical transplants;

(iii) Match the patients in priority order based on 'match probability' (see Keizer et al., 2005);

(iv) Minimize the length of the longest cycle or chain;

(v) Maximize the spread over transplant centers per cycle and chain;

(vi) Match the patient with the longest waiting time.

The Dutch criteria are based on European agreements governed in the convention on human rights and biomedicine Council of Europe (2002), which determines that the allocation of organs should be both 'optimal' and 'fair'. For this reason the criteria include factors related to the probability of obtaining a transplant (criteria (ii) and (iii)) and waiting time (criterion (vi)). The exact aim of criterion (ii) is to help establish a fair allocation across patient blood types by ensuring that patients of disadvantaged blood types, such as blood type O, receive as many transplants as possible (donors of the same blood type will be reserved for them whenever this is viable). Criterion (iii) establishes such fairness in a broader sense by taking into account the total match probability (as defined in Keizer et al. (2005)). The priority order *within* criteria (iii) and (vi) is based on the traditional priority mechanisms for allocating deceased donor kidneys. Criteria (iv) and (v) are of a logistical nature. The hierarchy among the criteria implies that every criterion should be optimized subject to the best possible score on previous criteria. For example, the number of blood type identical transplants (criterion (ii)) should be maximized under the condition that the total number of transplants is maximum (criterion (i)).

Because of the evolution of kidney exchange pools and the ways in which exchange can take place, and because of the advent of large multi-center exchanges and the requirement of multi-criteria optimization, there is a need for new techniques for kidney exchange clearing that facilitate long chains. The work presented in this paper makes the following contributions:

1. We develop a generic iterative branch-and-price algorithm for clearing kidney exchanges with a weighted or hierarchically ordered set of objective criteria;
2. We propose a polynomial solution method for the pricing problems as they result for a general class of criteria (which includes all criteria of the Dutch exchange);
3. The presented approach accommodates long, possibly non-simultaneous, unspecified donor chains at running times that are feasible in practice;

4. The approach allows for optimization for a set of transplantation centers, such as at a (inter-) national level, while taking individual rationality constraints of the participating transplantation centers into account.

This paper is organized as follows. First, Section 3.2 describes the multi-criteria kidney exchange problem mathematically. Section 3.3 details our iterative branch-and-price algorithm used to solve the multi-criteria kidney exchange clearing problem. In particular, Section 3.3.2 describes a new branching scheme and Section 3.3.3 describes how the pricing problem can be solved in polynomial time for a wide range of criteria. Section 3.4 discusses the setup of our simulations using actual kidney exchange data and Section 3.5 presents the computational results. Finally, Section 3.6 concludes the paper.

3.2 A kidney exchange model

In this section we formalize the concepts used in kidney exchanges and we mathematically define the problem under consideration.

3.2.1 Problem definition

Definition 3.2. *A kidney exchange pool N consists of two sets, i.e. $N = N_U \cup N_S$, where N_U refers to the set of all unspecified donors and N_S to the set of all incompatible specified donor-recipient pairs.*

Definition 3.3. *A kidney exchange graph $D = (N, A)$ has as its node set a kidney exchange pool N. There is an arc $a_{i,j} = (n_i, n_j) \in A$ from node $n_i \in N$ to node $n_j \in N_S$ if the donor corresponding to node n_i is compatible with the recipient corresponding to node n_j.*

Note that in any kidney exchange graph $D = (N, A)$, nodes in N_U, which correspond to donors without recipients, have no incoming arcs. We define a transplant cycle and a transplant chain as follows

Definition 3.4. *In any given kidney exchange graph $D = (N, A)$, a length-k cycle is an arc traversal $\langle n_1, \ldots, n_k \rangle$ such that $\{n_1, \ldots, n_k\} \subseteq N_S$ and such that $(n_k, n_1) \in A$ and, for every $1 \leq i < k$, $(n_i, n_{i+1}) \in A$.*

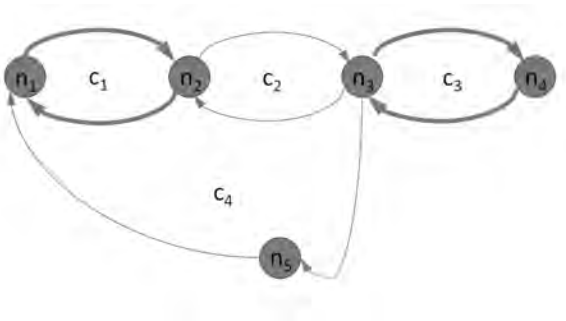

Figure 3.1: Kidney exchange example

Definition 3.5. *A length k chain is an arc traversal $\langle n_0, \ldots, n_k \rangle$ such that $n_0 \in N_U$ and $\{n_1, \ldots, n_k\} \subseteq N_S$ and for every $0 \leq i < l$, $(n_i, n_{i+1}) \in A$.*

In practice, there exist limits on the number of transplants that can be performed simultaneously within a cycle or chain segment. This implies a natural bound on the maximum cycle and chain length.

Definition 3.6. *For kidney exchange graph $D = (N, A)$ and $K \in \mathbb{N}$,*

$$C(K) := \left\{ c \subseteq N : \ c \text{ is a cycle or chain in } D \text{ with length at most } K \right\}$$

Note that, because chains can allow for the requirement of simultaneity to be relaxed, in general the limit on chains is greater than or equal to the the limit on cycles. Typically, chains use one or more non-simultaneous transplants to link several simultaneous segments of transplants. For ease of exposition, we use a single limit parameter in our notation. However, it is straightforward to use separate parameters and in the experiments in Section 3.5 we will do exactly this.

Definition 3.7. *Let $D = (N, A)$ be a kidney exchange graph, $K \in \mathbb{N}$, and $C(K)$ be defined as above. Then, any subset $M = \{c_1, c_2, \ldots, c_{|M|}\} \subseteq C(K)$, is called an exchange if $c_i \cap c_j = \emptyset$ for all, $1 \leq i, j \leq |M|$, $i \neq j$.*

Thus, an exchange is a collection of interdependent kidney transplants which can be feasibly performed together. In the remainder of the paper, we assume a kidney exchange graph $D = (N, A)$, and $K \in \mathbb{N}$ are given, and we denote with $\mathcal{M}$ the *exchange set*, i.e.

the set of all exchanges M as defined above. Thus, an exchange set $\mathcal{M}$ always implicitly defines a kidney exchange graph $D = (N, A)$, and $K \in \mathcal{N}$. Now that we have formally defined exchanges, and the exchange set, we proceed by considering the criteria by which exchanges $M \in \mathcal{M}$ are evaluated.

Definition 3.8. *For any given exchange set $\mathcal{M}$, a criterion is a function $f : \mathcal{M} \to \mathbb{R}$.*

We now arrive at the formal definition of the problem under consideration:

Definition 3.9. *For any given exchange set $\mathcal{M}$ and ordered set of criteria $\mathcal{I} = \{f_1, \ldots, f_{|\mathcal{I}|}\}$, a hierarchical multicriteria clearing problem is to find an exchange $M^* \in \mathcal{M}$ such that, for each $i = 1, \ldots, |\mathcal{I}|$, $M^* \in \mathcal{M}_i$ where $\mathcal{M}_i$ is recursively defined as $\mathcal{M}_i := \{M \in \mathcal{M}_{i-1} : f_i(M) \geq f_i(M'), \forall M' \in \mathcal{M}_{i-1}\}$ with $\mathcal{M}_0 := \mathcal{M}$.*

Note that the set of criteria used in the Dutch kidney exchange program are an ordered set of kidney exchange criteria which fit the above definition, as would be the sole criterion of maximizing the (weighted) number of transplants. Because any minimization criterion can be rewritten as a maximization criterion, the definition also accomodates for minimization criteria. Moreover, the definition also accommodates for individual rationality (or participation) constraints for hospitals as sometimes required in multi-hospital settings (Glorie et al., 2013).

Figure 3.1 illustrates an example of a kidney exchange clearing problem with 5 donor-recipient pairs, $n_1, \ldots, n_5$. The bound on the length of exchange cycles K is 4. The graph has 4 feasible cycles, $c_1 = \langle n_1, n_2 \rangle, c_2 = \langle n_2, n_3 \rangle, c_3 = \langle n_3, n_4 \rangle, c_4 = \langle n_1, n_2, n_3, n_5 \rangle$. There are two maximal exchanges given by $M_1 = \{c_1, c_3\}$ (highlighted) and $M_2 = \{c_4\}$. Although both exchanges have the same number of transplants, in the Dutch system exchange M_1 could be preferable over exchange M_2 by, for example, criterion (iv) in Definition 3.1: the maximum cycle length is 2 instead of 4.

3.2.2 Complexity of the clearing problem

We will now prove that the clearing problem is NP-hard. Although this was first proved by (Abraham et al., 2007), we present here an alternative proof which is an extension of the reduction from X3C to PARTITION INTO TRIANGLES given in Garey and Johnson (1979).

Consider the following decision problem:

Static k-EXCHANGE (SkE)
INSTANCE: A directed graph $D = (N, A)$ and a positive integer $k \leq |N|$.
QUESTION: Is there a partition of N into disjoint sets $C_1, C_2, \ldots, C_m$, such that each $C_i, i = 1, \ldots, m$ forms a directed cycle in D of length at most k?

We have the following theorem.

Theorem 3.1. *For $3 \leq k \leq |N|$ SkE is NP-Complete.*

Proof. We transform EXACT COVER BY 3-SETS (X3C) to SkE. The NP-Complete problem X3C is defined as

EXACT COVER BY 3-SETS (X3C)
INSTANCE: A finite set X with $|X| = 3q$ and a collection C of 3-element subsets of X.
QUESTION: Does C contain an *exact cover* for X, that is, a subcollection $C' \subseteq C$ such that every element of X occurs in exactly one element of C'?

Let the set X and the collection C of 3-element subsets of X be an arbitrary instance of X3C. We shall construct a graph $D = (N, A)$, such that a partition of N into disjoint sets $C_1, C_2, \ldots, C_m$, with each $C_i, i = 1, \ldots, m$ a directed cycle in D of length at most k, exists, if and only if C contains an exact cover for X.

The basic units of the X3C instance are the 3-element subsets in C. We can locally replace each such subset $c_i = \{x_i, y_i, z_i\} \in C$ with the collection A_i of edges shown in Figure 3.2. Then $D = (N, A)$ is defined by

$$N = X \cup \bigcup_{i=1}^{|C|} \{a_i[j_l] : 1 \leq j \leq n, 1 \leq l \leq 9\}$$

$$A = \bigcup_{i=1}^{|C|} A_i$$

Notice that the only nodes that appear in the edges belonging to more than a single A_i are those that are in the set X. In every A_i there are n diamond like structures of nodes, where $n = \lceil \frac{k-1}{12} \rceil$. It is not hard to see that this instance of SkE can be constructed in polynomial time from the X3C instance.

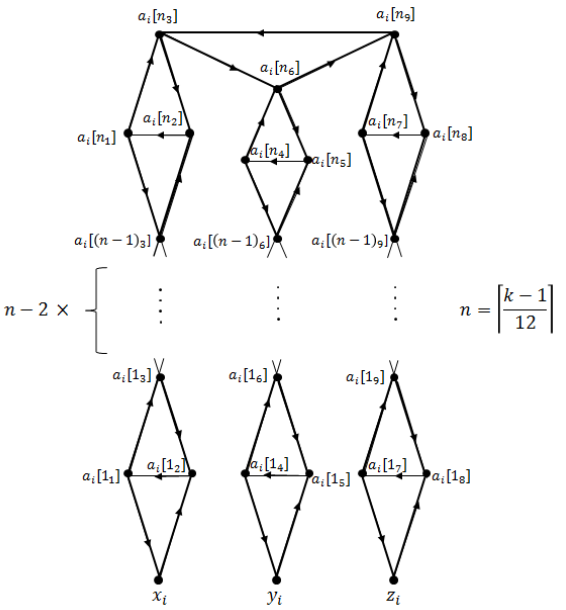

Figure 3.2: Local replacement for $c_i = (x_i, y_i, z_i) \in C$ for transforming X3C to SkE.

If $c_1, c_2, \ldots, c_q$ are the 3-element subsets from C in any exact cover for X, then the corresponding partition $N = C_1 \cup C_2 \cup \ldots \cup C_m$ of N is given by taking

$$\{a_i[1_1], a_i[1_2], x_i\}, \{a_i[1_4], a_i[1_5], y_i\}, \{a_i[1_7], a_i[1_8], z_i\}, \{a_i[n_3], a_i[n_6], a_i[n_9]\}$$

$$\left\{a_i[j_l], a_i[(j+1)_{l-1}], a_i[(j+1)_{l-2}]\right\}, j = 1, \ldots, n-1, l = 3, 6, 9$$

from the nodes meeting A_i whenever $c_i = \{x_i, y_i, z_i\}$ is in the exact cover, and by taking

$$\{a_i[j_l], a_i[j_{l-1}], a_i[j_{l-2}]\}, j = 1, \ldots, n, l = 3, 6, 9$$

from the nodes meeting A_i whenever c_i is not in the exact cover. This ensures that each element of X is included in exactly one 3-node cycle in the partition. Notice that cycles containing more than 3 nodes are never feasible because of the choice of the number n. Indeed, if there would be a cycle C' of length > 3, then the shortest such C' involves a directed path P_1 from s_i to t_i through the gadget corresponding to some subset p and a directed path P_2 from t_i to s_i through the gadget corresponding to some subset p', where $s_i \in \{x_i, y_i, z_i\}$ and $t_i \in \{x_i, y_i, z_i\} \setminus \{s_i\}$. The length of each of P_1 and P_2 is at least $3n + 1 + 3n$, so the length of C' is at least $12n + 2$. Because we have chosen $n = \lceil \frac{k-1}{12} \rceil$, it easily follows that $12n + 2 \geq k + 1$ and that hence C' is infeasible.

Conversely, if $N = C_1 \cup C_2 \cup \ldots \cup C_m$ of N is any partition of D into cycles of size k or less, the corresponding exact cover is given by choosing $c_i \in C$ such that $\{a_i[n_3], a_i[n_6], a_i[n_9]\} = C_j$ for some j, $1 \leq j \leq m$. We leave to the reader the straightforward task of verifying that the two partitions we have constructed are as claimed.

□

Corollary 3.1. *For $3 \leq k \leq |N|$ the hierarchical multicriteria clearing problem is NP-hard.*

3.2.3 Integer programming formulations

The clearing problem can be formulated as a mixed integer linear program. For example, for the single criterion of maximizing the number of transplants the clearing problem can be formulated using the so-called cycle formulation, which we describe below. Although alternative mixed integer programming formulations for the kidney exchange problem have also been investigated, the linear programming (LP) relaxation of the cycle formulation provides the strongest upper bound (Constantino et al., 2013).

Cycle formulation

The cycle formulation, which was first presented in Abraham et al. (2007), uses a binary decision variable x_c for each cycle and chain $c \in C(K)$ that is defined as:

$$x_c = \begin{cases} 1 & \text{if } c \in M^*, \\ 0 & \text{otherwise.} \end{cases}$$

Setting $x = \left[x_1, \ldots, x_{|C(K)|}\right]^T$, the integer program is given by:

P_0:

$$\max\ z_0(x) = \sum_{c \in C(K)} |c| \cdot x_c \tag{3.1}$$

$$\text{s.t.} \sum_{c \in C(K): n \in c} x_c \leq 1 \qquad \forall n \in N \tag{3.2}$$

$$x_c \in \{0, 1\} \qquad \forall c \in C(K)$$

In P_0, the objective (3.1) is to select a collection of cycles and chains that maximizes the number of transplants. The constraints (3.2) ensure that no patient or donor is contained in more than one selected cycle or chain.

The number of variables in the cycle formulation can be very large (see Table 3.1 which shows the number of cycles and chains in pools based on actual data from the Dutch kidney exchange program), particularly because the number of chains grows rapidly with the number of nodes. In an exchange pool with 200 nodes there can be over a billion chains up to length 6, thus the formulation requires at least that many variables. In contrast, Abraham et al. (2007) showed that, when dealing only with cycles up to length 3, this number of variables is often not even attained in pools of 5,000 nodes or more (see Table 2 in Abraham et al. (2007)).

Generalized cycle formulation

The cycle formulation above can be generalized to allow for many other practically relevant criteria, including each of the criteria (i)-(vi) mentioned in the introduction.

Consider a criterion $f_i \in \mathcal{I}$. As before, let $x = \left[x_1, \ldots, x_{|C(K)|}\right]^T$ denote the vector of decision variables that indicate whether a cycle/chain $c \in C(K)$ is selected. In addition, for $n_i, m_i \in \mathbb{N}$, let y_i denote a $n_i \times 1$ vector of auxiliary variables which are allowed to assume values in some subspace $F_i \subseteq \mathbb{R}^{n_i}$. Then, for $w_i \in \mathbb{R}^{|C(K)|}$, $v_i \in \mathbb{R}^{n_i}$, $A_i \in$

Nodes	Arcs	Cycles ≤ 4	Chains ≤ 4	Chains ≤ 6
10	50	0	1.0e+1	5.4e+1
20	192	8.00e+1	2.21e+2	1.34e+2
50	1087	2.04e+2	9.87e+3	2.51e+5
100	4443	5.07e+3	1.84e+5	2.44e+7
200	16412	1.00e+5	2.23e+6	1.34e+9
500	99501	8.58e+6	1.02e+8	5.83e+11

Table 3.1: Average number of cycles and chains over five random kidney exchange pools of the indicated size sampled from historical data of the Dutch national kidney exchange program

$\mathbb{R}^{m_i \times |C(K)|}$, $B_i \in \mathbb{R}^{m_i \times n_i}$, and $b_i \in \mathbb{R}^{m_i}$, the generalized cycle formulation is given by the following integer program:

P_i:

$$\begin{aligned} \max\ z_i(x, y_i) = \quad & w_i^T x + v_i^T y_i && (3.3) \\ \text{s.t.} \quad & (3.2) \\ & A_i x + B_i y_i \leq b_i && (3.4) \\ & x \in \{0,1\}^{|C(K)|} \\ & y_i \in F_i \end{aligned}$$

Here, the objective (3.3) is to maximize $z_i(x)$ with respect to f_i (note that if f_i were to be a minimization criterion, it can be rewritten as a maximization criterion by multiplying the objective coefficients with -1). As before, the constraints (3.2) ensure that no patient or donor is contained in more than one selected cycle or chain. The general constraints (3.4) allow for various relationships between the selected cycles x and the auxiliary variables y_i that are required to model f_i.

Ostensibly, the above formulations can also allow for multiple criteria by including a separate term in the objective function for each criterion under consideration. Each term is then multiplied with the relative weight attached to the criterion it models. As long as the weights are relatively close to each other this approach works well. However, if the criteria are hierarchically ordered, the required scaling of the weights will quickly lead to numerical instability which renders the program to be infeasible. This is, for example, the case with the six criteria used in the Dutch national program. Therefore, in the next subsection, we present a recursive formulation which models the criteria in the hierarchy without leading to numerical instability.

Recursive cycle formulation

In this subsection we present a recursive formulation modelling hierarchical criteria that does not suffer from numerical instability: the *recursive cycle formulation*. The idea is not to capture the hierarchical multi-criteria structure into a single integer program, but instead recursively define multiple programs $R_1, \ldots, R_{|\mathcal{I}|}$ which are linked together by 'objective propagation' constraints. This corresponds to a lexicographic optimization approach (see e.g. Isermann (1982); Rentmeesters et al. (1996)).

The first program in the recursion sequence is the generalized cycle formulation of criterion f_1. In case of the Dutch criteria, we have $R_1 := P_0$, where P_0 is the program we have defined before for the maximization of the number of transplants.

Then, denoting, in addition to the notation introduced above, the optimum value of R_i by z_i^*, the programs R_i, $i = 2, \ldots, |\mathcal{I}|$, are recursively defined as:

R_i:

$$\begin{aligned}
\max\ z_i(x, y_i) = \quad & w_i^T x + v_i^T y_i && && (3.5)\\
\text{s.t.} \quad & (3.2) && &\\
& A_j x + B_j y_j \leq b_j && j = 1, \ldots, i && (3.6)\\
& z_j(x, y_j) \geq z_j^* && j = 1, \ldots, i-1 && (3.7)\\
& x \in \{0,1\}^{|C(K)|} && &\\
& y_j \in F_j && j = 1, \ldots, i &
\end{aligned}$$

As in the generalized cycle formulation, the objective (3.5) is to maximize the single criterion f_i. However, the constraints (3.6) now include all the relationships required for modeling criteria $f_1, \ldots, f_i$. Constraints (3.7) are the objective propagation constraints, which link the program R_i to the programs $R_1, \ldots, R_{i-1}$, by propagating their corresponding objective function values.

The recursive cycle formulation naturally fits the definition of the hierarchical multi-criteria kidney exchange clearing problem. Indeed, the constraints (3.6) and (3.7) directly describe the sets $\mathcal{M}_i$, $i = 1, \ldots, |\mathcal{I}|$. The exchange corresponding to the solution of program $R_{|\mathcal{I}|}$ is the solution to the hierarchical multi-criteria kidney exchange clearing problem.

Step 0	Initialize $C(K)$ and $x = \left[x_1, \ldots, x_{\lvert C(K)\rvert}\right]^T$
FOR	$i = 1, \ldots, \lvert\mathcal{I}\rvert$ DO
Step i	Solve R_i on D: $z_i^* := \max_{x \in \{0,1\}^{\lvert C(K)\rvert}} f_i(x)$ s.t. (3.2), $f_1(x) \geq z_1^*$, …, $f_{i-1}(x) \geq z_{i-1}^*$
END FOR	
Output	$x^* := \operatorname{argmax}_{x \in \{0,1\}^{\lvert C(K)\rvert}} f_{\lvert\mathcal{I}\rvert}(x)$ s.t. (3.2), $f_1(x) \geq z_1^*$, …, $f_{\lvert\mathcal{I}\rvert-1}(x) \geq z_{\lvert\mathcal{I}\rvert-1}^*$ $M^* := \{c \in C(K) : x_c^* = 1\}$

Table 3.2: Iterative algorithm for solving the hierarchical multi-criteria kidney exchange clearing problem

3.3 Iterative solution approach

In this section we will develop an iterative branch-and-price algorithm for solving the hierarchical multi-criteria kidney exchange problem based on the recursive cycle formulation. The idea is to iteratively solve integer programs corresponding to the criteria in the hierarchy. If a program is solved, its objective function value is propagated to the integer program corresponding to the next criterion by means of an objective propagation constraint. Table 3.2 gives a schematic overview of this iterative approach, where R_i and $f_i(x) := f_i(\{c \in C(K) : x_c = 1\})$ respectively denote the integer program corresponding to criterion f_i and the objective function value of the exchange corresponding to $x = \left[x_1, \ldots, x_{\lvert C(K)\rvert}\right]^T$ under criterion f_i. Note that the algorithm is also valid when there is no hierarchy between the criteria and the criteria are captured into a single integer program. The algorithm then requires a single iteration.

3.3.1 Branch-and-price methodology

Because the integer programming formulations described in Section 3.2 with one variable per cycle and chain grow exponentially in the size of the exchange pool, the (recursive) integer programs $R_1, \ldots, R_{\lvert\mathcal{I}\rvert}$ included in the approach of Table 3.2 are solved using branch-and-price. The branch-and-price method starts with a limited subset $C \subseteq C(K)$

of cycles and chains and solves the linear program (LP) relaxation of the integer program (IP) under consideration using the corresponding restricted variable set. Whenever linear programming duality conditions imply that adding variables may improve the solution value, corresponding cycles and chains are generated and added to C. This process repeats until strong duality conditions are satisfied. By doing this repeatedly for each node in a branch-and-bound tree, an optimal integral solution can be obtained.

Generating columns for any of the LP relaxations to $R_1, \ldots, R_{|\mathcal{I}|}$ corresponds to generating cycles and chains in the kidney exchange graph. Let δ_n denote the dual value of the constraint corresponding to node $n \in N$ in (3.2). For the LP relaxation of R_i, $i = 1, \ldots, |\mathcal{I}|$, we have the following reduced cost r_c^i of a cycle or chain $c \in C(K) \setminus C$:

$$r_c^i = w_i[c] - \sum_{n \in c} \delta_n - \sum_{j=1}^{i} \sum_{k=1}^{m_i} A_j[k, c] \cdot \mu_{j,k} - \sum_{j=1}^{i-1} w_j[c] \cdot \nu_j \tag{3.8}$$

where, as before, δ_n denotes the dual value of the constraint corresponding to node $n \in N$ in (3.2), $\mu_{j,k}$ denotes the dual value of the k-th constraint modeling criterion j in (3.6), and ν_j denotes the dual value of the j-th objective propagation constraint in (3.7).

In order to establish LP-optimality we search for cycles with positive reduced cost in the kidney exchange graph (see Section 3.3.3 for details on how this can be accomplished). If no such cycle can be found, the LP has been solved to optimality. If the LP solution is fractional, we branch, restricting one or more variables in the values they can assume, and then resolve the LP. At each node of the branching tree, the LP solution provides an upper bound on the restricted problem of that node. An integral lower bound can be obtained by solving the IP with the columns generated for the LP. If, at any node, the LP upper bound is no better than the best lower bound, its subtree can be pruned. If the IP lower bound matches the upper bound at the root node, the problem has been solved to optimality.

3.3.2 Branch-and-bound

Branching

An important and essential part of any branch-and-price procedure is the branching scheme. In the best branching scheme investigated in Abraham et al. (2007) branching is performed on the cycles and chains in the kidney exchange graph. Whenever the LP solution is fractional, the cycle or chain whose corresponding variable has an LP value closest to 0.5 is selected and two branches are created, one in which the cycle's corresponding variable is set to 0, and one in which it is set to 1. Branches are then explored

using depth-first search. As there are are up to $\sum_{i=2}^{K} |N|^i$ cycles of length K or less in D, the branching tree may have exponential depth. We therefore propose to branch on the arcs, of which there can be only up to N^2. We consider two branching schemes based on the following definition:

Definition 3.10. *An arc $a \in A$ is fractional if*

$$x_a := \sum_{c \in C(K): a \in c} x_c$$

is fractional.

The existence of fractionally selected cycles need not immediately imply that a fractional arc exists. For instance, multiple fractional cycles might overlap, such that $x_a = 1$ for every arc $a \in A$. Fortunately, Theorem 3.2 establishes that this can never be true for all arcs whenever the LP solution is fractional.

Theorem 3.2. *There exists a fractional arc if and only if the LP solution is fractional.*

Proof. The first implication is trivial: if $a \in A$ is a fractional arc, then by definition of x_a, there must be at least one $c \in C(K) : a \in c$ for which x_c is fractional. To prove the other implication, suppose c_1 is a fractionally selected cycle containing arcs $a_1, a_2, \ldots, a_{|c_1|}$. If any arc $a \in c_1$ is not also covered by at least one other fractionally selected cycle, then $x_a = x_{c_1}$ and hence a is fractional. Therefore suppose there are one or more other fractional cycles which have at least one arc in common with cycle c_1. Now, let c_2 be such a fractional cycle containing, without loss of generality, arc $a_1 = (n_1, n_2)$ but not arc $a_2 = (n_2, n_3)$, and let $c_3, \ldots, c_m$ be all other fractional cycles containing arc a_1. There are two options: either $\sum_{i=1}^{m} x_{c_i} = 1$ or $\sum_{i=1}^{m} x_{c_i} < 1$. In the first case, $x_{a_1} = \sum_{i=1}^{m} x_{c_i} = 1$ so arc a_1, and hence node n_2, is totally covered, implying that no positively valued cycle $c \in C(K) \setminus \{c_1, c_3, \ldots, c_m\}$ can cover arc $a_2 = (n_2, n_3)$, and that therefore $x_{a_2} \in [x_{c_1}, 1 - x_{c_2}]$, making arc a_2 fractional. In the second case, $x_{a_1} = \sum_{c=1}^{m} x_c < 1$ and thus arc a_1 is fractional. This completes the proof. □

In our first branching scheme, we branch on groups of multiple arcs. If the LP solution is fractional, we select the node with the largest number of fractional out-arcs and then divide its out-arcs in two subsets, S_1 and S_2, and create a branch for each subset. In each branch, all the arcs of its corresponding subset are banned. The subsets S_1 and S_2 are

determined by adding arcs to S_1 in non-decreasing order of x_a value, until the sum of x_a values of arcs in S_1 is at least 0.5. The remainder of the arcs are added to S_2. Theorem 3.2 guarantees us that we can always find a node with at least one fractional out-arc.

In the second branching scheme, we branch on only one arc at a time. If the LP solution is fractional, we select the arc with fractional value closest to 0.5. We then create two branches: one in which the arc is banned, and one in which it is enforced. Again, Theorem 3.2 guarantees that a fractional arc always exists, and, moreover, that when we have branched on all fractional arcs, we have an integer solution.

In order to enforce an arc $a \in A$ in the master problem, we need to add the following constraint:

$$\sum_{c \in C(K): a \in c} x_c = 1 \tag{3.9}$$

Adding constraint (3.9) to the master problem changes the reduced cost of a cycle or chain. In particular, if $A^* \subseteq A$ is the set of enforced arcs, the reduced cost r_c^i of a cycle or chain $c \in C(K) \setminus C$ in problem R_i is now given by:

$$r_c^i = w_i[c] - \sum_{n \in c} \delta_n - \sum_{j=1}^{i} \sum_{k=1}^{m_i} A_j[k, c] \cdot \mu_{j,k} - \sum_{j=1}^{i-1} w_j[c] \cdot \nu_j - \sum_{a \in A^*} \mathbf{1}_{a \in c} \xi_a \tag{3.10}$$

where, in addition to the previously introduced notation, ξ_a is the dual value of constraint (3.9) and $\mathbf{1}_{a \in c}$ is an indicator function which is 1 if $a \in c$ and 0 otherwise.

Note that banning an arc in the master problem is trivial, because that arc can simply be removed from the graph.

Bounding

In all cases, before branching, integral upper and lower bounds can be derived from the last iteration of the algorithm. For example, in Step 2 of the iterative solution algorithm, the maximum number of blood type identical transplants can not be higher than the total number of transplants determined in Step 1. Nor can it be lower than the number of blood type identical transplants in Step 1's solution. These derived bounds are used to prune the irrelevant parts of the branching tree as soon as they violate the bounds.

If the objective is to maximize the number of transplants, an upper bound can be derived by determining in polynomial time the maximum number of transplants when $K = \infty$. If there is a low number of highly-sensitized patients (i.e. patients who are

crossmatch incompatible with many donors), Roth et al. (2007) have shown that this upper bound is tight.[2] As in Abraham et al. (2007) such an upper bound can be determined by finding a maximum weight matching in a bipartite graph with donors on one side and patients on the other. Let us denote this bipartite graph as $G = (U, V, E)$, with U denoting the patients, V denoting the donors, and E denoting the edges. Donors are connected to their own patients with a zero-weight edge and to all other compatible patients with an edge of weight 1.

For each edge $e \in E$, let x_e be defined as:

$$x_e = \begin{cases} 1 & \text{if } e \text{ is selected,} \\ 0 & \text{otherwise.} \end{cases}$$

A maximum weight matching can then be found in polynomial time by solving the following LP[3]:

$$\begin{aligned} \max \quad & \sum_{e \in E} w_e \cdot x_e & & \\ \text{s.t.} \quad & \sum_{e=\{u,v\} \in E} x_e = 1 & & \forall u \in U \\ \text{s.t.} \quad & \sum_{e=\{u,v\} \in E} x_e = 1 & & \forall v \in V \\ & x_e \in [0,1] & & \forall e \in E \end{aligned}$$

During the branching process the initial bounds may be improved upon by the LP solutions (which provide an upper bound), or by a primal heuristic for constructing a feasible integer solution (which provides a lower bound). In all branching schemes, we use, as a primal heuristic, the solution to the IP with the columns generated for the LP. If, at any node of the branching tree, the LP upper bound is no better than the best lower bound, that node's subtree can be pruned. If, at any node, the IP lower bound matches the upper bound at the root node, the problem has been solved to optimality.

[2] In their simulations Roth et al. (2007) use instances in which 10 % of the patients is highly sensitized, which in their study implies that these patients are crossmatch incompatible with 90 % of the donors.

[3] Although in principle a graph-based algorithm for maximum weight matching could also be used, for large instances it is often faster to solve the indicated linear program, possibly with delayed edge generation

3.3.3 Pricing

In Abraham et al. (2007) the pricing problem is solved by traversing the kidney exchange graph D in search for a positive price cycle. In the worst case, this procedure enumerates all cycles in D and therefore is of order $\mathcal{O}(|N|^K)$, which is exponential in the size of the input. In this section we present a polynomial algorithm to solve the pricing problem in $\mathcal{O}(K\,|N|\,|A|)$ time.

The algorithm requires that the reduced cost of a cycle can be expressed as a linear function of arc weights. Therefore, we first formulate the following lemma on the reduced cost of a cycle or chain in the recursive cycle formulation.

Lemma 3.1. *If the objective coefficients $w_j[c]$ and the constraint coefficients $A_j[k,c]$, $j = 1,\dots,i$, $k = 1,\dots,m_j$ for each cycle or chain $c \in C(K)$ in problem R_i can be described as linear functions of arc weights, then there exist weights $\pi_a^i \in \mathbb{R}$, for all arcs $a \in A$, such that, for every cycle and chain $c \in C(K)$,*

$$r_c^i = \sum_{a \in c} \pi_a^i \tag{3.11}$$

i.e. the reduced cost of c can also be described as a linear function of arc weights.

Proof. Let $w_i[c] = \sum_{a\in c} \alpha_i \omega_{i,a}$ and $A_j[k,c] = \sum_{a\in c} \beta_{i,j}\omega'_{j,k,a}$ for $j = 1,\dots,i$ and $k = 1,\dots,m_j$, then by (3.10),

$$\begin{aligned}
r_c^i &= w_i[c] - \sum_{n\in c}\delta_n - \sum_{j=1}^{i}\sum_{k=1}^{m_i} A_j[k,c]\cdot\mu_{j,k} - \sum_{j=1}^{i-1} w_j[c]\cdot\nu_j - \sum_{a\in A^*}\mathbf{1}_{a\in c}\xi_a \\
&= \sum_{a\in c}\alpha_i\omega_{i,a} - \sum_{n\in c}\delta_n - \sum_{j=1}^{i}\sum_{k=1}^{m_i}\sum_{a\in c}\beta_{i,j}\omega'_{j,k,a}\cdot\mu_{j,k} - \sum_{j=1}^{i-1}\sum_{a\in c}\alpha_j\omega_{j,a}\cdot\nu_j \\
&\quad - \sum_{a\in A^*}\mathbf{1}_{a\in c}\xi_a \\
&= \sum_{a=\{n,n'\}\in c}\left(\alpha_i\omega_{i,a} - \delta_{n'} - \sum_{j=1}^{i}\sum_{k=1}^{m_i}(\beta_{i,j}\omega'_{j,k,a})\cdot\mu_{j,k} - \sum_{j=1}^{i-1}(\alpha_j\omega_{j,a})\cdot\nu_j - \mathbf{1}_{a\in A^*}\xi_a\right) \\
&= \sum_{a=\{n,n'\}\in c}\pi_a^i
\end{aligned}$$

where

$$\pi_a^i = \alpha_i \omega_{i,a} - \delta_{n'} - \sum_{j=1}^{i} \sum_{k=1}^{m_i} (\beta_{i,j} \omega'_{j,k,a}) \cdot \mu_{j,k} - \sum_{j=1}^{i-1} (\alpha_j \omega_{j,a}) \cdot \nu_j - \mathbf{1}_{a \in A^*} \xi_a \tag{3.12}$$

with δ_n the dual value of the constraint (3.2) for node n, $\mu_{j,k}$ the dual value of the k-th constraint modeling criterion j in (3.6), ν_j the dual value of the j-th objective propagation constraint in (3.7), and ξ_a the dual value of constraint (3.9). □

The linear relationship between the objective and constraint coefficients and the arcs in D holds for most criteria used in practice. In particular, all of the Dutch criteria have this property. Also, the constraints required for branching on arcs have this property. Note, however, that the constraints required to branch on cycles (as used by Abraham et al. (2007)) do not satisfy this relationship, because they require constraints to enforce the inclusion of a single cycle.

Now, let us define a reversion operator as follows:

Definition 3.11. *For any directed cycle or chain* $c = \langle n_1, n_2, \ldots, n_{|c|} \rangle$*, the directed cycle (respectively chain)*

$$c^{-1} := \langle n_{|c|}, n_{|c|-1}, \ldots, n_1 \rangle$$

is the reverse of c*.*

The pricing problems can now be solved in polynomial time through the algorithm given in Table 3.3. The algorithm first constructs the arc set $\widetilde{A} \subseteq A$ of arcs that are not banned and then determines for each starting node $n \in N$ a shortest path up to length K in $\widetilde{D} = (N, \widetilde{A})$ (depending on whether node n corresponds to an unspecified donor or not) using an adapted version of the Bellman-Ford method (Bellman, 1958)(Ford, 1956). For each node $n \in N$ and $k = 0, 1, \ldots, K$ the algorithm calculates functions $f_k^n : N \to \mathbb{R} \cup \{\infty\}$ and $g_k^n : N \to N$ that respectively provide the weight of the shortest path between n and any other node $n' \in N$ using at most k arcs, and the predecessor of node $n' \in N$ on such a shortest $n - n'$ path.

The algorithm consists of four main steps. Before executing the main steps, Step 0 transforms the arc specific weights obtained from Lemma (3.1) such that the pricing problem becomes a minimization problem. Then, for each node $n \in N$, Step 1 initializes the functions f_k^n and g_k^n, Step 2 calculates the function values of f_k^n and g_k^n in case of a cycle (i.e. $n \in N_S$), and Step 3 calculates the function values in case of a chain (i.e.

$n \in N_U$). The final step, Step 4, checks whether there are cycles or chains with positive reduced cost and, if there are, constructs them in reverse from the function values of g_k^n.

As stated in Theorem 3.3 below, the algorithm is exact, i.e. it always finds a positive price cycle or chain if one exists. In fact, for each starting node it finds the maximum weight cycle or chain of length at most K. However, it might be the case that a cycle or chain returned by the algorithm contains a subcycle (and hence is not feasible for the master problem). In the case of such a compound cycle or chain, Theorem 3.3 guarantees us that the subcycle will always have a positive price. We can choose to abort the algorithm as soon as a positive price cycle or chain is found, or it can be run to completion, possibly resulting in multiple positive price cycles and chains being identified (*Nota bene*, if run to completion, the algorithm will output each cycle c^* up to $|c^*|$ times, therefore it may be desirable to filter the generated cycles for duplicates).

Before providing the theorem, we first introduce the following definition:

Definition 3.12. *For any directed cycle c composed of simple cycles $\sigma_1, \ldots, \sigma_m$ in $D = (N, A)$, and arc weights $\pi_a^i \ \forall \ a \in A$, the maximum simple cycle $S(c)$ is the cycle given by*

$$S(c) = argmax_{\sigma \in \{\sigma_1, \ldots, \sigma_m\}} \left\{ \sum_{a \in \sigma} \pi_a^i \right\}$$

Theorem 3.3. *$C^* \neq \emptyset$, and, for all $c^* \in C^*$, $S(c^*) \in C(K)$ and $r^i_{S(c^*)} > 0$, if and only if $\exists c \in C(K) : r_c^i > 0$.*

Proof. Analogous to the Bellman-Ford method, we have, for each $n, n' \in N_S$, $k = 0, \ldots, K$, that

$$\begin{aligned} f_k^n(n') &= \min \left\{ \sum_{a \in P} w'_a : P \text{ is an } n - n' \text{ walk traversing at most } k \text{ arcs} \right\} \\ &= \max \left\{ \sum_{a \in P} w_a : P \text{ is an } n - n' \text{ walk traversing at most } k \text{ arcs} \right\} \end{aligned}$$

Then, obviously,

$$\begin{aligned} c^*(n) &:= \{n', g^n(n'), g^n(g^n(n')), \ldots, n\}^{-1} \\ &= \text{argmax} \left\{ \sum_{a \in P} \pi_a^i : P \text{ is an } n - n \text{ walk traversing at most } k \text{ arcs} \right\} \end{aligned} \tag{3.13}$$

Step 0 Set $w'_a := -\pi^i_a \; \forall \; a \in \widetilde{A}$ as in (3.12), $C^* = \emptyset$

FOR EACH Node $n \in N$ DO

Step 1 Set $f^n_0(n) := 0$ and, $\forall \; n' \in N \backslash \{n\}$, $f^n_0(n') := \infty$ and $g^n_0(n') := \emptyset$

Step 2 IF $n \in N_S$ THEN

set, for $k = 0, \ldots, K-2$, and for all $n' \in N$,

$$\hat{a} = (n'', n') := \text{argmin}_{a=(u,n') \in \widetilde{A}} \{f^n_k(u) + w'_a\},$$

$$f^n_{k+1}(n') := \min \{f^n_k(n'), f^n_k(n'') + w'_{\hat{a}}\},$$

$$g^n_{k+1}(n') := \begin{cases} n'' & \text{if } f^n_k(n'') + w'_{\hat{a}} < f^n_k(n'), \\ g^n_k(n') & \text{otherwise.} \end{cases}$$

Step 3 ELSE IF $n \in N_U$ THEN

set, for $k = 0, \ldots, K-1$, and for all $n' \in N$,

$$\hat{a} = (n'', n') := \text{argmin}_{a=(u,n') \in \widetilde{A}} \{f^n_k(u) + w'_a\},$$

$$f^n_{k+1}(n') := \min \{f^n_k(n'), f^n_k(n'') + w'_{\hat{a}}\},$$

$$g^n_{k+1}(n') := \begin{cases} n'' & \text{if } f^n_k(n'') + w'_{\hat{a}} < f^n_k(n'), \\ g^n_k(n') & \text{otherwise.} \end{cases}$$

END FOR

Step 4 For $n, n' \in N_S$, if $(n', n) \in \widetilde{A}$ and $f^n_{K-1}(n') + w'_{\{n',n\}} < 0$,

$$C^* \rightarrow C^* \cup \left\langle n', g^n_{K-1}(n'), g^n_{K-2}(g^n_{K-1}(n')), \ldots, n \right\rangle^{-1},$$

and, for $n \in N_U, n' \in N_S$, if $f^n_K(n') < 0$,

$$C^* \rightarrow C^* \cup \left\langle n', g^n_{K-1}(n'), g^n_{K-2}(g^n_{K-1}(n')), \ldots, n \right\rangle^{-1}$$

Table 3.3: Polynomial pricing algorithm

is a, possibly compound, maximum weight cycle with length at most K. Let $\sigma_1(n), \ldots, \sigma_m(n)$ be the simple cycles composing $c^*(n)$ (if $c^*(n)$ itself is a simple cycle, $m = 1$ and $\sigma_1(n) = c^*(n)$). By definition, $S(c^*(n)) \in \{\sigma_1, \ldots, \sigma_m\} \subseteq C(K)$. Therefore, it remains to prove that $\exists n \in N_S : c^*(n) \in C^*$ and that, for all $n \in N_S : c^*(n) \in C^*$, $\sum_{a \in S(c^*(n))} \pi_a^i > 0$.

To prove the first part, let $c \in C(K)$ be a cycle with $\sum_{a \in c} \pi_a^i > 0$ and let $n \in c$. By (3.13) we then have that $\sum_{a \in c^*(n)} \pi_a^i \geq \sum_{a \in c} \pi_a^i > 0$, and, therefore

$$f_{K-1}^n(n') + w_{\{n',n\}} = \sum_{a \in c^*(n)} w'_a = -\sum_{a \in c^*(n)} \pi_a^i < 0$$

which implies that $c^*(n) \in C^*$ as desired.

To prove the second part, let $n \in N_S : c^*(n) \in C^*$. Then

$$\sum_{a \in c^*(n)} \pi_a^i = \sum_{a \in \sigma_1(n)} \pi_a^i + \ldots + \sum_{a \in \sigma_m(n)} \pi_a^i > 0.$$

Because of this, $\exists \sigma \in \{\sigma_1(n), \ldots, \sigma_m(n)\} : \sum_{a \in \sigma} \pi_a^i > 0$, and, by definition 3.12, $\sum_{a \in S(c^*(n))} \pi_a^i > 0$ as desired. The proof for chains is analogous. □

Corollary 3.2. *Given a kidney exchange graph $D = (N, A)$ and arc weights $\pi_a^i \ \forall \ a \in A$, a positive weight cycle or chain up to length K, if one exists, can be found in time $\mathcal{O}(K\,|N|\,|A|)$.*

Proof. The proof follows directly from the description of the algorithm in Table 3.3. □

3.4 Simulations

We test our algorithm using several realistic simulators. The first is a kidney exchange simulator based on historical data from the Dutch national kidney exchange program. This simulator is described in detail in (Glorie et al., 2013). The second is the simulator described in (Saidman et al., 2006) (and used in (Abraham et al., 2007)), which is the most commonly used generator for kidney exchange pools. This second simulator is based on US population data. We use the simulators to generate both static kidney exchange pools (individual pools sampled from the available patient-donor population) as well as dynamic sequences of pools and exchanges (pools that dynamically evolve by simulating arrivals sampled from the patient-donor population and by simulating removals due to exchanges and, for example, patient illness). In this section we will briefly explain the main aspects of the data and simulation procedures. Tables 3.6, 3.7 and 3.8 give an overview of the pool composition under the various simulators.

3.4.1 Static simulation with Dutch clinical data

The data for our first simulator is obtained from the Dutch Transplant Foundation Nederlandse Transplantatie Stichting (NTS) (2012) and originates from the empirical registry of the Dutch national kidney exchange program. It includes 438 incompatible patient-donor pairs who participated in Dutch kidney exchanges between October 2003 and January 2011. In addition it contains 109 unspecified donors who were screened at one of the seven Dutch transplant centers during that period. Each patient and donor has a blood type as well as a registration center. Donors also have a record of their antigen types, while patients have a record of the antigen types that are medically unacceptable to them. Patients and donors are marked as blood type or crossmatch (in)compatible based on the data. A static kidney exchange pool is generated at random from the data using sampling with replacement.

Using Table 3.6, which details the characteristics of the patients and donors in the data set described above, a pool with similar characteristics as the Dutch pool can be easily constructed by generating pairs and unspecified donors by sampling randomly from the categories listed in the table. Each category should then have a probability of being sampled equal to the percentage listed in the table.

3.4.2 Static simulation with US population data

We also perform simulations with US population data using the simulator described in (Saidman et al., 2006). The simulation is based on data from the United Network for Organ Sharing (UNOS) in the US. The simulator generates patients with a random blood type, sex, and probability of being crossmatch incompatible (this probability is called the percentage Panel Reactive Antibody (PRA)) with a randomly chosen donor. Each patient is assigned a potential donor with a random blood type and relation to the patient. If the patient and the potential donor are incompatible, they are added to the kidney exchange pool. Blood types and probabilities of crossmatch failure are then used to determine the compatibilities in the pool. Table 3.4 summarizes the probabilities as described in (Saidman et al., 2006). Because the original simulator did not include unspecified donors, we add to each pool a fixed percentage of unspecified donors (generated as above but without assignment to a patient).

Prob. blood type A	.3373
Prob. blood type B	.1428
Prob. blood type AB	.0385
Prob. blood type O	.4814
Prob. low PRA (5 %)	.7019
Prob. medium PRA (10 %)	.2
Prob. high PRA (90 %)	.0981
Prob. female	.409
Prob. spousal donor*	.4897
% unspecified donor**	4.5
* Applies to female patients only. Spousal PRA := 1 - .75 (1 - PRA)	
** Original simulator did not have altruistic donors	

Table 3.4: Probabilities in Saidman simulator

3.4.3 Sparse pools

Ashlagi and Roth (2012) recently found that the percentage of highly sensitized patients (i.e. patients with a high probability of crossmatch incompatibility with a randomly chosen donor) in practice can be significantly higher than assumed in (Saidman et al., 2006). A possible reason for a higher percentage of highly sensitized patients could be the use of more sensitive crossmatching techniques. Ashlagi and Roth (2012) describe an empirical distribution in which half of the patients have a very high PRA - between 95 and 100 % - and the other half have a very low PRA - between 0 and 5 % (see Table 1 in Ashlagi and Roth (2012)). Because of this a kidney exchange pool can in practice be much sparser than the pools generated by the Saidman simulator. We make some modifications to the Saidman simulator to reflect this phenomenon of sparse pools. In particular, we adjust the value for low PRA to 2.5 % and the value for high PRA to 97.5 % and we modify the frequencies such that the simulated pool contains approximately 50% highly sensitized patients. Table 3.5 summarizes the probabilities in the modified simulator.

Prob. blood type A	.3373
Prob. blood type B	.1428
Prob. blood type AB	.0385
Prob. blood type O	.4814
Prob. low PRA (2.5 %)	.7
Prob. high PRA (97.5 %)	.3
Prob. female	.409
Prob. spousal donor*	.4897
% unspecified donor	4.5
* Applies to female patients only. Spousal PRA := 1 - .75 (1 - PRA)	

Table 3.5: Probabilities in modified Saidman simulator

3.4.4 Dynamic simulations

We use the static simulators described above to perform dynamic kidney exchange simulations as described in (Glorie et al., 2013). The dynamic simulation procedure consists of repeated simulated arrivals and exchanges.

For the Dutch simulator we generate a population by sampling from the historical population (we generate the same number of arrivals as in the data set) and then assign each pair and each unspecified donor in the population a random arrival date. Arrival

Dutch simulator								
		Donor blood type						
		O		A		B		AB	
Patient blood type	O	% PRA 0-80:	10.6	% PRA 0-80:	24.1	% PRA 0-80:	3.8	% PRA 0-80:	.6
		% PRA 80-95:	.9	% PRA 80-95:	1.1	% PRA 80-95:	.1	% PRA 80-95:	.0
		% PRA 95-100:	.7	% PRA 95-100:	1.3	% PRA 95-100:	.2	% PRA 95-100:	.0
	A	% PRA 0-80:	5.8	% PRA 0-80:	6.8	% PRA 0-80:	5.3	% PRA 0-80:	.4
		% PRA 80-95:	.9	% PRA 80-95:	2.0	% PRA 80-95:	.3	% PRA 80-95:	.2
		% PRA 95-100:	.6	% PRA 95-100:	1.4	% PRA 95-100:	.3	% PRA 95-100:	.0
	B	% PRA 0-80:	2.3	% PRA 0-80:	6.1	% PRA 0-80:	1.0	% PRA 0-80:	.2
		% PRA 80-95:	.4	% PRA 80-95:	.5	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	.6	% PRA 95-100:	.6	% PRA 95-100:	.2	% PRA 95-100:	.0
	AB	% PRA 0-80:	.2	% PRA 0-80:	1.0	% PRA 0-80:	.0	% PRA 0-80:	.0
		% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0
	-	% Unspecified	10.3	% Unspecified	7.7	% Unspecified	.8	% Unspecified	.8

Table 3.6: Pool composition in the Dutch simulator (averages over 10 instances). % PRA refers to the percentage of the pool with which the patient is crossmatch incompatible.

Saidman simulator								
		Donor blood type						
		O		A		B		AB	
Patient blood type	O	% PRA 0-80:	4.5	% PRA 0-80:	29.1	% PRA 0-80:	12.3	% PRA 0-80:	2.7
		% PRA 80-95:	4.0	% PRA 80-95:	3.2	% PRA 80-95:	1.4	% PRA 80-95:	.0
		% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0
	A	% PRA 0-80:	3.2	% PRA 0-80:	2.2	% PRA 0-80:	8.5	% PRA 0-80:	2.2
		% PRA 80-95:	2.7	% PRA 80-95:	2.0	% PRA 80-95:	.9	% PRA 80-95:	.2
		% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0
	B	% PRA 0-80:	1.3	% PRA 0-80:	8.6	% PRA 0-80:	.4	% PRA 0-80:	1.0
		% PRA 80-95:	1.1	% PRA 80-95:	1.0	% PRA 80-95:	.4	% PRA 80-95:	.1
		% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0
	AB	% PRA 0-80:	.4	% PRA 0-80:	.3	% PRA 0-80:	.1	% PRA 0-80:	.0
		% PRA 80-95:	.3	% PRA 80-95:	.2	% PRA 80-95:	.1	% PRA 80-95:	.0
		% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0	% PRA 95-100:	.0
	-	% Unspecified	2.2	% Unspecified	1.5	% Unspecified	.6	% Unspecified	.2

Table 3.7: Pool composition in the Saidman simulator (averages over 10 instances). % PRA refers to the percentage of the pool with which the patient is crossmatch incompatible.

Modified Saidman simulator								
		Donor blood type						
		O		A		B		AB	
Patient blood type	O	% PRA 0-80:	2.4	% PRA 0-80:	16.3	% PRA 0-80:	7.1	% PRA 0-80:	2.6
		% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	11.9	% PRA 95-100:	9.1	% PRA 95-100:	3.1	% PRA 95-100:	1.1
	A	% PRA 0-80:	1.3	% PRA 0-80:	1.1	% PRA 0-80:	5.6	% PRA 0-80:	1.5
		% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	7.8	% PRA 95-100:	5.4	% PRA 95-100:	2.3	% PRA 95-100:	.7
	B	% PRA 0-80:	.5	% PRA 0-80:	5.7	% PRA 0-80:	.2	% PRA 0-80:	.6
		% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	3.2	% PRA 95-100:	2.4	% PRA 95-100:	1.0	% PRA 95-100:	.3
	AB	% PRA 0-80:	.1	% PRA 0-80:	.1	% PRA 0-80:	.0	% PRA 0-80:	.0
		% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0	% PRA 80-95:	.0
		% PRA 95-100:	.9	% PRA 95-100:	.6	% PRA 95-100:	.3	% PRA 95-100:	.1
	-	% Unspecified	2.1	% Unspecified	1.5	% Unspecified	.6	% Unspecified	.2

Table 3.8: Pool composition in the modified Saidman simulator (averages over 10 instances). % PRA refers to the percentage of the pool with which the patient is crossmatch incompatible.

dates are drawn uniformly, corresponding to a Poisson arrival process. In each exchange round, the optimization algorithm described in Section 3.3 implemented with the Dutch hierarchical criteria identifies a matching. The last donor of each chain in an exchange round donates to the waiting list (hence, this donor is not available for future exchange rounds). Proposed matches may fail with a probability depending on patient and donor characteristics. If matches fail this information is incorporated in the compatibility matrix and the optimization algorithm is rerun for the present exchange round. This process is repeated until a feasible matching is found. Patients and donors may leave the pool over time due to simulated attrition and reneging. For the precise probabilities we refer to (Glorie et al., 2013).

When using the simulator with US data we generate a population of size 10,000 and then, for every exchange, we generate a fixed number of arrivals by sampling with replacement from this population. In each exchange round, the optimization algorithm described in Section 3.3 implemented with the maximum number of transplants criterion identifies a matching. Match failure is simulated as above. We use this dynamic simulation to study the clearing time of pools in a dynamic state. We do this by considering the clearing time of the tenth exchange round.

3.5 Computational results

Our experiments were performed on a Windows 7 64-bit computer with a 3 GHz AMD Athlon II X2 processor and 4 GB of RAM. The iterative branch-and-price algorithm has been implemented in C#.NET and LP's and IP's are solved using CPLEX 12.5.

Table 3.9 displays the run time performance of our algorithm with the single objective of maximizing the number of transplants (all transplants have equal weight) on instances constructed by the simulator with Dutch clinical data described in Section 3.4.1. The performance of the different pricing and branching strategies described in Section 3.3 is compared on instances of various sizes. The cycle length limit is set to either 3 (short cycles) or 4 (long cycles) and the chain length limit is set to either 3 (short chains) or 6 (long chains).

In our comparisons we include the depth-first pricing algorithm with cycle branching as described in Abraham et al. (2007). In this algorithm, the kidney exchange graph is traversed for positive price cycles by exploring nodes in non-decreasing dual value order. Intermittently, the search path is pruned based on the fact that new nodes will have dual value as least as large as the current node.

In all instances the master problem is seeded with a starting collection of 10,000 random cycles and chains (generated by random walks from a randomly chosen node in the kidney exchange graph until a feasible cycle or chain is found). The collection of cycles and chains is managed such that whenever the problem contains more than 400,000 cycles and chains, the cycles and chains with the lowest reduced cost are deleted (excepting those that are branched on or have a non-zero LP value). Per pricing iteration up to 100 new cycles and chains are added (except in the depth-first pricing algorithm, where we adhered to the setting of 1 new cycle or chain per iteration, as advised in Abraham et al. (2007) and which, after tuning, we found to work best for this pricing algorithm).

The first column in Table 3.9 indicates the pool size. The second column contains the total run time in seconds. The third and fourth column respectively contain the time spent on solving LP's and IP's for the master problem. When branching is applied, the fifth column reports the number of processed nodes in the branch-and-bound tree over the total number of nodes in the tree; the sixth column reports the total time required for solving pricing problems.

As can be seen from the table, our algorithm is able to find optimal solutions in instances with 500 nodes – which contain around 5.83e+11 chains up to length 6 (see Table 3.1) – within two minutes. In almost all instances the polynomial pricing algorithm performs better than the depth-first pricing algorithm. In fact, using depth-first pricing, the algorithm is not able to solve the larger instances within the imposed time-limit of three hours (see the instance with 500 nodes), because the pricing takes too much time. Using polynomial pricing all instances can be solved fast. Subset arc branching appears to require the least amount of branching decisions of the various branching strategies, although the difference in performance is small. Often the optimal solution is already found in the root of the branch-and-bound tree.

Next, we perform experiments with instances constructed by the simulator with US population data described in Section 3.4.2-3.4.4. When we consider only cycles and chains up to length 3 all algorithms perform similarly, therefore we directly proceed and report results for cycles up to length 4 and chains up to length 6 ($K = 4$ and $L = 6$). We generate various instances using both static and dynamic simulation with the Saidman simulator and the modified Saidman simulator.

Tables 3.10 and 3.11 summarize the average performance characteristics over, respectively, the static and the dynamic instances. The columns in Table 3.10 and 3.11 are similar to the columns in Table 3.9, except that now, as not all versions of the algorithm are able to solve all the instances, the percentage of solved instances is reported in the last column.

The findings reported in Tables 3.10 and 3.11 are in line with the findings reported in Table 3.9 for static instances generated with Dutch data. Both for the instances generated by the Saidman simulator and the sparser instances generated by the modified Saidman simulator the polynomial pricing algorithm performs much better than the depth first algorithm, regardless of whether they are simulated as static or dynamic. In fact, when using depth-first pricing with cycle branching, many of the larger instances cannot be solved within the imposed time limit of three hours (this is the case for 20 percent of the instances with 500 nodes, and 80 percent of the instances with 1,000 nodes) while all of these instance can be solved within reasonable time when using polynomial pricing. As before, many instances can be solved in the root of the branching tree, but, in total, branching is now required for more instances. When branching is required, arc branching appears to be slightly more effective than subset arc branching because it leads to fewer branches on average (see the 1,000 node instances).

As (Ashlagi et al., 2011b) have shown, allowing longer cycles and chains is important to increase the number of transplants for the hardest to match patients. This is especially true if the pool is sparse. Allowing long cycles and chains may also be important for objectives other than maximizing the number of transplants, whether they are captured through a hierarchical objective function or through a single weighted objective function. By allowing longer cycles and chains these objectives may be improved.

Table 3.12 and Figure 3.3 display the long term effects of using the multiple hierarchical criteria used in the Netherlands. In particular, Table 3.12 shows the percentage of instances showing improvement in the i-th objective criterion and Figure 3.3 shows the relative difference on the total number of transplants, the average wait time, the number of highly sensitized patients (patients with PRA > 80) transplanted, and O patients transplanted versus (a) a policy using only the single criterion of maximizing the number of transplants, and (b) a policy using only short cycles and chains.

As we can see from Table 3.12, additional criteria often make a difference, even if they have a low hierarchical ranking. For instance, in our simulations, Dutch criterion (vi) constitutes an improvement in 34.5 % of the instances. While the long run improvement in the total number of transplants versus a single criterion policy aimed at just maximizing the number of transplants is small (see Figure 3.3), the improvement in terms of highly sensitized patients transplanted is significant. This - normally disadvantaged - group can receive up to 4.5 percent more transplants when using the Dutch allocation criteria. Also O type patients, which are another disadvantaged group, benefit by over 3 percent. Furthermore, Figure 3.3 shows how long cycles and chains may lead to a 9 percent improvement of average waiting time.

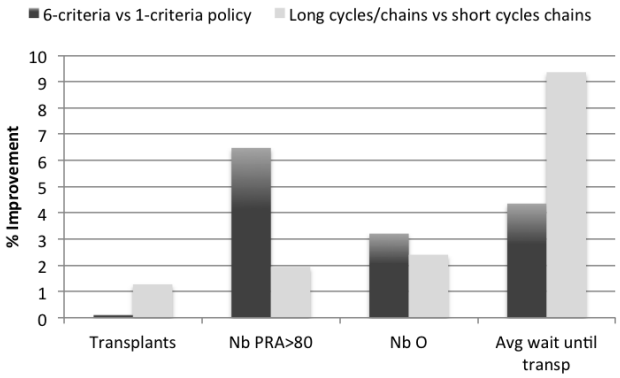

Figure 3.3: Long term effects using Dutch hierarchical criteria. Cycle limit is 4, chain limit is 6. Dark bars: comparing the 6-criteria policy versus the 1-criteria 'maximum transplants' policy. Light bars: comparing the 6-criteria policy versus the 6-criteria policy with cycles and chains limited to 3.

3.6 Conclusions

In this paper we have shown how to clear large multi-criteria kidney exchanges with long chains using a general and scalable exact algorithm. This is particularly important because, over the last years, kidney exchange has quickly increased as a modality for transplanting end stage renal disease patients with an incompatible living donor and long exchange chains have turned out to be increasingly important to help the most disadvantaged patients. Most kidney exchange programs not only seek to maximize directly the number of transplants, but also seek to optimize other objectives, such as fairness prescribed in international treaties (e.g. Council of Europe (2002)). For this reason many programs use a set of multiple, often hierarchical, optimization criteria. Using our algorithm, we can effectively deal with such criteria, even in large and sparse exchange pools that now begin to arise in practice.

To maximize the benefits from exchange it should be coordinated at an (inter-)national level. However, participation barriers for transplant centers may prevent such nationally coordinated kidney exchange from being established. To make such coordination possible then, participation constraints must be included. Our algorithm can also deal with such constraints by including them as a hierarchical objective at the highest level.

Mathematically, the algorithm consists of an iterative branch-and-price procedure. By using a general but effective class of integer programming formulations we are able to

optimally clear exchange pools with billions of cycles and chains within minutes. The key part of our algorithm is a polynomial pricing procedure for this class of formulations in combination with a branching strategy that branches on arcs or on subsets of arcs. These elements allow us to efficiently deal with long chains which would not be possible with depth-first pricing techniques suggested in previous research.

We hope our algorithm may serve as a reference solution framework for other researchers, so that solution methods and data can be shared, to the benefit of the patients suffering from end stage renal disease across the globe. Our approach is also easily applicable to other types of barter exchange markets besides kidney exchange and can therefore have implications for a broader class of allocation issues.

Pool size	Total time (s)	LP time (s)	IP time (s)	# nodes proc. / # nodes	Pricing time (s)
Depth first pricing with cycle branching, short cycles and chains					
10	.61	.04	.00	1 / 1	.00
20	.21	.04	.00	1 / 1	.00
50	1.11	.26	.00	7 / 13	.00
100	.78	.09	.28	1 / 1	.06
200	1.81	.52	.47	1 / 1	.36
500	54.92	32.59	.47	28 / 55	12.17
Depth first pricing with cycle branching, long cycles and chains					
10	.28	.05	.00	2 / 3	.00
20	.83	.17	.00	5 / 9	.00
50	.42	.13	.00	2 / 3	.00
100	7.52	.14	.27	1 / 1	6.81
200	730.65	9.30	.20	16 / 31	713.17
500	>10,800	-	-	-	-
Polynomial pricing with arc branching, short cycles and chains					
10	.33	.03	.00	1/1	.00
20	.20	.03	.00	1/1	.00
50	2.97	.91	.00	20/39	.00
100	.80	.09	.25	1/1	0.13
200	1.58	.17	.30	1/1	0.64
500	21.98	1.09	.69	1/1	18.08
Polynomial pricing with arc branching, long cycles and chains					
10	.27	.06	.00	2 / 3	.00
20	.94	.19	.00	6 / 11	.00
50	1.61	.53	.00	10 / 19	.00
100	.83	.13	.31	1 / 1	.08
200	2.78	.67	.30	1 / 1	1.33
500	103.67	21.44	4.53	24 / 47	35.72
Polynomial pricing with subset arc branching, short cycles and chains					
10	.16	.05	.00	1 / 1	.00
20	.16	.03	.00	1 / 1	.00
50	.50	.13	.00	3 / 5	.00
100	.70	.08	.22	1 / 1	.11
200	1.59	.17	0.30	1 / 1	.64
500	22.06	1.08	0.67	1 / 1	18.13
Polynomial pricing with subset arc branching, long cycles and chains					
10	.42	.09	.00	3 / 5	.00
20	.91	.22	.00	6 / 11	.00
50	1.20	.39	.00	7 / 13	.00
100	.88	.14	.31	1 / 1	.08
200	2.78	.67	.30	1 / 1	1.31
500	95.02	15.59	7.64	12 / 23	35.61

Table 3.9: Average performance characteristics over 10 randomly sampled static instances from historical data from the Dutch national kidney exchange program. The cycle length limit is set to either 3 (short cycles) or 4 (long cycles) and the chain length limit is set to either 3 (short chains) or 6 (long chains).

Pool size	Total time (s)	LP time (s)	IP time (s)	# nodes proc. / # nodes	Pricing time (s)	% Solved
Saidman simulator, Depth first pricing with cycle branching						
100	3.67	2.16	.11	1.8 / 2.6	1.26	100
200	180.26	24.41	.39	3.0 / 5.0	154.51	100
500	1270.82	191.80	.43	25.0 / 49.0	1067.03	80
1000	4109.97	556.64	1.81	58.5 / 116.0	3383.05	40
Modified Saidman simulator, Depth first pricing with cycle branching						
100	2.14	1.59	0.07	1.0 / 1.0	0.40	100
200	121.01	31.76	.30	1.0 / 1.0	87.98	100
500	2948.91	311.19	1.18	2.4 / 3.8	2634.55	80
1000	1760.15	120.33	15.36	11.0 / 6.0	416.34	20
Saidman simulator, Polynomial pricing with arc branching						
100	1.40	.84	.15	5.6 / 10.2	.09	100
200	1.58	.53	.53	1.0 / 1.0	.36	100
500	9.66	3.43	1.29	3.6 / 6.2	3.46	100
1000	102.36	23.78	13.94	10.8 / 20.5	52.07	100
Modified Saidman simulator, Polynomial pricing with arc branching						
100	.87	.35	.11	1.0 / 1.0	.31	100
200	92.08	34.36	.87	1.0 / 1.0	56.43	100
500	740.31	131.38	1.46	1.0 / 1.0	606.38	100
1000	1111.98	705.45	29.99	301.5 / 602	76.28	100
Saidman simulator, Polynomial pricing with subset arc branching						
100	.93	.48	.15	3.4 / 5.8	.09	100
200	1.59	.52	.56	1.0 / 1.0	.36	100
500	8.50	3.04	1.26	2.8 / 4.6	3.32	100
1000	180.55	43.06	21.20	30.0 / 59.0	79.07	100
Modified Saidman simulator, Polynomial pricing with with subset arc branching						
100	.90	.36	.12	1.0 / 1.0	0.31	100
200	33.92	9.94	.47	1.0 / 1.0	23.17	100
500	24.83	12.18	1.84	1.0 / 1.0	10.21	100
1000	1717.42	857.50	16.14	363.0 / 725.0	203.52	100

Table 3.10: Average performance characteristics over 10 randomly generated static instances generated with US population data. Cycle limit is 4, chain limit is 6.

Pool size	Total time (s)	LP time (s)	IP time (s)	# nodes proc. / # nodes	Pricing time (s)	% Solved
Saidman simulator, Depth first pricing with cycle branching						
100	52.57	1.82	.25	4.8 / 8.6	49.32	100
200	117.55	3.97	.58	4.4 / 7.8	110.70	100
500	6644.83	20.40	.77	1.0 / 1.0	6609.75	50
Modified Saidman simulator, Depth first pricing with cycle branching						
100	1.37	.76	0.04	4.0 / 7.0	0.06	100
200	790.68	3.45	.56	1.0 / 1.0	785.65	80
500	2449.93	187.54	2.18	93.0 / 47.0	2258.44	80
Saidman simulator, Polynomial pricing with arc branching						
100	4.98	.65	.24	3.8 / 6.6	3.41	100
200	9.95	.68	.38	1.0 / 1.0	7.68	100
500	1731.53	18.39	2.31	19.3 / 37.7	1685.6	100
Modified Saidman simulator, Polynomial pricing with arc branching						
100	1.24	.33	.14	2.6 / 4.2	.35	100
200	13.78	.82	.64	1.0 / 1.0	11.33	100
500	54.47	3.62	1.49	1.0 / 1.0	40.98	100

Table 3.11: Average performance characteristics over 10 randomly generated dynamic instances generated with US population data. Cycle limit is 4, chain limit is 6.

Criterion	i	ii	iii	iv	v	vi
% of instances showing improvement at step i	99.3	24.5	52.1	.3	.3	34.5

Table 3.12: Percent of instances showing improvement at step i in the i-th objective criterion of the Dutch hierarchical criteria. Cycle limit is 4, chain limit is 6.

Chapter 4

Coordinating unspecified living kidney donation and transplantation across the blood type barrier in kidney exchange[1]

4.1 Introduction

Living donor kidney transplantation is the preferred treatment for patients with end-stage renal disease. However, due to blood type and crossmatch incompatibility over 30 percent of living donors are incompatible with their intended recipient. Kidney exchange is a modality that identifies matches between such incompatible donor-recipient pairs that allow them to proceed with transplantation through a cyclic transplant procedure (de Klerk et al., 2011; Montgomery et al., 2006a, 2005; Park et al., 1999; Rapaport, 1986; Roth et al., 2006; Saidman et al., 2006; Segev et al., 2005b; De Klerk et al., 2010). Over recent years various countries have pursued nationwide implementation of kidney exchange (Wallis et al., 2011; Irwin et al., 2012).

Not all pairs can be matched through kidney exchange however. Alternative transplant modalities available to incompatible pairs include unspecified living donation and ABO incompatible (ABOi) transplantation. Unspecified living donation (Dor et al., 2011), alternatively known as altruistic or non-directed donation, facilitates chains of transplants in which each pair is further matched to another pair (Montgomery et al., 2006a; Roth et al., 2006). ABOi transplantation utilizes desensitization techniques to overcome ABO incom-

[1]This chapter is based on (Glorie et al., 2013).

patibility as a contraindication for transplantation (Tyden et al., 2005; Shin and Kim, 2011). However, despite the availability of these alternative modalities transplantation rates of highly sensitized patients and blood type O patients have remained persistently low (Roodnat et al., 2012).

This paper studies central coordination of unspecified donation and ABOi transplantation in kidney exchange. Important questions are whether such coordination should utilize domino paired donation (DPD) (Roodnat et al., 2010) or non-simultaneous extended altruistic donor (NEAD) chains (Rees et al., 2009), what the length of the segments in such chains should be, when they should be terminated, and how much time should be allowed between matching rounds. Furthermore, this paper compares the effects of coordinating the different modalities centrally or locally and independently.

In DPD, an unspecified donor donates to a recipient of an incompatible pair, and simultaneously the donor of the pair donates to the recipient of another pair, and so on, until the donor of the last pair in the resulting chain donates to a recipient on the waitlist (Roodnat et al., 2010). In NEAD chains, the donor of the last pair in the chain is recruited as a bridge donor who can start a new chain segment of incompatible pairs at a later time (Rees et al., 2009). Gentry et al. (Gentry et al., 2009) showed that, when the monthly renege rate of bridge donors is above 4 percent, DPD strategies yield more transplants than NEAD strategies. In their simulations DPD chain segments involved at most 2 incompatible pairs and NEAD chain segments involved at most 3 pairs. Interestingly, Ashlagi et al. (Ashlagi et al., 2011b,a) showed that when chain segments of longer length are allowed, non-simultaneous chains almost always outperform simultaneous chains. However, due to computational difficulty of optimization with longer chain segments, they only perform the analysis on an eight month time period.

Incentive problems appear to play an important role in establishing multi-center coordination (De Klerk et al., 2010). Fear for loss of in-house transplants, for example, might cause transplant centers to want to match some donors and patients locally so as to guarantee a certain number of in-house transplants (see Figure 4.1). One way to overcome such incentive issues is by implementing participation constraints which ensure that each transplant center can perform at least the same number of transplants in a national pool as that it can achieve on its own. Policies that implement such constraints are called individually rational (IR) (Curiel, 2010; Ashlagi and Roth, 2011b; Glorie et al., 2014d).

In this research we use specifically developed exact mathematical optimization software (Glorie et al., 2014d) to simulate and analyze multiple kidney exchange policies over a complete seven year time period. Our simulation uses actual data from the Dutch national kidney exchange program and features an accurate modeling of various types of match

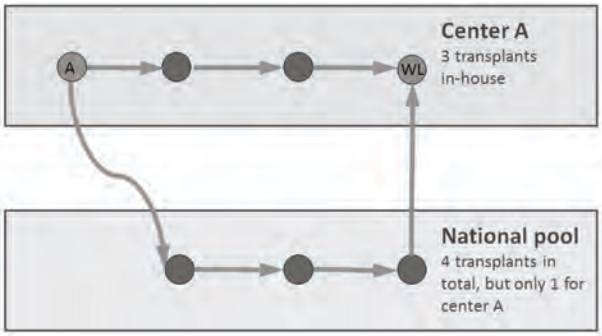

Figure 4.1: Potential incentive problems. An unspecified donor (A) is registered at center A, which can generate 3 in-house transplants. In a nationally optimized program, 4 transplants are generated, but only 1 of those transplants is performed by center A.

failure. Sensitivity analysis is performed on the composition of the population, the time unspecified and bridge donors wait before donating to the waitlist, the time between matching rounds, and donor renege rates.

Our analysis includes the policies investigated in Gentry et al. (Gentry et al., 2009) and Ashlagi et al. (Ashlagi et al., 2011b) for which, under the same settings, we find comparable results but we show that the benefits of longer chains depend considerably on the composition of the patient and donor population. Additionally, our analysis considers a variety of new IR policies that feature central coordination of both unspecified donation and ABOi transplantation for highly sensitized patients (with panel reactive antibody [PRA] > 80) (Tyden et al., 2005). We show that, by using these new policies, substantially more transplants can be obtained than under any of the previously investigated policies and than could be expected from any of the transplant modalities independently. We also show the importance of allowing the exchange pool to build up by allowing sufficient time between matching rounds.

4.2 Materials and methods

4.2.1 Data

This study uses empirical data from the Dutch national kidney exchange program. The data include 438 ABO blood type or crossmatch incompatible patient-donor pairs who participated in Dutch kidney exchanges between October 2003 and January 2011, as well as 109 unspecified donors who donated during that period. There are eight transplant centers with pair registrations ranging between 4-123 (median 47) and unspecified donor registrations ranging between 3-64 (median 7). Donor HLA types and unacceptable HLA mismatches are provided by the national reference laboratory for histocompatibility testing. The national reference laboratory identifies unacceptable HLA specificities on basis of a combination of a complement dependent cytotoxicity (CDC) and a solid phase antibody screening. Antibody specificities leading to a positive CDC crossmatch are considered to be a contraindication for transplantation and the HLA antigens recognized are defined as unacceptable mismatches. Table 4.1 details the patient and donor characteristics. In addition to center-reported PRA levels (which are based on the general population), the table includes kidney exchange donor population PRA levels which are computed using virtual crossmatches between each patient and all donors in the data set. In this paper, whenever we refer to a PRA level, we refer to these kidney exchange donor population based PRA levels.

	ABO blood type			
	A	B	AB	O
Patients (%)	30	15	1	54
Donors (%)	56	14	2	29
	PRA level w.r.t. general population (at time of entry)			
	0-9	10-79	80-100	
Patients (%)	78	17	5	
	PRA level w.r.t. kidney exchange donor population			
	0-9	10-79	80-100	
Patients (%)	48	35	17	

Table 4.1: Patient and donor characteristics

4.2.2 Simulation

Monte Carlo simulations (Ross, 2006) are used to compare different policies for unspecified donation in kidney exchange. Each simulation spans the period between 1 October 2003 and 23 December 2010 and involves a population of size 547 generated from the empirical data using sampling with replacement.

The arrivals of patient-donor pairs and unspecified donors are determined by assigning each pair and each unspecified donor in the population a random date in the simulation period. Arrival dates are drawn uniformly, corresponding to a Poisson arrival process. This appears to be a more realistic arrival process than the constant-size batch arrivals assumed in (Gentry et al., 2009) and (Ashlagi et al., 2011b): a Chi Square goodness of fit test on historical arrivals in our data set significantly rejects a fit with batch arrivals ($p < 0.0001$) but not with Poisson arrivals ($p=0.47$).

Kidney exchanges are conducted at regular time intervals (once per 3 months in our base case). Compatibility between patients and donors is based on blood type and virtual crossmatching. ABO incompatible transplantation may be considered for highly sensitized (PRA>80) patients with isoagglutinin titer of at most 1:256 (which corresponds to 60 % of these patients).

4.2.3 Market clearing

In each exchange, an exact optimization algorithm, described in (Glorie et al., 2014d), is run on the pool of incompatible pairs, unspecified donors and bridge donors in order to determine an allocation. The algorithm allows cycles involving up to 4 pairs and, depending on the analyzed policy, DPD chains or NEAD chain segments involving up to 6 pairs and 1 unspecified or bridge donor. In determining an allocation, the algorithm adheres

the allocation criteria used in the Dutch national kidney exchange program (Keizer et al., 2005). That is, the algorithm ranks solutions on six hierarchical criteria: (i) number of transplants, (ii) number of blood type identical transplants, (iii) match probabilities of matched patients (inverse ranking), (iv) longest cycle and chain length (inverse ranking), (v) smallest spread per cycle and chain over transplant centers, and (vi) longest wait time; the algorithm returns the highest ranking solution.

4.2.4 Policies

The policies considered in our simulation are distinguished by whether unspecified donation is coordinated locally or nationally (with or without IR requirement), by whether unspecified donors initiate DPD or NEAD chains (either involving a maximum of 3 or 6 pairs), and by whether ABO incompatible transplantation for highly sensitized patients (PRA > 80) is allowed.

If unspecified donation is coordinated locally, all pairs in a chain need to be registered at the same transplant center as the unspecified donor who initiated the chain. If unspecified donation is coordinated nationally, pairs in the chain may be registered at any transplant center.

IR policies mitigate incentive problems in multi-center coordination at a potential cost of a reduced number of transplants. Under an IR policy we first determine the maximum number of transplants that each center can achieve individually and then impose restrictions to the kidney exchange optimization algorithm to ensure that each center achieves at least this number.

4.2.5 Match failure, reneging and attrition

Incompatible pairs may leave the program if the pairs recipient gets transplanted in another program or leaves the program for psychological or medical reasons. Alternatively, the pairs donors may become ineligible or may reconsider participating. To model those cases, simulated attrition randomly removes 2 % of the incompatible pairs at the end of each month. This estimate is in line with earlier studies (Gentry et al., 2009; Ashlagi et al., 2011b) and empirical findings in the Dutch national kidney exchange program.

Also, there are various types of failure that may prevent kidney exchange matches from going forward to transplantation. These include positive crossmatch after a negative virtual crossmatch, desensitization failure, donor withdrawal and patient illness. Based on Dutch match failure data, we model these types of failure using both an exogenous

probability (12.5%) and an endogenous probability calculated by the following probit model (see Appendix A):

$$Pr[\text{Failure} : PRA] = \Phi\left(-1.5007 + 0.0170 \cdot PRA\right)$$

where Φ represents the cumulative distribution function of the standard normal distribution. If a failure occurs, the optimization algorithm is rerun for the current matching round using the updated information, as is current practice in the Netherlands.

4.2.6 Bridge donors

The last donor in a NEAD chain segment becomes a bridge donor, i.e. a donor whose intended recipient has already received a transplant and who can start a next NEAD chain segment in a later exchange. Bridge donors may renege if they decide not to donate or become ineligible. At the end of each month, simulated reneging removes a percentage of the bridge donors (e.g. 1 %). When a bridge donor does not start a new chain segment within a specified period of time (e.g. 3 months), the NEAD chain is ended and the bridge donor donates to the wait list. Unspecified donors are assumed not to renege, but if they do not initiate a DPD or NEAD chain within the specified period, they donate to the deceased donor waitlist. In concordance with (Ashlagi et al., 2011b), when we allow for DPD or NEAD chain segments longer than length four, these involve an intermediate short-term bridge donor after the first three transplants.

4.2.7 Base case

In the base case simulation, kidney exchanges are conducted once per three months (thirteen weeks), starting from 1 January 2004. There are a total of 29 kidney exchanges during the simulation period. Chain segments are limited to 3 pairs and 1 unspecified or bridge donor. The monthly probability of reneging for bridge donors is set to 1 %, which corresponds to the estimate made in (Ashlagi et al., 2011b) based on clinical experience in the US. As this may not be a reliable point estimate we also perform sensitivity analysis (see below). Short term bridge donors have a renege probability of 0.5 %. Unspecified donors and bridge donors are available for DPD or NEAD chains up to three months after their entry or recruitment date, after which they donate to the waitlist. The percentage of unspecified donors is 20 % and the percentage of highly sensitized (PRA>80) patients is 17 %.

4.2.8 Sensitivity analysis

Sensitivity analysis is used to assess the effects of changes in uncertain or variable factors on the simulation outcomes. This is done by performing repeated simulations while varying these factors. In particular, the patient-donor population, the bridge donor renege rate, the availability period of unspecified and bridge donors, and the timing between kidney exchanges are varied. Variety in the number of pairs and unspecified donors arriving each month is inherent to the design of the simulation procedure. For the patient-donor population we simultaneously vary the percentage of donors that are unspecified, considering values of 1 %, 5 %, and 20 %, and the percentage of highly sensitized patients, considering values of 10 %, 20 %, 30 %, 40 %, and 50 %. We consider renege rates of 1 %, 2 %, 5 % and 10 %, and unspecified donor availability periods of 3 months (13 weeks), 6 months (26 weeks) and 18 months (78 weeks). When varying the timing of exchanges, we use intervals of 1 week, 1 month (4 weeks), 2 months (8 weeks), 3 months (13 weeks), and 6 months (26 weeks). For the last case we adjust donor availability to match the time interval, in the other cases it is set to the default value of 3 months.

4.2.9 Statistical analysis

As in Gentry et al. (Gentry et al., 2009) 30 Monte Carlo simulations are run for each experiment and average results are reported. The results include (i) the total number of patients transplanted (including patients from the deceased donor waitlist), (ii) the total number of blood type O patients transplanted, (iii) the total number of highly sensitized (PRA $>$ 80) patients transplanted, and (iv) the average waiting time. For NEAD chains, any remaining bridge donors at the end of the simulation period are assumed to be able to donate directly to the deceased donor waitlist and hence their number is added to the total number of transplants. For all policies the improvement to Local DPD-4,3 (i.e. a local DPD policy with a maximum of 4 pairs per cycle and 3 pairs per chain), which is current practice in the Netherlands, is calculated. For the base case, 95 % confidence intervals (2.5 - 97.5 percentile) are also reported. Significance of results is tested using the sign test.

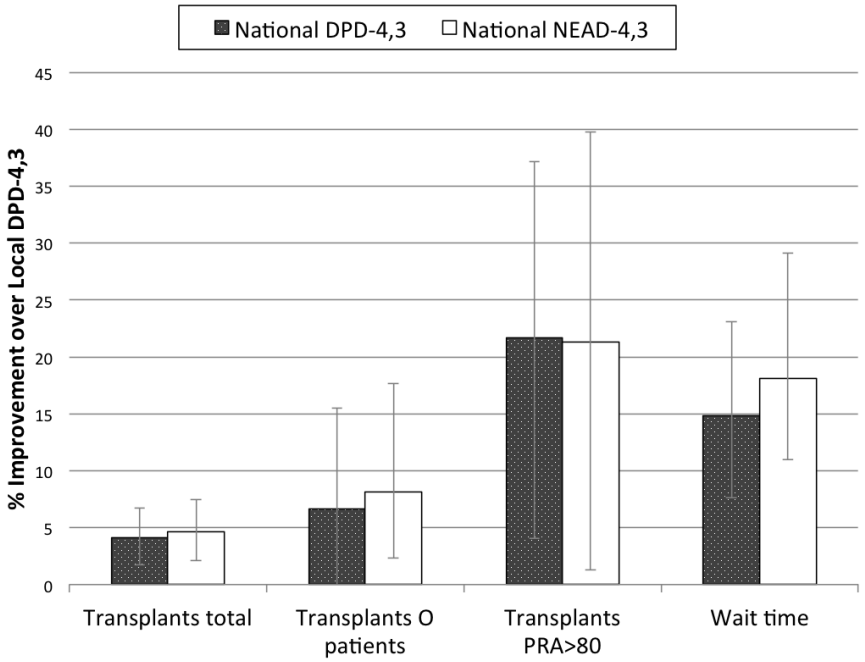

Figure 4.2: Relative performance for various kidney exchange policies with 95 % confidence intervals in a population with 20 % unspecified donors and 17 % patients with PRA>80.

4.3 Results

4.3.1 National coordination

Figures 4.2-4.4 display the performance of the various kidney exchange policies in the base case simulation. In particular, they show the improvement over Local DPD-4,3, which is representative of current practice in the Netherlands. Local DPD-4,3 produced an average of 429.2 transplants, including 109 transplants for wait list recipients, 143.2 transplants for ABO blood type O patients, and 46.5 transplants for highly sensitized patients (PRA > 80). This is similar to the actual number of transplants achieved historically in the observed time period. The average waiting time was 297.7 days (waiting time for unmatched patients is counted until the end of the horizon).

Figure 4.2 shows that on average the number of transplants increases by about 4.1 % under national DPD-4,3 and by about 4.6 % under national NEAD-4,3 (both with

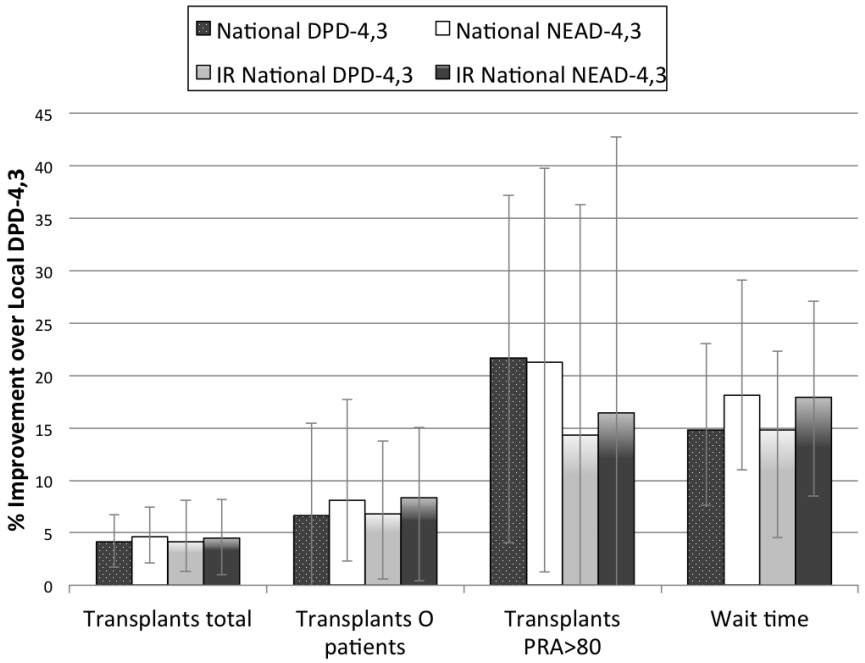

Figure 4.3: Relative performance for various kidney exchange policies with 95 % confidence intervals in a population with 20 % unspecified donors and 17 % patients with PRA>80.

$p < 0.001$). Particularly highly sensitized patients (PRA > 80) benefit from national coordination: they receive 21 % more transplants under both National DPD-4,3 and National NEAD-4,3, constituting almost all of the gains in the total number of transplants. Not only are patients transplanted more often, they are also transplanted faster: the average wait time for transplantation is reduced by 15 % under national DPD ($p < 0.001$) and by 18 % under national NEAD ($p < 0.001$).

Importantly, the restriction that national implementation is individual rational does not lead to a significant loss of transplants or to an significant increase in wait time, indicating that individual rational national coordination is a viable strategy (Figure 4.3).

4.3.2 Allowing longer chain lengths

Figure 4.4 shows the results of allowing unspecified donor chains to be of longer length (up to length 6). In contrast to the findings in Ashlagi et al. (Ashlagi et al., 2011b), in

our simulations allowing longer chains produces no significant difference in the number of transplants or waiting time (compare IR National DPD-4,6 and IR National NEAD-4,6 with IR National DPD-4,3 and IR National NEAD-4,3 in Figure 4.3). However, the composition of the kidney exchange population in our base case is different from theirs due to differences between the Dutch and the APD data. To understand the nature of these differences we will perform sensitivity analysis on the population composition (see below).

4.3.3 Allowing ABOi transplantation for highly sensitized patients

Figure 4.4 also shows the effect of allowing ABOi transplants for highly sensitized patients. When coordinated locally, allowing ABOi transplantation augments the total number of transplants with about 0.5 % ($p = 0.0081$). However, when utilized in a nationally coordinated policy together with any of the unspecified donation modalities, the increase in total transplants is approximately 10 % ($p < 0.001$) and the increase in transplants for highly sensitized patients is over 55 % ($p < 0.001$). This brings the probability of obtaining a transplant on par for all patient groups (the probability is 87 % for non-highly sensitized patients and 86 % for highly sensitized patients). These benefits require only a small number of ABOi transplants: on average 38 ABOi matches were made in the simulated policies, whereas historically 42 pairs that took part in the Dutch KPD program, but remained unmatched, eventually received an ABOi transplant outside the program.

4.3.4 Sensitivity analysis population composition

Figures 4.5-4.9 provide a sensitivity analysis on the population composition. For comparison, we have included the same policies as used in (Ashlagi et al., 2011b). As expected, the number of transplants decreases with the percentage of highly sensitized patients and increases with the percentage of unspecified donors. However, the number of transplants under policies allowing long chains decreases less fast (with respect to the percentage of highly sensitized patients) than the number of transplants under policies allowing only short chains, leading to larger differences. This is independent of whether the policy is DPD or NEAD. This explains the relative effectiveness of long chains in the simulations of (Ashlagi et al., 2011b).

The benefits of allowing ABOi transplantation increase with the percentage of donors that are unspecified. The benefits also increase with the percentage of highly sensitized

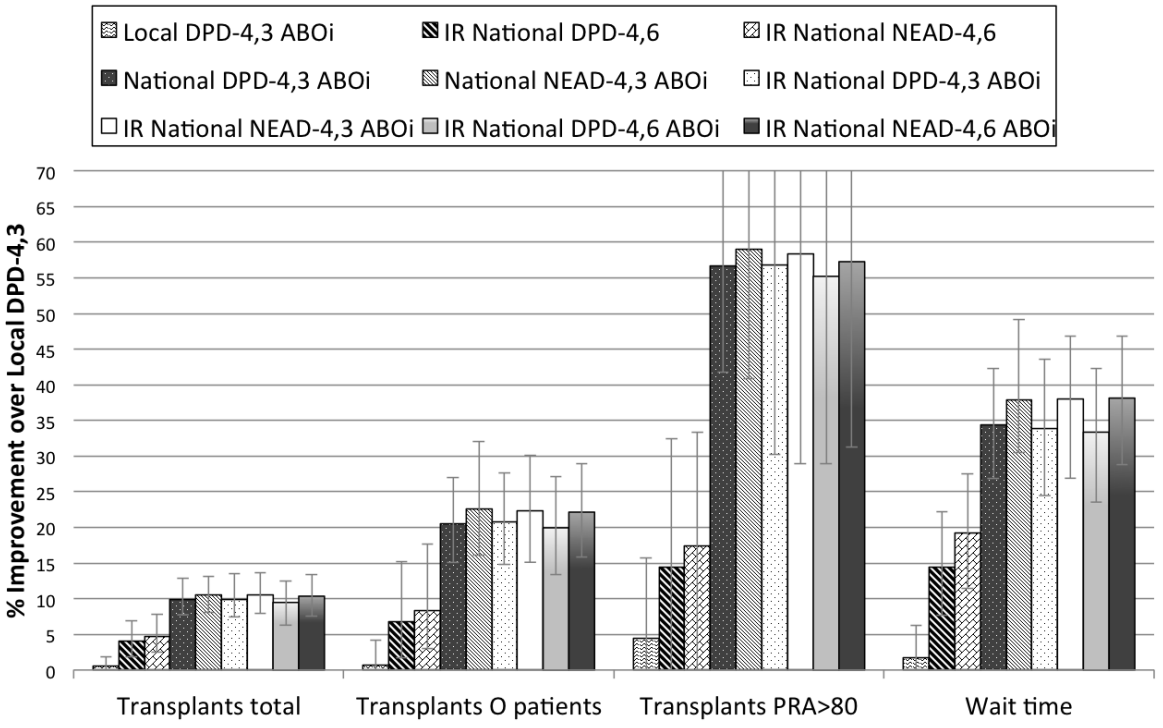

Figure 4.4: Relative performance for various kidney exchange policies with 95 % confidence intervals in a population with 20 % unspecified donors and 17 % patients with PRA>80.

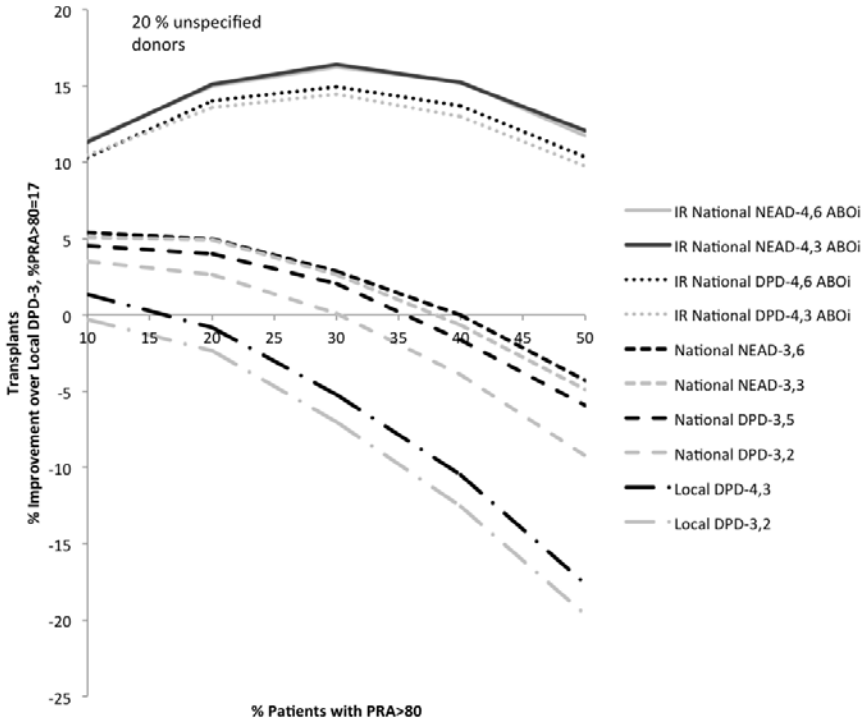

Figure 4.5: Sensitivity analysis on the percentage of highly sensitized patients when the percentage of unspecified donors is 20 %

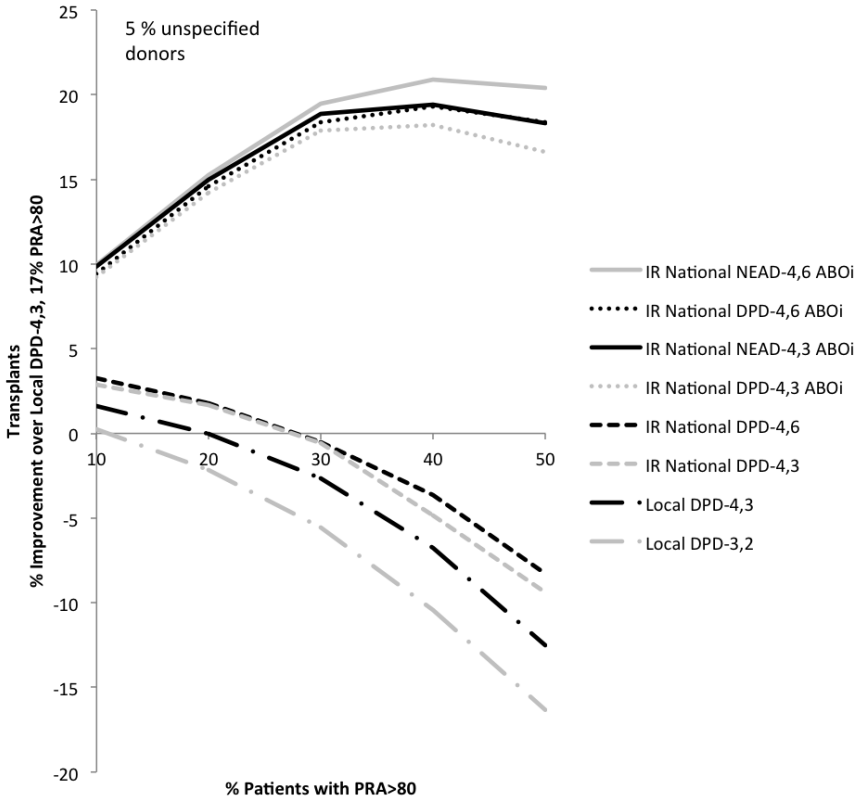

Figure 4.6: Sensitivity analysis on the percentage of highly sensitized patients when the percentage of unspecified donors is 5 %

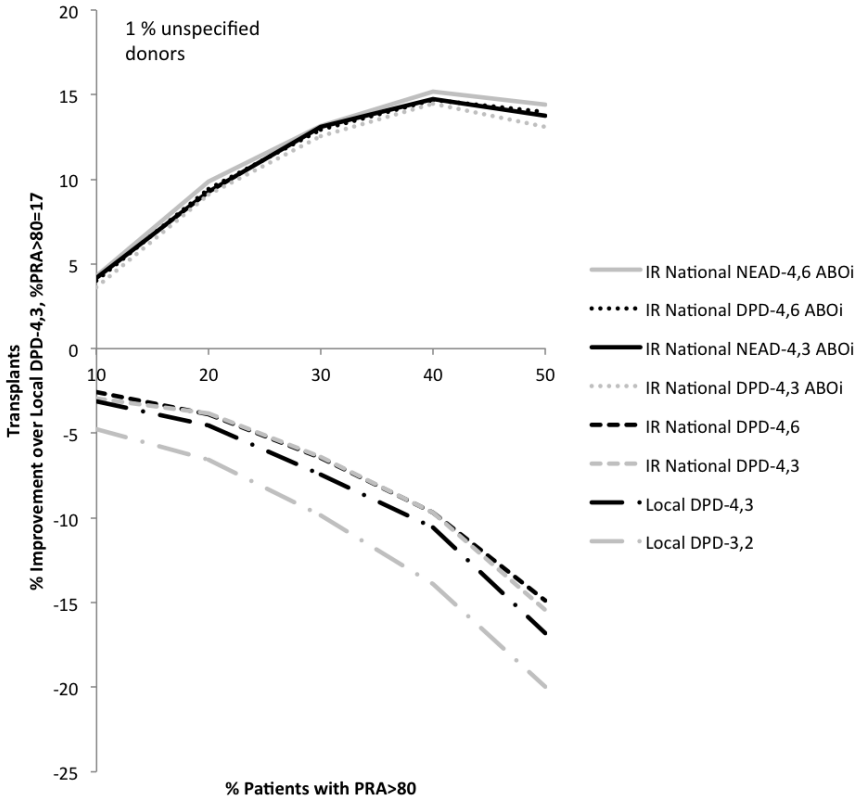

Figure 4.7: Sensitivity analysis on the percentage of highly sensitized patients when the percentage of unspecified donors is 1 %

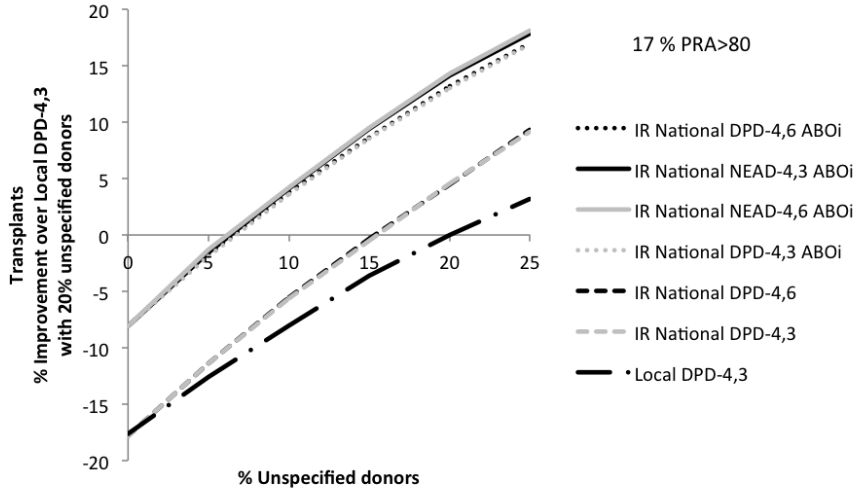

Figure 4.8: Sensitivity analysis on the percentage of unspecified donors while 17 % of patients is highly sensitized.

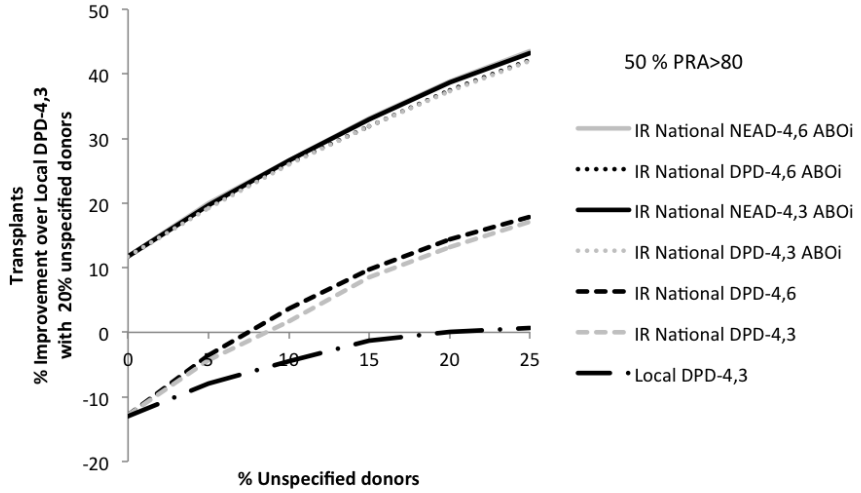

Figure 4.9: Sensitivity analysis on the percentage of unspecified donors while 50 % of patients is highly sensitized.

patients (they only start decreasing slightly when the percentage of these patients is over 30-40 %). The relative effectiveness of ABOi policies in populations with many highly sensitized patients is substantial. In all cases only a small number of ABOi transplants is required to obtain the benefits.

4.3.5 Sensitivity analysis unspecified and bridge donor availability (chain termination)

We also perform sensitivity analysis on the period during which unspecified donors and bridge donors are available for (continued) chain donation (see Figure 4.10). When the period is extended from 3 months until 18 months after the unspecified donors entry date or the bridge donors recruitment date, local DPD-4,3 achieves 1.1 % more transplants ($p < 0.001$). However - and this is notable - for all national policies an extended availability period does not have a significant effect on the number of transplants. The same holds for the number of transplants for blood type O and highly sensitized patients, as well as for the waiting time. As before, we performed this analysis for varying pool compositions and the pattern turns out to be independent of the number of unspecified donors. Even when only 1% of all donors is an unspecified donor, the benefits of a longer availability period are insubstantial and insignificant. This indicates that it is best to perform a waitlist donation or end an ongoing chain if no kidney exchange transplant options are available within 3 months (as this reduces the wait time for wait list recipients).

4.3.6 Sensitivity analysis timing of exchanges

Figure 4.11 presents sensitivity analysis on the time interval between exchanges. A longer time interval increases the number of transplants. When exchanges are run once per three months, as is currently done in the Netherlands, there are about 7 % ($p < 0.001$) more transplants than when exchanges are run once per month, regardless of the policy. An explanation for this is that additional time between kidney exchanges allows exchange cycles and chains to be formed that involve relatively more highly sensitized patients (33 % in the case of 3 months versus 1 month). The graphs for both transplant categories are equally concave, meaning that the increase in transplants diminishes as the time interval increases. The difference in transplants between the extremes, the near continuous weekly exchange policy and the bi-annual exchange policy, is 31 % (and 144 % if we decompose this to highly sensitized patients (not shown in the table)).

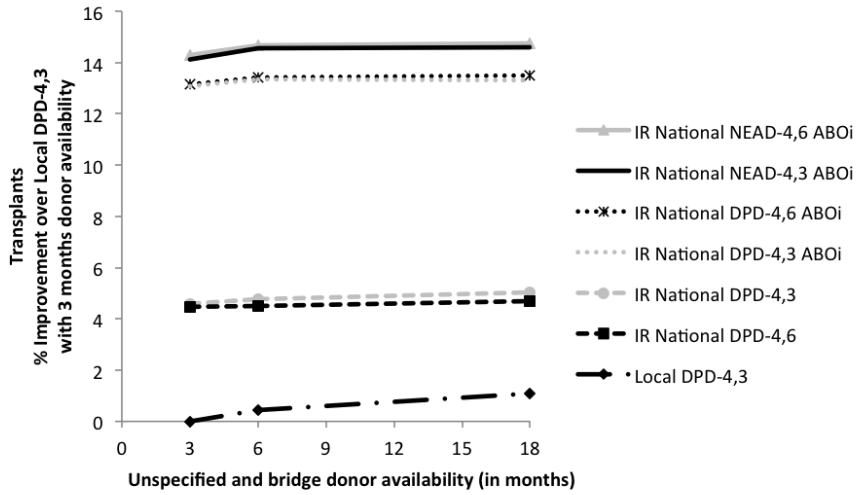

Figure 4.10: Sensitivity analysis on the time unspecified and bridge donors are available before donating to the waitlist

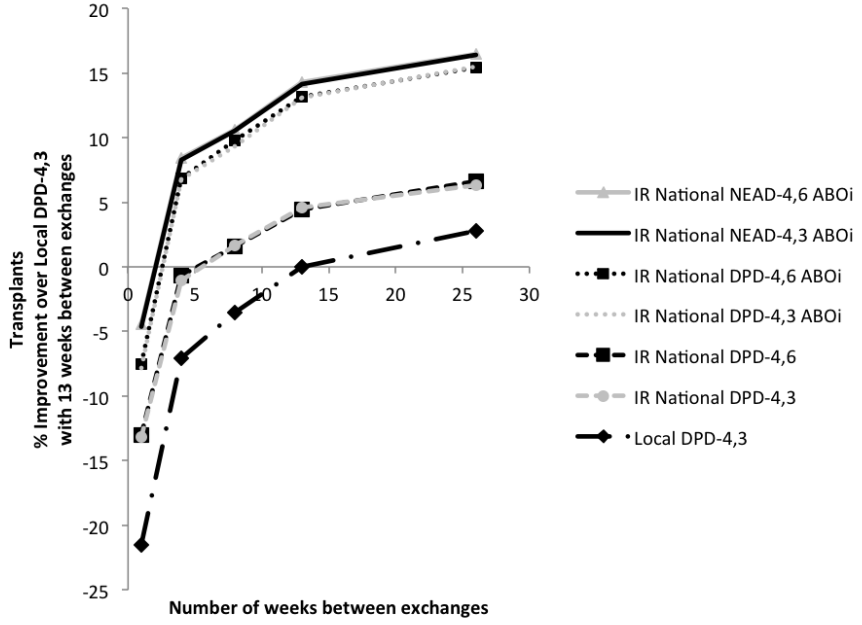

Figure 4.11: Sensitivity analysis on the time between exchanges

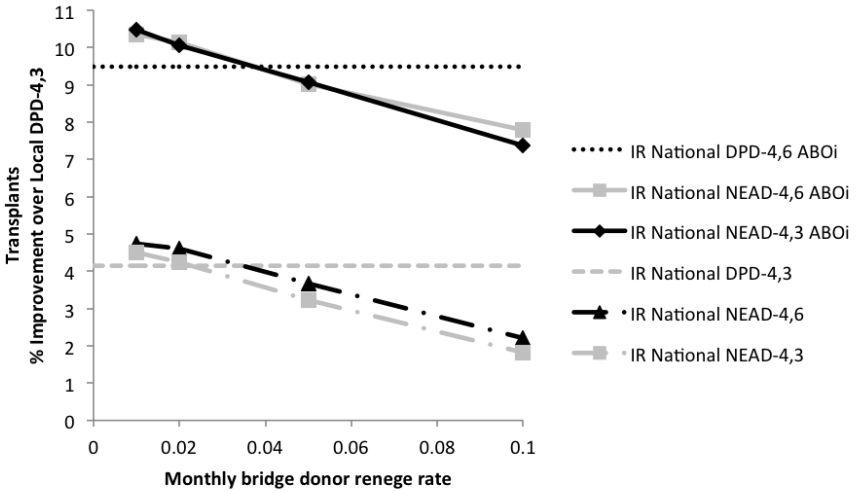

Figure 4.12: Sensitivity analysis on the renege rate

4.3.7 Sensitivity analysis renege rate

Figure 4.12 displays a sensitivity analysis on the renege rate. When the renege rate is under 3 %, NEAD chain policies slightly outperform equivalent DPD chain policies. However, when the renege rate increases beyond 3-4 %, NEAD chains lose bridge donors too frequently, resulting in a substantial advantage for DPD chain policies. These findings are in line with (Gentry et al., 2009) and (Ashlagi et al., 2011b). Overall, NEAD chains produce slightly more transplants for patients in the kidney exchange program, including highly sensitized patients with PRA > 80 and O patients, but less transplants for waitlist patients.

4.4 Discussion

In the recent history of transplantation medicine various novel modalities for transplanting patients with an incompatible living donor have been introduced. In this paper we presented a simulation study that considers the coordination of two of those modalities, unspecified donation and transplantation across the ABO blood type barrier, in kidney exchange. Clinical data and allocation criteria from the Dutch national kidney exchange program (de Klerk et al., 2011) have been used to perform the simulations and to determine donor-recipient matches. Our findings are therefore, at least in part, conditional

on these data and criteria. Extensive sensitivity analysis on the population composition, however, helps us understand the general implications.

Our results strongly suggest that there is clear synergy in the central coordination of unspecified donation and ABOi transplantation in kidney exchange, even when the latter is performed exclusively for highly sensitized patients. Only a few ABOi transplants are required to substantially increase the benefits of national unspecified donation policies. These benefits are in terms of total transplants, transplants for blood type O and highly sensitized patients, and waiting time, and are much larger than could be expected from any of the transplant modalities independently.

In our base case simulations the benefits of long unspecified donor chains are not significant. This contrasts with the recent study of (Ashlagi et al., 2011b) whose simulations suggest significant benefits of long chains. The difference in the outcomes is the result of differences in the composition of the patient-donor populations. The benefits of long unspecified donor chains increase with the percentage of highly sensitized patients. When we consider highly sensitized population compositions similar to those investigated in Ashlagi et al., we therefore do find significant benefits of long chains. Thus, whether it is best to perform shorter simultaneous chains or longer non-simultaneous chains, will not only depend on the risk of reneging but also on the population under consideration.

Interestingly, the benefits of allowing coordinated transplantation across the blood type barrier are present in all population compositions we investigated, despite the increased risk of match failure, and they become more substantial in populations with many highly sensitized patients. Importantly, the benefits include more equitable transplant opportunities among patients.

Another observation in this study is that allocating unspecified or bridge donors directly to the waitlist if they cannot initiate a chain segment within the next exchange round (in 3 months) reduces the waiting times for patients on the waitlist without reducing the benefits for patients in the kidney exchange program. This criterion for chain initiation and termination helps balance the fact that DPD and NEAD policies shift transplants away from patients on the deceased donor wait list to patients in the kidney exchange program. Finally, we find that the time between matching rounds has considerable impact on the number of transplants that can be achieved. Allowing more time means that the pool can build up and better exchange combinations can be identified.

Multi-center coordination of transplant modalities in kidney exchange is a difficult task. Nevertheless, the present study suggests that the synergy of simultaneously coordinating at least two such modalities, unspecified donation and transplantation across the blood type barrier, increases both the number and the equitability of transplants. Using

individual rationality guarantees for transplant centers may help to overcome some of the coordination difficulties with no harm to these benefits. Actual national experience and thorough evaluation of implementation will be necessary to fully understand real life effects.

Chapter 5

Health value analysis of allocation policies in kidney exchange[1]

5.1 Introduction

For patients suffering from end-stage renal disease (ESRD), kidney transplantation has been established as the preferred treatment (Wolfe et al., 1999). Compared to alternative renal replacement therapies, such as dialysis, it offers substantial advantages in terms of quality of life, patient survival, and costs (Port et al., 1993; Franke et al., 2003; Winkelmayer et al., 2002): on average, patients who receive a kidney transplant live 10 years longer than patients who remain on dialysis (Port et al., 1993), while the long term costs of transplantation are 4 to 5 times lower (Winkelmayer et al., 2002). Living donor transplantation (LTx) is the most effective treatment because graft survival after living donor transplantation is generally twice as good as graft survival after deceased donor transplantation (DTx)(SRTR, 2011).

Unfortunately, even though the number of living donor kidney transplants has increased over recent years (Segev, 2012) (in many countries, including the US and the Netherlands, the number of living donors has now surpassed the number of deceased donors[2]), the number of kidneys available for transplantation is still largely insufficient to meet demand: in Europe and the United States together, approximately 30 patients die each day while waiting for a kidney transplant (European Society for Organ Transplantation (ESOT), 2010; United States Organ Procurement and Transplantation Network (OPTN), 2011). A major part of the problem is that, even when a living donor is will-

[1] This chapter is based on (Glorie et al., 2014c).

[2] In fact, in the Netherlands more than half of the transplants now involve a living donor (Nederlandse Transplantatie Stichting (NTS), 2012)

ing to donate, in over 30 percent of the cases, the donor is incompatible with his or her intended recipient due to blood type or crossmatch incompatibility (Segev et al., 2005b).

Kidney exchange (KE) is a modality that allows incompatible patient-donor pairs to be matched with other incompatible pairs in order to proceed with transplantation through an exchange procedure. In such a procedure, the donor of the first pair should be compatible with the patient of the second pair, and the donor of the second pair should be compatible with the patient of the first pair. The pairs then switch donors so that both patients are able to receive a transplant (Rapaport, 1986). Kidney exchange procedures are not limited to pairwise exchange, but can involve exchange cycles, and exchange chains - which are initiated by altruistic donors - of arbitrary length. However, due to incentive reasons (in order to prevent donors from withdrawing consent after their intended recipient has received a transplant), all transplants in a cycle must be performed simultaneously. Because of the large potential for increasing the number of kidney transplants, many countries have now developed kidney exchange programmes (Park et al., 1999; Delmonico et al., 2004; Keizer et al., 2005; Petrini et al., 2007).

Typically, the allocation of donors to patients in kidney exchange programs is determined by a central authority. The allocation policy used by this authority has an important effect on the outcomes of the exchanges. It determines not only which patient-donor pairs are involved in an exchange but also with whom they exchange. In this paper we focus on health outcomes - in terms of quality adjusted life years (QALYs) - of various allocation policies proposed in the literature. Moreover, we compare these policies to an allocation policy that maximizes the discounted sum of the quality adjusted life years gained. Such a policy has been envisioned since the advent of kidney exchange programmes (Zenios, 2002; Abraham et al., 2007), but to our knowledge, this paper is the first to thoroughly model and evaluate it to centrally determine allocations in kidney exchange as it is available today. We calculate an upper bound on the maximum health value that can be achieved by any policy and show that our newly proposed policy comes much closer to this bound than the other policies investigated.

Use of quality adjusted life years is commonly accepted as a prime decision criteria for many medical interventions, following the framework of Health Technology Assessment (Hutton et al., 2006; Guindo et al., 2012). However, it may conflict with criteria that are currently used in most kidney exchange programs, such as maximizing the number of transplants (Wolfe et al., 2008; Zenios, 2002). In this paper we develop a Markov model for assessing the quality adjusted life years associated to particular kidney exchange policies. The transition probabilities in our Markov model are patient-donor specific functions related to characteristics as age, antigen mismatch, and gender. Using this model, we

conduct long term simulations with kidney exchange data from the Netherlands, which has the longest running national kidney exchange program (de Klerk et al., 2005). We then evaluate policies in terms of quality adjusted life years and on the outcomes for several traditional kidney exchange criteria such as equity, mortality and number of transplants.

This paper is organized as follows. Section 5.2 describes the Markov model for determining the health value outcomes. Section 5.3 describes the allocation policies under consideration. Then, Section 5.4 details the simulation procedure by which the policies are assessed. The results are presented in Section 5.5. Finally, Section 5.6 concludes.

5.2 An individualized health value model for kidney exchange

In order to assess the quality adjusted life years gained from any kidney exchange allocation rule, we develop a patient and donor specific Markov chain model (see e.g. (Thijms, 2003)). Markov chain models are commonly used in the literature to analyze health outcomes (see e.g. (de Wit et al., 1998)). A Markov chain model is a discrete statistical process characterized by a set of states, transition probabilities between states, and an initial distribution over states.

5.2.1 States

We define six states, consisting of five transient treatment states - (i) 'ESRD', (ii) 'Renal Function (RF) Recovery', (iii) 'LTx Recovery', (iv) 'DTx Recovery', and (v) 'KE Recovery' - and one absorbing state, (vi) 'Death'. The default treatment for ESRD is dialysis (i.e. ESRD patients who do not receive a transplant are assumed to be treated with dialysis). Recovery of renal function on dialysis is very rare, but may occur. In that case the patient transitions to the 'RF Recovery state'. The 'LTx Recovery' and 'DTx Recovery' states respectively represent recovery after a living and deceased donor transplant. The state 'KE Recovery' represents the situation in which the patient successfully receives a kidney exchange transplant. Although recovery after a kidney exchange transplant is in principle similar to recovery after any other living donor transplant, the 'KE Recovery' state is added separately to allow us to capture the impact of the present matching decision on the health outcomes by explicitly taking donor characteristics into account in the transition probabilities (see below), whereas the 'LTx Recovery' state represents a transplant from a presently unknown, future living donor. From each of the recovery states it is also possible for patients to return to the ESRD state. This can for instance

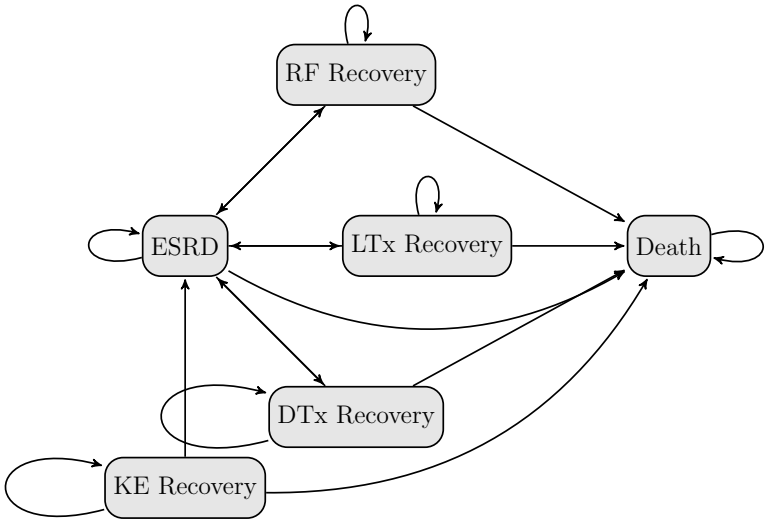

Figure 5.1: Individualized health value model: state space and transitions. The model consists of six states with patient and donor specific transition probabilities.

happen due to graft failure. Should a patient return to the 'ESRD' state from the 'KE Recovery' state, possible future living donor allocations (for which the involved donor is presently unknown) are modeled as transitions to the 'LTx Recovery' state (so this state also captures future kidney exchange transplants). Figure 5.1 displays the state space and possible transitions.

5.2.2 Transition probabilities

The transition probabilities are functions of patient and donor characteristics. Let us denote a patient-donor pair participating in kidney exchange as X-Y, where X is the patient and Y is the donor, and let N be the set of all patient-donor pairs. (NB. Patients without donors can be indicated as X-$\emptyset$, and donors without patients, such as altruistic donors, can be indicated as $\emptyset$-Y.) In kidney exchange, a patient can only receive a transplant from another donor if the patient's own donor donates to some other patient. Formally, an allocation $\mu : N \to N \cup \emptyset$ is a function such that if $\mu(X\text{-}Y) = W\text{-}Z$ then $\mu(W\text{-}Z) \neq \emptyset$ for all X-Y, W-$Z \in N$. This implies that if $\mu(X\text{-}Y) = \emptyset$, the pair X-Y is unmatched. We define:

$p_{ij}^{\mu}(X\text{-}Y) :=$

$Pr[\text{transition of } X \text{ from state } i \text{ to state } j | X \text{ receives a transplant from } \mu(X\text{-}Y)]$

Moreover, we have

$$p_{ii}^{\mu}(X\text{-}Y) := 1 - \sum_{j \neq i} p_{ij}^{\mu}(X\text{-}Y)$$

Transitions from the 'ESRD' state

At the start of the horizon, if a patient does not take part in a kidney exchange, he or she starts in the 'ESRD' state. From the 'ESRD' state patients have three recovery options: 'RF Recovery', 'LTx Recovery', and 'DTx Recovery'. As explained in Section 5.2.1, future kidney exchange transplants, for which the donor is unknown, are implicitly modeled through the 'LTx Recovery' state. The probability of obtaining a deceased or direct living donor kidney transplant for an ESRD patient depends on the availability of deceased and living donors, the probability of compatibility between patient and donor, and, for deceased and altruistic donors, the allocation policy. If a patient does not recover and does not die, it remains in the 'ESRD' state.

Transition to the 'DTx Recovery' state

The probability of compatibility is based on blood types and PRA level. The probability of obtaining a deceased donor transplant in a given period can be estimated by:

$$Pr[\text{DTx}|X\text{-}Y] = Pr[\text{DTx donor is allocated to blood type } BLO_X]\,(1 - PRA_X)$$

where the allocation probability can be calculated from historical data over a given period by:

$$Pr[\text{DTx donor is allocated to blood type } BLO_X] = \frac{\#\text{DTx transplants for blood type } BLO_X}{\#\text{patients of blood type } BLO_X \text{ on the waitlist}}$$

and where BLO_X and PRA_X respectively indicate the blood type and the PRA level (on a 0 to 1 scale) of patient X. In order to estimate the allocation probability we use historical Dutch data (see (Nederlandse Transplantatie Stichting (NTS), 2012)). Table 5.1 lists the annual allocation probabilities we use in our model per blood type category.

Blood type patient	Probability
O	.22
A	.24
B	.14
AB	.34

Table 5.1: Annual probability that a suitable deceased donor becomes available and is allocated to a patient of the indicated blood type

Transition to the 'LTx Recovery' state

The probability of obtaining a living donor kidney transplant can be calculated similarly. However, because participants in kidney exchange programs have likely exhausted their opportunities to find a compatible living donor (e.g. because they have asked most of their family members and friends), the probabilities for the general patient population are likely to be higher than the conditional probability for patients in a kidney exchange program. Preliminary simulation experiments confirm this. In our model we therefore adjust the general probabilities by a scaling factor. Our experiments suggest that a scaling factor of .5 results in outcomes in concordance with historical data.

The probability of obtaining a living donor transplant in a given period can be estimated by:

$$Pr[\text{LTx}|X\text{-}Y] = .5 \cdot Pr[\text{LTx donor is allocated to blood type } BLO_X]\,(1 - PRA_X)$$

where the annual allocation probabilities per blood type category are as listed in Table 5.2.

Blood type patient	Probability
O	.22
A	.27
B	.12
AB	.18
Scaling factor	.5

Table 5.2: Annual probability that a suitable living donor is available to a patient of the indicated blood type. For patients in a kidney exchange program the probabilities should be multiplied with the provided scaling factor.

Transition to the 'RF Recovery' state

The probability of recovery of renal function after dialysis treatment is estimated at 1.1 % based on recovery rates described in (Chu and Folkert, 2010).

Transition to the 'Death' state

Transition to the 'Death' state depends on patient survival. We obtain mortality rates for patients on dialysis from historical Dutch data (Registratie Nierfunctievervanging Nederland (Renine), 2012). The annual mortality rates for patients on dialysis depend on patient age and are respectively 3.3%, 11.4%, 17.4% and 28.5% for age categories 16-44, 45-64, 65-74 and above 75 years old.

Transitions from the 'KE Recovery' state

There are two possible transitions from the 'KE Recovery' state, transition to the 'ESRD' state and transition to the 'Death' state. If these two do not occur, patients remain in the 'KE Recovery' state.

Transition to the 'ESRD' state

Transition to the 'ESRD' state occurs if there is a match failure preventing transplantation, or if there is graft failure subsequent to the transplant.

There are various types of failure that may prevent kidney exchange matches from going forward to transplantation. These include positive crossmatch after a negative virtual crossmatch, desensitization failure, and patient or donor withdrawal for medical or other reasons. Based on Dutch match failure data and in line with the medical literature (Ashlagi et al., 2011b; Glorie et al., 2013), we model these types of failure using both an exogenous probability of 12.5% and an endogenous probability calculated by the following probit model:

$$Pr[\text{Failure}|X\text{-}Y] = \Phi(-1.5007 + 0.0170 \cdot \text{PRA}_X) \tag{5.1}$$

where Φ represents the cumulative distribution function of the standard normal distribution. For the derivation of these probabilities we refer to Appendix A.

In order to estimate the probability of graft failure, we build a model for graft failure based on the medical literature. In (Laging et al., 2012) and (Laging et al., 2014) Dutch data from 1990 to 2011 is used to identify factors influencing patient and graft survival. Recipient age, HLA mismatch, donor type (living or deceased) and transplant year are identified as significant factors. By employing all the parameters in (Laging et al., 2012) and (Laging et al., 2014) to filter all the effect factors except for time period after transplant, we can get the estimated fit function for cumulative graft failure hazard rate. Given a pair X-Y, the hazard rate $\lambda_{\text{graft}}(t|X-Y)$ in period t is:

$$\lambda_{\text{graft}}(t|X-Y) = 0.0418t \cdot \exp(\beta' VAR_{(X-Y)})$$

where $0.0418t$ is the estimated baseline hazard rate, the parameters β are as specified in Table 5.3, and $VAR_{(X-Y)}$ represents the relevant explanatory variables. For the transplant year variable the baseline is 2008, for all other variables it is 0.

Variable	Coefficient
RECIPIENT_AGE	-0.0160
HLA_MISMATCH	.1017
DUMMY_LIVING_DONOR	-.5058
TRANSPLANT_YEAR	-.0263

Table 5.3: Hazard rate parameters for graft failure

Transition to the 'Death' state

As before, transition to the 'Death' state depends on patient survival. We estimate the survival function similarly to the graft failure function described above. Again the relevant variables are obtained from (Laging et al., 2012). Given a pair X-Y, the hazard rate $\lambda_{\text{survival}}(t|X-Y)$ in period t is:

$$\lambda_{\text{survival}}(t|X-Y) = 0.00926t \cdot \exp(\beta' VAR_{(X-Y)})$$

where $0.00926t$ is the estimated baseline hazard rate, the parameters β are as specified in Table 5.4, and $VAR_{(X-Y)}$ represents the relevant explanatory variables. Again, for the transplant year variable the baseline is 2008, for all other variables it is 0.

Variable	Coefficient
RECIPIENT_AGE	.06859
DUMMY_LIVING_DONOR	0.5749
TRANSPLANT_YEAR	-.0608

Table 5.4: Hazard rate parameters for patient survival

Transitions from other states

Since donor specific information is not known in the other states in the model, graft failure and patient survival in these states are based on average donor characteristics. For the 'LTx Recovery' and 'DTx Recovery' states, we use the same graft survival and recipient survival functions described in Section 5.2.2, but evaluate these functions using mean values for the HLA mismatch (see Table 5.5).

Variable	Mean value
HLA_MISMATCH living	3
HLA_MISMATCH deceased	2.6

Table 5.5: Mean values of HLA mismatch

For the 'RF Recovery' state we estimate mortality rates and dialysis recommencement rates based on the numbers reported in (Craven et al., 2007). In particular, we estimate the 3 monthly mortality rate at 4.5 % and the 3 monthly dialysis recommencement rate at 13.5 %.

5.2.3 Distribution over states

Let $A^{\mu}(X\text{-}Y) = [p^{\mu}_{ij}(X\text{-}Y)]$ be the matrix of transition probabilities and let $I(k)$ denote the probability distribution over states after k transitions (the entries of $I(k)$ correspond to the states 'ESRD', 'RF Recovery', 'LTx Recovery', 'DTx Recovery', 'KE Recovery', and 'Death'). It then holds that $I(k+1)$ can be recursively computed as

$$I(k+1) = I(k) \cdot A^{\mu}(X\text{-}Y)$$

with $I(0) = [1, 0, 0, 0, 0, 0]$ in case $\mu(X\text{-}Y) = \emptyset$ and $I(0) = [Pr[\text{Failure}|X\text{-}Y], 0, 0, 0, 1 - Pr[\text{Failure}|X\text{-}Y], 0]$ otherwise. In other words, the initial distribution specifies a start from the 'ESRD' state if patient X remains unmatched under μ and a start from the 'KE Recovery' state if X is matched and there is no match failure, if there is match failure X remains in the 'ESRD' state. The match failure probability $Pr[\text{Failure}|X\text{-}Y]$ is as specified in equation (5.1).

5.2.4 Calculating QALYs gained

The Markov chain model is supplemented with information on quality of life per state. We use two scenarios based on (de Wit et al., 1998) and (Kontodimopoulos and Niakas, 2008). The 'optimistic' scenario is based on (de Wit et al., 1998), which assessed quality of life of patients with the EuroQol (EQ-5D) Instrument (EuroQol Group, 1990; Brooks, 1996) using Standard Gamble (Torrance et al., 1972) and Time Trade Off (Churchill et al., 1987). The 'pessimistic' scenario is based on (Kontodimopoulos and Niakas, 2008), which obtained estimates using the SF-36 Health Survey from which the preference based SF-6D utility index was derived (Ara and Brazier, 2008). Let $QoL(X)$ denote the quality of life of patient X per state. The discounted quality adjusted life years gained $Q(X\text{-}Y)$ for patient donor pair X-Y can be calculated as follows. Let $t = 1, 2, \ldots$ denote the time periods, and let δ indicate the discount rate. Assuming that transitions only take place at the end of a period, we have

$$Q(X\text{-}Y) = \sum_{t=0}^{\infty} QoL(X)^T I(t) \cdot \frac{1}{(1+\delta)^{(t)}}$$

In our case, the 'ESRD' state is assigned a quality of life of .63, all recovery states are assigned a quality of life of .90 in the optimistic scenario and .72 in the pessimistic scenario. The 'Death' state is assigned a quality of life of 0. Following the discussions in the medical community (Luce, 1995; Bonneux and Birnie, 2001; Rittenhouse, 1996; Gravelle and Smith, 2001; Jacobs et al., 1995), we use a discount rate for health benefits

that is lower than the current discount rate of costs. In particular, we use a discount rate for health benefits of 1 % per year in our optimistic scenario and 1.5 % per year in our pessimistic scenario.

For each patient we compute the total discounted QALYs for a period of 25 years from entry into the kidney exchange pool. We discount to the beginning of the horizon, which in our simulations will be 1 January 2004 (see Section 5.4). Periods before a patient's entry date are not counted.

5.3 Allocation policies

5.3.1 Policies

In the literature on kidney exchange, various allocation policies have been suggested (Ashlagi et al., 2011b; Keizer et al., 2005; Glorie et al., 2014d; Ferrari et al., 2011; Böhmig et al., 2013; Kim et al., 2007; Manlove and O'Malley, 2012; Kaplan et al., 2005; Hanto et al., 2008). In this regard it is important to make a distinction between allocation requirements that limit the number of feasible allocations, and thereby transplants, (e.g. requiring donors to be in the same age category or have the same CMV-EBV serology as their recipients) and actual allocation criteria that determine the selection of an allocation from the set of feasible allocations (e.g. maximum number of transplants between donors and recipients of the same blood type).

In line with current practice of kidney exchange programs, we focus on periodical allocation policies. These are policies where patient-donor allocations are determined periodically, i.e. after a certain amount of time has expired or after certain number of new pairs have entered the program. These policies contrast with dynamic policies, in which decisions are made dynamically and take into account the timing of exchanges and the fact that patients and donors enter and leave the kidney exchange pool over time, to optimize the desired allocation criteria in the long run.

Table 5.6 summarizes the policies under consideration. In our base case policy, we consider the most commonly used allocation criteria, which is to maximize the total number of transplants. The second policy we consider, is a hierarchical criterion policy, which refines the primary criterion of maximizing the total number of transplants by several tie breaking criteria. We consider the hierarchical criteria used in the Dutch kidney exchange program (Keizer et al., 2005; Glorie et al., 2014d), which ranks allocations on (i) number of transplants, (ii) number of blood type identical transplants, (iii) match probabilities of matched patients (inverse ranking), (iv) longest cycle and chain length

Policy	Criteria	Requirements*
MaxTrans	Maximize # transplants	None
Dutch	Dutch hierarhical criteria	None
MaxTrans_R	Maximize # transplants	HLA mismatch < 2, age difference < 10
Dutch_R	Dutch hierarhical criteria	HLA mismatch < 2, age difference < 10
MaxQaly	Maximize QALYs	None
* In addition to blood type and crossmatch compatibility		

Table 5.6: Allocation policies

(inverse ranking), (v) smallest spread per cycle and chain over transplant centers, and (vi) longest wait time, and selects the highest ranking allocation.

We consider two versions of each policy. In the first version only blood type and crossmatch compatibility are considered as allocation requirements. In the second version, additional requirements with respect to some common measures are formulated (see e.g. Lucan (2007); Kute et al. (2013); Kim et al. (2007); Ycetin et al. (2013); Glorie et al. (2014b)): in particular, we consider a maximum number of 2 HLA mismatches and a maximum age difference between donor and recipient of 10 years.

Finally we consider a policy which maximizes the total sum of discounted QALYs, as calculated with the Markov model described in Section 5.2, for the entire patient population.

In all policies listed above the maximum cycle and chain length is set to 3. In our experiments we will also consider longer limits and set the cycle limit to 4 and chain limit to 6 (except for the perfect information policy, where we set the limit to infinity). We will indicate this by appending the policy names with 'Long cycles and chains'.

5.3.2 Determining the allocation by mixed integer programming

Under the above allocation policies, for a given set of patient-donor pairs, the kidney exchange allocation problem corresponds to a cycle packing problem in a weighted directed graph in which the nodes represent patient-donor pairs, the arcs represent the compatibilities, and the weights on cycles in the graph correspond to priorities or weights on matchings (Abraham et al., 2007; Glorie et al., 2014d). The goal is to find a maximum weight exchange, i.e. a collection of non-overlapping cycles, such that no cycle exceeds the bound on the number of possible simultaneously feasible transplants.

Let $C(K, L)$ denote the collection of cycles and chains that are feasible with respect to the bound on cycle length K and the bound on chain length L. Next, let us introduce a binary decision variable x_c for each cycle and chain $c \in C(K, L)$ that is defined as:

$$x_c = \begin{cases} 1 & \text{if } c \text{ is selected,} \\ 0 & \text{otherwise.} \end{cases}$$

Let $x = \left[x_1, \ldots, x_{|C(K,L)|}\right]^T$ denote the vector of decision variables and let $w \in \mathbb{R}^{|C(K,L)|}$. The basic allocation problem can then be represented by the following Mixed Integer Program:

P_1:

$$\max z(x) = \sum_{c \in C(K,L)} w_c x_c \tag{5.2}$$

$$\text{s.t.} \sum_{c \in C(K,L): n \in c} x_c \leq 1 \qquad \forall n \in N \tag{5.3}$$

$$x_c \in \{0,1\} \qquad \forall c \in C(K,L)$$

Here, the objective (5.2) is to select a collection of cycles and chains that maximizes $z(x)$. The constraints (5.3) ensure that no patient or donor is contained in more than one selected cycle or chain. When the objective is to maximize the number of transplants, the weights w_c are equal to $|c|$.

For the other objective criteria listed in Table 5.6 the weights may be different and some additional variables and constraints may be needed. For a detailed description we refer to (Glorie et al., 2014d). In principle, all of the criteria mentioned above can be represented by the following general model. In addition to the decision vector x, let y denote a $n \times 1$ vector of auxilliary variables which are allowed to assume values in some subspace $F \subseteq \mathbb{R}^n$, for $n \in \mathbb{N}$. Also, for $m \in \mathbb{N}$, let $v \in \mathbb{R}^n$, $A \in \mathbb{R}^{m \times |C(K,L)|}$, $B \in \mathbb{R}^{m \times n}$, and $b \in \mathbb{R}^m$. Then the following MIP solves the allocation problem for a general class of objective criteria:

P_2:

$$\max z(x,y) = w^T x + v^T y_i \tag{5.4}$$

$$\text{s.t.} \quad Ax + By \leq b \tag{5.5}$$

$$x \in \{0,1\}^{|C(K,L)|}$$

$$y \in F$$

The constrains (5.5), which are formulated in a very general way, allow to model the objective criteria at hand. For instance, for the policy of maximizing the total sum of

discounted QALYs we set w_c equal to the total discounted QALYs for the entire cycle c if it is selected and define an auxiliary variable y_n for each node $n \in N$ that is defined as:

$$y_n = \begin{cases} 1 & \text{if } n \text{ is not selected,} \\ 0 & \text{otherwise.} \end{cases}$$

and we set v_n equal to the total discounted sum of QALYs for node i if it is not selected. The MaxQaly policy can then be solved by the following model:

P_3:

$$\begin{aligned} \max\ z(x,y) = & \sum_{c \in C(K,L)} w_c x_c + \sum_{n \in N} v_n y_n & & (5.6) \\ \text{s.t.} & \sum_{c \in C(K,L): n \in c} x_c + y_n = 1 & \forall n \in N & \\ & x_c \in \{0,1\} & & \forall c \in C(K,L) \\ & y_n \geq 0 & & \forall n \in N \end{aligned}$$

In all cases the above Mixed Integer Programs may be solved by a branch-and-price algorithm in which the cycles and chains are generated when this is required by their reduced cost criterion in the simplex method. For a detailed description we refer to (Abraham et al., 2007; Glorie et al., 2014d).

5.3.3 Determining the maximum possible gain in health value

We would like to understand how far away the periodical policies described in Table 5.6 are from the maximum possible gain in health value over a given time horizon. To this end we calculate an upper bound on the total discounted quality adjusted life years that could be gained over the horizon under consideration if we were to have perfect information at the beginning of the horizon. We do this by solving problem P_3 for the entire horizon at once. In this case, the weights w_c are set equal to the total discounted sum of QALYs for the entire cycle c if it is selected at the earliest possible date. This 'perfect information policy' represents essentially the best possible dynamic policy over the horizon.

5.4 Simulator

We evaluate health outcomes by simulations based on historical data from the Dutch national kidney exchange program. This simulator is described in detail in (Glorie et al., 2013). In this section we will briefly explain the main aspects of the data and simulation procedures.

5.4.1 Data

The data for our simulator is obtained from the Dutch Transplant Foundation and originates from the empirical registry of the Dutch national kidney exchange program. It includes 438 incompatible patient-donor pairs who participated in Dutch kidney exchanges between October 2003 and January 2011. In addition it contains 109 unspecified donors, i.e. donors without a specified recipient, who were screened at one of the seven Dutch transplant centers during that period. A patient is considered to be incompatible with a donor whenever the donor's blood type contains a protein that is not contained in the patient's blood type, or whenever the donor has a HLA type that is unacceptable to the patient, otherwise the patient and donor are compatible.

5.4.2 Simulations

Dynamic simulations are conducted by performing repeated Monte Carlo simulations. Each such simulation spans the period between 1 October 2003 and 23 December 2010 and involves a population of size 547 generated from the empirical data using sampling with replacement. The arrivals of patient-donor pairs and unspecified donors are determined by assigning each pair and each unspecified donor in the sampled population a random date in the simulation period. Arrival dates are drawn uniformly, corresponding to a Poisson arrival process. Matching rounds are conducted every three months, starting from 1 January 2004. In each matching round, an allocation is determined based on the specified allocation policy. The underlying optimization problem is solved by the algorithm described in (Glorie et al., 2014d) and as specified in Section 5.3. There are a total of 29 matching rounds during the simulation period. Proposed matches may fail to go forward to transplantation because a final crossmatch test between the donor and the intended recipient is positive, because of desensitization failure, or because of patient or donor withdrawal for medical, psychological or other reasons. Based on Dutch match failure data, we simulate this with both an exogenous probability and an endogenous probability depending on the patient and donor characteristics (see Appendix A). In

case of match failure the optimization algorithm is rerun with the updated compatibility information. This process is repeated until a feasible matching is found.

5.4.3 Statistical analysis

For each simulation run the total discounted quality adjusted life years gained are calculated using the model and approach described in Section 5.2. Then, for each policy the average results over 30 simulation runs are computed. Significance of difference in results between policies is tested using the sign test.

5.5 Results

Figures 5.2-5.6 display the outcomes of our simulations using the procedure described in Section 5.4.

Figure 5.2 shows the average health value per policy measured in discounted quality adjusted life years for the entire patient population (both transplanted and not transplanted patients). It is interesting to observe that the MaxTrans policy and the Dutch policy perform equivalently in both the optimistic and the pessimistic scenario. In the optimistic scenario, both policies result in an average of 9.7 discounted QALYs (7.7 in the pessimistic scenario), which is 3.6 QALYs more than if no kidney exchanges would be performed (2.5 QALYs in the pessimistic scenario). The additional hierarchical criteria included in the Dutch policy compared to the single criterion MaxTrans policy do not appear to result in a comparative gain in health value. Furthermore, the restricted versions of both policies, with requirements set so as to improve the transplant quality, turn out to be so restrictive that the average health value is comparable to not performing kidney exchanges at all.

On the other hand, if all matching decisions would be made based on perfect information so as to optimize the total health value, this would entail an average of 11.6 discounted QALYs gained (8.9 in the pessimistic scenario). This is a theoretical upper bound, however, since in practice perfect information is not at hand. If we were to employ our periodical MaxQaly allocation policy, which does not rely on perfect information and which is like the MaxTrans and the Dutch policy but with an objective of maximizing health value, an average of 10.3 discounted quality adjusted life years could be gained (8.0 in the pessimistic scenario). This is an increase of .6 discounted quality adjusted life years over current practice ($P < 0.0001$) and it is 32 % closer to the upper bound. Allowing longer cycle and chain lengths (up to length 4 cycles and length 6 chains) does increase

the health value gains slightly further and preserves the differences between the various policies.

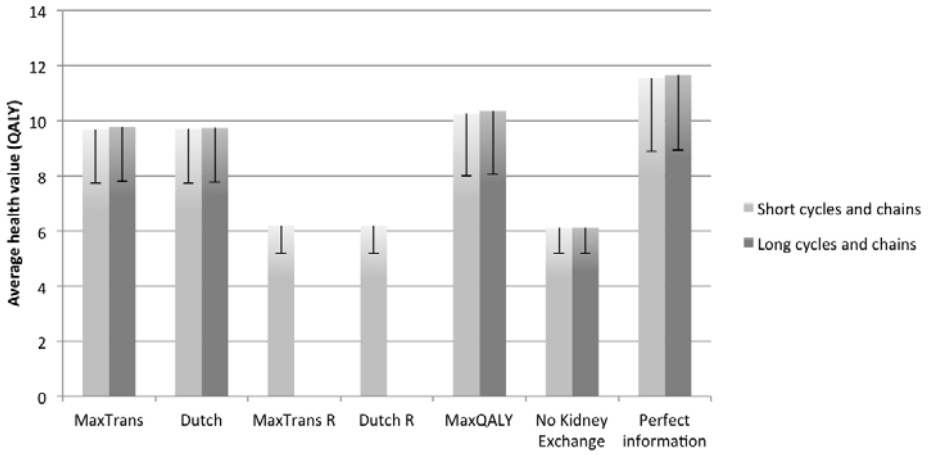

Figure 5.2: Average health value in discounted quality adjusted life years per policy in two scenarios. Bars correspond to the optimistic scenario and error bars correspond to the pessimistic scenario.

Next, we consider the number of transplants (Figure 5.3). The figure clearly shows that the average number of transplants achieved under the policies MaxTrans (352.5), Dutch (355.2), and MaxQaly (351.3) is not significantly different (P = .2923) and is similar in both scenarios. It also becomes evident how restrictive the restricted policies are, as under these policies almost no matches can be made. In case of perfect information however, 372.9 transplants could be achieved on average. The additional transplants achieved under this policy account for a large part of the gain in health value observed for this policy (Figure 5.2). Under the periodic policies (MaxTrans, Dutch and MaxQaly) there is therefore still potential to exploit dynamics to achieve more matches and hence generate more health value.

To provide more insights into the distribution of health value, we will also consider the health value for each of several patient groups. Figure 5.4 displays the average health value for matched and unmatched patients per policy. As expected, matched patients achieve a substantially higher health value than unmatched patients under all policies. It is interesting to see, however, that under the MaxQaly policy the unmatched patients achieve a significantly higher health value than under the MaxTrans and Dutch policy (6.7 versus, respectively, 5.2 and 5.1 in the positive scenario (P<0.0001) and 5.7 versus 4.5 and

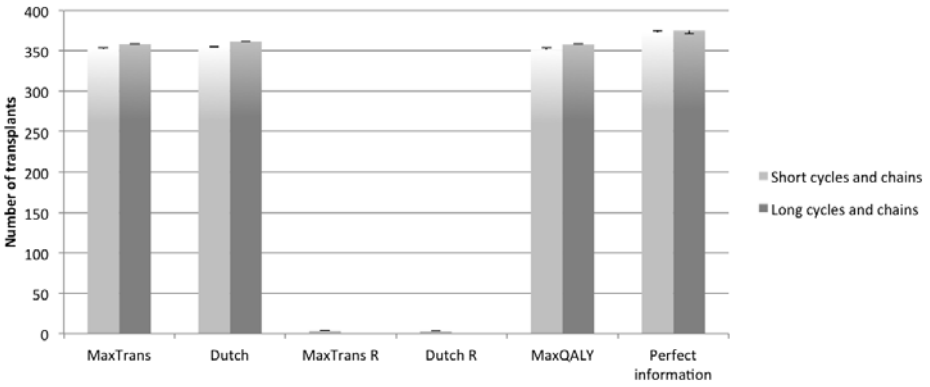

Figure 5.3: Average number of matches per policy in two scenarios. Bars correspond to the optimistic scenario and error bars correspond to the pessimistic scenario.

4.4 in the negative scenario (P<0.0001)). Matched patients, on the other hand, achieve a similar health value under these three policies (11.1 versus, respectively, 10.8 and 10.8 in the positive scenario (P<0.0001), and 8.5 for all three policies in the pessimistic scenario). This likely occurs because the patients with the worst prospects if they were to be left unmatched are matched under the MaxQaly policy. For both matched and unmatched patients it is theoretically possible to achieve an even higher health value, as is evidenced by the perfect information policy.

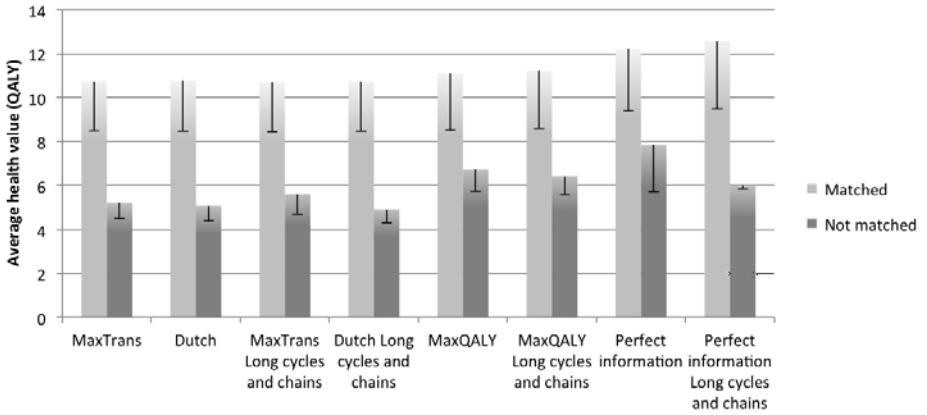

Figure 5.4: Average health value in discounted quality adjusted life years for matched and unmatched patients per policy in two scenarios. Bars correspond to the optimistic scenario and error bars correspond to the pessimistic scenario.

Figures 5.5 and 5.6 provide a distribution of the average health value over blood types and age categories. Overall, prospects are best for type AB patients and worst for type O patients. Type A and type B patients are in between. The distribution for the Dutch policy differs only marginally from the distribution for the MaxTrans policy. The MaxQaly policy, however, constitutes a higher health value for all blood types than under the Dutch policy. In particular, there is a substantial gain for type O patients (9.5 versus 8.7 in the optimistic scenario ($P < 0.0001$) and 7.4 versus 7.1 in the pessimistic scenario ($P < 0.0001$)).

For all policies we observe a substantial difference in health value for patients of different age. Even under the Dutch policy elderly patients have a substantially lower health value than younger patients. An important question is therefore whether elderly patients are not disproportionally disadvantaged compared to younger patients when a policy with the objective of maximizing the discounted sum of quality adjusted life years

is applied. Figure 5.6 shows that this need not be the case as, for short cycles and chains, the health value of patients of 75 years and older is equivalent under the MaxQaly policy and the Dutch policy in both scenarios. Equivalence also holds for long cycles and chains in the pessimistic scenario, but not in the optimistic scenario.

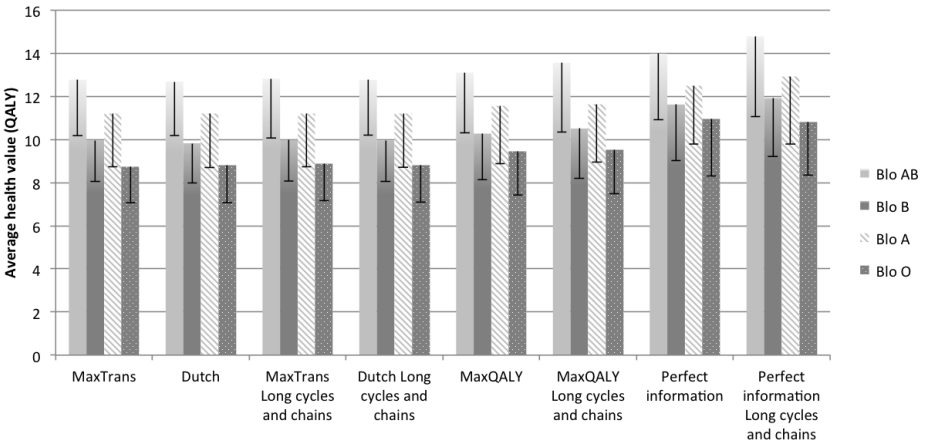

Figure 5.5: Average health value in discounted quality adjusted life years per blood type per policy in two scenarios. Bars correspond to the optimistic scenario and error bars correspond to the pessimistic scenario.

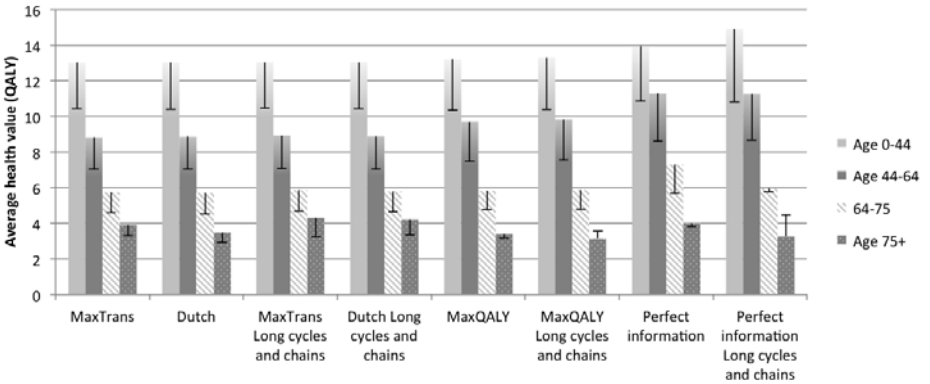

Figure 5.6: Average health value in discounted quality adjusted life years per age category per policy in two scenarios. Bars correspond to the optimistic scenario and error bars correspond to the pessimistic scenario.

5.6 Conclusion and discussion

In this paper we have performed a health value analysis of allocation policies for kidney exchange. The basis for our analysis is an individualized Markov health value model which can be linked to a mixed integer programming model. In combination with evidence based data and survival analysis, we have used discrete event simulation to compare existing policies to a new policy that aims to maximize health value. We have also calculated an upper bound on the maximum health value attainable by any policy.

Interestingly, we found that policies that directly impose allocation restrictions to increase the health outcomes - such as restrictions on the acceptable HLA mismatch or on the age difference between recipients and donors - may actually be detrimental to the total health value. This is particularly so if the imposed restrictions severely limit the recipient-donor matches that can be made. Also, we found that additional hierarchical allocation criteria beyond maximizing the number of transplants, in particularly those currently used in practice in the Dutch kidney exchange program, do not lead to a significant difference in health outcomes.

The health value policy we propose performs significantly better in terms of health outcomes than the other policies tested. Of course, use of quality adjusted life years may conflict with criteria that are currently used in most kidney exchange programs, such as maximizing the number of transplants. In particular, there may be concern that a focus on maximizing health value may be detrimental to the number of transplants that are performed. However, our findings do not indicate a significant effect on the number of transplants if our health value maximizing policy would be adopted.

Analyzing the allocations made under our proposed policy, we find that patients with relatively poor prospects if left unmatched are matched more often than in the other policies we tested. The result is that our proposed policy especially benefits quality of life for unmatched patients. In particular, type O patients benefit from the gains in health value. Furthermore, and perhaps non-obviously, we find that elderly patients need not be disadvantaged by using health value to determine allocations. For short cycle and chain lengths, the simulation results yield no significant difference in health outcomes for elderly patients between the proposed policy and the present Dutch policy. Hence, the proposed maximum health value policy need not reduce equity.

Although our health value policy improves on the other policies investigated, its performance is of course dependent on the way in which health value is measured and on the clinical data with which it is evaluated. Our individualized health value model is based on several models described in the medical literature and their underlying assumptions. Even

though these models and assumptions have been carefully reviewed and, where possible, tested with clinical data, there may be factors affecting health outcomes that lay beyond our health value model such as recipient health status at time of transplant, quality of patient and donor screening and preparation, and medical and psychological follow-up after transplant. The clinical data used in our simulations to evaluate the allocation policies is taken from the longest running national kidney exchange program in the world and we have used two scenarios for the parameter values for quality of life and the discount rate.

Finally, we note that even though the health value policy we propose improves substantially over current practice, further improvements in health outcomes are still possible. This is evidenced by our perfect information policy which serves as an upper bound on the maximum health value that can be achieved by any policy. We estimate that a further improvement of up to 12.6 % in health outcomes is possible with respect to our proposed policy. In line with what we have discussed above, further refinement of the health model and data form one direction for improvement. Another direction is for the matching algorithms to better anticipate information about future patient and donor arrivals. This appears to be particularly promising as end stage renal disease and participation in donor programs typically occur after lengthy health service trajectories. Optimization algorithms, such as the algorithm used in our perfect information policy, can then take information about future patients and donors into account when determining the allocation. The last direction we would like to mention is the inclusion of compatible pairs in kidney exchange programs by the promise of increased quality of life compared to a direct transplant.

In spite of the fact that the use of quality adjusted life years is commonly accepted as a primary decision criteria for many medical interventions, its use in deciding on allocations in kidney exchange may be controversial. We hope our research may provide guidance to policy makers as to what the consequences in terms of health outcomes will be when health value maximization is considered as a primary decision criterion. Conversely our study shows the impact on (loss of) health value, when other criteria are considered instead. As we believe that consideration of health outcomes is equally appropriate to consider as it is for many other health problems, we hope the proposed health value model may serve as a reference framework in future research, to the benefit of the patients suffering from end stage renal disease across the globe.

Chapter 6

Robust barter exchange[1]

6.1 Introduction

We consider the centralized organization of barter exchange markets. Barter exchange markets are markets in which agents seek to directly trade their goods with each other (Abraham et al., 2007; Glorie et al., 2014d). The trades in such markets consist of trading cycles in which each agent gives a good to the next agent in the cycle (Shapley and Scarf, 1974; Roth et al., 2007). Alternatively, the trades may consist of chains which are started by an agent that provides a good without requiring a good in return and end with an agent that receives a good without providing one (Anderson et al., 2014). Barter exchanges find a natural application in kidney exchange programs, which aim to enable transplants between incompatible donor-patient pairs (Rapaport, 1986; Roth et al., 2004; Glorie et al., 2014b). Other applications include house exchanges (in which agents seek to simultaneously buy each others houses, see for example www.besthouseswap.com), shift exchanges (e.g., between nurses in hospitals), intra-organizational skilled worker exchanges (e.g., between projects or departments), and book exchanges (see for example www.readitswapit.co.uk).

In this research we focus on barter exchange markets in which proposed transactions must be verified before they can proceed. Proposed transactions may fail to go forward if verification fails or if a participant withdraws. In housing markets, for example, it should be checked whether the participants in a transaction meet the financing requirements. In kidney exchange, proposed 'transactions' must be checked with a so-called crossmatch test to ensure the success of eventual transplants, and patients and donors may withdraw

[1]This chapter is based on (Glorie et al., 2014a).

at the last moment due to medical, psychological or other reasons (Delmonico et al., 2004; de Klerk et al., 2005; Glorie et al., 2013).

In order to prevent agents from withdrawing from the market after they have received their desired good, but before they have given up the good with which they came to the market, trades are typically organized simultaneously (Segev et al., 2005b; Glorie et al., 2014b). This poses a natural constraint on the length of trading cycles as they cannot exceed the number of logistically feasible simultaneous transactions.

In our setting, the market is cleared by a central authority (Roth et al., 2005a). The clearing problem for this authority is to select a set of agents in such a way that each selected agent can trade with another agent in the set (Abraham et al., 2007; Manlove and O'Malley, 2012; Constantino et al., 2013; Glorie et al., 2014d). The corresponding transactions are then verified (i.e. in kidney exchange the patient-donor pairs involved are notified and the final crossmatch tests are performed). In case one or more proposed transactions fail, a new set of agents may be selected. The new set should be as close as possible to the initial set in order to minimize the material and emotional costs of the alteration. The objective is to maximize the number of transactions going forward.

A possible approach to market clearing in uncertain markets is to consider the expected number of transactions that can go forward (see e.g. (Pedroso, 2013; Awasthi and Sandholm, 2009)). However, considering the expectation is not always tractable or desirable. For instance, in kidney exchange there is a class of patients who are highly sensitized, which means that these patients are compatible with only a very small fraction of kidney donors. The rare matching opportunities that exist for these patients should be protected against failure. Failure to match highly sensitized patients has led to the accumulation of these patients in kidney exchange pools and in substantially longer waiting times and higher mortality for these patients (Ashlagi et al., 2013). In this research we focus on robustness metrics (see e.g. (Ben-Tal et al., 2009)) that allow us to specify the desired level of protection from uncertainty. A substantial advantage of using robust optimization is that it requires no assumptions on the underlying probability distribution.

We consider various recourse policies that determine the allowed actions after an initial subset of transactions is proposed for verification. In our first policy, called simple recourse, we take into account costs (or missed gains) for failing transactions. Although this policy does not allow failing transaction cycles to be recovered, it does allow better decisions to be made regarding the set of transactions that is initially proposed because the possibility of failure is taken into account. In the second policy, called back-arcs recourse, we allow part of a failing transaction cycle to be recovered if the remaining participants in the cycle can trade among themselves. In our last policy, full recourse, we allow for a

complete recovery of the initial solution using alternative transactions. We develop robust models for each of the recourse policies. In all cases, the optimum clearing problem is a combinatorial optimization problem that is modeled as a vertex-disjoint cycle packing problem in an unreliable digraph. The arcs and nodes of this graph are subject to failure.

Barter exchange has received substantial attention in recent years, particularly due to the impact of kidney exchange. The clearing problem in barter exchange was first presented in (Shapley and Scarf, 1974). The idea of using trading chains in addition to trading cycles was presented in (Roth et al., 2004). (Roth et al., 2007) studied the relevant bounds on trading cycles due to simultaneous exchange. (Abraham et al., 2007) formulated the clearing problem with bounded cycles as a cycle packing problem in a digraph and provided a branch-and-price algorithm to solve it. Their approach worked well for trading cycles and chains involving up to three agents. (Glorie et al., 2014d) showed how the pricing problem could be solved efficiently in the cycle and chain length, thereby allowing the branch-and-price approach to scale better to longer cycles and chains. (Constantino et al., 2013) did a systematic comparison of several compact and non-compact formulations for barter exchange and concluded that the cycle packing formulation is strongest.

Failure in barter exchange was first considered in (Awasthi and Sandholm, 2009), which heuristically solved the online clearing problem using scenario sampling to minimize regret over several future scenarios. (Dickerson et al., 2012) presented an alternative heuristic learning approach to deal with uncertain future scenarios. Their approach relied on using weighted myopia. (Dickerson et al., 2013) studied optimizing the set of proposed transactions with probabilistic failures, but allowed no recourse to recover trading cycles. Their approach resembles our simple recourse policy in a probabilistic setting. (Molinaro and Ravi, 2013) and (Goel and Tripathi, 2012) considered failures in a bilateral exchange setting where transactions that verify positively must be executed.

Possibilities for recourse were considered in (Manlove and O'Malley, 2012). They introduced the notion of back-arcs recourse, as we use it in this paper, and gave preference to cycles containing back-arcs in the clearing problem. Back-arcs recourse was also considered by (Pedroso, 2013) in a stochastic optimization setting. However, their approach was computationally very expensive. To the extent of our knowledge, we are the first to explicitly consider failures and full recourse policies in an optimization model for barter exchanges.

We also would like to place our research in the general context of robust optimization. Robust optimization was first introduced by (Soyster, 1973). Under the assumption of 'unknown but bounded' data, the goal was to optimize the objective value while guar-

anteeing feasibility with respect to all realizations of the data within the considered 'uncertainty set'. Because Soyster's approach tends to provide very conservative solutions, Kouvelis and Yu (1997); Ben-Tal and Nemirovski (1997, 1998); El Ghaoui and Lebret (1997); El Ghaoui et al. (1998) developed new robust optimization frameworks for Integer Programming and Convex Programming that allow adjusting the size and shape of the uncertainty set to allow for a balance between feasibility and the attainable objective value. Both static and dynamic approaches to robust optimization have been considered (Bertsimas and Thiele, 2006). In a static uncertain optimization problem, all decisions have to be made before the actual realizations of the parameters are known. In a dynamic uncertain optimization problem, some decisions - the so-called 'recourse actions' - may be made after the parameters values are known (Ben-Tal et al., 2004; Atamturk and Zhang, 2007; Chen et al., 2007; Bertsimas and Caramanis, 2010). Dynamic problems are referred to as two-stage or multi-stage problems, depending on the number of stages in which the decisions can be made. (Ben-Tal et al., 2004) show that two-stage robust linear programming is computationally intractable and propose a tractable alternative referred to as affinely adjustable robust linear programming. Affinely adjustable robustness requires the recourse decision variables to be an affine function of the realizations of the uncertain parameters.

The problem considered in this paper can be classified as a two-stage dynamic uncertain optimization problem. In contrast to the robust optimization approaches discussed above, our focus is not on maintaining feasibility in all scenarios, but instead on maximizing the gains of trade in the worst-case scenario in our uncertainty set. Transactions that are infeasible after second stage recourse actions, are considered as lost transactions. As our problem, including the recourse actions, can be modeled by mixed integer programs, our solution approaches can be considered as generalizations of the above techniques for adjustable robust mixed integer programming. However, in our solution approaches we rely on the specific structure of our problem. The delayed scenario generation approach we use for our full-recourse policy may be applicable to general mixed integer uncertain optimization problems, provided that appropriate bounds can be derived for solving the scenario generation subproblem. Scenario generation has been considered in stochastic programming (see e.g. Casey and Sen (2005)), but to the extent of our knowledge we are the first to consider it for adjustable robust optimization.

The remainder of this paper is organized as follows. Section 6.2 provides a mathematical description of the robust exchange problem. It first presents a general model for market uncertainty and then details the simple recourse, back-arcs recourse, and full recourse policies. Sections 6.3, 6.4, and 6.5 describe our theoretical results for each of

these recourse policies. Section 6.6 considers a method to refine the robust solution by embedding the robust optimization criteria in a hierarchical set of criteria. Section 6.7 then provides computational results. Finally, Section 6.8 concludes.

6.2 Mathematical problem description

6.2.1 A model for market uncertainty

We model the exchange market as follows. Let $D = (N, A)$ denote an unreliable digraph where the node set N represents the agents and the arc set A represents the possible transactions (see Figure 6.1 for an example). Furthermore, let $N = N_S \cup N_U$ where N_S is the set of agents requiring a good in return for their own good, and N_U is the set of agents that provide a good without requiring a good in return. A *length-l cycle* is an arc traversal $\langle n_1, \ldots, n_l \rangle$ such that $\{n_1, \ldots, n_l\} \subseteq N_S$, $(n_l, n_1) \in A$ and, for every $1 \leq i < l$, $(n_i, n_{i+1}) \in A$. A *length l chain* is an arc traversal $\langle n_1, \ldots, n_l \rangle$ such that $n_1 \in N_U$, $\{n_2, \ldots, n_l\} \subseteq N_S$ and for every $1 \leq i < l$, $(n_i, n_{i+1}) \in A$. Next, let $k \in \mathbb{Z}_+$ denote the maximum size of trading cycles and chains[2]. Then a solution to the clearing problem corresponds to a set of vertex disjoint cycles and chains in D with length at most k.

Let $\mathfrak{U} \subseteq \mathcal{P}(N \cup A)$, where $\mathcal{P}(N \cup A)$ denotes the power set of $N \cup A$, be the collection of possible 'scenarios' of ultimately available nodes and arcs, i.e. the transactions that can go forward after verification. In what follows we consider $\mathfrak{U} := \{u \subseteq N \cup A : B\zeta^u \leq b, \zeta^u \in \{0,1\}^{|N|+|A|}\}$, where B is a given matrix, b is a given vector and where $\zeta^u = \left[\zeta^u_1, \ldots, \zeta^u_{|N|}, \zeta^u_{|N|+1}, \ldots, \zeta^u_{|N|+|A|}\right]^T$ with

$$\zeta^u_i = \begin{cases} 1 & \text{if } i \leq |N| \text{ and node } i \text{ is available in the recourse stage,} \\ 1 & \text{if } i > |N| \text{ and arc } i \text{ is available in the recourse stage,} \\ 0 & \text{otherwise.} \end{cases}$$

For ease of exposition we will denote with u_ζ the scenario specified by the vector ζ. Furthermore, we will denote with ζ^u_n and ζ^u_a the elements of ζ^u referring to, respectively, node $n \in N$ and arc $a \in A$. A scenario set can, for example, be characterized as the set of scenarios in which at most p % of nodes fail. This would correspond to the set $\mathfrak{U} := \{u \subseteq N \cup A : \sum_{n \in N} \zeta^u_n \geq |N|(1-p), \sum_{a \in A} \zeta^u_a \geq |A|, \zeta^u \in \{0,1\}^{|N|+|A|}\}$. We do not require the probability distribution over the set of scenarios to be known.

[2]Although, in some applications, the maximum cycle and chain length may be different, we use a single limit in this paper. This corresponds for instance to the maximum number of simultaneous transplants in kidney exchange.

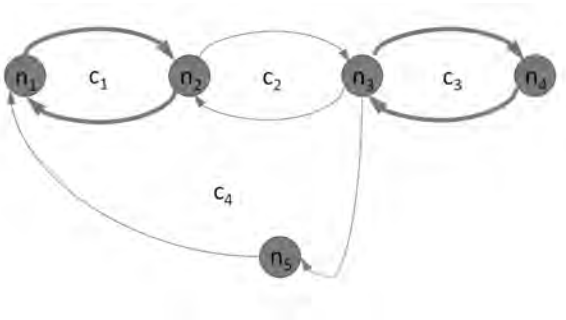

Figure 6.1: Example of an exchange market digraph. There are 5 agents, represented by the nodes $n_1, \ldots, n_5$. The arcs in the graph represent the possible transactions: an arc between nodes n_i and n_j indicates that agent n_j is interested in the good of agent n_i. The graph has 4 feasible trading cycles, $c_1 = \langle n_1, n_2 \rangle, c_2 = \langle n_2, n_3 \rangle, c_3 = \langle n_3, n_4 \rangle, c_4 = \langle n_1, n_2, n_3, n_5 \rangle$. A solution to the clearing problem could, for instance, consist of cycles c_1 and c_3 since these are vertex disjoint.

N.B. If we choose $\mathfrak{U} := \{N \cup A\}$, the above model corresponds to the standard deterministic exchange model as considered in (Abraham et al., 2007; Constantino et al., 2013; Glorie et al., 2014d).

6.2.2 The robust exchange problem

The robust exchange problem is to determine a solution to the clearing problem that is robust against market uncertainty.

Denote with $D^u = (N^u, A^u)$ the subgraph of D induced by a scenario $u \in \mathfrak{U}$. Furthermore, denote with $C(k)$ and $C^u(k)$ the set of all cycles and chains in, respectively, D and D^u with cardinality at most k. If $C^* \subseteq C(k)$ is a solution to the clearing problem in D (the planned solution which is proposed for verification) then if scenario $u \in \mathfrak{U}$ occurs after verification, an alternative solution $C^{*u} \subseteq C^u(k)$ in D^u may be considered (the effective solution).

Let us introduce decision variables

$$X_c = \begin{cases} 1 & \text{if cycle } c \in C(k) \text{ is selected in the planned solution,} \\ 0 & \text{otherwise.} \end{cases}$$

Then the robust exchange problem is given by

$$\max_{X} \min_{u \in \mathfrak{U}} R(X, u) \tag{6.1}$$

$$\text{s.t.} \sum_{c \in C(k): n \in c} X_c \leq 1 \qquad \forall\, n \in N \tag{6.2}$$

$$X \in \{0,1\}^{|C(k)|} \tag{6.3}$$

where $R(X, u)$ specifies the objective value attained under the recourse policy for the planned solution X and the scenario $u \in \mathfrak{U}$. The objective (6.1) is to maximize some objective value, as determined by the selected recourse policy (see below), in the worst case scenario. The packing constraints (6.2) guarantee that each agent can be involved in at most one trading cycle or chain.

Since the set of scenarios $\mathfrak{U}$ is finite, the robust exchange problem can alternatively be formulated as:

$RE(\mathfrak{U}) :=$

$$\max_{Z,X} \quad Z \tag{6.4}$$

$$\text{s.t.} \quad Z \leq R(X, u) \qquad \forall\, u \in \mathfrak{U} \tag{6.5}$$

$$\sum_{c \in C(k): n \in c} X_c \leq 1 \qquad \forall\, n \in N \tag{6.6}$$

$$Z \in \mathbb{R}_+ \tag{6.7}$$

$$X \in \{0,1\}^{|C(k)|} \tag{6.8}$$

Here, Z is an auxilliary decision variable and Constraints (6.5) specify that the worst case is taken with respect to the uncertainty set $\mathfrak{U}$.

6.2.3 Simple recourse

We will first consider the so-called simple recourse policy. In this policy we take into account costs (or missed gains) for failing transactions. In other words, under this policy the alternative solution that may be selected after verifying the planned transactions, consists only of the cycles and chains in the planned solution for which all nodes and arcs are available. Although this policy does not allow failing trading cycles or chains to be recovered, it ostensibly allows better decisions to be made regarding the set of transactions that is initially proposed because the possibility of failure is explicitly taken into account.

Let $f : A \to \mathbb{R}$ be a weight function over the arcs in D, such that $f(a)$ indicates the benefit associated to executing the transaction represented by the arc $a \in A$. Next, let $w_c := \sum_{a \in c} f(a)$ denote the benefit associated to executing a cycle or chain $c \in C(k)$, let X indicate a planned solution, and let $u \in \mathfrak{U}$. Then, the simple recourse policy is defined as:

$$\begin{aligned} R_{\text{Simple}}(X, u) &:= \sum_{c \in C(k)} w_c X_c - \sum_{c \in C(k): c \notin C^u(k)} w_c X_c \\ &= \sum_{c \in C(k)} w_c X_c - \sum_{c \in C(k)} (1 - \prod_{n \in c} \zeta_n^u \prod_{a \in c} \zeta_a^u) w_c X_c \\ &= \sum_{c \in \mathcal{C}(k)} (w_c X_c \prod_{n \in c} \zeta_n^u \prod_{a \in c} \zeta_a^u) \end{aligned} \tag{6.9}$$

If the weights w_c are set equal to the number of nodes in each cycle or chain $c \in C(k)$, then $R_{Simple}(X, u)$ equals the number of nodes belonging to cycles and chains that are in the planned solution X and are feasible in scenario u.

Although the simple recourse policy may appear to be very restrictive as it does not allow failing trading cycles or chain to be recovered, this restrictiveness corresponds to current practice in some kidney exchange programs. In these programs it is simply not possible to recover match failures in a timely fashion and the patients and donors involved in a failing cycle or chain are left in the exchange pool until the next matching round. By taking the possibility of failure already into account in the primary decision stage, the simple recourse model allows better decisions to be made even for those programs.

6.2.4 Back-arcs recourse

The next recourse policy we consider is the so-called back-arcs recourse policy (see Manlove and O'Malley (2012)). The idea is to allow part of a failing transaction cycle to be recovered if the remaining participants in the cycle can trade among themselves. We begin with the following definition:

Definition 6.1. *Let $D = (N, A)$ be a digraph and let c be a cycle in D. An arc $a = (i, j) \in A$ is a back-arc for c if $i \in c$ and $j \in c$ but $a \notin c$.*

As for the simple recourse policy, let $f : A \to \mathbb{R}$ be a weight function over the arcs in D, such that $f(a)$ indicates the benefit associated to executing the transaction represented by the arc $a \in A$. Also, let $w_c := \sum_{a \in c} f(a)$ denote the benefit associated to executing a cycle $c \in C(k)$.

Furthermore, let X indicate a planned solution, let $A(X) \subseteq A$ denote the set of arcs included in cycles and chains selected in X, and let $\hat{A}(X) \subseteq A$ denote the set of back-arcs for cycles selected in X. Finally, let $\hat{D}^u = (N^u, A^u \cap (A(X) \cup \hat{A}(X))$ denote the recourse graph in scenario $u \in \mathfrak{U}$ and denote with $\hat{C}^u(k)$ the set of all cycles and chains in $\hat{D}^u$ with cardinality at most k.

We introduce the following additional decision variables:

$$X_c^u = \begin{cases} 1 & \text{if cycle or chain } c \in C(k) \text{ is selected in the recourse solution} \\ & \text{under scenario } u \in \mathfrak{U}, \\ 0 & \text{otherwise.} \end{cases}$$

Then, the back-arcs recourse policy is defined as:

$R_{\text{Back-arcs}}(X, u) :=$

$$\max_{X^u} \sum_{c \in \hat{C}^u(k)} w_c X_c^u \tag{6.10}$$

$$\text{s.t.} \sum_{c \in \hat{C}^u(k): n \in c} X_c^u \leq 1 \qquad \forall\, n \in N^u \tag{6.11}$$

$$X^u \in \{0,1\}^{|C(k)|}$$

The recourse objective (6.10) maximizes the benefit of the transactions selected in the final solution given a specific scenario $u \in \mathfrak{U}$. Constraints (6.11) ensure that agents can be selected at most once in the final solution.

6.2.5 Full recourse

The last recourse policy we consider, called full recourse, allows for a complete recovery of the planned solution using alternative transactions. We are interested in determining a planned and alternative solution such that the number of nodes in the intersection of both solutions is maximized.

As in the back-arcs recourse policy, let us use the following additional decision variables:

$$X_c^u = \begin{cases} 1 & \text{if cycle or chain } c \in C(k) \text{ is selected in the recourse solution} \\ & \text{under scenario } u \in \mathfrak{U}, \\ 0 & \text{otherwise.} \end{cases}$$

Futhermore, let X indicate a planned solution and let $u \in \mathfrak{U}$. Then, the full recourse policy is defined as:

$R_{\text{Full}}(X, u) :=$

$$\max_{X^u} \sum_{c \in C^u(k)} \left(\sum_{n \in c} \sum_{c' \in C(k): n \in c'} X_{c'} \right) X_c^u \tag{6.12}$$

$$\text{s.t.} \sum_{c \in C^u(k): n \in c} X_c^u \leq 1 \qquad \forall\, n \in N^u \tag{6.13}$$

$$X^u \in \{0,1\}^{|C(k)|}$$

The recourse objective (6.12) maximizes the number of nodes selected in both the initial and the final solution given a specific scenario $u \in \mathfrak{U}$ (the quantity between parenthesis specifies the number of nodes of cycle c that are part of the initial solution). Constraints(6.13) ensure that nodes can be selected at most once in the final solution.

Alternatively, the full recourse function may be expressed directly in terms of the uncertainty vector ζ:

$R_{\text{Full}}(X, u) =$

$$\max_{X^u} \sum_{c \in C(k)} \left(\sum_{n \in c} \sum_{c' \in C(k): n \in c'} X_{c'} \right) X_c^u$$

$$\text{s.t.} \sum_{c \in C(k): n \in c} X_c^u \leq \zeta_n^u \qquad \forall\, n \in N \tag{6.14}$$

$$\sum_{c \in C(k): a \in c} X_c^u \leq \zeta_a^u \qquad \forall\, a \in A \tag{6.15}$$

$$X^u \in \{0,1\}^{|C(k)|}$$

Here constraints (6.14) guarantee that all nodes in the cycles in the final solution are available. Constraints (6.15) do the same for arcs.

6.3 Solving the robust exchange problem with simple recourse

In this section we consider solving the robust exchange problem with simple recourse. The first difficulty in solving the robust exchange problem, regardless of the form of recourse, is that the number of scenarios, and hence the number of constraints (6.5) in our formulation

(6.4)-(6.8), may be too large to solve the problem directly as a mixed integer program. However, given a planned solution X, we can compute the worst case scenario by solving:

$A(X) := \min_{u \in U} R(X, u) =$

$$\begin{aligned} \min_{\zeta} \quad & R(X, u_\zeta) && (6.16)\\ \text{s.t.} \quad & B\zeta \leq b && (6.17)\\ & \zeta \in \{0,1\}^{|N|+|A|} && (6.18) \end{aligned}$$

Let us call this problem the 'adversary's problem'. The objective (6.16) is to minimize the benefits after recourse actions are performed. Constraints (6.17) ensure that a scenario is selected within the uncertainty set $\mathfrak{U}$.

In case of simple recourse, the adversary's problem reads as follows:

$A_{\text{Simple}}(X) :=$

$$\begin{aligned} \min_{\zeta} \quad & \sum_{c \in C(k)} w_c X_c \prod_{n \in c} \zeta_n \prod_{a \in c} \zeta_a \\ \text{s.t.} \quad & B\zeta \leq b \\ & \zeta \in \{0,1\}^{|N|+|A|} \end{aligned}$$

Before we present our main result for the simple recourse policy, we need the following definition.

Definition 6.2. *Consider an unreliable digraph $D = (N, A)$. The setting in which at most p % of the nodes and arcs can fail is called homogenous failure. This corresponds to the uncertainty set $\mathfrak{U} := \{u \subseteq N \cup A : \sum_{n \in N} \zeta_n^u + \sum_{a \in A} \zeta_a^u \geq (|N| + |A|)(1-p), \zeta^u \in \{0,1\}^{|N|+|A|}\}$.*

Observe that in case of homogenous failure and simple recourse, only a single arc or node failure is required to completely cancel a cycle or chain. Hence, a straightforward strategy for the adversary is to cancel the $\lfloor p(|N| + |A|) \rfloor$ most valuable cycles. We can simplify the adversary's problem by replacing node and arc failure with cycle failure. We do this by introducing an additional decision variable $\zeta_c := \prod_{n \in c} \zeta_n \prod_{a \in c} \zeta_a$ for each cycle $c \in C(k)$ and rewrite the adversary's problem as:

$A_{\text{Simple}}(X) =$

$$\min_{\zeta} \sum_{c \in C(k)} w_c X_c \zeta_c \tag{6.19}$$

$$\text{s.t.} \sum_{c \in C(k)} \zeta_c \geq |C(k)| - \lfloor p(|N| + |A|) \rfloor \tag{6.20}$$

$$\zeta \in \{0,1\}^{|C(k)|} \tag{6.21}$$

We are now ready to present our main result for the simple recourse policy.

Theorem 6.1. *In case of simple recourse and homogenous failure, the constraint matrix associated to the adversary's problem $A_{Simple}(X)$ is totally unimodular.*

Proof. In case of simple recourse and homogenous failure, and after relaxing the integrality requirement (6.21) on the ζ variables, the constraint matrix associated with the adversary's problem as specified by (6.19), (6.20) in standard form is of the form

$$\begin{pmatrix} 1 & 1 & 1 & \dots & 1 \\ -1 & 0 & 0 & \dots & 0 \\ 0 & -1 & 0 & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \dots & -1 \end{pmatrix}. \tag{6.22}$$

Theorem 13.3 from (Steiglitz and Papadimitriou, 1982), gives sufficient conditions to prove that matrix (6.22) is totally unimodular.

The first requirement is that all the entries in the matrix belong to $\{-1, 0, 1\}$. This can be easily verified. Second, no more than two entries in the same column may be non-zero. This is also easy to verify. Finally, it must be possible to partition the rows of the matrix into two sets A and B such that: *i)* if a column has two entries of the same sign, their rows are in different sets; *ii)* if a column has two entries of different signs, their rows are in the same set. This is easily fulfilled if A contains all the rows and B is the empty set. □

Because of Theorem 6.1 there is no need to include the binary requirement (6.21) on the variables ζ that represent the cycles surviving in the worst case scenario. Every extreme point of the feasible region is integral. Then, using strong duality on the adversary's problem and letting v_0 denote the dual of constraint (6.20) and v_c, $c \in C(k)$, the dual

of the unit upper bounds imposed by (6.21), we can obtain an equivalent mixed integer programming formulation of the robust exchange problem:

$$\begin{aligned}
\max_{X,v} \quad & (|C(k)| - \lfloor p(|N| + |A|) \rfloor)\, v_0 - \sum_{c \in \mathcal{C}(k)} v_c \\
\text{s.t.} \quad & \sum_{c \in \mathcal{C}(k): n \in c} X_c \leq 1 \qquad \forall n \in N && \text{(6.23a)} \\
& v_0 - v_c \leq w_c X_c \qquad \forall c \in \mathcal{C}(k) && \text{(6.23b)} \\
& X_c \in \{0,1\} \qquad \forall c \in \mathcal{C}(k) \\
& v_0 \geq 0 \\
& v_c \geq 0 \qquad \forall c \in \mathcal{C}(k)
\end{aligned}$$

Although the above model is still a mixed integer program, its size is much more compact than the size of formulation (6.4)-(6.8).

6.4 Solving the robust exchange problem with back-arcs recourse

In this section we study how to solve the robust exchange problem with back-arcs recourse. Similar to how we analyzed the simple recourse policy, we begin by considering the adversary's problem:

$A_{\text{Back-arcs}}(X) :=$

$$\begin{aligned}
\min_{\zeta} \quad & R_{\text{Back-arcs}}(X, u_\zeta) \\
\text{s.t.} \quad & B\zeta \leq b \\
& \zeta \in \{0,1\}^{|N|+|A|}
\end{aligned}$$

Since the back-arcs recourse function $R_{\text{Back-arcs}}(X, u)$ as defined in (6.10)-(6.11) is a maximization problem, the adversary's problem is, in the general case, a non-linear optimization problem. However, we will consider a specific setting for which it can be solved efficiently.

Let us assume homogenous failure (see Definition 6.2), let $k = 3$ (this is the bound used in most kidney exchange programs (Roth et al., 2007)), and let $w_c = |N_S \cap c|$ for all $c \in C(k)$ (i.e. we want to maximize the number of agents that receive a good). As, by definition, back-arcs cannot exist for cycles of length 2 and back-arcs recourse is meaningless for chains of length 2, we then only have to consider recourse actions for cycles and chains of length 3. Without loss of generality, there are four possible configurations for back-arc reactions in cycles of size 3 that are illustrated in Figures 6.2 to 6.5, and four possible configurations for back-arc reactions in chains of size 3 that are illustrated in Figures 6.6 to 6.9. Note that, in the absence of failure, a length 3 cycle involves 3 agents from N_S, and a length 3 chain involves 2 agents from N_S.

In the first three cases for cycles, illustrated in Figures 6.2-6.4, a single node failure is sufficient to completely cancel the cycle (in the worst case). However, in the fourth case, illustrated in Figure 6.5, two node failures are required to completely cancel the cycle. Similarly, in the first three cases for chains, illustrated in Figures 6.6-6.8, a single node failure is sufficient, but in the last case, illustrated in Figure 6.9, two failures are required.

Because of the above, in the case of homogenous failure and $k = 3$, it is possible to solve the adversary's problem using a trivial greedy algorithm (i.e. cancel cycles and chains in order of the number of failures required per point of damage inflicted on the objective function). However, this would not help us as we want to include the adversary's problem in a mixed integer program for $RE(\mathfrak{U})$. Therefore, using the knowledge of our problem structure, we now proceed with the following steps:

1. Identify the cycles of length 3 with the structure of case 4; let $C'(3) \subset C(3)$ be the set of such cycles;

2. For each $c \in C'(3)$ create one auxiliary binary decision variables ζ_c^1 representing the first failure for c;

3. Reformulate the recourse function and the adversary's problem such that they satisfy the following conditions for each $c \in C'(3)$:

   i if $\zeta_c = \zeta_c^1 = 0$ then the benefit from c must be 0, i.e. the adversary completely cancels c and thus there is no *back-arc recourse*.

   ii if $\zeta_c = \zeta_c^1 = 1$ then the benefit from c must be 3, i.e. the adversary does not cancel c.

   iii if $\zeta_c = 1$ and $\zeta_c^1 = 0$ then the benefit from c must be 2, i.e., the adversary cancels c partially as two nodes can be recovered through *back-arc recourse*.

Similarly, we perform the following steps for chains:

1. Identify the chains of length 3 with the structure of case 8; let $C''(3) \subset C(3)$ be the set of such chains;

2. For each $c \in C''(3)$ create one auxiliary binary decision variable ζ_c^1 representing the first failure for c;

3. Reformulate the recourse function and the adversary's problem such that they satisfy the following conditions for each $c \in C''(3)$:

   i if $\zeta_c = \zeta_c^1 = 0$ then the benefit from c must be 0, i.e. the adversary completely cancels c and thus there is no *back-arc recourse*.

   ii if $\zeta_c = \zeta_c^1 = 1$ then the benefit from c must be 2, i.e. the adversary does not cancel c.

   iii if $\zeta_c = 1$ and $\zeta_c^1 = 0$ then the benefit from c must be 1, i.e., the adversary cancels c partially as one node can be recovered through *back-arc recourse*.

Following these lines, we rewrite the back-arcs recourse function as:

$$R_{\text{Back-arcs}}(X,u) = \sum_{c \in C(3) - (C'(3) \cup C''(3))} |c| X_c \zeta_c^u + \sum_{c \in C'(3)} X_c(\zeta_c^{1,u} + 2\zeta_c^u) + \sum_{c \in C''(3)} X_c(\zeta_c^u + \zeta_c^{1,u}) \tag{6.24}$$

It is straightforward to check that (6.24) satisfies the above conditions. Furthermore, note that the recourse function now has been reformulated as a linear function, whereas before it was a maximization problem (recall (6.10) and (6.11)).

Next, letting $b = \lfloor p(|N| + |A|) \rfloor$, we rewrite the adversary's problem as:

$A_{\text{Back-arcs}}(X) =$

$$\min_{\zeta} \sum_{c \in C(3) - (C'(3) \cup C''(3))} |c| X_c \zeta_c + \sum_{c \in C'(3)} X_c(\zeta_c^1 + 2\zeta_c) + \sum_{c \in C''(3)} X_c(\zeta_c^1 + \zeta_c) \tag{6.25}$$

$$\text{s.t.} \sum_{c \in C(3)} \zeta_c + \sum_{c \in C'(3) \cup C''(3)} \zeta_c^1 \geq |C(3)| + |C'(3)| + |C''(3)| - b \tag{6.26}$$

$$\zeta_c \geq \zeta_c^1 \qquad \forall c \in C'(3) \cup C''(3) \tag{6.27}$$

$$\zeta_c \leq 1 \qquad \forall c \in C(3) \tag{6.28}$$

$$\zeta_c \in \{0, 1\} \qquad \forall c \in C(3)$$

$$\zeta_c^1 \in \{0, 1\} \qquad \forall c \in C'(3) \cup C''(3)$$

Here, the objective (6.25) is to minimize the number of agents receiving a good under the back-arcs recourse policy as specified by (6.24). Constraint (6.26) specifies the adversary's uncertainty 'budget' in the homogenous failure setting. Constraints (6.27) ensure condition (ii) and (iii) are met by guaranteeing that cycles and chains of cases 4 and 8 are not cancelled entirely unless they contain two failures. Constraints (6.28) are redundant but are added to aid the exposition of the remainder of our analysis.

The next step is to relax the binary requirement on the adversary's variables ζ_c, ζ_c^1 and ζ_c^2 in order to get a lower bound on the robust exchange problem with back-arcs recourse. Let us denote the relaxed adversary's problem by $A'_{\text{Back-arcs}}(X)$. Note that by making this relaxation, the adversary has a larger set of feasible strategies and thus is potentially capable of inflicting more damage on the planned solution. This is the reason why we get a lower bound to the robust exchange problem by relaxing the integrality of the adversary's variables. Next, we can apply strong duality on $A'_{\text{Back-arcs}}(X)$ to achieve a linear formulation for the relaxed robust exchange problem:

$RE'_{\text{Back-arcs}}(\mathfrak{U}) =$

$$\max_{X,v}(|C(3)| + |C'(3)| + |C''(3)| - b))\, v_0 - \sum_{c \in C(3)} v_c \tag{6.29}$$

$$\text{s.t.} \sum_{c \in C(3): n \in c} X_c \leq 1 \qquad \forall n \in N$$

$$v_0 - v_c \leq |c| X_c \qquad \forall c \in C(3) - (C'(3) \cup C''(3)) \tag{6.30}$$

$$v_0 + v_c^1 - v_c \leq 2X_c \qquad \forall c \in C'(3) \tag{6.31}$$

$$v_0 + v_c^1 - v_c \leq X_c \qquad \forall c \in C''(3) \tag{6.32}$$

$$v_0 - v_c^1 \leq X_c \qquad \forall c \in C'(3) \cup C''(3) \tag{6.33}$$

$$X_c \in \{0, 1\} \qquad \forall c \in C(3)$$

$$v_0 \geq 0$$

$$v_c \geq 0 \qquad \forall c \in C(3)$$

$$v_c^1 \geq 0 \qquad \forall c \in C'(3) \cup C''(3)$$

The above formulation is a straightforward mixed integer program. Although we have argued that it provides a lower bound to the original robust exchange problem, one could question whether there exist situations in which the adversary is actually capable of using the relaxation to inflict more damage on the planned solution (and thus whether the integrality requirement was necessary to begin with). The following example shows us that this is indeed the case.

Example 6.1. *Consider the market digraph represented in Figure 6.10 in which at most 2 nodes can fail. We have the set of cycles* $C(3) = \{c_1 = \langle 1, 2\rangle, c_2 = \langle 2, 3\rangle, c_3 = \langle 1, 3\rangle, c_4 = \langle 4, 5\rangle, c_5 = \langle 1, 2, 3\rangle, c_6 = \langle 3, 2, 1\rangle\}$ *and* $C'(3) = \{c_5, c_6\}$.

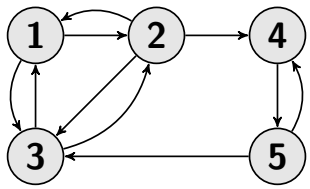

Figure 6.10:

The optimal solution to the robust exchange problem with back-arcs recourse $RE_{Back\text{-}arcs}(\mathfrak{U})$ *is to select cycles* c_4 *and* c_5 *with objective value equal to 2. Although the optimal solution for the relaxed robust exchange problem* $RE'_{Back\text{-}arcs}(\mathfrak{U})$ *leads to the same planned solution,*

the objective value is equal to 1.5, since the adversary variables need not be binary and will be chosen as follows: $\zeta_{c_1} = 1, \zeta_{c_2} = 1, \zeta_{c_3} = 1, \zeta_{c_4} = 0, \zeta^1_{c_5} = \zeta^2_{c_5} = \zeta_{c_5} = \frac{1}{2}, \zeta^1_{c_6} = \zeta^2_{c_6} = \zeta_{c_6} = 1$.

We are now ready to provide our main results for the back-arcs recourse policy.

Lemma 6.1. *Let X be an arbitrary feasible solution to the robust exchange problem. In case of back-arcs recourse, if the optimal solution value for the relaxed adversary's problem $A'_{Back\text{-}arcs}(X)$ is zero then the optimal solution value for the adversary's problem $A_{Back\text{-}arcs}(X)$ is also zero.*

Proof. For the optimal value to be zero, all ζ variables associated with selected cycles (for which $X_c = 1$) must be zero such that these cycles are completely cancelled and cannot be reconstructed. If this is feasible in the relaxed problem $A'_{\text{Back-arcs}}(X)$, this is also feasible under the binary requirement in $A_{\text{Back-arcs}}(X)$. □

Lemma 6.2. *Let X be an arbitrary feasible solution to the robust exchange problem and let $k = 3$. In case of back-arcs recourse and homogeneous failure, the adversary's budget constraint* (6.26) *evaluated in an optimal solution to the adversary's problem $A'_{Back\text{-}arcs}(X)$ is either binding or the optimal objective value is zero.*

Proof. By contradiction, assume that for a given X the optimal adversary's objective function is positive and that the optimal solution ζ^* is such that constraint (6.26) is not binding:

$$\sum_{c \in C(3)} \zeta_c + \sum_{c \in C'(3) \cup C''(3)} \zeta^1_c > |C(3)| + |C'(3)| + |C''(3)| - b$$

The first hypothesis implies that there is a cycle for which $X_c = 1$ and $\zeta^*_c > 0$. The second hypothesis implies that the slack variable associated to constraint (6.26) is positive. By complementary slackness, the optimal solution of the dual problem must have $v^*_0 = 0$. In particular, $v^*_0 = 0$ implies that the optimal objective function value of the dual (6.29) is non-positive. On the other hand, by strong duality, the primal and dual optimal values are to be equal which contradicts our hypothesis that the primal optimal value is positive. □

Lemma 6.3. *Let X be an arbitrary feasible solution to the robust exchange problem and let $k = 3$. In case of back-arcs recourse and homogenous failure, it holds that in an optimal solution ζ^* to the relaxed adversary's problem $A'_{Back\text{-}arcs}(X)$, for all $c \in C'(3)$ for which $X_c = 1$ we have $\zeta^*_c = \zeta^{1*}_c$.*

Proof. By constraint (6.27) $\zeta_c^* \geq \zeta_c^{1*}$. Additionally, the adversary's optimization problem is a minimization one and all the coefficients in the objective function are positive for ζ_c and ζ_c^1 where $X_c = 1$. Therefore, it is clear that in an optimal solution ζ_c will be as small as possible and thus equal to ζ_c^1. □

Theorem 6.2. *Consider the setting with back-arcs recourse and homogenous failure. Let* $k = 3$*, let* X *be an arbitrary feasible solution to the robust exchange problem and let* $b = \lfloor p(|N| + |A|) \rfloor$*. Furthermore, let* $F_3 := \{c \in C(3) - C'(3) : |c| = 3 \text{ and } X_c = 1\}$*,* $F_2 := \{c \in C(3) - C''(3) : |c| = 2 \text{ and } X_c = 1\}$*,* $F_{1.5} := \{c \in C'(3) : X_c = 1\}$*, and* $F_1 := \{c \in C(3) : |c| = 1, X_c = 1\} \cup \{c \in C''(3) : X_c = 1\}$*. If the optimal objective value is positive, there is an optimal solution* ζ^* *to the relaxed adversary's problem* $A'_{Back\text{-}arcs}(X)$ *that satisfies:*

- $|F_3^* := \{c \in F_3 : \zeta_c^* = 0\}| = n_3$ *with* $n_3 := \min(b, |F_3|)$*;*
- $|F_2^* := \{c \in F_2 : \zeta_c^* = 0\}| = n_2$ *with* $n_2 := \min(b - n_3, |F_2|)$*;*
- $|F_{1.5}^* := \{c \in F_{1.5} : \zeta_c^* = \zeta_c^{1*} = 0\}| = n_{1.5}$ *with* $n_{1.5} := \min(\lfloor \frac{b-n_3-n_2}{2} \rfloor, |F_{1.5}|)$ *and* $|F_{1.5}^{**} := \{c \in F_{1.5} : \zeta_c^* = \zeta_c^{1*} = \frac{1}{2}\}| = n'_{1.5}$ *with* $n'_{1.5} := 1_{\{n_{1.5} < |F_{1.5}| \text{ and } b-n_3-n_2 \text{ is odd}\}}$*.*
- $|F_1^* := \{c \in F_1 \cap C''(3) : \zeta_c^* = \zeta_c^{1*} = 0\} \cup \{c \in F_1 - C''(3) : \zeta_c^* = 0\}| = n_1 = n'_1 + n''_1$ *and* $|F_1^{**} := \{c \in F_1 \cap C''(3) : \zeta_c^* = \zeta_c^{1*} = \frac{1}{2}\}| = n'''_1$ *with* $n'_1 := |\{c \in F_1 \cap C''(3) : \zeta_c^* = \zeta_c^{1*} = 0\}|$ *and* $n''_1 := |\{c \in F_1 - C''(3) : \zeta_c^* = 0\}|$ *and* $2n'_1 + n''_1 + n'''_1 = \min(b - n_3 - n_2 - 2n_{1.5} - n'_{1.5}, |F_1|)$ *and* $n'''_1 := 1_{\{2n'_1 + n''_1 < \min(b-n_3-n_2-2n_{1.5}-n'_{1.5}, |F_1|)\}}$*.*
- *the variables associated with cycles not in* $F_3^* \cup F_2^* \cup F_{1.5}^* \cup F_{1.5}^{**} \cup F_1^* \cup F_1^{**}$ *are equal to 1.*

Proof. Suppose that the theorem conditions are satisfied. Then, since the optimal objective value is positive, by Lemma 6.2 it holds:

$$\sum_{c \in C(3)} \zeta_c + \sum_{c \in C'(3) \cup C''(3)} \zeta_c^1 = |C(3)| + |C'(3)| + |C''(3)| - b$$

We will prove the theorem by induction on b.

If $b = 0$, the equation above becomes

$$\sum_{c \in C(3)} \zeta_c + \sum_{c \in C'(3) \cup C''(3)} \zeta_c^1 = |C(3)| + |C'(3)| + |C''(3)|$$

and in order for the decision vector ζ^* to be feasible all its entries must be equal to one (binary). It follows that $n_3 = n_2 = n_{1.5} = n_1 = 0$ which is in accordance with the theorem statement.

Assume that the theorem holds for $b = i - 1 > 0$. Note that by the induction hypothesis, there is a cycle $\overline{c} \in F_3^* \cup F_2^* \cup F_{1.5}^* \cup F_1^* \cup F_{1.5}^{**} \cup F_1^{**}$ such that

$$\zeta_{\overline{c}}^* = 0 \qquad \text{if } \overline{c} \in C(3) \setminus (F_{1.5}^{**} \cup F_1^{**})$$

or

$$\zeta_{\overline{c}}^* = \zeta_{\overline{c}}^{1*} = \frac{1}{2} \qquad \text{if } \overline{c} \in (F_{1.5}^{**} \cup F_1^{**}) \quad \text{(applying Lemma 6.3).}$$

Taking into account that $\zeta_c^* < 1$ for all $c \in F_3^* \cup F_2^* \cup F_{1.5}^* \cup F_1^* \cup F_{1.5}^{**} \cup F_1^{**}$, by complementary slackness, $v_c^* = 0$. If we increase b by one unit, since constraint (6.26) is binding, the value of the dual variable v_0^* associated to the problem with $b = i - 1$ tell us how much the objective function decreases if $b = i$. Consider the cycle $\overline{c} \in F_3^* \cup F_2^* \cup F_{1.5}^* \cup F_1^* \cup F_{1.5}^{**} \cup F_1^{**}$ that is in the F_j^* with smallest index. There are four possible cases.

Case 1: $F_j^* \subset F_j$ **and** $j \geq 2$**.** Then, cycle $\overline{c}$ belongs to $C(3) - (C'(3) \cup C''(3))$. As noted before $v_{\overline{c}}^* = 0$ and thus, evaluating constraint (6.30) for $\overline{c} \in C(3) - (C'(3) \cup C''(3))$ leads to

$$v_0^* \leq j.$$

We conclude that the adversary's optimal objective value with $b = i$ decreases by at most j units in comparison with the case of $b = i - 1$. In fact, a decrease of exactly j units can be achieved by choosing an additional cycle $c \in (F_j - F_j^*)$ to be part of F_j^* (i.e put $\zeta_c = 0$). Note that this solution is feasible for the problem with $b = i$. Moreover, this optimal solution is in accordance with the theorem statement.

Case 2: $F_j^* = F_j$**,** $j = 3$ **and** $F_2 \neq \emptyset$**.** Using our induction hypothesis together with strong duality, constraints (6.30) to (6.33) come down to

$$
\begin{aligned}
v_0^* &\le 3 && \forall c \in F_3 && \\
v_0^* &= 2 + v_c^* && \forall c \in F_2 && \\
v_0^* &= 1 + v_c^* && \forall c \in F_1 - C''(3) && \\
v_0^* &= v_c^* && \forall c \in C(3) - (C'(3) \cup C''(3) \cup F_1 \cup F_2 \cup F_3) && \\
v_0^* - v_c^{1*} &= 1 && \forall c \in F_{1.5} && \\
v_0^* + v_c^{1*} - v_c^* &= 2 && \forall c \in F_{1.5} && \Rightarrow 2v_0^* - 3 = v_c^* \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C'(3) - F_{1.5} && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C'(3) - F_{1.5} && \Rightarrow 2v_0^* = v_c^* \\
v_0^* - v_c^{1*} &= 1 && \forall c \in F_1 \cap C''(3) && \\
v_0^* + v_c^{1*} - v_c^* &= 1 && \forall c \in F_1 \cap C''(3) && \Rightarrow 2v_0^* - 2 = v_c^* \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C''(3) - F_1 && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C''(3) - F_1 && \Rightarrow 2v_0^* = v_c^*
\end{aligned}
$$

Observe that setting $v_0^* = 2$ and the v_c^* accordingly is a dual feasible solution. Moreover, that dual solution is optimal: by the induction hypothesis the adversary's optimal value is

$$2|F_2| + 3|F_{1.5}| + 2|F_1 \cap C''(3)| + |F_1 - C''(3)|$$

and the dual objective function evaluated at the dual solution just described takes the same value

$$
\begin{aligned}
&(|C(3)| + |C'(3)| + |C''(3)| - b)\, v_0^* - \sum_{c \in C(3)} v_c^* \\
=&(|C(3)| + |C'(3)| + |C''(3)| - |F_3|)\, 2 - \sum_{c \in F_2} 0 \\
&- \sum_{c \in C(3) - (C'(3) \cup C''(3) \cup \{F_1 - C''(3)\} \cup \{F_1 \cap C''(3)\} \cup F_2 \cup F_3)} 2 - \sum_{c \in F_{1.5} \cup \{F_1 - C''(3)\}} 1 \\
&- \sum_{c \in \{C'(3) - F_{1.5}\} \cup \{C''(3) - F_1 \cap C''(3)\}} 4 \\
=&2|C(3)| + 2|C'(3)| + 2|C''(3)| - 2|F_3| - 2|C(3)| + 2|C'(3)| + 2|F_2| + 2|F_3| \\
&+2|C''(3)| + 2|F_1 - C''(3)| - 2|F_1 \cap C''(3)| - |F_{1.5}| - 4|C'(3)| + 4|F_{1.5}| \\
&-4|C''(3)| + 4|F_1 \cap C''(3)| - |F_1 - C''(3)| \\
=&2|F_2| + 3|F_{1.5}| + 2|F_1 \cap C''(3)| + |F_1 - C''(3)|
\end{aligned}
$$

Therefore, the optimal value of the relaxed adversary's problem with $b = i$ decreases by 2 units in comparison with the case of $b = i - 1$ and that decrease can be achieved by choosing an additional cycle $c \in (F_2 - F_2^*)$ to be part of F_2^* (i.e put $\zeta_c = 0$). Note that this solution is feasible for the problem with $b = i$ and it is in accordance with the theorem statement.

Case 3: $F_3^* = F_3$**,** $F_2^* = F_2$ **and** $F_{1.5}^* \cup F_{1.5}^{**} \subset F_{1.5}$**.** The proof is analogous to the previous case. Using the induction hypothesis together with strong duality, constraints (6.30) to (6.33) now come down to:

$$
\begin{aligned}
v_0^* &\leq 3 && \forall c \in F_3 && \\
v_0^* &\leq 2 && \forall c \in F_2 && \\
v_0^* &= 1 + v_c^* && \forall c \in F_1 - C''(3) && \\
v_0^* &= v_c^* && \forall c \in C(3) - (C'(3) \cup C''(3) \cup F_1 \cup F_2 \cup F_3) && \\
v_0^* - v_c^{1*} &= 1 && \forall c \in F_{1.5} - F_{1.5}^* \cup F_{1.5}^{**} && \\
v_0^* + v_c^{1*} - v_c^* &= 2 && \forall c \in F_{1.5} - F_{1.5}^* \cup F_{1.5}^{**} && \Rightarrow 2v_0^* - 3 = v_c^* \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C'(3) - F_{1.5} && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C'(3) - F_{1.5} && \Rightarrow 2v_0^* = v_c^* \\
v_0^* - v_c^{1*} &= 1 && \forall c \in F_1 \cap C''(3) && \\
v_0^* + v_c^{1*} - v_c^* &= 1 && \forall c \in F_1 \cap C''(3) && \Rightarrow 2v_0^* - 2 = v_c^* \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C''(3) - F_1 && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C''(3) - F_1 && \Rightarrow 2v_0^* = v_c^*
\end{aligned}
$$

Observe that setting $v_0^* = \frac{3}{2}$ and the v_c^* accordingly with the updated system of equations leads to a dual feasible solution. Moreover, that dual solution is optimal: by the induction hypothesis the adversary's optimal value is

$$3|F_{1.5}| - 3|F_{1.5}^*| + 2|F_1 \cap C''(3)| + |F_1 - C''(3)| - \frac{3}{2}|F_{1.5}^{**}|$$

Additionally, the dual objective function evaluated at the dual solution just described takes the same value:

$$
\begin{aligned}
&(|C(3)| + |C'(3)| + |C''(3)| - b)\, v_0^* - \sum_{c \in C(3)} v_c^* \\
=&(|C(3)| + |C'(3)| + |C''(3)| - |F_3| - |F_2| - 2|F_{1.5}^*| - |F_{1.5}^{**}|)\, \frac{3}{2} \\
&- \sum_{c \in C(3) - (C'(3) \cup C''(3) \cup \{F_1 - C''(3)\} \cup F_2 \cup F_3)} \frac{3}{2} - \sum_{c \in F_{1.5} - F_{1.5}^*} 0 \\
&- \sum_{c \in C'(3) - F_{1.5}} 3 - \sum_{c \in F_1 - C''(3)} \frac{1}{2} - \sum_{c \in F_1 \cap C''(3)} 1 - \sum_{c \in C''(3) - F_1} 3 \\
=&\frac{3}{2}|C(3)| + \frac{3}{2}|C'(3)| + \frac{3}{2}|C''(3)| - \frac{3}{2}|F_3| - \frac{3}{2}|F_2| - 3|F_{1.5}^*| - \frac{3}{2}|F_{1.5}^{**}| \\
&-\frac{3}{2}|C(3)| + \frac{3}{2}|C'(3)| + \frac{3}{2}|F_2| + \frac{3}{2}|F_3| + \frac{3}{2}|F_1 - C''(3)| + \frac{3}{2}|C''(3)| \\
&-3|C'(3)| + 3|F_{1.5}| - \frac{1}{2}|F_1 - C''(3)| - |F_1 \cap C''(3)| - 3|C''(3) - F_1| \\
=&3|F_{1.5}| - 3|F_{1.5}^*| + 2|F_1 \cap C''(3)| + |F_1 - C''(3)| - \frac{3}{2}|F_{1.5}^{**}|
\end{aligned}
$$

Therefore, the optimal value of the relaxed adversary's problem with $b = i$ decreases by $\frac{3}{2}$ units in comparison with the case of $b = i - 1$ and that decrease can be achieved by making $\zeta_{c'}^1 = \zeta_{c'} = 0$ for the $c' \in F_{1.5}^{**}$ if $|F_{1.5}^{**}| > 0$, and otherwise, by adding a cycle $c \in F_{1.5} - F_{1.5}^*$ to $F_{1.5}^{**}$ (i.e put $\zeta_c^1 = \zeta_c = \frac{1}{2}$). Note that this solution is feasible for the problem with $b = i$ and that it is in accordance with the theorem statement.

Case 4: $F_3^* = F_3$, $F_2^* = F_2$, $F_{1.5}^* = F_{1.5}$ **and** $F_1^* \cup F_1^{**} \subset F_1$**.** Again the proof is analogous. Using the induction hypothesis together with strong duality, constraints (6.30) to (6.33) now come down to:

$$
\begin{aligned}
v_0^* &\leq 3 && \forall c \in F_3 && \\
v_0^* &\leq 2 && \forall c \in F_2 && \\
v_0^* &= 1 + v_c^* && \forall c \in F_1 - (C''(3) \cup F_1^*) && \\
v_0^* &= v_c^* && \forall c \in C(3) - (C'(3) \cup C''(3) \cup F_1 \cup F_2 \cup F_3) && \\
v_0^* - v_c^{1*} &\leq 1 && \forall c \in F_{1.5} && \\
v_0^* + v_c^{1*} - v_c^* &\leq 2 && \forall c \in F_{1.5} && \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C'(3) - F_{1.5} && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C'(3) - F_{1.5} && \Rightarrow 2v_0^* = v_c^* \\
v_0^* - v_c^{1*} &= 1 && \forall c \in (F_1 \cap C''(3)) \ - (F_1^* \cup F_1^{**}) && \\
v_0^* + v_c^{1*} - v_c^* &= 1 && \forall c \in (F_1 \cap C''(3)) \ - (F_1^* \cup F_1^{**}) && \Rightarrow 2v_0^* - 2 = v_c^* \\
v_0^* - v_c^{1*} &= 0 && \forall c \in C''(3) - F_1 && \\
v_0^* + v_c^{1*} - v_c^* &= 0 && \forall c \in C''(3) - F_1 && \Rightarrow 2v_0^* = v_c^*
\end{aligned}
$$

Observe that now setting $v_0^* = 1$ and the v_c^* accordingly with the updated system of equations leads to a dual feasible solution. Moreover, that dual solution is optimal: by the induction hypothesis the adversary's optimal value is

$$2|F_1 \cap C''(3)| + |F_1 - C''(3)| - 2|F_1^* \cap C''(3)| - |F_1^* - C''(3)| - |F_1^{**}|$$

Additionally, the dual objective function evaluated at the dual solution just described takes the same value:

$$
\begin{aligned}
&(|C(3)| + |C'(3)| + |C''(3)| - b)\, v_0^* - \sum_{c \in C(3)} v_c^* \\
=&(|C(3)| + |C'(3)| + |C''(3)| - |F_3| - |F_2| - 2|F_{1.5}| - 2|F_1^* \cap C''(3)| - |F_1^* - C''(3)| - |F_1^{**}|)\, 1 \\
&- \sum_{c \in C(3) - (C'(3) \cup C''(3) \cup \{F_1 - C''(3)\} \cup F_2 \cup F_3)} 1 \\
&- \sum_{c \in C'(3) - F_{1.5}} 2 - \sum_{c \in F_1 - C''(3)} 0 - \sum_{c \in F_1 \cap C''(3) - F_1^* \cup F_1^{**}} 0 - \sum_{c \in C''(3) - F_1} 2 \\
=&|C(3)| + |C'(3)| + |C''(3)| - |F_3| - |F_2| - 2|F_{1.5}| - 2|F_1^* \cap C''(3)| - |F_1^* - C''(3)| - |F_1^{**}| \\
&-|C(3)| + |C'(3)| + |C''(3)| + |F_1 - C''(3)| + |F_2| + |F_3| \\
&-2|C'(3)| + 2|F_{1.5}| - 2|C''(3)| + 2|F_1 \cap C''(3)| \\
=&2|F_1 \cap C''(3)| + |F_1 - C''(3)| - 2|F_1^* \cap C''(3)| - |F_1^* - C''(3)| - |F_1^{**}|
\end{aligned}
$$

Therefore, the optimal value of the relaxed adversary's problem with $b = i$ decreases by 1 unit in comparison with the case of $b = i-1$ and that decrease can be achieved by making $\zeta_{c'}^1 = \zeta_{c'} = 0$ for the $c' \in F_1^{**}$ if $|F_1^{**}| > 0$, otherwise, by adding a cycle $c \in (F_1 \cap C''(3)) - F_1^*$ to F_1^{**} (i.e put $\zeta_c^1 = \zeta_c = \frac{1}{2}$) or by adding a cycle $c \in (F_1 - C''(3)) - F_1^*$ to F_1^* (i.e put $\zeta_c = 0$). Note that this solution is feasible for the problem with $b = i$ and that it is in accordance with the theorem statement.

□

Corollary 6.1. *In case of back-arcs recourse, homogenous failure and $k = 3$, the optimal value for the robust exchange problem $RE_{Back\text{-}arcs}(\mathfrak{U})$ is equal to the optimal value of the relaxed robust exchange problem $RE'_{Back\text{-}arcs}(\mathfrak{U})$ rounded up.*

Proof. The optimal value of the relaxed adversary's problem $A'_{\text{Back-arcs}}(X)$ rounded up gives a lower bound to the adversary's problem. By Theorem 6.2, there always exists an optimal solution to the relaxed adversary's problem in which at most 3 variables are fractional. In case of fractional variables, that optimal value is equal to some integer, say OPT, plus $\frac{1}{2}$ and thus the lower bound is $OPT + 1$. By making $\zeta_{c'} = 1 = \zeta_{c'}^1$ and $\zeta_{c'}^2 = 0$ we get a binary feasible solution for the adversary which has objective value equal to $OPT+1$. Since the objective values of $RE_{\text{Back-arcs}}(\mathfrak{U})$ and $RE'_{\text{Back-arcs}}(\mathfrak{U})$ respectively coincide with $A_{\text{Back-arcs}}(X)$ and $A'_{\text{Back-arcs}}(X)$, the corollary follows. □

6.5 Solving the robust exchange problem with full recourse

In this section we consider solving the robust exchange problem with full recourse. The methodology we develop works equally well for the forms of recourse discussed previously, particularly when the considered setting does not allow the theorems presented in the previous sections to be applied.

6.5.1 Delayed scenario generation

As discussed in Section 6.3, the first difficulty in solving the robust exchange problem, regardless of the form of recourse, is that the number of scenarios and hence the number of constraints (6.5) is typically prohibitively large. Therefore, in this section, we develop the concept of delayed scenario generation. The main idea is to start out with only a small set of scenarios and to generate additional scenarios only when required (i.e. when the corresponding constraint (6.5) is violated). As we will see, the scenario generation algorithm involves simultaneous row and column generation.

The delayed scenario generation algorithm is as follows:

Delayed scenario generation algorithm

1. Let $\bar{\mathfrak{U}} := \{N \cup A\}$.
2. Solve $RE(\bar{\mathfrak{U}})$.
3. Check if there exists a scenario $u \in \mathfrak{U} \backslash \bar{\mathfrak{U}}$ such that $RE(\bar{\mathfrak{U}} \cup \{u\}) < RE(\bar{\mathfrak{U}})$. If yes, go to 4, otherwise go to 5.
4. Set $\bar{\mathfrak{U}} := \bar{\mathfrak{U}} \cup \{u\}$ and go to 2.
5. Done.

Proposition 6.1. *The delayed scenario generation algorithm described above returns the optimal solution to the robust exchange problem* $RE(\mathfrak{U})$.

Proof. Because of the finiteness of $\mathfrak{U}$ the procedure terminates in a finite number of iterations. When it terminates, because of step 3, there exists no $u \in \mathfrak{U} \backslash \bar{\mathfrak{U}}$ such that $RE(\bar{\mathfrak{U}} \cup \{u\}) < RE(\bar{\mathfrak{U}})$. Hence, all constraints (6.5) are satisfied and the procedure returns the optimal solution to $RE(\mathfrak{U})$. □

Proposition 6.2. *Let $\{Z^*, X^*\}$ denote an optimal solution to the robust exchange problem $RE(\bar{\mathfrak{U}})$. Furthermore, let ζ^* denote an optimal solution of the adversary's problem $A(X^*)$ with objective value z^*. There exists a scenario $u \in \mathfrak{U} \backslash \bar{\mathfrak{U}}$ such that $RE(\bar{\mathfrak{U}} \cup \{u\}) < RE(\bar{\mathfrak{U}})$ if and only if $z^* < Z^*$.*

Proof. The proof follows directly from the observation that

$$A(X) = \min_{\zeta} \{R(X, u_\zeta) : B\zeta \leq b, \zeta \in \{0,1\}^{|N|+|A|}\} = \min_{u \in \mathfrak{U}} R(X, u)$$

□

6.5.2 Full recourse linearization

Step 2 in the scenario generation algorithm requires solving $RE(\bar{\mathfrak{U}})$ for a subset $\bar{\mathfrak{U}} \subseteq \mathfrak{U}$. For the case with full recourse we begin by substituting the full recourse function (6.12)-(6.13) in the robust exchange problem (6.1)-(6.3). The resulting robust exchange problem with full recourse is:

$$RE_{\text{Full}}(\mathfrak{U}) =$$

$$\begin{aligned}
\max_{Z,X} \quad & Z \\
\text{s.t.} \quad & Z \leq \sum_{c \in C^u(k)} \left(\sum_{n \in c} \sum_{c' \in C(k): n \in c'} X_{c'} \right) X_c^u && \forall\ u \in \mathfrak{U} \\
& \sum_{c \in C(k): n \in c} X_c \leq 1 && \forall\ n \in N \\
& \sum_{c \in C^u(k): n \in c} X_c^u \leq 1 && \forall\ u \in \mathfrak{U}, n \in N^u \\
& Z \in \mathbb{R}_+ \\
& X \in \{0,1\}^{|C(k)|} \\
& X^u \in \{0,1\}^{|C(k)|}
\end{aligned}$$

Observe that this is a non-linear mixed integer program. However, we can linearize it by introducing the following additional decision variables:

$$Y_n^u = \begin{cases} 1 & \text{if node } n \in N \text{ is selected in both the planned solution and the final} \\ & \text{solution under scenario } u \in \mathfrak{U}, \\ 0 & \text{otherwise.} \end{cases}$$

Then we can rewrite the full recourse function as:

$R_{\text{Full}}(X, u) =$

$$\max_{X^u, Y^u} \sum_{n \in N} Y_n^u \tag{6.35}$$

$$\text{s.t.} \quad Y_n^u \leq \sum_{c \in C(k): n \in c} X_c \qquad \forall\, n \in N \tag{6.36}$$

$$Y_n^u \leq \sum_{c \in C^u(k): n \in c} X_c^u \leq 1 \quad \forall\, n \in N^u \tag{6.37}$$

$$Y^u \in \mathbb{R}_+^{|N|}$$

$$X^u \in \{0,1\}^{|C^u(k)|}$$

As before, the objective (6.35) is to maximize the number of nodes in the intersection of the planned and the final solution given the scenario $u \in \mathfrak{U}$. Constraints (6.36) check whether a node is in the planned solution and constraints (6.37) check whether a node is in the final solution. The advantage of this formulation is that we can now again substitute the recourse function in the robust exchange problem (6.1)-(6.3) and write it as the following *linear* problem:

$RE_{\text{Full}}(\mathfrak{U}) =$

$$\max \; Z$$

$$\text{s.t.} \; Z \leq \sum_{n \in N} Y_n^u \qquad \forall\, u \in \mathfrak{U} \tag{6.38}$$

$$Y_n^u \leq \sum_{c \in C(k): n \in c} X_c \leq 1 \quad \forall\, u \in \mathfrak{U}, n \in N \tag{6.39}$$

$$Y_n^u \leq \sum_{c \in C^u(k): n \in c} X_c^u \leq 1 \quad \forall\, u \in \mathfrak{U}, n \in N^u \tag{6.40}$$

$$Z \in \mathbb{R}_+$$

$$Y^u \in \mathbb{R}_+^{|N|} \qquad \forall\, u \in \mathfrak{U}$$

$$X \in \{0,1\}^{|C(k)|}$$

$$X^u \in \{0,1\}^{|C^u(k)|} \qquad \forall\, u \in \mathfrak{U}$$

Here, constraints (6.2) and (6.5) are replaced by constraints (6.38), (6.39) and (6.40). The formulation above is a regular mixed integer program, albeit with a prohibitively large number of variables and constraints if the complete set $\mathfrak{U}$ is considered. Adding a

scenario u to the above formulation corresponds to simultaneously generating the relevant rows in (6.38), (6.39) and (6.40) and the relevant columns associated with the variables Y^u and X^u.

6.5.3 The scenario generation subproblem

Proposition 6.2 implies that step 3 in the delayed scenario generation algorithm - the scenario generation subproblem - is equivalent to solving the adversary's problem. We will now first study the complexity of the adversary's problem in case of full recourse.

In case of full recourse, the adversary's problem reads as follows:

$A_{\text{Full}}(X) =$

$$\min_{\zeta} \quad R_{\text{Full}}(X, u_\zeta) \tag{6.41}$$
$$\text{s.t.} \quad B\zeta \leq b \tag{6.42}$$
$$\zeta \in \{0,1\}^{|N|+|A|} \tag{6.43}$$

The adversary's problem as presented by (6.41) - (6.43) belongs to the class of 'interdiction problems', in particular it is a directed cycle interdiction optimization problem. Let us consider the following decision variant of the problem:

Problem 1. Directed Cycle Interdiction
Input: A digraph $G = (V, A)$, a budget b, an integer m.
Output: A subset $V' \subseteq V$ such that $|V'| \leq b$ and such that the maximum number of nodes covered by a disjoint collection of directed cycles in $G \setminus V'$ is at most m.

We will now first consider membership of the NP-class.

Theorem 6.3. *A solution for the Directed Cycle Interdiction problem can be verified in polynomial time.*

Proof. Given a set of nodes V', it can be verified in polynomial time that $V' \subseteq V$ and that $|V'| \leq b$. Furthermore, $G \setminus V'$ can be computed in polynomial time. Since the maximum number of nodes covered by disjoint directed cycles can be computed in polynomial time (for example by transforming $G \setminus V'$ to a perfect matching problem in a bipartite graph), it can be verified whether this number does not exceed m in polynomial time as well. □

Next we only need to consider NP-hardness. Let us consider the Feedback Vertex Set problem:

Problem 2. FEEDBACK VERTEX SET
Input: A digraph $G = (V, A)$, an integer l.
Output: A set of nodes $V' \subseteq V$ with $|V'| \leq l$ such that if we remove V' from G the remaining graph does not contain any directed cycles.

It is well known that the Feedback Vertex Set problem is NP-complete.

Theorem 6.4. *Feedback Vertex Set is a special case of Directed Cycle Interdiction.*

Proof. Let us take a Feedback Vertex Set instance and create a Directed Cycle Interdiction instance with the same graph, budget $b = l$ and parameter $m = 0$. Now the Directed Cycle Interdiction instance is a YES-instance if and only if there exists a Feedback Vertex Set. □

We now obtain our final complexity results for the Directed Cycle Interdiction problem and, subsequently, the adversary's problem.

Corollary 6.2. *In case of full recourse, the adversary's problem is NP-hard.*

Proof. From Theorem 6.3 and Theorem 6.4 it follows that the Directed Cycle Interdiction problem is NP-complete. Since the adversary's problem is a directed cycle interdiction *optimization* problem, the adversary's problem is NP-hard.

□

6.5.4 Solving the scenario generation subproblem

Let X^* denote an optimal solution to the robust exchange problem $RE(\bar{\mathfrak{U}})$. In case of full recourse, the adversary's problem $A_{\text{Full}}(X^*)$, which is equivalent to the scenario generation subproblem, may be solved exactly by branch-and-bound. Branching can be performed on the nodes and arcs in the exchange digraph D.

For any node t of the branch-and-bound tree let $u(t)$ denote any scenario in which the branching decisions made in t are respected, i.e. enforced nodes and arcs are available in the recourse stage and banned nodes and arcs are not. Then note that $R_{\text{Full}}(X^*, u(t))$ provides an integral upper bound for node t in the branch-and-bound tree. Furthermore, note that if $B\zeta^{u(t)} \leq b$ a lower bound can be obtained by solving either the adversary's problem for simple recourse $A_{\text{Simple}}(X^*)$ or the adversary's problem for back-arcs recourse

$A_{\text{Back-arcs}}(X^*)$ under the settings for which these can be solved efficiently (recall Section 6.3 and Section 6.4). If $B\zeta^{u(t)} > b$ a lower bound is equal to $+\infty$. Whenever for any node in the branch-and-bound tree the lower bound is no better than the best upper bound found so far, that node's subtree can be pruned. If, at any node, the upper bound matches the lower bound at the root node, the adversary's problem $A_{\text{Full}}(X^*)$ has been solved to optimality.

For some nodes in the branch-and-bound tree it is possible to obtain substantially better upper bounds than those obtained by solving $R_{\text{Full}}(X^*, u(t))$. This is particularly the case for nodes near the root of the branch-and-bound tree. In order to explain how to achieve these improved bounds, note that if the integrality of the recourse variables X^u in the full recourse problem $R_{\text{Full}}(X^*, \zeta)$ described by (6.12), (6.14), (6.15) is relaxed, the adversary's problem $A_{\text{Full}}(X^*)$ can be solved by rewriting the nonlinear min-max objective as a minimization problem by using the dual of the recourse problem. The resulting problem is a minimum vertex and arc cover problem with variable cost:

$$A'_{\text{Full}}(X) =$$

$$\min_{\zeta, W} \sum_{n \in N} \zeta_n W_n + \sum_{a \in A} \zeta_a W_a \tag{6.44}$$

$$\text{s.t.} \quad \sum_{n \in c} W_n + \sum_{a \in c} W_a \geq \sum_{n \in c} \sum_{c' \in C(k): n \in c'} X_{c'} \quad \forall\, c \in C(k) \tag{6.45}$$

$$B\zeta \leq b$$

$$\zeta \in \{0,1\}^{|N|}$$

$$W \in \mathbb{R}_+^{|N|+|A|}$$

Here, the variables W are the duals of constraints (6.14) and (6.15). The objective (6.44) is to find a minimum cost cover. Constraints (6.45) imply that all cycles that include nodes selected in the first stage must be covered.

The nonlinear terms $\sum_{n \in N} \zeta_n W_n$ and $\sum_{a \in A} \zeta_a W_a$ in the objective (6.44) may be linearized by introducing a variable $T_n := \zeta_n W_n$ for each $n \in N$ and a variable $S_a := \zeta_a W_a$ for each $a \in A$, and by imposing the additional constraints $T_n \geq W_n - M(1 - \zeta_n)$ for all $n \in N$ and $S_a \geq W_a - M(1 - \zeta_a)$ for all $a \in A$, where M is some sufficiently large number. In this case, setting $M := k$ is sufficient because constraints (6.45) imply that neither any W_n nor any W_a ever need to be larger than k. Applying these adjustments, we obtain the following mixed integer program:

$A'_{\text{Full}}(X) =$

$$
\begin{aligned}
\min_{\zeta,W,S,T} \quad & \sum_{n\in N} T_n + \sum_{a\in A} S_a \\
\text{s.t.} \quad & \sum_{n\in c} W_n + \sum_{a\in c} W_a \geq \sum_{n\in c} \sum_{c'\in C(k):n\in c'} X_{c'} && \forall\ c \in C(k) \\
& W_n + k\zeta_n - T_n \leq k && \forall\ n \in N \\
& W_a + k\zeta_a - S_a \leq k && \forall\ a \in A \\
& B\zeta \leq b \\
& \zeta \in \{0,1\}^{|N|} \\
& W \in \mathbb{R}_+^{|N|+|A|} \\
& S \in \mathbb{R}_+^{|A|} \\
& T \in \mathbb{R}_+^{|N|}
\end{aligned}
$$

The difference between the bound obtained by solving $R_{\text{Full}}(X^*, u(t))$ and the bound obtained by solving $A'_{\text{Full}}(X^*)$ is that the former accurately takes into account the recourse actions but underestimates the adversary's potential by using the scenario $u(t)$, whereas the latter overestimates the recourse actions because the recourse variables are relaxed but accurately takes into the adversary's potential to damage the planned solution.

Finally, note that it is possible to use the LP relaxations $R'_{\text{Full}}(X^*, u(t))$, $A'_{\text{Simple}}(X^*)$, and $A'_{\text{Back-arcs}}(X^*)$ when determining the bounds in the branch-and-bound procedure. While this may provide bounds that are less tight, it may save computation time. We have the following relationships:

$$R'_{\text{Full}}(X^*, u(t)) \geq R_{\text{Full}}(X^*, u(t)),$$

$$A'_{\text{Simple}}(X^*) \leq A_{\text{Simple}}(X^*),$$

$$A'_{\text{Back-arcs}}(X^*) \leq A_{\text{Back-arcs}}(X^*)$$

that hold in any branch-and-bound node t.

6.6 Refinement of the robust solution

In barter exchanges there may be multiple solutions that are optimal with respect to the chosen objective. This frequently occurs in kidney exchange for example, where the objective typically is to maximize the number of transplants but there are multiple ways in which the maximum number of transplants can be achieved (Manlove and O'Malley, 2012; Glorie et al., 2014d). Preliminary experiments suggest that this may also happen for our robust exchange models.

The most common approach to deal with multiple optimal solutions is to use a set of tie-breaking rules or secondary criteria (Manlove and O'Malley, 2012; Glorie et al., 2014d). A set of multiple objectives may be combined into a single objective function by including a separate term for each criterion under consideration. Each term is then multiplied with the relative weight attached to the criterion it models. It is very common in kidney exchange for the criteria to be hierarchically ordered (De Klerk et al., 2010; Manlove and O'Malley, 2012; Kim et al., 2007). The objective weights should then be scaled such that the first criterion is indeed more important than the second, the second criterion more important than the third, etc. Alternatively, in case of hierarchical criteria, an iterative lexicographic approach may be considered (Glorie et al., 2014d).

In Section 6.7, we compare the best (0 nodes fail) and worst case (p nodes fail) scenarios in the presence of a kidney exchange program that takes into account only the best scenario ($\mathfrak{U} = \{N \cup A\}$) and a kidney exchange program that takes into account all scenarios ($\mathfrak{U} := \{u \subseteq N \cup A : \sum_{n\in N} \zeta_n^u \geq |N|(1-p), \sum_{a\in A} \zeta_a^u \geq |A|, \zeta^u \in \{0,1\}^{|N|+|A|}\}$).

Frequently, an optimal solution to the optimistic program performs equally to an optimal robust solution in the worst case scenario. This is because there are typically multiple optimal robust solutions and thus we would like to select the one among them that performs best in the optimistic scenario.

In order to select the optimal solution for the robust exchange problem that performs best for the optimistic scenario we replace the objective function in (6.1) by

$$\max_{Z,X} Z + \varepsilon \sum_{c\in\mathcal{C}(k)} w_c X_c$$

with $\varepsilon > 0$.

The value of ε must be carefully chosen in order to avoid obtaining kidney exchange programs that are not robust, i.e, the second term in the new objective function should never be greater than the first term. Therefore, it is sufficient to set

$$\varepsilon = \frac{1}{\sum_{n \in N} \max_{c \in \mathcal{C}(k): n \in c} \frac{w_c}{|c|}} \tag{6.46}$$

Note that we can also add the term $\varepsilon \sum_{c \in \mathcal{C}(k)} w_c X_c$ to the objective function of the adversary's problem (6.16). This is equivalent to adding a constant, because in the adversary's problem the decision variables X are already determined/fixed. In this way the results we obtained for solving the robust exchange problem for the various forms of recourse still apply.

In a similar way, we can use objective weights to assign priority to specific groups of agents, such as highly sensitized patients in kidney exchange. In case of the full recourse policy, we can also use a more efficient formulation than adding another term to the objective function. Because of the structure of the recourse objective (6.35), we can replace the unit objective weights of the Y variables by scaled weights, such that the desired groups of agents are prioritized. In particular, in Section 6.7 we will use a scaling that prioritizes highly sensitized patients. If N^* denotes the set of highly sensitized patients, we replace the full recourse objective (6.35) by:

$$\max_{X^u, Y^u} \sum_{n \in N^*} Y_n^u + \sum_{n \in N \setminus N^*} \varepsilon Y_n^u + \varepsilon^2 \sum_{c \in \mathcal{C}(k)} w_c X_c \tag{6.47}$$

where ε is defined as above.

Given that highly sensitized patients have a particularly high probability of match failure compared to non-highly sensitized patients (see Appendix A), we explicitly consider arc failure for this patient group. In the next section we present the results that these small modifications lead us to.

6.7 Computational results

6.7.1 Instance generator

To evaluate the solution approach for the robust exchange problem described in this paper, we test it on several kidney exchange instances generated by the well known Saidman kidney exchange simulator (Saidman et al., 2006), which we have adjusted to include altruistic donors in addition to incompatible patient-donor pairs.

The simulator uses US population data from the United Network for Organ Sharing (UNOS). It generates patients with a random blood type, sex, and probability of being crossmatch incompatible (this probability is called the PRA level) with a randomly chosen

donor. Each patient is assigned a potential donor with a random blood type and relation to the patient. If the patient and the potential donor are incompatible, they are added to the kidney exchange pool. Blood types and probabilities of crossmatch failure are then used to determine the compatibilities in the pool. Table 6.1 summarizes the probabilities as described in (Saidman et al., 2006). As the original simulator did not include altruistic donors, we add to each pool a fixed percentage of altruistic donors (generated as above but without assignment to a patient).

Prob. blood type A	.3373
Prob. blood type B	.1428
Prob. blood type AB	.0385
Prob. blood type O	.4814
Prob. low PRA (5 %)	.7019
Prob. medium PRA (10 %)	.2
Prob. high PRA (90 %)	.0981
Prob. female	.409
Prob. spousal donor*	.4897
% altruistic donor**	4.5
* Applies to female patients only. Spousal PRA := 1 - .75 (1 - PRA)	
** Original simulator did not have altruistic donors	

Table 6.1: Probabilities in Saidman simulator

For our experiments we will generate 30 instances of 20, 50 and 100 nodes. Table 6.2 summarizes some characteristics of these instances.

We have implemented the robust exchange problem with simple, back-arcs, and full recourse in C#.NET. All instances were run using a computer equipped with a 2.3 GHz Intel Core i7 processor with 16 GB of RAM memory. All LPs and MIPs were solved using CPLEX 12.5.

6.7.2 Simple recourse

Table 6.3 describes our findings for the performance and run times of the simple recourse policy on various instances. The first column specifies the instance size in terms of the number of nodes. The second column specifies the maximum number of failures. The third and fifth column respectively specify the number of proposed transplants for the robust program (which anticipates failures) and the deterministic program (which does not anticipate failures). The fourth and sixth column specify the actual number of transplants

for these programs. The seventh column specifies the run time and the eighth column specifies the percent of instances in which the loss in transplants (= number of first stage matches minus number of actual transplants in the second stage) is lower than the maximum possible loss.

From Table 6.3 it becomes clear that all instances can be solved within very short run times. There is no substantial difference between the run times of the 1-failure and the 2-failures tests. Also, the number of transplants proposed in the robust and deterministic program is similar.

In the worst case scenario, we could lose at most 3 transplants per failing node or arc. Hence, in case of a single failure, at most 3 transplants can be lost. If the instance size is small, this loss can sometimes be restricted to less than 3 transplants (see the instances of size 20 in which 2.43 transplants are lost on average in the robust program, versus 3 in the deterministic program). However, for larger instance sizes (50 and 100) the loss of 3 transplants cannot be avoided by anticipation of failure. In case of two failures, at most 6 transplants can be lost. Again, this loss can be restricted if the instance size is small enough (in the instances of size 20 and 50 on average 4.33 and 5.83 transplants are lost respectively). Interestingly, in case the number of failures is higher, the percentage of instances in which the loss can be reduced increases substantially.

6.7.3 Back-arcs recourse

Table 6.4 summarizes our results for the back-arcs recourse policy.

Table 6.4 shows that, also for the back-arcs policy, all instances can be solved within very short run times. With the exception of the 20 node instance for the 1 failure setting, the transplant numbers are identical to the transplant numbers of the simple recourse policy. The same holds true for the percentage of instances with reduced loss. This indicates that in the worst case scenario the additional flexibility for recovering from failures provided by the back-arcs recourse is insufficient to reduce the losses compared to what could be gained by anticipating failures as by the simple recourse policy. The main reason is that, in nearly all instances, it is not possible to select only cycles with sufficient back-arcs to recover from a single node or arc failure. Therefore, in the worst case any of the selected 'non-robust' cycles will be cancelled.

6.7.4 Full recourse

Table 6.5 describes our findings for the performance and run times of the full recourse policy on various instances. In addition to the statistics reported for the simple and

back-arcs recourse policies, we now also report the average number of scenarios that is generated (column 6).

From Table 6.5 it becomes clear that, as expected, the running time for solving the full recourse problem increases strongly with the instance size and the number of failures. However, all instances can be solved within run times acceptable to kidney exchange programs in practice. Interestingly, the number of scenarios that needs to be generated is very small for all instances and does not show much variation.

Compared to the simple and back-arcs recourse policies, the number of transplants in the worst case scenario is higher for all instances. Also the percentage of instances with a reduced loss is substantially higher. In up to 86.67 percent of the instances it is possible to reduce the losses by combined anticipation of failure and a flexible response to failure.

6.7.5 Protecting highly sensitized patients

Table 6.6 describes our findings for the performance and run times of the refined full recourse policy which prioritizes highly sensitized patients on various instances. In all instances we allow at most 30 % of the arcs to highly sensitized patients to fail. The first row in the table reports the actual number of arc failures corresponding to this percentage. The second and third row report the number of first stage matches in respectively the robust and the deterministic program. The fourth and fifth row report the matches specifically for highly sensitized patients. Rows six and seven provide the number of transplants, i.e. the matches that can actually go forward, for highly sensitized patients. Rows eight to ten contain the run time statistics we also reported for the previously considered policies.

The first observation that can be made from Table 6.6 is that the total number of matches in any of the instances is not substantially different between the robust and the deterministic program. The deterministic program does tend to propose slightly more matches for highly sensitized patients, but substantially less of these matches go forward to transplantation. Moreover, the magnitude of this difference increases as the instance size grows. This indicates that the value of the robust program increases with the size of the kidney exchange program. Another observation is that, even though the tests consider a substantially larger number of failures than our previous tests, the run times are still likely to be acceptable to practice. Also, the number of scenarios that need to be generated increases when the instance grows from 20 to 50 nodes, but stays almost constant when the instance grows further to 100 nodes. Finally, the percentage of instances in which the

loss of transplants can be reduced also grows with the instance size. In the largest size programs it is possible to reduce the losses in 100 % of the tested instances.

6.8 Conclusions

In this research we have considered the centralized clearing of barter exchange markets in which proposed transactions must be verified before they can proceed. Proposed transactions may fail to go forward if verification fails or if a participant withdraws. We have modeled the clearing problem in these markets as a vertex-disjoint cycle packing problem in an unreliable digraph. The arcs and nodes of this graph are subject to failure.

Our research has many natural and interesting applications, of which kidney exchange is probably the most important. Deciding which donors get matched to which patients in kidney exchange can be a matter of life and death. Unfortunately, the present algorithms employed to clear kidney exchanges often leave highly-sensitized patients, who are hard to match, without a transplant. It has been the need to protect the rare transplant opportunities for these highly-sensitized patients that has motivated us in particular to consider the concept of a 'robust exchange'.

Other methodologies that aim to take market uncertainty into account, such as maximizing the expected number of transplants, typically disadvantage highly-sensitized patients as transactions involving these patients tend to have a high probability of failure. Under our 'robust exchange' methodology we aim to protect transactions against a large set of possible scenarios for failure. Our methodology allows in particular to protect the transactions for highly-sensitized patients.

In addition to protecting against failure, we explicitly consider the option of flexible response to failures. We do this by allowing recourse actions. We have considered three recourse policies - simple recourse, back-arcs recourse, and full recourse - which can be easily implemented in practice. Our clearing algorithm selects an optimal planned solution taking the possibility of recourse into account. If actual failures occur, our algorithm selects the optimal recourse action.

We have provided results for settings in which the problem of determining the optimal recourse action can be solved efficiently, whereas in general this requires time exponential in the input size. Moreover, we have shown that for these settings also the problem of determining the worst case scenario (taking into account the possibility of recourse) can be solved efficiently. These results apply to the simple recourse and back-arcs recourse policies, when trading cycles and chains are limited to three agents and failure is considered to be homogenous. For other settings and for the full recourse policy, we have

developed an advanced methodology for delayed scenario generation. In this methodology row and column generation are combined with a branch-and-bound algorithm.

We have tested our algorithms on various instances generated by the most commonly used kidney exchange simulator based on US population data. Our computational results show that instances of realistic size (the size of current kidney exchange pools), can be solved within run times that are acceptable to practice. More importantly, our results show that in a substantial number of instances, it is possible to actually protect patients against failures that prevent them from undergoing a transplant. In this regard, our algorithms may offer a significant improvement over current practice.

There are several opportunities to expand the research presented in this paper. Direct extensions include extending the experiments to different types of uncertainty sets that reflect heterogenous failure or that tail-off as scenarios become more extreme (as per the concept of globalized robustness (Ben-Tal et al., 2009)). Another direction would be to combine our solution approach with delayed generation of trading cycles and chains (Abraham et al., 2007; Glorie et al., 2014d). This would be particularly advantageous if the market size grows far beyond what it is today or if the bound on the trading cycles and chains becomes large.

There also remain general challenges to barter exchange markets that are important to mention. Dynamic market clearing - in which the market is not cleared by accumulating batches of agents and then maximizing the transactions per batch as is done in present exchanges, but in which the market is cleared while taking future arrivals into account - is a problem that has received attention but has not yet been solved optimally. Our model of market uncertainty can ostensibly be extended to take future arrivals into account. Another challenge is the internationalization of markets and the conflicts of interest that may arise between market participants (e.g. participation and incentive compatibility for hospitals and networks of hospitals in kidney exchange). Finally, we would like to mention that generalizations of our work could consider allowing monetary transfers and private information regarding agent preferences. While these factors may be less important in kidney exchange markets, they may be important in other markets such as house trading.

In conclusion, we hope our work may serve to improve allocations in barter exchange markets. In particular, we hope it may make allocations more reliable so agents can hold faith in the markets, and, in the case of kidney exchange, that the most disadvantaged patient groups can benefit by having more transplants made available to them.

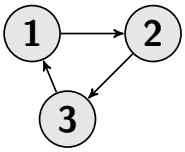

Figure 6.2: Case 1. Cycle without back-arcs. If one node or arc fails, the entire cycle fails and cannot be recovered.

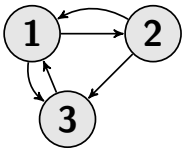

Figure 6.4: Case 3. Cycle with two back-arcs. If node 1 fails, the entire cycle fails and cannot be recovered. Therefore a single failure is sufficient to completely cancel the cycle.

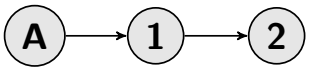

Figure 6.6: Case 5. Chain without back-arcs. If one node or arc fails, the entire chain fails and cannot be recovered.

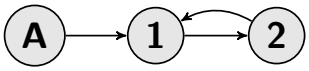

Figure 6.8: Case 7. Chain with one back-arc. If node 1 fails, the entire chain fails and cannot be recovered.

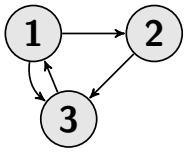

Figure 6.3: Case 2. Cycle with one back-arc. If node 1 or node 3 fails, the entire cycle fails and cannot be recovered. Therefore a single failure is sufficient to completely cancel the cycle.

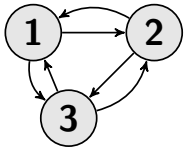

Figure 6.5: Case 4. Cycle with three back-arcs. If there is a single failure, the transactions can always be recovered for at least two nodes. However, if two nodes fail, the entire cycle fails and cannot be recovered. Therefore two failures are required to completely cancel the cycle.

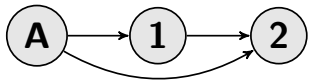

Figure 6.7: Case 6. Chain with one back-arc. If node A fails, the entire chain fails and cannot be recovered. Therefore a single failure is sufficient to completely cancel the chain.

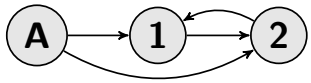

Figure 6.9: Case 8. Chain with two back-arcs. If there is a single failure, a transaction can always be recovered for at least one node. However, if two nodes fail, the entire chain fails and cannot be recovered. Therefore two failures are required to completely cancel the chain.

Nb nodes	Nb arcs	Nb cycles & chains	Nb cycles 0 back-arcs	Nb cycles 1 back-arc	Nb cycles 2 back-arcs	Nb cycles 3 back-arcs	Nb chains 0 back-arcs	Nb chains 1 back-arc	Nb chains 2 back-arcs
20	90.40	49.07	10.43	7.87	10.27	2.20	6.07	9.83	2.40
50	576.13	733.7	74.00	133.93	138.30	34.00	88.60	208.80	56.07
100	2367.20	6085.77	350.83	1047.3	1186.83	308.87	565.77	1994.37	631.80

Table 6.2: Average characteristics of 30 instances generated by the Saidman simulator with altruistic donors.

Nb nodes	Max nb failures	Robust nb proposed	Robust nb transplants	Det. nb proposed	Det. nb transplants	Time (s)	% of instances with reduced loss
20	1	7.43	5.00	7.43	4.43	.03	36.67
50	1	25.03	22.03	25.03	22.03	.14	.00
100	1	54.33	51.33	54.33	51.33	10.96	.00
20	2	7.43	3.10	7.43	1.43	.04	70.00
50	2	25.03	19.20	25.03	19.03	.95	16.67
100	2	54.33	48.33	54.33	48.33	10.31	.00

Table 6.3: Average performance characteristics for the simple recourse policy over 30 instances generated by the Saidman simulator with altruistic donors. The objective is to maximize the number of transplants. Cycle and chain limit is 3 and there is homogenous failure.

Nb nodes	Max nb failures	Robust nb proposed	Robust nb transplants	Det. nb proposed	Det. nb transplants	Time (s)	% of instances with reduced loss
20	1	7.43	5.03	7.43	4.43	.02	40.00
50	1	25.03	22.03	25.03	22.03	.14	.00
100	1	54.33	51.33	54.33	51.33	27.73	.00
20	2	7.43	3.10	7.43	1.43	.04	70.00
50	2	25.03	19.20	25.03	19.03	.95	16.67
100	2	54.33	48.33	54.33	48.33	9.28	.00

Table 6.4: Average performance characteristics for the back-arcs recourse policy over 30 instances generated by the Saidman simulator with altruistic donors. The objective is to maximize the number of transplants. Cycle and chain limit is 3 and there is homogenous failure.

Nb nodes	Max nb failures	Nb transplants	Det. nb transplants	Time (s)	Scenarios generated	% of instances with reduced loss
20	1	5.20	4.43	.33	2.33	60.00
50	1	22.27	22.03	3.93	2.37	23.34
100	1	51.50	51.33	85.64	2.9	20.00
20	2	3.40	1.43	2.74	2.6	86.67
50	2	19.63	19.03	114.93	2.8	53.33
100	2	48.76	48.33	3157.84	2.7	36.67

Table 6.5: Average performance characteristics for the full recourse policy over 30 instances generated by the Saidman simulator with altruistic donors. The objective is to maximize the number of transplants. Cycle and chain limit is 3 and there is homogenous failure.

	Nb nodes		
	20	50	100
Max nb arc failures	.43	6.13	22.46
Nb matches	7.80	26.30	57.13
Nb matches det.	7.83	26.47	57.42
Nb matches PRA ≥ 80	1.10	5.47	14.25
Nb matches PRA ≥ 80 det.	1. 17	6.10	15.21
Nb transplants PRA ≥ 80	.83	4.43	12.67
Nb transplants PRA ≥ 80 det.	.60	.20	.08
Time (s)	.49	157.25	5067.80
Scenarios generated	1.37	4.43	4.13
% of instances with reduced loss	16.67	96.67	100.00

Table 6.6: Average performance characteristics for the refined full recourse policy which prioritizes highly sensitized patients over 30 instances generated by the Saidman simulator with altruistic donors. Cycle and chain limit is 3 and at most 30 % of the arcs to highly sensitized patients (PRA ≥ 80) can fail.

Chapter 7

Summary and Conclusions

In this thesis we have considered the clearing problem in barter exchange markets. Our research has many natural and interesting applications, of which kidney exchange is probably the most important. Deciding which donors get matched to which patients in kidney exchange can be a matter of life and death. We have therefore focused in particular on kidney exchange markets. Our results are, however, easily applicable to other types of barter exchange markets.

We have started in Chapter 2 by providing an extensive literature review of the state of the art in kidney exchange clearing. We have shown that as the transplant community strives to balance quantity and equity of transplants to achieve the best possible outcomes, determining the right long-term allocation strategy in kidney exchange markets becomes increasingly important. Challenges we have identified include making full use of the various transplant modalities that are now available through integrated and optimized clearing software, encouragement of transplant centers to fully participate, improving transplant rates by focusing on the *expected* long run number of transplants, and selecting uniform allocation criteria to facilitate international pools.

In Chapter 3 we have considered solving the clearing problem with multiple objective criteria and long cycles and chains. We have shown that to achieve the best possible score on all criteria long cycles and chains are often needed, particularly when there are many hard-to-match patients. We have presented a generic iterative branch-and-price algorithm which can deal effectively with multiple criteria and side-constraints such as individual rationality constraints. We have shown how the pricing problem may be solved in polynomial time in the cycle and chain length for a general class of criteria and constraints. Our approach and its effects are demonstrated using simulations with kidney exchange data from the Netherlands and the US. We find that our algorithm is effective even for large realistic barter exchange markets.

In Chapter 4 we have studied various policy improvements for kidney exchange. We have shown that there is clear synergy in the central coordination of both unspecified donation and transplantation across the blood type barrier. Transplants can be increased by up to 10 % and by up to 22 % and 58 % for blood type O and highly sensitized patients respectively. Transplant centers can be encouraged to participate by including individual rationality constraints for the groups of patients and donors they represent. Implementing these constraints has negligible consequences for the long term outcomes that can jointly be achieved, and for individual objectives of the transplant centers, such as maximizing the number of transplants for the patients enrolled at a center. We have further shown that, although the best configuration of a national kidney exchange program depends on the composition of the patient-donor population, sufficient time between matching rounds is essential and that benefits of non-simultaneous extended altruistic donor chains are limited in case of low numbers of highly sensitized patients and sufficient unspecified donors. Furthermore, chains are best terminated when no further segment is part of an optimal exchange within 3 months.

In Chapter 5 we have considered the health outcomes of various allocation policies used in kidney exchange clearing. We have introduced an individualized health value model, which is a Markov process with patient-donor specific transition probabilities. We found that conventional allocation rules and criteria do not increase health value compared to a straightforward policy intended to maximize the number of transplants. However, we have also proposed a new policy intended to maximize health value. This model links the individualized Markov model to the branch-and-price algorithm described in Chapter 3. Under our newly proposed policy an improvement in quality adjusted life years of 6 % over current practice is possible. In particular, under this policy an improvement of 31 % is possible for the group of patients that are left unmatched. Furthermore, we have calculated an upper bound on the maximum health value that can be achieved by any allocation policy and have shown that our newly proposed policy comes 32 % closer to this bound than existing policies.

Finally, in Chapter 6 we have considered market failure. In particular, we have studied the clearing of barter exchange markets in which proposed transactions must be verified before they can proceed. For instance, in kidney exchange, patients and donors are prepared and crossmatch tests between each donor and selected recipient are performed. Proposed transactions may fail to go forward if verification fails or if a participant withdraws. In case one or more matches fail, a new allocation may be selected. The new allocation should be as close as possible to the initial set in order to minimize the material and emotional costs of the alteration. We have presented a robust optimization

approach that intends to maximize the number of agents selected in both the first and second allocation in a worst case scenario. Our methodology allows in particular the transactions for highly-sensitized kidney exchange patients to be protected. In addition to protecting against failure, we have explicitly considered the option of flexible response to failures. We have done this by allowing recourse actions. We have considered three recourse policies that can be easily implemented in practice. Our clearing algorithm selects an optimal planned solution taking the possibility of recourse into account. If actual failures occur, our algorithm selects the optimal recourse action. We have provided results for settings in which the problem of determining the optimal recourse action can be solved efficiently, whereas in general this requires time exponential in the input size. Moreover, we have shown that for these settings also the problem of determining the worst case scenario (taking into account the possibility of recourse) can be solved efficiently. For other settings we have developed an advanced methodology for delayed scenario generation. In this methodology, row and column generation are combined with a branch-and-bound algorithm. Computational results show that instances of realistic size (the size of current kidney exchange pools), can be solved within run times that are acceptable to practice.

Our results, especially those from Chapters 3 and 6, are applicable to general barter exchange markets, even when these markets allow for side payments. If prices are fixed (e.g. if agents have a fixed asking price for the goods they brought to the market and a maximum buying price for every good they are interested in) the results can be directly applied by taking prices into account when determining the possible transactions. If prices are not fixed but need to be determined by the market, auction techniques such as those used in combinatorial auctions may be required.

Based on the contributions made in this thesis, we see several interesting possible directions for future research. In addition to taking into account auction techniques to determine transfer prices, these include considering participation and incentive compatibility in international markets when national markets have different characteristics; considering the dynamic or online variant of the clearing problem to take future arrivals into account; considering stochastic allocation mechanisms such as lotteries; and considering coordination between related markets, such as the markets for living and deceased donor kidneys. We hope our research may serve as a reference framework to study these challenges.

Finally, and most importantly, we hope the findings described in this thesis may benefit the patients suffering from end stage renal disease across the globe.

Appendix A

Estimating the probability of match failure due to positive crossmatch[1]

In order to determine kidney exchange matches, compatibility between all patients and donors in the kidney exchange pool is analyzed by testing blood type compatibility and by performing a virtual crossmatch. Then, after a set of desirable recipient-donor matches is identified by a specialized computer algorithm, actual crossmatches are performed for all proposed recipient-donor matches. If a crossmatch is positive it means that the respective recipient-donor match fails to go forward to transplantation. The number of positive crossmatches after a negative virtual crossmatch can be substantial. In this appendix we estimate the probability of positive crossmatch after a negative virtual crossmatch on an individual level using Dutch clinical data.

Data

The available data include 438 ABO blood type or crossmatch incompatible patient-donor pairs who participated in Dutch kidney exchanges between October 2003 and January 2011, as well as outcomes of 331 crossmatch tests performed by the national reference laboratory for histocompatibility testing in Leiden. The data contain blood types of all patients and donors as well as center-reported patient PRA values at time of entry and, if available, at time of transplantation. Donor HLA types and recipient unacceptable HLA mismatches are also included. The national reference laboratory identifies unacceptable HLA specificities on basis of a combination of a complement dependent cytotoxicity (CDC) and a solid phase antibody screening. Antibody specificities leading to a positive

[1]This appendix is based on (Glorie, 2012).

CDC crossmatch are considered to be a contraindication for transplantation and the HLA antigens recognized are defined as unacceptable mismatches.

Because center-reported PRA levels are based on the general population, they may not accurately reflect the difficulty of finding compatible donors in the kidney exchange program. For that reason additional kidney exchange donor population PRA levels are computed based on virtual crossmatches between each patient and all donors in the data set. Throughout the rest of this appendix, whenever we refer to a PRA level, we refer to these kidney exchange donor population based PRA levels. Table A.1 details the patient and donor characteristics.

	ABO blood type			
	A	B	AB	O
Patients (%)	30	15	1	54
Donors (%)	56	14	2	29
	PRA level w.r.t. general population (at time of entry)			
	0-9	10-79	80-100	
Patients (%)	78	17	5	
	PRA level w.r.t. kidney exchange donor population			
	0-9	10-79	80-100	
Patients (%)	48	35	17	

Table A.1: Patient and donor characteristics

Table A.2 displays the number of positive crossmatch outcomes after a negative virtual crossmatch for each of the PRA level categories of Table A.1. The numbers clearly indicate that there is a relationship between the probability of a positive crossmatch after a negative virtual crossmatch and the PRA level.

	PRA level w.r.t. kidney exchange donor population		
	0-9	10-79	80-100
# Actual crossmatches	126	173	32
Positive (%)	6	31	44

Table A.2: Relation between positive crossmatch after a negative virtual crossmatch and PRA level

However, the crossmatch tests reported in Table A.2 are not all independent. Regularly, multiple crossmatch tests correspond to an individual patient. Multiple tests might, for example, be required when a patient's initial test is positive, or when a patient's crossmatch test is negative but the proposed transplant procedure cannot take place because

of a positive crossmatch for another patient involved in the procedure. We need to investigate the effects and significance of this dependence relation before making inferences.

Analysis

Table A.3 shows the outcomes of a χ^2 test for independence of the probability of a positive crossmatch test and the outcomes of previous crossmatch tests, per PRA category as in Table A.1. For each of the PRA categories, there is no significant evidence to reject the null hypothesis of independence. Therefore all the observed crossmatch results can be straightforwardly used to estimate the probability of a positive crossmatch within each PRA category, as was done in Table A.2.

Table A.4 shows the outcomes of a probit regression of the latent individual probability of a positive crossmatch on recipient PRA, recipient age, recipient blood type and recipient gender. Only the coefficient of recipient PRA is highly significant. We exclude the other factors and repeat the regression (Table A.5). Again, the coefficient of PRA is highly significant, as is the likelihood-ratio test for model fit. Figure A.1 shows a plot of the fitted probabilities. The non-linear relationship between the probability of a positive crossmatch and the PRA level is clearly visible. To assess whether this relationship is correctly modeled, we further diagnose a plot of the standardized residuals (Figure A.2). The standardized residuals behave nicely overall, showing only weak signs of heteroskedasticity for PRA values close to 0 and 100. This indicates that possibly the tails of the normal distribution do not correctly fit the distribution of the probabilities. However, a formal Lagrange Multiplier test reveals that the amount of heteroskedasticity is not significant (Table A.5). It therefore appears that

$$Pr[T_{i,j} = 1 : PRA_j] = \Phi\left(-1.5007 + 0.0170 \cdot PRA_j\right)$$

appropriately models the individual probability of a positive crossmatch.

Conclusion

In this appendix we have estimated the probability of virtual crossmatch failure in kidney exchange matching by relating this probability to the recipients PRA level. Our findings indicate that highly sensitized patients have a significantly higher probability of virtual crossmatch failure than non-highly sensitized patients. Moreover, we find that the non-linear relationship between the PRA level and the probability of virtual crossmatch failure is modeled appropriately by a homoskedastic probit model.

Crossmatch tests		Test 1	Test 2	Test 3	Test 4	Test 5	Test 6	Test 7	Total
PRA 0-9	Positives	4	2	1	0				7
	Negatives	79	31	8	1				119
	Total	83	33	9	1				126
	$\chi^2 = 0.69$		P = 0.124						
PRA 10-79	Positives	23	16	8	3	2	1	0	53
	Negatives	66	26	17	4	3	2	2	120
	Total	89	42	25	7	5	3	2	173
	$\chi^2 = 3.67$		P = 0.280						
PRA 80-100	Positives	8	3	2	1	0			14
	Negatives	11	5	1	0	1			18
	Total	19	8	3	1	1			32
	$\chi^2 = 2.85$		P = 0.417						

Table A.3: Test for independence

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-0.1970	0.4602	-1.9926	0.0463
PRA	0.0154	0.0031	4.9607	<0.0001
DUMMY_A	0.1649	0.1974	0.8358	0.4033
DUMMY_B	0.4868	0.2705	1.8000	0.0719
DUMMY_AB	0.8269	0.4202	1.9681	0.0491
AGE	-0.0133	0.0071	-1.8802	0.0601
DUMMY_MALE	-0.2317	0.1946	-1.1907	0.2338
Deviance	293.4677	Prob (Deviance)		<0.0001

Table A.4: Probit regression involving several recipient characteristics

Variable	Coefficient	Std. Error	t-Statistic	Prob.
C	-1.5007	0.1486	-10.1007	<0.0001
PRA	0.0170	0.0026	6.5340	<0.0001
Deviance	304.5770	Prob (Deviance)		<0.0001
LM-test	1.7514	Prob (LM-test)		0.1857
McFaddens R-squared	0.1342			

Table A.5: Probit regression involving only recipient PRA

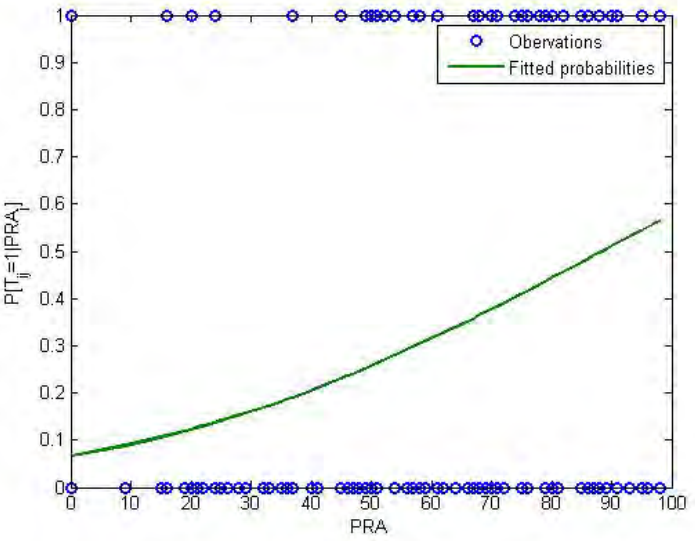

Figure A.1: Fitted probabilities

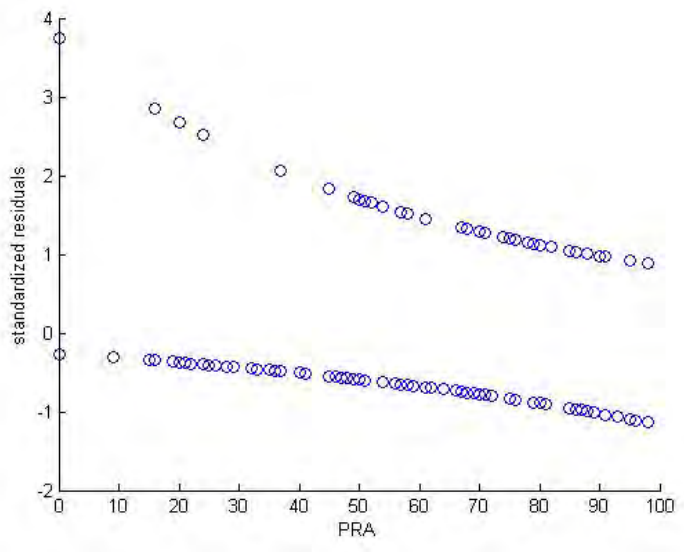

Figure A.2: Standardized residuals versus PRA

Although this model improves on the estimations made in previous literature (e.g. (Ashlagi et al., 2011b)), we do not claim that the PRA level is the sole explanatory factor for virtual crossmatch failures, nor that virtual crossmatch failure is the only cause of failure preventing kidney exchange matches from going forward to transplantation. There may be other factors which play a role, such as recipient health status and likelihood of withdrawal of incompatible donors, but their impact will likely be smaller than the impact of the PRA level, and as we did not have data available on these other factors, they were not explicitly included. Instead, these exogenous factors are captured by the constant terms in our model.

Additionally, our findings are conditional to our assumptions (although we applied multiple statistical test to verify these assumptions) and to our data (although comparison of our data (see Table A.3) with the data used in related literature (see Table 2 in (Ashlagi et al., 2011b)) suggests failure rates are comparable).

Considering the practical impact of failure of kidney exchange matches, particularly due to failure of virtual crossmatching, we hope the present findings may serve to improve kidney exchange simulations by taking into account virtual crossmatch failure more accurately, and thereby help policy makers select the best kidney exchange mechanisms.

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Nederlandse Samenvatting (Summary in Dutch)[1]

Vrijwel iedereen heeft weleens iets geruild. Van knikkers tot voetbalplaatjes tot wellicht een dienst met een collega. Dit ruilen gebeurt vaak één op één: men zoekt iemand die een object heeft dat hij of zij graag wil hebben én die geïnteresseerd is in het object dat men aanbiedt. Dit decentraal en paarsgewijs ruilen kost vaak veel tijd en is vaak niet erg efficient. Een gecentraliseerde markt, waarin iedereen zijn wensen kenbaar maakt aan een operator, kan veel tijd besparen en een betere allocatie van goederen mogelijk maken. Dit is met name het geval als er ruilcycli worden toegestaan waarin elke deelnemer een object geeft aan de volgende deelnemer in de cyclus en een object ontvangt van de voorgaande deelnemer. In de praktijk is er veelal een natuurlijke beperking op het aantal deelnemers in een ruilcyclus, bijvoorbeeld vanwege logistieke redenen. Dit proefschrift beschouwt het allocatieprobleem voor de marktoperator in dit soort ruilmarkten. In het bijzonder beschouwt het daarbij de markt voor nieruitwisseling, welke één van de meest impactvolle en geprofessionaliseerde ruilmarkten van dit moment is.

Er zijn in Nederland circa 60.000 patiënten met ernstige nierproblemen (Nierstichting Nederland, 2011). 6400 van hen zijn aan het dialyseren, wat betekent dat ze drie tot vijf keer per week naar een dialysecentrum moeten om hun bloed gedurende vier uur te laten zuiveren en onderworpen zijn aan een streng dieet. De kwaliteit van leven met dialyse is erg laag en het jaarlijkse overlijdenspercentage is 20 %. Het geprefereerde alternatief, transplantatie, is helaas niet voor iedereen beschikbaar. Per jaar kunnen slechts 860 patiënten op deze manier geholpen worden (Nederlandse Transplantatie Stichting (NTS), 2012).

De helft van het aantal transplantaties is postmortaal. Dat wil zeggen dat de transplantaties plaatsvinden met een orgaan van een overleden donor, waarvoor patiënten gemiddeld 4 jaar op de wachtlijst staan. De andere helft vindt plaats met een levende donor, zoals een broer of zus van de patiënt. Ruim 30 % van de levende donoren is

[1]Deze samenvatting is gebaseerd op (Glorie et al., 2012a).

echter incompatibel met de patiënt waaraan ze in eerste instantie zouden willen doneren. Om transplantatie voor deze groep patiënten toch mogelijk te maken is in 2004 een nieruitwisselingsprogramma opgericht. Dit programma stelt incompatibele paren in staat te ruilen van donor om zodoende op een indirecte manier toch door te gaan met transplantatie (Hoofdstuk 2).

Het nieruitwisselingsprogramma werkt als volgt. Stel, patiënt Anna heeft een nier nodig. Haar broer Bart wil haar graag helpen en een van zijn twee gezonde nieren doneren. Na enkele tests in het ziekenhuis blijkt echter dat de bloedgroepen van Bart en Anna niet compatibel zijn. Een transplantatie zou vrijwel onmiddellijk tot afstoting leiden. Elders in het land zitten Cynthia en Dirk met een soortgelijk probleem. Cynthia heeft na haar zwangerschap antistoffen aangemaakt tegen de cellen van Dirk. Hierdoor kunnen ook zij niet doorgaan met transplantatie. In een nationale database kunnen transplantatiedeskundigen echter constateren dat Cynthia en Bart *wel* compatibel zouden zijn, evenals Anna en Dirk. Zij stellen daarom voor dat beide paren, weliswaar anoniem, ruilen van donor via het nieruitwisselingsprogramma. Op deze manier zouden zowel Anna als Cynthia toch een transplantatie kunnen krijgen.

Tien jaar geleden hadden Anna en Cynthia niet geholpen kunnen worden. Gelukkig voor hen en vele andere patiënten was Nederland in 2004 het eerste land ter wereld met een nationaal nieruitwisselingsprogramma. Maar net als bij de toewijzing van postmortale organen rijst de vraag: wie krijgt een tranplantatie en wie niet? In ons voorbeeld ruilden Anna en Bart bijvoorbeeld met Cynthia en Dirk. Maar wellicht hadden zij ook kunnen ruilen met Eduardo en Floor. Wie gaat er dan voor, Cynthia of Eduardo?

Het ruilen binnen het nieruitwisselingsprogramma hoeft zich niet te beperken tot twee patiënt-donor paren. Er kunnen ook grotere ruilcycli gevormd worden. Een risico is echter dat een donor zich terugtrekt nadat zijn patiënt een nier heeft ontvangen. Dit zou de andere patiënten in de cyclus die nog niet getransplanteerd zijn, maar waarvan de donor reeds heeft gedoneerd, ernstig benadelen. Dit terugtrekken hoeft niet opzettelijk te gebeuren en kan bijvoorbeeld veroorzaakt worden door ziekte of zwangerschap van de donor.

Om benadeling van patiënten op deze manier te voorkomen zijn er een paar mogelijkheden: (1) alle transplantaties in een cyclus gelijktijdig uitvoeren, (2) in plaats van een ruilcyclus een ruilketen vormen die start met een Samaritaanse donor (een levende donor zonder specifieke patiënt) en eindigt met een donatie aan een patiënt op de postmortale wachtlijst, en (3) een patiënt in plaats van een directe transplantatie voorrang geven op de wachtlijst in ruil voor donatie door zijn levende donor. Opties (2) en (3) hebben als voordeel dat zij de ruilmogelijkheden vergroten, dit in tegenstelling tot optie (1). Bij

optie (1) is er namelijk een beperking op hoeveel paren kunnen deelnemen in een cyclus, ingegeven door het aantal operatiekamers en operatieteams dat simultaan beschikbaar is.

Hoe wordt hier in Nederland mee omgegaan? Wel, simultaniteit is een standaardvereiste voor ruilcycli (die om logistieke redenen uitgevoerd worden met maximaal vier paren) en Samaritaanse donorketens worden waar mogelijk regionaal per transplantatiecentrum gecoördineerd. De derde optie, wachtlijstprioriteit, is echter bij wet verboden omdat dit patiënten die reeds op de wachtlijst staan zou kunnen benadelen. Met deze maatregelen wordt gepoogd te zorgen dat er binnen een van de grootste nieruitwisselingsprogramma's ter wereld 'van ruilen geen huilen komt'.

Een belangrijk criterium bij het bepalen wie met wie ruilt is het helpen van het maximale aantal patiënten. Dit kan worden bereikt door het ruilvraagstuk te formuleren als een wiskundig optimaliseringsprobleem. Een bottleneck bij het oplossen van dit probleem is dat het aantal variabelen zeer groot kan zijn. Er zijn namelijk zeer veel mogelijke ruilcycli en ruilketens. Gelukkig is het door gebruik te maken van een zogeheten *branch-and-price* algoritme mogelijk snel een optimale oplossing te vinden, zelfs als er veel participanten in een ruilketen of cyclus kunnen deelnemen (Hoofdstuk 3).

Maximaliseren van het aantal transplantaties is niet het enige criterium. Want is een maximale oplossing ethisch gezien wel juist? Op Europees niveau is afgesproken dat er sprake moet zijn van zowel een optimale als een *rechtvaardige* verdeling (Council of Europe, 2002). Dit houdt in dat factoren als de kans op transplantatie en de wachttijd ook meegenomen moeten worden. Om op ons voorbeeld terug te komen: stel dat Eduardo antistoffen heeft tegen een zeer hoog percentage van alle donoren waardoor de kans op het vinden van een geschikte match zeer klein is, dan is het wellicht eerlijker om Bart aan Eduardo te laten doneren dan aan Cynthia.

De Nederlandse transplantatiestichting heeft de volgende zes hiërarchische beslissingsregels opgesteld waaraan een allocatie binnen het nieruitwisselingsprogramma moet voldoen:

1. het aantal transplantaties is maximaal;
2. het aantal bloedtype identieke transplantaties is maximaal;
3. de patiënt met de laagste matchkans wordt gematcht (iteratief voor elke transplantatie);
4. het aantal paren in de langste ruilcyclus is zo klein mogelijk;
5. de spreiding over transplantatiecentra in de minst gespreide ruilcyclus is zo groot mogelijk;

6. de patiënt met de langste dialysetijd wordt gematcht.

Het doel van criterium 2 is om patiënten met een lastig te matchen bloedtype te beschermen. Dit wordt vervolgens verfijnt door criterium 3 dat rekening houdt met een meer specifiek gedefiniëerde matchkans. Criteria 4 en 5 zijn logistiek van aard en criterium 6 spreekt voor zich. De hiërarchische opzet van de criteria sluit aan bij de traditionele prioriteitsmechanismen die worden gebruikt bij de toewijzing van postmortale organen aan patiënten op de wachtlijst.

Hoewel het toevoegen van deze criteria het optimalisatieprobleem computationeel lastiger maakt, blijft het gelukkig door het op een slimme manier uitvoeren van branch-and-price iteraties, waarbij de doelfunctiewaarden gepropageerd worden door het toevoegen van restricties, ook mogelijk om dit probleem snel tot optimaliteit op te lossen (Hoofdstuk 3).

De hierboven genoemde criteria zijn niet de enige mogelijkheid om tot een rechtvaardige ruil te komen. Als alternatief wordt ook wel een lotingsprocedure genoemd. Hoewel een dergelijke stochastisch mechanisme mooie theoretische eigenschappen heeft zoals het bieden van zoveel als mogelijk gelijke kansen voor patiënten, wordt zij in de praktijk echter (nog) nergens omarmd.

Daarnaast is het bijvoorbeeld mogelijk te matchen op basis van gezondheidswinst (Hoofdstuk 5). Naast het feit dat dit de voordelen van transplantatie maximaliseert, schept het ook een mogelijkheid voor de inclusie van compatibele paren in het nieruitwisselingsprogramma. Stel dat een compatibel echtpaar van wat oudere leeftijd, Greet en Henk, de mogelijkheid geboden wordt om te ruilen met de jongere Cynthia en Dirk. Dit zou er toe kunnen leiden dat Greet een betere kwaliteit orgaan krijgt en dat Cynthia niet ongematcht hoeft achter te blijven. Door compatibele paren een verbetering in levensverwachting te garanderen zouden de kansen voor alle patiënt-donor paren in het programma zo verbeterd kunnen worden.

Bij het bespreken van degenen die door het ruilen benadeeld kunnen worden hebben we ons direct gericht op de patiënt-donor paren. Maar zij zijn niet de enigen die er op achteruit kunnen gaan. De transplantatiecentra zelf dienen ook in acht genomen te worden, met name wanneer het gaat om het ruilen met Samaritaanse donoren. Een centrum steekt namelijk veel tijd en geld in de voorbereidende onderzoeken en opwerking van donoren. Met een Samaritaanse donor zou het centrum dan ook het liefst zoveel mogelijk van de eigen patiënten helpen. Dit vormt in veel landen een groot praktisch probleem bij het opzetten van een nationaal programma en is mogelijk een van de redenen waarom ruilketens in Nederland tot op heden lokaal worden gecoördineerd.

In Hoofdstuk 4 is gekeken naar de toevoeging van participatierestricties (garanties dat een transplantatiecentrum in een nationaal mechanisme minstens zoveel transplantaties kan verrichten als in een lokaal mechanisme) voor verschillende configuraties van het nieruitwisselingsprogramma. Hieruit blijkt dat dergelijke restricties geen negatieve consequenties hebben op de lange termijn. Bovendien wordt aangetoond dat onder landelijke multimodale coördinatie een toename in het aantal transplantaties mogelijk is van bijna 60 % voor de meest lastig te matchen patiënten.

Hoewel we het nieruitwisselingsprogramma tot dusver in een statische toestand hebben beschouwd, is het dat in werkelijkheid niet. Maandelijks melden zich nieuwe patiënten en donoren aan en verdwijnen reeds aangemelde paren (bijvoorbeeld door verergering van de ziekte, transplantatie buiten het programma om, etc). Deze dynamische context heeft implicaties voor de optimaliteits- en rechtvaardigheidscondities van optimale oplossingen.

In Hoofdstuk 4 hebben we ook gekeken naar de effecten van het veranderen van de tijd tussen allocatiebeslissingen. We ontdekten dat het belangrijk is om niet teveel tijd tussen beslissingen te laten zodat patiënten niet onnodig hoeven wachten, maar ook om voldoende tijd tussen beslissingen te laten zodat er zich voldoende ruilmogelijkheden voordoen. In het Nederlandse programma treft een drie-maandelijkse allocatiebeslissing hierin een goede balans.

In Hoofdstuk 7 hebben we in het bijzonder gekeken naar mogelijkheden om rekening te houden met de kans op het falen van een voorgestelde ruil, bijvoorbeeld door het op het laatste moment terugtrekken van een patiënt of donor of door het falen van een medische test ter controle van de compatibiliteit tussen donor en ontvanger. Wij hebben verschillende manieren voorgesteld om te reageren op een falende ruil, afhankelijk van de gewenste flexibiliteit. Het beschermen tegen marktfalen kan vooral belangrijk zijn voor de meest moeilijk-te-matchen patiënten.

Het aloude gezegde “van ruilen komt huilen” hoeft niet op te gaan voor het ruilen van nieren binnen het nieruitwisselingsprogramma. Integendeel, het programma biedt deelnemers de kans om te overleven in betere gezondheid. Dat brengt belangrijke optimaliseringsvraagstukken met zich mee. Ten eerste om te zorgen dat het maximaal aantal patiënten geholpen wordt, ten tweede om er voor te zorgen dat dit rechtvaardig, of zelfs zo rechtvaardig mogelijk gebeurt. Dankzij recente ontwikkelingen op het gebied van operations research zoals gepresenteerd in dit proefschrift blijven deze optimaliseringsvraagstukken praktisch oplosbaar, nu en in de toekomst als nieruitwisselingsprogramma’s verder groeien. Zo draagt operations research bij aan de kwaliteit en het behoud van leven van een groeiende populatie van patiënten.

About the author

Kristiaan Glorie (1987) holds a cum laude bachelor's and cum laude master's degree in Econometrics and Management Science from Erasmus University Rotterdam. In 2010 he started his PhD research at the Econometric Institute in the Erasmus School of Economics. Kristiaan has served as the PhD representative to the board of the Dutch network on the Mathematics of Operations Research (2011 and 2012) and, in the summer of 2013, he has been a visiting researcher at the MIT Sloan School of Management.

Kristiaan's research interests are at the intersection of Operations Research and Mechanism Design. He is particularly interested in the theory and application of combinatorial optimization problems involving uncertainty and human interaction. In addition to the research presented in this thesis, he has collaborated with other researchers to investigate route planning of unmanned aerial vehicles, management of sterile inventory, and house allocation mechanisms.

Kristiaan has published in several of the leading journals in his field, including *Manufacturing & Service Operations Management*, *Computers & Operations Research*, *Transplantation*, and *Transplant International*. He has presented his research at various international conferences, including IFORS, MATCH-UP, INFORMS Healthcare, and OR2013, as well as the national conferences of the Dutch transplant foundation and the Dutch network on the Mathematics of Operations Research. For the third chapter of this thesis, he has been awarded the second price in the 2013 Student Research Paper Contest in the Healthcare Applications Section of INFORMS.

After having finished his PhD trajectory, Kristiaan will start as an assistant professor in combinatorial optimization at the Department of Mathematics at the VU University Amsterdam. He will continue to work on combinatorial optimization problems and to apply his research in practice.

Kristiaan is married and is the father of a daughter.

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Design & layout: B&T Ontwerp en advies (www.b-en-t.nl) Print: Haveka (www.haveka.nl)

CLEARING BARTER EXCHANGE MARKETS

KIDNEY EXCHANGE AND BEYOND

Advanced computer assisted markets, otherwise known as smart markets, are becoming an important part of our modern society. This dissertation considers smart barter exchange markets, which enable people to trade a wide range of goods: from shifts, to houses, to kidneys. Centralized and computerized clearing is what makes these markets 'smart'. The market clearing problem is to match demand and supply so as to maximize the gains of trade. Trades, in this regard, need not be limited to pairwise swaps but may consist of trading cycles and chains involving multiple agents.

This dissertation presents several sophisticated market clearing algorithms that enable optimal clearing in large real-life barter exchange markets. With a particular focus on kidney exchanges, it shows how these algorithms can enable a significant alleviation of the present shortage of kidney donors and an improvement in health outcomes for kidney patients. State-of-the-art techniques are developed to allow the algorithms to be scalable, even when there are bounds on the number of simultaneous transactions, multiple objective criteria, and side constraints. Furthermore, innovative models and solution approaches are presented to allow market uncertainty, such as transaction failure, to be taken into account.

The research presented in this dissertation contributes to the advancement of scientific knowledge in combinatorial optimization and market design, particularly in the domains of mathematical programming and market clearing, and aids the establishment and operation of smart barter exchange markets in the field of kidney exchange and beyond.

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