Multi-Donor Organ Exchange

M. Utku Ünver

*Boston College*

(with Haluk Ergin and Tayfun Sönmez)

COMSOC-2016, Toulouse
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.
Human organs cannot be 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

The right lung is divided into three lobes, whereas the left lobe is divided into two lobes.

LDLLT involves donation of a lower lobe from each of two blood type and size compatible living donors.

- Finding two compatible donors is difficult, suggesting that gains from lung exchange might be considerable!

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.

Figure from Date et al. Multimedia Manual of Cardiothoracic Surgery 2005
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.
- 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.
Kidney Exchange: Among many

- Rapaport [1986] proposed the idea
- Ross et al. [1997] proposed ethical implementation grounds
- 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
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 is required (like kidneys).
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:

Ergin, Sönmez, Ünver

Multi-Donor Organ Exchange
Possible Two & Three-way Multi-Donor Exchanges

Two-Way:

Three-Way:
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: $k$

- $k = 1$: Kidney, Single-lobe liver
- $k = 2$: 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 (\( \ell \)) and small (\( s \)), \( \ell \) can only receive from \( \ell \), \( s \) can receive from both \( s \) and \( \ell \);
    - while patients and donors can have only \( A \) or \( O \) blood types.
Compatibility Partial Order

- **Compatibility**: 2 dimensional binary partial order on unit square: $\triangleright$
- **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
• 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. $Y \triangleright X$ and $Z \triangleright X \implies n(X - Y - Z) = 0$. 

Ergin, Sönmez, Ünver
Multi-Donor Organ Exchange
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 \( Y \in \{O, A, B\} \).

\[
\begin{align*}
A-A-B & \quad \leftrightarrow \quad B-B-A \\
A-O-B & \quad \leftrightarrow \quad B-O-A \\
A-B-B & \quad \leftrightarrow \quad B-A-A
\end{align*}
\]
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

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

Step 1

Step 2

Step 3
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:

\[
\begin{align*}
N_1 &= n(A - A - B) + n(A - O - B) + n(A - B - B) \\
N_2 &= n(A - O - B) + n(A - B - B) + n(B - B - A) + n(B - O - A) \\
N_3 &= n(A - A - B) + n(A - O - B) + n(B - O - A) + n(B - A - A) \\
N_4 &= n(B - B - A) + n(B - O - A) + n(B - A - A)
\end{align*}
\]
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.*
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.
Lemma 3: Consider a lung 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 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.
Three-way exchanges (in the Proposition)

- with $A - O - B$ types (Kind 2 in Proposition)
  
  $A - O - B \quad A - O - B$
  
  $B - A - B \quad \text{and} \quad B - A - A$
  
  $O - O - A \quad O - O - B$

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

- Symmetrically defined for $B - O - A$ and $B - A - A$ types
Step 1: Carry out the 2 & 3-way exchanges in Proposition among
maximize the number of transplants subject to the following
constraints ($\ast$):

(1) Leave at least a total of

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


(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.
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.
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
Theorem (Maximum Number of Patients Matched)

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

\[ m - i + \min\{n(A - O - B), s_B\} + \min\{n(B - O - A), s_A\}, \]

where \( i \in \{0, 1\} \), and

\[ m := m_A + m_B \text{ where} \]
\[ m_A := \min\{p_A, \left\lfloor \frac{d_A + d_O}{2} \right\rfloor, s_B\} \]
\[ s_B := 2n(B - O - A) + n(B - A - B) + 2n(B - A - A) \]
\[ m_B \text{ and } s_A \text{ symmetrically defined.} \]

\( m_A \): \#A patients that can be matched,
\( s_B \): 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

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>1-Donor Direct</th>
<th>1-Donor Exchange</th>
<th>2-Donor Direct</th>
<th>2-Donor Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>59.998</td>
<td>+35.032</td>
<td>+48.818</td>
<td>+26.096</td>
</tr>
<tr>
<td>(6.9937)</td>
<td></td>
<td>(7.5297)</td>
<td>(7.1265)</td>
<td>(5.8167)</td>
</tr>
<tr>
<td>2&amp;3-way</td>
<td>+49.198</td>
<td>+43.472</td>
<td>+34.796</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(10.37)</td>
<td>(7.1942)</td>
<td></td>
<td>(8.2052)</td>
</tr>
</tbody>
</table>

**Table:** Using Korean data, 500 simulations
## Lung Exchange Simulations

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Direct Donation</th>
<th>2-way</th>
<th>2&amp;3-way</th>
<th>2–4-way</th>
<th>2–5-way</th>
<th>Unrestricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.256</td>
<td>+0.292</td>
<td>or +0.452</td>
<td>or +0.506</td>
<td>or +0.52</td>
<td>or +0.524 (1.0298)</td>
</tr>
<tr>
<td></td>
<td>(1.0298)</td>
<td>(0.72925)</td>
<td>(1.0668)</td>
<td>(1.1987)</td>
<td>(1.2445)</td>
<td>(1.2604)</td>
</tr>
<tr>
<td>20</td>
<td>2.474</td>
<td>+1.128</td>
<td>or +1.818</td>
<td>or +2.176</td>
<td>or +2.396</td>
<td>or +2.668 (1.4919)</td>
</tr>
<tr>
<td></td>
<td>(1.4919)</td>
<td>(1.4183)</td>
<td>(2.0798)</td>
<td>(2.4701)</td>
<td>(2.7273)</td>
<td>(3.1403)</td>
</tr>
<tr>
<td>50</td>
<td>6.31</td>
<td>+4.956</td>
<td>or +8.514</td>
<td>or +10.814</td>
<td>or +12.432</td>
<td>or +16.506 (2.2962)</td>
</tr>
<tr>
<td></td>
<td>(2.2962)</td>
<td>(2.9759)</td>
<td>(4.5191)</td>
<td>(5.3879)</td>
<td>(5.9609)</td>
<td>(7.1338)</td>
</tr>
</tbody>
</table>

**Table:** Using Japanese Data, 500 simulations
### Simultaneous Liver-Kidney Exchange Simulations

<table>
<thead>
<tr>
<th>Liver Pool</th>
<th>SLK Patient Sizes</th>
<th>Sample Sizes</th>
<th>Direct Donation</th>
<th>Exchange Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KA</td>
<td>SLK</td>
<td>LA</td>
<td>KA</td>
</tr>
<tr>
<td>7.5%</td>
<td>535</td>
<td>35</td>
<td>430</td>
<td>244.09</td>
</tr>
<tr>
<td>15%</td>
<td>518</td>
<td>72</td>
<td>410</td>
<td>236.23</td>
</tr>
</tbody>
</table>

**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 $\mu$ 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 $\mu$ 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:

\[
\begin{align*}
\{ & A - O - B \\
& O \leftarrow O - A \}
\implies A - A - B \\

\{ & A - O - B \\
& O \leftarrow O - B \}
\implies A - B - B
\end{align*}
\]

Similarly for $B - O - A$ (like $B - A - A$ or $B - A - B$).
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 $A - B - A$, $A - B - B$, $B - A - B$, $B - A - A$:

- Step 1
- Step 2
- Step 3

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**

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

![Diagram](image)

Step 1

Step 2

Step 3

Every patient is matched.

---

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

![Diagram](image)

Step 1

Step 2

Step 3

Some A patients remain unmatched. At most one B-A-B or some A-B-A likes remain unmatched, but not both.
Above construction also proves 6-way Sufficiency Theorem