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Optimizing Kidney Transplantations: A Social Welfare Problem

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Contents

1 Abstract

In a perfect world, for any individual with End Stage Renal Disease there would be a perfectly functioning, compatible kidney ready to be transplanted. Obviously this is not the case for the vast majority of the population: as they apply for a kidney from a cadaveric donor, they wait for years before getting one; many resort to hemodialysis, which is only intended to be a temporary solution as it does not restore kidney functionality; the main cause of the streamlining of the waiting list pool is not the implementation of transplants: it is the deterioration of the medical condition of the candidates who become unsuitable for the surgery, and sometimes even their death. In this scenario, living donors come into play, and, although the shortage of graft remains an issue, from these altruistic gestures many lives are saved.

It becomes clear how kidney transplants are not exclusively about the quality of the National Health Service or the ability if the surgeons: it is both a social welfare and a market design problem. The approaches that are going to be presented in this work are tested and used algorithms that rely on notions from graph theory mechanism design: the ultimate goal is maximizing the number of transplants that can be carried out among the participants in the market, while ensuring quality of the grafts. Recurrent characteristics of these algorithms are strategy-proofness, i.e. individuals have incentives to join the market and declare their truthful preferences over the set of alternatives, and rationality. Particular attention will be put on the Italian case, through an analysis of the general and regulatory framework for Kidney exchanges, as well as of the main accomplishments reached since the 2005.

Three are the requirements that need to be accounted for, in market design: thickness, ensuring a wide range of possibilities and providing incentives to prospect applicants; absence of congestion, granting the candidates enough time to process and manage the transactions; safety, in joining the programs and disclose information. Nevertheless, the procedures in use are not exempt from critiques, mostly concerning ethical issues that will be explained extensively.

Given these premises, it is important to aknowledge the economist Alvin E. Roth, Nobel Prize laureate (2012), who, by applying game theory and market design to the

Kidney exchange problem, proposed many approaches to it (TTCC and pairwise exchange [1] [2]) and served as a reference in all subsequent works.

2 Introduction

According to a study conducted by the Italian Society of Nephrology, in 2018, 7% of the country's population suffers from Chronic Kidney Disease. Although not always life-threatening, it still is a concerning condition, as it is the forerunner of a much more serious one, referred to as End Stage Renal Disease (ESRD) and, thus, the complete failure of the organ. At this stage, patients are left with two options: on the one hand, dialysis, a medical treatment replacing kidney functionality; on the other hand, kidney transplantation, either from deceased or living donor, allowing recipients to recover and conduct a normal life. Both options have downsides: dialysis is extremely costly and puts many limitations in the everyday life; moreover, life expectancy is lower than in case of transplant; in order to carry out a transplant, instead, patients are required to enter the waiting list and wait for a period of time, averaging the 3 years, in order to find a compatible donor.

This waiting time is mainly due to the unavailability of sufficient cadaveric kidneys: as supply does not manage to keep up with demand and the gap keeps on widening, the urge of finding alternative solutions arises. One of the few available options would be to find a compatible living donor, genetically or emotionally related, with whom to conduct the operation. Until recently, all donors who were deemed incompatible with their elected recipient were excluded from the program, resulting in the loss of many potential viable organs: according to a study conducted by the University of Chicago, 10-20% of all donations cannot take place due to AB0-incompatibility, and another 15% donors are excluded becase of positive crossmatch (i.e. the recipient developed antibodies against some of the donor's antigens). Different approaches have been proposed over the years, with the intent of maximizing the number of viable pairings through the implementation of donation from living and deceased donor.

2.1 Criteria for compatibility

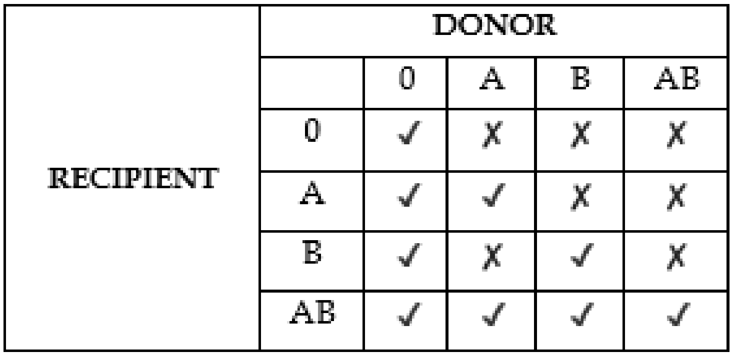
As incompatibility plays a crucial role in the allocation of kidneys, it is important to define what are the factors determining the feasibility of a matching. There are two such factors, that are:

1. **Blood AB0-type**: as in blood transfusion, blood-type compatibility is a funda-

mental requirement for the success of the transplant; blood type depends on the presence of two agglutinogens, i.e. antigens, on the surface of red blood cells: the presence of the A angglutinogen corresponds to type A; presence of the B determines the type B; the presence of both is typical of the type AB and their absence denotes the type 0. The introduction of any tissue from a donor whose blood type is incompatible with that of the recipient, immediately results in its rejection.

2. **Human Leukocyte Antigen (HLA) type**: HLA antigens are inherited in a random way; they are *allo*antigens, meaning that they are responsible of identifying and destroing non-self cells: this implies that major mismatches in the transplanted tissue are detected by the recipient's immune system and result in graft rejection. HLA type is determined by the combination of 6 proteins, 2 of type A, 2 of type B and 2 of type DR; compatibility can be measured in terms of mismatches in this protein structure and ranges from 0 to 6. In general, the more similar the type (i.e. the fewer the mismatches), the higher the chances of graft survival.

Another element to be consider prior to the operation, is the **degree of sensitization** of the patient, i.e. the presence of preformed antibodies to the HLA, that act as an immunological barrier. High degrees of sensitization (PRA> 80%) is associated with graft dysfunction, transplant rejection and poor survival rate. It has to be noted that sensitization can happen before (it can be developed as a consequence of blood transfusion, pregnancy etc.) but also after the transplant: it has been estimated that around 30% of the candidates for kidney transplant are pre-sensitized, while the insurgence of post-transplant sensitization would concern 20% of the recipients [3].



		DONOR			
		0	A	B	AB
RECIPIENT	0	✓	✗	✗	✗
	A	✓	✓	✗	✗
	B	✓	✗	✓	✗
	AB	✓	✓	✓	✓

Figure 1: AB0-type compatibility

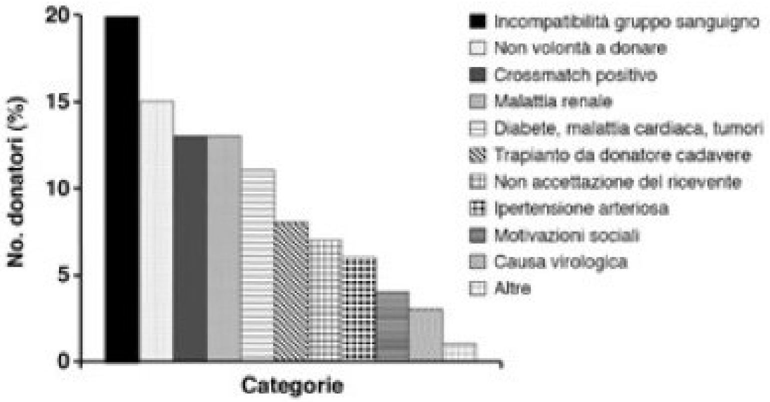


Figure 2: Causes for incompatibility;
source: Il trapianto di rene da donatore vivente: la modalità cross-over; Barsotti et al.; url: http://www.nephromeet.com/web/eventi/GIN/dl/storico/2009/4/488-498.pdf

3 Kidney transplant in Italy

3.1 The Italian framework

In Italy, the first kidney transplant, which was the first organ transplant ever to be finalized in the country, took place in 1966, as a kidney from an adult woman was implanted in a 17 year old girl. Over the years, as scientific progress allows to obtain ever more successful results and increased life expectancy, this practice have become more widespread, with 42 authorized centres spread across 16 regions. During the last 30 years, an interesting trend has been the gradual aging in both donors (30% of donors are reported to be over 70 y.o.) and recipients (transplant on patients over 75 y.o. is quite common). This trend underlined the necessity of finding methods for the optimization of the use of the "older" transplants (eg. dual kidney transplantation on a unique patient (1996), in order to compensate for the possible damages) and the design of suitable immunosuppressive therapies for the elderly. The donation from living donor became common practice starting from the 2000s [24].

From the latest CNT report [23], in 2018, **2.117 kidney transplant were conducted**, out of which 1.831 from deceased donor and the remaining (287) from living donor: this is the second highest result since 1992, after the 2017 peak. Although this number is slowly but steadily declining (-2.1% compared to 2017), the data concerning the waiting list are still alarming: by the end of 2018, **6.545 patients are waiting to be awarded an organ** and the average waiting time is 3.3 years. A positive note is the increase (+76.15%) in the number of the statement of intent for organ donation, that, by the end of 2018 were almost 4.5 million.

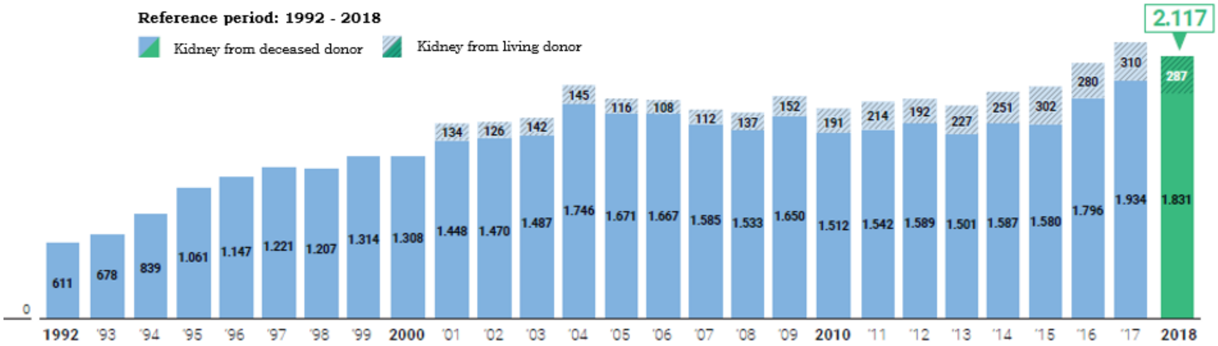


Figure 3: Data concerning kidney transplantation in Italy (1992 - 2018); *source: [23]*

3.2 Some milestones in kidney transplantation from living donors

The implementation of alternative algorithms for the allocation of organs, starting from a living donation, provided very positive results. Here are some of the most remarkable episodes of the latest years:

- 2005: first kidney transplant in cross-over mode (Centro Trapianti di Pisa);
- 2006: activation of the National cross-over program;
- 2015: first chain started from a Samaritan donation: five incompatible couples managed to effectuate a cross-over kidney transplant [31]; as of today, in Italy, there was a total of 8 Samaritan donations, starting chains of transplant involving 19 donor-recipient pairs;
- 2018: first international cross-over involving an Italian and a Spanish couple, made possible by the implementation of the South Alliance Transplant (SAT)[1]. [25];

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[1] Signed in 2012, this agreement brings together four countries, Italy, France and Spain, for the im-

- 2019: first cross-over among three couples in the same center (Azienda Ospedaliero-universitaria Careggi, Firenze); [26].

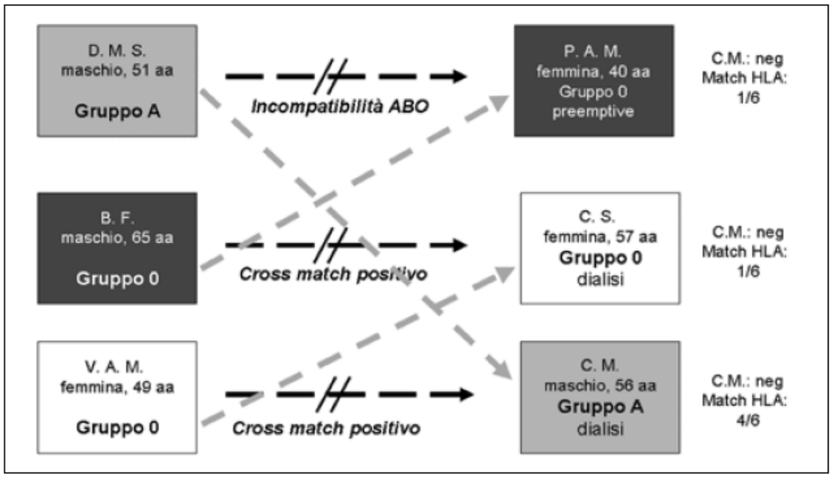

Figure 4: 2005 cross-over operation in Pisa; *source: Il trapianto di rene da donatore vivente: la modalità cross-over; Barsotti et al.; url: http://www.nephromeet.com/web/eventi/GIN/dl/storico/2009/4/488-498.pdf*

3.3 Allocation criteria

Operating CNT states that each transplantation center should provide a Charter of Services, containing the application requirements and the criteria for the priority of the patients on the waiting list. Although there is the intention of creating a unique set of rules to be adopted at a national level, individual centers are still connected to their own regulations.
Differences across transplantation centers mainly concern the weights attributed to the variables used for the scope of allocating the organ.
We here refer to the Charter provider by the A.O. of Perugia [27].

A distinction is made between *benefit* and *justice* criteria, that will both play a role in the decision-making process: the former favours the assignment of the graft to the

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plementation of cross-border kidney exchanges and sharing of common knowledge; the 14 hospitals and transplant centres participating to the program must comply with some common requirements and are subject to the same evaluation criteria;

recipients with the highest chances of success; the latter safeguards the rights of the patients that have spent the longest time in the waiting list, in response to their most probable medical decline and compatibility issues. A point system is then developed, in order to create a ranking among the candidates: some of these prioritization criteria will be useful in some of the models - in particular for the paired exchange mechanism proposed by Roth et al. [2] - that will be later analysed.
Benefit criteria take into account:

1. **Blood type**:
   - points awarded for incompatible pairs will be -1;
   - compatible (but different type) pairs have +1;
   - same type pairs are awarded +10 points.

Table 1: Blood type matches score

		DONOR			
		0	**A**	**B**	**AB**
RECIPIENT	**0**	10	-1	-1	-1
	A	1	10	-1	-1
	B	1	-1	10	-1
	AB	1	1	1	10

2. **HLA mismatch**: In the first stage, only 5/6 and 6/6 HLA matches are considered for eligibility; in case of no Full-House compatibility, the minimum requirement is that there is at least one DR-type antigen match.

Table 2: HLA mismatches score

		ANTIGEN TYPE		
		A	**B**	**DR**
MISMATCHES	**0**	10	20	30
	1	5	15	25
	2	0	0	0
	MAX	10	20	30

3. **Age**: Generally, the donor-recipient age difference shall not exceed 25 years; to reduce the disadvantage for the younger candidates, some revisions can be made: if

the patient is under 60 year old, older candidates undergo the 25-year-gap, while all younger candidates are considered eligible.

Justice criteria are instead:

1. **Anti-HLA Antibodies**: in other words, the aforementioned degree of sensitization, which is measures through the Panel-reactive Antibodies (PRA) test; highy-sensitized patients are harder to match, thus, in order to homogenize the list of candidates, they are assigned with some points:

Table 3: PRA score

PRA	SCORE
80-100%	20
60-79%	15
40-59%	10
20-39%	5
0-19%	0

2. **Waiting list seniority and years of dialysis**: Due to the clinical decline of the patients, for every month spent in the waiting list, they are assigned 0.1 points. Moreover, for every month of dialysis exceeding the waiting time they are awarded other 0.1 points.

In this dynamic model, the candidate with the overall highest score will then be assigned the kidney that has become available.

4 Introducing living donors: some solutions for incompatibility

Accepting donations from living donors has some evident benefits: first of all, the organ is well-functioning, which is not always the case with cadaveric kidneys, that may have been damaged by the same cause of death; this increases the possibilities of success and the rate of survival of both the graft and the recipient; secondly, this type of donation allows

the patient to receive the organ with virtually no delay and without depleting the pool of organs reserved for the waiting list candidates. The compatibility makes it impossible in a large number of situations to carry out the transplant due to the genetic factors and the recipient's conditions that have previously been discussed.
As a result, many different algorithms have been proposed in order to deal with this issue:

- **Top Trading Cycles and Chains (TTCC)**: is a mechanism proposed by Alvin E. Roth et al. in 2004 and is aimed at the definition of a directed graph for the allocation of kidneys from living donors; the participants to the program are the patients in need and their available donors; the couples can either be compatible or incompatible and the process could potentially increase the number and the quality of matches. It is, in fact, proven to return an allocation that lies in the core; the core is a concept from game theory: it represents one class of solutions for cooperative games; in particular, the fact that the allocation deriving from the TTCC mechanism lies in the core implies that the outcome that each participant could gain from joining the program is always at least as preferable as the one they would gain through smaller coalitions. TTCC therefore addresses the issue of individual satisfaction and provides incentives to participate.

  Moreover, the mechanism also makes it optimal for individuals to reveal their own preferences: this property, known as strategy-proofness, and the concept of core will be discussed throughout section 5.
  The main issue with this mechanism is its lack of practicality. Dealing with long chains proves to be challenging, primarily for two reasons: the presence of legislations, both in the U.S. [2], where the algorithm was initially proposed, and in Italy [3], forbidding the underwriting of a contract or any expression of consideration on organ donations; the requirements for carrying out multiple operations simultaneously, since every pair requires two surgeons, two operating rooms and so on. Simultaneity is necessary since, in absence of a contract, the couple who already underwent the surgery may reconsider its position about donation and interrupt the process.

- **Indirect exchange**: this method, also called *list exchange*, can be developed from

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[2] National Organ Transplant Act (1984) explicitly states: "It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human organ for valuable consideration for use in human transplantation if the transfer affects interstate commerce."

[3] Legge 1 aprile 1999 n. 91; Legge 11 dicembre 2016, n. 236

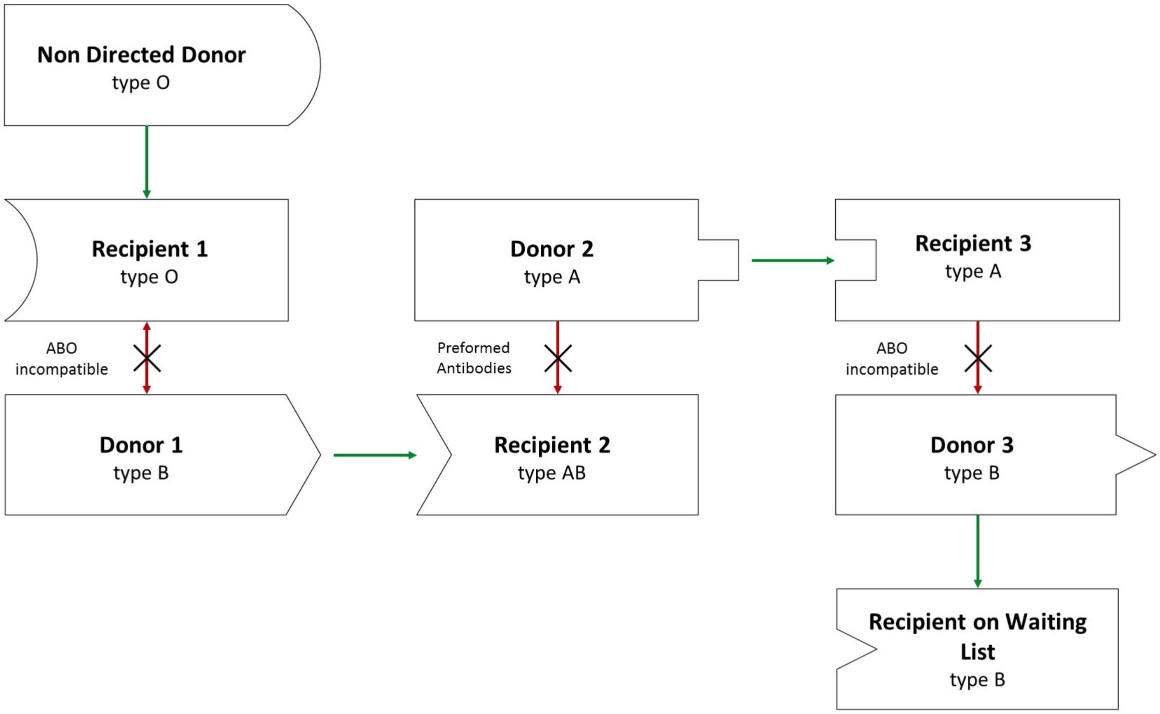

Figure 5: Model for a chain algorithm with the waiting list (W) option;
source: Presentation by Salvioli, M. and Lucchetti, R.

the TTC; in this algorithm, individuals, incompatible with their own donor and having preferences over the set of available donors, may not partake a cycle and end up in a w-chain. The w-chain is a subset of the directed graph in which the last member (head of the chain) points towards the waiting list; this implies that their donor will leave its kidney to another patient, while his elected patient will instead receive the priority in the waiting list; this mechanism is deemed as unethical, as the prioritization system damages those who, due to incompatibility issues (for example, type 0 patients, who are only compatible with same type tissues), have been candidates in the list for longer. Thus, this approach will not be further analysed in this paper;

- **Paired exchange**: is a mechanism proposed by Felix Rapaport, former director of the Transplantation Service at the State University of New York, in 1986, with the aim of increasing the number of performed kidney transplants across incompatible

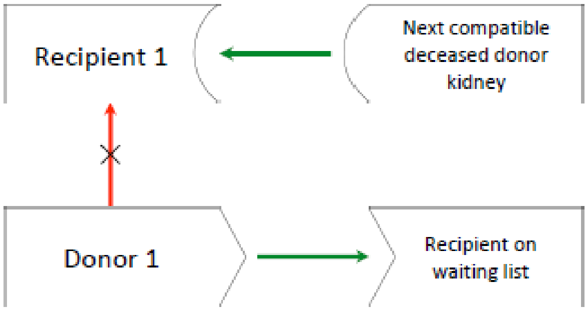

Figure 6: Model for the indirect exchange; patients exchange their incompatible donor for a priority in the waiting list
source: [6]

couples of donor and patient that can benefit from another couple's donation; the first KPD (i.e. Kidney Paired Donation) program was implemented in South Korea starting from 1991. The practice started spreading in Western countries starting from the late '90s: in the following sections, we will comment on the milestones made possible by the impementation of this algorithm. This approach has been reviewed by Roth in his pairwise kidney exchange. The development of such algorithm is based on two assumptions:

1. exchanges only concern pairs, i.e. two sets of patients and donors [4];
2. patients are indifferent among the compatible kidneys (based on the empirical evidence from studies[5] conducted in the U.S. concerning the similarity, in terms of graft survival probabilities, of all compatible organs; as remarked throughout the paper, this assumption is arguable as there is evidence of the contrary being true;

Considered as "ethical", the development of a theory systematically allocating compatible organs to incompatible pairs was developed with two types of strategy-proof approaches: a deterministic mechanism, which uses priority criteria similar to those

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[4] Although this is a limitation, as the number of exchanges that could be achieved from two pairs is lower than that obtainable from larger groups, the implementation of such a systematic mechanism could significantly increase the number of transplantation: Roth et al. analysed statistical data and assessed that, were pairwise exchange to be applied, live organ donations could increase by the 54% up to the 75% [2]

[5] Gjertson and Cecka (2000), Delmonico (2004)

currently used for cadaveric kidney allocation and, thus, may be easily adopted by transplant organization; a stochastic (egalitarian) mechanism, that, appealing to criteria of distributive justice, grants similar odds of getting a viable organ to all participant patients.

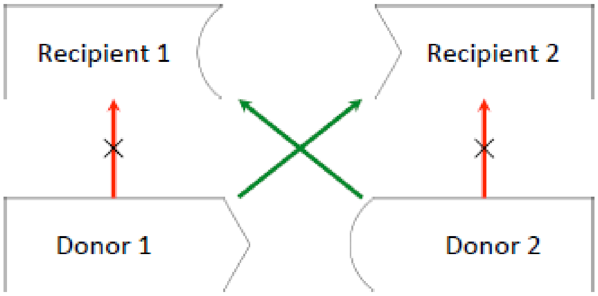

Figure 7: Model for the paired exchange; each recipient exchanges his own incompatible donor for the other pair's;
source: [6]

5 Top Trading Cycles and Chains

5.1 Developments of the original TTC mechanism

The idea of Top Trading Cycle was initially proposed by Nathan Gale, who developed an algorithm that allowed to allocate indivisible goods - houses, in literature -, among the agents, without using any means of payment. Later formalized by Shapley and Scarf (1974), this model will be referred to as the "Housing allocation problem". This kind of market shares some clear similarities with the one described for kidney exchange and can be used to maximize the number of donor-recipient couples that can be formed.
A Housing market consists of:

- a set of n agents
- a set of n indivisible objects (houses)
- a preference profile for each agent over the set of houses

Agents point to their first preference, while each house points to its owner. In the directed graph that is formed, all cycles are removed and the allocation of the house is carried out. The process is repeated until the market is cleared, i.e. until all houses are assigned to an agent.

The algorithm allows for an allocation that:

- is in the **core** of a suitable game associated to the problem (Shapley and Scarf, 1974) [6] : there is no coalition of agents that, through trading among theselves, is able to reach a more preferable outcome; in fact, they cannot possibly obtain houses that have already been allocated in previous cycles, as they are removed from the market; as every core allocation, it is individually rational and Pareto efficient;
- is the **unique** allocation in the core, under strict preferences (Roth and Postlewaite, 1977): supposing that the allocation were not to be the only one in the core, one would have to be more preferable to some players than the other; these players could avoid the least fortunate pairing through a coalition with members in the same cycle;
- is **truthful** (Roth, 1982): for any agent, declaring the true valuations is a dominant strategy.

A development of this algorithm is proposed by Abdulkadiroğlu and Sömnez (1999), who proposed two versions of a model for housing allocation in college campuses: *random-serial dictatorship with squatting rights* (RSD-SR) and *you request my house - I get your turn* (YRMY-IGYT). [9] [10]

The difference compared to the previous model is that some of the students are already owners of a house (and may be willing to switch), some others, freshmen, do not have any, and some houses are empty and ready to be assigned. So, in the kidney-transplant model, it would mean that some patients have a living donor, some do not and are on the waiting list, and some cadaveric organs are available for transplantation. In the model,

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[6] Shapley and Scarf, 1974: The allocation x produced by the top trading cycle algorithm is in the core. Proof: Supposing that no agent from cycles $C_1 ... C_j$ can be in a dominating coalition; then, if a is in cycle C_{j+1}, the only way to be better off through an allocation $y \succeq x$ would be by receiving a house assigned to a player b in the preceding cycles; but, by assumption, y cannot dominate x through a coalition containing b.

just like in the regular housing allocation, there are some strict preferences on the pool of goods (in the kidney model, preferences would be guided by the odds of success of the transplant), and players in the first round will be pointing to their first choice.
The RSD-SR is flawed: it is modeled in such a way that it provides no incentive for current tenants to enter the lottey, since the house they are assigned may be less-preferable than the one they would be giving up. We will therefore focus only on the second variant.

YRMH-IGYT gives priority on the choosing process to any existing tenant whose house is requested by some other player, so that he is *at least as satisfied* as he would have been prior to the operation, and bears some evident resemblence with the indirect exchange system. This is how it works:

1. students report their preferences over the houses;
2. a random order is picked;
3. following the order, students point and are assigned to their preferred house: if the house is empty, the process goes on; if the house previously belonged to an existing tenant, the latter receives priority right over the remaining houses, including his own;

From this process, some cycles will be created: students will be assigned to the house they are pointing to and the process will be repeated until the market is cleared.

5.2 Application to the Kidney Exchange problem

The application of the TTC to the kidney exchange problem was originally proposed by A. Roth, T. Sömnez and M. U. Ünver in 2004 [1]. Although deemed unfeasible due to practical reasons (operations would have to take place simultaneously, as U.S. legislation forbids the formulation of a contract over organ donations), it is nonetheless an interesting mechanism using the concept of chains and cycles for the maximization of the number of possible transplants. The improvement in welfare would not only concern the patients with a willing live donor, who would be directly involved in the program, but also those in the waiting list: in some cases it is also possible for one kidney from a living donor to be transplanted to one candidate from the list, as in the case of the indirect exchange.
One major difference between the dormitory and the kidney allocation problem is that

the first one is a static scenario, in which all houses - occupied or vacant - can be allocated among the participants, while in the other case that is not true: not all organs can be awarded at the same time and their availability constantly changes; this means that, in case one patient was left without donor, he can stay in the waiting list for a cadaveric kidney. It becomes important, for the scope of the analysis, to consider a given moment in time with given characteristics.
Within this framework, there will be:

- a set of donor-patient couples $\{(D_1, P_1), ..., (D_n, P_n)\}$
- a set of donors compatible with patient P_i: $D_i \subset D = \{d_1, ..., d_n\}$
- a strong preference relation R_i over $D_i \cup \{d_i, w\}$
  (d_i does not necessarily belong to D_i; w is the waiting list)

By the end of the process, each patient will be assigned either to a donor or to the waiting list. It should also be noted that no kidney can be assigned to more than one patient.
The implementation follows the same logic of the house allocation: each patient points to the most desirable donor (or, eventually, to the waiting list), each donor points to its designated patient, forming a directed graph. At the end of each round, cycles may form and they shall be eliminated by the graph.

Definition 5.1 *(**Directed Graph**) A directed graph, also called digraph, is an ordered pair $G = (V, A)$ in which the edges have a direction; the elements in the set V are called vertices; A is a set of ordered pairs of vertices called arrows, connecting one vertex to another.*

Definition 5.2 *(**Cycle**) A cycle is an ordered list of donors and patients $\{d'_1, p'_1, ..., d'_m, p'_m\}$ such that: d'_1 is matched to p'_2, d'_2 is matched to p'_3 and so on, and d'_m is matched to p'_1; cycles are unique, since each donor can point to one patient and each patient to one donor.*

Also chains can be formed: chains trigger the indirect exchange mechanism, as the last donor's organ will be devoted to the pool of candidates in the waiting list.

Definition 5.3 *(**Chain**) A chain is an ordered list of donors and patients $\{d'_1, p'_1, ..., d'_m, p'_m\}$ such that: d'_1 is matched to p'_2, d'_2 is matched to p'_3 and so on, and d'_m points to the waiting* *list; chains are not unique, so we draw a distinction with maximal chains, which are the longest sequences (no other agent can be added). Moreover, there can be multiple maximal chains, so in the allocation process some chain selection rules shall be taken into account, such as priority of the patient, geographical closeness etc.*

From a comparison with the mechanisms currently implemented for the kidney allocation problem, there are mainly four points in favour of the TTCC:

1. TTCC allows any donor-patient couples to benefit from trade: couples that are incompatible can obtain a viable organ, couples that are already compatible can find better matches;

2. compared to existing exchange programs, TTCC allows more than two couples to participate, thus minimizing the loss of potential donors and allowing for the possibility of obtaining superior matches;

3. compared to indirect exchange programs, which tend to select the minimal chain and benefit incompatible couples through prioritization in the waiting list, TTCC mechanism allows all couples to benefit from the incompatible couples;

4. compared to indirect exchange programs, TTCC does not harm type-0 patients in the waiting list.
   Type-0 kidneys are extremely rare: while they are compatible with all blood types patients, they represent the only viable option for 0-patients. It has been argued that prioritizing patients with a living donor patient would imply a decrease in the availability of this type of kidneys - as they would be compatible with any applicant - and an increase in the time spent by type-0 patients in the waiting list. This is not true: as supported by Roth in [1], TTCC does not deplete the pool of available type-0 kidneys and, instead, could potentially enlarge it.

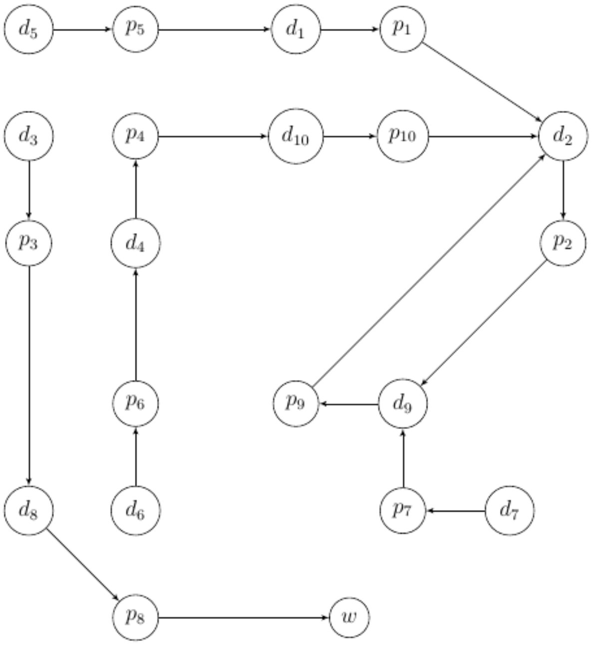
In the following example, the original approach by A. Roth was adopted: as in the house allocation case, donors point to their patient, patients point to the most compatible (and, thus, preferred) donor.

Example 5.1 *Let us imagine a framework with 10 patient-donor couples having the preference relations described in figure 8:*

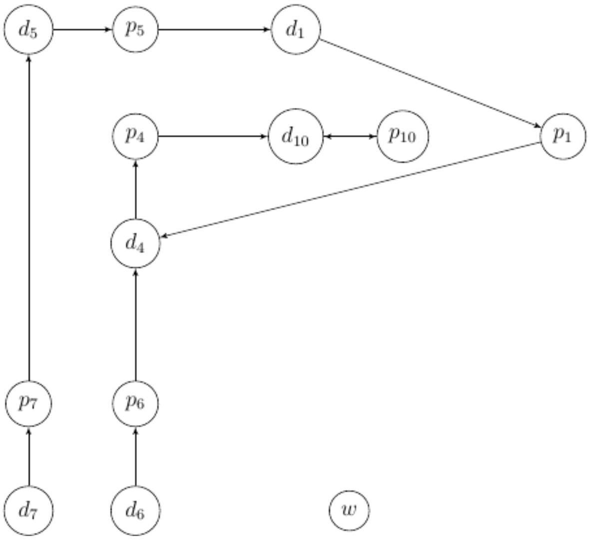
	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10
Preference relations	2	9	8	10	1	4	9	w	2	2
	4	2	9	w	7	6	5		9	10
	w		w		6	w	w		w	w
					w					

Figure 8: Example 5.1: Preference relations

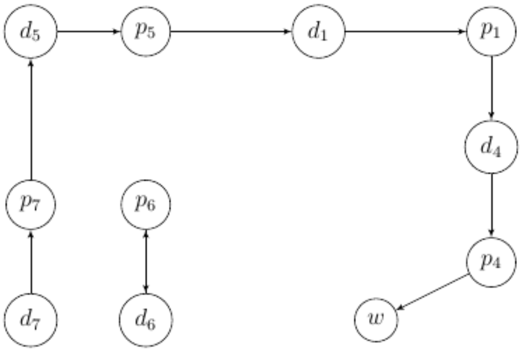
As we can see, patient p_8's first choice would be the waiting list: in this model we consider indirect exchange as a viable option, neglecting the ethical controversy connected to it; thus, by bringing a donor to the available pool, the patient is awarded a priority in the list, although entering it later than other candidates. From this list of preferences we obtain the following directed graph:



From a first observation, it will be possible to remove the cycle $\{d_2, p_2, d_9, p_9\}$ and the chain $\{d_3, p_3, d_8, p_8\}$. As a consequence of the removal of the cycle, p_1 and p_{10} - who were previously pointing to d_2 - and p_7 - who, instead, was pointing to d_9 - are forced to turn their attention to their second most preferable choices, respectively d_4, d_{10} and d_5. The *elimination of the chain bears no direct consequence on the graph; waitlist node w will not be eliminated;* p_3 *will be awarded the kidney from* d_8*, and the one from* d_3 *will be awarded to some candidate in the waitlist.*



As p_{10} *turns to* d_{10}*, the exchange between the couple will be carried out, leaving* p_4 *with his second option, i.e. the waitlist. We are left with two maximal chains:* $\{d_7, p_7, d_5, p_5, d_1, p_1, d_4, p_4\}$ *and* $\{d_6, p_6, d_4, p_4\}$*. Assuming the chain selection rule is the maximization of the length of the chain, the first chain will be implemented, resulting in a 4-couple exchange and* d_7*'s kidney to be left available for the waitlist.* p_6 *will then turn to its third preference, i.e.* d_6*, and the market will be cleared.*



6 Paired Exchange

6.1 Development of the Paired Exchange mechanism

Kidney Paired Donation mechanism was proposed by F. Rapaport in 1986: the rationale behind it was the possibility of maximizing transplants by creating successful matches, starting from the pool of donor-patient couples who applied for transplantation, but were ineligible due to AB0- or HLA-incompatibility. Although extremely simple, this allocation mechanism combines different fields (transplantation, graph theory and mechanism design) and has some interesting implications: as Roth, Sönmez and Ünver proved in their 2005 work [2], it is helpful for identifying viable matches and makes it a dominant strategy for all agents to reveal their own preferences (strategy-proofness). At the time of the writing, in the U.S. there existed no patient-donor specific list and no systematic algorithm for kidney allocation (nowadays, in Italy, such programs are present and the CNT is working towards expanding outside the national boundaries, allowing for cross-border operations; in the U.S., the Alliance for Paired Donation is operating in connecting transplantation centers in more than 27 States since 2006); moreover, the complexity of the logistics and the legal aspects, linked to the implementation of the TTCC mechanism proposed in their previous work, lead the three authors to the development of a different and more viable solution, involving only two couples at a time.

One major difference compared with the TTCC framework is the indifference of the patients between all compatible and between all incompatible kidneys; this leads to the preference relation:

$$\textit{compatible} \succ \textit{own} \succ \textit{incompatible}$$

Borrowing some concepts from graph theory, it is possible to build an undirected graph G, having as vertices the donor-patient; edges will connect only if there is a double coincidence of wants, i.e. if each patient can benefit from the other's available donor. Thus, the optimal solution for the problem would be the maximum-cardinality matching, i.e. one that maximizes the number of edges. It should be noted that the solution may not be unique; nevertheless, the solution to this cardinality matching problem will result in a unique matching number, $\nu(G)$, representing the number of pairwise exchanges resulting from the graph: this is a property inherent to the fact that the graph used in order to assess the matchings is a *matroid*.

6.2 Modeling the Pairwise Kidney Exchange Problem

Definition 6.1 *(**Pairwise Kidney Exchange Problem**) Let*

- $N = \{1, ..., n\}$ *be the set of patients having one or more incompatible donors;*
- $\succ_i$ *represent a strict preference;*
- $\sim_i$ *represent an indifference relation;*

A pairwise Kidney Exchange Problem is a pair $(N, \succsim_i)$*, where* $\succsim_i = (\succsim_i)_{i \in N}$ *denotes the patient preferences.*

From here, two patients i, j are said to be **mutually compatible** if and only if $i \succ_j j \cup j \succ_i i$: this is the required condition for a matching.

Definition 6.2 *(**Matching**) A matching* $\mu : N \rightarrow N$ *is a function such that:*

$$\mu(i) = j \iff \mu(j) = i, \forall i, j \in N$$

Moreover a matching is said to be individually rational if for any patient $i \in N$*,* $\mu(i) \neq i \Rightarrow \mu(i) \succ_i i$*. The set* M *includes all individually rational matchings for the problem* $(N, \succsim)$*.*

As only two-pair exchanges are accepted in this approach, it is possible to build a $|N| \times |N|$ matrix keeping track of all the possible matchings, keeping in mind that there could be multiple solutions to the maximum cardinality matching problem.

Definition 6.3 *(**Mutual Compatibility Matrix**) The mutual compatibility matrix is a symmetric,* $|N| \times |N|$ *matrix* $R = [r_{i,j}]_{i \in N, j \in N}$ *s.t.*

$$r_{i,j} = \begin{cases} 1 & \text{if } j \succ_i i \text{ and } i \succ_j j \\ 0 & \text{otherwise} \end{cases}$$

$$\forall i, j \in N.$$

This matrix will represent all the mutually compatible couples and will be of use in the handling of the ***reduced problem****; this problem is defined as a pair (V, R), with V being the set of vertices present in the network.*

Starting from such a matrix, it will be possible to analyse the problem recurring to the Undirected graph framework:

Definition 6.4 *(**Undirected Graph**) An undirected graph is a pair $G = (V, E)$, with V is a set of elements called vertices and E is a set of two-sets of vertices called edges or links.*

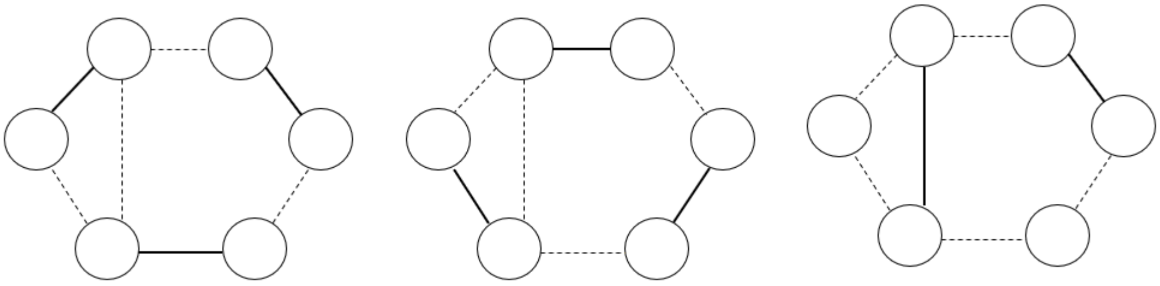
Definition 6.5 *(**Matching**, reformulation) Let (V, E) be a undirected graph, with the vertices V representing the incompatible donor-patient pairs; a matching M will be defined as a collection of edges, such that no vertex is covered more than once.*
Efficient matching are those maximising the number of edges in the graph: there cannot exist another matching $\eta \in N$ such that:

$$\eta(i) \succsim_i \mu(i) \forall i \in N$$

and

$$M_\eta \supset M_\mu$$

i.e. the set of patients matched by μ is maximal.
Denoting by ε the set of all Pareto-efficient matchings, then for any $\mu, \eta \in \varepsilon$, $|\mu| = |\eta|$.



(a) An efficient matching; $|\mu| = 3$

(b) An efficient matching; $|\mu| = 3$

(c) An inefficient matching; $|\mu| = 2$

Figure 9: For any Pareto-efficient matching, the number of matchings is maximal ($|\mu| = 3$)

6.3 Gallai-Edmonds Decomposition Lemma

First, let us define the concept of decomposition:

Definition 6.6 *(**Decomposition**) A decomposition of a graph G is a family $\mathcal{F}$ of edge-disjoint subgraphs such that the union of the edge sets of all components in the family $\mathcal{F}$ equals the edge set of the original graph:*

$$\bigcup_{F\in\mathcal{F}} = E(G)$$

or

$$E(F_1) \cup (...) \cup E(F_n) = E(G)$$

*If every graph in $\mathcal{F}$ is a cycle, then the decomposition is called a **cycle decomposition**; if instead all subgraphs are path, it will be called a **path decomposition**. Every simple graph can be reduced into a trivial path decomposition, as any edge, joining two vertices, is indeed a path.*

Starting from the previously characterized graph, it will be possible to identify the maximal matchings using the Gallai Edmonds Decomposition Lemma, which provides an important insight for the understanding of Pareto-efficient matchings.

Gallai and Edmonds provided a characterization of the maximum matchings by partitioning the nodes of the graph N- that, in our case, represented the incompatible donor-patient couples - in the following three cathegories:

1. *under-demanded* (N^u), if they are paired under certain Pareto-efficient matchings, but not under others:

$$N^u = \{i \in N : \exists \mu \in \epsilon s.t. \mu(i) = i\};$$

2. *over-demanded* (N^o), if they are matched at any Pareto-efficient matching but are mutually compatible with at least one under-demanded patient:

$$N^o = \{i \in N \setminus N^u : \exists j \in N^u s.t. r_{i,j} = 1\};$$

3. *perfectly matched* (N^p), if they are paired at any Pareto-efficient matching and are not mutually compatible with any under-demanded patient:

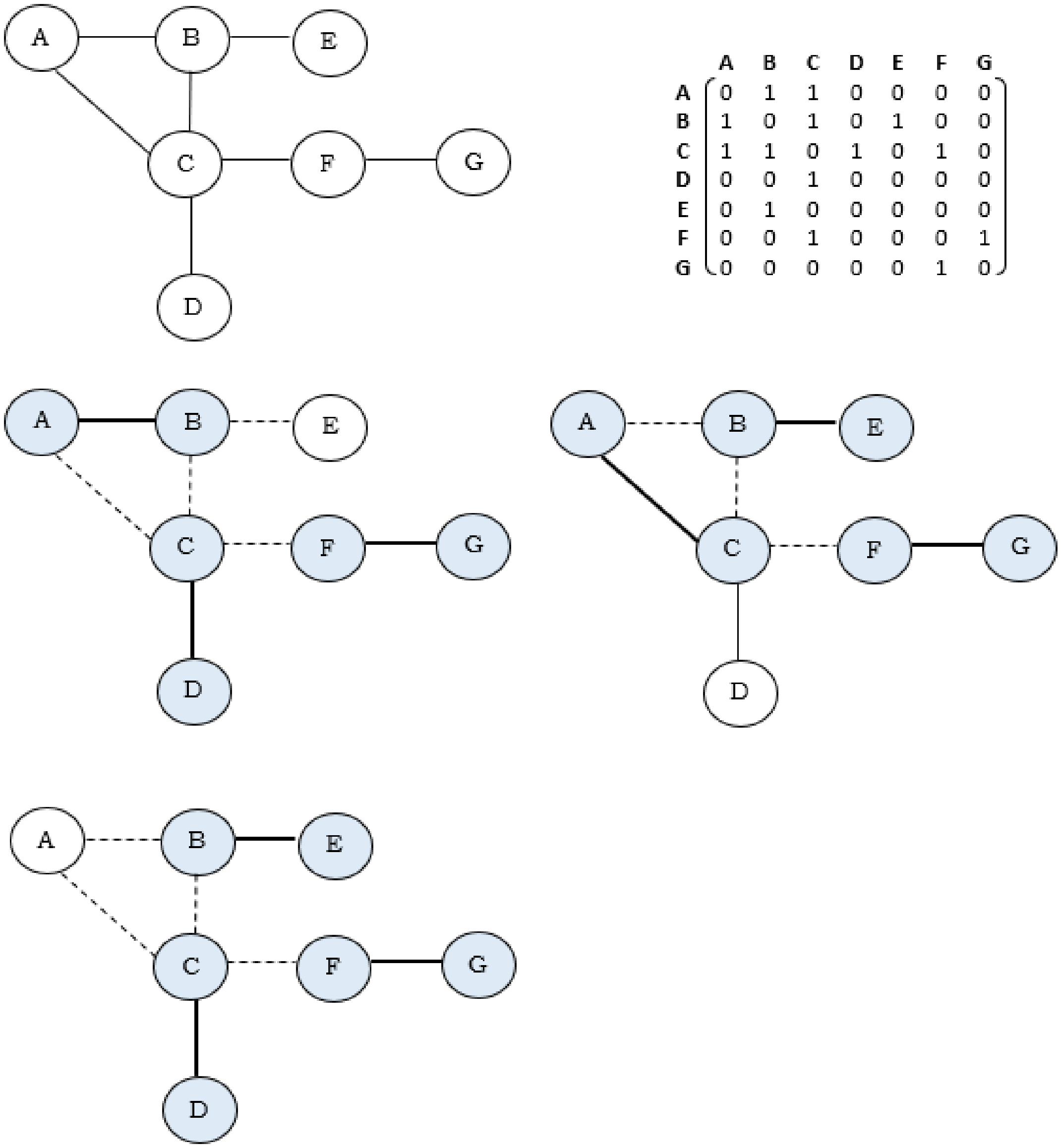
$$N^p = N \setminus (N^u \cup N^o).$$

According to the Gallai-Edmonds Decomposition theorem, every maximum matching of a network links:

- perfectly matched nodes to a perfectly matched node;
- over-demanded nodes to a under-demanded node.

Example 6.1 *Let us consider this* (N, R) *problem, with* $N = \{A, B, C, D, E, F, G\}$ *and* R *being represented by a 7x7 matrix;*
by any Pareto-efficient matching, with $|\mu| = 3$, *it is possible to notice that some nodes will be always included in the matchings, while some other will not; moreover, as predicted by the GED Lemma:*

- *node F is always paired with node G, as they are perfectly matched;*
- *the over-demanded nodes B and C are always connected to under-demanded elements (A and E)*



$$\begin{array}{c|ccccccc} & A & B & C & D & E & F & G \\ \hline A & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ B & 1 & 0 & 1 & 0 & 1 & 0 & 0 \\ C & 1 & 1 & 0 & 1 & 0 & 1 & 0 \\ D & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ E & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ F & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ G & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{array}$$

Figure 10: Example 5.1: This simple graph aims at providing an understanding of the GED Lemma and the deriving concept of over-demanded, under-demanded and perfectly matched.

The GED Lemma provides a further insight on the matching criteria: being all the over-demanded elements removed from the network, it is, in fact, possible to analyze partitioned **reduced subproblems** (I, R_I), with $I \subset V$ and $R = [r_{i,j}]_{i \in I, j \in I}$.
A reduced subproblem (I, R_I) is a component of (N, R) if there exist no edge connecting an patient $i \in I$ to a patient $j \in N \setminus I$. If the subproblem is a connected component - i.e. there exists a sequence of mutually compatible patients - and:

- $|I|$ is an even number, then the component is even and the all the patients will be perfectly matched;
- $|I|$ is an odd number the component is odd and there will be two possible outcomes:
    1. one under-demanded vertex is matched to an over-demanded one, while the remaining elements in the component (in an even number) will match be matched with each other;
    2. no element of the component will be matched with the over-demanded element; elements within the odd component will be matched but one will remain unmatched.

In this framework, some priority criteria would be introduced, in order for the exchange to be fair and maximize the welfare.

6.4 Priority Mechanisms

According to the points that have been brought forward in the previous section, in every Pareto-efficient matching, **all perfectly matched and all over-demanded donor-patient couples will find a match**.
What about the ones that are under-demanded?
After having analyzed it as a two-sided market [7], Roth et al. [2] propose two approaches:

1. deterministic mechanisms, based on the criteria currently adopted by hospitals and medical centres for the allocation of cadaveric kidneys;

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[7] they stress the differences between an induced two-sided matching market and a natural two-sided market: (1) while one side of the market is made out of over-demanded individual pairs of patients and their donors, the other is composed by a group of pairs, namely the members of the odd components; (2) the structure of the market is not defined exogenously, but on the basis of mutual compatibilities across patients, that are at the basis of the 0-1 preference relationships

these mechanisms account for some variables, such as the Anti-HLA Antibodies, waiting list seniority or years of dialysis, to establish a degree of urgency of the transplantation (ref. section 3.3); those patients who are deemed to be more urgent (i.e. to have a higher priority) will have higher possibilities of getting matched;

2. stochastic mechanisms, among which a particular focus is put on the egalitarian mechanism, based on the work [12] by Bogomolnaia and Moulin (2004).
   These approaches address the issue of equity in resource allocation problems with indivisibilities, relying on a lottery (λ), i.e. a probability distribution over the set of possible matchings; therefore, the expected utility from a lottery for any given patient ($u_i(\lambda)$) would be the probability of finding a match, and the utility profile would be defined as $u(\lambda) = (i_i(\lambda))_{i \in N}$.[4]

While the second method should provide all applicants with a equal possibility of being awarded a kidney, through the adoption of the first, a priority ordering will be generated; such an ordering will ensure the k^{th} patient to have the k^{th} priority.
The following part of the section will be dedicated to the analysis of the priority mechanism, as it is the one that is easier to implement in the current transplantation system. From [2] we obtain a definition of priority function:

Definition 6.7 *(**Priority function** It is defined as a priority function a non-negative function π that is increasing in priority (i.e. $\pi(i) \geq \pi(i+1)$).*

In other words, patients will be assigned a number, from 1 to n, with patient 1 being the one with the highest priority. Adding (or replacing a lower priority patient with) a higher priority patient automatically generates a preferred matching.

Definition 6.8 *(**Priority Matching**) A priority matching for a given problem (N, R) and an ordering $(1, ..., n)$ is one that:*

- *is maximal, with respect to the number of exchanges, and, thus, Pareto-efficient;*
- *always accounts for the level of priority.*

Priority mechanisms, implemented on matroids, are called **greedy**: they select, at every stage, the patient with the highest priority that solves the subproblem $max \sum_{i \in I} \pi(i)$. As only pairwise exchanges are considered, the optimization of each subproblem leads to the

optimal solution of the general problem (N, R).
Moreover, priority mechanisms are strategy-proof; since no patient has the possibility of accessing a better match by misrepresenting their preferences, the greedy algorithm provides incentives to:

- reveal all available donors:
  in case multiple donors were to be available, providing information on all of them allows the patient to gain more edges: having more connections would provide more probabilities of getting paired with another donor-patient couple;

- reveal all acceptable kidneys[8]:
  in many instances, proposed matches are rejected by surgeons and patients due to medical reasons; setting thresholds (such as limits on age difference, BMI, blood pressure) beforehand does not limit the chances of getting paired, as there exist multiple optimal solutions.

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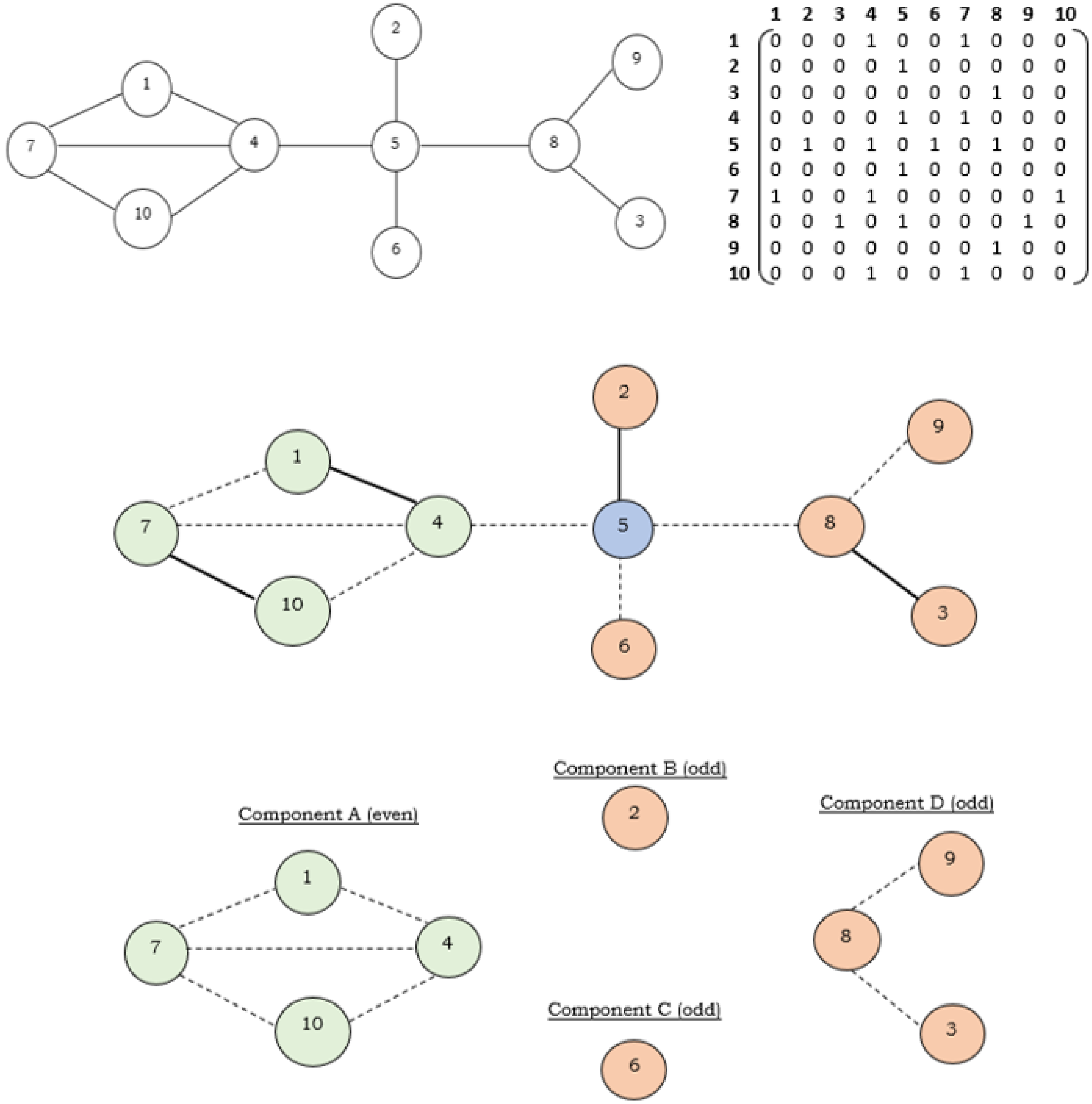
[8] as documented by Roth during the lecture held on Nov. 16th 2015 at the University of Berkeley, up to 2007 rejection rate was extremely high: as no rejection criterion was accounted for, only 15% of all matching offers were accepted by surgeons; they then moved to establishing, together with the surgeons, some thresholds on the donor physical condition, on all possible matchings; under this continuous optimization process, acceptance rates went up to 50% (as of 2015); source: Kidney Exchange: Algorithms and Incentives (url: `https://simons.berkeley.edu/talks/alvin-roth-2015-11-16`)



$$\begin{array}{c|cccccccccc} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\ \hline 1 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 2 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 4 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 \\ 5 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 0 \\ 6 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 7 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 8 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 9 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 10 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \end{array}$$

Figure 11: GED Lemma with priority constraints; while the even-component A is self-sufficient and all the nodes are perfectly matched, the over-demanded node 5 is conflicted among the odd-components B, C and D, which compete to be matched with 5.
Top priority is given to the component 2, the most "urgent"; 3 and 9 (in D) are in competition for being matched with 8: being $3 < 9$, 3 has the priority and will therefore receive the match.

7 Non-Simultaneous Extended Altruistic Donor

The Non-Simultaneous Extended Altruistic Donor (NEAD) is a mechanism made possible by the availability of one "free" donor; by altruistic, or "Samaritan" donor, we refer to a living donor offering his kidney to the community and not to a specific recipient, without any kind of remuneration or reciprocation.This kind of chains not only benefit the couples having a living donor available, but also the candidates for the cadaveric kidney waiting list: they, in fact, generally culminate with a living kidney being assigned to one of the applicants.

Although rare, as result from unconditional altruism, these gestures are not unprecedented: in the U.S., the first experimentation with NEAD dates back to July 2007 and allowed for the creation of a chain of 10 kidney transplants [13] [14]; in Italy, instead, the first donation took place in April 2015 and involved a chain of 6 donor-patient couples [30]; in total, there have already been eight cases, handled by the CNT. A more extended description of the cases will be reported in the following sections.

In Italy, these procedures are only applicable to the kidney exchanges and regulated by the rulings of the Italian National Committee for Bioethics (CNB) and the Italian National Institute of Health (ISS) [29]; although formally allowed by the law since 1967[9], the urge of formal regulation on this specific procedure was requested to the ISS in 2010, when three altruistic donors offered to donate their kidneys to the community.

On this issue, the CNB deemed the practice as:

> *"legitimate, as it is a supererogatory act, and as such ethically significant [...]; it does not involve higher risks, from a medical point of view, for the living donor, than those that can be found in other forms of ex vivo kidney removal"* [28].

In particular, it was also underlined how this transplant should not be considered as a substitute for those from deceased, blood- or emotionally-related living donors; additionally, it is required for it to comply with other fundamental criteria; namely:

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[9] Law No. 458, 26th of June 1967: "Kidney transplantation between living persons"; *"Notwithstanding the prohibition in Article 5 of the Civil Code, it is acceptable, without compensation, to offer a kidney for transplant purposes between living individuals. The exemption is allowed to parents, sons/daughters, adult twin or non-twin brothers/sisters of the patient, provided that the current law is respected. Only in the case the patient does not have the blood relatives mentioned in the previous paragraph or none of them is suitable or available, the exemption may be allowed also for other relatives or unrelated donors"*

- mutual anonimity, for the donor and the patient;
- full disclosure of the physical and psychological risks involved to the donor, prior to consent;
- involvement of a third party - thus independent from the Organ Transplant Centres, University Institutes, Hospitals in which the transplant will be conducted - in the assessment of the motivations as well as the clinical conditions of the donor;
- the recognition - as proposed in such instance - of the act of generosity through a prioritisation of the donor in the waiting list, shall they need a donation themselves;
- full respect of the guidelines provided by the CNB, in order to prevent illecit trades and compensations.

7.1 Practical Benefits from NEAD

The main advantage brought by the implementation of the NEAD, with respect to the more common paired exchanges, is the **non-simultaneity**. The introduction of an altruistic (or non-directed donor, as Roth defines it in [13]) relaxes the main assumption behind standard two- or three-way exchanges, that represented a limitation for the length of the chains: simultaneity means that, in order to execute n transplantations, $2n$ operating rooms and surgical teams are required, in order to prevent the couples entering the exchange from leaving the market as they receive the desired organ. This represents a big threat to the overall welfare.

Let us consider a two-way exchange, involving couple 1 and couple 2. Were couple 1 to abandon the market **after recipient 1 received the kidney** from donor 2, recipient 2 would be permanently damaged: it would be left without the compatible kidney from donor 1 and would be also deprived of its own, healthy donor, that would have been useful to enter future exchanges.

Starting an exchange from an altruistic donor defends the participants from such circumstance, by ensuring that each couple receives a kidney before giving away its own: ND-donor grants recipient 1 with the kidney; donor 1, then refuses to donate; although not receiving the elected, compatible kidney, recipient 2 still has donor 2 available and will be able to find another mutually compatible couple in future allocations.

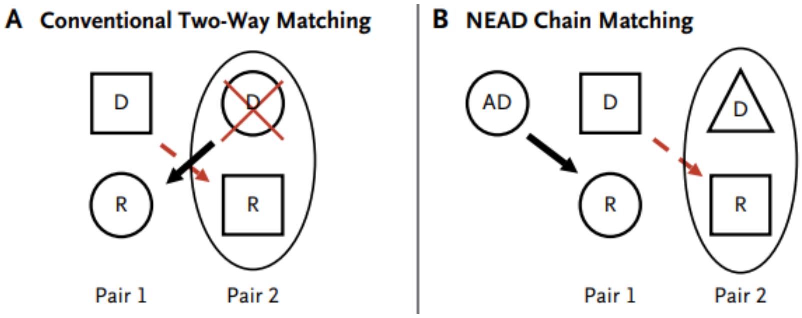

Figure 12: The impact of reneging in a two-way VS. a NEAD chain matching; source: [14]

When taking into consideration a more complex case, in which a whole chain is involved, the reneging of one of the parties could interrupt the ND-chain, but would not damage the exchange process: in the worst case scenario, an unfair behaviour hinders the donation of the final kidney to the waiting list applicants, thus the social benefits would only be shared among those contained in the Kidney-paired exchange pool.

It should be noted that, in the NEAD case, couples actually have a higher incentive to breach the agreement; however the social cost of that action would be far less onerous than in the two-way exchange. This leads Roth to state that, although risky, this approach is worth exploring as it bears some significant benefits, among which there is also the unlocking of longer chains, that allow for the inclusion of couples that would not have been otherwise reached (more specifically the highly sensitized patients, with a PRA[10]>80%;). That is the case, for example, of the chain accomplished in 2012 by the National Kidney Registry in the U.S., in which 30 couples were involved.

In [15], a comparison is conducted between NEAD chains and short cycles on the basis of empirical data; according to it, NEAD supposedly allows for the optimization of the results: short cycles are not able to ensure as many transplants (12% less than following the other approach) and waiting time would be increased in 30% of the cases.

The increased social welfare brought by TTCC and, in general, chain exchanges, compared to pairwise exchanges, is also stressed by Salvioli, Lucchetti and Torelli in [6] [11].

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[10] Panel Reactive Antibody

[11] Starting from a dataset provided by the Nord Italia Transplant program (NITp) about incompatible donor-patient couples from 2001 to 2013, they used algorithms to run simulations and build potential mutually compatible couples and cycles/chains across applicants; they accounted for the variables determinant for compatibility (HLA- & HB0-compatibility), patients' preferences over the set of donors (age difference, HLA mismatches) and bonus points (same transplant center, same blood type or perfect HLA

7.2 First Samaritan Donation in the U.S. (July 2007)

The world's first Samaritan donor-initiated chain [14] was initiated in the U.S. in July 2007 and carried out by the Alliance for Paired donation (APKD).

The APKD is a non-profit organization, connecting more than 70 transplantation centers across 27 States; founded in the year 2000 by Dr. Micheal Rees, it uses the algorithm developed by Alvin Roth to identify two-, three- or four-way exchanges, as well as chains, starting from the database of all applicants. Apart from the completion of the first NEAD chain, APKD accomplished many other remarkable projects: it managed the transplantation of a 16-couple chain exchange and it was also the first organization to generate intercontinental chains.

This first donor, a 28-year-old man from Michigan, registered for donating in 2006 and was finally matched in April 2007: this initiated chain has brought together 10 couples (and 11 donors, among which, 5 were *bridge* donors).

It is defined as "bridge" a donor whose elected recipient has already received a compatible kidney but who does not donate immediately; generally, kidney removal is carried out from one week to three months after the transplantation. The causes of the delay can be different: as in the 2007 case, there could be difficulties in finding a compatible match, or desensitization treatments may be required. The introduction of such donors involves some additional risks: for example, it may happen that, if unsuitable for the surgery, forced to wait for longer periods of time or unsatisfied with the results of the transplant in the recipient, donors may have more incentives for reneging, thus interrupting the chain.

The non-simultaneity, deemed, at that time, controversial, was not the only peculiarity of the process: first, in three cases, kidneys (instead of donors) were shipped to the recipients, bearing no apparent short-term consequences; secondly, some of the constraints considered fundamental for the compatibility were relaxed: two recipients were in fact able to receive from donors with minor AB0 or HLA incompatibilities by undergoing some preliminary therapies; thirdly, the inclusion of compatible couples arose some questions about whether it would be fair for the other participants.

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match).

The difference in the results was clear: with 24 viable transplants and 7 prioritized patients out of the pool of 38 candidates, the TTCC produced a far better outcome than paired exchanges (only 16 matches, and 20 being excluded due to the absence of mutually compatible pairs).

To address this last issue, Rees et al. state in [14]:

> *"In addition to increasing the quantity of living-donor transplantations, NEAD chains may improve the quality of the matches. To find twoway exchanges between pairs, the computer must seek pairs with reciprocal compatibilities, and [...] such pairs do not necessarily result in the best possible matches that could have been arranged."*

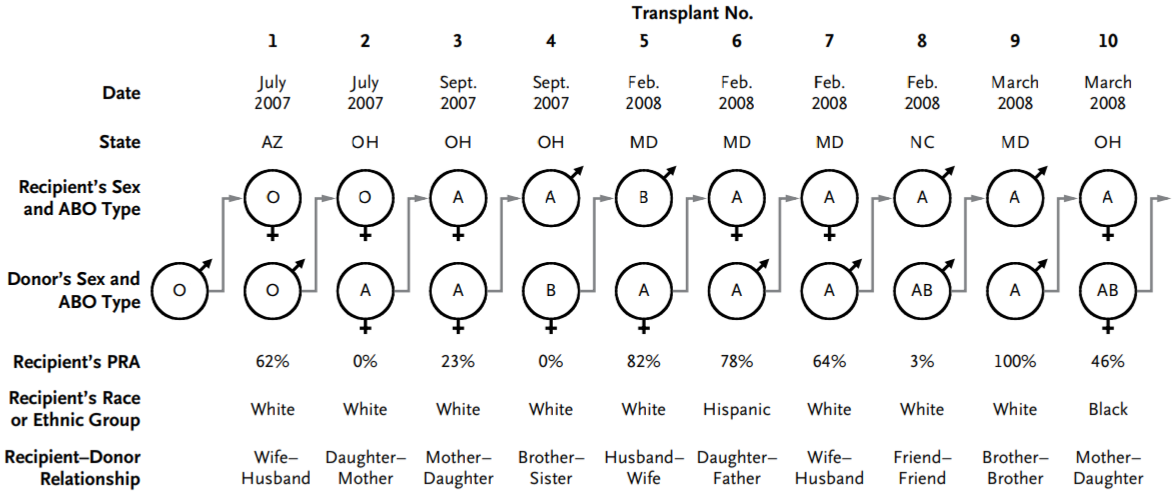

Figure 13: Scheme of the first NEAD initiated by the APKD in 2007
source: [14]

7.3 First Samaritan Donation in Italy (April 2015)

On April 7th 2015, a 56-year-old woman, after having undergone a thorough examination process [12], became the first Italian Samaritan donor. Starting from her, the CNT was indeed able to build a six-people chain, among which the first five had an incompatible living donor available, while the last was a candidate for the waiting list for cadaveric donations. The procedure, of the duration of 72 hours, entailed the execution of six nephrectomies and six transplantations.

During similar procedures, it becomes clear the role of coordination of the players: apart

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[12] including three phases: a clinical evaluation; a psychological/psychiatrical screening; an overall evaluation by a national committee;

from the cohesion of the transplantology network and health institutions, the participation of the traffic police becomes pivotal for the quick and safe delivery of the organs, as most shipments are on-road.

Ever since this first altruistic donor, there have been other seven cases of chains of this type, with the latest being reported by the CNT on June 4th 2019: in total, these cross-over procedures, saw the participation of 19 donor-patient couples and the effectuation of 26 transplantations.

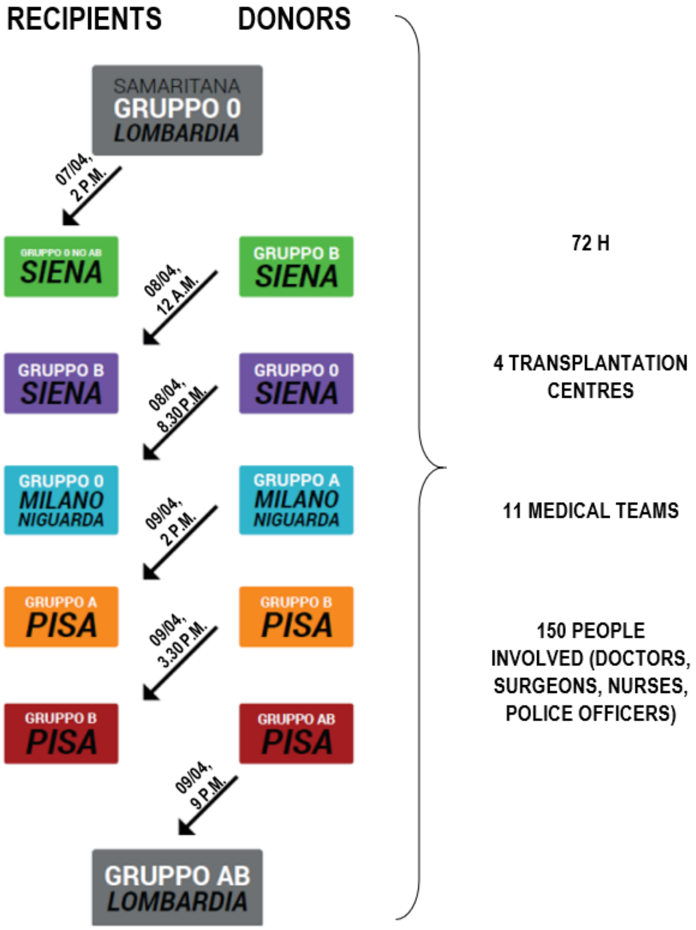

Figure 14: Summary of the chain started from the first samaritan donation in April 2015; source: [31]

8 Initiating Chains from Deceased Donors

The DECK (DECeased Kidney) paired exchange program is an approach that uses deceased donors to initiate kidney exchange chains. Although some precedents can be found in literature, as in [18],[19] and [20], this program has been first implemented in March 2018 in the Padua University Hospital, on the basis of the algorithm developed in the Mathematics Department of the University of Padua under the direction of Prof. Antonio Nicolò. [33]

Prof. Paolo Rigotti, head of the Kidney Transplant unit of the Padua University Hospital, comments on this:

> *"The novelty of the program implemented yesterday lies on the fact that for the first time the program started from a deceased kidney donor. Considering that the number of deceased donors in a single transplant center by far exceeds that of available living donors, this will allow to increase the size of the pool of potential compatible donors to be used to start a greater number of chains that would account for incompatible couples and patients that would find it difficult to receive a transplant" [34]*

Much like in the Altruistic donor case, this new procedure brings forward some advantages: it, in fact, maximizes and optimizes the viable pairings, thanks to the absence of the simultaneity constraint; moreover, excluding the ethical concerns that were raised by the NEAD chains about the nature and the motivation behind the spontaneous donation, it is more likely to meet the approval of a greater number of hospitals and transplantation centers.

The algorithm uses directed graphs for the detection of cycles and chains in different moments in time, with the objective of maximizing the number of transplants; this goal is synthesized in the characteristic equation: $\sum_{e \in E} v_e$, i.e. in the maximization of the *active* edges in the set at any iteration of the process.

In particular, these iterations are triggered by the introduction of a new donor-patient couple (cycle) or by the availability of a new kidney from deceased donor (chain).

The program, that is, at the moment, limited to the center of Padua and the procurement region of Veneto, was presented to the Veneto Regional Authority's Bioethical Committee in November 2017 and received its approval, as it conforms to the principle of benevolence and has clear social value [17].

Retrospective simulations[13] have been conducted on the basis of the data concerning the Padua University Hospital: the relevant results obtained (illustrated in figure 16) lead the team to the first DECK program implementation in March 2018.

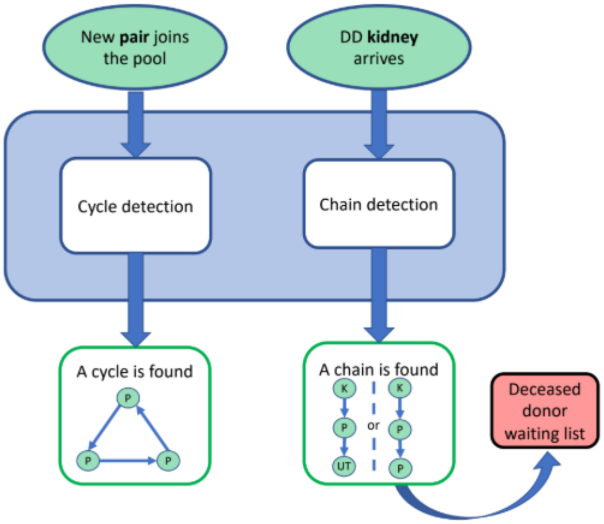

Figure 15: A description of the DECK algorithm; *source: [16]*

8.1 Theoretical Framework

The **nodes** of the graph are partitioned into:

- Pair nodes (P);
  these nodes represent the donor-patient couples that are, by any means, not compatible (NT pairs) and those who could be matched only after a desensitization procedure (DS pairs)[14].

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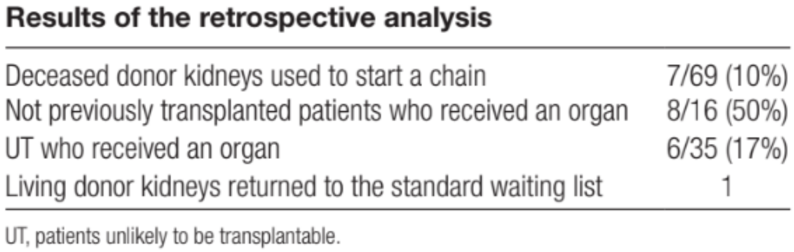
[13] The database used referred to the timespan Jan. 2012 - Dec. 2014; the program therefore included:

- 16 NT pairs, who could not be matched during those 3 years;
- 30 DS pairs, subject to some restrictions;
- 35 UT patients;
- 69 high quality K, i.e. kidneys with a life expectancy similar to the one of the recipient[**?**];

Restrictions on the DS: (1) a 6-month time limit to find a match, at the end of which recipients are expected to undergo desensitization and transplant from the intended donor; (2) a restriction to the quality of kidneys, limited to living donor kidneys.

[14] Desensitization helps reduce minor incompatibilities; nevertheless, the authors of [16] consider it to be undesirable as it: (1) weakens the patient, already undergoing dialysis; (2) is costly for the patient.



Results of the retrospective analysis

Deceased donor kidneys used to start a chain	7/69 (10%)
Not previously transplanted patients who received an organ	8/16 (50%)
UT who received an organ	6/35 (17%)
Living donor kidneys returned to the standard waiting list	1

UT, patients unlikely to be transplantable.

Figure 16: Results from the 2017 retrospective analysis on the implementation of the DECK procedure;
source: [17]

- Unlikely Transplantability, immunized patients (UT);
  The Nord Italia Transplant program defines this category as the set of those patients who have spent more than five years in the deceased donor waitlist or more than seven years on dialysis due to high immunization, which generally corresponds to a PRA>80%. Several UT patients may have already undergone other transplants, as they are one of the main causes for immunization.
- Kidneys (K) from deceased donors.

The edges represent the compatibility of the nodes; in particular, as only some directions are allowed (edges can start from or point to pairs; can point to patients or start from kidneys), the authors refer to E_X^- as the inbound edges, while to E_X^+ as the outbound edges. Depending on whether the compatibility translates into a transplant in a given moment t, the edges can assume value:

$$v_e = \begin{cases} 1 & \text{"active" edge, if transplant} \\ 0 & \text{"inactive" edge, otherwise} \end{cases}$$

Therefore, based on the aforementioned allowed directions for each specific type of node, it is possible to formulate some constraints:

- for P nodes:
  $$\sum_{e \in E_X^-} v_e - \sum_{e \in E_X^+} v_e \in \{0,1\} \forall X \in K;$$

and

$$\sum_{e \in E_X} v_e \in \{0, 1, 2\};$$

i.e. a pair can either have:

- an inbound edge: the pair receives a kidney and donates to an applicant to the waiting list for cadaveric kidneys (in absence of a node representing this last option, no edge will result in the graph);

  $$\textstyle\sum_{e \in E_X^-} v_e - \sum_{e \in E_X^+} v_e = 1 \text{ and } \sum_{e \in E_X} v_e = 1;$$

- an inbound and an outbound edge: the pair is matched to another pair; a paired exchange will occur;

  $$\textstyle\sum_{e \in E_X^-} v_e - \sum_{e \in E_X^+} v_e = 0 \text{ and } \sum_{e \in E_X} v_e = 2;$$

- no edge: at time t there is no compatible node;

  $$\textstyle\sum_{e \in E_X^-} v_e - \sum_{e \in E_X^+} v_e = 0 \text{ and } \sum_{e \in E_X} v_e = 0$$

- for UT nodes and K nodes:

  $$\sum_{e \in E_X} v_e \in \{0, 1\};$$

  i.e. a UT patient (a Kidney) can either have:

  - an inbound (outbound) edge: it can only receive (be donated);

    $$\textstyle\sum_{e \in E_X} v_e = 1;$$

  - no edge: there is no compatible match;

    $$\textstyle\sum_{e \in E_X} v_e = 0;$$

- Moreover, another constraint is added on the graph representations that include the kidneys that would be allocated to the pool of UT patients in the deceased waiting list:

  $$\sum_{X \in UT} (\sum_{e \in E_X^-} v_e) - \sum_{X \in K} (\sum_{e \in E_X^+} v_e) \geq 0$$

  this constraint prioritizes those highly immunized patients that have no available donor and therefore are harder to match.

8.2 Cycle and Chain Detection

As depicted in figure 15, the two underlying mechanisms that allow for kidney allocation among participants are cycle and chain detection. Let us analyse these two procedures in detail.

- **Cycle Detection**: cycle detection starts at time t as soon as a new pair joins the existing pool $P(t)$; pairs will be the only "players" in this specific case.
  From the compatibility graph, maximal cycles containing the newly introduced pair are identified.
  A new undirected graph, called *cycle graph*, is built: the nodes represent the cycles (generally of size two or three, in response to the simultaneity requirement); the edges will connect two nodes if the cycles represented by those nodes share at least one pair.
  From then on, it is possible to pick cycles using a coloring problem: it will not be possible, for obvious reasons, to choose and implement two adjacent cycles; the procedure is optimal when the cardinality of the cycles is maximized.
  By assumption, cycle detection will only look at the cycles containing the new pair: all other cycles should, in fact, have been implemented in advance.

- **Chain Detection**: chain detection is triggered by the availability of a new kidney K from a deceased donor; that will be the start of the chain, that will involve all three participants: pairs, patients and kidneys.The final objective will be to find the longest chain possible, given the present situation.
  As cycles should have already been implemented, the result of chain detection is assued to be an acyclical path (which, empirically, may not always be the case).
  Chain detection and implementation should also account for additional constraints, to favour those patients who are less likely to find a donor in the short-term:
  - in presence of multiple maximal chains, preference should be given to the one, if present, ending with a UT patient;
  - in case of chain initiated from a blood type 0 deceased donor kidney, the chain should end either with a donation to a UT patient or to a type-0 patient in the standard waiting list.

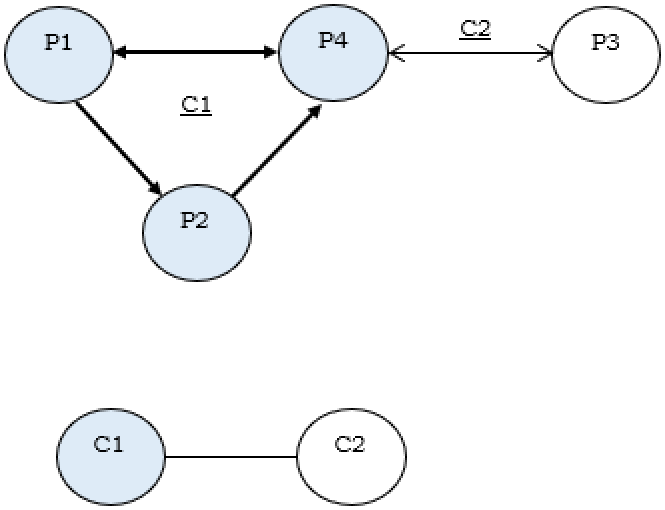


Figure 17: Example of compatibility and cycle graph for cycle detection;
The newly introduced pair (P4) is a part of a 2-way (C2) and 3-way (C1) cycles; as maximal cardinality is sought, C1 is preferred to C2.

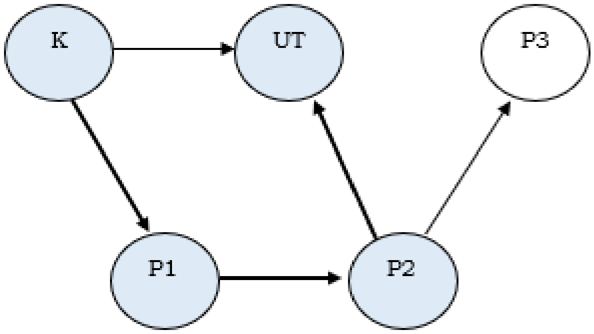


Figure 18: Example of compatibility graph;
The graph is acyclical and maximal chains are of size 3; as there exist 2 maximal chains, priority is given to the one culminating with a UT patient.

8.3 First DECK Implementation

The implementation of world's first chain from deceased donor was initiated on March 14th 2018 and involved one incompatible pair and one applicant to the deceased donor waiting list, for a total of 2 transplants.

The chain-initiating kidney recipient is a 53-year-old man with Berger's disease, whose incompatibility with the intended donor, his 53-year-old wife, was due to a complement-

dependent cytotoxicity (CDC) positive crossmatch; having already undergone a first, unsuccessful kidney transplant in 2003, and hemodialysis since 2017, the patient was added to the DECK list of candidates, together with his donor, in February 2018; after careful examination of the physical and psychological conditions of both of them, the following month, the pair was assigned a kidney from deceased donor.
The kidney was respected the "high quality" standard: it was removed from a 28-year-old man who died after a head trauma, with no record of specific medical conditions that could be relevant for the compatibility. The operation was successful and the patient discharged after having recovered normal renal function.
The kidney removal from the living donor, his wife, was carried on March 16th without any complication or damage on the donor.
The kidney was then transplanted on a patient in the waiting list: the 47-year-old man suffered from Schoenlein Henoch purpura, a condition often leading to chronic kidney disease and kidney failure. Without prior transplants and having undergone almost five years of dialysis, he too, without any complication, recovered full renal function.

Following the steps of this first procedure and adopting the same algorithm, another DECK program was initiated on August 9th 2018 from the availability of a deceased kidney in Genova. This chain was made possible thanks to the participation of three couples from two cities, Bari and Padua, and ended with a donation to a candidate in the waiting list.

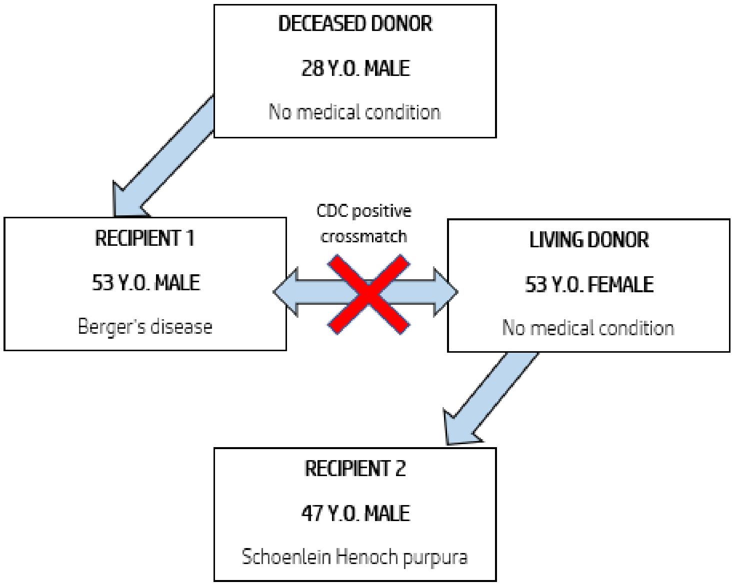


Figure 19: First DECK implementation in Italy: the pair, husband and wife, received a kidney from a living donor and donated its own to a candidate on the waiting list

9 Conclusions

The mechanisms that have been analysed throughout this work are an application of theoretical sciences to real life, and, although some some only bring forward incremental changes, their impact is, potentially, revolutionary. Let us just consider some data: according to Roth et al. (2007), the implementation of three-way exchanges would allow a 20% increase in the realisable transplants; the implementation of chains, especially from altruistic donors, include otherwise unreachable patients: an incredible example is the NEAD chain implemented in the University of Alabama at Birmingham, which started from a Samaritan and, in five years (2013-2018), connected 101 incompatible couples across 12 States in the U.S.; the spreading of the DECK procedure, that, based on the pool used for the retrospective analysis, was able to match 50% of the patients that would not have been awarded a kidney using standard procedures.

Some issues still remain. Firstly, the logistics: as of today, the implementation of cycles larger than three pairs would represent a challenge in terms of the space, equipment and teams required for the simultaneous implementations; secondly, the ethical implications, sparkling debates on the impact these practices bear on those patients on the waiting list having difficulties in finding matches and the true motivations behind living donations; other sources of concerns regard the thickness of the ”market” and the uneveness in the distribution of these programs, which have reached the upper bound in the U.S. while they are still developing in most European countries.

Another threat is posed by ”players” that have not been accounted for, in the analysis of these procedures: hospitals and surgeons. Their goal is maximizing the surgeries that take place within the single transplant center in order to meet the necessities of as many patients as possible, and to avoid costs related to the transfer of the patient/donor/organ. Therefore, the interests of hospitals may collide with those of society as a whole, leading to sub-optimal allocations. Let us suppose a center has three patients suitable for a three-way exchange (3 transplants), and that two of them, if integrated in programs from other centers, could allow the implementation of two three-way exchanges (6 transplants); the first center would prefer keeping those two patients for the internal program, even if, from a welfare perspective, it would be the least efficient option. This ”selfishness” may hinder the development of a centralized clearinghouse; on this issue, Micheal Rees, the director of the APKD, comments:

> *“As you predicted, competing matches at home centers is becoming a real problem. Unless it is mandated, I’m not sure we will be able to create a national system. I think we need to model this concept to convince people of the value of playing together”*

What is the future for the kidney exchange problem?
First of all, the trend seems to point to the development of ever-inclusive programs: this would increase the pool of participants and, consequently, the quantity and quality of the performed transplants; disregarding cultural and political constraints, the benefits from a nationally implemented program would be evident: Jayme Locke, surgical director of the Incompatible Kidney Transplant Program in UAB’s School of Medicine and coordinator of the world’s longest chain, estimates that it could potentially double the number of transplants from living donors (from 8.000 to 16.000).
Moreover, borders are being crossed: International program have been developed in the U.S. and in Europe as well: a remarkable example of a program including Italy is the South Alliance Transplant.
Additionally, a proposal for a Global Kidney Exchange (GKE) Program was advanced by Rees and Roth in 2015: the idea was to allow kidney exchanges between High Income Countries (HIC) and Low and Middle Income Countries (LMIC), providing opportunities also to people without financial means; due to several concerns about the program (one being the fact that it would provide funding to the poorer country’s patient, thus violating the principle of non-payment), the program was not accepted by European NCAs [37], but still it was implemented in the U.S. within the framework of the APKD: the first GKE procedure, involving a Filipino donor-patient couple, took place in 2015.
Another possible improvement for the Kidney Exchange programs is the inclusion in the donor-patient pool of compatible couples: this strategy is currently adopted by the Methodist Transplant Institute in San Antonio (TX), one of the leading transplantation center in the United States. As illustrated in [21] and [38], incompatible pairs would not be the only ones to benefit from this procedure: all compatible couples can in fact be paired only with kidneys of superior quality (eg. from a younger donor), thus associated with a higher survival rate.

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