Dual-Donor Organ Exchange

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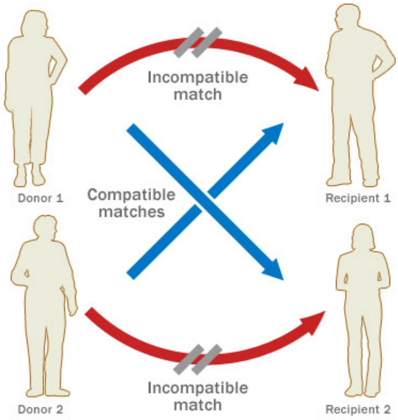
Introduction

- **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.


Incompatible
match
Donor 1
Compatible
matches
Recipient 1
Donor 2
Incompatible
match
Recipient 2

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.
- Moreover, in many occasions, each live-donor transplant for these organs requires the involvement of two donors.

Live-Donor Lobar Lung Transplants

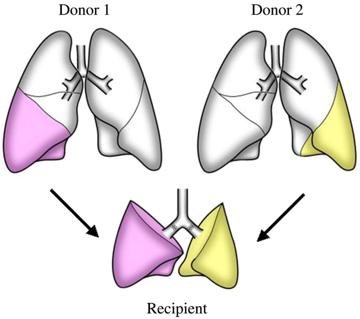


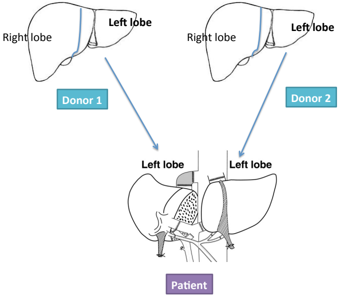
Figure from Date et al. Multimedia Manual of Cardiothoracic Surgery 2005

- 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.

Live-Donor Lung Transplants

- In Japan around 20 patients receive transplants a year. The number is increasing.
- Size compatibility and blood-type compatibility are required. No consensus on tissue-type compatibility, many transplant centers do not check.

Dual-Graft Liver Transplants



- Patient needs roughly at least 40% of his own liver size to survive.
- Donor needs at least 30% remnant liver volume to survive. Usually right lobe is 60+%, left lobe is 40-% of liver.
- Occasionally, the left lobe mass falls below 30%. Donor cannot donate right lobe and a single left lobe is too small for patient.
- Then two lobes are needed for a patient from two donors.

Dual-Graft Liver Transplants

- 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.
- 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 <u>two</u> 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

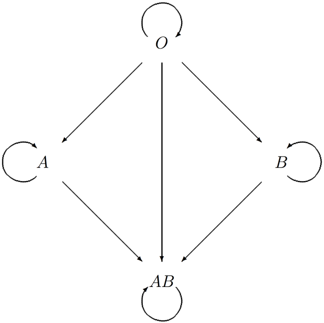
- **Kidney Exchange**: Among many
  - Rapaport [1986] proposed the idea
  - Ross et al. [1997] proposed ethical implementation grounds
  - Roth, Sönmez, Ünver [2004, 2005, 2007] introduced optimization, matching, and market design techniques
  - Segev et al. [2005] simulated gains, approval of the optimization techniques among doctors
  - Roth 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] showed asymptotic gains from 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).



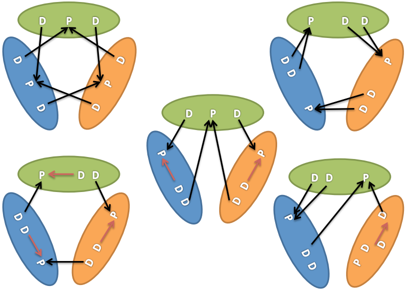
Multi-donor Exchange

- 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:

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]

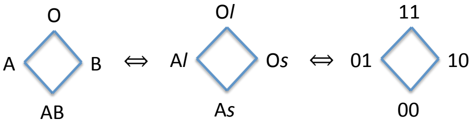
Model 1: Multi-Donor Organ Exchange Model

- 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



No Size Comp — No B Antigen — **Compatibility Partial Order**
Binary Partial Order on Unit Square

- **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 $Z \trianglerighteq X \implies n(X - Y - Z) = 0$.

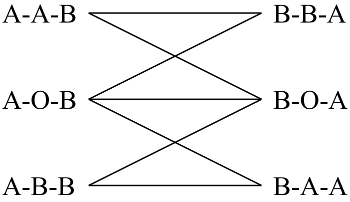
Two-way Multi-Donor Exchange

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 $Y, Y' \in \{O, A, B\}$.



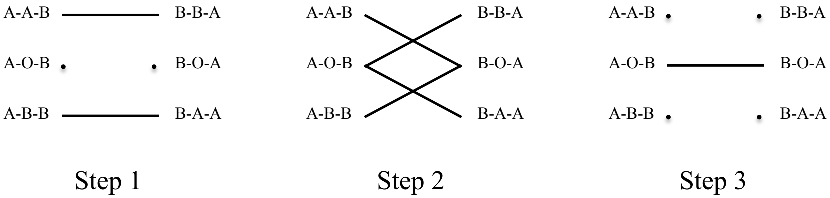
Sequential Two-way Multi-Donor Exchange Algorithm

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.

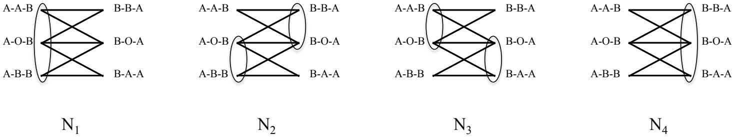
Sequential Two-way Multi-Donor Exchange Algorithm



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:*

$$
\begin{aligned}
N_1 &= n(A-A-B) + n(A-O-B) + n(A-B-B) \\
N_2 &= n(A-O-B) + n(A-B-B) + n(B-B-A) + n(B-O-A) \\
N_3 &= n(A-A-B) + n(A-O-B) + n(B-O-A) + n(B-A-A) \\
N_4 &= n(B-B-A) + n(B-O-A) + n(B-A-A)
\end{aligned}
$$



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

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

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

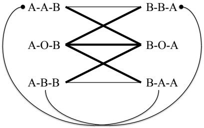
Proposition

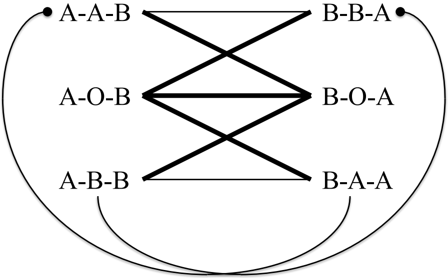
Consider a multi-donor exchange problem that satisfies the long run assumption, and suppose $n = 3$. Then, there exists an optimal matching that consists of exchanges summarized in the following figure where:

(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.*




A-A-B
B-B-A
A-O-B
B-O-A
A-B-B
B-A-A

Three-way exchanges (in the Proposition)

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

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

- 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

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

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

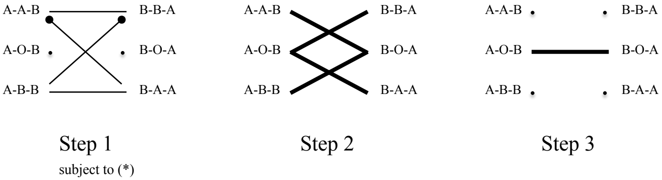
$B-B-A$ and $B-A-A$ types unmatched.

Two & Three-Way Multi-Donor Exchange Algorithm

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.



Optimal Two & Three-Way Multi-Donor Exchange

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.

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

Welfare Gains from Dual-Graft Liver Exchange

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 (1.0298)	+0.292 (0.72925)	or +0.452 (1.0668)	or +0.506 (1.1987)	or +0.52 (1.2445)	or +0.524 (1.2604)
20	2.474 (1.4919)	+1.128 (1.4183)	or +1.818 (2.0798)	or +2.176 (2.4701)	or +2.396 (2.7273)	or +2.668 (3.1403)
50	6.31 (2.2962)	+4.956 (2.9759)	or +8.514 (4.5191)	or +10.814 (5.3879)	or +12.432 (5.9609)	or +16.506 (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.
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  - 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**