ABSTRACT

This paper on the UNOS Liver Allocation Model (ULAM) describes the building of a simulation model that supports policy evaluation for a national medical problem. The modeling and simulation techniques used in building ULAM include: fitting donor and patient arrival processes having trend and cyclic rate components using non-homogeneous Poisson processes (NHPPs) having exponential rate functions which may include both a polynomial and some trigonometric components; fitting distributions to data on transition times between states of medical urgency, application of variance reduction techniques using common random-number streams and prior information; organizing data structures for efficient file searching and ranking capabilities; the use of bootstrapping techniques for attribute sampling; the building of submodels employing biostatistical procedures such as Kaplan-Meier and logistic regression; and the characterization of performance measures within a complex political, economic and social environment. ULAM provides a means for producing quantitative information to support the selection of a liver allocation policy.

DESCRIPTION OF THE MEDICAL PROBLEM

Organs for transplantation are a scarce resource. The number of people who donate organs has not kept pace with increasing demand. Thousands of people wait for organs every year, with many dying while they wait. The list of waiting patients continues to grow at a faster rate than the number of donors.

How to allocate such a scarce and valuable resource is indeed complex. Much is at stake among doctors, Organ Procurement Organizations (OPOs), transplant centers, and, without question, the potential recipients. Issues revolve around what is an equitable, efficient and effective means of organ distribution. The United Network for Organ Sharing (UNOS) has the responsibility for setting policy to make this trade-off between medical utility and justice among patients. (Pritsker et al 1995)

PROJECT OBJECTIVE

The objective of the project is to develop the UNOS Liver Allocation Model (ULAM) for comparing proposed alternative allocation policies. The operative word in the objective is “comparing” as it allows the elimination of components which are presumed to not have an impact on the comparison of policies.

A model specification document was written which describes the entities, events and component models for arrival streams of donors and patients, the patient status change process, the offering and acceptance of grafts by doctors/patients and the relist and survivability functions relating to patient post-transplantation status. A specification for the reports and displays to be included within ULAM was also detailed. The policies to be evaluated initially using
ULAM were limited to those prescribed in terms of patient health status and the geographical areas where patients wait. SLAM SYSTEM (Pritsker Corporation 1992) was selected as the simulation language for ULAM because of its flexibility and advanced data structure capabilities. The specification was approved by the Allocation Modeling Oversight Committee of UNOS.

OVERVIEW OF ULAM

Figure 1 presents an overview of ULAM. Starting on the left of Figure 1, we see that the arrivals to the system are donars and patients. Either historical or generated streams of arrivals can be processed with ULAM. Historical information was available from 1990-1994. To fit the interarrival distributions of donors to 65 OPOs and patients to 132 Liver Transplant Centers, we used an estimation procedure employing a non-homogeneous Poisson process (NHPP) having a rate function that is exponential-polynomial-trigonometric with multiple periodicities. For example, given the time $t_i$ for the $i$th patient to arrive at transplant center 2 (expressed in days since the start of January 1, 1991), the distribution function for the next arrival time $t_{i+1}$ is

$$F_{t_{i+1}}(t) = 1 - \exp\left[-\int_{t_i}^t \lambda(z)dz\right],$$

where $\lambda(z) = -4.2747 + 0.00096752z + 0.15562 \sin(z+2\pi/365+1.9728)$

$+ 1.2617 \sin(z+2\pi/7+0.45698)$

$+ 2.3340 \sin(z+2\pi/2.4037).$

Notice that the three trigonometric rate components represent cyclic effects with periods of one year, one week, and one day, respectively.

The characteristics of the donors are determined using a bootstrapping technique which randomly selects the characteristics of a generated donor from the 1990 to 1994 donors. The characteristics of a donor include: age, weight, sex and blood type. The listing of a patient at multiple transplant centers is allowed in accordance with UNOS policies.

For the initial waiting list of patients, ULAM includes the actual waiting lists that existed at the beginning of each year from 1992 through 1994. A patient is added to the waiting list when the patient arrives. A patient is transplanted and taken off the waiting list when an organ is offered and accepted for that patient. An allocation policy selects a subset of waiting patients in accordance with their medical status and proximity to the donor location and ranks the patients in the subset by points assigned based on medical status, blood type compatibility and waiting time. This requires patient waiting lists to be organized by medical status transplant center location. The definitions of medical urgency status are:

- **Status 1**: Patients must be in an Intensive Care Unit (ICU) due to acute or chronic liver failure and have a life expectancy of less than 7 days without a transplant.
- **Status 2**: Patients have been continuously hospitalized in an acute care bed for at least five days, or are ICU bound.
- **Status 3**: Patients require continuous medical care.
- **Status 4**: Patients are at home and functioning normally and for whom liver transplantation would be an elective procedure.
- **Status 7**: A patient listed as Status 7 is temporarily inactive; however, the patient continues accruing waiting time up to a maximum of 30 days.
- **Status 8**: A patient died while waiting for a transplant.
- **Status 9**: A patient has been removed from the waiting list and is no longer considered as part of the UNOS system.

The policies employ a point ranking scheme where waiting time points are based on the rank of the longest waiting patient in the waiting list, that is, $10^*(1+N-R)/N$ where $N$ is the number of patients in the list and $R$ is the patient's rank. The patient with the longest waiting time has rank $N$. In addition, points are assigned based on status (24, 18, 12, 6)

![Image of Figure 1: Overview of ULAM](image-url)
and on blood type compatibility (10, 5, 0). This necessitates creating and reranking of the lists at every graft arrival. With as many as 6,000 patients on the waiting list and approximately 4,000 donors per year, the procedure for implementing the ranking of patients according to the allocation policy requires efficient data structures and computational procedures. A model built prior to ULAM required 4 hours on UNOS’s mainframe computer for a 1 year run which ULAM performs in 40 seconds on a notebook computer.

When a donor arrives, the quality of the organ recovered from the donor is assessed. Data available at UNOS permits the modeling of organ quality as a function of the age of the donor. The organ is then offered to the patient ranked highest by the allocation policy. The probability of accepting an organ by the doctor/patient is a function of recipient status. ULAM includes a Monte Carlo procedure for this acceptance process, where the probability of acceptance is a function of the medical status of the patient and the quality of the organ offered. If the organ is not accepted, then the next highest ranking patient is offered the organ. This continues until the organ is accepted or all patients have been considered.

A patient is removed from the waiting list when transplanted with an organ which is referred to as a graft. The future status of the transplanted patient is then determined by comparing the time-to-patient relist with the time to patient death. Relist functions have been developed for each medical status using a technique developed by Kaplan and Meier (1974). The relist data was derived from the 1991-92 time period which allowed a two year follow-up period to determine if a patient was relisted. For this same time period, the patient’s mortality following the transplant was determined. A logistic regression approach was employed for determining the mortality rate as a function of: (a) transplant center volume (number of transplants per year); (b) patient condition as reflected by the patient’s medical status; and (c) whether the patient had a previous transplant.

Status Change Event

As patients wait for a transplant, their medical status changes. When a nonhistorical patient arrives in the model an initial probability table is used to assign a medical urgency status to the patient. To model status change, a transition probability matrix, that is, a Markov chain, is constructed which models the probability of a change from one status to another in one day. The transition probabilities are estimated from a count of the number of times a daily transition was made from one status to another divided by the total number of daily transitions from the particular status. More advanced techniques for modeling status change are currently being investigated.

User Interfaces and Output Variables

To build or modify ULAM, the standard SLAMSYSTEM modeler’s interface is used. To run ULAM, SLAMSYSTEM’s user interface was adapted to select policies and to specify control parameters such as run length, number of runs and data sources. From the user interface, the outputs of ULAM can be browsed. The outputs used in evaluating allocation policies fall into the following categories:

Medical Utility
* Number of people transplanted
* Percentage of patients surviving transplantation
* Number of pre- and post-transplant deaths
* Surrogate measures of costs
* Number of patient-days in each medical status
* Percentage of transplants by medical status
* Distance the organs travel

Justice
* Percentage of patients transplanted by status
* Waiting time by patient and regional characteristics
* Number of pediatric patients transplanted

LIVER ALLOCATION POLICIES

Many allocation policies have been suggested. ULAM has been run for over 20 different policies. Five policies were selected for detailed assessment. Three of the policies specify a grouping of waiting patients according to a geographical area and a medical urgency status, for example, consider local patients in Status 1 (L1) first, then local patients in Status 2 (L2), etc. For policy specifications, local means patients waiting at Transplantation Centers associated with the OPO at which a donor arrives. Regional means the current UNOS regions.

Policy 1 is the current allocation policy and is designed to balance patient need for a transplant with successful transplant outcome. In order to limit organ travel distance, the policy allocates liver organs to the local patients first, followed by regional patients, and then patients on the national list. Patients who have the highest medical urgency for a liver transplant are looked at first in any given level. Status 3 and 4 patients are grouped together. Codes for each policy are given in the following form: [L1,2,3/4, R1,2,3/4; N1,2,3/4].

Policy 3.2 allows for broader sharing of liver organs to Status 1 and then Status 2 patients on a local and regional basis. Local allocation to Status 3 patients is made prior to national allocation to Status 1 patients. No transplants are made to Status 4 patients. [L1, R1, L2, R2, L3, N1, R3, N2, N3]

Policy 5 allocates liver organs to local Status 1 patients first then national Status 1 patients followed by local Status 2 patients and national Status 2 patients, followed by local Status 3 and 4 patients, followed by
national Status 3 and 4 patients. This policy resembles a single national list and allows broader national sharing to the most medically ill patients. [L1, N1, L2, N2, L3/4, N3/4]

Policy 20 and 21 use a different scheme to distribute liver organs. They are based on circles around the donor hospital that contain a fraction of the total list of patients waiting. Policy 20 has circles of 5, 20 and 100 percent and Policy 21 has circles of 15 and 100 percent.

ANIMATION, VERIFICATION AND VALIDATION

An animation was developed which illustrates the flow of grafts to patients. Figure 2 is a snapshot of the animation screen showing the delivery of liver grafts to patients in accordance with UNOS regions. The color of the grafts and patients indicate their blood types. Also shown on the animation are the total distance traveled by all grafts and the current simulated time. A second animation shows a dynamic table which updates the number of transplants, pre-transplant deaths and patients removed from the waiting list by UNOS region. The animation helped to verify that ULAM operates the way it was intended.

ULAM was validated by comparing each component model output as well as the total system model output to actual results over the 1992-94 time period. For example, for the donor streams, the stochastic process that was generated over four years (1991-94) was fitted with three years of data (1991-93) and used to project 1994 donor arrivals. The projection of 1994 was deemed acceptable.

To gain acceptance for the model, ULAM was presented to many individuals and groups within the transplantation community at various UNOS committee meetings. Each UNOS meeting is open and outside interested parties, and other modelers were in attendance. Their suggestions and recommendations were considered and included in ULAM after careful evaluation. Acceptance of the model was obtained through a review of the component models and through reviews of the outputs of ULAM for the various policy comparisons for which ULAM was built. This acceptance/auditing step is an important part of the simulation modeling process. (Withers, Pritsker, and Withers 1993)

ULAM OUTPUTS AND PERFORMANCE MEASURES

An overview of the policy comparisons for five policies assessed is given in Figure 3. These results are for generated donor and patient arrivals during 1995 through 1997 for 10 runs. These outputs show that the number of non-repeated transplants, that is, the number of different patients that are transplanted, differs over the five policies. The difference increases as a policy transplants the sicker patients which have a higher relist probability. When a patient is relisted, a numerically lower medical urgency status is typically assigned, giving relisted patients a higher priority for transplantation. This is reflected in the model output in terms of the number of different patients transplanted as well as the number of Status 1 patients transplanted. Pediatric patients usually are assigned a numerically lower medical urgency status and this is reflected in the number of pediatric transplants that occur for those policies that transplant Status 1 and Status 2 patients nationally prior to treating Status 3 patients locally or regionally.

The number of days in status is a cost-related measure, as it indicates the number of days patients would be in the hospital and in intensive care units. It can be seen that there are a large number of patient-days in Status 3 which requires continuous medical monitoring and, if these patients are in the hospital, would reflect an added cost for those policies that have a low percentage of transplants for Status 3 patients.

The share type measures relate to the use of grafts locally. Currently there is a debate in the transplantation community as to whether a low percentage of grafts used locally would adversely affect the donor rate. If it does, there is a secondary effect, not included in ULAM, of a potential decrease in the donor arrival rate for such policies. In the outputs presented in Figure 3, the percent of transplants locally and regionally is given in accordance with the OPO definition of local and regional boundaries even though states, super-regions and percent circles may be used in the allocation policy. Distance measures may have an impact on transplantation survival rates as the longer a graft is delayed before its use, the greater its possible deterioration.

With regard to death measures, ULAM presents quantitative information reflecting the intuitive and experiential nature of the different policies. Expectations were that the current policy would experience more pre-transplant deaths because it is not
Figure 3. ULAM Policy Comparisons for 1995-97.

Figure 4. Policy equity analysis by region historical data 1992-94.
oriented to transplanting national Status 1 patients before local and regional patients. Policy 5 is more oriented to transplanting Status 1 patients first. Policy 3.2 is a compromise, and the output measures reflect this. By transplanting less sick patients, the number of post-transplant deaths is decreased and the quantitative values for this are shown. The total number of deaths occurring during the three year simulation period indicates the largest difference is 100 deaths between policies 5 and 1. For these two policies, the difference in the waiting list at the end of the simulation is 1076 patients. The larger number of patients waiting at the end of the simulation reflects a negative performance for the policy. In an attempt to quantify deaths that occur after the simulation, the time of death for those patients transplanted was projected and then discounted back to the end of the simulation. For those on the waiting list, a projection of the number of pre-transplant deaths occurring after the simulation under the condition of no donor arrivals was made. This involved performing a Markov chain analysis to determine the expected number of deaths on a given day after the simulation period and then discounting it back to the final day of the simulation period. An analytic model was developed for this purpose to arrive at the discounted after simulation waiting list deaths. Results for a discount factor of 0.2 are shown in Figure 3. This use of an analytic model is an example of the use of prior information (the method of conditional expectations) as a variance reduction technique.

If the discounted after simulation "deaths" are added to the total pre- and post- transplant deaths, then the total simulation period "deaths" show a surprising similarity for the five policies evaluated. Another surprising result is that the number of patients removed from the list over the three year period are all similar. This was not the case for 1 and 2 year runs. These results were not expected as the five policies selected for evaluation were considered to be different with regard to the death measures included in the analysis.

Measures of justice to patients are currently being developed. Figure 4 shows a portion of the analysis of policy equity across regions for simulation runs based on historical data from 1992-94. Figure 4 shows the population in a region and the number of donors. At the lower left of Figure 4, the correlation between donors and population is seen to be 0.977. For each policy the import/export of organs is presented where a negative number indicates an import into the region. It can be seen that different policies result in large differences in import/export values. To compare policies, the absolute deviation from an average is computed and shown in the row/ave.dev. For this measure it is seen that Policy 1 has the smallest deviation from the average. Similar policy equity analyses were performed for regional transplants, patient-days waiting to obtain a transplant, and averaged values of patient-days waiting by number of transplants, population and waiting list size.

Based on the outputs produced by ULAM, it was decided not to make a policy change at the current time.

SUMMARY

The process of modeling and simulation has been accepted by the UNOS transplantation community. ULAM has demonstrated how the formal modeling and simulation process can produce outputs that support policy evaluation for a national medical problem. Confidence in the model and its outputs for comparing alternative policies has been established. Refinements and extensions will further boost this confidence and the use of modeling and simulation in the transplantation community.

From a technical point of view, ULAM includes many advanced capabilities available from the simulation community. Common random-number streams and prior information are used as variance reduction techniques. Interarrival times and holding times were fit using developed techniques and programs. Bootstrapping methods were employed for attribute sampling. Statistical techniques were used for output variable estimation. SLAMSYSTEM with its capability for complex data structure development has produced a 240 to 1 decrease in running time, and SLAMSYSTEM's user interface provides a means to allow non-simulation personnel to make runs, to modify inputs in component modules, and to browse the outputs.

ULAM is a simulation program that is supporting the transplantation community in the evaluation of alternative policies which will yield improved medical utility and greater justice for waiting liver transplantation patients.

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