IISE Transactions on Healthcare Systems Engineering

ISSN: 2472-5579 (Print) 2472-5587 (Online) Journal homepage: https://www.tandfonline.com/loi/uhse21

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To cite this article: Mahdi Fathi & Marzieh Khakifirooz (2019): Kidney-related operations research: A review, IISE Transactions on Healthcare Systems Engineering, DOI: 10.1080/24725579.2019.1640318

To link to this article: https://doi.org/10.1080/24725579.2019.1640318

Accepted author version posted online: 08 Jul 2019.
Published online: 06 Aug 2019.

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IISE TRANSACTIONS ON HEALTHCARE SYSTEMS ENGINEERING
https://doi.org/10.1080/24725579.2019.1640318

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Kidney-related operations research: A review

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ABSTRACT

Operations research and optimization in healthcare and disease modeling have received significant attention in the last three decades. This article 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 article is concluded by offering some research direction to fill in the gaps in the literature.

ARTICLE HISTORY
Received 8 February 2019
Accepted 1 July 2019

KEYWORDS
Acute kidney injury; chronic kidney disease; graph theory; kidney disease; kidney transformation; Markov decision process; operations research; phase-type distribution; queueing 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 research 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 article surveys some selected OR topics that appeared in kidney-related studies. The main objective of the article is to introduce the models rather than only a collection of the related literature. The topics on kidney problems in this article 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 ninth 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 to be 50% more likely 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 white 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), representing 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 cases of 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 one in three 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 10 years, on average. The more lasting cure is transplantation. Considering that selling and buying organs in most of society are prohibited, there is a mismatch in supply and demand. In the United States, 79000 patients are waiting for a kidney transplant, while, in 2008,

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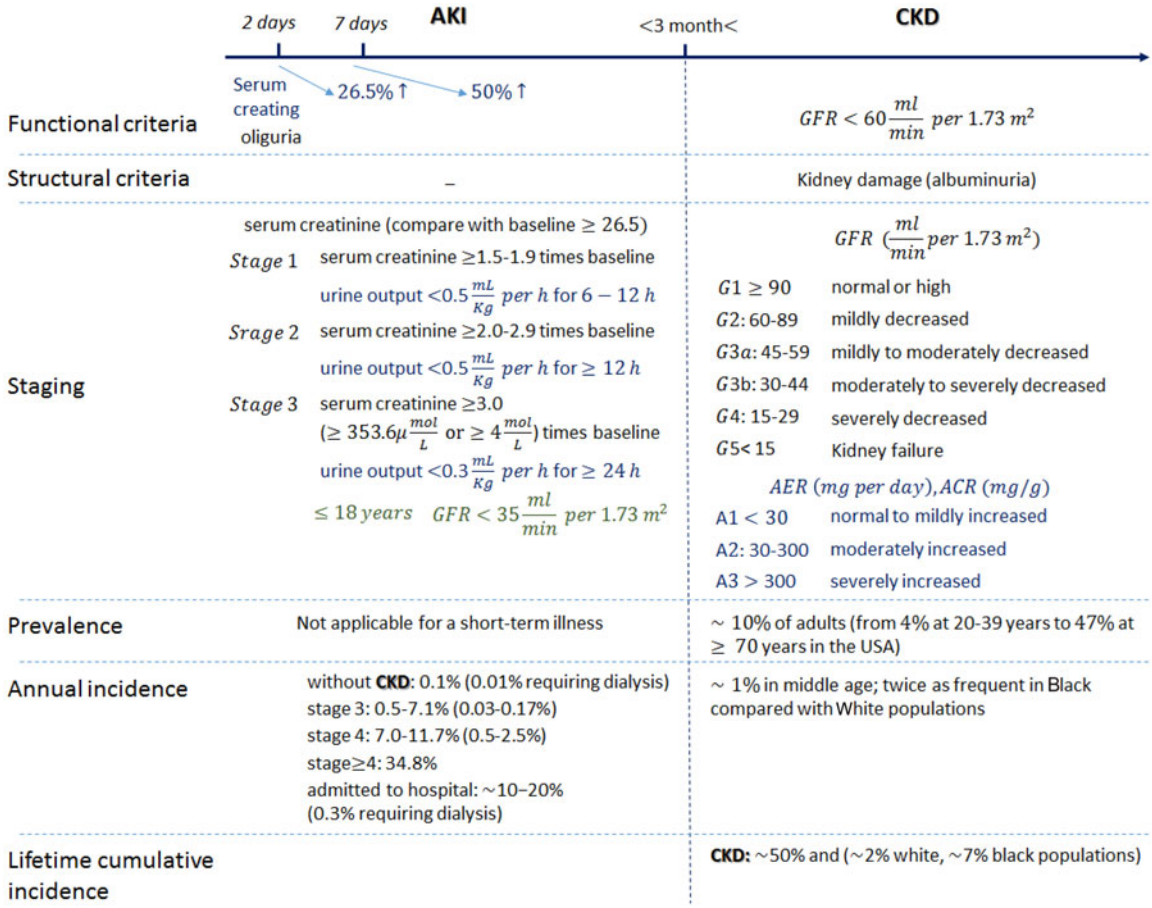


Figure 1. Burden, stages, and definitions of CKD and AKI (information extracted from Kellum and Prowle (2018)).

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 patient's 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 availability.

One of the most severe kidney diseases is AKI. AKI is a sudden failure of the kidney and happens in people who are already sick and in the hospital. Unlike CKD, AKI is often reversible if treated quickly. However, AKI patients who overcome kidney problems in the hospital have a danger of developing CDK, leading to 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),[1] "Albumin Excretion Rate" (AER),[2] and "Albumin-to-Creatinine Ratio" (ACR) criteria.[3]

[1]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.
[2]AER is a test to describe how much kidney leaks albumin into the urine per 24 hours.
[3]ACR is an annual test after a diagnosis of diabetes or HBP, comparing the amount of albumin in the sample against its concentration of creatinine.

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 show 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 in terms of 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 conditions (such as rare diseases) cause a problem for the kidney and lead to kidney disease (Levey *et al.*, 2007; Mallappallil *et al.*, 2014)?
- How is kidney disease 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 or Anemia (Asar *et al.*, 2016)?
- How can we speed up the evaluation process and find a transplant match (Anderson *et al.*, 2015a)?

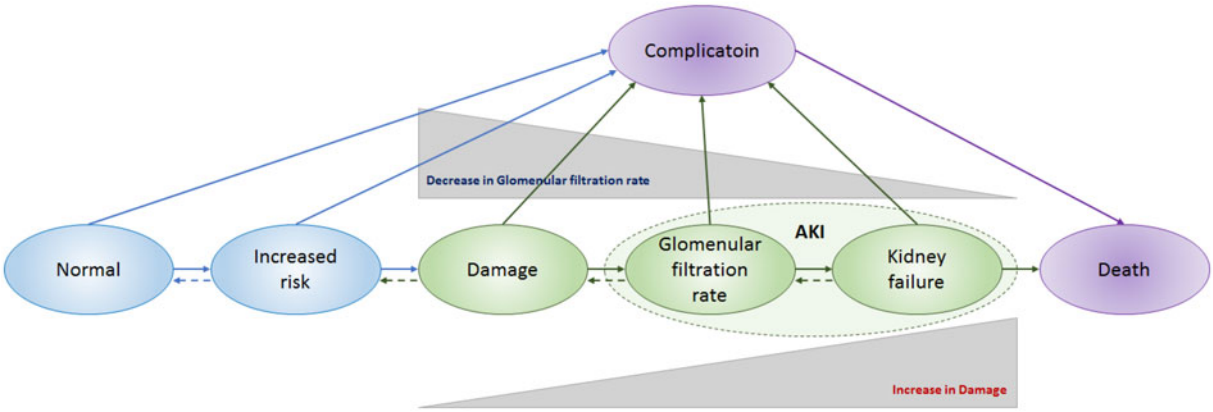


Figure 2. Kidney disease progression process (Eckardt *et al.*, 2013).

- How can we manage the waiting list and multiple listing for the kidney transplant (Alvelos *et al.*, 2019a)?
- 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 that addresses kidney problems from an OR perspective. Among the reviewed literature, those with novel solutions for modeling kidney problems are selected for further discussion in this article.

Kidney-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 article, 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 are studied from statistical inferences, and therefore we eliminate this topic in current research.

Unlike kidney transplant topics, 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, stones, and infection. The majority of research looks at these phenomena from a data science (DS) perspective, and OR has barely been applied.

The remainder of this article is organized as follows. Section 2 describes the kidney exchange problem and its modeling through graph theory. The kidney transplantation problem is addressed in Section 3. Section 4 surveys stochastic modeling of kidney disease and transformation of CKD to AKI. The MDP for kidney disease screening and treatment is presented in Section 5. Finally, we conclude the article with 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 OR techniques to the 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 the OR perspective.

As shown in Fig. 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. There are also 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 mean 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 follows:

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

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 dedicated to the kidney exchange problem, mainly focused on integer programming and stochastic programming. Table 1 summarizes some highlighted recent works in this domain.

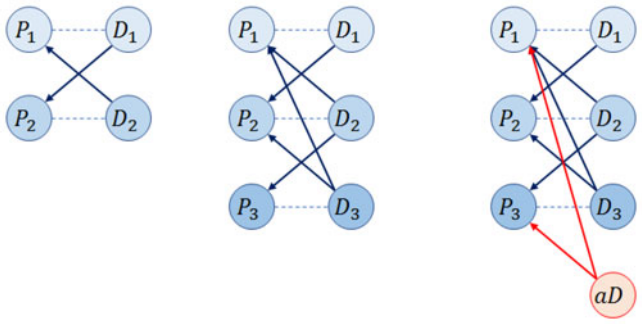


Figure 3. From left to right, a two-way exchange, a three-way exchange, and a three-way exchange with an altruistic donor; kidney transfer represented by arrows.

The graph theory model in the kidney exchange problem maximizes the number of possible kidney transplants by finding maximum weight packing of vertex-disjoint cycles and chains for a given weighted digraph with limited length of cycles L (typically $2 \leq L \leq 5$) (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); and Huang (2010)). Moreover, the traditional economic theory and integer programming view of the kidney exchange problem may lead to 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[4] for minimizing allocation disparities.

2.1. Discussion graph theory and the 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 offers the benefit 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, graph theory 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 flows change with time. Therefore, a static graph may only represent a system and the prerequisite for building detailed dynamical models. Also, graph-theoretic methods are data-driven rather than model-driven, which means that each updated or new data set requires a new graph model. In addition, graph theory is not a problem-free approach; it 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.

[4]MATLAB code is available at https://sites.google.com/site/joshmikemath/code

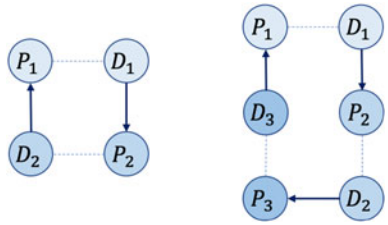


Figure 4. From left to right, a cycle of two-way exchange, and a three-way exchange in a kidney transfer graph.

3. Queueing models for kidney transplantation

Kidney transplantation depends on a national kidney allocation policy as a national plan that manages the list of all people across the country waiting (approximately 3-5 years) for a 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 of how to distribute a donor's kidneys depends on 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). 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 time for solid-organ transplantation is a vital issue 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); and Perlman *et al.* (2018). Although their observation is inconsistent, recipients with blood type *O* in comparison to type *A*, and *A* in comparison to *AB*, wait longer. Also, patients with blood type *B* sometimes wait slightly longer than patients with type *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 kidneys (Stanford *et al.*, 2014; Perlman *et al.*, 2018).

Table 1. Recent trends in kidney exchange problem from an OR perspective.

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

3.1. Ahn and Hornberger's *1996* Model

Ahn and Hornberger's 1996 model offers organ quality-based kidney transplantation, in which patients have a choice to accept or reject the kidney. As shown in Fig. 5, they considered five states (with transition probabilities based on issued graft survival rates[5] 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 a 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 one-year graft survival rate ($x > d$) and then either (1) have a successful transplantation ($QALY_3$), or (2) have a failed transplantation ($QALY_4$). The patient may not find a donor with a satisfying one-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 one-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, $i, j = 1, \ldots, 5$.

[5]Graft survival rate is an estimate of the probability of the transplant kidney functioning at a finite time after transplantation.

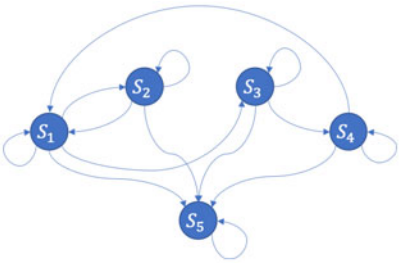


Figure 5. State transition diagram for Ahn and Hornberger's model.

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

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

3.2 Su and Zenios's *2005* Model

Su and Zenios (2005) considered the patient choice on kidney allocation based on a sequential stochastic assignment model. When a kidney is offered to a patient, it could be accepted or rejected, and the 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:

1. The candidates and the donor are equally well-informed about kidney types and the reward functions.
2. Candidates may discount future rewards using a discount factor $\delta \leq 1$, while the donor is interested in long-run average rewards.
3. 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.
4. 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 $i = 1, \ldots, m$ has been assigned to type $j = 1, \ldots, n$ kidney, we get a reward of R_{ij}. For $i \in \{1, \ldots, m\}$, p_i is the proportion of type i patient, and for $j \in \{1, \ldots, n\}$, 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 $a^* = \{a_{ij}\}_{i=1}^{m} j = 1^n$ 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 the 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 rejects the kidney j, and accepts the next offer, the second-best policy under discrete kidney types would be as follows:

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

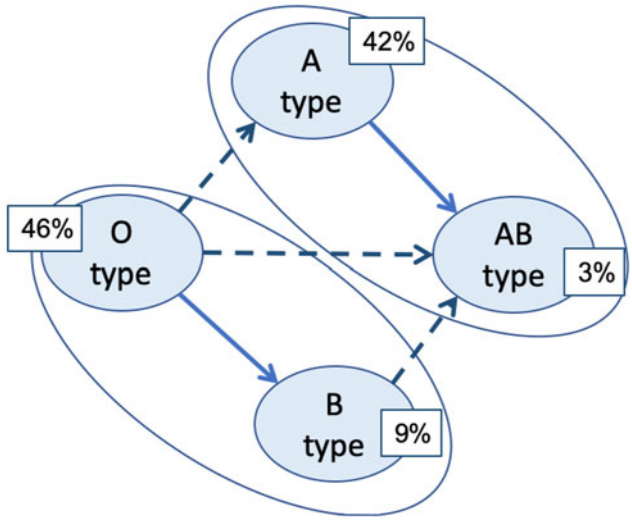


Figure 6. Kidney compatible pairs and their percentages; dashed lines show cross-match–incompatible pairs. (Stanford *et al.*, 2014)

The model with patient choice considers the incentive compatibility constraint and replaces the "supply balance demand" constraint with the inequality constraint.

3.3. Stanford et al.'s *2014* 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 Fig. 6, allowable pairs and rejected compatible pairs are represented by solid and dashed arrows, respectively. Based on Fig. 6, O to AB is not favored medically, B to AB would conduct 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.

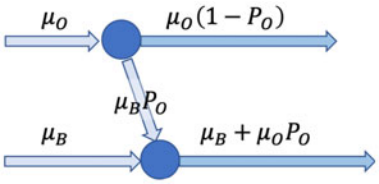


Figure 7. Kidney transplantation aggregation rate for type *O* and *B* kidneys (Stanford *et al.*, 2014).

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 follows:

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

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* engaged for receivers with kidney *O* follows a Poisson process with rate $\mu_O(1-P_O)$, and the kidney type *O* 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 Fig. 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 leads 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.'s *2018* 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 kidneys of type *O* exists and there is no type *B* kidney.

Perlman *et al.* (2018) modeled this situation with the assumption of allocating 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) to assess the completion of kidney transplantation. They modeled the problem by assuming two Poisson processes for the 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

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

For $n = 0$:

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

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

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

For $n = N$:

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

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 a "best-fit rule" for the HLA issue. Human tissue cells include antigens that are immunologically related to a specific candidate. This antigen is called the 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, 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 are denoted by $f_i = P(H=i), i = 0, 1, 2, ..., I$, and $F_i = P(H \le i)$, where $F_I = 1$. Assume the value of transplantation between a stochastic candidate and arriving kidney is X; therefore, 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:

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

where

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

Proof: Refer to 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 involved in kidney transplantation, such as ethical (how to get approval from a donation, equity amongst the various patients), economic (how to buy and stop the black market), and logistical (how to store the organ, how to balance supply and demand effectively). In this section, models that consider 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 reflecting socially ethical concerns; 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 a kidney by the patient based on his/her situation (running a fever, or on vacation). For example, consider this issue when the patient is not always available to receive the kidney and his/her state is dynamic. Although Ahn and Hornberger's (1996) model provides a semi-Markov decision process for this situation, in their model they only considered a single patient facing an infinite stream of kidney offers. Therefore, studies such as the work of Su and Zenios (2004) involving a situation where there are n patients who face a stream of m ($m \le n$) kidneys sequentially could be more practical in a real setting. With the

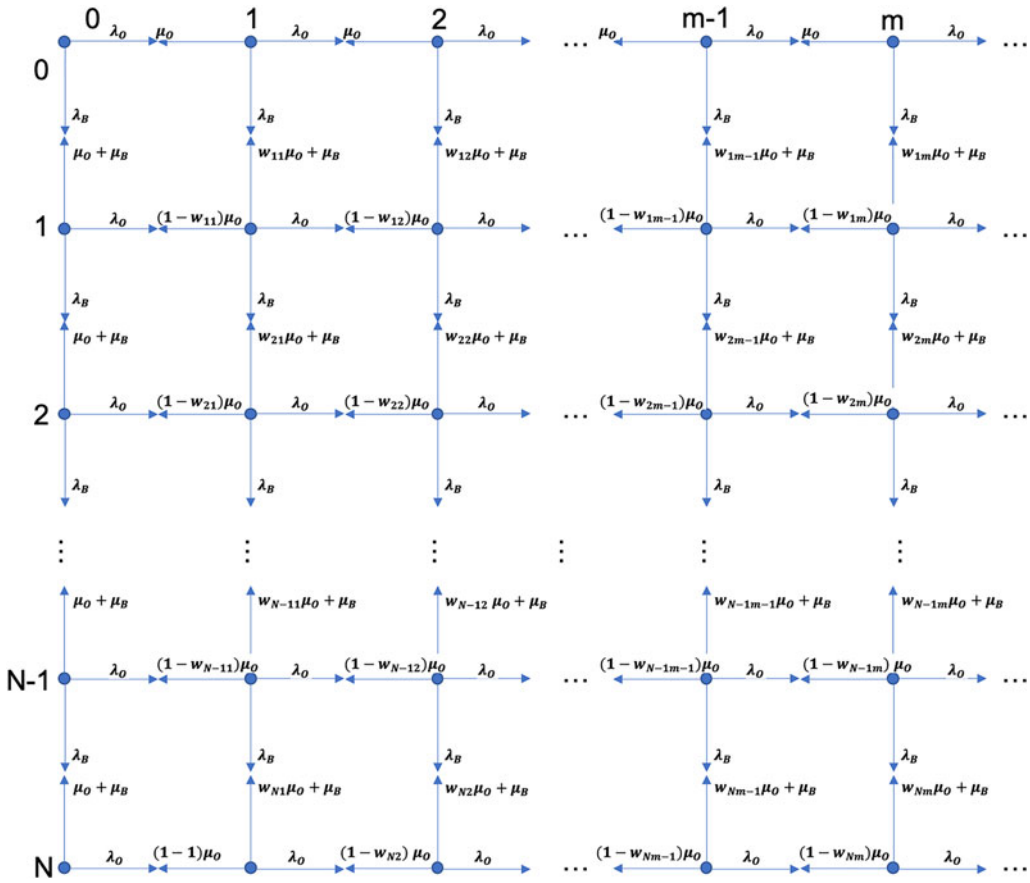


Figure 8. Kidney transplantation state transition diagram (Perlman *et al.*, 2018)

case of n patients and m ($m \leq n$) kidneys, the factor of waiting time comes into consideration for patients; for instance, sometimes patients do not wait for the best match, and they select the semi-best. Therefore, patients' decisions are not independent of each other; the time-homogeneous assumption (independent increments) which Su and Zenios (2004) consider in their study does not work in a real application. The case would be more complicated when there are k types of organs (for instance, kidney, liver, pancreas, etc.).

For optimal allocation of arriving kidneys for transplantation, almost all the mentioned models are considered the national pool of donors for the local patients. Therefore, it is hard to say which method works 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 the kidney is first 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. Regarding this limitation, there is no international waiting list for organ transplantation, and patients are allowed to register on multiple lists to increase their chance (Ata *et al.*, 2016). Therefore, giving a rank or score to local, regional, national, and then worldwide compatibility could help with implementation of the optimally allocating kidney transplantation algorithm on a global level.

In addition to the main models for kidney transplantation discussed earlier, extensive efforts have been carried out in 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). In addition, there is a high risk after AKI for the propagation of CKD. Therefore, CKD and AKI are strongly associated. Despite the fact that other risk factors, such as age, race or ethnic group, genetic factors, hypertension, diabetes, and metabolic syndrome affect 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).

Table 2. Literature on kidney transplantation from a 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 incomplete information and unstable patients' decisions	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 per transplantation for kidney storage policy	Considering multiple-type double-ended queues, where candidates are distinguished by their HLA compatibility	Not considering blood compatibility
Perlman *et al.* (2018)	Providing a dynamic allocation model of flexible resources for calculating the optimal probabilities of 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-organ transplantation, and mortality rate	Improving geographic equity when patients can register on 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 waiting times for all blood types	Considering ABO-incompatible (or cross-match–incompatible)	ABO-incompatible cannot achieve equity; not considering the 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 proposing 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
Su and Zenios (2004)	Modeling incorporates patients' individual problems in organ accept/reject decisions with the last-come-first-served (LCFS) queueing policy	Considering a pool of n patients who face a stream of m ($m \leq n$); 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-candidates, 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 an 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 acceptance or rejection of kidney by the patient based on his/her situation	Introducing the QALY index based on patient-specific rating for being in different health states	Only considering a single patient facing an infinite stream of kidney offers

However, the long-term effects of AKI remain an open research area.

There are several papers about stochastic modeling of kidney diseases with a 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 of 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) and 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 Fig. 9 and summarized in Table 3 with five states for the CKD model, which are equivalent to stages $G2-G5$ in Fig. 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 death, although each stage of CKD can gradually transform to a worse stage with absorbing state λ.

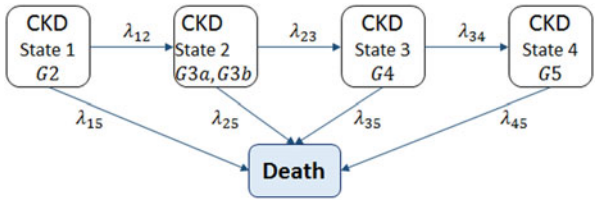


Figure 9. CKD progression process with five stages. *G2*−*G5* reference the staging formation in Fig. 1.

According to Fig. 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 the 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:
$$P\left(X_{n+1}=j|X_n=i, X_{n-1}=i_{n-1}, ..., X_0=i_0\right) = P(X_{n+1}|X_n=i)$$
$$P_{ij} = P\left(X_{n+1}=j|X_n=i\right)$$
3. Transition probabilities: P_{ij} (each transition probability is a function of the state of health and the treatment):
$$P_{ij} \geq 0, \quad \sum_{j=0}^{\infty} P_{ij} = 1$$
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:
$$\begin{cases} \pi_j = \sum_{i=0}^{n} \pi_i P_{ij}, \quad j = 0, 1, ..., n \\ \sum_{i=0}^{n} \pi_i = 1 \end{cases}$$
6. 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 follows:

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 is 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,

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

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 that 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 confirm 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 Fig. 10.

As Fig. 10 shows, AKI patients can be healed, be released without restoration of renal function, or can die. Additionally, patients who seem relieved, may in the future develop CKD or cardiovascular disease (CVD) (dashed lines in Fig. 10). 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 the Markov model for AKI to CKD transition using seven states. The states include normal kidney function, AKI, CKD,

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	*G2*
2	Kidney damage with a moderate reduction in GFR	30–59	*G3a* and *G3b*
3	Kidney damage with a severe reduction in GFR	15–29	*G4*
4	ESRD implying Renal Replacement Therapy (RRT) (regardless of GFR)	<15	*G5*
5	Death		

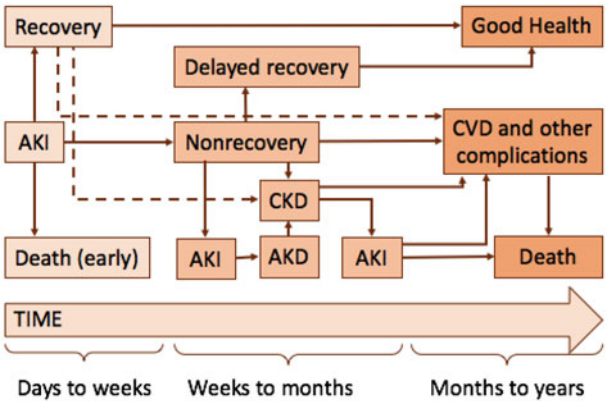


Figure 10. Potential patient outcomes following AKI (Kellum and Prowle, 2018).

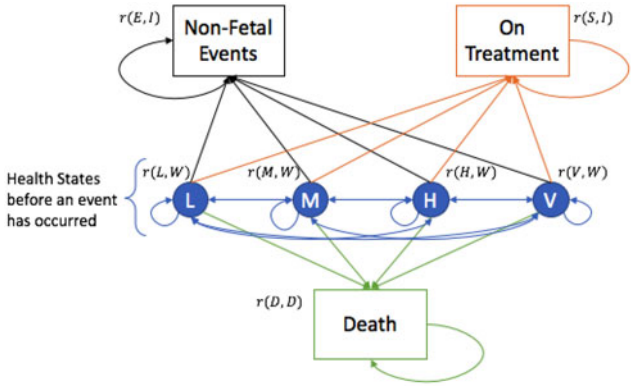


Figure 11. State transition diagram of MDP for kidney disease screening and treatment.

ESRD—including dialysis, transplant, and no RRT—, and death. For more specifications on data and investigation, refer to Petrovic *et al.* (2015) and Kerr *et al.* (2014).

4.3. Discussion on Stochastic modeling of kidney disease

Advantage: Patients with renal disease 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 of 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 Fig. 1) based on the degree of severity or frequency.

Thirdly, patients with more severe AKI are sicker. Therefore, the transformation to CKD by other diseases may not directly cause 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 kidney disease, such as progression of CKD to AKI. Therefore, stochastic modeling for kidney disease progression can indirectly affect 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 disease and cannot fully recover 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 in order 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 Fig. 11.

- 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 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 a living state (s_t, m).

Therefore, the optimality equation is

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

where $\lambda \sum_{\forall s_{t+1}} p(s'_t|s_t, W) v_t(s'_t, m), r(s_t, W), R(s_t, I),$ and $p(s'_t|s_t, W)$ 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, a 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 Fig. 1. in Van Arendonk et al. (2015) for more detail in the 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 for its applications in liver transplantation see Alagoz *et al.* (2007) and Batun *et al.* (2018).

5.1. Discussion on MDP for kidney disease screening and treatment

Advantage: MDP can find optimal solutions for 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 visiting a doctor regularly. Even so, it is possible that a patient for the first time goes under treatment when in the high state of disease progression.

The other limitation of the MDP model is that all 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 a 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 issue in kidney disease screening and treatment using an MDP approach is the "curse of dimensionality," which means that the number of states that must be included in the calculation of the solution increase exponentially quickly as the size of the problem increases.

6. Conclusion

OR techniques have been playing an important role in solving kidney problems. 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 article. As a conclusion and for a future research direction, we attempted to have a broader vision for solving kidney problems from an OR perspective. These problems are barely indicated in literature with an analytic context and are known as critical obligations for the kidney specialist. In this 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. Kidney operation frames depend on the ordering, but kidney disease usually happens before ordering. However, research only has investigated 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 as a new variable of bargaining power, and game-theoretical approaches can simulate this situation.
3. The case of the kidney exchange is also included in 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 addition, there are several operations techniques used in different kidney research, such as forecasting and data-driven models, which are under the scope of statistical inferences and are not investigated in this article. Despite the 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. 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 a 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 humans 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 humans 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 problems in which decisions can be available from different sources and can 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, a kidney's operation system can be used as a bio-inspired optimization algorithm for a population-based optimization approach to assist in OR-related problems. The approach is called a kidney inspiration algorithm (KIA) and it reflect some ideas from the structure of the nephron. For more information, one can refer to Jaddi *et al.* (2017); Jaddi and Abdullah (2018); Behmanesh (2016); Taqi and Ali (2017).

Acknowledgment

The authors would like to thank Prof. Panos M. Pardalos, Prof. Azra Bihorac, Prof. Parta Hatamizadeh, and Prof. Amir Kazory for providing a visiting research opportunity for studying kidney disease at the PRISMA Group at the Division of Nephrology, Hypertension, & Renal Transplantation, Department of Medicine, University of Florida. Also, we would like to thank Prof. John A. Kellum of the Department of Critical Care Medicine, University of Pittsburgh, for his constructive discussion about an earlier version of the article, the paradigm of AKI to CKD, and its future research direction.

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References

Aalen, O. O. (1995) Phase-type distributions in survival analysis. *Encyclopedia, of Biostatistics*, **22**(4), 447–463.

Aalen, O. O., Farewell, V. T., De Angelis, D., Day, N. E. and Nöel Gill, O. (1997) A Markov model for HIV disease progression including the effect of HIV diagnosis and treatment: Application to AIDS prediction in England and Wales. *Statistics in Medicine*, **16**(19), 2191–2210.

Abellán, J., Armero, C., Conesa, D., Pérez-Panadés, J., Martínez-Beneito, M., Zurriaga, O., García-Blasco, M. and Vanaclocha, H. (2006) Analysis of the renal transplant waiting list in the país Valencià (spain). *Statistics in Medicine*, **25**(2), 345–358.

Abraham, D. J., Blum, A. and Sandholm, T. (2007) Clearing algorithms for barter exchange markets: Enabling nationwide kidney exchanges. In *Proceedings of the 8th ACM Conference on Electronic Commerce ACM*, San Diego, California, USA — June 11-15, 295–304.

Ahn, J.-H. and Hornberger, J. C. (1996) Involving patients in the cadaveric kidney transplant allocation process: A decision-theoretic perspective. *Management Science*, **42**(5), 629–641.

Alagoz, O., Hsu, H., Schaefer, A. J. and Roberts, M. S. (2010) Markov decision processes: A tool for sequential decision making under uncertainty. *Medical Decision Making*, **30**(4), 474–483.

Alagoz, O., Maillart, L. M., Schaefer, A. J. and Roberts, M. S. (2007) Choosing among living-donor and cadaveric livers. *Management Science*, **53**(11), 1702–1715.

Alvelos, F., Klimentova, X. and Viana, A. (2019*a*) Maximizing the expected number of transplants in kidney exchange programs with branch-and-price. *Annals of Operations Research*, **272**(1-2), 429–444.

Alvelos, F., Klimentova, X. and Viana, A. (2019*b*) Maximizing the expected number of transplants in kidney exchange programs with branch-and-price. *Annals of Operations Research*, **272**(1-2), 429–444.

Amdur, R. L., Chawla, L. S., Amodeo, S., Kimmel, P. L. and Palant, C. E. (2009) Outcomes following diagnosis of acute renal failure in US veterans: Focus on acute tubular necrosis. *Kidney International*, **76**(10), 1089–1097.

American Kidney Fund (n.d.) http://www.kidneyfund.org/. (accessed September 21, 2018).

Andersen, P. K., Hansen, L. S. and Keiding, N. (1991) Assessing the influence of reversible disease indicators on survival. *Statistics in Medicine*, **10**(7), 1061–1067.

Anderson, R., Ashlagi, I., Gamarnik, D., Rees, M., Roth, A. E., Sönmez, T. and Ünver, M. U. (2015a) Kidney exchange and the alliance for paired donation: Operations research changes the way kidneys are transplanted. *Interfaces*, **45**(1), 26–42.

Anderson, R., Ashlagi, I., Gamarnik, D. and Roth, A. E. (2015b) Finding long chains in kidney exchange using the traveling salesman problem. *Proceedings of the National Academy of Sciences*, **112**(3), 663–668.

Anwar, N. and Mahmoud, M. R. (2014) A stochastic model for the progression of chronic kidney disease. *International Journal of Engineering Research and Applications*, **4**(11), 08–19.

Asar, Ö., Ritchie, J., Kalra, P. A. and Diggle, P. J. (2016) Short-term and long-term effects of acute kidney injury in chronic kidney disease patients: A longitudinal analysis. *Biometrical Journal*, **58**(6), 1552–1566.

Ata, B., Skaro, A. and Tayur, S. (2016) Organjet: Overcoming geographical disparities in access to deceased donor kidneys in the United States. *Management Science*, **63**(9), 2776–2794.

Bandi, C., Trichakis, N. and Vayanos, P. (2019) Robust multiclass queuing theory for wait time estimation in resource allocation systems. *Management Science*, **65**(1), 152–187.

Barone, M., Avolio, A. W., Di Leo, A., Burra, P. and Francavilla, A. (2008) ABO blood group-related waiting list disparities in liver transplant candidates: Effect of the meld adoption. *Transplantation*, **85**(6), 844–849.

Batun, S., Schaefer, A. J., Bhandari, A. and Roberts, M. S. (2018) Optimal liver acceptance for risk-sensitive patients. *Service Science*, **10**(3), 320–333.

Behmanesh, R. (2016) Nephron algorithm optimization: Inspired of the biologic nephron performance. *International Journal of Applied Metaheuristic Computing*, **7**(1), 38–64.

Bellman, R. (1966) Dynamic programming. *Science*, **153**(3731), 34–37.

Bertsekas, D. P., Bertsekas, D. P., Bertsekas, D. P. and Bertsekas, D. P. (1995) *Dynamic Programming and Optimal Control*, Vol. **1**, *Athena Scientific, Belmont, MA*.

Bertsimas, D., Farias, V. F. and Trichakis, N. (2013) Fairness, efficiency, and flexibility in organ allocation for kidney transplantation. *Operations Research*, **61**(1), 73–87.

Best, N., Richardson, S. and Thomson, A. (2005) A comparison of bayesian spatial models for disease mapping. *Statistical Methods in Medical Research*, **14**(1), 35–59.

Biro, P., Manlove, D. F. and Rizzi, R. (2009) Maximum weight cycle packing in directed graphs, with application to kidney exchange programs. *Discrete Mathematics, Algorithms and Applications*, **1**(04), 499–517.

Brandeau, M. L., Sainfort, F. and Pierskalla, W. P. (2004), *Operations Research and Health Care: A Handbook of Methods and Applications*, Vol. 70, Springer Science & Business Media.

Chawla, L. S., Eggers, P. W., Star, R. A. and Kimmel, P. L. (2014) Acute kidney injury and chronic kidney disease as interconnected syndromes. *New England Journal of Medicine*, **371**(1), 58–66.

Chen, H. H., Duffy, S. W. and Tabar, L. (1996) A Markov chain method to estimate the tumour progression rate from preclinical to clinical phase, sensitivity and positive predictive value for mammography in breast cancer screening. *The Statistician*, **45**(3), 307–317.

Chen, J. S. and Prorok, P. C. (1983) Lead time estimation in a controlled screening program. *American Journal of Epidemiology*, **118**(5), 740–751.

Constantino, M., Klimentova, X., Viana, A. and Rais, A. (2013) New insights on integer-programming models for the kidney exchange problem. *European Journal of Operational Research*, **231**(1), 57–68.

Conway, R. W., Maxwell, W. L. and Miller, L. W. (2003) *Theory of Scheduling*, Courier Corporation.

Danovitch, G. M. and Cecka, J. M. (2003) Allocation of deceased donor kidneys: past, present, and future. *American Journal of Kidney Diseases*, **42**(5), 882–890.

Denton, B. T. (2013) *Handbook of Healthcare Operations Management*, Vol. 184, New York: Springer.

Dickerson, J. P., Kazachkov, A. M., Procaccia, A. D. and Sandholm, T. (2017) Small representations of big kidney exchange graphs. In *AAAI*, 487–493.

Dickerson, J. P. and Sandholm, T. (2017) Multi-organ exchange. *Journal of Artificial Intelligence Research*, **60**, 639–679.

Donaghy, R. and Marshall, A. (2006) Using patient survival time and dynamic clinical variables to determine characteristics of the hidden phases in a Coxian phase-type distribution. *In Statistical Latent Variables Models in the Health Sciences*, 31–32.

Donnelly, C., McFetridge, L. M., Marshall, A. H. and Mitchell, H. J. (2017) A two-stage approach to the joint analysis of longitudinal and survival data utilising the Coxian phase-type distribution. *Statistical Methods in Medical Research*, **27**(12), 3577–3594.

Duffy, S. W., Chen, H.-H., Tabar, L. and Day, N. E. (1995) Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. *Statistics in Medicine*, **14**(14), 1531–1543.

Eckardt, K.-U., Coresh, J., Devuyst, O., Johnson, R. J., Köttgen, A., Levey, A. S. and Levin, A. (2013) Evolving importance of kidney disease: From subspecialty to global health burden. *The Lancet*, **382**(9887), 158–169.

Elalouf, A., Perlman, Y. and Yechiali, U. (2018) A double-ended queueing model for dynamic allocation of live organs based on a best-fit criterion. *Applied Mathematical Modelling*, **60**, 179–191.

Esfandiari, H. and Kortsarz, G. (2018) A bounded-risk mechanism for the kidney exchange game. *Discrete Applied Mathematics*, **243**, 46–53.

Fackrell, M. (2009) Modelling healthcare systems with phase-type distributions. *Health Care Management Science*, **12**(1), 11–26.

Faissol, D. M., Griffin, P. M. and Swann, J. L. (2009) Bias in Markov models of disease. *Mathematical Biosciences*, **220**(2), 143–156.

Freedman, R., Schaich Borg, J., Sinnott-Armstrong, W., Dickerson, J. and Conitzer, V. (2018) Adapting a kidney exchange algorithm to align with human values. In *Proceedings of the 32nd AAAI Conference on Artificial Intelligence*.

Ghariblou, S., Salehi, M., Magnani, M. and Jalili, M. (2017) Shortest paths in multiplex networks. *Scientific Reports*, **7**(1), 2142.

Gjertson, D. W., Terasaki, P. I., Takemoto, S. and Mickey, M. R. (1991) National allocation of cadaveric kidneys by hla matching: Projected effect on outcome *and costs*. New England Journal of Medicine, **324**(15), 1032–1036.

Glander, P., Budde, K., Schmidt, D., Fuller, T. F., Giessing, M., Neumayer, H.-H. and Liefeldt, L. (2010), 'The blood group O problem in kidney transplantation—time to change?. *Nephrology Dialysis Transplantation*, **25**(6), 1998–2004.

Grams, M. E., Sang, Y., Coresh, J., Ballew, S., Matsushita, K., Molnar, M. Z., Szabo, Z., Kalantar-Zadeh, K. and Kovesdy, C. P. (2016) Acute kidney injury after major surgery: A retrospective analysis of veterans health administration data. *American Journal of Kidney Diseases*, **67**(6), 872–880.

Green, P. J. and Richardson, S. (2002) Hidden Markov models and disease mapping. *Journal of the American Statistical Association*, **97**(460), 1055–1070.

Hamouda, E., El-Metwally, S. and Tarek, M. (2018) Ant lion optimization algorithm for kidney exchanges. *PloS One*, **13**(5), 1–23.

Hauskrecht, M. and Fraser, H. (2000) Planning treatment of ischemic heart disease with partially observable Markov decision processes. *Artificial Intelligence in Medicine*, **18**(3), 221–244.

He, Q. M. (2014) *Fundamentals of Matrix Analytic Methods*, Vol. 365, Springer.

Huang, C.-C. (2010) Circular stable matching and 3-way kidney transplant. *Algorithmica*, **58**(1), 137–150.

Hussey, J., Parameshwar, J. and Banner, N. (2007) Influence of blood group on mortality and waiting time before heart transplantation in

the United Kingdom: Implications for equity of access. *The Journal of Heart and Lung Transplantation*, **26**(1), 30–33.
Jackson, C. H., Sharples, L. D., Thompson, S. G., Duffy, S. W. and Couto, E. (2003) Multistate Markov models for disease progression with classification error. *Journal of the Royal Statistical Society: Series D (The Statistician)*, **52**(2), 193–209.
Jaddi, N. S. and Abdullah, S. (2018) Optimization of neural network using kidney-inspired algorithm with control of filtration rate and chaotic map for real-world rainfall forecasting. *Engineering Applications of Artificial Intelligence*, **67**, 246–259.
Jaddi, N. S., Alvankarian, J. and Abdullah, S. (2017) Kidney-inspired algorithm for optimization problems. *Communications in Nonlinear Science and Numerical Simulation*, **42**, 358–369.
Kay, R. (1986) A Markov model for analysing cancer markers and disease states in survival studies. *Biometrics*, **42**(4), 855–865.
Kellum, J. A. and Prowle, J. R. (2018) Paradigms of acute kidney injury in the intensive care setting. *Nature Reviews Nephrology*, **14**(4), 217–230.
Kerr, M., Bedford, M., Matthews, B. and O'donoghue, D. (2014) The economic impact of acute kidney injury in England. *Nephrology Dialysis Transplantation*, **29**(7), 1362–1368.
Kleinrock, L. (1975) *Queueing Systems*, Wiley, New York.
Koh, H. C., Tan, G. et al. (2011) Data mining applications in healthcare. *Journal of Healthcare Information management*, **19**(2), 65.
Lakshmi, C. and Iyer, S. A. (2013) Application of queueing theory in health care: A literature review. *Operations Research for Health Care*, **2**(1-2), 25–39.
Lee, H., Chung, S., Cheong, T. and Song, S. (2018) Accounting for fairness in a two-stage stochastic programming model for kidney exchange programs. *International Journal of Environmental Research and Public Health*, **15**(7), 1491.
Lee, K.-M., Min, B. and Goh, K.-I. (2015) Towards real-world complexity: An introduction to multiplex networks. *The European Physical Journal B*, **88**(2), 48.
Levey, A., Atkins, R., Coresh, J., Cohen, E., Collins, A., Eckardt, K.-U., Nahas, M., Jaber, B., Jadoul, M., Levin, A. et al. (2007) Chronic kidney disease as a global public health problem: Approaches and initiatives–a position statement from kidney disease improving global outcomes. *Kidney International*, **72**(3), 247–259.
Levey, A. S., Levin, A. and Kellum, J. A. (2013) Definition and classification of kidney diseases. *American Journal of Kidney Diseases*, **61**(5), 686–688.
Liefeldt, L., Budde, K. and Glander, P. (2011) Accumulation of elderly ESRD patients with blood group O on the waiting list. *Transplant International*, **24**(10), e83–e84.
Lin, M., Wang, J., Feng, Q. and Fu, B. (2019) Randomized parameterized algorithms for the kidney exchange problem. *Algorithms*, **12**(2), 50.
Luo, L., Small, D., Stewart, W. F. and Roy, J. A. (2013) Methods for estimating kidney disease stage transition probabilities using electronic medical records. *eGEMs*, **1**(3), 1–17.
Mallappallil, M., Friedman, E. A., Delano, B. G., McFarlane, S. I. and Salifu, M. O. (2014) Chronic kidney disease in the elderly: Evaluation and management. *Clinical Practice (London, England)*, **11**(5), 525.
Marshall, G. and Jones, R. H. (1995) Multi-state models and diabetic retinopathy. *Statistics in Medicine*, **14**(18), 1975–1983.
Mdala, I., Olsen, I., Haffajee, A. D., Socransky, S. S., Thoresen, M. and Blasio, B. F. (2014) Comparing clinical attachment level and pocket depth for predicting periodontal disease progression in healthy sites of patients with chronic periodontitis using multi-state Markov models. *Journal of Clinical Periodontology*, **41**(9), 837–845.
Mehta, R. L., Kellum, J. A., Shah, S. V., Molitoris, B. A., Ronco, C., Warnock, D. G. and Levin, A. (2007) Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. *Critical Care*, **11**(2), R31.
Mike, J. L. and Maroulas, V. (2019) Combinatorial hodge theory for equitable kidney paired donation. *Foundations of Data Science*, **1**(1), 87–101.
Moni, M. A. and Liò, P. (2014) ComoR: A software for disease comorbidity risk assessment. *Journal of Clinical Bioinformatics*, **4**(1), 8.
Nuijten, M., Andress, D. L., Marx, S. E. and Sterz, R. (2009) Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: A US perspective. *Current Medical Research and Opinion*, **25**(5), 1221–1234.
Obenshain, M. K. (2004) Application of data mining techniques to healthcare data. *Infection Control & Hospital Epidemiology*, **25**(8), 690–695.
Orlando, L. A., Belasco, E. J., Patel, U. D. and Matchar, D. B. (2011) The chronic kidney disease model: A general purpose model of disease progression and treatment. *BMC Medical Informatics and Decision Making*, **11**(1), 41.
O'Rourke, M. F. and Safar, M. E. (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney. *Hypertension*, **46**(1), 200–204.
Ozrazgat-Baslanti, T., Thottakkara, P., Huber, M., Berg, K., Gravenstein, N., Tighe, P., Lipori, G., Segal, M. S., Hobson, C. and Bihorac, A. (2016) Acute and chronic kidney disease and cardiovascular mortality after major surgery. *Annals of Surgery*, **264**(6), 987–996.
Petrovic, S., Bogavac-Stanojevic, N., Lakic, D., Peco-Antic, A., Vulicevic, I., Ivanisevic, I., Kotur-Stevuljevic, J. and Jelic-Ivanovic, Z. (2015) Cost-effectiveness analysis of acute kidney injury biomarkers in pediatric cardiac surgery. *Biochemia medica*, **25**(2), 262–271.
Perlman, Y., Elalouf, A. and Yechiali, U. (2018) Dynamic allocation of stochastically-arriving flexible resources to random streams of objects with application to kidney cross-transplantation. *European Journal of Operational Research*, **265**(1), 169–177.
Phelan, P., O'Kelly, P., O'Neill, D., Little, D., Hickey, D., Keogan, M., Walshe, J., Magee, C. and Conlon, P. (2010) Analysis of waiting times on Irish renal transplant list. *Clinical Transplantation*, **24**(3), 381–385.
Puterman, M. L. (2014), *Markov Decision Processes: Discrete Stochastic Dynamic Programming*, John Wiley & Sons.
Raghupathi, W. (2016) Data mining in healthcare. In *Healthcare Informatics: Improving Efficiency through Technology, Analytics, and Management*, CRC Press, Boca Raton, FL, 353–372.
Rais, A. and Viana, A. (2011) Operations research in healthcare: A survey. *International Transactions in Operational Research*, **18**(1), 1–31.
Reddy, B. P., Walters, S. J., Duenas, A., Thokala, P. and Kelly, M. P. (2019) A role for mcda to navigate the trade-offs in the national institute for health and care excellence's public health recommendations. *Operations Research for Health Care* (in press).
Rexius, H., Nilsson, F. and Jeppsson, A. (2002) On the allocation of cardiac allografts from blood group O donors. *Scandinavian Cardiovascular Journal*, **36**(6), 342–344.
Rifkin, D. E., Coca, S. G. and Kalantar-Zadeh, K. (2012) Does aki truly lead to ckd?. *Journal of the American Society of Nephrology*, **23**(6), 979–984.
Rodina-Theocharaki, A., Bliznakova, K. and Pallikarakis, N. (2012) Markov Chain Monte Carlo simulation for projection of end stage renal disease patients in Greece. *Computer Methods and Programs in Biomedicine*, **107**(1), 90–96.
Rojas, E., Munoz-Gama, J., Sepúlveda, M. and Capurro, D. (2016) Process mining in healthcare: A literature review. *Journal of biomedical informatics*, **61**, 224–236.
Roth, A. E., Sönmez, T. and Ünver, M. U. (2004) Kidney exchange. *The Quarterly Journal of Economics*, **119**(2), 457–488.
Santos, N., Tubertini, P., Viana, A. and Pedroso, J. P. (2017) Kidney exchange simulation and optimization. *Journal of the Operational Research Society*, **68**(12), 1521–1532.
Schaefer, A. J., Bailey, M. D., Shechter, S. M. and Roberts, M. S. (2005) Modeling medical treatment using Markov decision processes. In *Operations Research and Health Care*, Springer, 593–612.
Snyder, S. and Pendergraph, B. (2005) Detection and evaluation of chronic kidney disease. *Interventions*, **100**(1), 24–25.
Stanford, D. A., Lee, J. M., Chandok, N. and McAlister, V. (2014) A queuing model to address waiting time inconsistency in solid-organ transplantation. *Operations Research for Health Care*, **3**(1), 40–45.

Stanford, D. A., Renouf, E. M. and McAlister, V. C. (2008) Waiting for liver transplantation in Canada: Waitlist history 2000–2004 and sensitivity analysis for the future. *Health Care Management Science*, **11**(2), 184–195.

Steimle, L. N. and Denton, B. T. (2017), Markov decision processes for screening and treatment of chronic diseases. In *Markov Decision Processes in Practice*, Springer, 189–222.

Su, X. and Zenios, S. (2004) Patient choice in kidney allocation: The role of the queueing discipline. *Manufacturing & Service Operations Management*, **6**(4), 280–301.

Su, X. and Zenios, S. A. (2005) Patient choice in kidney allocation: A sequential stochastic assignment model. *Operations research*, **53**(3), 443–455.

Su, X. and Zenios, S. A. (2006) Recipient choice can address the efficiency-equity trade-off in kidney transplantation: A mechanism design model. *Management Science*, **52**(11), 1647–1660.

Sweeting, M., Farewell, V. and De Angelis, D. (2010) Multi-state Markov models for disease progression in the presence of informative examination times: An application to hepatitis C. *Statistics in Medicine*, **29**(11), 1161–1174.

Taqi, M. K. and Ali, R. (2017) OBKA-FS: An oppositional-based binary kidney inspired search algorithm for feature selection. *Journal of Theoretical and Applied Information Technology*, **95**(1), 9–23.

Tomar, D. and Agarwal, S. (2013) A survey on data mining approaches for healthcare. *International Journal of Bio-Science and Bio-Technology*, **5**(5), 241–266.

Van Arendonk, K. J., Chow, E. K., James, N. T., Orandi, B. J., Ellison, T. A., Smith, J. M., Colombani, P. M. and Segev, D. L. (2015) Choosing the order of deceased donor and living donor kidney transplantation in pediatric recipients: a Markov decision process model. *Transplantation*, **99**(2), 360–366.

Xu, H., Moni, M. A. and Liò, P. (2015) Network regularised cox regression and multiplex network models to predict disease comorbidities and survival of cancer. *Computational Biology and Chemistry*, **59**(Part B), 15–31.

Yoo, I., Alafaireet, P., Marinov, M., Pena-Hernandez, K., Gopidi, R., Chang, J.-F. and Hua, L. (2012) Data mining in healthcare and biomedicine: a survey of the literature. *Journal of medical systems*, **36**(4), 2431–2448.

Zaric, G. S. (2013) *Operations Research and Health Care Policy*, Springer.

Zenios, S. A. (2002) Optimal control of a paired-kidney exchange program. *Management Science*, **48**(3), 328–342.