Graph-Based Optimization Algorithm and Software on Kidney Exchanges

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***Abstract*—Kidney transplantation is typically the most effective treatment for patients with end-stage renal disease. However, the supply of kidneys is far short of the fast-growing demand. Kidney paired donation (KPD) programs provide an innovative approach for increasing the number of available kidneys. In a KPD program, willing but incompatible donor–candidate pairs may exchange donor organs to achieve mutual benefit. Recently, research on exchanges initiated by altruistic donors (ADs) has attracted great attention because the resultant organ exchange mechanisms offer advantages that increase the effectiveness of KPD programs. Currently, most KPD programs focus on rule-based strategies of prioritizing kidney donation. In this paper, we consider and compare two graph-based organ allocation algorithms to optimize an outcome-based strategy defined by the overall expected utility of kidney exchanges in a KPD program with both incompatible pairs and ADs. We develop an interactive software-based decision support system to model, monitor, and visualize a conceptual KPD program, which aims to assist clinicians in the evaluation of different kidney allocation strategies. Using this system, we demonstrate empirically that an outcome-based strategy for kidney exchanges leads to improvement in both the quantity and quality of kidney transplantation through comprehensive simulation experiments.**

***Index Terms*—Kidney exchanges, optimal matches, software.**

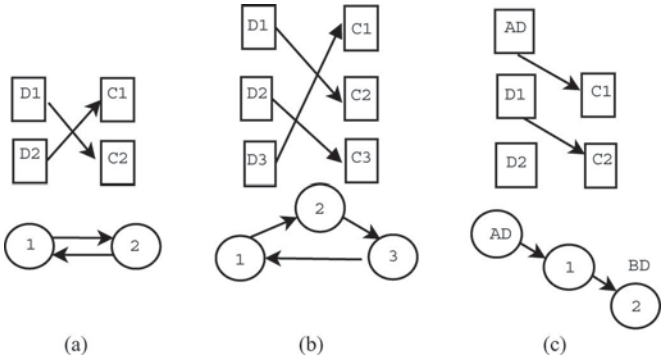

Fig. 1. Illustration of three types of kidney exchanges: (a) two-way cycle-based exchange, (b) three-way cycle-based exchange, and (c) a chain-based exchange initiated by an AD. (Top) In the graphs, donors (D) and their willing but incompatible candidates (C) are shown in the same numbered pairs, and arrows denote the kidney transplant from donor (D) to the compatible candidate (C). (Bottom) Graphs are the corresponding graphical representation of three cases. BD is a bridge donor that triggers another chain-based exchange in a future run.

I. Introduction

In comparison to dialysis, kidney transplantation has been proven to be a more effective treatment for most patients with end-stage renal disease. However, in response to the growing demand, there is a serious shortage in supply of transplantable kidneys. As a result, more than 90 000 patients were waiting for kidney transplantation by the end of 2011 [11]. Although deceased donation and living donation are the two sources of kidneys for transplantation, the number of living-donor transplantation has increased more rapidly in recent years. This is fortuitous since transplants from live donors generally have a higher chance of success than those from deceased ones [13]. Unfortunately, biological incompatibility, such as ABO blood type mismatch or the presence of human leukocyte antigen (HLA) antibodies [9], prevents many intended living-donor transplants from being performed. Therefore, kidney paired donation (KPD) programs [13], also referred to as kidney exchanges, are established to circumvent these incompatibilities by allowing incompatible living paired donors–candidates to swap organs, thus facilitating the chance of transplantation with the willing donors' kidneys.

Two and three-way pair exchanges, illustrated in Fig. 1(a)–(b), are the most common organ allocation exchanges in traditional KPD programs involved with only cycle-based exchanges. In these situations, the candidate (C) of one pair is compatible with and receives the kidney of the donor (D) from another pair. Recently, a chain of kidney exchanges triggered by an altruistic donor (AD), shown in Fig. 1(c), has drawn much attention because chain-based exchanges can be advantageous compared with the traditional cycle-based exchanges. These chains not only relax the reciprocal and simultaneous requirements of a traditional KPD program but also tend to achieve many more transplants [2], [12].

The goal of kidney exchanges is to make optimal decisions to achieve the maximum overall benefit for all kidney candidates (patients) in the exchange pool. In the current literature, most researchers focus on developing optimal matching algorithms for either cyclic pair or chain exchanges. In the field of

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paired donation study, the most well-known algorithm is to use an integer program (IP) to select the optimal matches among incompatible pairs based on the maximum number (or maximum utility) of transplants [1], [4], [10], [13]–[15], [17]. According to Li *et al*. [7], in order to determine the best matches for improving both the quantity and quality of patients' life after transplantation, accounting for uncertainty in KPD program is essential. They proposed a probability-based utility measure to access a variety of uncertainties in KPD, so that the optimality is based on the overall expected utility of exchanges. This paper will apply their method of expected utility to develop an algorithm and software. Other researchers explore theoretical analysis and real application issues on chain exchanges, such as the algorithmic efficiency or optimal length of chains, the benefit and computational limitation of integrating chains into KPD program, etc. [2], [6]. An overall review of KPD is referenced in [18]. However, it remains unknown as how best to utilize all the forms of simultaneous exchange cycles and nonsimultaneous exchange chains, given the fact that both paired donor–candidates and ADs can be added to exchange databases [2]. In addition, there is an urgent need for public software to evaluate these KPD strategies and statistical algorithms so as to improve clinical decision making.

In this paper, we consider a graphical model to determine optimal matches for KPD program, in which both cycle and chain exchanges are involved. Through comprehensive simulation experiments performed on our novel computerized decision support software, we demonstrate and confirm the superior performance of the method of expected utility [7] accounting for exchange uncertainties, in comparison to the existing strategies for kidney exchanges. The major contributions of this paper are summarized as follows.

1) Applying a graph-based maximum expected utility model proposed by [7], we relax the current strategy of a KPD program in which optimal matches are selected for both exchange cycles and chains by allowing both operational uncertainty and contingency plans.
2) We consider the comparison between two allocation algorithms, termed as *MEU-Parallel* and *MEU-Sequential*, which, respectively, search simultaneously and sequentially for donor–candidate pairs and/or ADs to *M*aximize the *E*xpected *U*tility of exchanges.
3) More importantly, we develop a computerized system which enables us conveniently to evaluate and compare different organ allocation strategies and effectiveness of policy. In particular, we build a user-friendly graphical interface which provides easy communication between clinicians and computer tools, thus facilitating convenience and quality of clinical decision making.

The remainder of the paper is organized as follows. We first present the relevant mathematical formulation and algorithm for kidney exchanges in detail in Section II. Then, a descriptive outline of computerized decision support software is presented in Section III. In Section IV, we discuss extensive simulation experimental evaluation and results using this system. Finally, we conclude and propose future work in Section V.

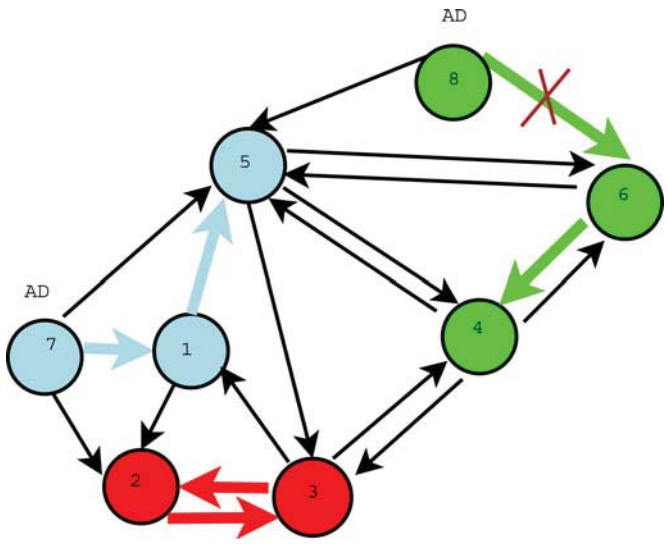

Fig. 2. Toy kidney exchanges program with six incompatible pairs $(1, 2, 3, 4, 5, 6)$ and 2 ADs $(7, 8)$, including 5 two-way cycles ($\{2, 3\}$, $\{3, 4\}$, $\{4, 5\}$, $\{4, 6\}$, $\{5, 6\}$), 4 three-way cycles ($\{1, 2, 3\}$, $\{3, 4, 5\}$, $\{4, 5, 6\}$, $\{1, 5, 3\}$), and 17 AD chains with size limited to 3 ($\langle 7, 1\rangle$, $\langle 7, 2\rangle$, $\langle 7, 5\rangle$, $\langle 8, 5\rangle$, $\langle 8, 6\rangle$, $\langle 7, 1, 2\rangle$, $\langle 7, 1, 3\rangle$, $\langle 7, 1, 5\rangle$, $\langle 7, 2, 3\rangle$, $\langle 7, 5, 3\rangle$, $\langle 7, 5, 4\rangle$, $\langle 7, 5, 6\rangle$, $\langle 8, 5, 3\rangle$, $\langle 8, 5, 4\rangle$, $\langle 8, 5, 6\rangle$, $\langle 8, 6, 4\rangle$, $\langle 8, 6, 5\rangle$). In this example, the cycles and chains are restricted to size $L = 3$ or less.

II. KPD Formulation and Algorithm

A. Mathematical Formulation

A kidney exchange problem can be represented as a directed graph $G = (V, E)$. Fig. 2 shows an example. Let $|V|$ be the number of vertices (nodes) and $|E|$ the number of edges in the graph, where $|.|$ denotes cardinality. Each vertex in the graph G represents an incompatible donor–candidate pair (e.g., vertex 1) or an AD (e.g., vertex 7). Each directed edge from vertex i to j indicates that the donor kidney in vertex i is compatible with the candidate in vertex j (e.g., $7 \rightarrow 1$). In this directed graph, each edge can be assigned a weight representing the *edge utility* u_{ij} of the kidney transplant from the donor in vertex i to the candidate in vertex j. In addition, an *edge probability* p_{ij} can be included for each edge to characterize the chance of an actual successful kidney transplant from i to j. In this discussion, we assume that the probability associated with edges are independent [7]. In this paper, both u_{ij} and p_{ij} are assumed given; however, these utilities and probabilities can be estimated in practice using clinical data. For example, edge utility u_{ij} could be obtained from medical-outcome-based utility, such as the estimated total number of incremental years of life from transplant (LYFT) [19], which was proposed in the allocation policy for deceased donor kidney transplants. On the other hand, the edge probability p_{ij} can be estimated through a logistic regression modeling approach, based on clinical data from multiple existing KPD programs. Detailed discussion regarding edge utility and edge probability can be found in [7].

The goal of optimization for kidney exchanges is to find a collection of mutually disjoint cycles and/or chains that achieve maximum utility on the graph G. Therefore, the task of optimizing matches on graph can be realized by solving the following

IP problem:

$$\max \sum_{c \in C_L} x_c \mathrm{EU}_c \tag{1}$$

$$\text{s.t.} \begin{array}{l} x_c \in \{0,1\} \ \ \forall c \in C_L \\ \sum_{c \in C_L(i)} x_c \leq 1 \ \ \forall i \in V \end{array}$$

where C_L is the set of exchange cycles or chains in graph G with size limited to L or less, $C_L(i)$ is the set of exchange cycles or chains in C_L that contain vertex i, and x_c is a vector of indicators representing whether the cycle or chain c is to be chosen executed for transplant ($x_c = 1$) or not ($x_c = 0$). The constraints in Equation (1) indicate that no cycle or chain candidate can be involved in more than one exchange. Here, EU_c is the expected utility of cycle or chain c. In our setting, the calculation of EU_c based on u_{ij} and p_{ij} for all possible cycles or chain set configurations has been discussed in [7]. The expected utility is defined by an example in the following: for a cycle $c = \{i, j, k\}$ of length 3, $\mathrm{EU}_c = (u_{ij} + u_{jk} + u_{ki}) p_{ij} p_{jk} p_{ki}$; for a chain $< i, j, k >$, $\mathrm{EU}_c = (u_{ij} + u_{jk}) p_{ij} p_{jk}$. The optimization problem in (1) is an IP problem that can be solved to find the optimal matches for different allocation algorithms. For instance, given all $u_{ij} = 1$ and $p_{ij} = 0.1$ except $p_{71} = 0.5$, $p_{15} = 0.5$, $p_{86} = 0.5$, $p_{64} = 0.5$, $p_{23} = 0.5$, and $p_{32} = 0.5$, the optimal solution of cycles and chains can be found by computer and is highlighted in Fig. 2: $\{2, 3\}$, $\langle 7, 1, 5 \rangle$, and $\langle 8, 6, 4 \rangle$. Note that not all the identified cycles and chains will lead to actual operations. Empirically, over 70% of computer-identified matches fail to yield transplants [2]. If the lab match run suggests one transplant fails (e.g., edge $8 \rightarrow 6$ is broken), then the entire chain exchange $\langle 8, 6, 4 \rangle$ is labeled as a failure in the existing methods [1]. As an alternative, the authors in [7] suggest a method with fall-back option; in this case, if $8 \rightarrow 6$ fails, we can try the kidney exchange between six and four. If all other matches are successful, transplants now include $\{2, 3\}$, $\langle 7, 1, 5 \rangle$, and $\{6, 4\}$.

B. Algorithm

Fig. 3 gives a schematic description for a complete process of kidney exchanges with ADs. The details are described in the following steps.

1) At time $t = 0$, there is an initial number of n to form the pool of kidney exchanges, including $P_{\mathrm{AD}}\%$ of ADs and $1 - P_{\mathrm{AD}}\%$ of incompatible donor–candidate pairs.
2) Construct a directed graph $G = (V, E)$ with each vertex representing an incompatible donor–candidate pair or an AD, and each edge from vertex i to j denoting that there is a possible match between the donor in vertex i to the candidate in vertex j.
3) Assign *edge utility* u_{ij} and *edge probability* p_{ij} to each match pair of donor i and candidate j.
4) Invoke one of the kidney allocation algorithms:
   I) *MEU-Parallel*: do the following steps a–e for all cycles and chains simultaneously;
   II) *MEU-Sequential*: do the following steps a–e for all cycles or chains sequentially. It includes two versions: i) *MEU-Sequential-1*: first perform steps a–e for cycles, then for chains; ii) *MEU-Sequential-2*: first perform steps a–e for chains, then for cycles.
   The algorithmic steps proceed as follows.
   a) Find set of exchange cycles and/or chains c in graph G using the depth-first search algorithm, and then compute the expected utility u_c according to the combination configuration of set c.
   b) Solve (1) with respect to indicator x_c representing the optimal virtual (i.e., computer identified) donor–candidate matches.
   c) In the real lab match, a virtual transplant may not be viable. Simulate such uncertainty via a Bernoulli trial with the probability of success equal to that edge probability. If such a Bernoulli trial yields occurrence of 1, the transplant is determined as a successful operation; otherwise it fails.
   d) Compute the number of successful transplants and associated utility of kidney transplants.
   e) Remove the vertices of donor–candidate pairs and/or ADs of successful transplants and remove edges for failed matches returning to the pool from graph G, thus the resulting end vertices of chains become bridge donors (BDs) [12] as new ADs in the next match run.
5) Given arrival rate λ and departure rate μ based on a Poisson process at time $t = t + 1$, generate the new incompatible

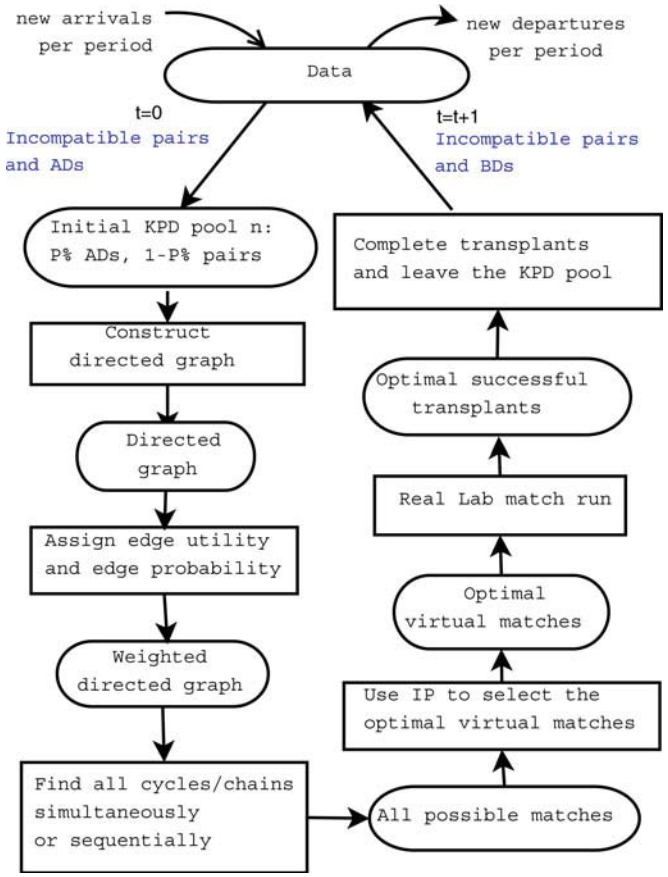

Fig. 3. Flow diagram of process for kidney exchanges.

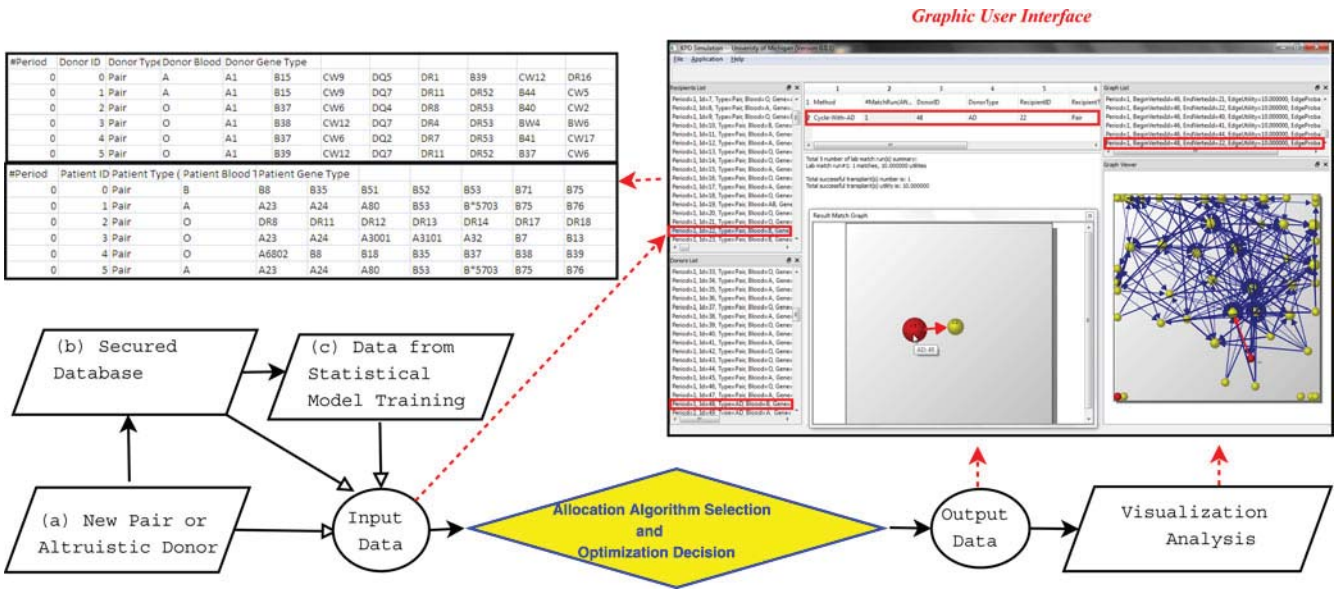

Fig. 4. Flowchart of computerized decision support system for kidney exchange program.

donor–candidate pairs and ADs, then go back to step 1 for the next match run.

Intuitively, *MEU-Parallel* obtains the optimal matches in terms of maximum expected utility in a global view, but the associated computational time is expensive. *MEU-Sequential* finds the solution in a two-step procedure to achieve optimal result, but runs faster. We will further show the difference between them through experiments in Section IV.

III. KPD Computerized Support System

A. Computerized System

In order to implement and compare different kidney allocation algorithms, we developed a novel computerized decision support system that appropriately reflects real world kidney exchange programs. A flowchart of such a system is illustrated in Fig. 4. In the system, we defined three basic components:

1) *Data Input:* The system deals with a collection of data records and files from different input sources, including a) individual user's input data, b) the existing secured KPD database, such as from the University of Michigan's KPD database that can only be accessed by specified approval, and (c) simulation data generated from statistical models based on a list of relative features, such as blood type, HLA antigens, etc.
2) *Optimal Decision Model:* Utilizing donor and candidate input data, the system launches inquiries to a computation server in an independent process to make optimal solutions as described in Section II.
3) *Output Data:* The system produces, displays, and visualizes results, such as optimal matches between donors and patients, number of transplants, and patients' waiting time, in a user-friendly graphical interface through tables, figures, and texts.

B. Graphical User Interface Software

We also developed a graphical user interface (GUI) to support easy communication between front-end inputs or outputs and back-end computation algorithms of our computerized decision support system. In detail, the current GUI supports the following features:

1) *Data extraction and save*: It currently allows displaying all input or output data in a file or from a database.
2) *Data simulation*: It allows simulating KPD pools based on characteristics of donors and candidates following certain probability distributions described in the literature or derived from real data.
3) *Parameter definition*: It allows multiple parameters to be used and defined by users in the algorithms, including the initial total number of pairs and ADs, percentage of ADs, arrival rate, departure rate, edge probability, edge utility, etc. Also, the types, maximal and minimal bounds of all parameters are checked by certain validation rules.
4) *Multiple allocation algorithms selection*: It holds multiple built-in KPD allocation algorithms discussed in Section IV-C to be selected based on user's interests. Different models can share the same parameters and therefore the system allows the user to easily compare and evaluate results.
5) *Simulation execution*: The system can compile an allocation algorithm and graphical interface using a unified C++ program so as to efficiently compute and generate results.
6) *Graph visualization manipulation*: Through GUI, the information of optimal matches between patients and donors will be visualized in a main window. The user can highlight every compatible donor–candidate pair, emphasize different vertices and edges using versatile colors, shapes or sizes (e.g., a red vertex could indicate an AD, and a red edge represents a cycle or chain match), mark the corresponding original input data in separate subwindows,

and zoom in to view details or zoom out to see the entire graph. Moreover, unselected matches can be muted, and leave matches of interest being highlighted.

7) *Dynamics match run monitor*: If desired, any number of match runs may be performed, providing useful information for further exploration and visualization of a KPD program.

These features clearly show that our developed GUI system provides a very powerful tool to help clinicians more easily analyze and assess the kidney exchanges program.

IV. Illustrative Simulation and Results

A. Input Data and Parameters

To illustrate our computerized support system, we present some simulation results in this section. First, we generated candidate and donor data separately for the following experiments in order to investigate our algorithm. Candidates are sampled at random with replacement from the University of Michigan (UM) KPD database, which had 115 incompatible donor–candidate pairs. This database provides us the representative patients' ABO blood type and HLA sensitivities useful to characterize each sampled candidate. Donors, on the other hand, are generated following population distributions of ABO blood types and HLA gene types. The distribution of ABO blood types is drawn from the U.S. population distribution: $O(44\%)$, $A(42\%)$, $B(10\%)$, and $AB(4\%)$ [16]; the distribution of an HLA is derived from HLA haplotypes frequencies of the U.S. population [8]. Through random sampling, we can appoint ADs directly from the set of drawn donors as well as create an incompatible donor–candidate pair if either their ABO blood types are mismatched or there is an HLA incompatibility. In this way, candidate and donor samples reflect the real-world data. Second, parameters needed for data generation, including an initial number of n with percentage of ADs P_{AD} and percentage of pairs $1-P_{\mathrm{AD}}$, are specified for the first match run. Third, a directed graph $G=(V,E)$ involving edge utility and edge probability is created by simulating characteristics of candidates and donors. For purpose of example, the edge utility is simulated from a uniform distribution on interval $U[\min,\max]$. In this paper, also for illustrative convenience, we simulated values of edge utility from $U[1,1]$, $U[10,20]$, or $U[10,30]$ and edge probability from $U[0.1,0.5]$, respectively. Then, for a given graph, we applied the depth-first search method to find all cycles and chains with size restricted up to 3 because longer cycles or chains result in substantial logistic burden and expensive computational cost, and do not in reality lead to significantly more transplants [1], [6]. Then, we obtained the optimal solution to (1). Finally, whether or not each selected match would in fact yield a transplant is determined by computer simulation. This accounts for the uncertainty in the actual cross match and other friction such as sickness and donor/recipient preferences.

B. Evaluation and Optimal Decision Model

In practice, there exist other considerations of clinical importance for KPD program, such as avoiding long waiting time for donors or candidates, considering Blood type O donors for Blood type O candidates as priority, etc. [3], [18]. We here in use maximizing the number or utility of transplants for our illustration. Thus, we evaluated the kidney exchange results using two criteria: the *number of transplants* to reflect the quantity of patient's life years saved and the *claimed utility* to indicate the quality of patient's life after transplants. The higher the number of transplants or the claimed utility, the higher the benefits for the kidney transplant patients. For each allocation algorithm, we conducted 100 replicates, and reported, the averaged number of transplants and the averaged claimed utility.

TABLE I
Comparison of Average Number of Transplants (ANT) and Average Number of Transplants Initiated by ADs (ANTAD) by Four Methods 1) *MN*, 2) *MEU-Parallel*, 3) *MEU-Sequential-1*, and 4) *MEU-Sequential-2* for Static Kidney Exchange in Various Data Pool Sizes (n) and Percentage of ADs (P_{AD}) Over 100 Runs

Method	*Pool Size*	$P_{AD}=0\%$	$P_{AD}=5\%$
Name	n	ANT	ANT(ANTAD)
MN	50	0.5	0.8 (0.4)
MEU-Parallel		0.8	1.6 (0.7)
MEU-Sequential-1		0.8	1.9 (0.8)
MEU-Sequential-2		0.8	1.7 (0.7)
MN	100	1.1	1.7 (0.7)
MEU-Parallel		1.8	3.5 (1.7)
MEU-Sequential-1		1.8	3.9 (1.8)
MEU-Sequential-2		1.8	3.7 (1.7)
MN	200	2.4	3.6 (1.5)
MEU-Parallel		3.9	7.7 (3.5)
MEU-Sequential-1		3.9	8.3 (3.7)
MEU-Sequential-2		3.9	8.1 (3.6)

C. Output Results

In this section, we discussed four allocation algorithms available in the computerized support system that incorporate ADs into KPD program. Algorithm *MN* [1] searches the cycles and chains simultaneously so as to obtain the *M*aximum *N*umber of transplants (i.e., with all $u_{ij}=1$) or maximum utility of transplants. On the other hand, *MEU-Parallel*, *MEU-Sequential-1*, and *MEU-Sequential-2* are executed according to the steps, described in Section II, to maximize the expected utility of transplants. Notice that the difference between *MN*-based and *MEU*-based methods lies in the fact that the former does not consider uncertainty and fall-back option, while the latter does. Since each algorithm has more than one parameter to vary, we ran the four algorithms under same parameter settings in order to compare them fairly.

In the first illustrative experiment, we investigated a static KPD program for only one time match run (i.e., $k=1$). Table I reports the average number of transplants for the four methods with two varying parameters, initial size of the KPD pool (n), and percentage of ADs P_{AD}. Here, we used $U[1,1]$ for the distribution of edge utility and $U[0.1,0.5]$ for the distribution of edge probability. To understand the effect of the initial size of the KPD pool (n) on the number of transplants while holding P_{AD} constant, Table I clearly suggests that the number of transplants increases by about 100% as the size of the initial KPD pool doubles. On the other hand, to investigate the number of transplants with respect to the percentage of ADs (P_{AD}) while keeping n

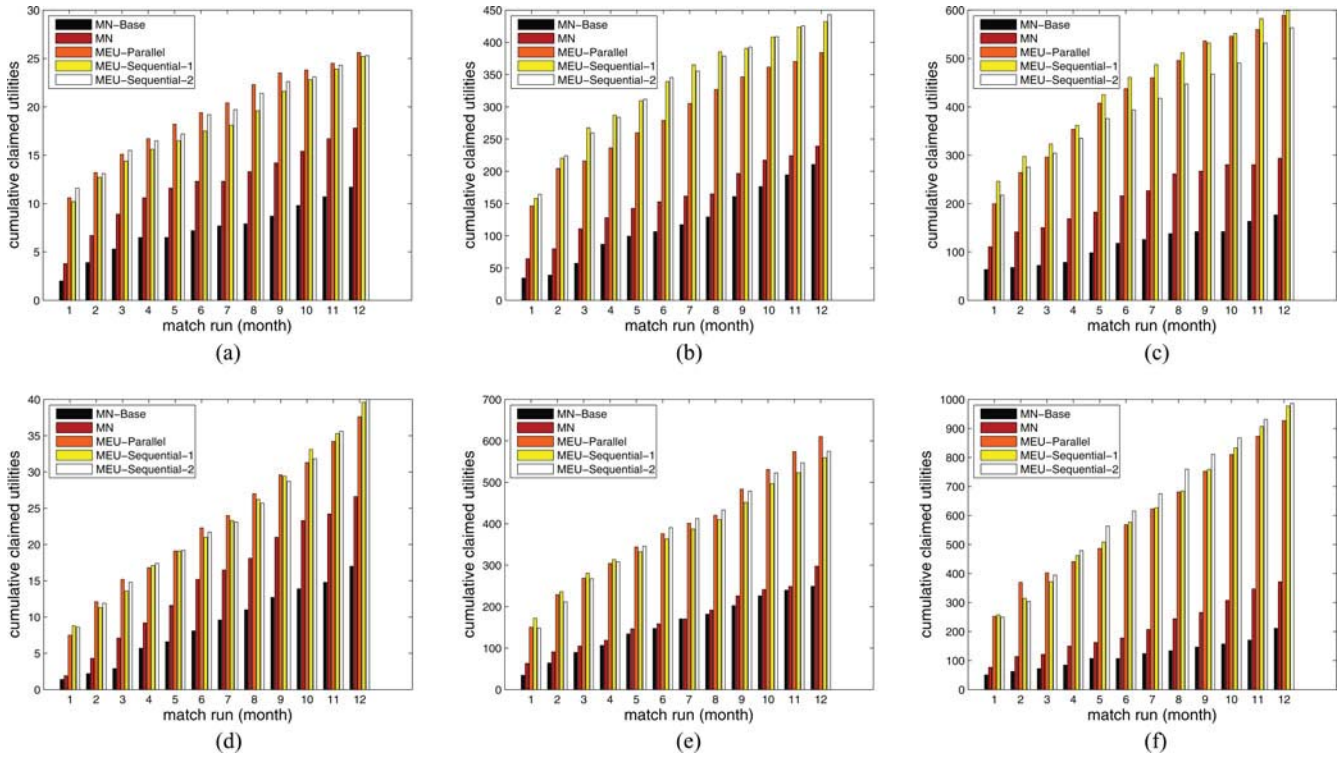

Fig. 5. Comparison of cumulative claimed utility over time in month (number of match runs) among five allocation algorithms: *MN-Base*, *MN*, *MEU-Parallel*, *MEU-Sequential-1* and *MEU-Sequential-2*. Different edge utility uniform distribution U, arrival rate λ and, departure rate μ are set as follows: (a) $U[1,1]$, $\lambda = 10$ and $\mu = 5$, (b) $U[10,20]$, $\lambda = 10$ and $\mu = 5$, (c) $U[10,30]$, $\lambda = 10$, and $\mu = 5$, (d) $U[1,1]$, $\lambda = 20$ and $\mu = 10$, (e) $U[10,20]$, $\lambda = 20$ and $\mu = 10$, (f) $U[10,30]$, $\lambda = 20$ and $\mu = 10$.

fixed, Table I shows that the average number of donor–candidate matches rises by at least 50% when the percentage of ADs is 5%. Theoretically, if $P_{\mathrm{AD}} = 0\%$, the average number of transplants is almost the same for all three *MEU*-based methods. The result is verified in Table I. Again with $P_{\mathrm{AD}} = 5\%$, the average number of transplants generated by ADs, shown in parentheses of Table I, indicates that more than 40% of matches are produced by exchange chains. For example, using the *MEU-Sequential-1* method, $3.7/8.3 = 44.58\%$ of transplants are produced by ADs initiated chains when $n = 200$ and $P_{\mathrm{AD}} = 5\%$. It is clear that involving ADs in the KPD program can significantly improve the quantity of transplants. Additionally, all *MEU*-based methods outperform method *MN* in all the cases because such methods incorporate operational uncertainties and allow contingency plans when the virtual match run fails [7].

In the second illustrative experiment, we focused on the dynamics of kidney exchanges. In an evolving KPD program, some new pairs or ADs will enter into the KPD pool and some will leave the pool due to transplantation refusal, illness, or willing withdrawal. Thus, new match runs are frequently and regularly performed over time. Using a Markov process, we considered that a dynamic KPD program has an arrival rate λ and a departure rate μ. We conducted $k = 12$ match runs, mimicking the scenario that there is one match run per month within a year. Fig. 5(a)–(f) display the cumulative claimed utility obtained by five methods implemented in the computerized support system, over the situations where arrival rate varies from $\lambda = 10$–20 and departure rate changes from $\mu = 5$–10. These five methods are as follows: 1) *MN-Base* [1] (i.e., method without considering ADs), 2) *MN* [1] (i.e., method incorporating ADs), 3) *MEU-Parallel*, 4) *MEU-Sequential-1*, and 5) *MEU-Sequential-2*. Other parameters were set as: $n = 200$, $P_{\mathrm{AD}} = 5\%$, $U[0.1, 0.5]$, $U[1,1]$, $U[10,20]$ or $U[10,30]$. From each vertical panel of Fig. 5, it is evident that the cumulative claimed utility increases if the number of arrivals is more than that of departures in the KPD pool (i.e., $\lambda = 10, \mu = 5$ to $\lambda = 20, \mu = 10$). Note that the cumulative claimed utility is equal to the cumulative claimed number of transplants when edge utility follows $U[1,1]$. Additionally, the cumulative claimed utility for 12 match runs using the four approaches with ADs is at least 10% higher than that of the method without ADs (i.e., *MN-base*). Moreover, the three *MEU*-based methods clearly outperformed the other two *MN*-based methods over time. In summary, through the simulation studies on both static and dynamic programs, the *MEU*-based methods incorporating ADs steadily outperformed the other allocation algorithms in terms of both quantity and quality of kidney exchanges.

Finally, in the third illustrative experiment, we compared the computing time of computerized matching processes as given by three *MEU*-based algorithms in one match run. From a theoretical perspective, the complexity of IP programming related to (1) is associated with two parameters: a) size of variables x_c determined by the number of possible exchanges (i.e., number of cycles and chains), and b) number of constraints determined by the number of vertices (i.e., size of KPD pool). In all

TABLE II
COMPARISON OF THE AVERAGE NUMBER OF CYCLE AND CHAIN EXCHANGES (IN NUMBERS) AND AVERAGE COMPUTATION TIME FOR OPTIMIZATION (IN SECONDS) BY THREE METHODS *MEU-Parallel*, *MEU-Sequential-1*, AND *MEU-Sequential-2* FOR STATIC KIDNEY EXCHANGES WITH ADS PROGRAM IN VARIOUS KPD POOL SIZES OVER 100 RUNS

	100	200	300	400	500
MEU-Parallel (numbers)	563	3,557	11,403	36,097	58,192
MEU-Sequential-1 (numbers)	**461**	**2,666**	**8,093**	**25,605**	**38,516**
MEU-Sequential-2 (numbers)	476	2,995	9,265	29,753	45,860
MEU-Parallel (seconds)	0.15	5.99	86.10	1,330.30	3,991.34
MEU-Sequential-1 (seconds)	**0.09**	**2.37**	**27.26**	**395.83**	**1,085.01**
MEU-Sequential-2 (seconds)	0.11	3.40	42.20	634.30	1,874.96

experiments, we used Gurobi optimization software [5], and ran C++ programming on a Linux Ubuntu 10.04 machine with Quad 3-GHz Intel Xeon processors and 4-GB RAM. Table II shows a summary of computing time with varying numbers of KPD pool (i.e., number of constraints), and possible exchanges (i.e., size of variables). It is seen that the total number of cycle and chain exchanges increases significantly if the KPD pool size increases from $n = 100$ to 500. The top three rows of Table II list the average number of exchanges with cycle/chain size limited to 3 over 100 simulation runs. The results show that the two *MEU-Sequential* methods found a smaller number of exchanges than *MEU-Parallel*. The reason is that these two *MEU-Sequential* methods first search either cycles or chains so that compatible matches would be removed from a KPD pool, leading to approximately a 15% decrease in the total number of exchanges. It is evident that method *MEU-Parallel* is the slowest because it needs to find the largest number of exchanges. Moreover, *MEU-Sequential-1* runs faster than *MEU-Sequential-2*. The time required for optimization in the two *MEU-Sequential* methods is about only 45% of the *MEU-Parallel* method except $n = 100$. For example, method *MEU-Sequential-1* spends only about 18 min while method *MEU-Parallel* needs more than 1 h to find the optimal results at $n = 500$. It indicates that method *MEU-Sequential* may be a more efficient approach to reach for optimal matches if a relatively large number of incompatible pairs and ADs are involved in a KPD program, which may be set up as a default option of allocation algorithm.

V. CONCLUSION AND FUTURE WORK

In this paper, we investigated an expected-utility-based graph model designed to increase the mutual benefits in kidney exchanges. The simulations, closely imitating the real application of a computerized exchange system, have suggested that utilizing both paired donors–candidates, and ADs can increase both quantity and quality of kidney transplants. All algorithms discussed in this paper have been fully integrated into a novel GUI software package, which will be released to the public through the necessary Institutional Review Board (IRB) regulations on the website.

Our future plan will focus on the incorporation of additional existing and/or new KPD allocation algorithms into the current system. Also, we plan to develop modeling of some important system parameters as functions of practical donor or candidate characteristics, and evaluate the differences and relationships among these parameters in terms of their impacts on the quantity and quality of transplants. In addition, we will investigate the evolution of KPD program using an online stochastic optimization algorithm, so the KPD computerized system will have more flexibility and practicality to facilitate clinical practice. Another direction of future work is to improve the software based on feedback from clinical users.

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Authors' photographs and biographies not available at the time of publication.