Matching theory for kidney transplantation

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May 21\textsuperscript{st} 2015
Every ten minutes, someone is added to the national transplant waiting list in the USA

Organ Procurement and Transplantation Network
On average, 21 people die each day while waiting for a transplant in the USA

Organ Procurement and Transplantation Network
Despite advances in medicine and technology the gap between supply and demand continues to widen

Organ Procurement and Transplantation Network
Transplant waiting list in Italy
Kidney disease

*Harrison’s Principles of Internal Medicine*, 17th Ed, 2008
Functions

- removal of waste products of metabolism through the production of urine
- regulation of electrolytes
- maintenance of acid–base balance
- regulation of blood pressure
- secretion of hormones
Chronic kidney disease

renal function <60 ml/min/1,73 m² for over 3 months

(normal value: 120-130 ml/min/1,73 m²)
Chronic kidney disease

Hypertension

Diabetes

Chronic kidney disease
Chronic kidney disease

In the USA:

- 13% of the population
- 15 - 30% of old people
- 50% of people who suffer from metabolic or cardiovascular diseases

have a kidney damage
Complications

- Fatigue
- Anemia
- Diminished urine output
- Hypertension
- Heart failure
- Bone disorder
- Death
Diseases associated to the kidney and urinary tract cause approximately 830,000 deaths annually (12th highest cause of death)

Approximately 1.8 million people currently have access to renal replacement therapy
Renal replacement therapy

- Dialysis
- Kidney transplant
Dialysis

- replaces only 10% of renal function
- does not correct the compromised endocrine functions of the kidney
- 4 hours, 3 times a week
- 17000 - 40000 € per year
Kidney transplant
Kidney transplant

DONOR
functioning kidneys

RECEIVER
non-functioning kidneys
Kidney transplant

- total replacement of renal function
- longer life expectancy with respect to people on dialysis
- good quality of life
90% of kidney transplant patients are able to return to work.
Kidney transplant

Women can get pregnant
Sean Elliott and Alonzo Mourning made history by returning to play in the NBA following the surgery.
Sources of kidneys

- Deceased donors
- Living donors

<table>
<thead>
<tr>
<th></th>
<th>1-Year-Follow-Up</th>
<th>5-Year-Follow-Up</th>
<th>10-Year-Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grafts, %</td>
<td>Patients, %</td>
<td>Grafts, %</td>
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<tr>
<td>Deceased donor</td>
<td>89</td>
<td>95</td>
<td>67</td>
</tr>
<tr>
<td>Living donor</td>
<td>95</td>
<td>98</td>
<td>80</td>
</tr>
</tbody>
</table>

Mean rates of graft and patient survival for kidneys transplanted in the USA from 1992 to 2002
Transplant activity in Italy

![Graph showing transplant activity in Italy from 2001 to 2013]

- **Deceased donor**
- **Living donor**

- **2001**: 1448, 134
- **2002**: 1470, 126
- **2003**: 1487, 142
- **2004**: 1746, 145
- **2005**: 1671, 116
- **2006**: 1667, 108
- **2007**: 1585, 112
- **2008**: 1533, 138
- **2009**: 1650, 151
- **2010**: 1512, 191
- **2011**: 1542, 214
- **2012**: 1589, 190
- **2013**: 1501, 226
<table>
<thead>
<tr>
<th>Kidney disease</th>
<th>Kidney exchange</th>
<th>Pairwise exchange</th>
<th>Top Trading Cycles and Chains</th>
</tr>
</thead>
</table>

Compatibility
Compatibility

The major problem in organ transplantation is **rejection**, during which the body has an immune response to the transplanted organ, possibly leading to transplant failure and the need to immediately remove the organ from the recipient.

Transplant rejection can be reduced by use of immunosuppressant drugs after transplant and by determining the **compatibility** between donor and recipient.
Compatibility

There are actually three tests that are done to evaluate compatibility between recipient and donor (living or deceased):

- ABO blood type test
- Comparison of HLA antigens
- Screen for antibodies
Compatibility

There are actually three tests that are done to evaluate compatibility between recipient and donor (living or deceased):

- ABO blood type test
- Comparison of HLA antigens
- Screen for antibodies
Blood typing

There are 4 different blood types: the most common blood type in the population is type O (40%), the next most common is blood type A (36%), then B (17%), and the rarest is blood type AB (7%).

The blood type of the donor must be compatible with the recipient. The rules for blood type in transplantation are the same as they are for blood transfusion.
### Blood typing

<table>
<thead>
<tr>
<th>Recipient’s blood type</th>
<th>Donor’s blood type</th>
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<tbody>
<tr>
<td></td>
<td>O</td>
</tr>
<tr>
<td>O</td>
<td>✓</td>
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<tr>
<td>A</td>
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<tr>
<td>B</td>
<td>✓</td>
</tr>
<tr>
<td>AB</td>
<td>✓</td>
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</table>
Blood typing

Blood type O is considered the **universal donor**, because people with blood type O can give to any other blood type.

Blood type AB is called the **universal recipient** because they can receive an organ or blood from people with any blood type.
HLA typing

HLA stands for human leukocyte antigen

HLA are proteins that are located on the surface of the white blood cells and other tissues in the body.
# HLA typing

## Identified antigens

<table>
<thead>
<tr>
<th>HLA-A</th>
<th>HLA-B</th>
<th>HLA-C</th>
<th>HLA-D</th>
<th>HLA-DR</th>
<th>HLA-DQ</th>
<th>HLA-DP</th>
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</tbody>
</table>

Marsh, Nomenclature for factors of the HLA system, 2010
Out of over 100 different antigens that have been identified, there are six that have been shown to be the most important in organ transplantation. Of these six antigens, we inherit three from each parent.

Except in cases of identical twins and some siblings, it is rare to get a six-antigen match between two people, especially if they are unrelated. The chance of a perfect or six-antigen match between two unrelated people is about one in 100,000.
HLA typing

Recipient’s HLA Antigens

Donor’s HLA Antigens

We count HLA matches/mismatches, with a possible range from 0 to 6
HLA typing

Kidneys have been transplanted between two people with no matching antigens without a rejection episode. In other cases where all six antigens matched, recipients have suffered from rejection.

There is no way to predict who will experience a rejection episode, but it has been observed a higher incidence of graft failure due to rejection with a lower degree of HLA compatibility. Living donors with a 6 antigen match also allow the opportunity for decreased immunosuppression.
Mean rate of graft survival
5-Year-Follow-Up

Cellular and Molecular Immunology, 2007
Preformed antibodies

Immunologic incompatibility occurs when transplant candidates are exposed to foreign (nonself) human leukocyte antigens (HLA) through blood transfusion, pregnancy, and/or prior transplantation. Exposure to foreign HLA leads many patients to develop anti-HLA antibodies, which cause reactivity against potential organ donors.
Preformed antibodies

Recipient serum is tested against donor cells to determine if the recipient has preformed antibodies against any antigens on the donor’s cells.

A positive result means that the recipient has responded to the donor and that the transplant should not be carried out. A negative result means that the recipient has not responded to the donor and therefore transplantation should be safe.
Preformed antibodies

Recipient’s Antibodies

A1  A3  A24  A36  A80  B14  B47  DR1  DR9

Donor’s HLA Antigens

A2  A24  B7  B35  DR1  DR53

INCOMPATIBLE
There is a test you need to take that will determine how easy or difficult it will be to find a compatible person. The test is called **PRA** (panel reactive antibody).

PRA is a blood test that measures the level of antibodies in the recipients blood. The more antibodies you have, the more difficult it will be to find a compatible donor.
A person’s PRA can be anywhere from 0% to 99%. Your PRA represents the percent of the population that the antibodies in your blood would react to and reject the kidney.

For example, having a PRA of 25 means that 25% of the population will not be able to donate a kidney to you, because the antibodies present in your blood would attack the transplanted kidney and can cause immediate rejection.
PRA’s levels

- LOW PRA: <10%
- MEDIUM PRA: 10-80%
- HIGH PRA: > 80% (*highly sensitized* patients)
Patients with a high degree of sensitization often have great difficulty in finding an organ donor to whom they will not have a significant immunologic reaction, which could lead to early and severe rejection of the allograft if transplantation were to occur.
Approximately 16 percent of patients currently on the waiting list are highly presensitized to HLA. Many of these patients have potential living donors that are excluded because of the presence of preformed HLA antibodies.

Similarly, based upon the distribution of blood groups in the United States, approximately one-third of potential living donors are excluded because they are ABO incompatible with their intended recipient.

Solutions

- densensitization protocols
- kidney exchange
Kidney exchange, as a mechanism to facilitate living donor kidney transplantation, is a concept first introduced by Rapaport in 1986 as a solution to the shortage of deceased donor organs.

Rapaport proposed an international registry whereby eligible and willing but ABO-incompatible living donors could donate via exchange facilitated through this registry.
Kidney disease

Kidney exchange

Pairwise exchange

Top Trading Cycles and Chains

History

Wallis CB, *Kidney Paired Donation*, 2011
Kidney exchange in the USA
Percentage of living donor transplants from paired donation

# Transplants from kidney exchange in Italy

<table>
<thead>
<tr>
<th>YEAR</th>
<th>NUMBER OF TRANSPLANTS</th>
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<tbody>
<tr>
<td>2005</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>2</td>
</tr>
<tr>
<td>2010</td>
<td>2</td>
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<tr>
<td>2011</td>
<td>4</td>
</tr>
<tr>
<td>2012</td>
<td>2</td>
</tr>
<tr>
<td>2014</td>
<td>2</td>
</tr>
</tbody>
</table>

Centro Nazionale Trapianti
"Conventional" Kidney Exchange

Recipient 1
- type A

Donor 1
- type B

Recipient 2
- type B

Donor 2
- type A

ABO incompatible
List Exchange

Recipient 1
- type O

Next Appropriate Deceased Donor Kidney
- type O

Donor 1
- type B

Recipient on Waiting List
- type B

ABO incompatible
Closed Chain

Non Directed Donor
  type O

Recipient 1
  type O

Donor 1
  type B

Recipient 2
  type AB

Donor 2
  type A

Recipient 3
  type A

Donor 3
  type B

Recipient on Waiting List
  type B
Open Chain

Non Directed Donor
type O

Recipient 1
type O

Donor 1
type B

Recipient 2
type A

Recipient 2
Preformed Antibodies

Recipient 3
type A

Donor 3
type B

Recipient 4
type B

Donor 4
type A

Donor 3 waits until a suitable match is found before donating.
A kidney exchange problem is a matching problem consisting of:

- a set of incompatible patient-donor pairs \( N = \{1, \ldots, n\} \)
- a profile (≿) of ordered lists of all donors’ kidneys, one list for each patient
Characteristics of the model

- Constraints on the size of exchanges
- List exchange
- Compatible pairs
- Patients’ preferences
Pairwise exchange

Roth AE, *Pairwise kidney exchange*, 2005
Characteristics of the model

- Constraints on the size of exchanges: exchanges involve two patients
- List exchange: no
- Compatible pairs: no
- Patients’ preferences: 0–1 preferences
0–1 preferences

For any recipient $i \in N$:

- for any patient $j$ with a compatible donor for patient $i$ we have $j \succ_i i$,
- for any patient $j$ without any compatible donor for patient $i$ we have $i \succ_i j$,
- for any patients $j, h$ each of whom has a compatible donor for patient $i$ we have $j \sim_i h$,
- for any patients $j, h$ neither of whom has a compatible donor for patient $i$ we have $j \sim_i h$.

($\succ_i$ denotes the strict preference relation and $\sim_i$ denotes the indifference relation induced by $\succeq_i$)
Each patient is indifferent between all compatible donors and between all incompatible donors, except she strictly prefers her donor to any other incompatible donor, and any compatible donor to her own donor.

A pairwise kidney exchange problem is a pair \((N, \succsim)\), where \(\succsim = (\succsim_i)_{i \in N}\) denotes the list of patient preferences.
Compatibility

We consider the case in which an exchange can involve only two pairs.

Definition

Patients $i, j \in N$ are **mutually compatible** if $i \succ_j j$ and $j \succ_i i$. That is, two patients are mutually compatible if each one has a donor whose kidney is compatible for the other patient.
Definition

A matching $\mu : N \rightarrow N$ is a function such that: $\mu(i) = j$ if and only if $\mu(j) = i$ for any pair of patients $i, j \in N$.

For each matching $\mu$ and patient $i \in N$, $\mu(i) = i$ means that the patient $i$ remains unmatched. For any matching $\mu$ and pair of patients $i, j \in N$, $\mu(i) = j$ means that patient $i$ receives a compatible kidney from the donor of patient $j$ and patient $j$ receives a compatible kidney from the donor of patient $i$. 
### Definition

The matrix \( R = [r_{i,j}]_{i \in N, j \in N} \) defined by

\[
    r_{ij} = \begin{cases} 
        1 & \text{if } j \succ_i i \text{ and } i \succ_j j \\
        0 & \text{otherwise}
    \end{cases}
\]

for any pair of (not necessarily distinct) patients \( i, j \in N \) is called **mutual compatibility matrix**.

We will refer to the pair \( (N, R) \) as the **reduced problem** of \( (N, \succ) \).

Occasionally it will be helpful to think of the reduced problem as a graph.
$G = (N, R)$ is a graph whose vertices $N$ are the patients (and their incompatible donors), and whose edges $R$ are the connections between mutually compatible pairs of patients; i.e. there is an edge $(i, j) \in R$ if and only if $r_{i,j} = 1$. 
Graphs
A matching then can be thought of as a subset of the set of edges such that each patient can appear in at most one of the edges.
With this alternative representation if \((i, j)\) is an edge in the matching \(\mu\), patients \(i\) and \(j\) are matched by \(\mu\) and, if patient \(i\) does not appear in any edge in the matching \(\mu\), she remains unmatched.

We need a **mechanism**, a systematic procedure that selects a matching for each problem.
### Individual rationality

**Definition**

A matching $\mu$ is **individually rational** if for any patient $i \in N$, $\mu(i) \neq i$ implies $\mu(i) \succ_i i$.

Let $\mathcal{M}$ be the set of individually rational matchings for the problem $(N, \succeq)$. 
A matching $\mu \in \mathcal{M}$ is **Pareto-efficient** if there exists no other matching $\eta \in \mathcal{M}$ such that $\eta(i) \succeq_i \mu(i)$ for all $i \in N$ and $\eta(i) \succ_i \mu(i)$ for some $i \in N$.

In the present setting, $\mu$ is Pareto-efficient if and only if the set $M_\mu = \{ i \in N : \mu(i) \neq i \}$ of patients matched by $\mu$ is maximal, i.e. if there does not exist any other matching $\eta \in \mathcal{M}$ such that $M_\eta \supset M_\mu$.

Let $\mathcal{E}$ be the set of Pareto-efficient matchings for the problem $(N, \succeq)$. 
Non-efficient matching
Efficient matching
For any matching $\mu \in \mathcal{M}$, let $|\mu| = |M_\mu| = |\{i \in N : \mu(i) \neq i\}|$ denote the number of patients who are matched with another patient.

**Lemma**

For any pair of Pareto-efficient matchings $\mu, \eta \in \mathcal{E}$, $|\mu| = |\eta|$.

If exchange is possible among more than two pairs, the conclusion of the Lemma no longer holds.
\[ D \succ_A A \succ_A B \sim_A C, \]
\[ C \succ_B B \succ_B A \sim_B D, \]
\[ D \succ_C C \succ_C B \sim_C A, \]
\[ B \succ_D A \succ_D D \succ_D C. \]
The experience of transplant centers is mostly with the priority allocation systems used to allocate cadaver organs. It is therefore natural to consider how priority mechanisms would function in the context of live kidney exchange.
Definition

A priority ordering is a permutation of patients such that the kth patient in the permutation is the patient with the kth priority.
Priorities may depend on quantifiable patient characteristics such as the patient’s PRA, which is correlated with how difficult it will be to find a compatible kidney for that patient. (So it might be desirable, for example, for a high PRA patient to have a high priority for a compatible kidney in the relatively rare event that one becomes available).

**Definition**

A non-negative function $\pi : N \rightarrow R_+$ is a *priority function* if it is increasing in priority, i.e. if $\pi(i) \geq \pi(i + 1)$. 
A priority mechanism produces a matching as follows, for any problem \((N, R)\) and priority ordering \((1, 2, ..., n)\) among the patients:

- **STEP 0:** \(E^0 = \mathcal{M}\)

- **STEP k:** for every \(k \leq n\) we define \(E^k \subseteq E^{k-1}\):
  \[
  \begin{aligned}
  E^k &= \begin{cases}
  \{ \mu \in E^{k-1} : \mu(k) \neq k \} & \text{if } \exists \mu \in E^{k-1} : \mu(k) \neq k \\
  E^{k-1} & \text{otherwise}
  \end{cases}
  
  \end{aligned}
  \]

We refer to each matching in \(E^n\) as a **priority matching**, and a **priority mechanism** is a function which selects a priority matching for each problem.
A priority matching matches as many patients as possible starting with the patient with the highest priority and following the priority ordering, never “sacrificing” a higher priority patient because of a lower priority patient. By construction, a priority matching is maximal, and hence Pareto-efficient, i.e. $E^n \subset E$. 
Example

STEP 0 = \{(1, 5)(2, 4); (1, 5)(3, 4); (2, 5)(3, 4); (2, 4)(3, 5)\}
STEP 1 = \{(1, 5)(2, 4); (1, 5)(3, 4)\}
STEP 2 = \{(1, 5)(2, 4)\}
STEP 3 = \{(1, 5)(2, 4)\}
STEP 4 = \{(1, 5)(2, 4)\}
STEP 5 = \{(1, 5)(2, 4)\}
Example

STEP 0 = \{(1, 5)(2, 4); (1, 5)(3, 4); (2, 5)(3, 4); (2, 4)(3, 5)\}
STEP 1 = \{(1, 5)(2, 4); (1, 5)(3, 4)\}
STEP 2 = \{(1, 5)(2, 4)\}
STEP 3 = \{(1, 5)(2, 4)\}
STEP 4 = \{(1, 5)(2, 4)\}
STEP 5 = \{(1, 5)(2, 4)\}
Strategy-proofness

The first issue has to do with patients who have multiple incompatible donors willing to donate on their behalf. The second issue involves revealing which compatible kidneys the patient is willing to accept.

**Theorem**

A priority mechanism makes it a dominant strategy for a patient to reveal both:

- her full set of acceptable kidneys,
- her full set of available donors.
Strategy-proofness

A patient maximizes her chance of being included in an exchange by revealing all of her willing donors and by accepting her full set of compatible kidneys.

These two conclusions have the same cause. A patient enlarges the set of other patients with whom she is mutually compatible by coming to the exchange with more donors, and by being able to accept a kidney from more of those other patients’ donors.
Gallai–Edmonds decomposition

The following partition of the set of patients is key to the structure of the set of Pareto-efficient matchings. Partition $N$ as \{ $N^U$, $N^O$, $N^P$ \} such that:

$$
N^U = \{ i \in N : \exists \mu \in \mathcal{E} \text{ such that } \mu(i) = i \},
$$

$$
N^O = \{ i \in N \setminus N^U : \exists j \in N^U \text{ such that } r_{i,j} = 1 \},
$$

$$
N^P = N \setminus (N^U \cup N^O).
$$

$N^U$ is the set of patients for each of whom there is at least one Pareto-efficient matching which leaves her unmatched. $N^O$ is the set of patients each of whom is not in $N^U$ (i.e., each of whom is matched with another patient at each Pareto-efficient matching) but is mutually compatible with at least one patient in $N^U$. $N^P$ is the set of remaining patients (i.e., the set of patients who are matched with another patient at each Pareto-efficient matching and who are not mutually compatible with any patient in $N^U$).
Kidney disease

Kidney exchange

Pairwise exchange

Top Trading Cycles and Chains
Definition

Consider the reduced problem \((N, R)\). For \(I \subset N\), let \(R_I = [r_{i,j}]_{i,j \in I}\). We refer to the pair \((I, R_I)\) as the **reduced subproblem** restricted to \(I\).
Let \((I, R_I)\) be the reduced subproblem of \((N, R)\) with \(I = N \setminus N^O\).
Let \((I, R_I)\) be the reduced subproblem with \(I = N \setminus N^O\) and let \(\mu\) be a Pareto-efficient matching for the original problem \((N, R)\). We have:

1. For any patient \(i \in N^O\), \(\mu(i) \in N^U\);
2. For any even component \((J, R_J)\) of \((I, R_I)\), \(J \subseteq N^P\) and for any patient \(i \in J\), \(\mu(i) \in J \setminus \{i\}\);
3. For any odd component \((J, R_J)\) of \((I, R_I)\), \(J \subseteq N^U\) and for any patient \(i \in J\) it is possible to match all remaining patients in \(J\) with each other (so that any patient \(j \in J \setminus \{i\}\) can be matched with a patient in \(J \setminus \{i, j\}\)). Moreover for any odd component \((J, R_J)\), either
• one and only one patient $i \in J$ is matched with a patient in $N^O$ under the Pareto-efficient matching $\mu$ whereas all remaining patients in $J$ are matched with each other so that $\mu(j) \in J \setminus \{i, j\}$ for any patient $j \in J \setminus \{i\}$, or

• one patient $i \in J$ remains unmatched under the Pareto-efficient matching $\mu$ whereas all remaining patients in $J$ are matched with each other so that $\mu(j) \in J \setminus \{i, j\}$ for any patient $j \in J \setminus i$. 
Top trading cycles and chains

Roth AE, *Kidney exchange*, 2004
Characteristics of the model

- Constraints on the size of exchanges: **no constraints**
- List exchange: **yes**
- Compatible pairs: **yes**
- Patients’ preferences: **strict preference relation over** $D \cup \{w\}$
### Preferences

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\( p = \text{patient (recipient)} \)
\( d = \text{donor} \)
\( w = \text{waiting list} \)
The outcome of a kidney exchange problem is a matching \( \mu \) of kidneys/waitlist option to patients such that:

1. each patient is either assigned a kidney or the waitlist option \( w \), and

2. no kidney can be assigned to more than one patient although the waitlist option \( w \) can be assigned to several patients.
Algorithm

1. Initially all kidneys are available and all agents are active. At each stage of the procedure:
   - each remaining active patient points to the best remaining unassigned kidney or to the waitlist option \( w \), whichever is more preferred, based on his preferences
   - each remaining passive patient continues to point to his assignment
Step 1

Diagram:

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2. There is either a cycle, or a w-chain, or both. By definition, a cycle can neither intersect with another cycle nor with a w-chain.
(2a) Proceed to Step 3 if there are no cycles. Otherwise locate each cycle and carry out the corresponding exchange. Remove all patients in a cycle together with their assignments.

(2b) Each remaining patient points to its top choice among remaining kidneys. There is either a cycle, or a w-chain, or both. Proceed to Step 3 if there are no cycles. Otherwise locate all cycles, carry out the corresponding exchanges, and remove them.

(2c) Repeat Step 2b until no cycle exists.
Step 2
Step 2
Step 2
3. If there are no pairs left, then we are done. Otherwise, each remaining pair initiates a w-chain. Some of these w-chains may intersect and others may not.
(3a) If each remaining w-chain is minimal, then each remaining patient points to the wait list option w. In this case carry our the basic indirect exchanges and we are done.

(3b) Otherwise select only one of the chains with the **chain selection rule**. The assignment is final for the patients in the selected w-chain. In addition to selecting a w-chain, the chain selection rule also determines:

- whether the selected w-chain is removed and the associated exchange is immediately carried out, or
- the selected w-chain remains in the procedure although each patient in it is passive henceforth.
4. Each time a w-chain is selected, a new series of cycles may form. Repeat Steps 2 and 3 with the remaining active patients and unassigned kidneys until no patient is left.
Examples of Chain Selection Rules

a. Choose minimal w-chains and remove them.
b. Choose the longest w-chain and remove it.
c. Choose the longest w-chain and keep it.
d. Prioritize patient-donor pairs in a single list. Choose the w-chain starting with the highest priority pair and remove it.

e. Prioritize patient-donor pairs in a single list. Choose the w-chain starting with the highest priority pair and keep it.
f. Prioritize the patient-donor pairs so that pairs with O blood-type donor have higher priorities than those who do not. Choose the w-chain starting with the highest priority pair; remove it in case the pair has an O blood-type donor but keep it otherwise.
Kidney disease
Kidney exchange
Pairwise exchange
Top Trading Cycles and Chains

Step 3
Step 3
Step 3
«60 lives, 30 kidneys, all linked »