Matching theory for kidney transplantation

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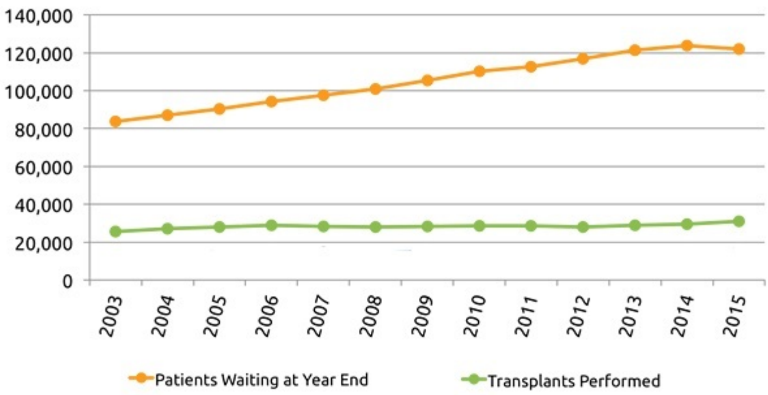
- Every ten minutes, someone is added to the national transplant waiting list in the USA
- On average, 22 people die each day while waiting for a transplant

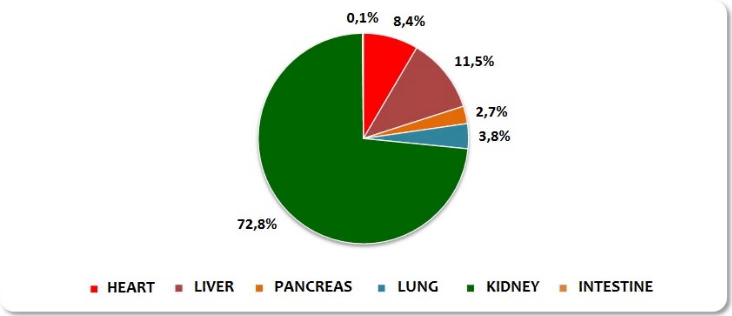


Despite advances in medicine and technology the gap between supply and demand continues to widen

Transplant waiting list in Italy

PATIENTS ON WAITING LIST IN ITALY AT 31/12/2016

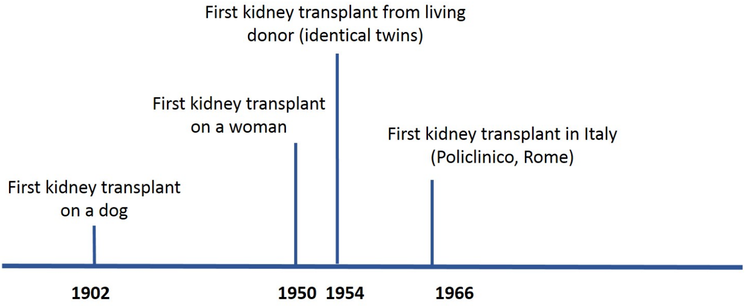
8856



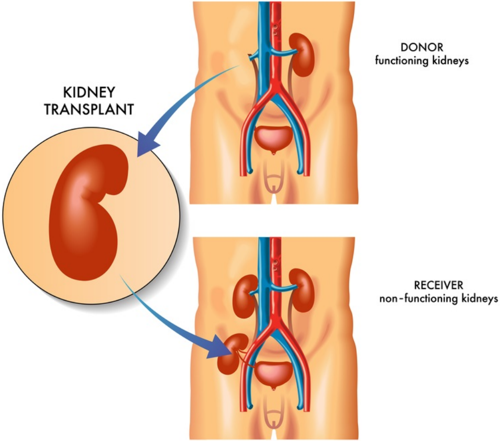
Statistics

- In the USA 13% of the population have a kidney damage (15-30% of old people)
- Diseases associated to the kidney and urinary tract cause approximately 830,000 deaths annually (12^{th} highest cause of death)
- Approximately 1.8 million people currently have access to renal replacement therapy:
  - dialysis
  - kidney transplant

Kidney transplant


First kidney transplant from living donor (identical twins)
First kidney transplant on a woman
First kidney transplant in Italy (Policlinico, Rome)
First kidney transplant on a dog
1902
1950
1954
1966

Kidney transplant



- total replacement of renal function
- longer life expectancy with respect to people on dialysis
- good quality of life

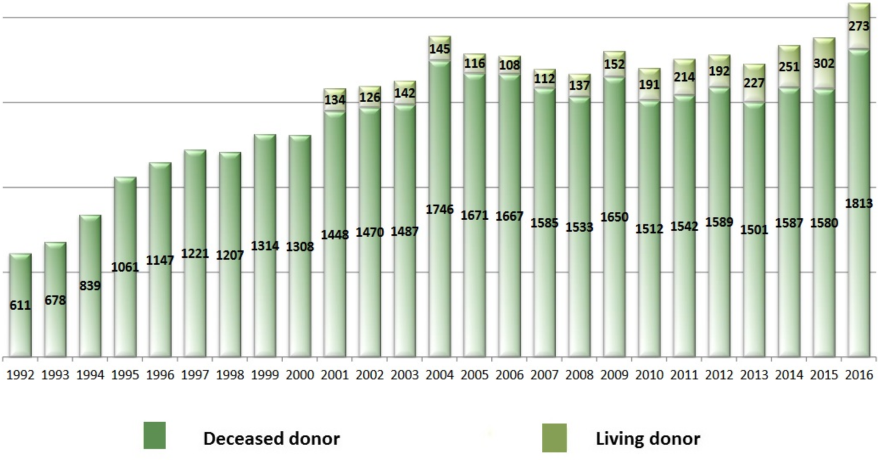
Kidney transplant

Women can have children after receiving a kidney from a donor

Kidney transplant

- Sean Elliott was the first NBA player coming back to play professionally after a kidney transplant.
- Alonzo Mourning received a kidney from a living donor in 2003 and won the NBA finals with Miami Heat in 2006.

Transplant activity in Italy



Compatibility

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

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

Blood typing

Recipient's blood type	Donor's blood type			
	0	A	B	AB
0	✓	✗	✗	✗
A	✓	✓	✗	✗
B	✓	✗	✓	✗
AB	✓	✓	✓	✓

HLA typing

HLA stands for human leukocyte antigen

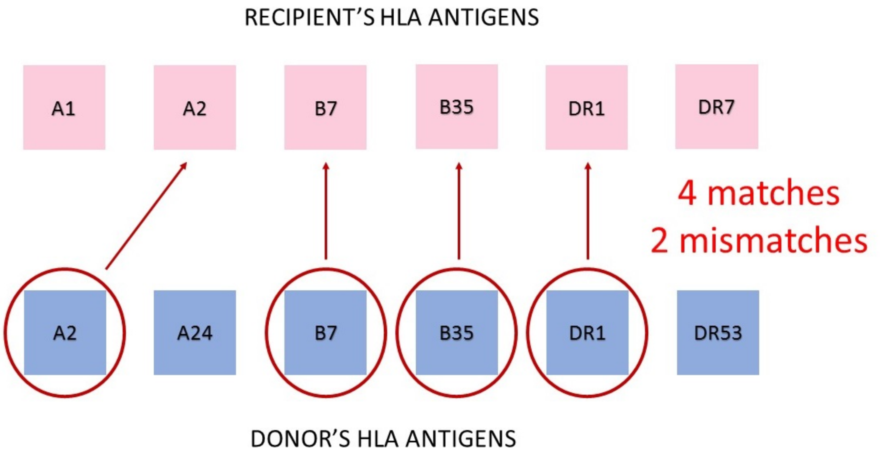
HLA are proteins that are located on the surface of the white blood cells and other tissues in the body.

HLA typing - identified antigens

HLA-A	HLA-B		HLA-C	HLA-DR	HLA-DQ	HLA-DP
A1	B5	B51(5)	Cw1	DR1	DQ1	DPw1
A2	B7	B5102	Cw2	DR103	DQ2	DPw2
A203	B703	B5103	Cw3	DR2	DQ3	DPw3
A210	B8	B52(5)	Cw4	DR3	DQ4	DPw4
A3	B12	B53	Cw5	DR4	DQ5(1)	DPw5
A9	B13	B54(22)	Cw6	DR5	DQ6(1)	DPw6
A10	B14	B55(22)	Cw7	DR6	DQ7(3)	
A11	B15	B56(22)	Cw8	DR7	DQ8(3)	
A19	B16	B57(17)	Cw9(w3)	DR8	DQ9(3)	
A23(9)	B17	B58(17)	Cw10(w3)	DR9		
A24(9)	B18	B59		DR10		
A2403	B21	B60(40)		DR11(5)		
A25(10)	B22	B61(40)		DR12(5)		
A26(10)	B27	B62(15)		DR13(6)		
A28	B2708	B63(15)		DR14(6)		
A29(19)	B35	B64(14)		DR1403		
A30(19)	B37	B65(14)		DR1404		
A31(19)	B38(16)	B67		DR15(2)		
A32(19)	B39(16)	B70		DR16(2)		
A33(19)	B3901	B71(70)		DR17(3)		
A34(10)	B3902	B72(70)		DR18(3)		
A36	B40	B73				
A43	B4005	B75(15)		DR51		
A66(10)	B41	B76(15)		DR52		
A68(28)	B42	B77(15)		DR53		
A69(28)	B44(12)	B78				
A74(19)	B45(12)	B81				
A80	B46	B82				
	B47					
	B48	Bw4				
	B49(21)	Bw6				
	B50(21)					

Six antigens are relevant in kidney transplantation
(we inherit three from each parent)

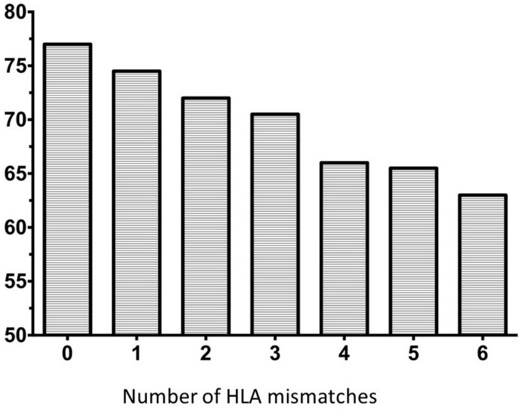
HLA typing



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

Mean rate of graft survival

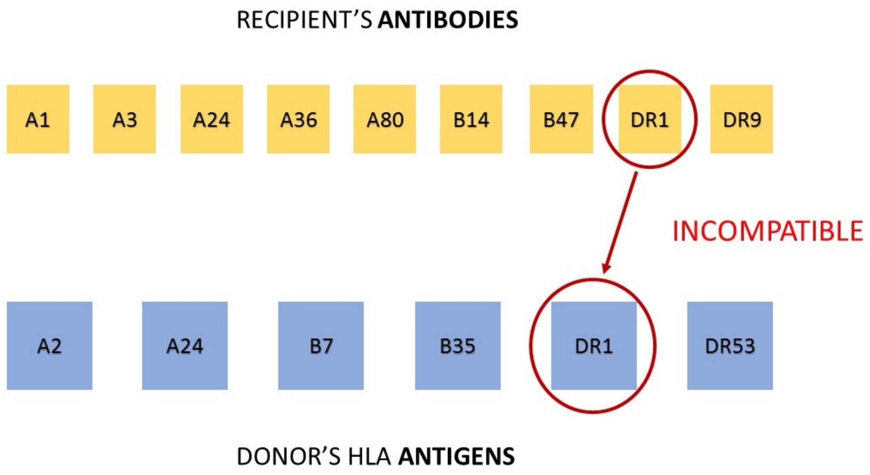
5-Year-Follow-Up



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



PRA

The **PRA** test determines is an index to show easiness to find a compatible donor. The PRA measures the level of antibodies in the recipients blood:

- LOW PRA: <10%
- MEDIUM PRA: 10-80%
- HIGH PRA: > 80% (**highly sensitized** patients)

- Approximately 16 percent of patients currently on the waiting list have high PRA. Many of these patients have potential living donors that are excluded because of the presence of preformed HLA antibodies.

- Approximately one-third of potential living donors are excluded because they are ABO incompatible with their intended recipient.

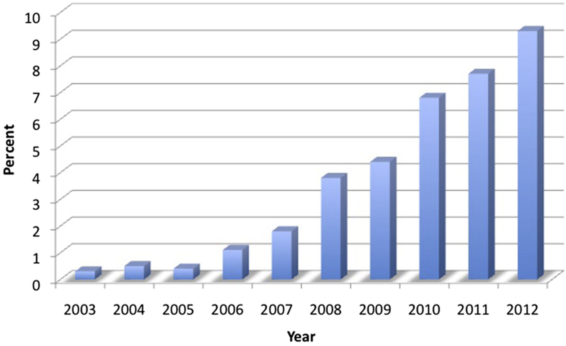
Solutions

- densensitization protocols
- kidney exchange

Kidney exchange in the USA

Percentage of living donor transplants from paired donation

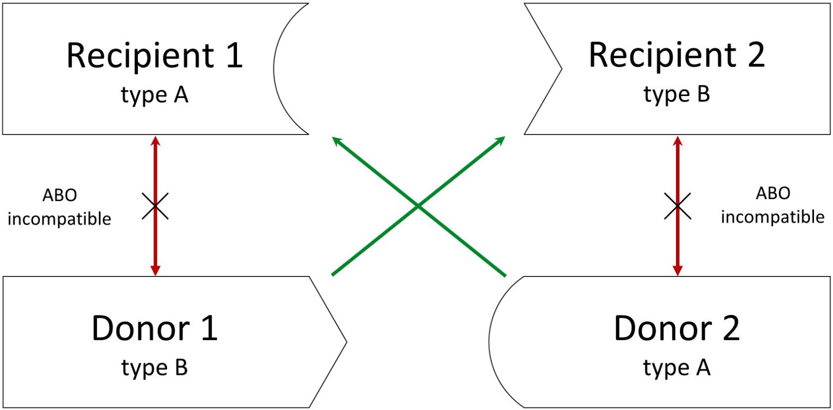
The idea of kidney exchange was introduced by Rapaport in 1986



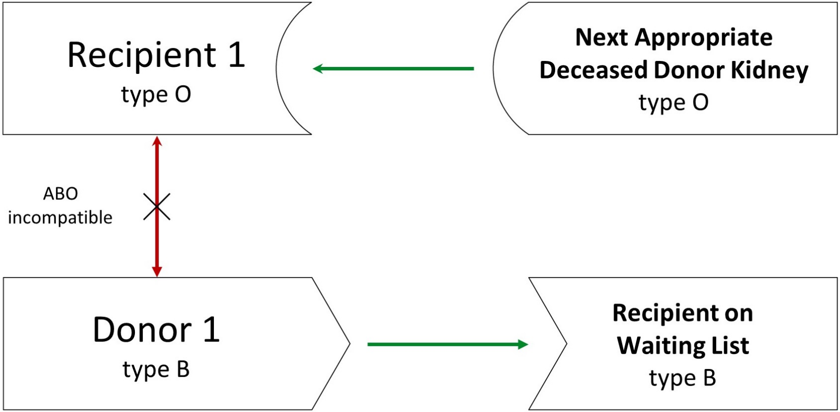
Transplants from kidney exchange in Italy

YEAR	NUMBER OF TRANSPLANTS
2005	3
2007	2
2010	2
2011	4
2012	2
2014	2

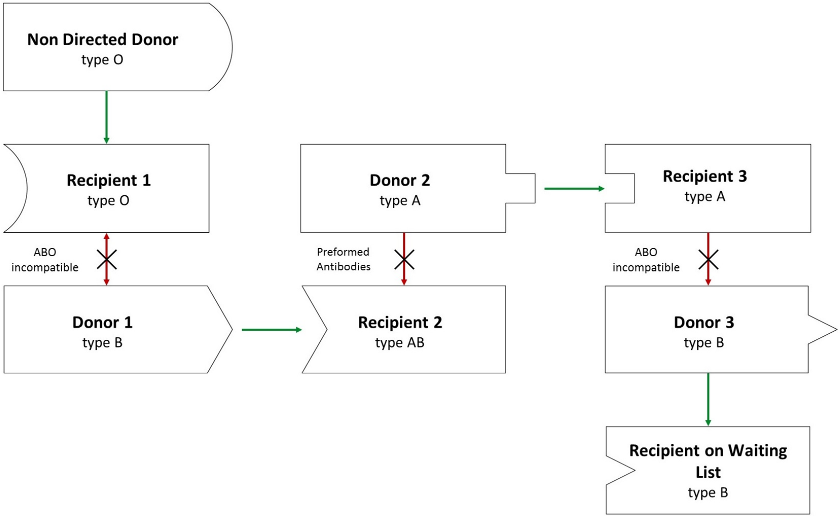
"Conventional" Kidney Exchange



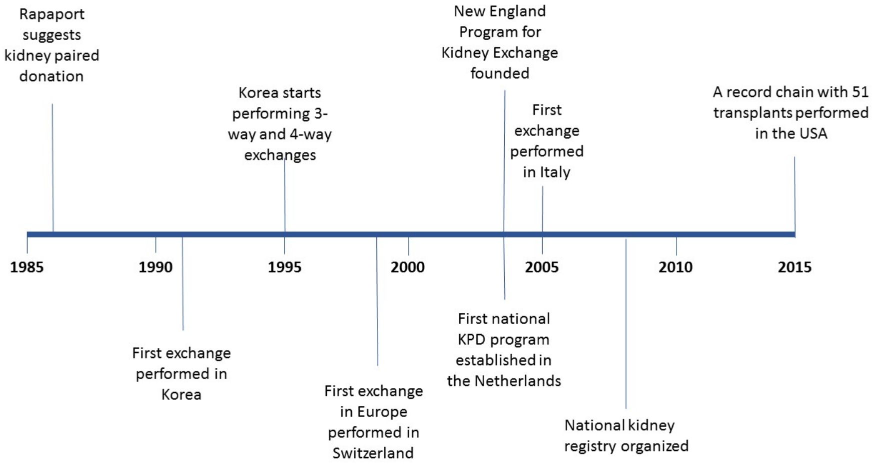
List Exchange



Chain


Non Directed Donor
type O
Recipient 1
type O
ABO
incompatible
Donor 1
type B
Donor 2
type A
Preformed
Antibodies
Recipient 2
type AB
Recipient 3
type A
ABO
incompatible
Donor 3
type B
Recipient on Waiting
List
type B

History


Rapaport suggests kidney paired donation
Korea starts performing 3-way and 4-way exchanges
New England Program for Kidney Exchange founded
First exchange performed in Italy
A record chain with 51 transplants performed in the USA
1985
1990
1995
2000
2005
2010
2015
First exchange performed in Korea
First exchange in Europe performed in Switzerland
First national KPD program established in the Netherlands
National kidney registry organized

A kidney exchange problem is a **matching problem** consisting of:

- a set of patient-donor pairs $N = \{1, ..., n\}$
- a profile ($\succsim$) of ordered lists of all donors' kidneys, one list for each patient

Pairwise exchange

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**

Compatibility matrix and graph

- In the symmetric compatibility matrix 1 means that the two patient-donor pairs are mutually compatible
  - for example: the entry AE=1 means that a kidney exchange between couple A e and couple E is possible
- Edges in the graph have the same meaning

$$
\begin{array}{c c}
 & \begin{array}{ccccc} \mathbf{A} & \mathbf{B} & \mathbf{C} & \mathbf{D} & \mathbf{E} \end{array} \\
\begin{array}{c} \mathbf{A} \\ \mathbf{B} \\ \mathbf{C} \\ \mathbf{D} \\ \mathbf{E} \end{array} &
\begin{bmatrix} 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 & 1 \\ 1 & 1 & 1 & 1 & 0 \end{bmatrix}
\end{array}
$$

Compatibility matrix and graph

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$$
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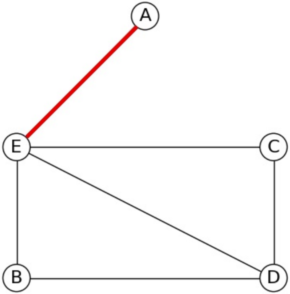
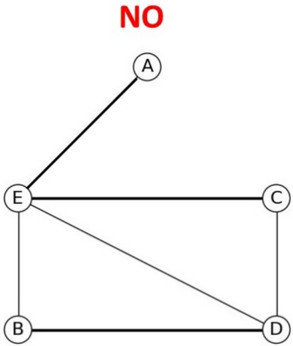
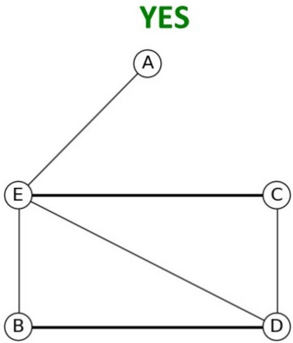
\begin{array}{c} \mathbf{A} \\ \mathbf{B} \\ \mathbf{C} \\ \mathbf{D} \\ \mathbf{E} \end{array} &
\begin{bmatrix} 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 & 1 \\ 1 & 1 & 1 & 1 & 0 \end{bmatrix}
\end{array}
$$



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.

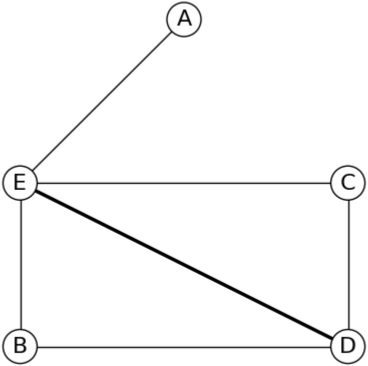




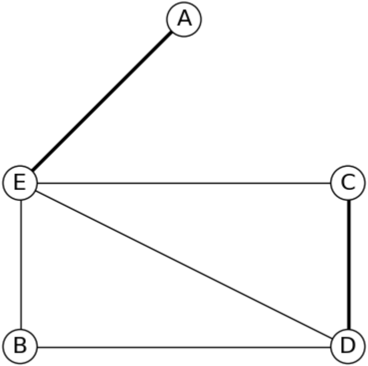
Efficiency

A matching μ is efficient if it is not possible to add to it another edge to it to built a bigger matching.

Non-efficient matching

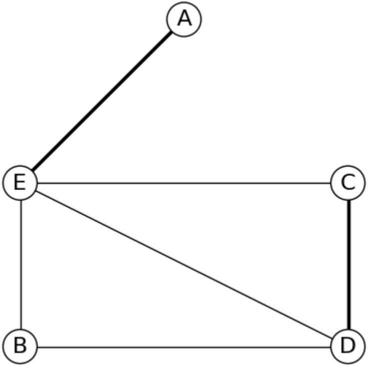


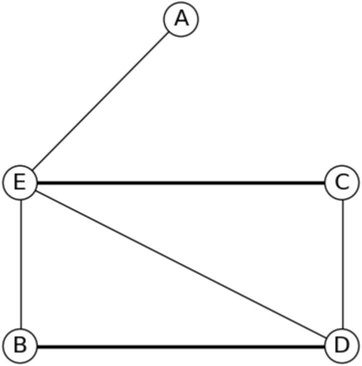
Efficient matching



Efficient matching

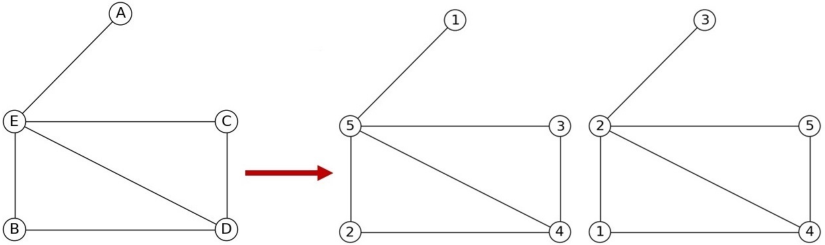
All efficient matchings have the same number of edges and there can be more than one efficient matching:



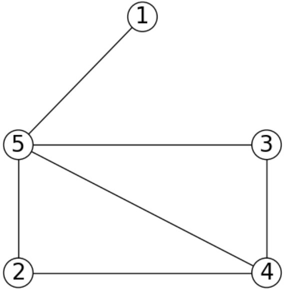


Definition

*A **priority ordering** is a permutation of patients such that the kth patient in the permutation is the patient with the kth priority.*

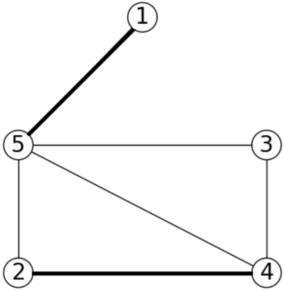


Example: priority mechanism



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

Example: priority mechanism



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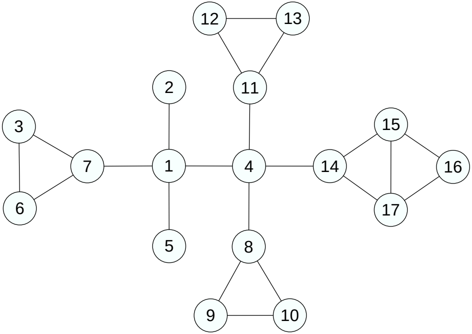
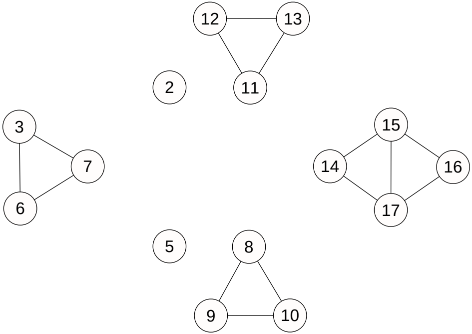
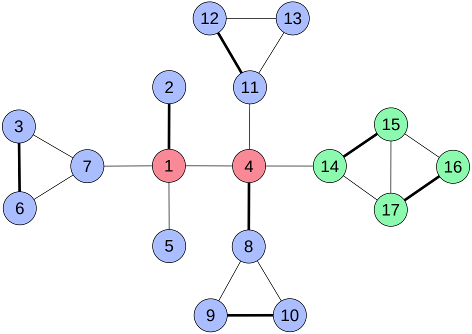


- Identify those patients who would receive a transplant in any maximal matching (overdemanded)
- remove them from the graph



The reduced graph has

- some odd components (underdemanded)
- some even components (perfectly matched)



- perfectly matched patients are matched with each other
- each overdemanded is matched to an underdemanded (priority ordering)
- the remaining underdemanded are matched with each other (priority ordering)

Top trading cycles and chains

Preferences

P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	D10	D3	D9	D3	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

$$p = patient(recipient); d = donor; w = waitinglist$$

Preferences of patient 1:

1. donor of patient 9
2. donor of patient 4
3. her own donor (there are no other compatible donors)

Preferences

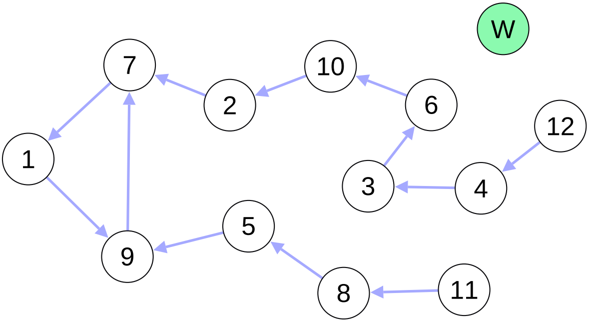
P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	D10	D3	D9	D3	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

$$p = patient(recipient); d = donor; w = waitinglist$$

Preferences of patient 2:

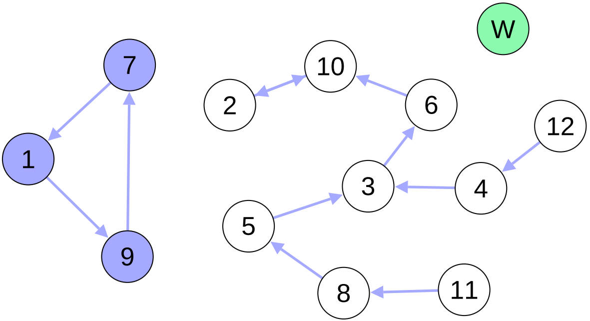
1. donor of patient 7
2. donor of patient 10
3. waiting list (there are no other compatible donors)

Step 1



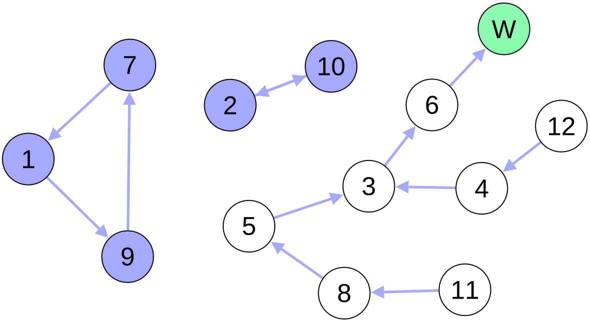
P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	D10	D3	D9	D3	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

Step 2



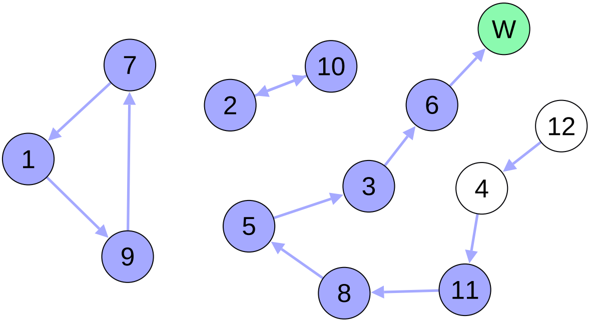
P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	$\boxed{\text{D10}}$	D3	D9	$\boxed{\text{D3}}$	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

Step 2



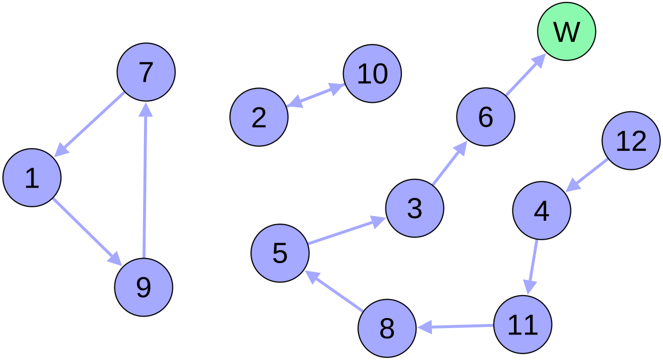
P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	D10	D3	D9	D3	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

Step 3



P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
D9	D7	D6	D3	D9	D10	D1	D5	D7	D2	D8	D4
D4	D10	D3	D9	D3	W	D9	D3	W	D3	D1	D12
D1	W		D11	D8		D7	D11		W	D5	
			W	D2			D8			W	
				D5							

Final matching



Recursive Algorithm

Good Samaritan donors

- With Good Samaritan donation, a person donates a kidney to an unknown recipient, starting a chain of transplants
- Chains starting with a samaritan can be very long, since transplant in this case, differently from the case of cycles, need not be contemporary

- Oriented graph $G(V, E)$;
- $V = \{1, ..., n\}$ set of the incompatible donor-recipient couples and samaritan donors (vertices);
- $E = \{1, ..., m\}$ set of the possible transplants (edges);
- $in(v)$ set of the edges that point to node v;
- $out(v)$ set of outgoing edges from node v;
- $w(e)$ weight associated with edge e.

- We introduce the following binary variable:

$$y_e = \begin{cases} 1 & \text{if edge e is in the final matching,} \\ 0 & \text{otherwise} \end{cases}$$

- we further add a 0-weighted edge from every node corresponding to an incompatible pair to every node corresponding to a samaritan donor; as a result, the algorithm needs to explicitly find only cycles (not chains).

This algorithm uses a recursive formulation:

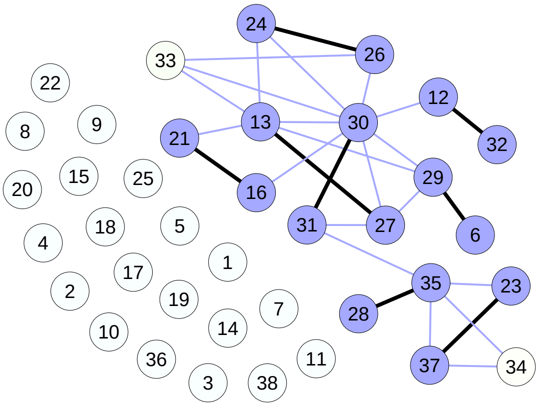
Maximize weighted flow s.t.

- total flow out of a pair is at most the total flow that goes into a pair;
- total flow out of an altruistic donor is at most 1;
- total flow that goes into a pair is at most 1;
- flow on each edge is binary.

(constraints can be introduced to eliminate those cycles which are too long)

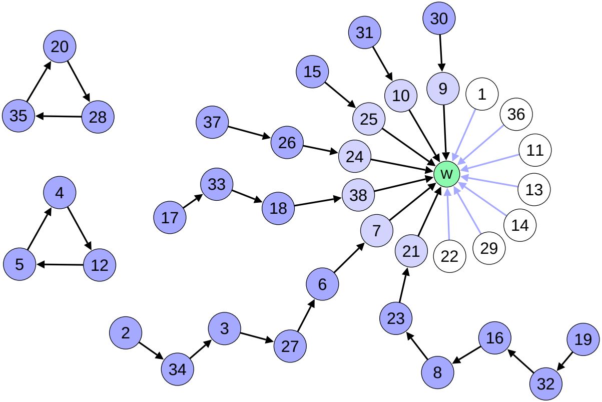
Results

Pairwise exchange



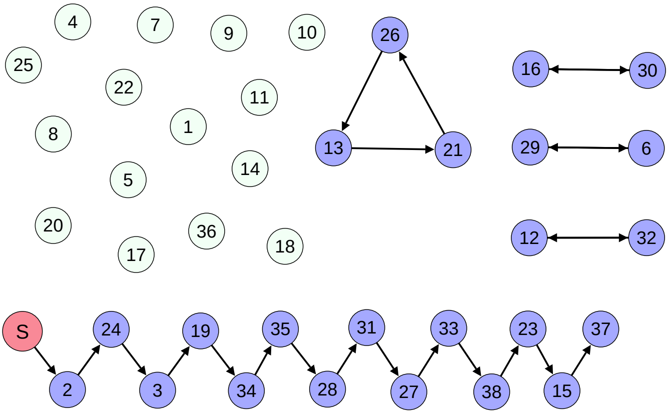
8 exchanges $\longrightarrow$ 16 transplants

TTCC



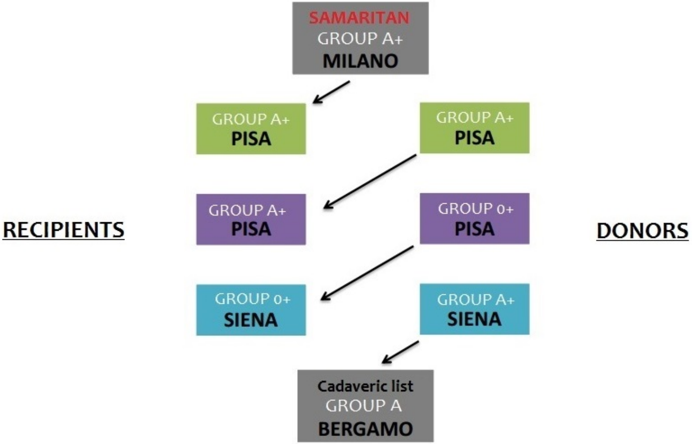
$\begin{cases} \text{2 cycles (6 transplants)} \\ \text{7 chains (18 transplants)} \end{cases} \longrightarrow$ 24 transplants

The recursive algorithm



$\begin{cases} \text{1 cycle (3 transplants)} \\ \text{3 exchanges (6 transplants)} \\ \text{1 chain (14 transplants)} \end{cases} \longrightarrow$ 23 transplants

A chain in Italy in 2016



«60 lives, 30 kidneys, all linked »

One of the longest chain performed in the Usa starting with a samaritan donor
(New York Times 2012)

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