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A BIOLOGICALLY BASED DISCRETE-EVENT SIMULATION MODEL OF LIVER TRANSPLANTATION IN THE UNITED STATES FOR PEDIATRIC AND ADULT PATIENTS

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ABSTRACT

We describe the framework of a discrete-event simulation of the national liver allocation system that incorporates the stochastic, disease-specific natural histories of pediatric and adult patients independent of allocation policies. This model will extend our previous work that only considered adult patients and organs. Our model will consist of patient and organ generators, a natural history progression module, and pre- and post-transplant survival estimation modules. While this is still a work in progress, our model will produce various statistics, such as the number of deaths while waiting for a liver, waitlist additions, the number of transplants performed, the number of wasted livers, and estimates of pre- and post-transplant survival at every time point for every patient.

1 INTRODUCTION

Since its inception in 1963, liver transplantation has been the only life-sustaining therapy for end-stage liver disease (ESLD), with the demand for livers far exceeding the supply. As of March 2011, there were 16,141 patients on the United States liver waiting list, with only 5,763 transplants having been performed in 2010 (United Network for Organ Sharing 2011). Of these patients waiting, 539 patients were pediatric ($<$ 18 years old) and in 2010, 517 pediatric liver transplants were performed. The growing discrepancy between the number of patients waiting for a liver and the number of patients offered livers has led to a reevaluation of organ donation and allocation policies, and necessitates the use of objective methodology to evaluate policy changes.

Our model relies on a discrete-event simulation (DES) with user-defined organ donation and allocation policies. This work builds on our existing DES (Shechter et al. 2005) by including pediatric patients and organs in the model and relaxing several restrictive assumptions; additionally, this model utilizes a revised algorithm for updating patients' natural histories. Given that children often have different disease

etiologies, clinical presentations and natural histories than adults, and that they may compete with adults for donor livers, it is imperative that they are accurately represented by the model. In addition, allocation policies for pediatric organs differ from those for adult organs. For example, only children may appeal for an exception to their health-based prioritization in order to move up on the waiting list. Also, children may receive a split portion of an adult donor liver. Given these policy differences between pediatric and adult patients, it is important that the simulation be able to evaluate policy changes independently for both children and adults.

The purpose of this study is to develop a comprehensive and clinically realistic model of liver disease that includes both children and adults who need transplantation, which can be used to evaluate alternative liver allocation policies.

1.1 Prior Models

There have been several modeling efforts in the past. In 1995, the United Network for Organ Sharing (UNOS) developed the first computerized simulation of the liver allocation process, known as the UNOS Liver Allocation Model (ULAM). ULAM is a DES with Monte Carlo events that was developed to evaluate several policy changes, including whether to implement national or regional waiting lists (Pritsker et al. 1995). Later, the Scientific Registry of Transplant Recipients (SRTR) developed a series of simulation models known as Simulation Allocation Models (SAMs) to understand the effect of several policy changes, including whether to implement a Model for End-stage Liver Disease score for livers and whether to mandate regional sharing of livers if local candidates are healthier (Thompson et al. 2004). While these simulation models have been able to successfully evaluate some policies, they were calibrated with the current policies and were unable to simulate pre-transplant natural histories that differed from those of real patients. A model that is built on current policies compromises an unbiased evaluation of arbitrary policy changes and the effect such changes have at the patient level.

We previously developed a DES that could accurately recreate the stochastic nature of individual patients' natural histories and evaluate nearly arbitrary policy changes with minimal bias (Shechter et al. 2005). This work was used to successfully model the progression of liver disease, organ allocation, organ acceptance, the timing of living-donor transplantation, and informed the development of complex Markov decision processes for evaluating the choice between living donation and waiting on the deceased donor list (Alagoz et al. 2004, Alagoz et al. 2007b, Alagoz et al. 2007a). This prior model was validated by comparing the difference in the model-predicted changes in patient natural histories and transplant outcomes to those of actual patients, which was deemed clinically insignificant by a panel of experts (Shechter et al. 2005). While this model contributed to our understanding of the challenges associated with liver transplant decision-making, it was calibrated with data from the mid 1990s, excluded children and did not fully describe how organs were accepted and rejected by recipients, how donor livers could be split, the use of living donors, and how patients were relisted after graft failure. Additionally, the time between updates in the previous model did not depend on patient age group, disease group, and location (which ranges from a patient remaining at home waiting for a transplant to being in the intensive care unit). Finally, this model's natural history module did not consider the entire duration of a patient's illness when updating his health state; for example, the model treated a patient with hepatitis C who had been ill for days to weeks the exact same as a patient who had chronic hepatitis C for years, as long as their laboratory and clinical profiles were similar. Medically, this was an invalid assumption, as the patient with chronic disease is likely to deteriorate at a slower rate than the patient with acute disease.

2 MODEL

The overall structure of the model is presented in Figure 1. First, the patient generator initializes either a pediatric or adult patient. The natural history module updates the patient's health while he is waiting for a transplant. The organ generator initializes either a deceased- or living-donor liver and determines whether

or not it can be split (the liver has a unique regenerative ability that allows it to be split and transplanted into two patients). Livers are allocated according to user-defined inputs. Pre-and post-transplant survivals are estimated at every time point for every patient by the survival module.

2.1 User-defined Inputs

Selection and allocation rules are entirely configurable so that various policies can be tested. For example, the user might determine the patient's position on the waiting list by using his Model for End-stage Liver Disease (MELD) or Pediatric End-stage Liver Disease (PELD) score if he is an adult or child respectively. Similarly, the likelihood that a patient on the waiting list will accept an offered liver could be determined by a logistic regression based on patient and donor organ characteristics. Other user-defined inputs include the criteria for splitting livers, the acceptability of marginal organs (i.e., organs that may be contraindicated for transplantation in some patients), and the definition of "similar" clinical profiles (discussed in Section 2.3).

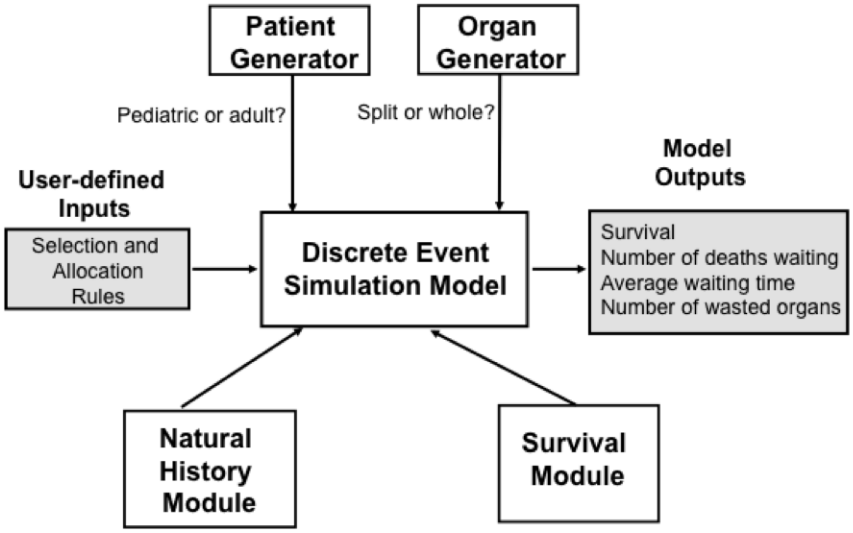

Figure 1: Basic DES Structure. There are four main modules of the simulation: a patient generator, an organ generator, a natural history module and a survival module. Users define selection, allocation, and acceptance rules, and the model produces various statistics including patient survival, the number of deaths waiting for a liver, the mean waiting time, and the number of wasted organs.

2.2 Patient and Organ Generation

When a simulated patient arrives on the waiting list, his initial clinical characteristics are taken from a real patient's initial characteristics from the UNOS database of over 150,000 patient registrations. (Patients may have multiple registrations resulting from multi-center listings, reneging, and retransplantation needs). These characteristics include age, gender, race, and various laboratory values. On the basis of these characteristics, he is placed on the waiting list at a position determined by the user-defined priority rule.

When a deceased- or living-donor organ arrives, its initial clinical characteristics are taken from a real donor organ's initial characteristics from the UNOS database. These characteristics include age, sex, race, donor region, blood type, and cytomegalovirus (CMV) antibody status. If the organ is suitable for transplantation, it is then determined whether it will be split, and ultimately, enter the patient-organ matching process. If a patient accepts the liver, he will enter the post-transplant state. Otherwise, his natural history is updated in the manner described in the Section 2.3.

2.3 Natural History

It is very important to accurately model a patient's natural history, because his transplant timing decision will depend on his disease trajectory. For example, if a patient's health is progressively improving, it may be beneficial for him to wait and reject an offered liver, as transplantation imposes substantial risk both during and after the procedure. Similarly, if a patient's health is progressively deteriorating, he may not benefit from transplantation and the donated organ may be better suited for another patient. The natural history module of our DES consists of updating every patient's health at distinct time points prior to transplantation. The time between updates depends on patient age group, disease group, and location. It ranges from six hours for children with acute liver failure to 30 days for outpatient adults with chronic liver disease. Patient health state is defined as a vector of clinical characteristics that are commonly used to evaluate the severity of liver disease in both children and adults. This vector of clinical covariates consists of continuous measures such as total bilirubin, serum creatinine, albumin, and international normalized ratio (INR), as well as discrete measures such as patient age group, location (e.g., intensive care unit, hospital, and home), presence or absence of encephalopathy, and ascites.

Clinical data are often subject to various inconsistencies that make it difficult to incorporate into a DES. For example, some data are recorded at irregular time intervals, missing one or more clinical values, and contain different levels of detail for different patients. We resolve many of these difficulties by fitting each laboratory value for every patient in the UNOS dataset to a continuous function that can be sampled at regular intervals using cubic spline interpolation. By using laboratory values estimated from cubic splines, a simulated patient waiting for a transplant can have his health state updated at arbitrary intervals. This method of cubic spline interpolation for clinical data is described in (Alagoz et al. 2005).

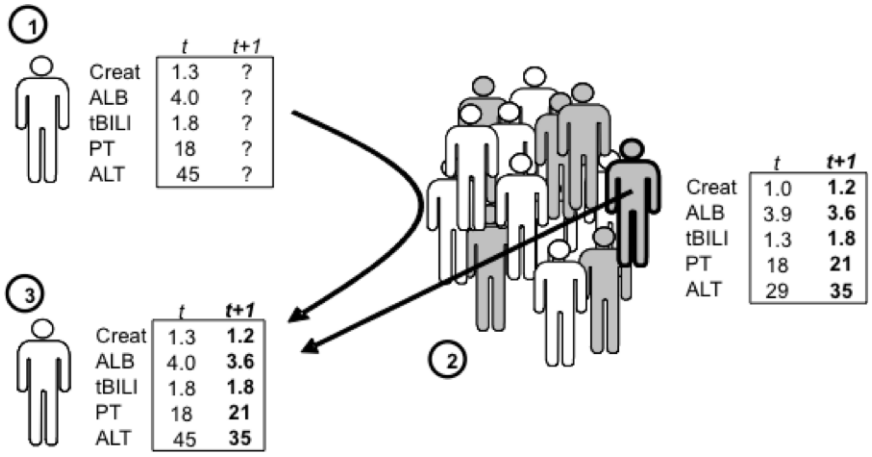

Figure 2: Updating a patient's natural history. 1) Consider a 42 year old male with hepatitis C at time t. 2) Among all 40-50 old male patients with hepatitis C at time t', we uniformly sample one with a "similar" laboratory profile. 3) The "similar" patient's values at time $t'+1$ become the current patient's values at time $t+1$ and the process repeats.

In the natural history module, we predict the vector of clinical covariates for each patient i at time $t+1$ given his health at time t, until the patient is either transplanted or dies. In other words, we seek $\mathbf{X}_{i,t+1} = f(\mathbf{X}_{i,t})$ over the time points in $\{0,1,2,\ldots min(T_i-1, D_i-1)\}$, where T_i is the time of patient i's transplant and D_i is the time of patient i's pre-transplant death. When a simulated patient i arrives on the waiting list at time $t=0$, his initial vector of clinical covariates, $\mathbf{X}_{i,0}$ is taken from a real patient who is uniformly sampled from the UNOS dataset. Once patient i has been initialized, we update his vector by choosing values from an empirical distribution of all "similar" patients within the UNOS dataset with the same, or related age group and disease etiology. To determine the subset of similar patients within the

dataset, we first assign a truncated normal distribution over the range of times covered by the relevant cubic spline estimates, with a mean time equal to our simulated patient's current time, and a standard deviation of 24 hours. Once we draw a particular time point t', we collect the all patients, j whose vectors of covariates $\mathbf{X}_{j,t'}$ are similar to that patient i's vector $\mathbf{X}_{i,t}$. A patient's vector at the chosen time t' is considered similar to our simulated patient i's vector at time t if $\mathbf{X}_{j,t'}$ falls within a hypercube centered at $\mathbf{X}_{i,t}$. The dimensions of the hypercube have been established and validated by a panel of leading hepatologists (Alagoz et al. 2005). Once we have the subset of patients at time t' that fall within the hypercube and are hence "similar" to our patient at time t, we select a patient j' from this subset according to a normalized distance from $\mathbf{X}_{i,t'}$ and assign his vector of covariates at time $t'+1$ to patient i's at time $t+1$, i.e. $\mathbf{X}_{i,t'+1} \leftarrow \mathbf{X}_{j,t'+1}$. To ensure that the patient's covariates over time represent an adequate sampling of many different patients, we impose that that if the number of patients in this subset is less than three, first increase the standard deviation of the distribution of times by 24 hours, and only then increase the acceptable range of covariate distances. If patient i is not transplanted and does not die (based on probabilities determined from our pre-transplant survival probabilities, discussed in Section 2.4), this process repeats for the next time period. If the patient is transplanted, he enters the post-transplant, alive state. Otherwise, he enters the absorbing state death. This process of updating a patient's natural history is illustrated in Figure 2.

2.4 Survival Models

Whether awaiting a liver from either a deceased or living donor, there is a chance that the potential recipient will die prior to receiving a transplant offer. Standard survival models such as Cox regressions cannot be used to estimate pre-transplant survival because the same conditions that increase a patient's likelihood of dying also increase the patient's likelihood of moving up the waiting list and getting transplanted. In other words, when a patient becomes sicker and more likely to die, he is more likely to receive an organ and become censored from the analysis. To resolve this problem of informed censoring, we use a competing risks survival model to predict the risk of death in the absence of transplantation (Chang and Callaghan 2008). Additionally, if the acutely injured liver recovers, we are able to determine factors responsible for the liver's improvement.

Post-transplant survival is estimated with a Cox proportional hazards model, similar to the model used in our prior work (Roberts et al. 2004). To simulate the possibility of graft failure, the model generates a patient survival time and a graft survival time. If the patient survival is less than the graft survival, the patient dies and exits the simulation. If the graft survival is less than the patient survival, the patient is relisted in the simulation at a time before the graft failure time. We estimate both disease-specific models, in which survival for each disease group is calculated separately, and a general model, in which a disease group variable is included in the overall model.

3 EXPECTED MODEL OUTPUTS

Our model will calculate individual patient survival with and without transplant at every time point, in addition to overall statistics such as the number of deaths while waiting for a liver, waitlist additions, the number of liver transplants performed, and the number of wasted livers. Knowing survival with and without a transplant at every time point will allow us to optimize transplant timing decisions for both pediatric and adult patients. It will also allow us to evaluate current prioritization schemes such as the MELD and PELD scores, which are currently used to determine a patient's position on the waiting list.

4 LIMITATIONS AND FUTURE DIRECTIONS

This is still a work in progress, and therefore model output is still pending. One difficulty often encountered when working with clinical data is that information is recorded irregularly and is generally more complete during disease exacerbations. For example, when a patient is in the intensive care unit (ICU), data might collected daily, or even hourly. When a patient is at home however, data are only collected weekly, or

monthly. This makes the spline fitting method a necessary, but inherently imperfect option. Additionally, ESLD has several dozen etiologies for both children and adults, some of which are extremely rare. Due to limited data, a separate analysis for each diagnosis is not possible. Hence, we must reduce adult diagnoses to a group of five categories and pediatric diagnoses to a group of 10 categories that have been validated by a panel of leading hepatologists.

5 CONCLUSIONS

We will use this DES to determine the optimal time to perform a liver transplant for both pediatric and adult patients. We will also use our survival models to determine whether the MELD and PELD scores are indeed accurate predictors of pre- and post-transplant survival, and if not, develop alternative scoring systems. Other policies we wish to consider are whether suitable livers should be split, and if so, whether they should be split before or after being offered to the recipient. Changes to the organ donation policy will also be evaluated, such as the effect on liver transplant outcomes if the United States replaces its opt-in donation policy with an opt-out one. The robustness of our model to evaluate nearly arbitrary policies on a societal, individual, and biological level will make it an invaluable resource in informing the transplant community and its policymakers.

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REFERENCES

Alagoz, O., C. L. Bryce, S. Shechter, A. Schaefer, C.-C. H. Chang, D. C. Angus, and M. S. Roberts. 2005. "Incorporating Biological Natural History in Simulation Models: Empirical Estimates of the Progression of End-Stage Liver Disease". *Medical Decision Making* 25 (6): 620–632.

Alagoz, O., L. M. Maillart, A. J. Schaefer, and M. S. Roberts. 2004. "The Optimal Timing of Living-Donor Liver Transplantation". *Management Science* 50 (10): 1420–1430.

Alagoz, O., L. M. Maillart, A. J. Schaefer, and M. S. Roberts. 2007a. "Choosing Among Living-Donor and Cadaveric Livers". *Management Science* 53 (11): 1702–1715.

Alagoz, O., L. M. Maillart, A. J. Schaefer, and M. S. Roberts. 2007b. "Determining the Acceptance of Cadaveric Livers Using an Implicit Model of the Waiting List". *Operations Research* 55 (1): 24–36.

Chang, C.-C. H., and F. M. Callaghan. 2008. "Use of Classification Tree Techniques To Determine the Likelihood of Pretransplant Death Among Patients Awaiting Liver Transplantation". In *Proceedings of the 2008 Joint Statistical Meetings*. Denver, Colorado: The American Statistical Association.

Pritsker, A. A. B., D. L. Martin, J. S. Reust, M. A. Wagner, O. P. Daily, A. M. Harper, E. B. Edwards, L. E. Bennett, J. R. Wilson, M. E. Kuhl, J. P. Roberts, M. D. Allen, and J. F. Burdick. 1995, December. "Organ transplantation policy evaluation". In *Proceedings of the 1995 Winter Simulation Conference*, edited by C. Alexopoulos, K. Kang, W. R. Lilegdon, and D. Goldsman, WSC '95, 1314–1323. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.

Roberts, M. S., D. C. Angus, C. L. Bryce, Z. Valenta, and L. Weissfeld. 2004. "Survival after liver transplantation in the United States: A disease-specific analysis of the UNOS database". *Liver Transplantation* 10 (7): 886–897.

Shechter, S. M., C. L. Bryce, O. Alagoz, J. E. Kreke, J. E. Stahl, A. J. Schaefer, D. C. Angus, and M. S. Roberts. March/April 2005. "A Clinically Based Discrete-Event Simulation of End-Stage Liver Disease and the Organ Allocation Process". *Medical Decision Making* 25 (2): 199–209.

Thompson, D., L. Waisanen, R. Wolfe, R. M. Merion, K. McCullough, and A. Rodgers. 2004. "Simulating the Allocation of Organs for Transplantation". *Health Care Management Science* 7:331–338. 10.1007/s10729-004-7541-3.

United Network for Organ Sharing 2011. "View Data Reports". Information accessed on March 25, 2011, http://www.unos.org/data.

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