Published in final edited form as:

Stat Biosci. 2018 April ; 10(1): 255–279. doi:10.1007/s12561-018-9214-7.

Valuing Sets of Potential Transplants in a Kidney Paired Donation Network

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Abstract

In kidney paired donation (KPD), incompatible donor-candidate pairs and non-directed (also known as altruistic) donors are pooled together with the aim of maximizing the total utility of transplants realized via donor exchanges. We consider a setting in which disjoint sets of potential transplants are selected at regular intervals, with fallback options available within each proposed set in the case of individual donor, candidate or match failure. We develop methods for calculating the expected utility for such sets under a realistic probability model for the KPD. Exact expected utility calculations for these sets are compared to estimates based on Monte Carlo samples of the underlying network. Models and methods are extended to include transplant candidates who join KPD with more than one incompatible donor. Microsimulations demonstrate the superiority of accounting for failure probability and fallback options, as well as candidates joining with additional donors, in terms of realized transplants and waiting time for candidates.

Keywords

Kidney Paired Donation; Organ Exchanges; Expected Utility; Network Analysis; Fallback Options; Waiting Time

1 Introduction

Kidney transplant candidates with willing but incompatible donors can join a *kidney paired donation* (KPD) program, in which donors and candidates are pooled with the goal of finding transplant opportunities through the exchange of donors (Park et al. 1999; Rapaport 1986). According to the Organ Procurement and Transplantation Network (OPTN),

approximately 500–600 transplants per year have come from KPD programs in the United States since 2012 (Organ Procurement and Transplantation Network 2017). These programs improve the quality of life of recipients and greatly reduce costs versus continued dialysis (Irwin et al. 2012; Laupacis et al. 1996).

In KPD, transplants are realized via one of two methods. In a *cycle* of size ℓ comprising ℓ incompatible donor-candidate pairs, the donor from one pair donates to the candidate in the next pair along the cycle, with the ℓ th donor closing the cycle by donating to the original candidate (Roth et al. 2005). In a *chain* of length ℓ the first transplant is initiated by a *non-directed* (or “*altruistic*”) donor (NDD), who is not associated with any particular candidate but willing to donate a kidney for the benefit of a candidate in the program (Adams et al. 2002; Gentry et al. 2009; Melcher et al. 2013). Successive transplants result from the donor associated with the transplanted candidate donating to the following candidate along the chain, for a total of ℓ transplants. The donor associated with the ℓ th recipient can act as an NDD and initiate a new chain at a future time (Ashlagi et al. 2011; Rees et al. 2009). As is evident, each pair or NDD can only participate in a single cycle or chain.

Transplant opportunities between donors and candidates in a KPD program are identified through a preliminary assessment of compatibility, the *virtual crossmatch*, and are referred to as *virtual matches* (VM). These assessments are based on readily available characteristics such as blood types, candidate sensitivity to human leukocyte antigens (HLA) of the donor, as well as preferences of the donors and candidates (Ashlagi et al. 2011). Regularly, the KPD initiates a *match run*, wherein a set of non-overlapping cycles and chains, based on these VMs, is selected to pursue for transplantation (Li et al. 2014b). The aim is typically to choose a set of cycles and chains such that the number of transplant opportunities is maximized (Roth et al. 2004), representing the optimal *solution* to the KPD. Alternatively, one can assign a *utility* to each VM such that an optimal solution maximizes the sum of the utilities involved. The utility may, for example, be higher for a VM involving a candidate who has spent a long time waiting for a transplant within the program, or who is otherwise difficult to transplant due to their blood type, HLA sensitivities, or general health (Li 2012).

An identified VM can fail to proceed to transplantation for a number of reasons, such as sickness, pregnancy or death of the candidate or donor, scheduling issues, unanticipated candidate or donor preferences, or if a confirmatory laboratory crossmatch contradicts the presumed compatibility of the VM (Kher 2016; Li et al. 2014b). We refer generally to these situations in this context as *failures*, which can be associated with the donor, candidate or match. If a proposed exchange is found to fail within a cycle, the entire cycle is no longer viable and must be abandoned. Similarly, chains cannot proceed to their originally determined length, though it may be administratively permissible for them to be transplanted up to the point of failure.

In the case of such failures, there may be the opportunity for immediate recourse to alternative transplant options. In particular, within a chosen cycle or chain, one can immediately fall back to any sub-cycle or sub-chain that remains viable once failures in the originally selected cycle or chain are determined (Li et al. 2014a). Planning for *fallback*

options has been shown in simulations to increase substantially the number of realized transplants within a KPD program (Bray et al. 2015).

Recent work has considered selecting more general *transplant arrangements*, subsets of pairs and NDDs that may not themselves be simple cycles or chains, but which allow for many possible immediate fallback options in the case of failures (Bray et al. 2015; Klimentova et al. 2016; Li et al. 2014b). After confirming availability of donors and candidates and viability of VMs in such an arrangement, one would proceed to transplantation with the optimal set of remaining sub-cycles and sub-chains. As before with cycles and chains, the question is how to discern which of these arrangements should be selected at each match run. Under this formulation, the aim at each match run would be to select those arrangements that maximize the total utility one should expect, accounting for the probability of failures and exploiting the availability of fallback options. The assignment of an appropriate *expected utility* to each transplant arrangement is the key quantification used in decision-making for KPD. Such calculations have been examined in recent literature in various contexts (Alvelos et al. 2016; Bray et al. 2015; Dickerson et al. 2013; Klimentova et al. 2016; Li et al. 2014b; Pedrosa 2014), though these evaluations are mostly restricted to simple cycles, with or without fallback options.

In this work, we develop methods to calculate expected utilities of transplant arrangements in KPD involving both pairs and NDDs, and taking account of fallback options. Section 2 describes methods for calculating the expected utility for general transplant arrangements, as well as simulation-based methods for estimating expected utilities in cases where computational complexity for exact calculation is high. Section 3 explores the advantages and limitations of each method through numerical experimentation. Section 4 extends these methods to cases where candidates can have several associated incompatible donors. Section 5 presents an experiment assessing the benefits of multiple-donor pairs to KPD in terms of realized transplants and waiting time. Section 6 concludes the paper with discussion and commentary.

2 Computation of Expected Utilities

2.1 Mathematical Model of KPD Programs

In this section, we consider a KPD program consisting only of single donor-candidate pairs and NDDs. Situations that allow for candidates with several associated donors are examined in Section 4.

We first outline a detailed mathematical model for such a KPD program. We represent the pairs and NDDs and their VMs as a directed graph $G = (V, E)$. The vertex set $V = V^P \cup V^A$ comprises the set of donor-candidate pairs, V^P , and the set of NDDs, V^A (where A stands for altruistic). The edge set is given by:

$$E = \{(i, j) : i \in V, j \in V^P, i \neq j, \text{VM from donor of } i \text{ to candidate of } j\}.$$

As noted, there is an important element of uncertainty in a KPD program in that a selected exchange may not lead to a completed transplant due to the unavailability of the donor or the

candidate, or because compatibility is overturned by a thorough laboratory crossmatch. Let $q_i \in [0, 1]$ denote the probability that both the donor and candidate of pair $i \in V^P$ are available through to transplantation¹; similarly for NDDs, q_i denotes the probability that NDD $i \in V^A$ is available. Let $p_e \in [0, 1]$ denote the probability of VM $e \in E$ proving to be viable. Assume that failure of any given pair is independent of failure of any other pair, and that VM failures, conditional on availability of the pairs involved, are independent of each other as well. Finally, let the utility of $e \in E$ be given by $u_e \in \mathbb{R}^+$.

A transplant arrangement $S = (V_S, E_S)$ is a subgraph of G such that $V_S = V_S^P \cup V_S^A \subseteq V$, where $V_S^P = V^P \cap V_S$, $V_S^A = V^A \cap V_S$, and $E_S \subseteq \{(i, j) \in E \mid i, j \in V_S\}$. The arguments and methods in this paper are applicable to any class of transplant arrangements of interest. In particular, the class of cycles and chains can be represented in this way, restricting the edge sets of the subgraphs to include only those VMs directly involved in the cycle or chain. For fixed values of x, y , and L , $\max(x, y) \leq L$, we will focus our attention on a broad set of transplant arrangements represented by subgraphs S of size $|V_S| \leq L$, where each vertex is involved in at least one cycle of size at most x , or at least one chain of length at most y . In addition, we require vertices within these subgraphs to be connected in such a way that any partition into two non-empty parts will result in the loss of at least one sub-cycle of size at most x or sub-chain of length at most y . We refer to these as *locally relevant subgraphs* (LRS) and denote the class of all such subgraphs of G as $LRS(x, y, L)$.

The idea behind the LRS is that it is easier to evaluate many smaller KPD subsets than a single large network. Thus, we are essentially partitioning the original KPD into smaller LRS-based subgraphs, which each admit transplant possibilities and are easier to process individually. Using the LRS as the basis of selection also allows us to readily utilize available transplant fallback options when donors, candidates or edges fail. Such subgraphs are more thoroughly examined in Wang et al. (2017), where methods of enumeration are also developed. We note that, since large cycles and chains are prone to failure (Bray et al. 2015), there is little advantage to considering large values of x and y . Accordingly, we will typically constrain cycles to size at most 3 and chains to length at most 3 ($x = y = 3$), although the methods apply to larger values of x and y as well.

The optimization problem of interest is as follows. For $S \in LRS(x, y, L)$, let EU_S represent its expected utility under the probability model defined previously. Subsequent sections of this paper will focus on the calculation of EU_S for all $S \in LRS(x, y, L)$, as necessary input to the optimization problem. For each vertex $i \in V$, let $LRS_{(i)} = \{S \in LRS(x, y, L) : i \in V_S\} \subseteq LRS(x, y, L)$, the set of all LRSs in $LRS(x, y, L)$ that involve vertex i . Define a decision variable Y_S , with $Y_S = 1$ if $S \in LRS(x, y, L)$ is selected, and $Y_S = 0$ otherwise. The problem of selecting the optimal set of disjoint LRSs in G can then be formulated as the following integer programming problem (Roth et al. 2004, 2005):

¹Please refer to the appendix for a complete list of notation used in this manuscript.

$$\begin{aligned}
& \max_{\{Y_S\}} \sum_{S \in LRS(x, y, L)} Y_S EU_S \quad (1) \\
& \text{subject to } \sum_{S \in LRS(i)} Y_S \leq 1, \forall i \in V, \\
& Y_S \in \{0, 1\}, \forall S \in LRS(x, y, L).
\end{aligned}$$

Thus, our aim is to select disjoint LRSs in $LRS(x, y, L)$ so as to maximize the sum of their expected utilities. The restrictions guarantee that no pair or NDD can appear in more than one LRS. For large problems with many overlapping LRS options, the optimization, though possibly computationally extensive, can be routinely carried out using integer programming software such as Gurobi (Gurobi Optimization Inc. 2017).

Suppose we select the transplant arrangement $S \in LRS(x, y, L)$. After confirming availability of donors and candidates and viability of transplants, we obtain $\bar{S} = (V_{\bar{S}}, E_{\bar{S}})$, the so-called *observed subgraph* of S , where $V_{\bar{S}} \subseteq V_S$ and $E_{\bar{S}} \subseteq \{e \equiv (i, j) \in E_S : i, j \in V_{\bar{S}}\}$. Let $\mathcal{C}_{\bar{S}}$ be the set of all cycles and chains remaining in $\bar{S}$. If $c = (V_c, E_c) \in \mathcal{C}_{\bar{S}}$, its utility is $U_c = \sum_{e \in E_c} u_e$. Transplants are ultimately realized through the disjoint cycles and chains remaining in $\mathcal{C}_{\bar{S}}$ that maximize the utility. With our previous constraints on x, y , and L , this solution can be formally obtained by solving an integer programming problem as in (1), in which $LRS(x, y, L)$ is replaced with $\mathcal{C}_{\bar{S}}$, S is replaced with c , and EU_S is replaced with U_c . See Roth et al. (2007) and Li (2012) for details on this procedure.

For cycles or chains, the following shorthand notation is useful. We indicate a cycle of size ℓ by the ordered ℓ -tuple $c = \langle i_1, \dots, i_\ell \rangle$, which indicates that the donor of pair i_k has a VM with the candidate of pair i_{k+1} for $k = 1, \dots, \ell - 1$, and the donor of pair i_ℓ has a VM with the candidate of pair i_1 , where $i_1, \dots, i_\ell \in V^P$. We denote the vertices involved in the cycle by $V_c = \{i_1, \dots, i_\ell\}$ and the edges as $E_c = \{(i_k, i_{k+1}) : k = 1, \dots, \ell\} \cup \{(i_\ell, i_1)\}$. Similarly a chain of length ℓ is denoted by $c' = \langle i_0, i_1, \dots, i_\ell \rangle$, where the donor at i_k has a VM with the candidate at i_{k+1} for $k = 0, \dots, \ell - 1$, with $i_0 \in V^A$ and $i_k \in V^P$, $k = 1, \dots, \ell$. We have that $V_{c'} = \{i_0, \dots, i_\ell\}$ and $E_{c'} = \{(i_k, i_{k+1}) : k = 0, \dots, \ell - 1\}$.

All cycles and chains contained in S , along with all disjoint combinations thereof, comprise the set of *potential solutions*, $\mathcal{C}_S^*$. Enumeration of cycles and chains in an LRS is accomplished using a depth first search. Assuming reasonable size constraints on the LRS, potential solutions can be obtained by systematically examining each possible combination of cycles and chains, eliminating those with overlapping vertex sets. As useful shorthand, we let potential solution $C^* = (V_{C^*}, E_{C^*}) \in \mathcal{C}_S^*$, be represented in graph notation, where the vertex set V_{C^*} and edge set E_{C^*} are the unions of the edge and vertex sets of its constituent cycles and chains. The utility of C^* is given by $U_{C^*} = \sum_{c \in E_{C^*}} u_c$, the sum of the utilities of the cycles and chains forming that potential solution.

As an illustration, Figure 1 depicts an LRS of size 6 made up of two NDDs, $V_A = \{1, 2\}$, represented by two black vertices, and four incompatible donor-candidate pairs, $V^P = \{3, 4, 5, 6\}$, represented by four white vertices. The LRS is denoted $S = (V_S, E_S)$, where $V_S = V_S^A \cup V_S^P = \{1, 2, 3, 4, 5, 6\}$, and $E_S = \{(1, 6), (2, 3), (2, 4), (3, 4), (4, 5), (4, 6), (5, 4)\}$.

Letting $x = 3$ and $y = 3$, we have that the chains within S are

$c'_1 = \langle 1, 6 \rangle, c'_2 = \langle 2, 3 \rangle, c'_3 = \langle 2, 3, 4 \rangle, c'_4 = \langle 2, 3, 4, 5 \rangle, c'_5 = \langle 2, 3, 4, 6 \rangle, c'_6 = \langle 2, 4 \rangle, c'_7 = \langle 2, 4, 5 \rangle, c'_8 = \langle 2, 4, 6 \rangle$

along with the cycle $c_1 = \langle 4, 5 \rangle$. Assuming an equal utility of 1 for each VM, we have that

$U_{c'_1} = U_{c'_2} = U_{c'_6} = 1, U_{c'_3} = U_{c'_7} = U_{c'_8} = U_{c_1} = 2$, and $U_{c'_4} = U_{c'_5} = 3$. In addition to the

individual cycles and chains listed above, there are other potential solutions arising from combinations of these cycles and chains. The potential solutions, 17 of them in this case, are listed in Table 1 as sets of disjoint cycles and chains.

As presented, the potential solutions are arranged in a non-increasing order of their utilities. The first two of these potential solutions represent ideal scenarios where all four candidates would get transplanted. For potential solutions with the same utility, a secondary criterion might be added in order to determine their precedence. Note that all vertices of S can participate in a cycle of size 3 or less, or a chain of length 3 or less, and that the graph is connected such that any partition of the vertex set will result in the loss of a valid sub-cycle or sub-chain. These are defining features that characterize this arrangement as a suitable LRS.

2.2 Exact Calculation of LRS Expected Utility

In this section, we describe a method for deriving EU_S for $S \in LRS(x, y, L)$. The crux of this calculation hinges on considering each *observable subgraph* in S and determining its maximum utility as described in the previous section. Then EU_S is obtained by multiplying the probability of observing each subgraph by its maximum utility, and taking the sum over all such subgraphs.

Consider vertex subset $\bar{V} \subseteq V_S$. The probability that only the vertices represented by $\bar{V}$ remain available for transplantation is given by

$$P(\bar{V}) = \prod_{i \in \bar{V}} q_i \prod_{i \in V_S / \bar{V}} (1 - q_i)$$

Let $S_{\bar{V}} = (\bar{V}, E_{\bar{V}})$ denote the subgraph induced by $\bar{V}$, where the edge set $E_{\bar{V}}$ is given by $E_{\bar{V}} = \{e = (i, j) \in E_S : i, j \in \bar{V}\}$. Now consider an edge subset $\bar{E} \subseteq E_{\bar{V}}$. The probability that the VMs and only the VMs represented by $\bar{V}$ are viable for transplantation is given by

$$P(\bar{E} \mid \bar{V}) = \prod_{e \in \bar{E}} p_e \prod_{e \in E_{\bar{V}} / \bar{E}} (1 - p_e).$$

With $\bar{S} = (\bar{V}, \bar{E})$ the observed subgraph of S , its solution can be obtained through the integer programming optimization in (1), but may be deduced by simple inspection in the case of graphs with reasonable size constraints, such as in Figure 1.

Let $C_{\bar{S}}^*$, with utility $U_{C_{\bar{S}}^*}$, represent the solution corresponding to $\bar{S}$. The expected utility of S

is obtained by aggregating all of the individual utilities for each observable subgraph, multiplied by the probability that subgraph would actually arise. That is,

$$EU_S = \sum_{\bar{V} \subseteq V_S} \sum_{\bar{E} \subseteq E_{\bar{V}}} P(\bar{V})P(\bar{E} | \bar{V}) U_{C_{\bar{S}}^*} = \sum_{\bar{V} \subseteq V_S} P(\bar{V}) \sum_{\bar{E} \subseteq E_{\bar{V}}} P(\bar{E} | \bar{V}) U_{C_{\bar{S}}^*}.$$

We illustrate the steps for the above method of calculating expected utility for the LRS depicted in Figure 2. Here, we denote the probability of success of $e = (i, j) \in E_{\bar{V}}$, $i, j \in \bar{V}$ and its utility by $p_e \equiv p_{ij}$ and $u_e \equiv u_{ij}$ respectively. There are three possible chains, denoted by $c'_1 = \langle 1, 2 \rangle$, $c'_2 = \langle 1, 2, 3 \rangle$, $c'_3 = \langle 1, 2, 3, 4 \rangle$, and one possible cycle, denoted by $c_1 = \langle 2, 3, 4 \rangle$. Table 2 summarizes the calculations required for each observable subgraph with at least one remaining viable cycle or chain. The expected utility is obtained by multiplying the values in the $P(\bar{V})$, $P(\bar{E} | \bar{V})$, and $U_{C_{\bar{S}}^*}$ columns in each row, and then taking the sum across all the

rows.

In cases where we are restricted to selecting only cycles or chains, without recourse to fallback options, the above formulas can be simplified. For cycles, if any of the donors or candidates involved are unable to proceed to transplantation, or any of the VMs are proven unviable, the cycle cannot proceed. Let $c = \langle i_1, \dots, i_\ell \rangle$ be a cycle of size ℓ , $e_1 = (i_\ell, i_1)$, $e_k = (i_{k-1}, i_k)$, $k = 2, \dots, \ell$ and p_{e_k} and q_{i_k} the probability of success of VM e_k and the probability of availability of pair i_k , respectively, for $k = 1, \dots, \ell$. Also, $U_c = \sum_{k=1}^{\ell} u_{e_k}$ is the utility of the cycle. The expected utility of c is given by:

$$EU_c = \left(\prod_{k=1}^{\ell} q_{i_k} p_{e_k} \right) U_c.$$

In some transplant centers, it may be administratively permissible for chains to be transplanted up to the first point of failure (Montgomery et al. 2006; Rees et al. 2009; Roth et al. 2006). As such, an appropriate expected utility calculation must take this nuance into account, and allow fallbacks for chains to direct sub-chains only. Consider a chain $c' = i_0, \langle i_1, \dots, i_\ell \rangle$ of length ℓ . Let $u'_k = \sum_{t=1}^k u_{e_t}$, with $U_{c'} = u'_\ell = \sum_{t=1}^{\ell} u_{e_t}$. The expected utility calculation for chains in this context, adapted from Dickerson et al. (2013), is given by

$$EU_{c'} = q_{i_0} \left\{ \sum_{k=1}^{\ell-1} (1 - q_{i_{k+1}} p_{e_{k+1}}) \left(\prod_{t=1}^k q_{i_t} p_{e_t} \right) u'_k + \left(\prod_{k=1}^{\ell} q_{i_k} p_{e_k} \right) U_{c'} \right\}. \quad (2)$$

The first summand in (2) is the sum of expected utilities for the chain reaching i_k for $k \in \{1, \dots, \ell-1\}$ (i.e. failure occurs before the transplant to i_{k+1}). The second summand is the utility gained if all transplants in the chain are realized.

2.3 Calculating Expected Utility through Inclusion-Exclusion

While intuitive, the method in Section 2.2 requires searching through every observable vertex-edge subset within each LRS under review. As there are $2^{|V_S|}$ possible vertex subsets within S , where each vertex subset $\bar{V}$ induces a subgraph which itself has $2^{|E_{\bar{V}}|}$ possible edge subsets, computations can quickly become prohibitive for even moderately sized LRSs. Fortunately, due to the restricted size of the LRS, enumerating the cycles and chains in an LRS and determining the potential solutions is straightforward. Here, we use the method of inclusion-exclusion to calculate the probabilities that each potential solution will be realized (i.e. viable and the best choice for transplantation), which can then be used to calculate the overall expected utility of the LRS.

Suppose S is an LRS with $|\mathcal{C}_S^*| = K$ potential solutions, denoted $C_1^*, C_2^*, \dots, C_K^*$. Without loss of generality, we suppose that these potential solutions have been arranged in non-increasing order of their total utilities. Thus $U_{C_1^*} \geq U_{C_2^*} \geq \dots \geq U_{C_K^*}$.

We represent $C_k^* = (V_{C_k^*}, E_{C_k^*})$ in graph notation. With a slight abuse of notation, we also let

C_k^* represent the event that potential solution C_k^* is viable, so that:

$$P(C_k^*) = \prod_{i \in V_{C_k^*}} q_i \prod_{e \in E_{C_k^*}} p_e. \quad (3)$$

Further, the joint event that both $C_{k_1}^*$ and $C_{k_2}^*$ are viable, denoted here by $C_{k_1}^* C_{k_2}^*$, $k_1, k_2 \in \{1, \dots, K\}$, can be identified similarly based on whether each distinctive vertex and edge is involved in at least one of the two options. In other words, the vertex set and edge set are given by $V_{C_{k_1}^*} \cup V_{C_{k_2}^*}$ and $E_{C_{k_1}^*} \cup E_{C_{k_2}^*}$, respectively. It follows that

$$P(C_{k_1}^* C_{k_2}^*) = \prod_{i \in V_{C_{k_1}^*} \cup V_{C_{k_2}^*}} q_i \prod_{e \in E_{C_{k_1}^*} \cup E_{C_{k_2}^*}} p_e. \quad (4)$$

The joint probabilities of any 3, 4, ..., K potential solutions being viable can all be calculated in a similar manner.

For $k = 1, \dots, K$, we evaluate the probability P_k that the potential solution C_k^* is selected as the optimal solution for S . Notably, C_k^* will be preferentially selected only if those potential solutions $C_{k'}^*$, $k' = 1, \dots, k-1$, with higher utilities are not viable. With the convention that the difference between two sets A and B is denoted by $A - B = \{x \in A : x \notin B\}$, it follows that $P_1 = P(C_1^*)$, and $P_k = P\left(C_k^* - \bigcup_{t=1}^{k-1} C_t^*\right)$, $k = 2, \dots, K$. Applying the idea of inclusion-exclusion, we obtain

$$\begin{aligned}
 P_k &= P\left(C_k^* - \bigcup_{t=1}^{k-1} C_t^*\right) \\
 &= P(C_k^*) - P\left(C_k^* \cap (C_1^* \cup C_2^* \cup \dots \cup C_{k-1}^*)\right) \\
 &= P(C_k^*) - \sum_{t=1, \dots, k-1} P(C_k^* C_t^*) + \sum_{t_1, t_2 \in \{1, \dots, k-1\}, t_1 \neq t_2} P(C_k^* C_{t_1}^* C_{t_2}^*) \pm \dots (-1)^{k-1} P(C_1^* \dots C_{k-1}^*),
 \end{aligned}
 \tag{5}$$

where each probability term can be calculated as described above in (3) and (4). The expected utility can then be calculated as

$$EU_S = \sum_{k=1}^K P_k U_{C_k^*}. \tag{6}$$

Returning to our previously worked example from Section 2.2, suppose we prefer the cycle c_1 over the long chain c'_3 (i.e. $u_{23} + u_{34} + u_{42} > u_{12} + u_{23} + u_{34}$). Our potential solutions, in order, are then given by $C_1^* = c_1$, $C_2^* = c'_3$, $C_3^* = c'_2$, $C_4^* = c'_1$, with

$$U_{C_1^*} = u_{23} + u_{34} + u_{42}, U_{C_2^*} = u_{12} + u_{23} + u_{34}, U_{C_3^*} = u_{12} + u_{23} + u_{34}, \text{ and } U_{C_4^*} = u_{12} + u_{23}.$$

Using inclusion-exclusion as in (5), the probability of each solution being selected is given by $P_1 = P(C_1^*)$, $P_2 = P(C_2^*) - P(C_1^* C_2^*)$, $P_3 = P(C_3^*) - P(C_1^* C_3^*) - P(C_2^* C_3^*) + P(C_1^* C_2^* C_3^*)$, and $P_4 = P(C_4^*) - P(C_1^* C_4^*) - P(C_2^* C_4^*) - P(C_3^* C_4^*) + P(C_1^* C_2^* C_4^*) + P(C_1^* C_3^* C_4^*) + P(C_2^* C_3^* C_4^*) - P(C_1^* C_2^* C_3^* C_4^*)$. The

values of each of these probability terms are given in Table 3.

Using inclusion-exclusion in this manner is preferable to the method from Section 2.2 when the number of potential solutions is small relative to the number of observable subgraphs. Here, we avoid having to calculate the probability and utility of every observable vertex-edge subset of the original LRS, many of which will have no remaining cycles or chains and thus do not contribute to the expected utility calculation.

2.4 Matrix Formulation

Incorporating ideas from the previous methods, we can formulate a simple matrix implementation for calculating expected utility to simplify computations and reduce calculation time. Suppose $\mathcal{S}$ is an LRS with K potential solutions, denoted by $C_1^*, C_2^*, \dots, C_K^*$, ordered such that $U_{C_1^*} \geq U_{C_2^*} \geq \dots \geq U_{C_K^*}$. As a convention, we will let $C_0^* = \emptyset$, with $U_{C_0^*} = 0$. Also, let H represent the number of observable subgraphs of $\mathcal{S}$.

We construct matrices $\mathbf{A}$ and $\mathbf{B}$ representing the subgraphs and the potential solutions of $\mathcal{S}$ respectively as follows. Suppose the vertices in $V_{\mathcal{S}}$ and edges in $E_{\mathcal{S}}$ are numbered $1, \dots, |V_{\mathcal{S}}|$ and $|V_{\mathcal{S}}|+1, \dots, |\mathcal{S}|$, respectively, where $|\mathcal{S}| = |V_{\mathcal{S}}| + |E_{\mathcal{S}}|$. Let the h -th subgraph $\mathcal{S}_h = (V_h, E_h)$ be an observable subgraph of $\mathcal{S}$. The probability of observing the subgraph $\mathcal{S}_h$ is:

$$P(\mathcal{S}_h) = \prod_{i \in V_h} q_i \prod_{i \in V_{\mathcal{S}}/V_h} (1 - q_i) \prod_{e \in E_h} p_e \prod_{e \in E_{V_h}/E_h} (1 - p_e).$$

Denote a vector of binary variables by $A_h = [a_{1h} \ a_{2h} \ \dots \ a_{|\mathcal{S}|h}]^T \in \{0, 1\}^{|\mathcal{S}|}$, where the h -th element is given by

$$a_{ih} = \begin{cases} 1 & (i \in V_h), \ 1 \leq i \leq |V_{\mathcal{S}}| \\ 1 & (i \in E_h), \ |V_{\mathcal{S}}| + 1 \leq i \leq |\mathcal{S}|. \end{cases} \quad (7)$$

Each vector A_h characterizes a subgraph by both its vertices and edges. Let $\mathbf{A} = [A_1, \dots, A_H]$, the $|\mathcal{S}| \times H$ matrix of all possible valid subgraphs within the LRS. Similarly, let $\mathbf{B} = (b_{ik})$ be the $|\mathcal{S}| \times K$ matrix characterizing the potential solutions of $\mathcal{S}$, constructed analogously to $\mathbf{A}$, where the (i, k) -th element is given by

$$b_{ik} = \begin{cases} 1 & \left(i \in V_{C_k^*} \right), \ 1 \leq i \leq |V_{\mathcal{S}}| \\ 1 & \left(i \in E_{C_k^*} \right), \ |V_{\mathcal{S}}| + 1 \leq i \leq |\mathcal{S}| \end{cases} \quad (8)$$

Let $\mathbf{W} = (w_{kh}) = \mathbf{B}^T \mathbf{A}$, where w_{kh} gives the number of nodes and edges common between potential solution k and subgraph h . Also, let $\mathbf{B}^T \mathbf{1} = \mathbf{t}$, where $\mathbf{1}$ is a vector of ones. For each subgraph h , $h = 1, \dots, H$, let

$$k_h = \begin{cases} \min \{k \in 1, \dots, K : t_k = w_{kh}\} & \text{if } \exists k \in 1, \dots, K \text{ st. } t_k = w_{kh} \\ 0 & \text{o.w.,} \end{cases}$$

be the preferred potential solution for that subgraph. The expected utility is then given by

$$EU_S = \sum_{h=1}^H U_{C_{k_h}^*} P(S_h).$$

In this manner, we avoid having to solve for the solution within each observed subgraph each time, as in Section 2.2. Here we require the list of potential solutions as in 2.3.

2.5 Estimating Expected Utility by Monte Carlo Sampling

Exact calculations given in the previous sections can become computationally prohibitive as the size of transplant arrangements, and thus the number of internal fallback options or potential solutions, is allowed to increase. The LRS in Figure 1, for example, has 370 observable subgraphs and 17 potential solutions. The inclusion-exclusion method involves calculating up to 2^{17} terms for the alternating sums. Enumerating the subgraphs and determining the optimal potential solution as in Section 2.4 is an improvement, but still involves a significant amount of calculation. In such cases, it may be preferable or even necessary to approximate the expected utility of the LRS. With sufficient accuracy, the proposed estimate can be used in place of an exact expected utility.

Due to the presumed independence between pair failures, as well as VM failures between available pairs, a simple procedure for estimating the expected utility of a transplant arrangement is based on a Monte Carlo procedure that samples separately whether each pair or NDD succeeds, followed by whether each VM between successful pairs and NDDs succeeds. This yields a sampled subgraph, the utility of which is determined by a maximum utility selection among its cycles and chains, as in Section 2.2. Alternatively, we can again exploit the fact that we can determine all potential solutions and their precedence within the LRS. Thus for a sampled subgraph, we check the potential solutions $C_1^*, \dots, C_2^*, \dots, C_K^*$ in sequence and select the first that appears viable.

This sampling procedure can be implemented using straightforward matrix multiplication. Consider sampled subgraphs $S_n = (V_n, E_n)$, $n = 1, \dots, N$, where N is the number of sampled subgraphs, and let $\tilde{A}_n = [\tilde{a}_{1n} \tilde{a}_{2n} \dots \tilde{a}_{|S_n|}]^T$ be a vector of binary variables similar to that shown in (7), where in this case:

$$\tilde{a}_{in} = \begin{cases} 1 & (i \in V_n), 1 \leq i \leq |V_S| \\ 1 & (i \in E_n), |V_S| + 1 \leq i \leq |S|. \end{cases}$$

Let $\tilde{\mathbf{A}} = [A_1, \dots, A_N]$, the $|S| \times N$ matrix of sampled subgraphs (note that this is not the same as $\mathbf{A}$ from Section 2.4). Let $\mathbf{B}$ be the same as described by (8) in Section 2.4. The product $\tilde{\mathbf{W}} = \mathbf{B}^T \tilde{\mathbf{A}}$, where $\tilde{w}_{kn}$ gives the number of nodes and edges common between potential solution k and sample subgraph n . For each n , let

$$k_n = \begin{cases} \min \{k \in 1, \dots, K : t_k = \tilde{w}_{kn}\} & \text{if } \exists k \in 1, \dots, K \text{ st. } t_k = \tilde{w}_{kn} \\ 0 & \text{o.w.} \end{cases}$$

be the preferred potential solution for subgraph n . The estimated expected utility is therefore given by

$$\widehat{EU}_S = \frac{1}{N} \sum_{n=1}^N U_{C_{k_n}^*}.$$

3 Comparison of Expected Utility Methods

We performed simulation experiments to evaluate the expected utility calculation methods presented in Section 2. In the first experiment, Table 4 displays the running time needed to estimate the expected utility for an LRS of size 3, 4 and 5 comprised only of pairs in which every donor is found to match every other candidate (i.e. the underlying graph is complete). With $x = 3$, the number of potential solutions is 5, 17 and 65, respectively. Note that the reported running times for the estimation method are based on 1000 Monte Carlo sample subgraphs of the LRS. The pair failure probability was set to 0.5 for all pairs, and the VM failure probability was set to 0.2 for all edges. Note also that cycles within the LRS were constrained to a maximum size of 3.

From Table 4, it is clear that exact expected utility calculations become prohibitive as the size of the subgraph and the number of potential solutions increase. With complete graphs, even for an LRS of size 4, estimation of the expected utility is preferred over exact calculations. It should be noted, however, that observing a complete graph of large size would be uncommon in practice. These complete-graph experiments correspond to the most computationally challenging scenarios.

In a second experiment, we generated LRSs comprised of exactly 5 pairs with either 9, 10, 11 or 12 VMs. 10,000 LRSs of each specified number of VMs were generated at random, and their expected utilities were calculated both by inclusion-exclusion and by estimation based on 1,000 sampled subgraphs. Failure probabilities were the same as in the previous experiment. Figure 3 displays expectations and standard errors of the relative difference in

expected utility values obtained by estimated methods $\widehat{EU}_S$, and by exact methods, EU_S , split based on the number of potential solutions admitted (note that the relative difference in expected utility is given by the difference in estimated and exact expected utilities, divided by the exact expected utility). For Figure 3, among each group of LRSs with at least 1,000 generated LRSs based on the number of potential solutions, a random sample of 1,000 LRSs were selected and used for the display. Note that precision will increase with the number of samples, with estimation standard error being of order $1/\sqrt{N}$ (recall N represents the number of graph samples generated to estimate the expected utility).

Figure 4 shows boxplots comparing the difference of the natural logs of the run-times for calculating estimated and exact expected utility. Note that values above 0 indicate the time required to estimate the expected utility is less favorable than the time required for the exact computation. For a given number of VMs, the superiority of estimation increases as the number of potential solutions increases. Such results may be utilized to determine suitable thresholds at which to switch between estimating and calculating the expected utility in practice.

Finally, we compare solutions obtained by exact expected utility and estimated expected utility using either 100 or 1000 iterations, for LRSs in a pool of 100 single-donor pairs (no NDDs). Pairs are generated as follows. Candidate information is based on data from 380 incompatible donor-candidate pairs from the Alliance for Paired Donation. Donor blood types are randomly generated based on their marginal probabilities in data of kidney transplant recipients from the Scientific Registry of Transplant Recipients. HLA information for donors is randomly generated based on population HLA profile frequency from the Bone Marrow Transplant Registry (Majers et al. 2007). If the donor generated through this procedure is found to be compatible with the candidate, we re-generate donor characteristics until an incompatible donor is obtained. LRSs are constrained to maximum size of 4 with cycles up to size 3.

In order to introduce more variability to the expected utility assignments, instead of optimizing in terms of number of transplants, we assign a utility value for each match from a continuous uniform distribution with bounds (1, 10). All candidates are assumed to fail with probability 0.25, donors with probability 0.10, and matches with probability drawn from a continuous uniform distribution with bounds (0, 0.25). Each donor is assessed for compatibility with all other candidates by virtual crossmatch, and the best LRS solution in terms of expected utility is produced. For each estimated utility solution, we calculated the corresponding exact expected utility of the selected subsets.

For each estimated expected utility solution, we calculated the corresponding exact expected utility of the selected subsets. Across 50 such generated pools, the average relative difference between the exact expected utility solution and the true expected utility of the estimated solution, using 100 iterations per LRS, is 0.0104, corresponding to a roughly 1% loss in expected utility due to the approximation. For the estimated solution using 1000 iterations per LRS, this average relative difference drops to 0.0012, for a roughly 0.1% loss in the expected utility.

It should be noted that it is possible to measure the accuracy of the approximation, based on the simulated values of the observed utility in each iteration for each LRS. That is, we can construct a confidence interval for the true expected utility, which could aid in choosing an appropriate number of iterations to employ in the estimation.

4 Extending the KPD Model for Multiple Donors

The previous formulation assumes that each transplant candidate joins a KPD with a single incompatible donor. Often, however, a transplant candidate may join with more than one donor, and organ exchanges can involve any one of these donors. By introducing new transplant opportunities, additional donors benefit both their candidate and the KPD program as a whole. Multiple donors also introduce additional fallback options for their candidate, thereby increasing the frequency of transplant arrangements and potential solutions in which the candidate is involved. We will continue to use the term “pair” in this context to refer to a transplant candidate and the set of his or her associated incompatible donors.

To reflect the possibility of multiple donors for each candidate, we consider the original KPD network $G = (V, E)$, but allow each individual vertex to have multiple edges to each other vertex. In other words, G is now a directed multigraph. Let $V = V^P \cup V^A$ as before. For pair $i \in V^P$, let r_i represent the candidate (the r refers to “recipient”), and $D_i = \{d_{i1}, \dots, d_{iM_i}\}$ represent the collection of $M_i - 1$ incompatible donors associated with candidate r_i . Note that for NDD $i \in V^A$, $D_i = \{d_{i1}\} \equiv d_i$. Let E_{ij} be the set of all VMs e_{imj} between donors d_{im} , $m = 1, \dots, M_i$ in $i \in V$, and the candidate r_j in $j \in V^P$. That is, $\forall i \in V, j \in V^P, i \neq j$, we have that

$$E_{ij} = \{e_{imj} \equiv (d_{im}, r_j) : m \in \{1, \dots, M_i\}, \text{VM from donor } m \text{ of } i \text{ to candidate of } j\}.$$

It follows that $E = \bigcup_{i \in V, j \in V^P, i \neq j} E_{ij}$. Let $u_{imj} \in \mathbb{R}^+$ represent the utility of the potential transplant from donor d_{im} to candidate r_j , and $p_{imj} \in [0, 1]$ its probability of success. The probabilities of being available through to transplantation associated with d_{im} and r_i are denoted as q_{im}^d and q_i^r respectively.

Figure 5 gives an example of an LRS involving a multiple donor pair. The LRS has three vertices, where vertex 1 has 2 donors, $D_1 = \{d_{11}, d_{12}\}$, and vertices 2 and 3 each have a single donor, $D_2 = \{d_{21}\}$ and $D_3 = \{d_{31}\}$. There are three potential solutions to this LRS. Two cycles of size 3 are possible between pairs 1, 2 and 3, with the first transplant taking place between either donor d_{11} or d_{12} to candidate r_2 . The final potential solution is a cycle of size 2 between pairs 1 and 3, though this cycle is contingent on the availability of d_{11} , since d_{12} is not compatible with r_3 as is evident by the absence of an edge e_{123} .

Again, we focus on the locally relevant subgraphs $LRS(x, y, L)$ for selection. For the purpose of optimization, we can reduce the multigraph G to a simple directed graph $G' = (V, E')$, by collapsing the possible multiple edges from one vertex to another into a single edge, such that $e = (i, j) \in E' \Leftrightarrow E_{ij} \neq \emptyset$. In this way, optimization proceeds as in (1).

We require an appropriate assignment of expected utility to each LRS that takes fallback options into account, including the additional fallback options offered by multiple donors. As in the single donor case, we can enumerate each potential solution within a given LRS and use the inclusion-exclusion method to calculate the probabilities needed for expected utility calculation. Suppose we have K potential solutions, denoted $C_1^*, \dots, C_K^*$, arranged in decreasing order of their total utilities $U_{C_1^*} \geq \dots \geq U_{C_K^*}$. Note that potential solutions consisting of the same vertices but with different donors facilitating the transplants are distinct. Let $C_k^* = (V_{C_k^*}, E_{C_k^*})$ represent the event that C_k^* is viable. Considering the probability associated with the specific donor involved in each transplant, the probability that the potential solution is viable is given by:

$$P(C_k^*) = \prod_{i,j \in V_{C_k^*}} \prod_{\substack{e \equiv e_{imj} \in E_{C_k^*} \\ m \in \{1, \dots, M_i\}}} q_{im}^d q_{jm}^r p_e.$$

The higher-order joint probabilities are calculated analogously to (4). The probability P_k that the potential solution C_k^* is realized within this LRS is therefore given by (5) and the expected utility is calculated as (6). Similarly, the matrix formulation and Monte Carlo estimation described in Sections 2.4 and 2.5 are also generalized in a straightforward fashion.

5 Experiment: Assessing the Value of Multiple Donors

This section presents the results of a microsimulation experiment that examines the advantage of our expected utility assignments, taking account of fallback options and allowing candidates to join with multiple donors. We perform 200 iterations of a dynamic KPD program under a variety of settings. We are primarily concerned with the number of transplants realized as well as waiting times for candidates in the simulated KPD programs.

The simulation follows a similar setup to Ashlagi et al. (2011) and Bray et al. (2015). In practice, the duration between successive match runs varies by KPD program, with some waiting as little as a few days to as long as 3 months between match runs. Here, donor-candidate pairs and NDDs join our simulated KPD in continuous time by a Poisson process over 8 months, with a match run occurring at the end of each month. A mean of 25 vertices join each month, with a 1 in 25 chance that each vertex added is an NDD. Pairs are generated in a similar fashion to our simulations at the end of Section 3. For each candidate r_i , either one or two associated donors are randomly generated such that $P(M_i = 2) = 1 - P(M_i = 1) = \rho$, where M_i represents the number of associated donors for pair i . Donors are generated until the specified number of incompatible donors are obtained (those that are found to be compatible with the candidate are discarded). In our simulations, we consider settings with $\rho \in \{0, 0.2, 0.4\}$. We compare results when selection is based on LRSs, versus

simple cycles or chains only. We also assess the difference between candidates who joined with two donors as opposed to one.

VM failure rates are set according to the panel reactive antibody (PRA) value of the candidate, a measure of the candidates' assumed compatibility with the general population, as in Ashlagi et al. (2011) and Bray et al. (2015). A utility value of 1 is assigned to each VM, meaning the outcome of interest is effectively the number of realized transplants.

Availability of candidates and donors for transplantation are assumed to follow independent homogeneous Markov processes described below. Suppose candidates and donors can be in one of three states: "active", representing active status in the KPD and availability for transplant; "inactive", representing individuals who are not available for transplantation but remain in the program; or "withdrawn", meaning permanent removal from the program due to sickness, death or other extenuating circumstances. The transitions between these states can be specified by the intensity matrix (suppose 1="active", 2="inactive", 3="withdrawn"):

$$Q = \begin{pmatrix} 0 & \lambda_1 & \mu_1 \\ \lambda_2 & 0 & \mu_2 \\ 0 & 0 & 0 \end{pmatrix}$$

where the ij -th entry specifies $q_{ij} = \lim_{h \rightarrow 0^+} P(X(t+h) = j | X(t) = i)/h$ (note that $i \neq j$), and $X(t)$ represents the state occupied at time t .

When a new pair/NDD joins the pool, each of the new donors is assessed for compatibility with all candidates currently in the program by virtual crossmatch, and all donors currently in the program are assessed for compatibility with the new candidate. Each individual donor and candidate joins the pool in the active state. The time an individual donor or candidate spends in the active state follows an exponential distribution with rate $\lambda_1 + \mu_1$. At the end of this time interval, the individual moves to the inactive state with probability $\lambda_1/(\lambda_1 + \mu_1)$ or is withdrawn from the pool with probability $\mu_1/(\lambda_1 + \mu_1)$. Similarly, we assume the time spent in the inactive state follows an exponential distribution with rate $\lambda_2 + \mu_2$, after which the individual either becomes active again with probability $\lambda_2/(\lambda_2 + \mu_2)$, or is withdrawn from the pool with probability $\mu_2/(\lambda_2 + \mu_2)$. This process continues until the individual is withdrawn or to the end of the timeline, whichever comes first.

We assume the individuals are in the active state 80% of the time and in the inactive state 20% of the time, and that the overall withdrawal rate is approximately 2%. Further, we assume that $\mu_2 = 3\mu_1$, such that withdrawals are three times as likely while inactive than while active. These two conditions make it so that $\mu_1 \approx 0.014286$ and $\mu_2 \approx 0.04286$. Values for λ_1 and λ_2 were chosen to correspond to average times of about 4 months and 1 month in the active and inactive states respectively, such that $\lambda_1 = 0.25$ and $\lambda_2 = 1$. A pair is available for a match run if both the candidate and at least one donor is available, otherwise, it is not included in the match run. NDDs are assumed to be available throughout the simulation.

At each match run, the optimal solution, consisting of either cycles and chains or LRSs, depending on the current setting, is collected. LRSs are constrained to a maximum of size 4,

with cycles constrained to size 3, and chains to length 3, namely $x = 3, y = 3, L = 4$. Each cycle/chain/LRS is then assigned a (expected) utility value. In the setting where only cycles and chains are considered, a simple utility is assigned to each, while exact expected utilities are calculated for the LRS setting.

Transplantation here is assumed to take place immediately prior to the next match run, with the interim time representing the time needed to assess compatibility and availability. Each selected transplant arrangement (cycle, chain, or LRS) is evaluated and failures are determined. Candidates and donors who were selected but become unavailable in the interim are marked as failed for the remainder of the evaluation. For all VMs that remain, success probabilities are updated after evaluation, to 1 if successful and 0 otherwise, for use in future calculations. In the cycles and chains setting, we allow fallbacks to the second donor, as well as sub-chains of the original chain. In the LRS setting, the best remaining option within each LRS is selected for transplantation. Transplanted candidates and their associated donors are then removed from further consideration, while pairs and NDDs that were included in transplant arrangements but not involved in an exchange are returned to the KPD to participate in the next match run. For transplanted chains, the final donor is retained as a bridge donor, acting as an NDD in future match runs.

Results are shown in Table 5. As expected, we observe improvement, in terms of proportion of candidates transplanted, in the LRS approach over the classical strategy based on simple cycles and chains. Two-donor candidates are shown to be more likely to receive transplants in all settings as well. Kaplan-Meier curves showing the candidate waiting time until transplantation under each simulation setting are shown in Figure 6, with $\rho = 0$ on the left, $\rho = 0.2$ in the center, $\rho = 0.4$ on the right. We observe a greater proportion of candidates with two donors receiving transplants across the timeline of the simulation compared to candidates with a single donor, in both the cycles and chains and LRS settings.

6 Discussion

This work concerns the calculation of expected utility for transplant arrangements in a KPD program, assuming pursuit of fallback options between selection and transplantation. We explore exact and sampling-based methods for assigning expected utility values to transplant arrangements in settings where all candidates join with a single incompatible donor, and also consider the setting where candidates can join with more than one donor. It is clear that transplant arrangements involving many fallback options should be preferred in a KPD program. It is also beneficial for candidates, as well as the KPD as a whole, to participate in KPD with several donors.

The issue of searching for the relevant transplant arrangements, as well as searching for cycles and chains within these arrangements, are themselves interesting problems to consider. These operations can be computationally expensive, so procedures that streamline this process are beneficial in practice. The strategy of decomposing a large KPD network into a set of small cohesive subgraphs with high numbers of fallback options is desirable to make the proposed utility calculations useful and practically appealing. Algorithms for

searching graphs for subgraphs relevant to the KPD problem have been studied in Wang et al. (2017).

We assume independence between the three sources of potential failure, that is the donor(s), candidate, and VM. There are clearly factors that may affect the probability of availability after identification of a suitable exchange for reasons such as unanticipated scheduling issues, candidates becoming pregnant or too ill to proceed to transplantation, etc. But there do not exist sufficient data to estimate these probabilities accurately. Fumo et al. (2015) report on investigations into failed transplant offers, though these relate largely to crossmatch failures and candidate refusals, as opposed to donor or candidate-specific failures. Future studies to explore probability assignments in greater detail, preferably developing a statistical model of probabilities from clinical data, may be warranted, though data supporting more complicated models may not be easily available. We have found that simply having a constant value for each subject, representing an average probability of available subjects, is enough to direct choice toward subsets with many fallback options, and preliminary investigations suggest that the advantages of fallback options are robust to probability assignment, in cases where values are over- or under-estimated, and improve the performance of the selection mechanism. We plan to investigate the issue of robustness in future work.

Acknowledgments

This research was supported by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) through grant number R01-DK093513. We thank the editor and reviewer for their careful reading of the manuscript and their helpful comments and suggestions.

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7 Appendix: Glossary and Notation

We include a glossary of terms in Table 6, as well as a list of notation used in Table 7, in the order of appearance in the text.

Table 6

Glossary of Terms

Chain	Transplant arrangement wherein an NDD donates to a candidate, whose donor donates to another candidate, and so on.
Cycle	Transplant arrangement wherein the donor from a first donor-candidate pair donates to the candidate in the next pair along the cycle, with the final donor closing the cycle by donating to the original candidate
Expected Utility	Utility one expects to obtain from a transplant arrangement, accounting for failure probabilities and fallback options
Failure	When a selected donor, candidate, or match is unable to proceed to transplantation due to issues such as sickness, pregnancy, death, or lab crossmatch overruling presumed compatibility of the proposed transplant
Fallback Options	Set of sub-cycles and sub-chains within a given transplant arrangement that can potentially be realized after accounting for failures
Kidney Paired Donation (KPD)	Pooled donor-candidate pairs and NDDs with the goal of facilitating new transplant opportunities through the exchange of donors
Locally Relevant Subgraph (LRS)	Type of transplant arrangement that satisfies a set of properties, namely that every pair/NDD is involved in a sub-cycle or sub-chain; more detail on the properties of the LRS are given in Wang et al. (2017)
Match Run	Time at which the pool of pairs and NDDs is assessed for compatibility and transplant arrangements are selected for transplantation
Non-Directed (Altruistic) Donor (NDD)	Donor who joins KPD altruistically, i.e. not for the benefit of any candidate in particular
Observed (Observable) Subgraph	Set of pairs/NDDs and VMs remaining within a transplant arrangement after evaluation for failures (observable subgraphs are subgraphs of pairs/NDDs and VMs that can be observed within the transplant arrangement)
Potential Solution	Disjoint set of sub-cycles and sub-chains within a transplant arrangement that may be selected as the observed solution after failures are determined
Solution	Optimal set of transplant arrangements within a KPD, or optimal set of cycles and chains within an LRS or observed subgraph of an LRS
Transplant Arrangement	Set of pairs/NDDs and VMs that acts as the basis for selection; examples include cycles, chains, and LRSs
Utility	Value of a VM, relative to others
Virtual Match (VM)	Potential transplant between a donor and candidate, identified by virtual crossmatch

Table 7**Notation**

Section 2.1	$G = (V, E)$	Graph representation for KPD; pairs/NDDs comprise the vertex set, and VMs comprise the edge set
	V^P, V^A	Set of donor-candidate pairs and NDDs respectively
	i, j	Indices representing vertices
	e	Index representing an edge
	q_i	Probability of success of pair i
	p_e	Probability of success of match e
	u_e	Utility of match e
	$S = (V_S, E_S)$	Graph representation for a transplant arrangement, typically an LRS
	x, y, L	Maximum length/size of cycle, chain, and LRS respectively
	ℓ	Index representing length
	$LRS(x, y, L)$	Class of LRSs in G , under the length/size constraints x, y, L
	$c = (V_c, E_c) = \langle i_1, \dots, i_\ell \rangle$	Graph and shorthand notation for a cycle of size ℓ
	$c' = (V_{c'}, E_{c'}) = \langle i_0, i_1, \dots, i_\ell \rangle$	Graph and shorthand notation for a chain of length ℓ
	EU_S	Expected utility of LRS S
	$LRS_{(i)}$	Collection of LRSs in $LRS(x, y, L)$ that involved vertex i
	Y_S	Decision variable for selection of LRS S
	$\bar{S} = (V_{\bar{S}}, E_{\bar{S}})$	Graph representation for an observed subgraph of S
	$\mathcal{C}_{\bar{S}}$	Set of cycles and chains in observed subgraph $\bar{S}$
	U_c	Utility of a cycle
	$\mathcal{C}_S^*$	Set of potential solutions of S
	$C^* = (V_{C^*}, E_{C^*})$	Graph representation for a potential solution
	U_{C^*}	Utility of a potential solution
Section 2.2	$P(\bar{V})$	Probability that only vertices represented by $\bar{V}$ succeed to transplantation
	$S_{\bar{V}} = (\bar{V}, E_{\bar{V}})$	Subgraph of S induced by $\bar{V}$
	$P(-/\bar{V})$	Probability that only edges represented by $-$ succeed to transplantation, given vertices represented by $\bar{V}$ are successful
	$C_{\bar{S}}^*$	Solution for observed subgraph $\bar{S}$
	$U_{C_{\bar{S}}^*}$	Utility of the solution for observed subgraph $\bar{S}$
	$EU_c, EU_{c'}$	Expected utility of a simple cycle or chain
Section 2.3	K	Number of potential solutions in an LRS
	$P(C_k^*)$	The probability that potential solution C_k^* will be viable for transplantation
	P_k	The probability that potential solution C_k^* will be realized
Section 2.4	A, B	Matrix representations of subgraphs of and potential solutions of S respectively

	H	Number of observable subgraphs
	h	Index for observable subgraph
	$S_h = (V_h, E_h)$	Graph representation of an observable subgraph of S
Section 2.5	$\tilde{\mathbf{A}}$	Matrix representation of a set of sampled subgraphs of S
	N	Number of sampled subgraphs
	n	Index for subgraph samples
	$S_n = (V_n, E_n)$	Graph representation of a sampled subgraph of S
Section 3	$EU^*, \widehat{EU}$	Exact expected utility and estimated expected utility for comparative experiments
Section 4	r_i	Candidate associated with pair i
	$D_i = \{d_{[m], m=1, \dots, M_i}\}$	Donors associated with pair i
	M_i	Number of donors associated with pair i
	m	Index for donors
	E_{ij}	Set of edges between vertices i and j
	e_{imj}	Match from d_{im} to candidate r_j
	u_{imj}, p_{imj}	Utility and probability of match e_{imj}
	q_{im}^d, q_i^r	Success probabilities for donor m and candidate of pair i
	$G' = (V, E')$	Reduced graph notation for KPD involving multiple donor pairs
Section 5	ρ	Probability that candidate joins simulation with second donor
	$Q, \lambda_1, \lambda_2, \mu_1, \mu_2$	Intensity matrix and state transition specifications for Markov process describing availability of individuals (candidates and donors) in simulation experiment

Fig. 1.
Example of an LRS of size 6 made up of two NDDs $V^A = \{1, 2\}$ (in black), and four incompatible donor-candidate pairs $V^P = \{3, 4, 5, 6\}$ (in white).

Fig. 2.
LRS Example for Exact Expected Utility Calculation.

Fig. 3.
Relative difference in expected utility, split by number of potential solutions.

Fig. 4. Runtime comparison for exact and estimated methods, split by number of potential solutions.

Fig. 5.
Illustration of a Multiple Donor LRS.

Fig. 6.
Kaplan-Meier Curves for Wait Times of Candidates across 200 Simulations.

Table 1

Potential LRS Solutions and their Utilities.

Potential Solutions	Utility ($U_{C_i^*}$)
$\{c'_1, c'_2, c_1\}, \{c'_1, c'_4\}$	4
$\{c'_1, c'_3\}, \{c'_1, c'_7\}, \{c'_1, c'_8\}, \{c'_1, c_1\}, \{c'_2, c_1\}, \{c'_4\}, \{c'_5\}$	3
$\{c'_1, c'_2\}, \{c'_3\} \{c'_7\}, \{c'_8\}, \{c_1\}$	2
$\{c'_1\}, \{c'_2\}, \{c'_6\}$	1

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Table 2

Exact Expected Utility Calculation for Example LRS.

∇	$\mathbf{P}(\nabla)$	$\mathbf{P}(\nabla)$	C_S^*	U
$\{1, 2\}$	$q_1 q_2 (1 - q_3)(1 - q_4)$	$\{(1, 2)\}$	c'_1	u_{12}
$\{1, 2, 3\}$	$q_1 q_2 q_3 (1 - q_4)$	$\{(1, 2)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(1, 2), (2, 3)\}$	c'_2	$u_{12} + u_{23}$
$\{1, 2, 4\}$	$q_1 q_2 (1 - q_3) q_4$	$\{(1, 2)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(1, 2), (4, 2)\}$	c'_1	u_{12}
$\{2, 3, 4\}$	$(1 - q_1) q_2 q_3 q_4$	$\{(2, 3), (3, 4), (4, 2)\}$	c_1	$u_{23} + u_{34} + u_{42}$
$\{1, 2, 3, 4\}$	$q_1 q_2 q_3 q_4$	$\{(1, 2)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(1, 2), (2, 3)\}$	c'_2	$u_{12} + u_{23}$
$\dots$	$\dots$	$\{(1, 2), (3, 4)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(1, 2), (4, 2)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(1, 2), (2, 3), (3, 4)\}$	c'_3	$u_{12} + u_{23} + u_{34}$
$\dots$	$\dots$	$\{(1, 2), (2, 3), (4, 2)\}$	c'_2	$u_{12} + u_{23}$
$\dots$	$\dots$	$\{(1, 2), (3, 4), (4, 2)\}$	c'_1	u_{12}
$\dots$	$\dots$	$\{(2, 3), (3, 4), (4, 2)\}$	c_1	$u_{23} + u_{34} + u_{42}$
$\dots$	$\dots$	$\{(1, 2), (2, 3), (3, 4), (4, 2)\}$	$c_1 \text{ or } c'_3$	$\max\{u_{12} + u_{23} + u_{34}, u_{23} + u_{34} + u_{42}\}$

Table 3

Probabilities for Terms in Inclusion-Exclusion Expected Utility Calculation for Example LRS.

Term	Probability	Term	Probability
$P(C_1^*)$	$q_2 q_3 q_4 p_{23} p_{34} p_{42}$	$P(C_2^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34}$
$P(C_1^* C_2^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$	$P(C_3^*)$	$q_1 q_2 q_3 p_{12} p_{23}$
$P(C_1^* C_3^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$	$P(C_2^* C_3^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34}$
$P(C_1^* C_2^* C_3^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$	$P(C_4^*)$	$q_1 q_2 p_{12}$
$P(C_1^* C_4^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$	$P(C_2^* C_4^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34}$
$P(C_3^* C_4^*)$	$q_1 q_2 q_3 q_4 p_{12} p_{23} p_{34} p_{42}$	$P(C_1^* C_2^* C_4^*)$	$q_2 q_3 q_4 p_{23} p_{34} p_{42}$
$P(C_1^* C_3^* C_4^*)$	$q_2 q_3 q_4 p_{23} p_{34} p_{42}$	$P(C_2^* C_3^* C_4^*)$	$q_2 q_3 q_4 p_{23} p_{34}$
$P(C_1^* C_2^* C_3^* C_4^*)$	$q_2 q_3 q_4 p_{23} p_{34} p_{42}$		

Table 4

Time (in milliseconds) to calculate expected utility for all-pairs complete LRSs.

Expected Utility Method	3 Pairs	4 Pairs	5 Pairs
All Subsets Calculation	1.00	182.21	4.42×10^6
Inclusion-Exclusion	0.16	1237.18	(Not Completed)
Monte Carlo Estimation (1000 Iterations)	1.34	2.53	4.85

Table 5

Average Proportion of Transplanted Candidates over 200 Simulations.

ρ	Donors	Cycles And Chains			LRS		
		Avg. Prop. of Candidates Transplanted	Std. Error	Std. Error	Avg. Prop. of Candidates Transplanted	Std. Error	Std. Error
0	1	0.158	0.006	0.006	0.226	0.006	0.006
0.2	1	0.168	0.006	0.006	0.230	0.006	0.006
	2	0.260	0.012	0.012	0.399	0.012	0.012
0.4	1	0.180	0.006	0.006	0.233	0.006	0.006
	2	0.266	0.008	0.008	0.409	0.010	0.010