Multi-Donor Organ Exchange

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Introduction

- **Kidney Exchange** became a wide-spread modality of transplantation within the last decade.
- More than 500 patients a year receive kidney transplant in the US along through exchange, about 10% of all live-donor transplants.
- In theory **live donor organ exchange** can be utilized for any organ for which live donation is feasible.

Institutions

- Human organs cannot received or given in exchange for "valuable consideration" (US, NOTA 1984, WHO)
- However, **live donor kidney exchange** is not considered as "valuable consideration" (US NOTA amendment, 2007)
- **Livers** and **lungs** are two of the other organs for which live donation is feasible.
- Live-donor liver and lung donations are common especially in regions where **deceased donation possibilities are limited**, such as Japan, South Korea, and Hong Kong.

Live-Donor Lobar Lung Transplants

- **Lungs:** Two donors each donate to a single patient a lobe of their lungs (less than 1/4th of total lung volume) to a donor. Lung lobes enlarge but do not regenerate.
    - In Japan around 40 patients receive transplants a year.
    - Cystic fibrosis disease is especially suitable for lung transplantation; most patients are typically juvenile.

Live-Donor Lobar Lung Transplants

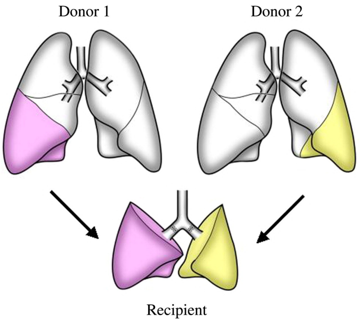


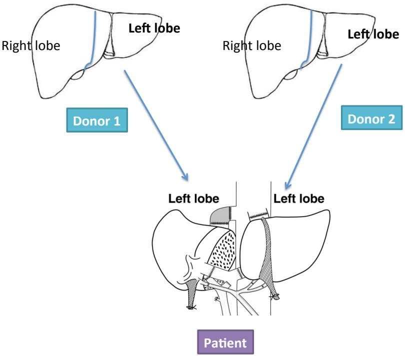
Figure from Date et al. Multimedia Manual of Cardiothoracic Surgery 2005

- Size compatibility and blood-type compatibility are required. No consensus on tissue-type compatibility, many transplant centers do not check.

Dual-Graft Liver Transplants

- The donor needs at least 30% remnant liver mass to survive. Usually right lobe is 60%, left lobe is 40% of the mass. In theory, either could be transplanted (but right is riskier for donor.)
- Patient needs roughly at least 40% of his own liver size to survive.
- Occasionally, the left lobe mass falls below 30%. Then donor cannot donate right lobe. And a single left lobe is usually too small for any patient.
- Then two lobes are needed for a patient from two donors.
  - In Korea, around 10% of the patients at the biggest center receive dual lobe liver transplants Potential is 20% of all live-donor liver transplants in Korea (850 per year).
  - In China, by live donation mandate of 2010, live donation is increasing. "Voluntary donation programs" became nationwide in 2013. Given the prevalence of Hep-B related end-stage liver disease in Asia, we would expect this phenomenon being very relevant.

Dual-Graft Liver Transplants



- Only Blood-type compatibility is required. Tissue-type incompatibility is not an issue for liver. Even though one lobe could be too small, two are enough in most cases. Size incompatibility is not an issue.

Simultaneous Liver-Kidney Transplants

- 7.5-15% of end-stage liver disease patients need also kidney transplantation.
- Simultaneous transplantation has been more effective than sequential transplantation for long term survival.
- Each KLT patient requires two designated live-donors, one for kidney and one for liver.
- Live donors are favored over deceased donors.

Contribution

- We introduce a new transplant modality to the attention of scientific community: **Multi-donor organ exchange**
- We model **multi-donor** organ exchange as matching problems to
  - characterize the maximum number of patients that can be saved under different institutional constraints and
  - find simple algorithms to find optimal exchanges.
- We simulate gains from exchange for dual-graft livers, simultaneous liver-kidney, and lungs to show that
  - **Dual-graft liver exchange** results gains **comparable** with single-graft liver exchange and dual-graft direct donation
  - **Lung exchange** can **quadruple** the number of patients who receive live donor lung donation, much more than kidney exchange.
  - An **integrated SLK** exchange program can **triple** gains of an **isolated SLK** exchange; and **quadruple** the number of SLK transplants even under 2&3-way exchanges.

Literature

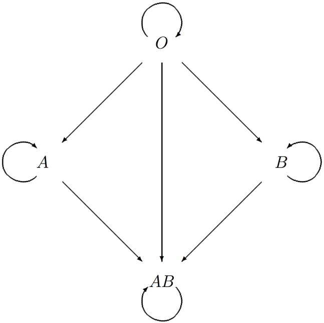
- **Kidney Exchange**: Among many
  - Rapaport [1986] proposed the idea
  - Ross et al. [1997] proposed ethical implementation grounds
  - Roth, Sönmez, Ünver [2004, 2005, 2007] introduced optimization, matching, and market design techniques
  - Segev et al. [2005] simulated gains, approval of the optimization techniques among doctors
  - Saidman et al. [2006] proposed non-simultaneous NDD chains
  - Abraham, Blum, Sandholm [2007] designed an efficient algorithm for the NP-complete computational problem
  - Rees et al. [2010] proof of concept of non-simultaneous NDD-chains
  - Ünver [2010] dynamically optimal clearinghouses
  - Sönmez & Ünver [2014,2015] and Nicolò & Rodriguez-Alvaréz [2014] compatible pairs in exchange
  - Roth, Sönmez, Ünver[2005] and Ashlagi & Roth [2014] multi-hospital exchange programs

Literature

- **Liver Exchange**: Only three papers
  - Hwang et al. [2010] proposed the idea and documented the practice in South Korea since 2003
  - Chen et al. [2010] documented the program in Hong Kong
  - Dickerson & Sandholm [2014] simulated gains from liver exchange and proposed joint liver+kidney exchange
- **Multi-Donor Exchange**: Ours is the first
  - Dual-Graft Liver Exchange
  - Lung Exchange
  - Simultaneous Liver-Kidney Exchange

Blood-Type Compatibility

- Blood-type compatibility is required (like kidneys).

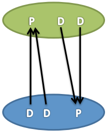


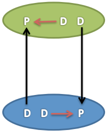
Multi-donor Exchange

- Finding two compatible donors is difficult.
- **Multi-donor exchange** can substantially increase the number of transplants.

Possible Two&Three-way Multi-Donor Exchanges

Two-Way:

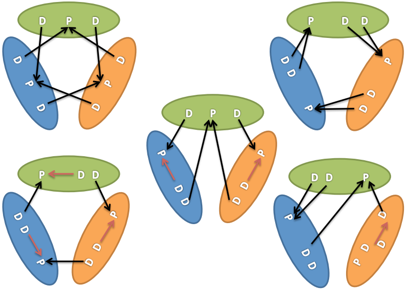




Possible Two&Three-way Multi-Donor Exchanges

Two-Way:

Three-Way:



Umbrella Model for Organ Exchanges

- Each patient in need of an organ has **k** attached donors
  - If all of them are compatible with her, she receives from them;
  - Otherwise, she participates in **exchange**
- Preferences: Dichotomous over compatible donors
- Compatibility:
  - Blood-type: Kidneys, Lungs, Livers
  - Tissue-type: Kidneys, possibly Lungs
  - Size: Lungs, Single-lobe Livers (roughly: each patient can get grafts from donors that are at least as heavy/tall as herself; the constraint could be more detailed for livers) Not a problem for dual-graft and juvenile lung transplantation.
- Number of Required Donors: **k**
  - $\mathbf{k} = \mathbf{1}$: Kidney, Single-lobe liver
  - $\mathbf{k} = \mathbf{2}$: Lung, Dual-graft liver, Kidney/Liver
- **Model 0: Kidneys** Roth, Sönmez, Ünver [2005]

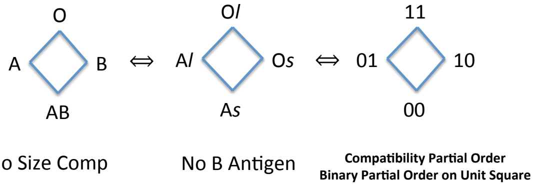
Model 1: Multi-Donor Organ Exchange Model

- We abstract away from size compatibility at first

Blood types:	O, A, B, AB
Blood-type incompatibility:	✓
Tissue-type incompatibility:	X
Size incompatibility:	X
Number of donors:	2

- Exact model for dual-graft liver exchange
- Exact model for lung exchange for juveniles (cystic fibrosis) – Donor size is not an issue
- For adult lung transplants, there is an equivalent interpretation: A, O are the most common blood types, making up of 80% of the world population. In this interpretation,
  - suppose there are two types of agents large (ℓ) and small (s), ℓ can only receive from ℓ, s can receive from both s and ℓ;
  - while patients and donors can have only A or O blood types.

Compatibility Partial Order



- **Compatibility**: 2 dimensional binary partial order on unit square: $\trianglerighteq$
- **Model 1a**: A blood antigen is the first dimension, B blood antigen is the second dimension. For $X \in \{A, B\}$
  - No X antigen $\equiv 1$
  - Has X antigen $\equiv 0$
- **Model 1b**: Size replaces antigen B in dimension 2 in the partial order.
  - $\ell \equiv$ No B antigen
  - $s \equiv$ Has B antigen

Multi-Donor Exchange Problem - Model 1a

- **Set of blood types** $\mathcal{B} = \{O, A, B, AB\} = \{11, 01, 10, 00\}$ **set of compatibility types**.
- A **patient-donors triple** is denoted by the blood types of its patient and donors respectively as $X - Y - Z = X - Z - Y \in \mathcal{B}^3$
- **Set of triple types** $\mathcal{B}^3$

Definition

A **multi-donor exchange problem** is a vector of non-negative integers $\mathcal{E} = \{n(X - Y - Z) \mid X - Y - Z \in \mathcal{B}^3\}$ such that for all $X - Y - Z \in \mathcal{B}^3$
(1) $n(X - Y - Z) = n(X - Z - Y)$ and
(2) $Y \trianglerighteq X$ and $Z \trianglerighteq X \implies n(X - Y - Z) = 0$.

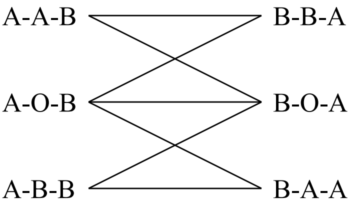
Two-way Multi-Donor Exchange

Lemma (Participation Lemma for Two-way Exchanges)

In any given multi-donor exchange problem, the only types that could be part of a two-way exchange are

$$A - Y - B \text{ and } B - Y - A$$

for all $Y \in \{O, A, B\}$.



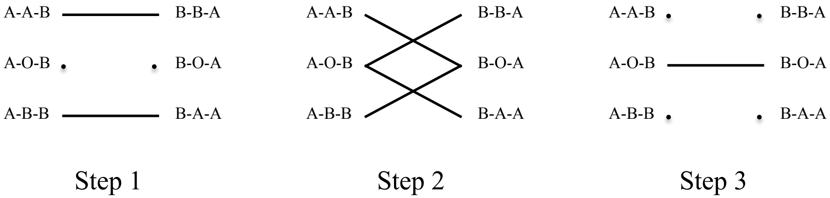
Sequential Two-way Multi-Donor Exchange Algorithm

Step 1: Match the maximum number of $A-A-B$ and $B-B-A$ types.
Match the maximum number of $A-B-B$ and $B-A-A$ types.

Step 2: Match the maximum number of $A-O-B$ types with any subset of the remaining $B-B-A$ and $B-A-A$ types.
Match the maximum number of $B-O-A$ types with any subset of the remaining $A-A-B$ and $A-B-B$ types.

Step 3: Match the maximum number of the remaining $A-O-B$ and $B-O-A$ types.

Sequential Two-way Multi-Donor Exchange Algorithm

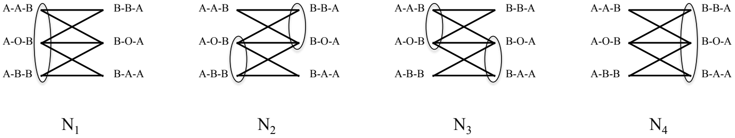


Optimal Two-way Multi-Donor Exchange

Theorem (Optimal Two-way Multi-Donor Exchange)

Given a multi-donor exchange problem, the sequential two-way multi-donor exchange algorithm maximizes the number of two-way exchanges. The maximum number of transplants through two-way exchanges is $2\min\{N_1, N_2, N_3, N_4\}$ *where:*

$$N_1 = n(A-A-B) + n(A-O-B) + n(A-B-B)$$
$$N_2 = n(A-O-B) + n(A-B-B) + n(B-B-A) + n(B-O-A)$$
$$N_3 = n(A-A-B) + n(A-O-B) + n(B-O-A) + n(B-A-A)$$
$$N_4 = n(B-B-A) + n(B-O-A) + n(B-A-A)$$



Larger Multi-Donor Exchanges

- Participation Lemma can be generalized to larger exchanges.
- In addition to the earlier types, some types with O blood type patients can be matched!

Lemma (Participation Lemma for All Exchanges)

Fix a multi-donor exchange problem and $n \geq 2$. Then, the only types that could be part of an n-way exchange are

$$O - Y - A, \quad O - Y - B, \quad A - Y - B, \quad \text{and} \quad B - Y - A$$

for all $Y \in \{O, A, B\}$. Furthermore, every n-way exchange must involve one A and one B patient.

Larger Multi-Donor Exchanges

- We will make the following assumption for the remaining results on multi-donor exchange.

Assumption (Long Run Assumption)

Regardless of the exchange technology available, there remains at least one "unmatched" patient from each of the two types $O-O-A$ and $O-O-B$.

Optimal Two & Three-way Multi-Donor Exchange

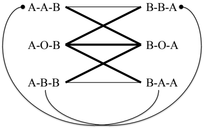
Proposition

Consider a multi-donor exchange problem that satisfies the long run assumption, and suppose $n = 3$. Then, there exists an optimal matching that consists of exchanges summarized in the following figure where:

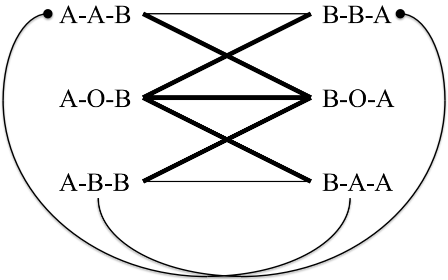
(1) *A regular (non-bold/no dotted end) edge between two types represents a 2-way exchange involving those two types.*

(2) *A bold edge between two types represents a 3-way exchange involving those two types and a $O - O - A$ or $O - O - B$ type.*

(3) *An edge with a dotted end represents a 3-way exchange involving two types from the dotted end, and one type from the non-dotted end.*



Optimal Two & Three-way Multi-Donor Exchange



Three-way exchanges (in the Proposition)

- with $A - O - B$ types (Kind 2 in Proposition)

$$\begin{array}{c} A - O - B \\ B - A - B \\ \mathbf{O - O - A} \end{array} \quad \text{and} \quad \begin{array}{c} A - O - B \\ B - A - A \\ \mathbf{O - O - B} \end{array}$$

- with 1 $A - B - B$ and 2 $B - A - A$ types (Kind 3 in Proposition)

$$\begin{array}{c} A - B - B \\ B - B - A \\ B - B - A \end{array}$$

- Symmetrically defined for $B - O - A$ and $B - A - A$ types

Sequential Two & Three-Way Multi-Donor Exchange Algorithm

Step 1: Carry out the 2 & 3-way exchanges in Proposition among $A-A-B$, $A-B-B$, $B-B-A$, and $B-A-A$ types to maximize the number of transplants subject to the following constraints $(*)$:

(1) Leave at least a total of

$$\min\left\{n(A-A-B)+n(A-B-B), n(B-O-A)\right\}$$

$A-A-B$ and $A-B-B$ types unmatched.

(2) Leave at least a total of

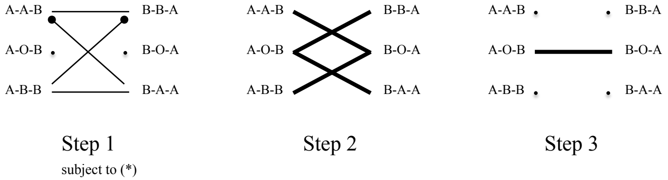
$$\min\left\{n(B-B-A)+n(B-A-A), n(A-O-B)\right\}$$

$B-B-A$ and $B-A-A$ types unmatched.

Step 2: Carry out the maximum number of 3-way exchanges in Proposition involving $A-O-B$ types and the remaining $B-B-A$ or $B-A-A$ types.

Carry out the maximum number of 3-way exchanges in Proposition involving $B-O-A$ types and the remaining $A-A-B$ or $A-B-B$ types.

Step 3: Carry out the maximum number of 3-way exchanges in Proposition involving the remaining $A-O-B$ and $B-O-A$ types.



Theorem (Optimal Two & Three-way Multi-Donor Exchange)

Given a multi-donor exchange problem satisfying the long run assumption, the sequential two & three-way multi-donor exchange algorithm maximizes the number of transplants through two and three-way exchanges.

Sufficiency of 6-way Exchange

Theorem (6-way Sufficiency Theorem)

Consider a multi-donor exchange problem satisfying the long run assumption. Then, there exists an optimal matching which consists only of exchanges involving at most 6-way exchanges.

Lack of Sufficiency of Less than 6-way Exchanges

Example

There are
3 blood type O patients and 6 blood type O donors,
2 blood type B patients and 4 blood type B donors, and
1 blood type A patient and 2 blood type A donors.
Hence, for optimality, each patients receives a graft from each of two donors of exactly his own blood type, and all are matched.

Triple types are:

1. $A - O - B$ needs to be in the same exchange as both Patients 2 & 3
2. $B - O - A$
3. $B - O - A$
4. $O - O - B$ needs to be in the same exchange as one of Patients 1, 2, 3
5. $O - O - B$ needs to be in the same exchange as one of Patients 1, 2, 3
6. $O - O - B$ needs to be in the same exchange as one of Patients 1, 2, 3

The blue argument along with the red arguments imply that a 6-way exchange is necessary. ▸ Simulations

Optimal Exchange

Theorem (Maximum Number of Patients Matched)

The number of patients matched in an optimal matching is given by

$$\overline{m} - \mathbf{i} + \min\{n(A-O-B), \overline{s}_B\} + \min\{n(B-O-A), \overline{s}_A\},$$

where $\mathbf{i} \in \{0,1\}$, *and*
$\overline{m} := \overline{m}_A + \overline{m}_B$ *where*
$\overline{m}_A := \min\{p_A, \lfloor \frac{d_A + d_O}{2} \rfloor, \overline{s}_B\}$
$\overline{s}_B := 2n(B-O-A) + n(B-A-B) + 2n(B-A-A)$
$\overline{m}_B$ *and* $\overline{s}_A$ *symmetrically defined.*

$\overline{m}_A$: $\#A$ patients that can be matched,
$\overline{s}_B$: Max. $\#A$ patients that can be potentially matched with the help of B patients,
p_A : $\#A$ patients, and d_X : $\#X$ donors

Dual-Graft Liver Exchange Simulations					
Sample Size	**1-Donor Direct**		**1-Donor Exchange**	**2-Donor Direct**	**2-Donor Exchange**
250	59.998 (6.9937)	**2-way**	+35.032 (7.5297)	+48.818 (7.1265)	+26.096 (5.8167)
		2&3-way	+49.198 (10.37)	+43.472 (7.1942)	+34.796 (8.2052)

Table: Using Korean data, 500 simulations

Welfare Gains from Lung Exchange

Lung Exchange Simulations						
Sample	**Direct**	**Exchange Technology**				
Size	**Donation**	**2-way**	**2&3-way**	**2–4-way**	**2–5-way**	**Unrestricted**
10	1.256	+0.292	or +0.452	or +0.506	or +0.52	or +0.524
	(1.0298)	(0.72925)	(1.0668)	(1.1987)	(1.2445)	(1.2604)
20	2.474	+1.128	or +1.818	or +2.176	or +2.396	or +2.668
	(1.4919)	(1.4183)	(2.0798)	(2.4701)	(2.7273)	(3.1403)
50	6.31	+4.956	or +8.514	or +10.814	or +12.432	or +16.506
	(2.2962)	(2.9759)	(4.5191)	(5.3879)	(5.9609)	(7.1338)

Table: Using Japanese Data, 500 simulations

Welfare Gains from Simultaneous Liver-Kidney Exchange

Simultaneous Liver-Kidney Exchange Simulations												
SLK Patient Fraction in Liver Pool	Sample Sizes			Direct Donation			Exchange Regime					
							Isolated			Integrated		
	KA	SLK	LA	KA	SLK	LA	KA	SLK	LA	KA	SLK	LA
7.5%	**535**	**35**	**430**	244.09	2.426	67.982	+151.34	+1.352	+53.26	or +154.48	+7.468	+54.264
		$n = 1000$		(11.783)	(1.5222)	(7.8642)	(14.841)	(1.5128)	(9.5101)	(14.919)	(2.4366)	(9.5771)
15%	**518**	**72**	**410**	236.23	5.076	64.874	+146.18	+4.108	+50.084	or +152.17	+14.74	+52.376
		$n = 1000$		(11.605)	(2.2646)	(7.5745)	(14.758)	(2.6883)	(9.3406)	(14.986)	(3.5175)	(9.3117)

Table: Using Korean Data, 500 Simulations

Conclusion

- We introduce a new transplant modality to the attention of scientific community: **multi-donor organ exchange**
- We model **multi-donor** organ exchange as matching problems to
    - characterize the maximum number of patients that can be saved under different institutional constraints and
    - find simple algorithms to find optimal exchanges.
- We simulate gains from exchange for dual-graft livers, simultaneous liver-kidney, and lungs to show that
    - **Dual-graft liver exchange** results gains **comparable** with single-graft liver exchange and dual-graft direct donation
    - **Lung exchange** can **quadruple** the number of patients who receive live donor lung donation, much more than kidney exchange.
    - An **integrated SLK** exchange program can triple gains of an **isolated SLK** exchange; and **quadruple** the number of SLK transplants even under 2&3-way exchanges.

Current Direction

- Incentive problems in liver exchange
- Dual-graft liver exchange/single-lobe exchange integration: model, ethical issues.
- Implementation: **Japan**

Lemma (Optimality Limit)

In a given exchange problem, if all $A-Y-B$ and $B-Y-A$ for $Y \in \{O, A, B\}$ can be matched perfectly in a matching μ in exchanges among themselves, then an optimal matching matches exactly

$$n(A-A-B)+n(A-B-B)+2n(A-O-B)$$
$$+n(B-A-A)+n(B-A-B)+2n(B-O-A)$$

patients. Such an optimal matching can be formed inserting in every exchange in μ for any $A-O-B$ or $B-O-A$ triple, one $O-O-A$ or $O-O-B$ type triple.

- We refer to this operation treating an $A-O-B$ triple like an $A-A-B$ or $B-A-A$ triple

$$\left\{ \begin{array}{c} A-O-B \\ O-O-A \end{array} \right\} \Longrightarrow A-A-B$$

$$\left\{ \begin{array}{c} A-O-B \\ O-O-B \end{array} \right\} \Longrightarrow A-B-B$$

- Similarly for $B-O-A$ (like $B-A-A$ or $B-A-B$)

Optimal Multi-Donor Exchange Algorithm

- If we can find an algorithm simultaneously satisfying

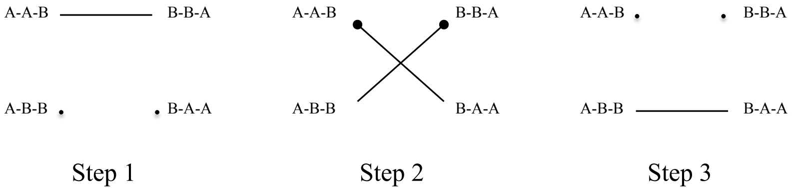
Obj. 1. match types $A - Y - B$, $B - Y - A$ for all $Y \in \{O, A, B\}$ with each other in two and three-way exchanges optimally, and

Obj. 2. maximize the number of $A - O - B$ and $A - B - O$ that can be matched in any matching

  then we can insert for each $A - O - B$ and $B - O - A$ used one additional $O - O - B$ or $O - O - A$ using the above Reduction depending on how each $A - O - B$ and $B - O - A$ was treated in the above matching.

- This operation yields, by Optimality Limit Lemma above, an optimal matching only with **6 or less-way exchanges**.

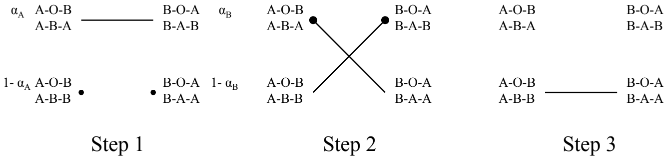
- Since we will classify $A-O-B$ as $A-B-A$ or $A-B-B$ and vice versa for $B-O-A$, inspect matching $A-B-A$, $A-B-B$, $B-A-B$, $B-A-A$:



- We then find out how to classify $A-O-B$ and $B-O-A$ so that we maximize their matches and total matches subject to Obj. 1 and Obj. 2.

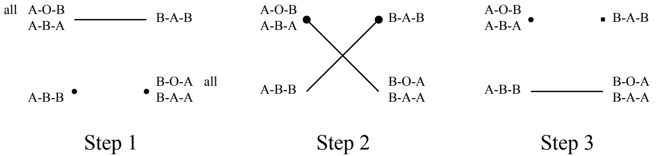
Optimal Multi-Donor Exchange Algorithm

Case 1 **if there are comparable A and B patients**



Every patient is matched.

Case 2.1 **if there are too many A patients**



Some A patients remain unmatched.
At most one B-A-B or some A-B-A likes remain unmatched, but not both.

Sufficiency of 6-way Revisited

- Above construction also proves 6-way Sufficiency Theorem