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Mahdi Fathi

Marzieh Khakifirooz

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Kidney-Related Operations Research: A Review

Mahdi Fathi

Department of Industrial and Systems Engineering, Mississippi State University, Starkville, MS, USA

Marzieh Khakifirooz

School of Science and Engineering, Tecnológico de Monterrey, Monterrey, Mexico

***Abstract*–Operations research and optimization in healthcare and disease modeling have received significant attention in the last three decades. This paper surveys several perspectives of operations research techniques in kidney disease, such as graph theory, queueing theory, Markov chain, and Phase-Type distribution (PTD). The kidney related problems include kidney exchange problem, the modeling of kidney disease progression, kidney transplantation, and the complex relationship between Chronic Kidney Disease (gradual loss of kidney function over time) and Acute Kidney Injury (sudden episode of kidney failure in a few hours or a few days). Each section is summarized by some discussion regarding the limitation of proposed methods in the literature. Finally, the paper is concluded by offering some research direction to fill in the gaps in the literature.**

Keywords: Kidney Disease, Kidney Transformation, Operations Research, Chronic Kidney Disease, Acute Kidney Injury, Phase-type Distribution, Queueing Theory, Markov Decision process, Graph Theory.

1 Introduction

From underdeveloped to developed societies, the perfection of healthcare and medical services are one of the far-reaching goals for governments. How to

decide the best location of medical centers? How to manage the service time in the emergency division? How to select the best route for ambulances? How can the medical service cover the target population? These are a few questions that Operations Research (OR) could provide a solution to tackle. The applications of OR are far broader than to answer the aforementioned questions. A useful review of the past researches can quickly be acquainted with the underlying implementation and numerous methodologies of OR in healthcare management and medical services. There are some review papers in this area such as OR techniques (Rais and Viana 2011; Brandeau et al. 2004), queueing theory application (Lakshmi and Iyer 2013), operations management (Denton 2013), healthcare policy (Zaric 2013) and data mining techniques (Obenshain 2004; Koh et al. 2011; Yoo et al. 2012; Tomar and Agarwal 2013; Raghupathi 2016; Rojas et al. 2016). However, there is a gap in the literature that focuses on a specific disease and discusses the details of the models for different challenges connected to that disease.

This paper surveys some selected OR topics that appeared in kidney-related studies. The main objective of the paper is to introduce the models rather than only a collection of the related literature. The topics on kidney problems in this paper include the kidney exchange problem, the modeling of kidney disease progression, kidney transplantation and the complex relationship between chronic kidney disease (CKD) and acute kidney injury (AKI).

According to the annual report of the American kidney fund in 2015 (*American Kidney Fund* n.d.), kidney disease is the 9th leading reason for death in the United States. A predicted 31 million Americans (10% of the adult population) have CKD, and 9 out of 10 Americans who have stage 3 CKD (moderately decreased kidney function) do not identify it. CKD is more prevalent among females than males. Males with CKD are expected 50% more to have their CKD turn into kidney failure. Moreover, some nationalities are at higher danger for kidney failure, for example, the risks for African Americans, Native Americans, and Asians are almost 4, 1.5, and 1.4 times higher than whites Americans. Hispanics are approximately 1.5 times as expected to be diagnosed with kidney failure in comparison to non-Hispanics. The first and

second leading causes of kidney failure are diabetes and high blood pressure (HBP), which make 44% and 28.4% of all current evidence of kidney disease, respectively. In 2012 diabetes and HBP were the first cause of 239,837 and 159,049 kidney failure patients. An estimated 29.1 million people have diabetes; 8.1 million of them do not know they have it, and around 70 million (29%) people have HBP — that is every 1 in 3 American adults. Approximately 40% of people with diabetes can get CKD.

Kidney diseases are prevalent in the world and often are lethal. Dialysis is a temporary solution for those waiting for a kidney transplant; however, it is expensive, and the quality of life would be low. In addition, only 12% of patients with dialysis will survive for more than ten years, on average. The more lasting cure is transplantation. Considering that selling and buying organs in most of society are prohibited, it makes supply and demand mismatch. In the United States, 79000 patients are waiting for a kidney transplant, while only in 2008, 4268 patients died during the waiting time. Besides the higher risk compared to the bid in the kidney transplant market, there are obstacles regarding incompatibility even from patients' family as a voluntary live-donor kidney transplant. Medically, compatibility is circumscribed both by blood type (*O*, *A*, *B*, or *AB*) and by existing tissue antibodies. Type *O* can accept only type *O*, type *A* only type *O* or *A*, type *B* only type *O* or *B*, and type *AB* any donor. However, the percentages of blood types are not equivalent, and therefore, for some groups with a higher risk for kidney disease, there is less offer than others.

One of the most severe kidney diseases is AKI. AKI is a sudden failure of kidney and happens in people who are already sick and in the hospital. Unlike CKD, AKI is often reversible if treats quickly. However, AKI patients who overcome kidney problem in the hospital have a danger of growing CKD and death (Kerr et al. 2014).

Figure 1 shows the standardized definitions and diagnostic criteria of AKI and CKD, including functional and structural criteria, staging, burden including prevalence and annual incidence, and lifetime cumulative incidence. The

measurement indexes are adjusted based on “Glomerular Filtration Rate” (GFR) [3], “Albumin Excretion Rate” (AER) [4], and “Albumin-to-Creatinine Ratio” (ACR) criteria [5].

Figure 2 shows the determinants related to the kidney disease progression process, including death (purple), grades of disease (green), and kidney disease (blue). Horizontal arrows show the transitions between stages (kidney outcomes). Solid and dashed arrows are showing kidney disease progression and remission, respectively. Gray triangles present constant variations in GFR and kidney loss. The transitions status reveals that if the status of disease is monitored weekly, then any change with duration less than or equal to three months is suspected of being AKI and more than three months to be the CKD. There is a big challenge in kidney problems for discovering the kidney disease propagation, the relationship between AKI and CKD, and renal healthcare management, which OR would be a useful tool to employ. OR techniques can answer several vital questions in this area, such as:

- How can factors such as diabetes, HBP, family history, race-ethnicity, obesity, age, smoking, history of AKI, and heart disease increase the risk of kidney disease? How can other health condition (such as rare disease) cause a problem for kidney and lead to kidney disease? (Levey et al. 2007; Mallappallil et al. 2014)
- How kidney disease is preventable from the medical test and symptoms? (Snyder and Pendergraph 2005)
- What are the causes of kidney failure? How can kidney disease cause a problem for the rest of the body, such as bone disease and Anemia? (Asar et al. 2016)
- How can we speed up the evaluation process and find a match for transplant? (Anderson et al. 2015a)
- How can we manage the waiting list and multiple listing for the kidney transplant? (Alvelos et al. 2019 *a*)
- What is the waiting time for the kidney transplant for each group of kidneys? (Bandi et al. 2019)

and many other questions. Therefore, considering the tremendous needs for optimal decision making in kidney problems despite the complexity, dynamicity, and time management challenges, this study aims to review the literature which addresses the kidney problems from OR perspective. Among the reviewed literature, those with novel solutions for modeling kidney problems are selected for further discussion in this paper.

Kidney's related problems are classified into two major groups, kidney disease, and kidney transplant. Kidney transplant topics investigated in the literature include 1) kidney transplant allocation, 2) survival model for life years from transplant (LYFT), 3) waiting list and time management, and 4) exchange model for paired donations, spousal, and living unrelated donors. In this paper, we review the kidney exchange model in Section 2, and transplant allocation and queuing models in Section 3. Challenges regarding survival analysis of LYFT mainly studied from statistical inferences, and therefore, we eliminate this topic in current research.

Unlike the kidney transplant topics, the kidney disease encompasses broader research topics including kidney disease causes and risk factors, disease types, symptoms, tests, prevention and treatment, kidney failure and several other topics such as kidney cancer, stone, and infection. The majority of research look at these phenomena from data science (DS) perspective, and the application of OR has barely been applied.

The remainder of this paper is organized as follows. Section 2 describes the kidney exchange problem and its modeling trough graph theory. The kidney transplantation problem is addressed in Section 3. Section 4 surveys stochastic modeling of kidney disease and transformation CKD to AKI. The MDP for kidney disease screening and treatment is presented in Section 5. Finally, we conclude the paper and future research directions in Section 6.

2 Graph Theory and Kidney Exchange Problem

Kidney exchange is a global innovation program that allows patients to swap willing but incompatible donors. Maximizing the mutual benefit for a given pool

of mismatched sets, measured by the number of possible kidneys, is the goal of this program (Constantino et al. 2013). There are several motives for applying the OR techniques in kidney exchange problem. For instance, when the donor and recipient are incompatible, or when donors do not come with paired patients and are willing to donate a kidney without asking for one in return. Such donors are called altruistic donors. Roth et al. (2004) first described the classic kidney exchange problem from OR perspective.

As shown in Figure 3 for three incompatible pairs $(P1, D1), (P2, D2)$ and $(P3, D3)$, organizing exchanges between some pairs of patients *P* and donors *D* is a critical responsibility, especially when an altruistic donor *aD* is available. In the simplest case, two patient/donor pairs are matched together, each donor giving to the other pair's patient and they make a cycle of length 4. Larger exchange cycles, such as the three patient/donor pairs shown in Fig 4.

To maximize the pair-exchange rate, assume *G*(*V*, *E*) be a directed graph with weighted edges, where vertex *V* represents a donor/recipient pair, and weighted edges *E* means donors and recipients' compatibility measurement. Consider *C* and w_c denote the set of cycles in the graph with most $|V|-1$ length, and the weight of cycle *c* which is equal to the sum of all edge weights in the cycle, respectively. The decision variable in each cycle is x_c,

$$x_c = \begin{cases} 1 & \text{if cycle } c \text{ is in the center} \\ 0 & \text{otherwise,} \end{cases}$$

and the problem is to find a cycle cover of the graph with maximum weight. The mathematical formulation is as follow:

$$\left\{ \max \sum_{c \in C} w_c x_c, st: \sum_{c: v \in C} x_c \le 1, \forall v \in V, x_c \in \{0,1\} \right\}$$

The constraint guarantees that a recipient and donor need one kidney to exchange, and each *V* of the graph can be in at most one cycle.

To solve the aforementioned optimization problem, extensive efforts have been done on kidney exchange problem for descends, mainly focused on

integer programming and stochastic programming. Table 1 summarizes some highlighted recent works in this domain.

The graph theory model in kidney exchange problem maximizes the number of possible kidney transplant by finding maximum weight packing of vertex-disjoint cycles and chains for a given weighted digraph with limited length of cycles L (typically $2 \le L \le 5$) (Lin et al. 2019). The kidney exchange problem is NP-hard which means that there is not a polynomial time exact algorithm for it (for the complexity investigation of kidney exchange problem refer to Abraham et al. (2007); Biro et al. (2009); Huang (2010)). Moreover, the traditional economic theory and integer programming view for kidney exchange problem face systematic inequity in exchange for certain unmatched patients. Recently Mike and Maroulas (2019) studied inequity within the distribution of kidney allocation among patients and proposed a Hodge cycle algorithm[6] for minimizing allocation disparities.

2.1 Discussion on Graph Theory and Kidney Exchange Problem

Advantages: Graph theory contains many well-established properties that can be used to improve the computational performance of programs dealing with graphs. Utilizing graph theory benefits of testing compatibility in order to build the entire kidney pair donation, before making allocation decisions. In particular, the lack of bias (e.g., due to location, ethnicity, or blood type) achieved by cycle allocation could shorten wait times for sensitized patients.

Disadvantages: Although, recent advances in graph theory have afforded some advantages over traditional methods such that considering correlations across the network among the nodes. However, it is costly in computation when it comes to large-scale data. Moreover, the kidney exchange problem has a dynamical nature, and the abstraction to graphs can show temporal aspects of information flow among nodes and links. However, these flow change with time. Therefore, a static graph only could be a system represented and the prerequisite for building detailed dynamical models. Also, graph-theoretic methods are data-driven rather than model-driven. Which

means each updated or new data set requires a new graph model. In addition, graph theory is not problem-free approach, is based on sophisticated mathematical techniques that require rational choices at various steps of the analysis. For instance, when there is a need to choose among several possible strategies to reconstruct the networks, consider the dynamic weight for nodes, or use a threshold for links or statistical controls, graphs do not always lead to a convergent or consistent outcome.

3 Queueing Models for Kidney Transplantation

The kidney transplantation relays upon national kidney allocation policy as a national plan which manages the list of all the people across the country, waiting (approximately 3-5 years) for the kidney transplant. This program ensures that deceased donors' kidneys are distributed fairly using a transparent system depending on how well you match with the available kidney and how many donors are available in your local area. The decision for distributing donors' kidneys is a combination of blood-type and antibody matching, time with kidney failure, and a few other factors (such as heart disease, not being strong enough to endure an operation, infection, obesity, smoking or substance abuse) that give people priority on the list (including being a child or being a past live kidney donor) with giving the propriety to longer waiting time. The main purpose of this program is to reduce regional variability in access to transplantation and improve the outcomes for individual kidneys that are transplanted.

Waiting time includes time spent after starting dialysis prior to being registered on the waiting list. Candidates are registered on the waiting list once they have a GFR value less than or equal to 20 ml/min or have begun dialysis.

The waiting times for solid-organ transplantation is a vital issue which is studied by Rexius et al. (2002); Danovitch and Cecka (2003); Hussey et al. (2007); Barone et al. (2008); Stanford et al. (2008); Glander et al. (2010); Phelan et al. (2010); Liefeldt et al. (2011); Elalouf et al. (2018); Perlman et al. (2018). Although their observation is inconsistent,

the recipients with blood type *O* in compared to type *A*, and *A* in comparison to *AB* wait longer. Also, patients with blood type *B* are sometimes waiting slightly longer than *O*. This problem is known as the blood type *O* problem occurring in various organ types with different waiting times as reported in several studies in the United States (Barone et al. 2008), and Ireland (Phelan et al. 2010).

Therefore, despite the regulation for kidney transplantation, optimal decision making can be categorized based on two main problems:

- Optimal threshold level to accept a transplant (Ahn and Hornberger (1996): single patient) (Su and Zenios (2004): multiple patients).
- Optimally allocating different types of stochastically arriving kidney (Stanford et al. 2014; Perlman et al. 2018).

3.1 Ahn and Hornberger (1996)'s Model

Ahn and Hornberger (1996)'s model offers organ quality-based kidney transplantation, which patients have a choice to accept or reject the kidney. As shown in Figure 5, they considered five states (with transition probabilities based on issued graft survival rates [7] of patients in the U.S.): alive on dialysis waiting for a transplant (s_1), alive on dialysis with no option for transplantation (s_2), successful transplant (s_3), transplant failed (s_4), death (s_5), where only at state s_1 patient can decide to accept or reject the kidney.

Their problem focused on finding the minimum threshold level for patient for deciding to accept or reject the kidney. They introduced the Quality-Adjusted Life Year (QALY) index based on patient-specific ratings for being in various health states. Such that, if the expected 12 months of graft survival rate for the kidney-patient pair exceeded the threshold, the patient accepted the transplant; otherwise, the patient rejected it.

To estimate graft survival rate, Gjertson's logistic-regression model (Gjertson et al. 1991) is considered with several independent futures including age,

gender, ethnic group, original disease-causing end-stage renal disease (ESRD), number of transfusions, graft number, highest panel reactive antibody level, year of transplant, use of cyclosporine to prevent rejection, center of transplantation, donor relationship (i.e., cadaver versus living-related), Human Leukocyte Antigen (HLA) mismatches, and cold ischemia time.

Let x be the graft survival rate and d the minimum accepted threshold level. The decision parameter d can be estimated using one-year graft survival rate. By starting from s_1, a patient may accept a donor who provides the minimum 1-year graft survival rate ($x > d$) and then either (1) have successful transplantation ($QALY_3$), or (2) have failed transplantation ($QALY_4$). The patient may not find a donor with a satisfying 1-year graft survival rate ($x < d$), and may undergo the QALY of dialysis as either (1) qualified for transplantation ($QALY_1$) or (2) unqualified for transplantation ($QALY_2$), or death ($QALY_5 = 0$) which mathematically can be represented as:

$$QALY_1 = \alpha \int_d^1 (xQALY_3 + (1-x)QALY_4) f(x)dx + \alpha \int_0^d f(x)dx(p_{11}QALY_1 + p_{12}QALY_2) + QOL_1,$$

and respectively $QALY_2$, $QALY_3$ and $QALY_4$ are equal to:

$$QALY_2 = \frac{QOL_2 + \alpha p_{21} QALY_1}{1 - \alpha p_{22}},$$

$$QALY_3 = \left[\frac{1-\alpha^{12}}{1-\alpha}\right](QOL_3 - (1-x)\mathrm{Imm}) + \alpha^{12}\left[\frac{QOL_3 - (1-x)\mathrm{Imm}}{1-\alpha p_{33}}\right] + \left[\frac{\alpha p_{34}}{1-\alpha p_{33}} QALY_4\right],$$

$$QALY_4 = \left[\frac{1-\alpha^6}{1-\alpha}\right] QOL_4 + \alpha^6 \left(\delta QALY_1 + (1-\delta)\left[\frac{QOL_4}{1-\alpha p_{44}}\right]\right),$$

where

$f(x)$: probability function of 1-year graft survival for a pool of donors' kidneys.

QOL_i: monthly quality-of-life score assigned to each state, $0 \le QOL_i \le 1$.

Imm: quality-of-life adjustment for side effects of immunosuppressive drugs.

$1-\alpha$: monthly fixed discount rate (> 0).

p_{ij}: monthly transition probability from s_i to s_j, $i, j = 1,...,5$.

δ: probability of being eligible for re-transplantation 6 months after a failed transplant

Therefore, the minimum acceptable of 1-year graft survival rate, d, is obtained by maximization of $QALY_1$.

3.2 Su and Zenios (2005)'s Model

Su and Zenios Su and Zenios (2005) considered the patient choice on kidney allocation based on sequential stochastic assignment model. When a kidney offers to a patient, it could be accepted or rejected, and patient can join the candidate queue for future transplantation. Patients accept a kidney offer by maximizing their expected reward.

The following assumptions are considered in their model:

(a) The candidates and the donor are equally well informed about kidney types and the reward functions.

(b) Candidates may discount future rewards using a discount factor $\delta \le 1$, while the donor is interested in long-run average rewards.

(c) The reward for a type i patient receiving a kidney x is $R_i(x)$, which is the same as the reward obtained by the donor.

(d) At the end of the planning horizon, the reward of a patient who has not received an offer is zero.

To estimate the optimal reward function for each patient, assume m different type of transplant candidates to be assigned to n different type of kidneys. If a transplant patient of type $i = 1,...,m$ has been assigned to type $j = 1,...,n$ kidney, we get a reward of R_{ij}. For $i \in \{1,...,m\}$, p_i is the proportion of type i patient, and for $j \in \{1,...,n\}$, q_j is the relative frequency of type j kidney.

Therefore, partition policy can be shown by a_{ij} and the fraction of type j kidneys assigned to type i candidates is calculated by $\frac{a_{ij}}{\sum_{i=1}^{m} a_{ij}}$. An optimal partition policy $a^* = \{a_{ij}\}_{i=1\,j=1}^{m\ n}$ as the first-best policy is a solution of the following mathematical problem:

$$\begin{aligned} \max_{a_{ij}} \quad & \sum_{i=1}^{m}\sum_{j=1}^{n} a_{ij} R_{ij} \\ st: \quad & \sum_{i=1}^{m} a_{ij} = q_j, \quad \forall j \\ & \sum_{j=1}^{n} a_{ij} = p_i, \quad \forall i \end{aligned}$$

Now, consider the situation that patient wants to reject a kidney offer. In order to penalize a patient from rejecting too many organs, if patient type i rejects kidney type j, he is moved down to the end of the queue, and that kidney is wasted. Assume that patients use a discount factor δ to discount future values. If patient i reject the kidney j, and accepts the next offer, the second-best policy under discrete kidney types would be as follow:

$$\begin{aligned} \max_{a_{ij}} \quad & \sum_{i=1}^{m}\sum_{j=1}^{n} a_{ij} R_{ij} \\ st: \quad & \sum_{i=1}^{m} a_{ij} \le q_j, \quad \forall j \\ & \sum_{j=1}^{k} a_{ij} \le p_i, \quad \forall i \\ & a_{ij}\left(R_{ij} - \left(\frac{\delta\sum_{j=1}^{n} a_{ij}}{1-\delta(1-\sum_{j=1}^{n} a_{ij})}\right)^{n}\left(\frac{\sum_{j=1}^{n} a_{ij} R_{ij}}{\sum_{j=1}^{n} a_{ij}}\right)\right) \ge 0, \quad \forall i, j \end{aligned}$$

The model with patient choice considers the incentive compatibility constraint and replace the “supply balance demand” constraint by the inequality constraint.

3.3 Stanford et al. (2014)’s Model

Stanford et al. (2014) proposed a queueing model for stochastically-arriving kidney allocation to arbitrary transplantation applicants. Their model considers blood type compatibility. As shown in Figure 6, allowable pairs and rejected compatible pairs represented by solid and dashed arrows, respectively. Based on Figure 6, *O* to *AB* are not favored medically, *B* to *AB* would conduct to further transfers from *O* to *B*, and *O* to *A* has disadvantages for candidates *O*. The resulting policy allows type *O* organs to be transplanted into type *B* recipients for a small fraction P_O, and type *A* organs to be transplanted into type *AB* recipients for another small fraction P_A.

The model of Stanford et al. (2014) presented an idealized transplant queue model by the most critical criteria in waiting time. Patients are assigned to the waiting queue for candidates with kidney type *i*, $\{i = O, A, B, AB\}$ based on a renewal process (see Kleinrock (1975)).

Consider T_i as the time between successive placements for First-Come-First-Served (FCFS) patients in single server queue *i* expressing the type *i* kidney availability. Then, the stationary waiting time distribution function for placing patient in the *i*th queue is as follow:

$$F_i(t) = Pr\{T_i \le t\}; t \ge 0; \quad i = O, A, B, AB.$$

They also assumed the cadaveric supply for all kidney types to meet the demand with $GI/M/1$ queue stability condition as

$$\frac{1}{\mu_i E\{T_i\}} = \rho < 1; \quad i = O, A, B, AB.$$

The consecutive time for availability of the same type of kidney (called sojourn time) is exponentially distributed with rate μ_i as:

$$P_i(w \ge t) = e^{-\mu_i(1-r_0)t}; \quad t \ge 0,$$

where *w* in $GI/M/1$ is the arrival time until service completion for the arbitrarily chosen patient, called waiting times on the “Array of Idealized

Transplant Queues" (AITQ) wait lists. $r_0 = m(-\mu_i(1-r_0)), 0 \le r_0 \le 1, W_i = \frac{1}{\mu_i(1-r_0)}$ is the average of sojourn time, and $m = \int_{x=0}^{\infty} e^{xt} dF_i(t)$ is the moment generating function.

Considering only type *O* and *B* queues, applying the Poisson processes' properties (Conway et al. 2003), the kidney type *O* is engaged for receivers with kidney *O* follows a Poisson process with rate $\mu_O(1-P_O)$, and the kidney type *O*s is available for receivers with kidney *B* follows a Poisson process with rate $\mu_O P_O$.

Moreover, the aggregated process of deceased donor organs available for type *B* recipients is a Poisson process at rate $\mu_B + \mu_O P_O$ (see Figure 7). To ensure achieving fair access for all recipients, equalize the mean sojourn times W_O and W_B, for type *O* and *B* kidney

$$W_O = (\mu_O(1-P_O-r_0))^{-1} = W_B = (\mu_B(1-r_0)+\mu_O P_O)^{-1},$$

which lead to the same probabilities of waiting time for a transplant if:

$$P_O = \frac{(R-1)(1-r_O)}{2R},$$

where $R = \frac{\mu_O}{\mu_B}$.

3.4 Perlman et al. (2018)'s Model

The queueing model of Stanford et al. (2014) assumes allocation of a constant portion of kidney *O* to *B* with equal expected transplantation queueing time for *B* and *O*. However, this situation is not applicable when only kidney of type *O* exists, and there is no type *B* kidney.

Perlman et al. (2018) modeled this situation with the assumption of allocating of arriving kidney *O* to applicant *O*. They modeled the problem as a dynamic flexible-resource allocation problem and a queueing performance measure called "Expected Value of Transplantation" (EVT) for assessing the

completion of kidney transplantation. They modeled the problem by assuming two Poisson processes for kidney candidate, the properties of their model are as follows:

- Kidney candidate in a queueing system has independent Poisson processes S_O and S_B with λ_O and λ_B rates.
- For each S_O and S_B process, there is a waitlist Q_O and Q_B respectively.
- Kidneys resources R_O and R_B are arriving independently with Poisson rates μ_O and μ_B, respectively.
- $L_O = m$, for $m = 0,1,2,\ldots$, and $L_B = n$, for $n = 0,1,\ldots,N$ are the queue length of S_O and S_B, respectively.
- R_B is allocated to S_B in Q_B. If $Q_B = 0$ the unit will be lost.
- R_O is allocated to either S_B or S_O.
- S_B is correlated to L_O and L_B. If $L_B = L_O = 0$, the R_O is missed.

The system's steady-state probability is

$$P_{n,m} = P(L_B = n, L_O = m), \quad n = 0,1,\ldots,N; \quad m = 0,1,2,\ldots$$

where $w_{n,m}$ is the probability of allocating R_O to S_B in state ($L_B = n, L_O = m$), then

$$\begin{cases} w_{0,m} = 0 & \text{if } L_B = 0, \quad R_O \text{ is allocated only to } S_O \qquad \forall m \geq 1 \\ w_{n,0} = 1 & \text{if } S_O = 0, \quad R_O \text{ is allocated to } S_B > 0 \qquad n = 1,\ldots,N \end{cases}$$

For $n = 0$:

$$\begin{cases} m = 0; & P_{0,0}(\lambda_O + \lambda_B) = P_{0,1}\mu_O + P_{1,0}(\mu_O + \mu_B) \\ m \geq 1; & P_{0,m}(\lambda_O + \lambda_B + \mu_O) = P_{0,m+1}\mu_O + P_{0,m-1}\lambda_O + P_{1,m}\left(w_{1,m}\mu_O + \mu_B\right) \end{cases}$$

For $1 \leq n \leq N-1$:

$$\begin{cases} m = 0; & P_{n,0}(\lambda_O + \lambda_B + \mu_O + \mu_B) = P_{n-1,0}\lambda_A + P_{n,1}(1 - w_{n,1})\mu_O + P_{n+1,0}(\mu_O + \mu_B) \\ m \geq 1; & P_{n,m}(\lambda_O + \lambda_B + \mu_O + \mu_B) = P_{n,m-1}\lambda_O + P_{n-1,m}\lambda_B + P_{n,m+1}(1 - w_{n,m+1})\mu_O + \\ & \qquad P_{n+1,m}(w_{n+1,m}\mu_O + \mu_B) \end{cases}$$

For $n = N$:

$$\begin{cases} m = 0; & P_{N,0}(\lambda_O + \mu_O + \mu_B) = P_{N,1}(1 - w_{N,1})\mu_O + P_{N-1,0}\lambda_B \\ m \geq 1; & P_{N,m};(\lambda_O + \mu_O + \mu_B) = P_{N,m-1}\lambda_O + P_{N,m+1}(1 - w_{N,m+1})\mu_O + P_{N-1,m}\lambda_B \end{cases}$$

Figure 8 represents the state transition diagram for kidney transplantation.

By solving the balanced equations, the mean number of S_O is $E[L_O]$. Then, the mean sojourn time for S_O by applying Little's law is

$$E[W_O] = \frac{E[L_O]}{\lambda_O}$$

Proof: Refer to equations 11-14 in Perlman et al. (2018).

In addition, Perlman et al. (2018) developed a queueing performance measurement based on "best-fit rule" for HLA issue. Human tissue cells include antigens that are immunologically related to a specific candidate. This antigen is called HLA system. In their model, a kidney in a particular queue will be delivered to the candidate with the highest HLA match in the waiting line. The HLA match is operationalized when a kidney appears and is assigned to Q_B or Q_O queue; then, the kidney is transferred to the best fit one, based on the histocompatibility degree to each candidate with I levels of tissues, independently of his location in the queue. The incompatible HLA features between a random applicant and stochastically-arriving kidney can be considered as a random variable H.

The probability of having i mismatches between a random candidate and arriving kidney denoted by $f_i = P(H = i), i = 0,1,2,...,I$, and $F_i = P(H \leq i)$, where $F_I = 1$. Assume the value of transplantation between a stochastic candidate and arriving kidney is X, therefore, the life of a transplanted applicant lives longer than x fixed years, and for $H = i$ mismatches denoted by x_i; if $i < j$, then $x_i > x_j$. We have $P(X = x_i) = P(H = i) = f_i$, and $E[X] = \sum_{i=0}^{I} f_i x_i$.

Therefore, the obtained EVT from allocating a kidney based on the best-fit rule can be calculated through the following theorem.

Theorem:

$$EVT_{best-fit} = \frac{\mu_B}{\mu_B+\mu_O} EVT_B + \frac{\mu_O}{\mu_B+\mu_O}[\sum_{m=1}^{\infty} P_{O,m} E[X^*_{(m)}] + \sum_{n=1}^{N} P_{n,O} E[X^*_{(m)}] + \sum_{n=1}^{N}\sum_{m=1}^{\infty} P_{n,m} C_{n,m}]$$

where

$$\begin{cases} EVT_B = \sum_{n=0}^{N} P_{n,\cdot} E[X^*_{(n)}], \\ EVT_O = \sum_{m=0}^{\infty} P_{\cdot,m} E[X^*_{(m)}], \\ C_{n,m} = w_n E[X^*_{(n)}] + (1-w_n) E[X^*_{(m)}], \\ X^*_{(n)} = \max\{X_1, X_2, ..., X_n\}. \end{cases}$$

Proof: Refer Perlman et al. (2018) (Equations 7 and 15 can be used for calculation of $P_{n\cdot}$ and $E[X^*_{(n)}]$).

3.5 Discussion on Queueing Models for Kidney Transplantation

There are many medical and non-medical issues such as ethical (how to get approval from a donation, equity amongst the various patient), economic (how to buy[8] and stop black-market), and logistical (how to store the organ[9], how to balance supply and demand effectively[10]) involved in kidney transplantation. In this section, models which considered medical phenomena (acceptance rules such as blood matching and tissue matching) and non-medical phenomena (logistic issues and kidney allocation) for kidney transplantation are discussed. However, there are more non-medical issues which social ethics bring them into account; for instance, considering equity among different groups of patients in terms of race, age, and gender.

Another non-medical issue is acceptance or rejection of kidney by the patient based on his/her situation (running a fever, or on vacation). Consider this issue, the patient is not always available to receive the kidney and his/her state is dynamic. Although Ahn and Hornberger (1996)'s model provides a semi-Markov decision process for this situation, however, in their model they

only considered a single patient who facing an infinite stream of kidney offers. Therefore, studies such as the work of Su and Zenios (2004) on a situation where there are n patients who face a stream of m ($m \leq n$) kidneys sequentially could be more practical in a real setting. With the case of n patients and m ($m \leq n$) kidneys, the factor of waiting time comes to consideration for patients, for instance, sometimes patients do not wait for the best to match, and they select the semi-best to match regards to the high ask and bid in the market. Therefore, patients' decisions are not independent of each other or better to say the assumption such as time-homogeneous (independent increments) which Su and Zenios (2004) are considered in their study does not work in the real application. The case would be more complicated when there are k types of organs (for instance, kidney, liver, Pancreas, etc.)

For optimally allocating arriving kidney for transplantation, almost all models are considered the national pool of donors for the local patients. Therefore, it is hard to say which method is working better when different benchmark data and national/regional regulations in each country/region come into consideration. However, the rule of allocation priority was not considered in most of the studies. A brief description of the allocation rule is that, first the kidney is offered to an identical blood-type zero-antigen mismatched local patient, then regionally and then nationally. Then it is offered to a blood-type compatible zero-antigen mismatched patient using the same geographic hierarchy. Finally, the kidney is offered to all other blood-type compatible candidates ranked according to their total number of points of priority around the world. Regards this limitation, there is no international waiting list for organ transplantation, and patients are allowed to register in multiple lists to increase their chance (Ata et al. 2016). Therefore, giving a rank or score to local, regional, national, and then worldwide compatible could help for implementation the optimally allocating kidney transplantation algorithm in worldwide level.

In addition to the main models for kidney transplantation discussed earlier, extensive efforts have been done on this area, mainly focused on queueing

models for modeling, patient choice, priority consideration, geographical aspects, and compatibility issues. Table 2 summarizes some highlighted works in this domain.

4 Stochastic Modeling of Kidney Disease Progression

The most critical risk factor for AKI is pre-existing CKD, which increases the risk of kidney failure 10 times in comparison with the absence of CKD (Eckardt et al. 2013; Chawla et al. 2014). Besides, there is a high risk after AKI for the propagation of CKD. Therefore, CKD and AKI are strongly associated. Despite this fact that other risk factors such as age, race or ethnic group, genetic factors, hypertension, diabetes, and metabolic syndrome are effecting on the severity of kidney disease, understanding the full implications of risk factors on kidney disease modifiers such as severity of AKI, stage of CKD, number of episodes, and duration of AKI is essential. Therefore, the acute changes in kidney function that characterize an AKI event can be modeled by a stationary stochastic process (Asar et al. 2016). However, the long-term effects of AKI remain an open research area.

There are several papers about stochastic modeling of kidney diseases with hidden Markov model (Luo et al. 2013), Markov process model (Nuijten et al. 2009; Orlando et al. 2011; Anwar and Mahmoud 2014), Monte Carlo simulation (Rodina-Theocharaki et al. 2012), Coxian PTD (Donnelly et al. 2017), and multistate Markov model (Faissol et al. 2009; Green and Richardson 2002; Jackson et al. 2003; Sweeting et al. 2010; Best et al. 2005). Additionally, many modeling methods have been studied for multiple different states disease progression such as HIV disease (Aalen et al. 1997), breast cancer (Duffy et al. 1995; CHEN and PROROK 1983; Chen et al. 1996), Hepatocellular carcinoma (Kay 1986), Liver cirrhosis (Andersen et al. 1991), and diabetic retinopathy (Marshall and Jones 1995), periodontal disease progression (Mdala et al. 2014). For more details on stochastic modeling, one can refer to He (2014); Fackrell (2009).

Following this section, we introduce the stochastic modeling of CKD progression and Markovian paradigm of AKI to CKD.

4.1 CKD Modeling

An example of life expectancy and progression process of a CKD patient is shown in Figure 9 and summarized in Table 3 with five states for the CKD model which are equivalent to stages $G2-G5$ in Figure 1. This example proposes a stochastic model that describes the progression process of CKD based on GFR to estimate the kidney functionality level and discover the stage of kidney disease, to predict the expected spent time in each stage of the disease progression and to estimate the life expectancy of a CKD patient. Figure 9 indicates that at any stage of CKD there is a probability and a transition that CKD eventuates to the death, although each stage of CKD can gradually transform to the worse stage with absorbing state *λ*.

According to Figure 9, the transition rate matrix of CKD progression represents the rates of transition from one state to another as *V*.

$$V=\begin{pmatrix} -\lambda_{12}-\lambda_{15} & \lambda_{12} & 0 & 0 & \lambda_{15} \\ 0 & -\lambda_{23}-\lambda_{25} & \lambda_{23} & 0 & \lambda_{25} \\ 0 & 0 & -\lambda_{34}-\lambda_{35} & \lambda_{34} & \lambda_{35} \\ 0 & 0 & 0 & -\lambda_{45} & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0. \end{pmatrix}$$

It can be noticed that λ_{ij} is independent of time because CKD process is homogeneous with respect to time. Consider the probability of being in one of the states of the process at the beginning of the treatment as $\pi(0)=(\pi_{01},\pi_{02},\pi_{03},\pi_{04},0)$, where the first four are transient states and the last is absorbing. We can model the CKD process as a discrete-time Markov chain with the following properties:

1. Stochastic process $\{X_n : n=0,1,2,...\}$ takes values in $\{0,1,2,...\}$.
2. Memoryless property:

$$P(X_{n+1}=j \mid X_n=i, X_{n-1}=i_{n-1},..., X_0=i_0)=P(X_{n+1} \mid X_n=i)$$
$$P_{ij}=P(X_{n+1}=j \mid X_n=i)$$

3. Transition probabilities: P_{ij} (each transition probability is a function of the state of health and the treatment):

$$P_{ij} \geq 0, \qquad \sum_{j=0}^{\infty} P_{ij}=1$$

4. Transition probability matrix: $P=[P_{ij}]$
5. Stationary distribution of CKD process

   - A finite number of states: Solve explicitly the system of equations as:

$$\begin{cases} \pi_j=\sum_{i=0}^{n} \pi_i P_{ij}, \quad j=0,1,...,n \\ \sum_{i=0}^{n} \pi_i=1 \end{cases}$$

   - An infinite number of states: Guess a solution to recurrence:

$$\begin{cases} \pi_j=\sum_{i=0}^{\infty} \pi_i P_{ij}, \quad j=0,1,... \\ \sum_{i=0}^{\infty} \pi_i=1 \end{cases}$$

In general, we can model this type of process with PTDs. The definition of PTD is as follow:

Definition: Consider n + 1 states of a continuous time Markov chain (CTMC), where $n \geq 1$, such that the states $1,...,n$ are transient states and state 0 is an absorbing state. The definition of transient and observing states are as follows:

$$\begin{cases} P_{ii}<1 & \text{transient state} \\ P_{ii}=1 & \text{observing state} \end{cases}$$

Moreover, assume we have an initial starting probability of n + 1 stages with the vector of probability $(\alpha_0, \boldsymbol{\alpha})$ where α_0 is a scalar, and $\boldsymbol{\alpha}$ is a $1 \times n$ vector.

Therefore, the continuous PTD is the distribution of time from the starting state to the absorbing state. The PTD process can be represented as a transition rate matrix Q as,

$$Q = \begin{bmatrix} 0 & \mathbf{0} \\ \mathbf{S}^0 & S \end{bmatrix},$$

where S is an $n \times n$ matrix and $\mathbf{S^0} = -S\mathbf{1}$, and $\mathbf{1}$ represents an $n \times 1$ vector with every element being 1. Hence, X as the time distributed variable until the process enters to the absorption state is a PTD denoted by $PH(\alpha, S)$, with the following properties:

1. The distribution function of X: $F(x) = 1 - \boldsymbol{\alpha} \exp(Sx)\mathbf{1}$.
2. The density function of X: $f(x) = \boldsymbol{\alpha} \exp(Sx)\mathbf{S^0}, \quad x > 0$.

   It is usually assumed the probability of process starting in the absorbing state is zero (i.e. $\alpha_0 = 0$).

3. The moments of the distribution function: $E[X^n] = (-1)^n n! \boldsymbol{\alpha} S^{-n} \mathbf{1}$.

Previously, PTD application has been used in healthcare (Aalen 1995; Fackrell 2009). In addition, PTD can model the CKD by considering creatinine level, body mass index, blood pressure, and other factors in each stage of disease and developing novel Bayesian regression models for progression prediction (Donaghy and Marshall 2006).

4.2 Paradigm of AKI to CKD: A Markov Modeling Perspective

Many kidney disease investigations presented a confirmation about a connection between AKI, CKD, and ESRD (see Amdur et al. (2009); Ozrazgat-Baslanti et al. (2016); Grams et al. (2016)). Moreover,

Kellum and Prowle (2018) discussed the paradigm of AKI and its potential outcomes for the patient, as shown in Figure 10.

As Figure 11 is illustrated, AKI patients can be healed, be released without restoration of renal function, or can be died. Additionally, patients who are seeming relieved, may in the future realize CKD or Cardio-Vascular Disease (CVD) (dashed lines in Figure 11). Although reports on in-hospital events and consequences confirm the transformation of AKI to CKD, the pathways influencing these results are virtually undiscovered. Because of the extraordinary complexity, not all connections can be displayed for AKI and CKD.

Kerr et al. (2014) proposed a structure of Markov model for AKI to CKD transition by the seven states. The states are including normal kidney function, AKI, CKD, ESRD -including dialysis, transplant, and no RRT-, and Death as illustrated in Figure 11. For more specifications on data and investigation, one can refer to Kerr et al. (2014) and Mehta et al. (2007).

4.3 Discussion on Stochastic Modeling of Kidney Disease

Advantage: Patients with renal diseases show diversity in disease progression. Although the factors that affect disease progression are not apparent, stochastic factors such as modifying genes, environmental factors, gene expression, and somatic mutations are probably involved. Therefore stochastic modeling of kidney disease is the best way to show the propagation and transformation of illness.

Disadvantage: There is no doubt that stochastic modeling of kidney disease can explain the probability of AKI propagation to CKD, and CKD transformation to a higher state or death. However, there is some opinion in the literature (Rifkin et al. 2012) that observed AKI–CKD associations should be considered noncausal as long as they are based on epidemiologic or observational studies. Therefore, to find whether stochastic models are appropriate for showing a causal relationship between AKI and CKD, some assumptions are essential.

Firstly, there is an unknown gap when AKI happens before CKD. Investigation on the distribution of this hidden gap is vital as domain knowledge to estimate the probability of AKI propagation to CKD.

Secondly, AKI severity or frequency is an essential index in the transformation of AKI to CKD. Therefore, like CKD modeling, AKI stochastic modeling is required to explain the change in AKI from stage 1 to 3 (see Figure 1) based on the degree of severity or frequency.

Thirdly, patients with more severe AKI are sicker. Therefore, the transformation to CKD may cause by other diseases not directly AKI. Hence, other severe diseases causing CKD should be considered in the model.

Accurate prediction of graft survival rate after kidney transplant is limited by the complexity and heterogeneity of risk factors influencing on kidney disease such as progression of CKD to AKI. Therefore, stochastic modeling for kidney disease progression can indirectly effects on resource allocation for a kidney transplant.

5 MDP for Kidney disease screening and treatment

Clinicians are willing to figure out which treatment is beneficial for a patient who has chronic diseases and cannot be fully recovered but can be treated by medical screening, surgical treatment, and medication. However, medical decisions are complicated because of the critical situation in different groups of patients. For instance, aged people usually have various chronic conditions, and medication for one disease may affect their other illnesses. OR techniques such as MDP are strong mechanisms to examine patient data and information to manage screening and surgery and medical treatment choices.

MDP is a mechanism for subsequent stochastic decision making which starts with a Markov model for disease (including states, transition probabilities, rewards) and overlays a decision process on the model that defines allowable

"actions" at each period and each state. The MDP's goal is to find the optimal action in each state at each period to maximize "rewards" (Alagoz et al. 2010; Hauskrecht and Fraser 2000; Steimle and Denton 2017; Schaefer et al. 2005). An optimal solution for MDP involves a decision based on optimal action as a policy and concerning some reward function at each potential state and each period of the problem.

For designing MDP for kidney disease modeling, consider the following assumptions:

- health status in the state transition diagram before an event has occurred: $s_t, s'_t \in S = \{L, M, H, V, D\} = \{$ Low, Medium, High, Very High, Dead $\}$, as shown in Figure 12.
- treatment state (on or off medication): $m \in \{0,1\}$, If m = 0, the patient is not currently on medication, and if m = 1, the patient is currently on the medication.
- action space: $a_{(s_t,m)} = \begin{cases} \{I, W\} & \text{if } m = 0 \\ \{W\} & \text{if } m = 1 \end{cases}$. For each medication, at each epoch, medication can be initiated (I) or can be delayed (W) for at least one period. Action $a_t \in a_{(s_t,m)}$ denotes the action taken if a patient is in living state (s_t, m).

Therefore, the optimality equation is

$$v_t(s_t, m) = max\left[R(s_t, I), r(s_t, W) + \lambda \sum_{\forall s_{t+1}} p(s'_t \mid s_t, W) v_t(s'_t, m) \right],$$

where $\lambda \sum_{\forall s_{t+1}} p(s'_t \mid s_t, W) v_t(s'_t, m)$, $r(s_t, W)$, $R(s_t, I)$, and $p(s'_t \mid s_t, W)$ are expected future reward with $\lambda \in [0,1)$ as discount factor, one period reward, discounted future rewards on treatment starting at age t, and transition probabilities, respectively (Steimle and Denton 2017).

According to Steimle and Denton (2017) there are three types of decision making perspectives to obtain the optimal reward. Firstly, patients want to maximize expected QALYs. From another perspective, the third-party payer

(i.e., insurance company) is willing to minimize the expected costs of treatment and health services. However, society perspective seeks to maximize the weighted combination of expected patient rewards for QALYs minus medical treatment and health services' expenses. Society's objective function includes rewards for QALYs and costs.

Moreover, Van Arendonk et al. (2015) developed a MDP model including five patient states the waitlist (W), post-transplant with a deceased donor kidney (TD), post-transplant with a living donor kidney (TL), alive after two graft failures (GF), or deceased (D) (refer to Figure 1. in Van Arendonk et al. (2015) for more detail in model).

For more details on MDP for kidney disease screening and treatment, one can refer to Bellman (1966); Puterman (2014); Bertsekas et al. (1995) and its applications in liver transplantation Alagoz et al. (2007); Batun et al. (2018).

5.1 Discussion on MDP for Kidney disease screening and treatment

Advantage: MDP can find optimal solutions to sequential and stochastic decision problems. The significant advantage of MDP is its flexibility. MDP is flexible with all classes of problems involving complex, stochastic, and dynamic decisions. MDP not only provides the consequences of a policy, but it also guarantees that no better policy exists.

Disadvantage: The main drawback of the MDP model for kidney disease screening and treatment is that the patient (agent) receives reward $r(s_t, W)$ every time that is visited at state s_t in a clinical center. Thus, in order to estimate an accurate transition matrix for each state, patients need to visit medical centers regularly, and their health status should be recorded. However, in a real scenario, especially when patients are in the early stage of disease they are not used to visit a doctor regularly. Even, it is possible that a patient for the first time goes under treatment when is in the high state of disease progression.

The other limitation of the MDP model is that all the state variables relevant for decision making are assumed to be observed without noise, while real-world data are always prone to noise. Furthermore, there might be situations that cannot be detected directly using the medical test, especially when the disease is at a very early stage. In this case, the state observed by the MDP is no longer Markovian, and hence, the value of the computed policies will no longer be accurate.

The last, but the least important issue in kidney disease screening and treatment using MDP approach is the “curse of dimensionality,” which means that the number of states that must be included in the calculation of the solution increases exponentially quickly as the size of the problem increases.

6 Conclusion

OR techniques have been playing an important role in solving kidney problems for descents. Hereupon, a systematic review of recent advances of OR techniques for solving kidney problems holds promise for comparing the advantage and limitation of existing models, as has been developed in this paper. As a conclusion and future research direction, we attempted to have a broader vision for solving kidney problem from OR perspective. These problems are barely indicated in literature with analytic context and are known as critical obligations for kidney specialist. Following we discuss some of the highlighted topics in this chain.

1. Finding an optimal matching policy for fully dynamic kidney exchange is an open problem from both the theoretical and computational points of view. Because kidney operation frames depend on the ordering, but the kidney disease usually happens before ordering. However, researches only investigated on waiting time for “hard to match” groups (kidney type “B” and “O”). Therefore, the OR techniques can be used to model and predict the order time.
2. Despite this fact that “a donor does not have an incentive to donate unless his paired patient receives a kidney”, incentives at the patient or

donor level have not been explored thoroughly in the kidney exchange literature. In fact, the kidney exchange is included a new variable of bargaining power, and game-theoretical approaches can simulate this situation.

3. The case of kidney exchange is also included the logistical issues when the operational constraints involve assembling the resources to coordinate and conduct complicated surgical procedures across many hospitals. This phenomenon is not only for “hard to match” groups but involved the “easy to match” groups as well. Therefore, new constraints as logistical capabilities are required to be considered for minimizing the waiting time for the operation.
4. Since kidney allocation policies are often made by a committee rather than a single expert, it is important to investigate if kidney allocation will be acceptable by a group of experts. Operations methods for opinion aggregation may be used to facilitate group decision making.
5. Adaptation of the theoretical results from kidney problems to models of lung, liver, and multi-organ exchange would also be of practical use.

In additions, there are several operations techniques used in different kidney researches such as forecasting and data-driven models which are under the scope of statistical inferences and we are not investigated on them in this paper. Despite this fact that data-driven models are supporting the foundation of decision making with OR techniques, in the content of statistical inferences and data science approaches, we suggest the following future research directions:

1. Applying PTD in CKD modeling by considering creatinine level, body mass index, blood pressure, and other factors in each stage of kidney disease and developing novel Bayesian regression models for progression prediction.
2. Developing a framework to consider a more precise analysis of all diseases derived from kidney problems into the body. In order to study this, a multiplex network (Lee et al. 2015; Ghariblou et al. 2017; Xu

et al. 2015) for considering a multi-layer analysis of kidney diseases is required.

3. Developing a model of comorbidity between AKI and CKD with the latent variable modeling. For comorbidity study of AKI diseases, we can consider Sepsis-associated AKI, surgery-associated AKI, AKI associated with renal hypoperfusion, and Nephrotoxic AKI as diseases in each layer (see Moni and Liò (2014)).
4. Analyzing the correlation between kidney diseases and other human diseases (as an example, refer to O'Rourke and Safar (2005) for the correlation between aortic stiffening and microvascular disease in brain and kidney).
5. Defining and classifying kidney diseases to different domains based on structure, function, causes, duration, and outcomes according to Levey et al. (2013). kidney diseases are different in comparison to other diseases because of the silent nature of the kidney (Levey et al. 2013). Therefore, developing such a classification system would help to identify kidney diseases in human with comorbidity relation to other diseases a list of kidney diseases are available at http://www.kidney.nyc/types-of-kidney-disease/. Developing a classification system for kidney diseases based on comorbidity with other diseases in the human would be vital for treatment and disease modeling.

There are many factors to be considered in healthcare cost-effectiveness decision-making (Reddy et al. 2019). OR techniques such as multiple-criteria decision analysis (MCDA) are very advantageous in kidney decision-making problem which decisions can be available from different sources to be integrated in a structured way. Moreover, MCDA techniques should be chosen based upon the context, restrictions and risk of the decision problem.

In this study we review some OR related techniques of kidney disease and healthcare management. However, kidney's operation system can be used as bio-inspired optimization algorithm for population-based optimization approach to assist OR related problems. The approach is called kidney

inspiration algorithm (KIA) and it is reflected some ideas from the structure of the nephron. For more information, one can refers to Jaddi et al. (2017); Jaddi and Abdullah (2018); Behmanesh (2016); Taqi and Ali (2017).

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Notes

[1]Corresponding author: fathi@ise.msstate.edu, Department of Industrial and Systems Engineering, Mississippi State University, 260 McCain Hardy Rd, Starkville, MS, USA, 39762

[2]mkhakifirooz@tec.mx

[3]GFR is a test used to check how well the kidneys are working. Specifically, it estimates how much blood passes through the glomeruli each minute.

[4]AER is a test to describe how much kidney leaks albumin into the urine per 24 hours.

[5]ACR is an annual test after a diagnosis of diabetes or HBP which comparing the amount of albumin in the sample against its concentration of creatinine

[6]MATLAB code is available at

https://sites.google.com/site/joshmikemath/code

[7]Graft survival rate is an estimate of the probability of the transplant kidney functioning at a finite time after trans- plantation

[8]organ procurement and transplantation network, https://optn.transplant.hrsa.gov/

[9]United Network for Organ Sharing, https://unos.org/

[10]Organ procurement organizations, http://www.aopo.org/

Fig. 1 Burden, stages, and definitions of CKD & AKI (information extracted from Kellum and Prowle (2018))

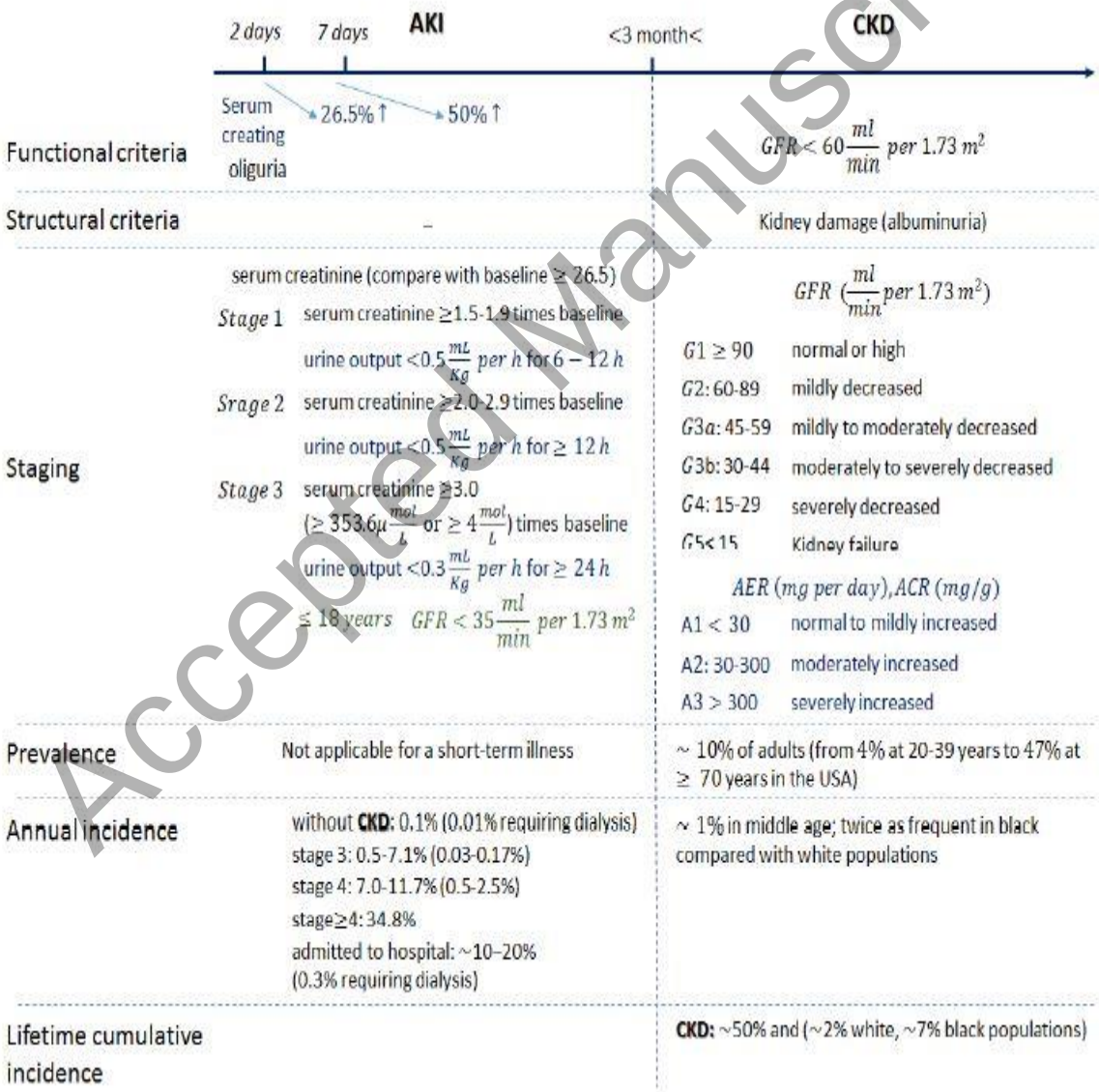

Fig. 2 Kidney disease progression process (Eckardt et al. 2013).

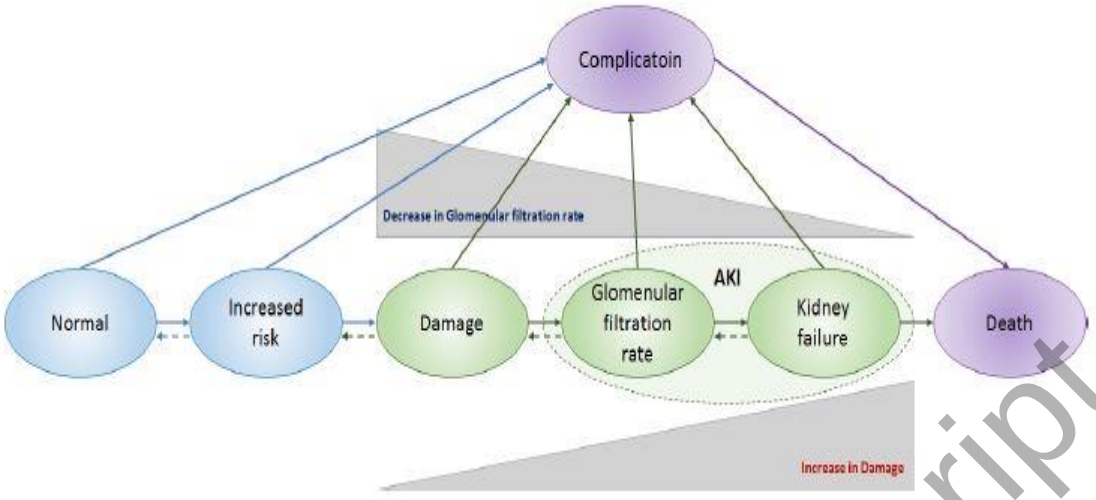

Fig. 3 From left to right, a 2-way exchange, a 3-way exchange, and a 3-way exchange with an altruistic donor; Kidney transfer represented by arrows.

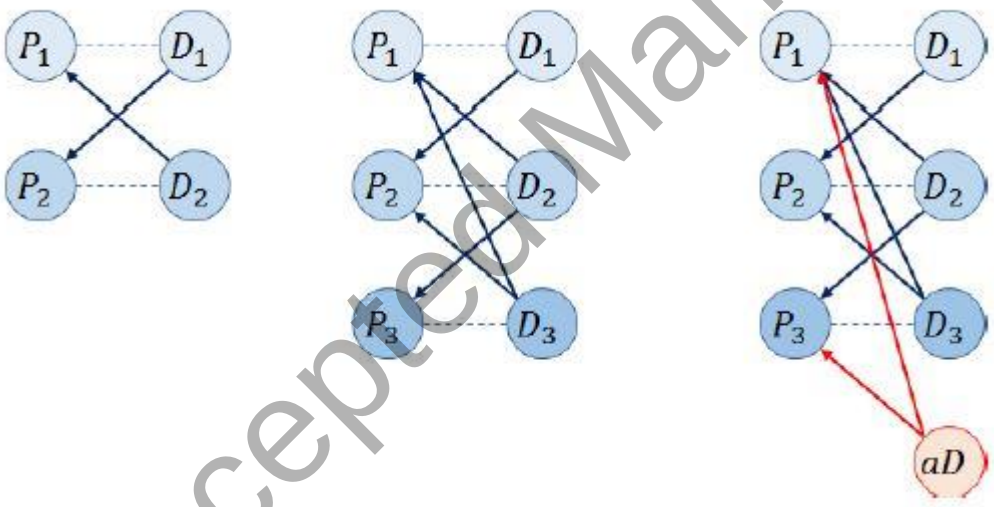

Fig. 4 From left to right, a cycle of 2-way exchange, and a 3-way exchange in kidney transfer graph.

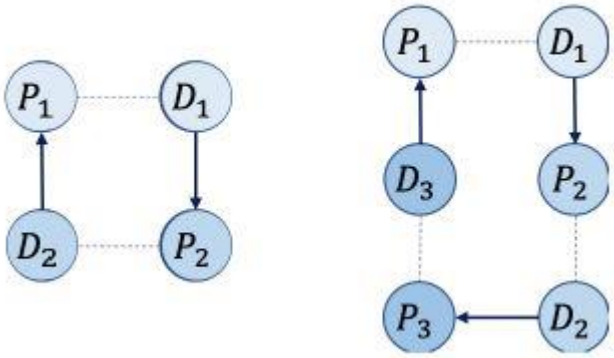

Fig. 5 State transition diagram for Ahn and Hornberger's model

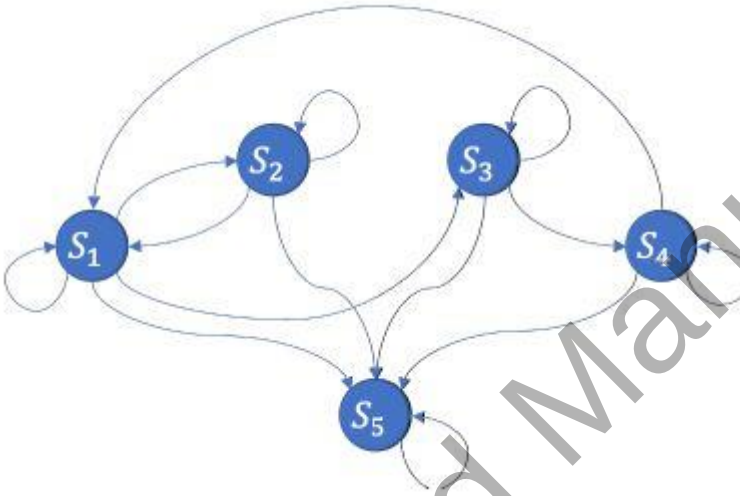

Fig. 6 Kidney compatible pairs and their percentages; dash lines show cross-match–incompatible pairs. (Stanford et al. 2014)

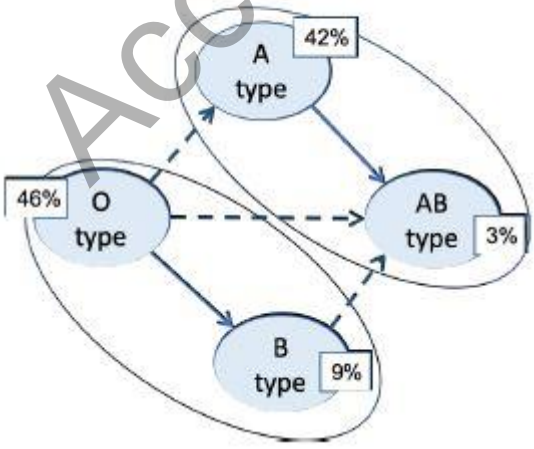

Fig. 7 Kidney Transplantation aggregation rate for type *O* and *B* kidneys (Stanford et al. 2014).

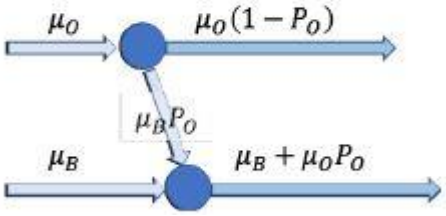

Fig. 8 Kidney Transplantation State Transition Diagram (Perlman et al. 2018)

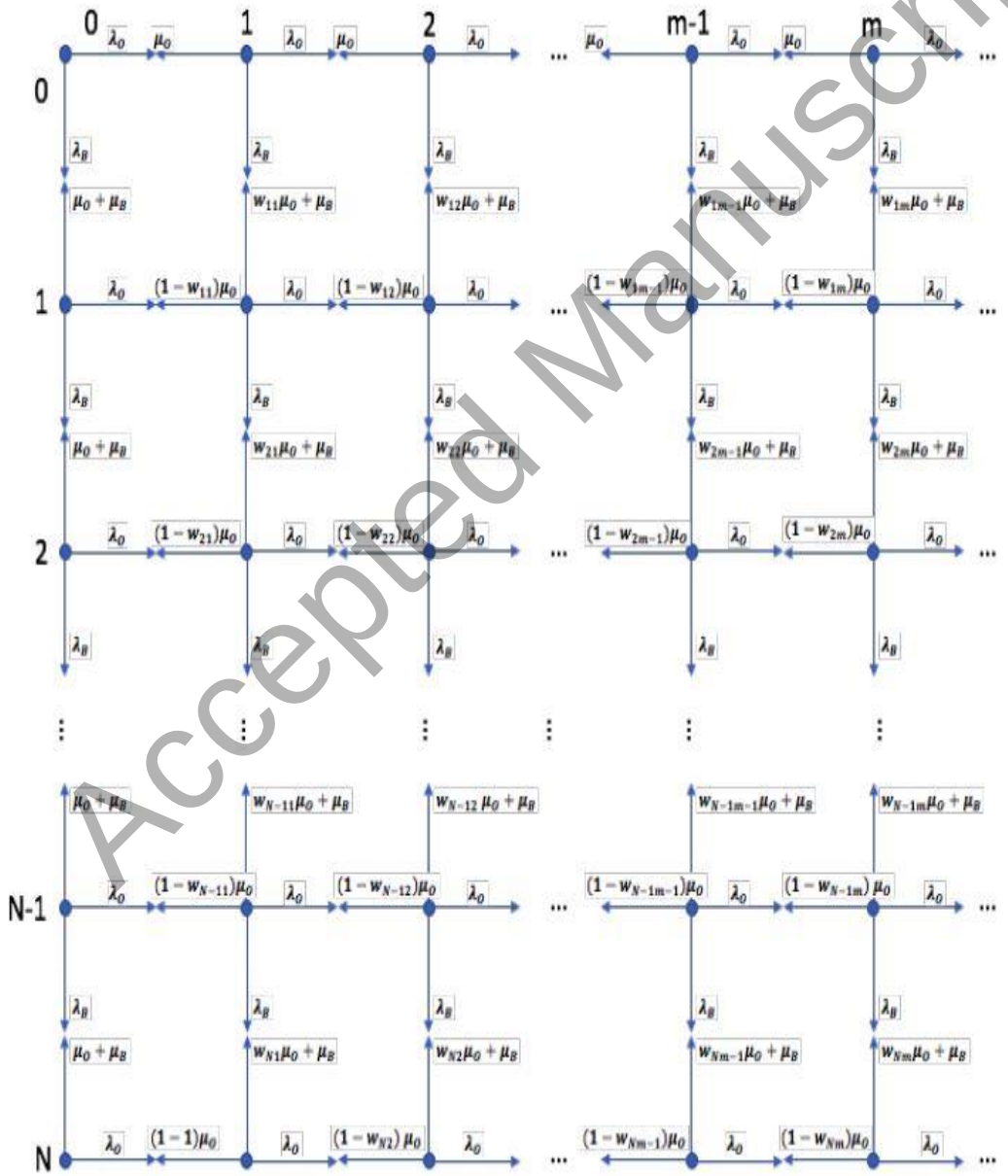

Fig. 9 CKD progression process with five stages. $G2-G5$ are referencing to the staging formation in Figure 1.

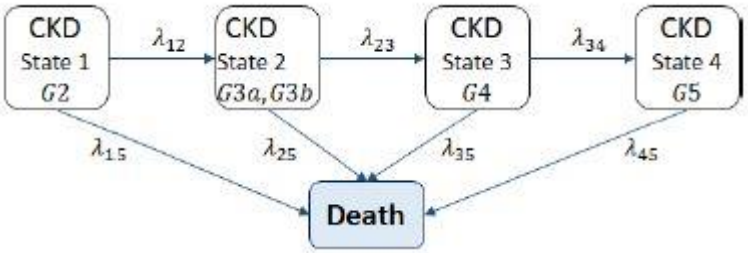

Fig. 10 Potential patient outcomes following AKI (Kellum and Prowle 2018)

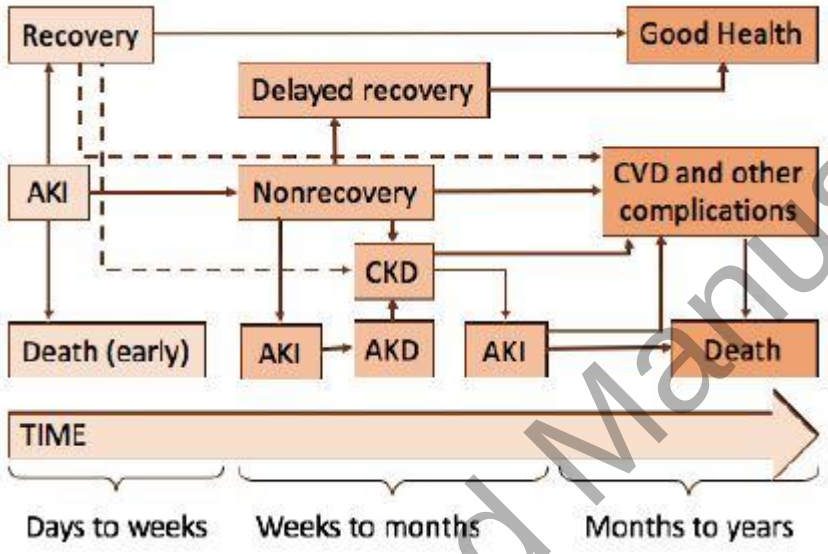

Fig. 11 AKI to CKD Markov Model (Kerr et al. 2014)

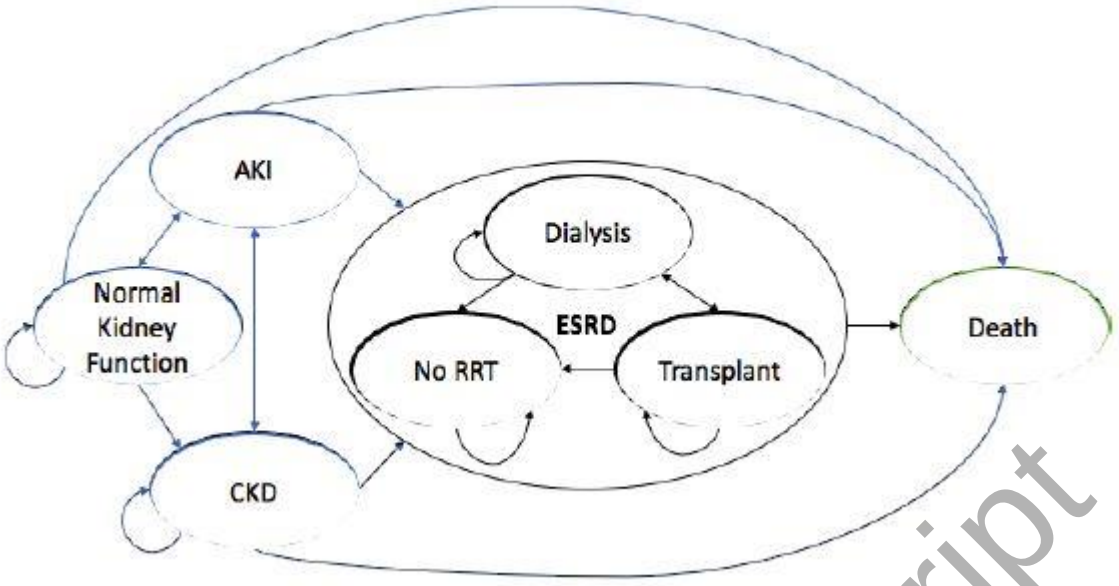

Fig. 12 State Transition Diagram (Steimle and Denton 2017)

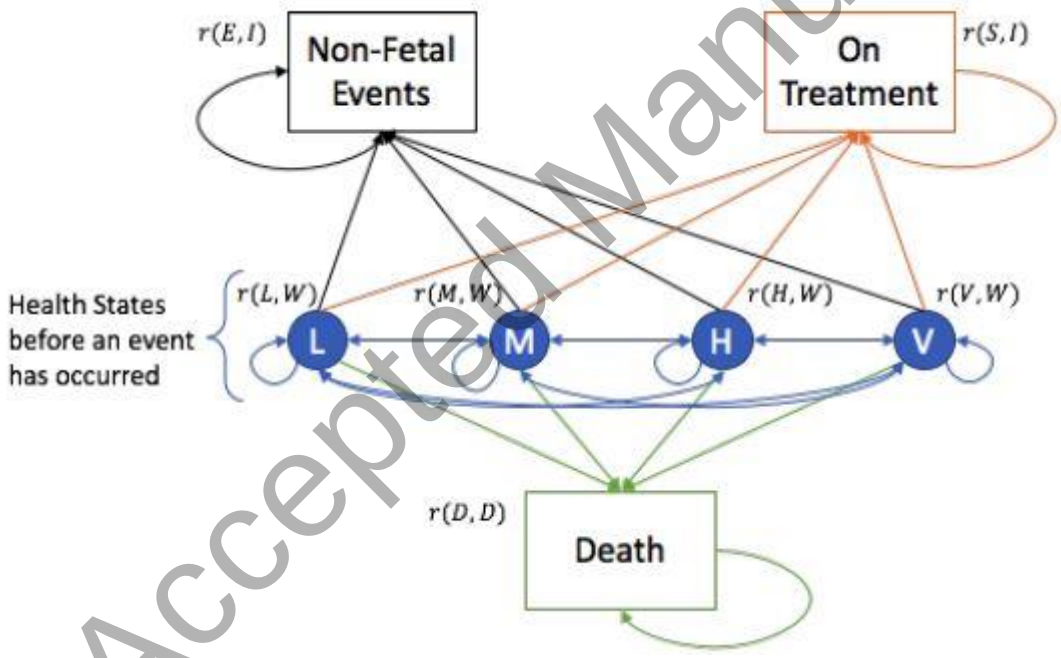

Table 1 Recent trends in kidney exchange problem from OR perspective

Reference	Methodology	Key Contribution
Alvelos et al. (2019 *b*)	branch-and-price algorithm	consider probabilities of failure of vertices and of arcs and the objective of maximizing the

Reference	Methodology	Key Contribution
		expected number of transplants
Freedman et al. (2018)	integer programming	give weight to patient attributes to determine priority
Esfandiari and Kortsarz (2018)	graph matching based on 2-approximation randomized truthful mechanism	low utility variation for pairwise kidney exchange problem
Hamouda et al. (2018)	a bio-inspired stochastic-based Ant Lion Optimization	maximizing the number of feasible cycles and chains in kidney exchange pool pairs; adaptability for online exchanges and the integration of weights for hard-to-match patients;
Lee et al. (2018)	two-stage stochastic programming method using the total utility in the first stage and the sum of the penalties for failure in the second stage	take fairness to be the degree to which individual patient-donor pairs feel satisfied
Dickerson et al. (2017)	integer programming	encode the kidney exchange compatibility graph by a constant number of patient and donor attributes
Santos et al. (2017)	integer programming	match pairs of specific patient–donor blood type, particularly, O-blood type patients. Including different

Reference	Methodology	Key Contribution
		types of matches in the problem (i.e., incompatible pairs, altruistic donors, and compatible pairs). find the best interval between matches
Dickerson and Sandholm (2017)	integer programming with steady-state nationwide scale using a specialized tree search algorithm based on the branch-and-price framework	multi-organ exchange: include liver lobes, either in conjunction with, or independently of, presently fielded kidney exchange
Anderson et al. (2015b)	integer programming inspired by the traveling salesman	prevent the long cycles appearing in solutions

Table 2 Literature on kidney transplantation from queueing theory perspective, summary, advantages, and disadvantages.

Reference	Main Contribution	Advantage	Disadvantage
Bandi et al. (2019)	estimating waiting times in multiclass, multiserver kidney allocation queuing systems	dealing with incompleteness information and unstable decision of patients	considering a closed queuing system model for patient arrival and waiting time
Elalouf et al. (2018)	proposing an allocation model based on best histocompatibility fit and maximizing expected reward	considering multiple-type double-ended queues, where candidates distinguish by	not considering blood compatibility

Reference	Main Contribution	Advantage	Disadvantage
	per transplantation for kidney storage policy	their HLA compatibility	
Perlman et al. (2018)	providing a dynamic allocation model of flexible resources for calculating the optimal probabilities kidney cross-transplantation	considering dependency between allocation probabilities and system's states; estimating expected value of transplantation based on HLA fit	only considering type *B* and *O* kidneys in the model
Ata et al. (2016)	studying the impact of the multiple listing of ESRD patients based on metrics such as waiting times, multi organs transplantation, and mortality rate	improving geographic equity when patients can register in multiple lists	not considering transplants across compatible blood types, allowing nonstationarities in the arrivals of organs and patients
Stanford et al. (2014)	considering a model for restricted cross-transplantation and comparable	considering ABO-incompatible (or cross-match–incompatible)	ABO-incompatible cannot achieve equity; not considering the

Reference	Main Contribution	Advantage	Disadvantage
	waiting times for all blood types		priority patients
Bertsimas et al. (2013)	developing a data-driven method for designing national policies for the allocation of deceased donor kidneys	flexible in selecting desired priority criteria and fairness constraints with maximizing medical efficiency	not categorizing and ranking patients within the group
Abellán et al. (2006)	modeling a real renal transplant waiting list with $M/M^X/1$	considering the heterogeneity in the daily number of arrivals with robust queueing model $M/M^X/1$	complexity in queueing model due to patient leave (i.e., death), move to other waiting list, or being special patient (i.e., children)
Su and Zenios (2006)	considering adverse selection and propose a mechanism-design based on patients' truth-telling report of their kidney types	candidates who wait longer receive better kidneys; developing a choice-based kidney allocation system with candidates' choice	implementation of a choice-based system requires new payment mechanisms

Reference	Main Contribution	Advantage	Disadvantage
Su and Zenios (2004)	modeling incorporate patients' individual problems in organ accept/reject decisions with the last-come-first-serve (LCFS) queueing policy	considering a pool of n patients who face a stream of m ($m \le n$); modeling patient queue as an $M/M/1$ with homogeneous patients and exponential reneging	considering time-homogeneous character (independency) between patients' decisions
Zenios (2002)	proposing a double-ended queueing model for autonomous kidney exchange system with two types of donor-candidate, accompany with a Brownian approximation to perform an indirect exchange	considering the mix of direct and indirect exchanges for maximizing the expected total discounted QALY of the candidates	In autonomous exchange system, participants experience excessive waits; the exchange program's success depends on maximizing the social welfare of the participants, and minimizing the risk of participant resentment
Ahn and Hornberger (1996)	providing a semi-Markov decision process for	introducing the QALY index based on	only considering a single patient who facing an

Reference	Main Contribution	Advantage	Disadvantage
	acceptance or rejection of kidney by the patient based on his/her situation	patient-specific rating for being in different health states	infinite stream of kidney offers

Table 3 Progression process of CKD based on GFR

State No.	State Name	GFR, ml/min	Equivalent stage in Figure 1
1	Kidney damage with mild reduction in GFR	60-90	*G*2
2	Kidney damage with a moderate reduction in GFR	30-59	*G*3*a* and *G*3*b*
3	Kidney damage with a severe reduction in GFR	15-29	*G*4
4	ESRD implying Renal Replacement Therapy (RRT) (regardless of GFR)	<15	*G*5
5	Death		