Living Donor Lobar Liver/Lung Exchange

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Kidney Exchange and Market Design

 Kidney exchange, originally proposed by Rapaport (1986), has become a major source of kidney transplantations with the introduction of optimization/market design techniques to kidney exchange by Roth, Sönmez, & Ünver (2004, 2005, 2007).

- A handful of transplants from kidney exchanges in the US prior to 2004, increased to 93 in 2006 and to 553 in 2010.
- Currently transplants from kidney exchanges in the US accounts for about 10% of all living donor kidney transplants.



Figure from Massie et al AJT 2013

Organs with Living Donor Transplantation

- While a kidney is the most common organ donated by living donors, it is not the only one.
- Living Donor Liver Transplantation:
 - Individuals can donate parts of liver, which has the ability to regenerate and regain full function.

The regeneration can occur within weeks of the transplant.

• Second most common organ in the US for living donation accounting for about 5% of liver transplantations in 2013.

This rate has peaked at about 10% in 2001, and declined since then.

- Korea and Japan lead the world in the number of living donor liver transplantations.
- First Liver Exchange has been carried out in South Korea in 2003.

Organs with Living Donor Transplantation

• Living Donor Lung Transplantation:

• There are 5 lung lobes and a living donor can donate a lobe to someone in need of a lung transplant.

The lung lobe does not regenerate, but the remaining lung tissue expands to fill the donated area.

• While living donor lung donation was introduced in the US, most living donor lung transplantations are carried out in Japan.

In 2013, about a third of lung transplantations in Japan were from living donors.

• We are the first to propose and analyze living donor lung exchange.

Literature on Living Donor Organ Exchange

• Kidney Exchange By now numerous. Some key contributions are:

- Rapaport (1986): Proposed the concept
- Ross et al. (1997): Generated renewed interest in the concept
- Roth, Sönmez, & Unver (2004, 2005, 2007): Introduced optimization and market design techniques to kidney exchange
- Segev et al. (2005): Further advocated use of optimization
- Saidman et al. (2006): Proposed non-simultaneous NDD chains
- Abraham, Blum, & Sandholm (2007): Focus on computational aspects for NP-hard versions of the problem
- Rees et al. (2010): Proof of concept for NDD chains

Literature on Living Donor Organ Exchange

• Liver Exchange Only three papers we are aware of

- Hwang et al. (2010): Introduced the concept and have been practicing liver exchange in South Korea since 2003
- Chan et al. (2010): Hong Kong became the second country to practice liver exchange
- Dickerson & Sandholm (2014): Simulated gains from liver exchange and proposed joint liver+kidney exchange
- Lung Exchange Nothing so far
 - Surprisingly, South Koreans who practiced not only the first kidney exchange but also the first liver exchange, and Japanese who championed living donor lung donation have not invented lung exchange yet!

Contributions of this Paper

- Propose living donor lung exchange as a lung transplantation modality
- Formulate an analytical model on lung exchange and provide optimal lung exchange algorithms
- Formulate an analytical model on liver exchange and provide optimal liver exchange algorithms
- Analyze the impact of size constraints on liver exchange
- Simulate gains from exchange for the lung and the liver
 Show that marginal contribution of exchange is considerably higher for the lung in comparison with kidney or liver

Living Donor Liver Transplantation

• Due to cultural differences, living donor liver transplantation is considerably more common than deceased donor liver transplantation in Asian countries.



Annual liver transplant activity per million population

Figure from Chen et al Nature Reviews Gastroenterology & Hepatology 2013

Segmental Anatomy of Liver



Graft Selection for Living Donor Liver Transplantation



Donor Mortality: 0.5% Size: 60% Most risky! Donor Mortality: 0.1% Size: 40% Often too small Donor Mortality: Rare Size: 20% Only pediadric

Increased Use of Right Lobe over Time

- Since the left lobe of the donor is often too small for the patient, right lobe transplantations have increased over time, despite fivefold mortality risk.
- This is possibly at odds with the oath all physicians pledge to keep: Primum non nocere – First, cause no harm.



Figure from Shimada et al The Journal of Medical Investigation 2005

Decline of Living Donor Liver Transplants in the US

- Indeed, the death of a living donor in 2001 contributed significantly to the decline of living donor liver transplants in the US:
 - US Living Donor Liver Transplants in 2001: 524
 - US Living Donor Liver Transplants in 2013: 252

The New York Times

Archives

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Liver Exchange: Hitting Two Birds with One Stone

- Liver exchange may be used to reduce the number of right lobe donations while at the same time increasing the number of donations!
- First liver exchange was conducted in South Korea in 2003 (Hwang et al 2010).

Other countries following their example include Hong Kong and Turkey.



Living Donor Lobar Lung Transplantation

- Living donor lobar lung transplantation (LDLLT) was introduced in 1992 by Dr. Vaughn Starnes, a transplant surgeon at the University of Southern California.
- Deceased donor lungs have not been able to meet the increasing needs for these organs and hundreds of patients die each year while waiting for lung transplantation.
- Initially the procedure was reserved for critically ill deteriorating patients who would have died without this intervention. The indication now has been expanded to include cystic fibrosis, and other end-stage lung disease patients.

Living Donor Lobar Lung Transplantation

- 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

An "Umbrella" Living Donor Organ Exchange Model

- Patients: Each patient needs $k \in \mathbb{Z}_{++}$ units of a specific organ.
- Donors: Each patient has k donors, each to donate 1 unit of the given organ.
- Outcome/Matching: An assignment of donors to patients such that each patient is assigned exactly *k* units of the given organ.
- Preferences: Dichotomous
 - There is a good outcome and a bad outcome for each patient.
 - Patient is indifferent between good outcomes; indifferent between bad outcomes; and prefers any good outcome to any bad outcome.
 - Each organ (or donor) is either compatible or incompatible with a given patient.
 - An outcome is good for a patient is he is assigned k compatible organs, and it is bad otherwise.

An "Umbrella" Living Donor Organ Exchange Model

- Compatibility: Depending on the given organ, compatibility may depend on the following factors.
 - Blood-type compatibility: Kidney, liver, lung.
 Patents can receive donations only from blood-type compatible donors.
 - Tissue-type compatibility: Kidney, possibly lung. Patient shall not have preformed antibodies to donor tissue (i.e. no positive crossmatch).
 - Size compatibility: Liver, lung. Donor organ (or graft) shall be "big enough" for the patient.

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- Baseline Model: Kidney Exchange (Roth, Sönmez & Ünver 2005, 2007)
 - Donor number: k = 1.
 - Blood-type compatibility: \checkmark
 - Tissue-type compatibility: \checkmark
 - Size compatibility:

Blood-type Compatibility

- Human blood may have the following red cell antigens: A, B.
- Human body produces antibody anti-A in the absence of antigen A and antibody anti-B in the absence of antigen B.
- There are four blood-types:
 - A (antigen A and antibody anti-B)
 B (antigen B and antibody anti-A)
 - AB • O

- (antigens A and B) (antibodies anti-A and anti-B)
- Hence, in the absence of other complications:
 - Type O organs can be transplanted into any patient;
 - type A organs can be transplanted into type A or type AB patients;
 - type B organs can be transplanted into type B or type AB patients;
 - type AB organs can only be transplanted into type AB patients.

Representation of Blood-type Compatibility

- $\mathcal{B} = \{O, A, B, AB\}$: The set of blood types with generic elements $X, Y, Z \in \mathcal{B}$.
- Donation partial order ⊵:

 $X \trianglerighteq Y \iff$ blood type X can donate to blood type Y



Graphical Representation:

 $X \trianglerighteq Y \iff$ there is a downward path from blood type X to blood type Y

Lung Exchange Model

• Lung exchange differs from kidney exchange in two key ways: Presence of two donors and size compatibility.

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- Views on the importance of tissue-type compatibility differ in lung transplantation community and it is not a requirement for transplantation at many centers.
- As a first approximation, we will abstract away from size compatibility and focus on the implications of a second donor in lung exchange.
- A Simplified Lung Exchange Model:
 - Donor number: k = 2.
 - Blood-type compatibility: \checkmark
 - Tissue-type compatibility: X
 - Size compatibility:
- Patient representation:

A triple of blood types $X - Y - Z \in \mathcal{B}^3$ X: blood type of the patient Y, Z: blood types of the donors

Alternative Interpretation of the Lung Exchange Model

85% of the US population is of blood types A or O.
 For some ethnicities 100% of the population is of blood types A or O (eg. Aborigines).

Hence a model with only 2 blood types is of some interest.

- An Equivalent Lung Exchange Model:
 - Blood types: A, O
 - Donor number: k = 2.
 - Blood-type compatibility: \checkmark
 - Tissue-type compatibility: X
 - Size compatibility: \checkmark with two types large (I) and small (s)
- Compatibility: A donor can donate to a patient if and only if
 - (1) the patient is blood type compatible with the donor, and
 - (2) the donor is not strictly smaller than the patient.

Alternative Interpretation of the Lung Exchange Model

The Partial Order $\stackrel{\sim}{\succeq}$ on $\{O, A\} \times \{I, s\}$

The Partial Order \geq on $\{O, A, B, AB\}$



 $\tilde{\underline{\triangleright}} \text{ is isomorphic to } \underline{\triangleright} \text{ if } \\ \text{we identify} }$

- OI with O,
- AI with A,
- Os and B, and
- As with AB.

• Think of being large as the lack of antibody anti-B!

Lung Exchange Problem

- Definition: A lung exchange problem is a vector of nonnegative integers $\mathcal{E}_{lung} = \{n(X - Y - Z) : X - Y - Z \in \mathcal{B}^3\}$ such that: (1) $\forall X - Y - Z \in \mathcal{B}^3$ n(X - Y - Z) = n(X - Z - Y)(2) $\forall X - Y - Z \in \mathcal{B}^3$ $Y \supseteq X$ and $Z \supseteq X \implies n(X - Y - Z) = 0$.
- Here n(X Y Z) denotes the number of patients of type X Y Z and
 - (1) the first condition simply means that there is no difference between types X Y Z and X Z Y, whereas
 - (2) the second condition means that compatible pairs do not participate in exchange.

Two-way Lung Exchange

• Two patients can participate in two-way lung exchange if their donors can be partitioned such that two donors can donate to first patient and the remaining two donors can donate to the second patient.

Lemma 1: In any given lung exchange problem, the only types that could be part of a two-way exchange are A - Y - B and B - Y' - A where $Y, Y' \in \{A, B, O\}.$



Two-way Lung Exchange Algorithm

• Consider the following sequential two-way lung 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.

Two-way Lung Exchange Algorithm



Optimal Two-way Lung Exchange

Theorem 1: Given a lung exchange problem, the sequential lung exchange algorithm maximizes the number of two-way exchanges. The maximum number of transplants through two-way exchanges is 2 min{N₁, N₂, N₃, N₄} 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 Exchanges

• We have seen earlier that every two-way exchange must involve one blood type A and one blood type B patient.

The following Lemma generalizes this observation to larger exchanges:

• Lemma 2: Fix a lung exchange problem and $n \ge 2$. Then, the only types that could be part of an *n*-way exchange are

O-Y-A, O-Y-B, A-Y-B, and B-Y-A

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

Three-way Lung Exchange

• We will make the following assumption about the types O - O - Aand O - O - B for the remaining results on lung exchange.

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 Three-way Lung Exchange

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:

- 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.

Two & Three-Way Lung Exchange Algorithm

• Consider the following sequential two & three-way lung exchange algorithm:

Step 1: Carry out the 2 & 3-way exchanges in Lemma 3 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 Lung Exchange Algorithm

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



Optimal Two & Three-Way Lung Exchange

• Theorem 2: Given a lung exchange problem satisfying the long-run assumption, the sequential two & three-way lung exchange algorithm maximizes the number of transplants through two and three-way exchanges.

Sufficiency of 6-way Exchange

• Theorem 3: Consider a lung 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

- The following example shows that Theorem 3 fails to hold for n < 6.
 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 lung lobe from two donors of exactly his own blood type.

Patient 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 to give a transplant for all 6 patients.

Liver Exchange Model

• Liver exchange differs from kidney exchange in two key ways:

- The lack of tissue-type compatibility, and
- the presence of size compatibility.
- In the absence of size compatibility the scope for liver exchange would be very limited: The only viable exchange would be between
 - a blood type A patient with blood type B donor and
 - a blood type B patient with blood type A donor.
- A Liver Exchange Model:
 - Donor number: k = 1.
 - Blood-type compatibility: ✓
 - Tissue-type compatibility: X

• Size compatibility: \checkmark with two types large (I) and small (s)

Liver Exchange Model

•
$$\underbrace{\{O, A, B, AB\}}_{\mathcal{B}} \times \underbrace{\{I, s\}}_{\mathcal{S}}$$
: Set of individual types

- Compatibility: A donor can donate to a patient if and only if
 - (1) the patient is blood type compatible with the donor, and
 - (2) the donor is not strictly smaller than the patient.





An Equivalent Representation

- Consider the following two partially ordered sets:
 - (1) The liver donation partial order \succeq on $\mathcal{B} \times \mathcal{S}$, and
 - (2) the standard partial order ≥ over the corners of the three-dimensional cube {0,1}³.





An Equivalent Representation



- Note that (B × S, ⊵) and ({0,1}³, ≥) are order isomorphic, where the order isomorphism associates each individual type τ ∈ B × S with the following vector X ∈ {0,1}³:

Liver Exchange Problem

- For notational transparency, we will work with the equivalent representation $(\{0,1\}^3,\geq)$.
- Definition: A liver exchange problem is a vector of nonnegative integers $\mathcal{E}_{liver} = \left\{ n(X Y) : X Y \in \left(\{0, 1\}^3\right)^2 \right\}$ such that

$$\forall X - Y \in (\{0,1\}^3)^2$$
 $\underbrace{Y \ge X \implies n(X - Y) = 0}_{\text{no compatible pairs}}.$

- Here n(X Y) denotes the number of pairs of type X Y.
- Lemma 4: In any liver exchange problem, the only types that could be part of a two-way exchange are

$$X - Y \in \left(\{0,1\}^3\right)^2$$
 such that $X \ngeq Y$ and $Y \gneqq X$.

Possible Two-Way Liver Exchanges



Two-way Liver Exchange Algorithm

• Consider the following sequential liver exchange algorithm:

Step 1: Match the maximum number of X - Y and Y - X types for all $X, Y \in \{0, 1\}^3$.

Step 2: Match the maximum number of 100 - 011, 010 - 101, and 001 - 110 types, without matching them to each other.

Step 3: Match the maximum number of 100 - 011, 010 - 101, and 001 - 110 types *among each other*.

Liver Exchange Algorithm: Step 1



Liver Exchange Algorithm: Step 2



Liver Exchange Algorithm: Step 3



Optimal Two-way Liver Exchange

• Theorem 4: Given a liver exchange problem, the sequential liver exchange algorithm maximizes the number of two-way exchanges.

Welfare Effects of Liver Size Constraints on Donation

• Patient Survival Data (Lo et al. 1999):

 $\begin{array}{l} \mbox{Graft Weight Ratio} \geq 0.4 \ (\cong \mbox{Graft/Body Weight Ratio} \geq 0.08): \ 95\% \\ \mbox{Graft Weight Ratio} < 0.4 \ (\cong \mbox{Graft/Body Weight Ratio} < 0.08): \ 40\% \end{array}$

- Donor Mortality(Chan et. al 2012): Left Lobe Living Donor Liver Transplantation: 0.1% Right Lobe Living Donor Liver Transplantation: 0.5%
- Liver Lobe Weight Ratio (Florman & Miller 2006): Left Lobe Weight / Liver Weight: ≈ 40% Right Lobe Weight / Liver Weight: ≈ 60%

Welfare Effects of Liver Size Constraints on Donation

- Based on these numbers, most donors feel obliged to donate their more risky right liver lobe, so that graft weight ratio exceeds the threshold 40%.
- Chan et. al 2012 argue that reducing the 40% threshold will not only increase living donor liver donation but also reliance on the left liver lobes for liver transplantation.
- While this is clearly correct in the absence of liver exchange, it may fail to hold in its presence.

A Model on Impact of Liver Size Constraints on Donation

- In this section, we consider a model with a continuum of agents.
- Baseline model (no liver size constraint)
 - Baseline population: $\Lambda_1 = \left\{ \lambda_1(X Y) : X Y \in \mathcal{B}^2 \right\}$
 - $\lambda_1(X Y)$: Mass of patient-donor pairs with blood types X Y in Λ_1
- Next, suppose that there exist ℓ ≥ 2 possible sizes 1,..., ℓ,
 i.i.d. across agents with probabilities p₁,..., p_ℓ.
- Induced model (with liver size constraint)
 - Induced population: $\Lambda_2 = \left\{ \lambda_2 (Xs - Ys') : Xs - Ys' \in (\mathcal{B} \times \{1, \dots, k\})^2 \right\}$
 - $\lambda_2(Xs Ys')$ Mass of pairs where the patient has blood type X, size $s = \lambda_1(X Y)p_sp_{s'}$: the donor has blood type Y, size s'

Liver Exchange

A Model on Impact of Liver Size Constraints on Donation

- Compatibility:
 - Baseline model: Blood type compatibility only
 - Induced model: Blood type compatibility + size compatibility Donor size should be at least as large as patient size
- Long Run Assumption on Λ_1 :

$$\forall X, Y \in \mathcal{B}, \qquad Y \trianglerighteq X \implies \lambda_1(X - Y) \ge \lambda_1(Y - X)$$

Incompatible pairs "accumulate" over time while compatible pairs leave after a short while due to transplantation.

• Patient-donor types:

- Type I: X = Y (O − O, A − A, B − B, AB − AB)
 Type II: Y ▷ X (A − O, B − O, AB − O, AB − A, AB − B)
- Type III: $X \triangleright Y$ (O A, O B, O AB, A AB, B AB)
- Type IV: $X \not \cong Y$ and $Y \not \cong X$ (A B, B A)
- $p^* = \sum_{l=1}^{k} p_l(\sum_{i=l}^{k} p_i)$: Odds that a random patient-donor pair is size compatible

Impact of Liver Size Constraints on Donation

Theorem 5: Given the long run assumption, the number of transplants through direct donation and two-way exchange in populations Λ_1 and Λ_2 are given as follows:

$$\Lambda_{1}: \underbrace{\lambda_{1}(Type \ I) + \lambda_{1}(Type \ II)}_{\text{transplants via direct donations}} + \underbrace{2 \min\{\lambda_{1}(A - B), \lambda_{1}(B - A)\}}_{\text{transplants via 2-way exchanges}}$$

$$\Lambda_{2}: \underbrace{p^{*}\lambda_{1}(Type \ I) + p^{*}\lambda_{1}(Type \ II)}_{\text{transplants via direct donations}} + \underbrace{2(1 - p^{*})\lambda_{1}(Type \ II) + 2\min\{\lambda_{1}(A - B), \lambda_{1}(B - A)\}}_{\text{transplants via 2-way exchanges}}$$

Therefore the removal of liver size constraints (1) increases transplants from direct donation, (2) decreases transplants from exchanges, and (3)

#Transplants(Λ_1) $\geq \#$ Transplants(Λ_2) $\iff \lambda_1$ (Type I) $\geq \lambda_1$ (Type II)

Welfare Gains from Left Lobe Liver Exchange

Average Numbers of Patients Matched										
			Exchange Technology							
Sample Size	Weight Threshold	Direct Donation	2-way	2&3-way	2&3&4-way	Unrestricted				
20	0%	12.476	0.792	0.792	0.792	0.792				
	0.60%	12	1.06	1.13	1.134	1.134				
	0.80%	9.678	1.576	1.864	1.932	1.952				
50	0%	31.518	2.7	2.7	2.7	2.7				
	0.60%	30.248	3.628	4.074	4.132	4.14				
	0.80%	24.362	6.012	7.58	8.008	8.212				
100	0%	63.288	6.316	6.316	6.316	6.316				
	0.60%	60.646	8.312	9.512	9.67	9.684				
	0.80%	48.826	14.668	19.42	20.616	21.002				

Welfare Gains from Lung Exchange

Average Numbers of Patients Matched										
			Exchange Technology							
Sample	Size	Direct		2&	2&3&	2&3&				
Size	Constraint	Donation	2-way	3-way	4-way	4&5-way	Unrestricted			
10	Х	4.364	0.492	0.66	0.71	0.734	0.738			
	\checkmark	1.564	0.356	0.476	0.552	0.574	0.576			
20	Х	8.852	1.472	2.072	2.328	2.434	2.462			
	\checkmark	3.156	1.148	1.7	2.058	2.254	2.472			
50	Х	22.42	4.688	6.862	7.836	8.31	8.446			
	\checkmark	8.092	4.936	8.028	10.286	11.858	15.534			