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Innovative Applications of O.R.

Deciding kidney-offer admissibility dependent on patients' lifetime failure rate

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ABSTRACT

We use developments in full-information *optimal stopping* to decide kidney-offer admissibility depending on the patient's age in treatment, on his/her estimated lifetime probabilistic profile and his/her prospects on the waiting list. We allow for a broad family of lifetime distributions – the Gamma – thus enabling flexible modeling of patients survival under dialysis. We fully automate an appropriate recursive solution in a spreadsheet application. It yields the optimal *critical times* for acceptance of offers of different qualities, and the ensuing expected value-to-go as a function of time. The model may serve both the organizer of a donation program for planning purposes, and the particular surgeon in making the critical decision at the proper time. It may further serve the potential individual recipient, practicing present-day *patient-choice*. Numerical results and their discussion are included.

1. Introduction

The US UNOS (United Network for Organ Sharing), the ERBP (European Renal Best Practice) and the Eurotransplant organization outline policies by which kidneys of the deceased are allocated locally, regionally and nationally (Eurotransplant manual, 2014; ERBP, European Renal Best Practice; US HRSA/OPTN, 2008a). They emphasize that the final decision to accept a particular organ remains the prerogative of the transplant surgeon and/or physician responsible for the care of the candidate in parallel, a*patient choice* practice has developed in recent years. Often, the choice is relegated to the patient (See Ahn & Hornberger, 1996; Su & Zenios, 2004a; 2004b; 2006; US HRSA/OPTN, 2008a and references therein). Patient-choice, particularly with regard to transplantation, benefits from hired professional advice. Because minor-quality kidneys are repeatedly refused for transplantation by patients on the waiting list and by their surgeons, excessive organ wastage is generated. To cope with this problem UNOS issued the ECD (Expanded Criteria Donor) policy, so kidneys from marginal donors are reserved for patients who declare in advance their willingness to accept such organs (US HRSA/OPTN, 2008a). Recently, *shared decision making* in kidney transplantation has been advocated impressively by Gordon et al. (2013). The question to be asked is what scientific and fact-based decision aids exist to help the individual in making such a critical decision, or the organizer of a donation program in assessing the future outlook of a pool of individual patients. The lack of accurate aids is explained by the immense difficulty of the analysis of a regulated dual donor-recipient streams (see Boxma, David, Perry, & Stadje, 2011; Yuan, Feldhamer, Gafni, Fyfe, & Ludwin, 2002; Zenios, Cherow, & Wein, 2000). Consequently, alternative decision-analytic approaches are sought. Such directions are heuristics - but still more analytically sound than the extant *point system*. For example, Yuan et al. (2002) suggest a *fuzzy logic* approach. The authors show, by way of example, that the fuzzy logic based policy is closer to an expert's (a medical practitioner) opinion than the policy attained by the UNOS point system. The authors, Chun and Sumichrast (2006) suggest a "rank based" approach for a selection problem applied to kidney allocation. The model proposed in the present work provides an analytical tool to help bridge the said decision-aid analytical gap, accompanied by an easy to use Excel workbook. The model and the software should prove useful to the individual patient, the consultant, the physician, and the social planner. We focus on the prospects of the *individual* patient. Optimizing the case of the single candidate (see e.g. Hornberger & Ahn, 1997) applies directly to patient-choice. As we show, it may further serve as a building block in the analysis of the dual (donor-recipient) queueing system at large. We ask for the patient's optimal, time-dependent, acceptance-rejection policy for kidneys of various quality, as a function of his/her blood-type (ABO) and immunological tissue characteristics (HLA). This policy depends also on the individual's deteriorating lifetime distribution under dialysis, and we assume that this lifetime distribution is *Gamma*(α, θ) with the shape parameter α being some integer (*Erlang* distribution). We use the recent study by

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Bendersky and David (2015) in full-information *optimal stopping* to suggest a computational scheme which determines the optimal policy for the patient in question, in terms of *critical times*. The *Gamma* has long been popular in survival analysis and in medical research, with practical examples dating back to the 1950's (Collett, 2003; Lawless, 2011; Lee & Wang, 2003). The two-parameter Gamma family furnishes enough agreement in fitting it to many relevant datasets (Gupta & Kunda, 1999), and it admits ordering in distribution and in hazard rate, with respect to the shape parameter. Yet, due to the fact that the Gamma has no closed form for its cumulative distribution function, researchers preferred sometimes the *Weibull* or the *generalized exponential*. Still, in our case we show that letting the shape parameter be a positive integer (the Gamma becoming Erlang) we can compute both the value functions and critical times while providing enough flexibly for the modeling of different profiles of deterioration.

Our model relies on the quantification of rewards from each candidate and kidney-donation matching, on the ABO and HLA distribution in the population to which donors belong, and on the donation rate μ. In fact, to pass from the realm of the single candidate to that of the competitive world, we propose, by way of approximation, to use a value of "effective μ" – an expected average rate of future offers which become available to the specific candidate in question. This figure is to be assessed via databases such as UNOS's or the ERA-EDTA's. The effective μ will also have to take into account the candidate's position in the queue. The present exposition is supported by real data regarding the above mentioned factors.

In Section 2 we briefly outline the determinants of successful transplantation. Section 3 provides basics of the needed temporal modeling. Section 4 outlines the analysis of the stopping problem for Gamma deterioration, and the single-candidate decision algorithm. Section 5, accompanied with the appendices to this paper, demonstrates the use of the Excel application with numerical examples. These examples are then followed by a discussion, and Section 6 concludes the paper. We emphasize at the outset that the random offer value X in our model may not be based on HLA (Human Leukocyte Antigens, see below) match levels, but rather on *any finite set of real values of kidney quality, as perceived by the decision-maker.* In particular, it may be based on subjective probabilities or on utilities as perceived by the client and/or his/her advisor within the praxis of patient choice. As the HLA remains a significant factor in the allocation of live kidneys worldwide, and because real-life data with respect to tissue matching are available, we base our presentation on this criterion.

2. Success in transplantation

We begin by discussing the major factors that influence the success in kidney transplantation. These factors function in most allocation systems in prioritizing the pool of waiting candidates vis-à-vis any pending donor kidney.

2.1. The HLA tissue matching

Human tissue cells contain antigens that vary from person to person and are immunologically relevant to the specific organ. The system of these antigens is known as the HLA system. It can be subdivided into two groups: Class I that contains A, B or C antigens, which are present in body cells that have a nucleus, and Class II that contains antigens of the types DP, DR and DQ which are present only in the membranes of the cells responsible for triggering the immune system. The A, B,...,DQ antigens are arranged in sites A, B,...,DQ respectively. Every HLA site contains two *alleles*. Since the 80's, from the entire HLA genetic complex, sites A, B and DR were considered transplant relevant antigens. If transplanted into another individual, they can cause an immune response that can lead to the rejection of the *graft*. Yet, different medical centers put different emphases on the three sites, so that the same match combination may score differently. Part of the question is whether the benefit from HLA matching is worth the economic and social costs, including the rationing of fewer donor organs to black recipients (see Held et al., 1994; Vereestraeten et al., 1999). Lefaucheur et al. (2010) is an example for recent years renewed emphasis on the HLA matching for graft survival. In this exposition, we assume that any A, B or DR donor antigens which do not match the recipient can trigger an immune response. The higher the total number of such antigens, the lower the chance of a successful transplant. So, seven possible match-levels are possible - zero (all 6 alleles, aranged in three sites, do match) to six mismatches (none match). In assessing the future prospects of a given candidate, the HLA gene-distribution in the relevant donor population is assumed to be known.

One comprehensive source concerning histocompatibility testing is Cecka and Reid (2005).

2.2. ABO blood type

The blood types of the donor and the recipient must also match. In allocation systems worldwide O donors go to O recipients exclusively, except for the case when there is a recipient with a zero antigen mismatch. (UNOS and Eurotransplant have a similar ABO-B rule for donors and recipients). The incorporation of the ABO match probability to the tissue match probability of a random donor to a given candidate is routine (see Barnes & Miettinen, 1972). In our model, this probability may simply multiply the relevant donor arrival rate to yield an effective μ. (Since a Poisson process with rate μ and a probability p of counting any arrival yields a Poisson process with rate μp. See also Section 3.2 below). One may assume statistical independence between tissue classification and blood type.

2.3. Preferred candidates: pediatric, long waiting and sensitized (PRA)

Pediatric patients are allocated extra score points. Also, each extra year on the waiting list credits the candidate with extra points. These two quantifying criteria may also be taken into account by an effective μ. There is an additional determinant factor in transplantation, called PRA (Panel Reactive Antibodies). It refers to a periodical immunological check of each candidate (Cecka & Reid, 2005; Eurotransplant manual, 2014). Although the PRA status is included in allocation systems, we choose not to include it in the present exposition.

2.4. x-*year graft survival, QALY, and discounted-QALY*

Let us denote the reward for a given candidate from a random offer by X, a discrete random variable. In this presentation X is a one-to-one function of I, the total number of mismatches in the HLA A, B and DR sites combined. Medical assessments as to how to translate the number of HLA-mismatches I to X vary, mainly because controversy surrounds the question of what gain needs to be measured. See Gold, Siegel, Russell, and Weinstein (1996) for the prevailing notions of *QALY* (quality-adjusted life-years), *QALE* (quality-adjusted life expectancy) and *discounted-QALY* (see also Evans, Tavakoli, & Crawford, 2004 for a critique). The present work adopts an alternative measure, that of (post-transplant) 3-*years graft-survival*. Table 1 below summarizes the distribution of X which is used for the numerical examples in Section 5. The sources of these data are indicated in Section 5.1 and in Appendix A.

3. Temporal modeling with gamma deterioration

Obviously, the deteriorating profile of lifetime under dialysis treatment must be reflected in any prescriptive model for acceptance-rejection of a kidney for transplant. David and Yechiali (1985) used dynamic programming to show that if the lifetime of