

A Bayesian Optimization Approach to Estimating Expected Match Time and Organ Quality in Kidney Exchange

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Abstract

Kidney exchanges allow patients with end-stage renal disease to find a lifesaving living donor by way of an organized market. However, not all patients are equally easy to match, nor are all donor organs of equal quality—some patients are matched within weeks, while others may wait for years with no match offers at all. Knowledge of expected waiting time and organ quality affects medical and insurance decisions. This work presents a principled method to estimate the expected quality of the kidney that a specific patient who enters an exchange will receive, as well as how long it will take to find that match. Estimation is performed via a novel Bayesian-optimization-based approach that learns a model of a computationally complex underlying Monte Carlo simulator. With a limited number of expensive simulation trajectories, the model produces results that are acceptable in practice. With access to fast and accurate sampling, medical professionals could have near-instantaneous access to valuable insight regarding a patient’s expected outcome in a kidney exchange system.

1 Introduction

Renal disease affects millions of people worldwide, with a societal burden comparable to that of diabetes (Neuen et al. 2013). A patient with end-stage renal failure requires one of two treatments to stay alive: either frequent and costly filtration and replacement of their blood, known as dialysis, or the reception of a new organ via transplantation from a donor with one or more healthy kidneys. The latter option is often preferable due to increased quality of life and other health outcomes (Santos et al. 2015).

Donor kidneys are obtained from one of three sources: the deceased donor waiting list, where cadaveric kidneys are harvested from deceased donors with still-healthy kidneys; ad-hoc arrangement between a compatible living donor and a patient; and, recently, *kidney exchanges*, a type of organized market where patients swap willing donors with other needy patients (Roth, Sönmez, and Ünver 2004; 2005a; 2005b). Kidney exchanges, while still quite new, result in increased numbers and quality of transplants (Sönmez, Ünver, and Yenmez 2017); furthermore, their design is a success story for fielded AI research (Abraham, Blum, and Sandholm 2007; Ashlagi and Roth 2014; Anderson et al. 2015; Dickerson and Sandholm 2015; Hajaj et al. 2015; Toulis and Parkes 2015; Manlove and O’Malley 2015).

The act of getting a kidney transplant is time sensitive, and affects healthcare and lifestyle decisions; furthermore, the expected quality of the kidney—if any—received by a patient affects the decision to accept or reject a particular match offer, and may be used to (de)prioritize patients in a matching mechanism (Bertsimas, Farias, and Trichakis 2013). Thus, decision support systems that incorporate donor and patient features and quantify or predict the value of a current or future offered kidney are valuable to practitioners. The Kidney Donor Profile Index (KDPI) (Rao et al. 2009) and the Living Kidney Donor Profile Index (LKDPI) (Massie et al. 2016) are well known and used to assess deceased- and living-donor kidneys, respectively. However, no method (nor system) currently exists to find the expected quality of a donated kidney in a kidney exchange.

This paper presents a Bayesian-optimization-based system that takes as input features of a patient and his or her paired donor and returns an estimate of (i) the expected quality of and (ii) expected waiting time for a matched kidney offer. The use of modern tools from machine learning and combinatorial optimization is required due to the NP-hard and APX-hard nature of even the most basic problems in kidney exchange (Abraham, Blum, and Sandholm 2007; Biró and Cechlárová 2007; Biró, Manlove, and Rizzi 2009; Luo et al. 2016; Jia et al. 2017). Our method uses a realistic but expensive black box Monte Carlo simulator to produce estimates of match quality and time to match for a specific patient and donor; it samples new points in the space intelligently, balancing overall computational time with the accuracy of prediction for a new patient and donor. That prediction can be done in real or near-real time, a requirement for such a decision support system. We give a proof of concept implementation on a reduced but realistic set of features in the kidney exchange setting, and show that the method learns the necessary functions well.

2 Preliminaries

In this section, we briefly overview the standard model of kidney exchange. The most-used model represents a kidney exchange as a directed graph $G = (V, E)$, called a *compatibility graph*. Here, each patient and paired donor who enter the pool are represented as a single vertex. Then, a directed edge is drawn from vertex v_i to vertex v_j if the patient at vertex v_j wants the donor kidney of vertex v_i . Weights $w_e \in \mathbb{R}$

represent the utility of an individual kidney transplant represented by an edge e , and are also used to (de)prioritize specific classes of patient (Dickerson, Procaccia, and Sandholm 2014; UNOS 2015).

Kidney exchanges rely on one of two types of structures to match patients: cycles and chains. First, a k -cycle c consists of exactly k patient-donor pairs (vertices), each connected by an edge in a cycle; here, each pair in c receives the kidney from the previous pair. Second, a k -chain begins with a non-directed donor, who enters the pool without a patient and gives her kidney to a patient with a paired donor, who gives to another patient with a paired donor, and so on k times.¹ Modern exchanges derive the majority of their utility from chains (Montgomery et al. 2006; Rees et al. 2009; Anderson et al. 2015; Ashlagi et al. 2017).

A *matching* M is a set of disjoint cycles and chains in a compatibility graph G ; $M \in \mathcal{M}$, the set of all legal matchings. No donor can give more than one of her kidneys, necessitating the disjointness of cycles and chains—although recent work explores multi-donor donation (Ergin, Sönmez, and Ünver 2017; Farina, Dickerson, and Sandholm 2017). Given the set of all legal matchings \mathcal{M} , the *clearing problem* finds the matching M^* that maximizes utility function $u : \mathcal{M} \rightarrow \mathbb{R}$ (e.g., for maximum weighted matching, $u(M) = \sum_{c \in M} \sum_{e \in c} w_e$). Formally: $M^* \in \arg \max_{M \in \mathcal{M}} u(M)$. Ongoing research in the AI/Economics literature uses utility functions to enforce incentive properties via mechanism design (Ashlagi and Roth 2014; Li et al. 2014; Hajaj et al. 2015; Blum et al. 2017; Mattei, Saffidine, and Walsh 2017).

Finding a maximum weight (capped-length) cycle and chain packing is NP-hard (Abraham, Blum, and Sandholm 2007; Biró, Manlove, and Rizzi 2009), and is also hard to approximate (Biró and Cechlárová 2007; Luo et al. 2016; Jia et al. 2017). In practice, integer program (IP) formulations are used to clear large exchanges (Abraham, Blum, and Sandholm 2007; Dickerson, Procaccia, and Sandholm 2013; Glorie, van de Klundert, and Wagelmans 2014; Anderson et al. 2015; Dickerson et al. 2016). Formally, denote the set of all legal chains of length no greater than K and cycles of length no greater than L by $\mathcal{C}(L, K)$. Then, solve the following integer program:

$$\max \sum_{c \in \mathcal{C}(L, K)} w_c x_c \quad s.t. \quad \sum_{c: v \in c} x_c \leq 1 \quad \forall v \in V,$$

where $x_c \in \{0, 1\}$ is a binary variable for every $c \in \mathcal{C}(L, K)$, and $w_c = \sum_{e \in c} w_e$. The final matching is the set of chains and cycles c such that $x_c = 1$. We use this integer program as a subsolver in this work.

3 Estimating the Quality of a (Future) Organ

In this section, we formally specify our model for quantifying the quality of an organ, as well as our method for predicting the expected quality of that organ given a black box

¹In fielded kidney exchanges, cycles are limited in size to, typically, 3; all surgeries in a cycle must be executed simultaneously, so longer cycles are nearly impossible to plan. Chains, however, can be much longer (or effectively endless) in practice.

exchange simulator. As defined, the model and method are applicable to any related online set packing problem (Emek et al. 2012); however, given our application, we motivate the model in the context of kidney exchange.

We associate with each patient-donor pair a vector $\mathbf{I} = \{X_1, \dots, X_n\}$ representing the features of that pair (e.g., blood types of the patient and donor, sex, age, body mass index (BMI), lifestyle choices, and so on). Our process begins when such a patient-donor pair arrives and wishes to know the expected quality $E[Q]$ of the kidney that they would receive through KPD, for some random variable $Q \in \mathbb{R}$ representing quality. Let

$$M(\mathbf{I}) \rightarrow \{O_1, \dots, O_d\}$$

denote the feature set of the donor who is matched with the patient-donor pair. Because the function $\mathbf{I} \rightarrow E[Q]$ is not necessarily continuous, and is—in practice—very difficult to model, we assume, as it is standard, $E[Q] = \sum_{i=1}^l Y_i$ for some independent random variables Y_i . Thus, if the set of functions

$$\{\mathbf{I} \rightarrow E[Y_1], \dots, \mathbf{I} \rightarrow E[Y_l]\}$$

can be modeled accurately using a practical number of samples, $E[Q]$ can be estimated by linearity of expectations.

Computing $E[Q]$, the Expected Organ Quality

Let A denote a static value, and B denote a random variable. Let $A \triangleright B$ denote that the value of B is affected by A , or more rigorously,

$$p(B|A) \neq p(B)$$

Let \triangleright be the complement of \triangleright . For all $k \in [l]$, $\exists M_k \subseteq M(\mathbf{I})$ such that $\forall M_i \in M, M_i \triangleright Y_k$. For all k , one of two cases occurs. First, $Y_k = f_k(M_k)$ for some function f_k . Let S_1 denote the set of Y_k where this applies. Second, $\exists I_k \subseteq \mathbf{I}$ such that $Y_k = f_k(I_k, M_k)$. Let S_2 denote the set of Y_k where this applies. Y_k can only depend on \mathbf{I} and $M(\mathbf{I})$, as all features pertaining to quality depend on the features of the patient and the features of the donor. Thus, we wish to find or accurately estimate

$$F_k(\mathbf{I}, M) \rightarrow E[Y_k] \quad \forall k$$

Given these functions and the input vector \mathbf{I} , $E[Q]$ is, at least, feasible to compute.

Each function F_k falls under two cases: $\mathbf{I} \triangleright M_k$, or $\mathbf{I} \triangleright M_k$:

- First, suppose that $\mathbf{I} \triangleright M_k$. We wish to compute $F_k = E[Q]$. Here, we are given $p(M_k)$. In the case that $Y_k \in S_1$, we can simply compute F_k using $p(M_k)$. In the case that $Y_k \in S_2$, where we are given

$$F_k(\mathbf{I}, M) = \int \cdots \int_{M_k} f_k \left(I_k, \bigcup_{i=1}^l M_k^i \right) p \left(\bigcup_{i=1}^l M_k^i \right) \prod_{i=1}^l dM_k^i$$

for $M_k^i \in M_k$, more computationally intensive methods are required, as discussed below.

- Second, suppose that $\mathbf{I} \triangleright M_k$, the use of a realistic simulator capable of producing samples of $M(\mathbf{I})$ is necessary to produce an estimate of $F_k(\mathbf{I}, M)$. The estimation

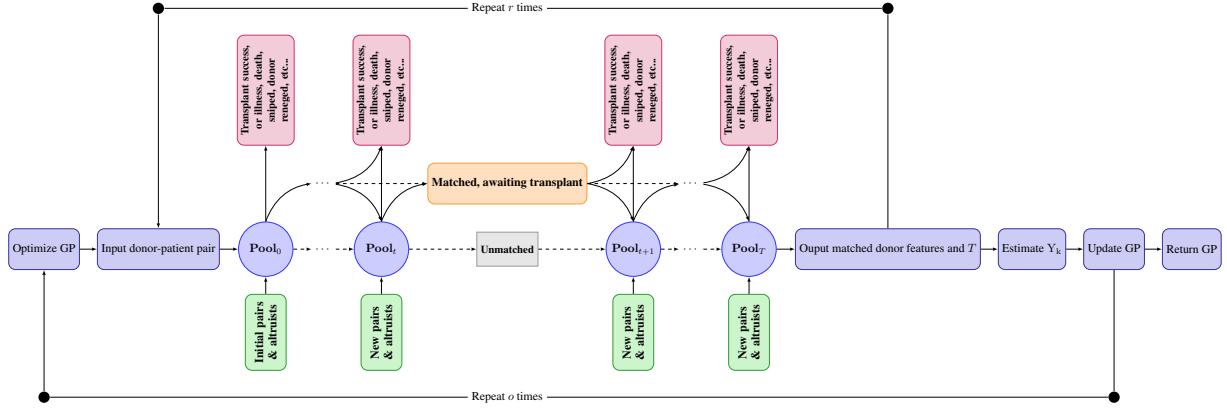


Figure 1: Estimating F_k when $\mathbf{I} \triangleright M_k$

must not rely on the simulation to compute values, as in practice, running time would be too large. Thus, information must be precomputed, such that values of the function can be returned instantaneously later. In this paper, we will use a modified Bayesian optimization approach to estimate F_k (Pelikan, Goldberg, and Cantú-Paz 1999; Snoek, Larochelle, and Adams 2012).

However, note that there is a special subset of cases within this general set of cases. In the following, we assume that $Y_k \in S_2$, however, the same applies to the case where $Y_k \in S_1$. If $f_k(I_k, M_k)$ is a conditional function with c cases, it cannot be accurately modeled by a Gaussian Process. Without loss of generality, let

$$f_k(I_k, M_k) = \begin{cases} f_k^1(I_k, M_k), & \text{if } C_k^1(I_k, M_k) \\ f_k^2(I_k, M_k), & \text{if } C_k^2(I_k, M_k) \\ \vdots & \vdots \\ f_k^c(I_k, M_k), & \text{otherwise} \end{cases}$$

where each function $C_k^i(I_k, M_k)$ is a mutually exclusive boolean valued function. In this case, the Bayesian optimization method is required to learn each of the $F_k^i(\mathbf{I}, \mathbf{M}) \rightarrow \mathbb{E}[f_k^i(I_k, M_k)]$. For $1 \leq i \leq c$, $\Pr[C_k^i(\mathbf{I}, \mathbf{M})]$ must be learned through the Bayesian optimization method. Assuming this can be learned,

$$F_k(\mathbf{I}, \mathbf{M}) = \sum_{i=1}^c \Pr[C_k^i(\mathbf{I}, \mathbf{M})] F_k^i(\mathbf{I}, \mathbf{M})$$

by linearity of expectations, and we are done.

Estimating F_k

Bayesian optimization (BO) utilizes Gaussian Processes (GP) to maximize an unknown function, in this case, the expected output of a realistic simulator. The acquisition function is used to select the best point on the function to sample that would lead us to the absolute maximum. Examples include Expected Improvement (EI), Lower Confidence Bound (LCB), and Maximum Probability of Improvement (MPI); Brochu, Cora, and De Freitas (2010) give an in-depth

overview of techniques. A kernel (covariance) function is used to interpolate between known values of the function, and determine the confidence at each point. While BO offers a method to maximize a function where getting output is time consuming, maximizing F_k is not what we are concerned with. We wish to learn F_k using this method instead, by taking as output the GP of the BO.

Modifications to Bayesian Optimization In order to learn the function F_k , rather than maximize it, we must change the acquisition function to solely value points based on their confidence. By greedily reducing variance on the GP, we can learn the function. At any point, the GP returns both the mean and the variance at that point. Thus, the acquisition function that would greedily reduce variance on the GP is the one that returns just the variance of the point. To optimize the acquisition, the limited-memory BFGS optimization algorithm is used (Andrew and Gao 2007). The kernel function used for the GP is the radial basis function (RBF) kernel, given by

$$K(\mathbf{x}, \mathbf{x}') = \exp\left(-\frac{\|\mathbf{x} - \mathbf{x}'\|^2}{2\sigma^2}\right)$$

While this kernel fits our use case, as points that are close together on the function are correlated, the covariance estimate given by the kernel will not be accurate unless the σ parameter is properly set. We use a Markov Chain Monte Carlo (MCMC) method to learn the kernel's σ hyperparameter. To compute the acquisition function, we compute the integrated expected variance at each point. The BO terminates and returns the GP after o optimization iterations.

Black Box Monte Carlo Simulation Our overarching goal is to learn a function $\mathbf{I} \rightarrow \mathbb{E}[Q]$, or some approximation thereof. This is done via a combination of the Bayesian-optimization-based approach to estimate F_k given above and a realistic simulator that mimics a particular use case. Here, that simulator mirrors a generic, large kidney exchange. We build on a known kidney exchange codebase,² and augment

²All code, including *all* data to reproduce experimental results, is available at <https://github.com/ndurvasula/KPDMetric>

the realistic dynamic kidney exchange simulator built there to mimic our setting. In each optimization iteration, the realistic simulator is run r times, so as to estimate the expected output of the simulator (see Figure 1). This estimate is then fed into the Bayesian optimization framework, and repeated o times for satisfactory convergence.

4 Computing Expected LKDPI and Matching Time in a Kidney Exchange

Our motivation in this paper is, in part, due to the widespread usage of the Kidney Donor Profile Index (KDPI) to quantify the value of deceased-donor kidneys, and the increasing use of the new Living Kidney Donor Profile Index (LKDPI) to quantify the value of living-donor kidneys (Rao et al. 2009; Massie et al. 2016). Roughly speaking, both the KDPI and the LKDPI are metrics used to compute the expected life-time (quality) of a kidney that is donated from a donor D to a patient P .

Because we build on the LKDPI metric in this paper, we formally restate its calculation below.

$$\begin{aligned}
Q = & -11.30 \\
& + 1.85 * [(\text{donor age} - 50) \text{ if donor age} > 50] \\
& - .381 * \text{donor eGFR} \\
& + 1.17 * \text{donor BMI} \\
& \quad (+22.34 \text{ if donor is African-American}) \\
& \quad (+14.22 \text{ if donor has history of cigarette use}) \\
& + 0.44 * \text{donor systolic blood pressure} \\
& \quad (-21.68 \text{ if donor and patient are ABO incompatible}) \\
& \quad (-10.61 \text{ if donor and patient are unrelated}) \\
& + 8.57 * (\# \text{HLA-B mismatches}) \\
& + 8.26 * (\# \text{HLA-DR mismatches}) \\
& - 50.87 * [\min(\text{donor to patient weight ratio}, 0.9)]
\end{aligned}$$

Here, the estimated glomerular filtration rate (eGFR), body mass index (BMI), blood type (ABO) compatibility, and human leukocyte antigen (HLA) are all integral or real values determined by physical medical testing. In a real kidney exchange, these features would all affect with which and how many donors a particular patient matched.

Unlike a standard ad-hoc living-donor donation, in a donation through a kidney exchange, the features of the end donor are unknown, and are generated through a stochastic process (affected by, among other things, the matching policy of an exchange, competition between exchanges, competition between an exchange and the deceased donor waiting list, uncertainty over future entrants to the pool, and so on). In this work, we aim to predict the expected LKDPI of the kidney that the patient would receive, as well as how long it will take to receive that kidney, given information regarding the kidney exchange and the feature set of the patient and the paired donor. Let I_l denote the features:

- Patient Blood Type
- Patient HLA-B vector
- Patient HLA-DR vector

Let I_m denote the features used in matching: for the UNOS matching policy:

- Patient Blood Type
- Paired Donor Blood Type
- Patient CPRA

Here, the Calculated Panel Reactive Antibodies (CPRA) is a score in $[0, 1]$ roughly representing the fraction of donors, drawn from a general population, that would *not* be a match for a particular patient (i.e., a CPRA score of 1 signals extreme difficulty in matching).

Let \mathbf{I} denote $I_l \cup I_m$. We compute $E[Q]$ as previously stated, by computing $F_k(\mathbf{I}) \forall k$.

However, while not a feature necessary for computing the quality of a the kidney, the matching time is also relevant information in making a decision regarding holding out for a better matched kidney in an exchange system. Let T denote the matching time. Unlike the features required for quality computation, $\mathbf{I} \triangleright T$, therefore in computing the matching time, the Bayesian Optimization approach as described in section 2 is implemented. If testing returns positive results for this method, the method can be shown to be functional for all features Y_k where $\mathbf{I} \triangleright M_k$.

Bayesian Optimization for Match Time Computation

The function mapping the features of a patient-donor pair to matching time in our simulated kidney exchange was learned through the described method. We use GPyOpt (2016), an open source Bayesian optimization platform for Python. We modified GPyOpt to change the acquisition to return the variance at the point. Then, for all 16 blood type pair combinations for patient-donor pairs who enter the exchange, we performed Bayesian optimize over patient CPRA for $o = 20$ iterations. For each blood type pair combination, $E[T]$ is estimated based on $r = 32$ trajectories in a realistic simulator, with the following exceptions:

- Due to increased stochasticity in the results of the simulations for the blood type pair combinations AB-A, A-B, and AB-AB, where X-Y denotes a donor patient pair with donor of blood type X, and patient of blood type Y, we simulate with an increased number of trajectories in order to make the function feasible to optimize.
- For the AB-A donor-patient pair, we simulate with 64 trajectories, and for the A-B and AB-AB donor-patient pairs, we simulate with 128 trajectories. This is in part due to the higher noise that arises from entering a hard-to-match patient-donor pair into the exchange system.

We emphasize that this paper’s experimental results serve as a proof of concept for the proposed method; in practice, a more computationally intensive simulation would be required before deploying the proposed system.

5 Experimental Results

We now experimentally validate the proposed method using a realistic kidney exchange simulator and a reduced feature

set, as a proof of concept. In practice, one would include 25-30 features before making a policy recommendation; however, as this section will show, even using a reduced feature set validates the method.

Experimental Setup

After constructing the Gaussian processes (GPs) as described in Sections 3 and 4, we tested them by comparing the match time returned by the GP and the match time returned by the realistic simulator after r trajectories. To test the 16 generated GPs (1 per blood type pair in $\{O-O, O-A, \dots, AB-B, AB-AB\}$), the domain of CPRA $[0, 1]$ is partitioned uniformly into 4 zones $\{[0, .25), [.25, .5), [.5, .75), [.75, 1)\}$. In each zone, 5 random trials are done, with $r = 32$ trajectories each, with the exceptions of the blood type pairs listed as special cases in Section 4.

Results

We briefly overview our experimental results. Figure 2 shows the estimated expected mean residual of our estimated function when compared to our simulated test of the value of that function in weeks, calculated over all blood type combinations. First, the learned function fits the true (simulated) function quite well, for CPRA values far from 1. As the CPRA value approaches 1, the residuals increase; this is to be expected, because higher CPRA values result in more uncertainty in the ability to find any match at all. Indeed, a CPRA of 1 indicates zero probability of finding a match; in a case like this, waiting time becomes infinity, and the function to be estimated becomes ill-defined.

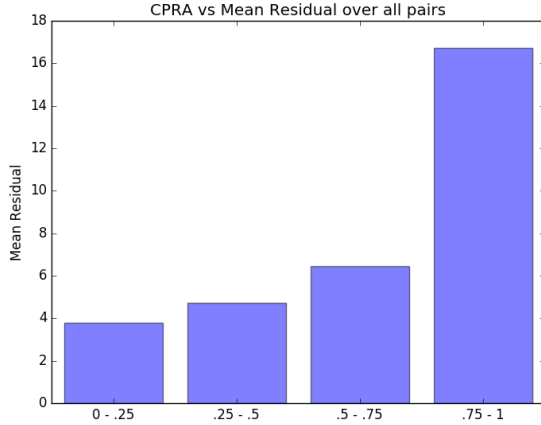


Figure 2: Mean residual in weeks over all blood type pairs

Figure 3 shows the distribution on the function mapping patient CPRA for the blood type combination O-AB in arbitrary units, the acquisition function (in red) in arbitrary units, and the point at which the acquisition is optimized (the solid red line going down). We see that uncertainty is quite low, even after a small number of (expensive) black box function queries.

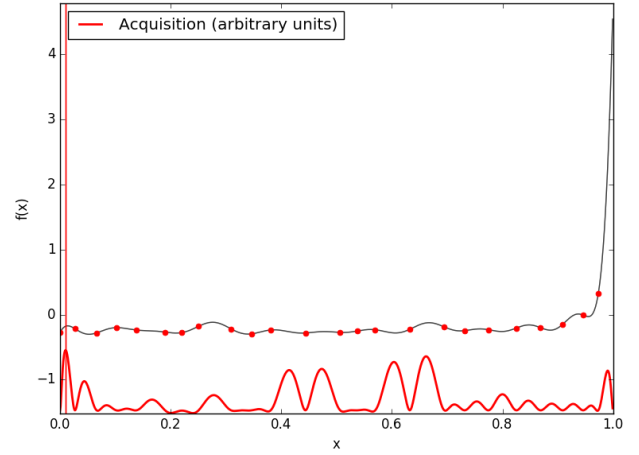


Figure 3: GP for O-type paired donor and AB-type patient (in arbitrary units)

Figure 4 shows the mean residual in weeks over CPRA for the blood type combination O-AB. The O-AB pair is, in some sense, the easiest pair to match; its donor has the “universal” blood type O, and its patient has no blood type constraints. Indeed, we see that the model estimates the waiting time and quality of this “easy” patient-donor pair quite well, albeit with the same expected spike toward uncertainty as the patient CPRA increases.

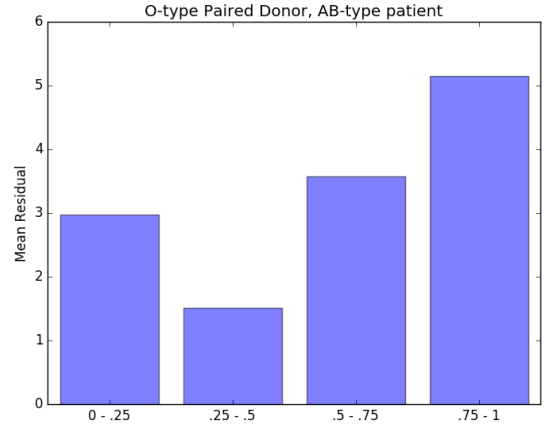


Figure 4: Mean residual in weeks

Figure 5 shows the distribution on the function mapping patient CPRA for the blood type combination AB-O in arbitrary units, the acquisition function (in red) in arbitrary units, and the point at which the acquisition is optimized (the solid red line going down). Figure 6 shows the mean residual in weeks over CPRA for the blood type combination AB-O. We focus on this particular case because the AB-O pair is a complement to the O-AB pair; while the latter is easy to match, the former has a relatively constrained donor (type

AB donors can only give to type AB patients), and a relatively constrained patient (type O patients can only receive from type O donors).

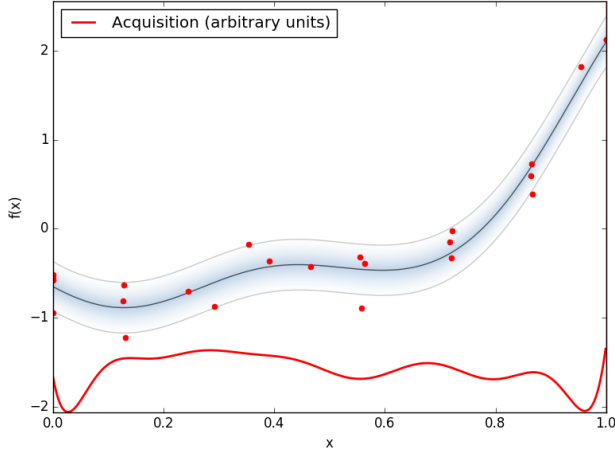


Figure 5: GP for AB-type paired donor and O-type patient (in arbitrary units)

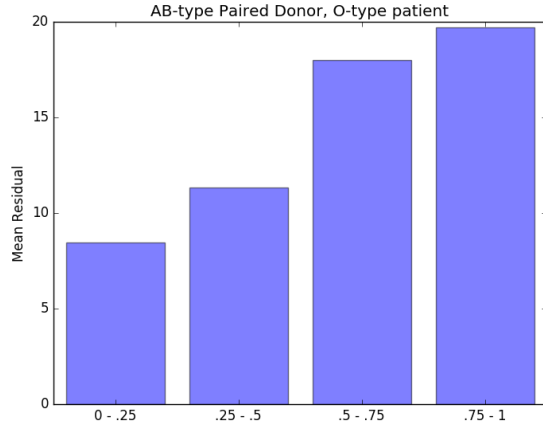


Figure 6: Mean residual in weeks

We performed this experiment for all 16 combinations of patient and donor blood types. Figure 2 gives a high-level quantitative overview of those results; qualitatively, results followed this visualization. In general, higher CPRA leads to greater uncertainty. Similarly, harder to match patients and harder to match donors also lead to greater uncertainty. However, throughout, our method was able to learn a close approximation to the underlying function of interest—even using commodity hardware.

Discussion

Overall, even with a limited amount of trajectories, the Gaussian Process (GP) provides accurate predictions. As the CPRA increases, the mean residual increases, as the match

time output increases in stochasticity with respect to an increase in CPRA. With harder to match blood types (such as the AB-type donor, O-patient donor patient pair), the stochasticity in the result was larger as well, resulting in a higher mean residual. However, as seen in Figure 5, the GP is capable of handling this, by estimating the probability distribution on that value (using a Gaussian prior). Thus, to a certain extent, the GP is capable of handling stochastic outputs.

While this proof of concept demonstrates the promise of this system in a toy environment, before making a policy recommendation or deploying a support tool in practice, we note that:

- the number of trajectories r should be (much) greater, for greatly reduced stochasticity, and thus far smaller mean residuals from the GP to the realistic simulator; and
- the number of features considered should be much higher, and informed by experts in the field.

Yet, given these proof of concept experimental results, we feel confident that—given all F_k —a decision support system can be deployed for use by practitioners, in order to give patients and their willing donors this information on demand.

6 Conclusions & Future Research

This paper presented a principled method to estimate the expected quality of the kidney that a specific patient who enters an exchange will receive, as well as how long it will take to find that match. Knowledge of expected waiting time and organ quality affects medical and insurance decisions. Estimation was performed via a novel Bayesian-optimization-based approach that learns a model of a computationally complex underlying Monte Carlo simulator, which in turn represents a potentially discontinuous function. With a limited number of expensive simulation trajectories, the model produced reliably accurate results in our proof-of-concept setting, supporting further investigation. With access to fast and accurate sampling, medical professionals could have near-instantaneous access to valuable insight regarding a patient’s expected outcome in a kidney exchange system.

The clear future research direction is to determine, via a combination of feature selection methods and expert opinion, the set of features necessary to completely characterize the expected waiting time and kidney quality function our method aims to learn. The model presented, and the proof-of-concept experiments performed, support more intense computational experiments. Similarly, one might use the application of LKDPI presented here to design more socially beneficial mechanisms in the face of strategic agents, perhaps incentivizing agents to perform in a specific way to increase overall social welfare; this area of research, particularly in the context of kidney exchange, is still open (Ashlagi and Roth 2014; Toulis and Parkes 2015; Hajaj et al. 2015; Blum et al. 2017).

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