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INCORPORATING BIOLOGY INTO DISCRETE EVENT SIMULATION MODELS OF ORGAN ALLOCATION

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ABSTRACT

We describe a discrete event simulation model of the national liver allocation system. This model differs from previous modeling efforts in that it considers the natural history of the disease independently of any particular patient priority scheme, thus allowing an unbiased appraisal of various allocation schemes. We provide the basic structure of the model, which consists of patient and organ generators, a survival module, and a disease progression module. The model provides various outputs such as patient survival, financial cost, and the number of wasted organs. We describe our model of patient survival with and without a transplant. We discuss some difficulties estimating model parameters due to a lack of appropriate medical data, and how these difficulties were overcome. We close with conclusions and directions for further research.

1 INTRODUCTION

The allocation of scarce donated organs is both an increasingly complex clinical and social problem as well as an excellent example of the general problem of optimization under constraints, which is a common analysis structure in engineering but has been used rarely in medical care. In the case of livers, for example, there are now over 4,000 liver transplant procedures performed each year in the U.S. (UNOS 1999), but this represents only a fraction of the potential transplants as the number of people on the waiting list now exceeds 17,000 (UNOS 2002). The growth of the waiting list has produced substantial debate about the mechanisms for allocating organs to potential recipients, with issues of fairness, efficiency and regional versus national interests complicating the discussion (Ubel and Loewenstein 1996, McMaster 2000).

Our modeling efforts rely on discrete event simulation (DES) instead of a randomized control trial, which is the more standard experimental design in medical research. However, because transplantation has been widely adopted and considered effective, it would be impossible to "randomize" patients between treatment and non-treatment. Furthermore, we focus on many questions, such as the optimal timing of transplantation, that are not suitable to randomization. Although the issues we raise pertain to all vital organ transplantation procedures, our work and this paper focus specifically on liver transplantation.

The purpose of this project is to inform this debate with a rigorous, clinically realistic model of end stage liver disease (ESLD) that is adequately robust to predict the expected effects of different selection and organ allocation rules in terms of life expectancy, size of waiting list, number of wasted organs, and other relevant outcome characteristics of the transplantation process. Although the model is designed to incorporate costs and quality of life, those components, which are not central to the design and structure of the model, will not be discussed here. Instead, we focus on background and basic structure, two of the most fundamental components/estimates of the model (survival both with

and without transplantation given patient characteristics), model outputs, and limitations and future directions. In this paper we report the methods by which we have included clinical realism into a DES model of the organ allocation system, and present a series of modeling issues that arise through the desire for clinical realism.

1.1 Prior Modeling Efforts

There have been two prior modeling efforts designed to address these issues. Over 10 years ago, The United Network for Organ Sharing (UNOS) developed the UNOS Liver Allocation Model (ULAM). This model used discrete event simulation to model the process by which candidates are listed, organs are made available for transplantation, and the matching criteria between these processes (Pritsker et al. 1995). The model has primarily been used to estimate the effects of changing from a regional to national waiting list. In a similar effort, a private research consulting firm, CONSAD, constructed a simulation model to incorporate several additional characteristics (technology advance, survival improvement) to address many of these same issues (CONSAD 1995). A potential flaw in both of these modeling efforts is that the description of natural history (how patients become "sicker") was estimated entirely through probability distributions that describe how patients move through the *existing* priority scheme for allocation, preventing an unbiased analysis of any organ allocation scheme significantly different than the current mechanism.

1.2 Basic Structure of the Model

The major motivation for the structure of the simulation model is the need to separate the modeling of the biology and natural history of the disease from the allocation and selection mechanism. This allows an arbitrarily large set of allocation rules to be examined. Another motivation for the direct and clinically realistic modeling of the biology is the need for transplant clinicians to have faith in the results. Any policy based on models that clinicians believe to be overly simplistic or that do not include factors that clinicians know to be relevant to prognosis will be intellectually (and pragmatically) ignored.

The basic structure of the model is presented in Figure 1. A patient generator and an organ generator create patients with liver disease and organs for donation according to the empiric probability distributions found within the UNOS database. A survival module and a disease progression module predict the time-course of individual patients as they progress through their disease, and estimate pre- and post-transplant mortality and retransplantation. Standard DES techniques are used to match patients to organs from a queue (the waiting list). Organ allocation policies are implemented as user-defined inputs.

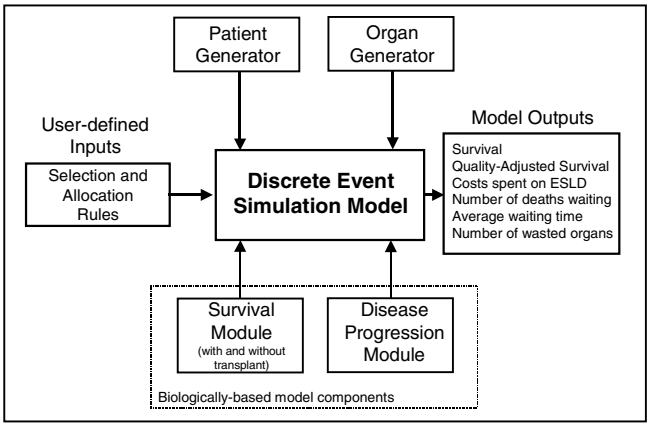

Figure 1: Basic Structure of the DES Model

DES traditionally uses random draws from distributions, because it is essentially a "time-to-event" technique. However, several model-derived events (e.g., patients receiving an organ) are stochastic and not predictable in the absence of model operations.

2 SURVIVAL IN THE ABSENCE OF LIVER TRANSPLANTATION

The progression of disease in patients awaiting a particular medical intervention (liver transplantation) is important to incorporate in the DES model because it allows us to understand the net gain or reduction in survival based on different timing decisions. The right timing matters, as the transplant procedure itself poses varying risks to the patient in terms of short-term outcomes and long-term survival depending on the course of illness. Essentially, patients need to be "sick enough" but not "too sick" to benefit from transplantation. Because the supply of donor organs is severely limited, suboptimal timing of the procedure impacts both the transplant recipient and other candidates who might have received greater benefit (in terms of either life expectancy or quality-adjusted life expectancy) had they received the transplant instead.

For the purpose of this model, we describe disease progression as the time course of a series of clinical variables that predict future survival. In the case of organ transplantation, this natural history might begin with the date that a patient is placed on the transplant waiting list ($t = 1$) and continue until date of death in the absence of transplantation ($t = T_i$ for each patient i). At $t = 1$, individuals start with a specific set of values for the vector of clinical covariates. We then want to "age" the clinical variables in subsequent time periods as members of the cohort progress through the simulation. In other words, for any patient i, we want to predict the covariate vector at time $t+\Delta t$, given information provided at time t, that is, $\boldsymbol{X}_{i,t+\Delta t} = f(\boldsymbol{X}_{i,t})$. The predicted values of the covariates need to be incremented and updated by the expected amount that

would occur in the time that has transpired. We continue updating the variables for each time period until either transplantation or death. Because of the chaotic and stochastic nature of changes in clinical status, we cannot simply predict the average level of change of a variable, but need specific changes proportional to the extent to which changes of a given magnitude occur.

Theoretically, this goal is a straightforward one. In practice, however, clinical data are not compatible with estimating disease progression in this way. Although hospitals maintain pre-transplant information over time for potentially large patient cohorts, our experience has identified at least five shortcomings with the structure of the data. First, the panel is unbalanced and does not contain the same number of observations (timepoints) for each patient. Some patients are observed only once while others have several hundred timepoints in the data set. Second, the intervals between observations frequently do not match the cycle length of the model. For example, liver function may be recorded daily during a hospital admission, but not more than monthly or yearly in the outpatient setting. When this occurs, we need an estimate of the clinical covariates at appropriate intervals matching the model's cycle length. Third, data are not collected at random times during the pre-transplant period. Instead, laboratory tests are typically ordered when patients experience problems and seek treatment, giving us the greatest level of detail during atypical, highly skewed periods (the sickest times in a patient's natural history). Fourth, dimensionality of the vector $\boldsymbol{X}_{i,t}$ matters. Liver function, and the effect of liver disease on other important physiological functions, are not scalar measures; we define it in terms of four continuous measures that change over time (total bilirubin, creatinine level, albumin, and prothrombin time), as well as several binary variables indicating the presence of risk factors (e.g., diabetes, ascites). The dimension of $\boldsymbol{X}_{i,t}$ is important both in terms of the number of values we must predict and because the covariates are correlated with one another (i.e., the off-diagonal terms of the covariance matrix are not zero). Fifth, complete clinical data are not measured at every time point. Our original natural history database contains more than 50,000 records, but whereas values for creatinine are available 80% of the time, information for albumin is complete less than 30% of the time.

Our approach for updating clinical covariates over time is to choose values from an "empirical distribution" of all similar types of patients. An example of a single variable in a single patient is illustrated in Figure 2. We begin by using the patient's pre-transplantation data for time periods $t \in [1, T_i]$ to estimate a spline function (either an interpolating spline function that exactly connects the observed data points or a smoothing spline function that chooses an approximate fitted value), spanning T_i days and providing us with an estimate of the vector $\boldsymbol{X}_{i,t}$ at any intervening time point. In our example, every patient has 4

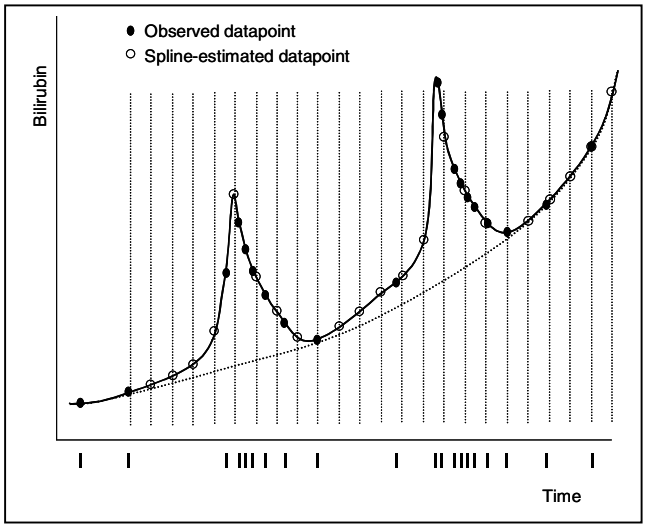

Figure 2: Hypothetical Example of Natural History Data Problems

such spline functions, one for each continuous clinical covariate used to measure liver function (total bilirubin, creatinine level, albumin, and prothrombin time).

For patient i moving through the simulation model with $\boldsymbol{X}_{i,t}$, we provide an estimate of $\boldsymbol{X}_{i,t+\Delta t}$ (where the interval Δt is based on the cycle length of the simulation model) in the following manner. We choose all patients from the database with covariates that "look like" (according to a defined nearness criterion) those of patient i at some point during their natural history. We randomly select one of these patients and use the values of his spline function Δt days later as the updated values for $\boldsymbol{X}_{i,t+\Delta t}$. If patient i is not transplanted and does not die in the next cycle of the model, the covariate vector will again be updated by forming a new empirical distribution based on patients who are now clinically similar to $\boldsymbol{X}_{i,t+\Delta t}$.

There are several desirable features of this approach. First, the panel can be unbalanced and patients are not required to have the same number of timepoints, although they are required to have a minimum of two timepoints. Second, the interval Δt between observations is not important because the spline function allows us to estimate values for clinical covariates for any desired cycle length. Third, we do not need to know the covariance matrix among the clinical covariates because all four spline functions for every individual are anchored at the same beginning and ending timepoints. Although we cannot specify the exact relationship among the clinical measures, we know that they are correlated and the spline functions essentially provide us with an empirical estimate of how the measures move together over time. Fourth, although the vector for the first and last time point must contain complete data for all four covariates, partial data is acceptable for the intervening observations. Certainly, more detail is always preferred, but we do not have to discard observations for encounters that per-

formed only a subset of laboratory tests. An obvious limitation of this method is that our current measure of "nearness" only takes into account the level of the variables in the covariate vector and ignores the rate of change. Future nearness measures will incorporate first derivative or rate of change in the parameter as well whenever a third timepoint for each patient is available.

3 SURVIVAL AFTER TRANSPLANTATION

There are two survival issues: pre-transplant survival and post-transplant survival. The pre-transplant survival issue considers the possibility of patient death prior to transplantation, typically due to a complication of end-stage liver disease. Our model must accurately estimate the post-transplant survival given biological characteristics of the patient, the quality of the graft (transplanted organ), and patient-graft interactions at time of transplant. Furthermore, any model of post-transplant survival must consider the possibility that the graft will fail, requiring further transplantation.

Because of its prevalence in estimating patient survival, our model uses a Cox Proportional Hazards model to estimate the survival probability distributions (Cox 1972). The Cox model produces a *baseline* hazard function, and then adjusts this function depending on the covariates that describe the patient and organ characteristics. While the Cox model is frequently utilized in the medical literature to estimate patient survival, most of these models are used to compare survival between groups or describe survival as a function of covariates. Our model requires a *specific* survival time for an individual given a set of clinical characteristics for each patient who receives a transplant. Therefore, our model generates a pseudorandom observation from the survival function. One advantage of our approach is that the entire distribution is considered rather than just its mean. To simulate the possibility of rejection and organ loss, the model generates two survival times: one for the patient, and another for the graft. If the patient survival is shorter than the graft survival, the patient dies and is no longer considered in the system. The graft is discarded as well since organs are never transplanted more than once. If, however, the graft fails before the patient, then the patient requires another transplant and is relisted in the simulation. This is not an insignificant possibility; approximately 11% of transplanted patients are later retransplanted (UNOS 1999). Clearly, simply replacing the survival times by their expectations is unsatisfactory.

4 MODEL OUTPUTS AND APPLICATIONS

Once a working model incorporates biology, we can use it to calculate survival both with and without a transplant at any (every) point in the patient's trajectory and optimize the timing decision for choosing to transplant. This clearly ignores the donor organ shortage and the fact that a donor liver may not be available at the time considered optimal; nevertheless, it provides a much-needed clinical benchmark by which we can compare current practice.

After validating the model by replicating the existing liver allocation system, we can test the effects of changing the liver allocation policy.

5 LIMITATIONS AND FUTURE DIRECTIONS

There are several difficulties in modeling natural history. The procedure above describes estimating the natural history of a homogeneous condition, but it becomes more complicated for heterogeneous conditions. ESLD has more than 60 diagnoses and etiologies; the rate of liver deterioration varies with diagnosis. A national clinical oversight committee of transplant clinicians aggregated these clinical diagnoses into 10 categories for the purpose of estimating survival. For modeling purposes we have grouped those into 5 broad diagnostic categories. In addition, we apply different cycle lengths depending on whether the patient is out of the hospital (cycle length = 30 days) or in either the hospital or the intensive care unit (cycle length = 1 day). Therefore, we have created 15 (5 aggregate diagnoses $\times$ 3 locations) empirical distributions from which we draw the updated covariate vectors. As a result, there are less data (fewer patients, fewer timepoints) on which to develop the empirical distribution and compute the updated vectors.

The other major limitation associated with the natural history model is the availability and completeness of data for estimating spline functions and updating the clinical covariates. The transplant candidate registry maintained by UNOS provides a list of all liver transplant candidates, but currently records no clinical data until transplantation. The Liver Transplant Database developed by NIDDK only collects natural history data at two timepoints, the time of listing and at transplantation. Therefore, the only database available to us with sufficient natural history detail is based on patients at our own institution, the University of Pittsburgh Medical Center (UPMC). UPMC is historically the largest transplant center in the country; however, its patients may not represent the ESLD population in general, biasing our current estimates of disease progression towards sicker patients. Nevertheless, the work presented here serves as a "proof of concept" for estimating natural history and incorporating disease progression into DES models. Our future research agenda includes efforts to construct a multi-site database across several representative transplant centers nationally and collect standardized clinical data on liver transplant candidates throughout the pre-transplant period.

In addition, Chang, Weissfeld and Valenta have shown that Cox models may contain biases in those variables that vary dynamically (Weissfeld et al. 2000). Basic assumptions imposed by Cox models, such as proportional hazards, may

not be satisfied when modeling post-transplant survival. Further enhancements to the survival model component will allow the effect of covariates to vary over time.

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