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SIMULATING MEDICAL DECISION TREES WITH RANDOM VARIABLE PARAMETERS

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ABSTRACT

This paper describes many of the issues that arise when incorporating the distribution of the uncertainty of the parameters into a medical decision tree. Most importantly, two different formulations of simulations of the tree yield two very differently distributed measures of the value of a tree. One measure is transaction-based reflecting the perspective of an individual patient, while the other provides the distribution of the global average value of the tree. Additionally, much care must be taken to represent duplication or other forms of dependence of distributions properly when calculating the tree average of stochastic trees. Finally, a practical example of a decision tree with random variable parameters, comparing the cost-effectiveness of using a new imaging agent to existing post-myocardial infarction testing protocols is presented.

1 INTRODUCTION

Decision analysis consists of a number of quantitative methods to aid in choosing among alternative decisions (Raiffa, 1968). Traditional decision analysis is used to indicate decisions favoring good outcomes even though there is risk surrounding the decision. Sometimes the risk is objective as in gambles with known odds, such as tossing dice or playing a lottery. More often though, the risk is subjective, based on limited data and uncertain theories. With further study and interpretation of new information, risk assessments can always be refined. Furthermore, the value of each possible outcome of a decision, whether measured in costs and benefits or utility, is usually variable. Traditional sensitivity analysis has simply varied parameters over a reasonable range of their possible values.

As the number of treatment options and policy choices have exploded and the cost of conducting research has skyrocketed, the "best" treatment for all clinical situations cannot be determined by conducting randomized controlled trials. Therefore, traditional decision analysis, in combination with sensitivity analysis, has become a standard methodology for using existing data and expert opinion to examine effectiveness and cost-effectiveness issues in health care. See Weinstein and Stason (1977) and Sox, et al. (1988) for discussion of the methodology and Udvarhelyi et al. (1992) for a bibliography and evaluation of the use of cost-effectiveness analyses in the medical literature. Beck and Pauker (1983) extended medical decision tree methodology to consider discrete-time Markov process-based models; which is helpful when the timing of a treatment is a critical variable. Recently, Hazen (1992) has defined stochastic trees as a technique for solving continuous-time Markov cycle trees. However, there are still no widely accepted techniques for incorporating variability in the estimates of the parameters of a decision tree.

Section 2 of this paper contrasts traditional decision analysis with simulation and other methods to evaluate decision trees when the uncertainty of the parameters is incorporated into the model. Section 3 describes other issues and controversies that must be addressed when undertaking a medical decision analysis. An example analyzing choices of testing protocols for patients following a heart attack is presented in Section 4.

2 DECISION ANALYSIS METHODOLOGIES

2.1 A Classic Decision Tree

A decision tree is composed of nodes containing estimates of outcome measures connected by probabilistic branches. According to Sox et al. (1988) creating a decision tree involves formulating a decision problem, assigning probabilities and measuring outcomes. Subsequently, the decision analysis involves calculating the expected value of each alternative, choosing the alternative with the highest expected value, and using sensitivity analysis to examine the conclusions. Figure 1 shows a much simplified tree for the costs after coronary angiography for patients after myocardial infarction, as depicted by the SMLTREE decision analysis package (Hollenberg 1989). Similar trees for other strategies (e.g., treadmill testing) must be built and evaluated in order to compare treatment protocols. For a more complete decision analysis of patient management strategies following myocardial infarction see Dittus et al. (1987, 1988).

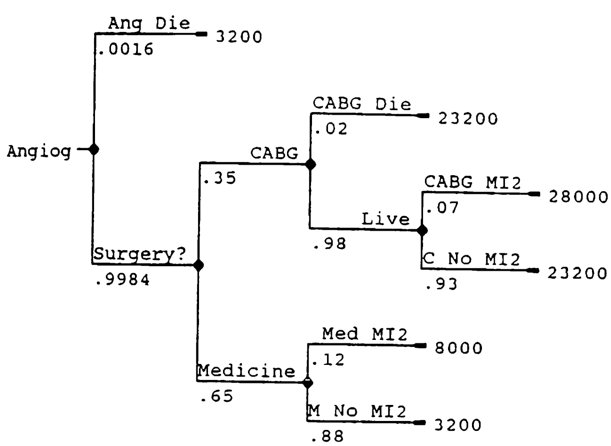

Figure 1: A Simple Decision Tree

A major shortcoming of this technique is the inability to model the variability inherent in the costs or utilities of various outcomes or to quantify the uncertainty in the subjective estimation of branching probabilities. For instance in the example in Figure 1, \$20000 is used as an estimate of the cost of bypass surgery, but it actually varies between \$16000 and \$26000. Similarly, various studies have found operative mortality from more than 4% to under 1%; thus there is uncertainty in our knowledge. Traditional sensitivity analysis deals with this by systematically varying one or two parameters (branch probability or outcome measure). However, when there is uncertainty in the estimates of many parameters, it becomes difficult to conduct and interpret sensitivity analyses. Thus other approaches for including uncertainty will be examined.

2.2 Incorporating Uncertainty

When data exist, information about variability should not be ignored as in a decision tree that uses only point estimates of the tree parameters. Even when data are sparse, a domain expert should be able to estimate a range and most likely value (mode) which is at least as good as the estimate of the mean. Much recent work done on input modeling for discrete event simulation is also applicable to modeling decision tree parameters. Vincent and Law (1991), Kelton et al. (1990) and Avramidis and Wilson (1989) offer techniques for choosing appropriate distributional forms and appropriate parameters when data are available. DeBrota et al. (1989a, 1989b) provide an approach to visual interactive fitting when data are scant and gathering additional data is too expensive or otherwise infeasible.

Whenever possible, a random sample of each input process should be gathered. When enough data can be obtained appropriate statistical distributions can be fit. However, just a good representation of the prominent features of existing data and expert opinion is often sufficient for a valid model. Klein and Baris (1991) describe many of the relevant considerations for selecting suitable distributions to represent sources of uncertainty in a large-scale systems analysis.

2.3 Analyzing trees with random parameters

Assuming that it is desirable to model the uncertainty in the parameters of a decision tree, there is still no generally accepted method to analyze the resulting tree. Most commonly, logical networks (of which trees are a special case) with variability would be analyzed by simulation. A general tool for this type of simulation, SLN, was introduced by Roberts and Klein (1984a) and applications of the methodology were described in Roberts and Klein (1984b). However, this type of simulation can be very time consuming, both in building and debugging the model and in computer time to execute sufficient observations to distinguish alternatives. Doubilet et al. (1985) described using Monte Carlo simulation to do what they call "probabilistic sensitivity analysis" and Hollenberg (1989) has added a few distribution choices to the SMLTREE software to perform what he calls "Second order Monte Carlo analyses". Other approaches have been taken by Katz and Hui (1989) and Willard and Critchfield (1986). However, none of these techniques perform both 1) the averaging out of a stochastic tree by sampling from all distributions and averaging the sampled values and 2) repeatedly following a transaction along a random path from the tree root to a leaf.

Eisenhut et al. (1991) developed an algorithm that uses up to four moments of all the input parameter distributions to compute exactly (to the limits of machine accuracy) the moments of the averaged-out value for a binary tree. Using these computed moments, an approximation to the distribution of that averaged-out value can be obtained. The analytical solution is limited to binary trees (that is, trees in which each node has at most two children); but each non binary node in any non binary tree can be converted into an equivalent sequence of binary nodes by an appropriate conditioning analysis (Doubilet et al. 1985).

While developing software to obtain the distribution of the averaged-out value of a tree analytically, it became obvious that this distribution is very different from the distribution obtained by usual Monte Carlo simulation. However, it was discovered that a tree can be simulated by two different methods. The method that directly parallels the analytical method has each observation representing the averaged-out value of the tree obtained by taking all branches in appropriate proportions. The usual transaction-based Monte Carlo simulation procedure focuses on the outcome of a single individual as he advances through a given realization of the tree along a single path from the root node to a leaf node. Each path is randomly selected according to the branching probability distributions. Both methods yield the same expected overall outcome, but the variance of the transaction-based distribution generally will be much larger, and it will usually be multi-modal. Both simulation methods and the analytical technique are available in the TreeModeler software (Dittus et al. 1990, Klein and Dittus 1991). Interpretations of these different distributions will be given in section 3.3. Finally, by combining two trees into a "super tree", the distribution of the difference between a pair of trees can be computed using either the transaction-based or tree average method.

A final technique for analyzing decision trees is with spreadsheet models. Palisade Corporation (1990) has created a series of add-in functions called @RISK which can be used with Microsoft Excel or Lotus 123. It provides over thirty distribution functions that can be substituted for the values in any spreadsheet cell. Additionally, there are statistical functions that allow for correlation between cells, a simulation command that systematically evaluates the distribution functions and several procedures for viewing the results. With @RISK a skilled spreadsheet programmer should be able to obtain either transaction-based or a tree-average view of a decision tree entered into a spreadsheet.

3 MEDICAL DECISION MAKING ISSUES

3.1 Outcome Measures

Decisions frequently require two or more simultaneous outcome measures on a tree. In medical decisions, the length and quality of life and direct health care costs are commonly used measures of relevant clinical outcomes and resource utilization needed to calculate a cost-effectiveness measure. Keeney and Raiffa (1976) offers a good discussion of multi-criterion decision issues.

Early work in the medical decision analysis field measured outcomes in terms of the effects on intermediate variables, such as the cost per degree of blood pressure lowering. Subsequently, analyses extended the outcomes to include the number of lives saved, translating the intermediate variables into a specific clinical outcome of direct importance to the individual, e.g. survival. Length of survival was clearly important and so the relevant cost-effectiveness measure to compare alternative strategies of care later became cost per year of life saved. Finally, to include the important consideration of the quality of life, years of life saved can be adjusted to reflect the quality of life, e.g. the use of quality adjusted life years. The quality adjustments are usually utilities. Of paramount importance is that none of these outcome measures are known with certainty and empirical studies explicitly describe the probabilistic nature of these outcomes. Thus a model that can directly reflect these uncertainties may provide a better understanding of the clinical implications of alternative decisions. Similarly, costs will vary by patient, usually widely. A model that can reflect the variation in costs can provide a better overall understanding of the cost implications of alternative decisions.

3.2 Dependence and Duplication

It is important to note that medical decision trees often have repeated or similar subtrees. For instance, a patient undergoing coronary angiography will have the same procedure-related risk regardless of what tests may have preceded it. When random variables are used in trees, then in any one iteration of a simulation of the tree, these must be represented as duplicates and not merely independent replications from a common distribution. This kind of duplication may even occur across trees and it's important to handle it properly especially when doing a pairwise comparison to find the distribution of the difference between to trees. Subtrees, with duplicated nodes and distributions, as well as pairwise comparisons are handled explicitly in TreeModeler. @RISK has facilities to include correlation coefficients, so it should be able to represent duplication as well as less complete dependence. More experience using this tool is needed.

3.3 Interpreting Simulation Results

The usual Monte Carlo simulation procedure is transaction based. It expands on the traditional technique of risk analysis, which describes the cumulative probabilities of each possible outcome. Groups of transaction-based observations can be averaged, and the distribution of those averages should correspond to the expected outcome value for that size of group.

The distribution that results from averaging out a tree with random variable parameters, as with the Eisenhut et al. (1991) algorithm, corresponds to the global (population) distribution of the outcome measure of the process being modeled. The procedure to simulate this measure is to sample from every distribution in the tree, making sure duplicate variables are only sampled once per iteration. Then on each iteration a traditional averaging out is done for the tree with the sampled values. The averaged-out value corresponds to the expected cost or reward for the entire relevant population of patients or clients (more generally called transactions) as they experience the process represented by the tree.

4 EXAMPLE: POST-MI MANAGEMENT

Over the last six years at Regenstrief Institute, a number of decision analysis models have been built to compare strategies for the management of patients following an asymptomatic myocardial infarction (heart attack without complications). Since only certain subgroups of these patients appear to benefit from interventions such as coronary artery by-pass surgery, the problem becomes one of finding the most effective and/or cost-effective way to identify these subgroups. Early spreadsheet models of this problem are described in detail in Dittus et al. (1987, 1988).

4.1 Input Data

Four kinds of data are needed to parameterize these models. First, patient subgroups are defined by combinations of functional status, the presence or absence of ischemia, and the number of occluded vessels (coronary anatomy). Data from a synthesis of several years of the medical literature are used to calculate the true prevalence of each subgroup. Angiography is a gold standard for determining coronary anatomy and functional status is measured by the left ventricular ejection fraction. Ischemia is somewhat more subjective, but measured by a test such as exercise thallium scintigraphy.

Second, sensitivities and specificities of each test must be converted to conditional probabilities. For instance, what is the chance of a positive treadmill test for a patient with ischemia, 2-vessel disease and good function? While overall sensitivities are reasonably well known, their allocation among the subgroups is somewhat subjective so it is important for the model to reflect the uncertainty here.

Information about the probabilities of survival, and second infarctions for medical and surgical treatment is obtainable from the literature. Operative mortality and mortality data for testing procedures such as angiography are also widely available. Adapting these for each subgroup is again somewhat subjective, though less so than for sensitivity data.

Finally, cost data were obtained both from local institutions and national Medicare data. The Medicare data samples are large enough to fit cost distributions. The models only look at short term results; so alive, die and second infarction are the only relevant health states to which an effectiveness measure (utility) needs to be assigned.

4.2 Alternative Models

At the time of the published spreadsheet models, the effect of functional status on medical and surgical survival rates had not been determined. So, when its effect on survival was quantified, we were compelled to add functional status to our subgroup classifications. Then the TreeModeler software reached a state where it could be used to incorporate some of the knowledge we had about the distributions of the model parameters. However, the cost-effectiveness of the various strategies were different enough that knowing the distributions did not change the recommendations, merely increased the certainty that they were correct.

Shortly thereafter, imaging agents which produce clearer pictures and thus better sensitivity and specificity than thallium scans have become available. For presentation purposes and to verify the TreeModeler results, an SMLTREE version of the model was created. Most recently, the model has been put back into a spreadsheet form and @RISK functions are being used to include uncertainty. This should make it easier to maintain when new information becomes available and to adapt when new testing strategies and treatment alternatives become available.

4.3 Output Distributions

Some of the input data in the current model is too preliminary to report results here. However, examples of the types of distributions available and their interpretations will be presented for the simplified tree in Figure 1. The averaged out value is $10,678, but unless the variability on the input parameters is modeled, there is no way to know how likely it is to be less costly than an alternative procedure with an averaged out value of $11,000. After adding appropriate variability to the inputs and evaluating with TreeModeler, histograms representing distributions of costs for the three types of analyses described above were produced. The distribution of the averaged out value as displayed in Figure 2 corresponds to a confidence interval on the long term average cost of the angiography strategy for the population modeled. It would be most useful for a national health policy maker.

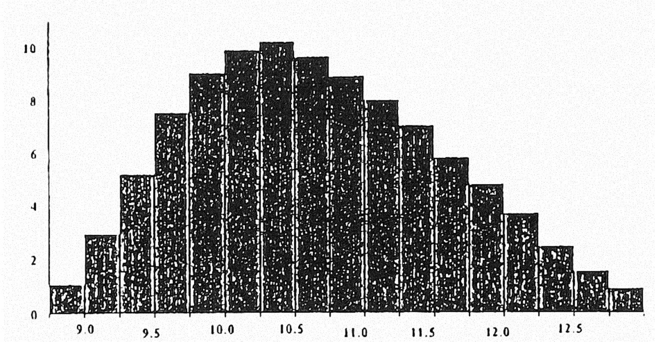

Figure 2: The Tree Average Distribution

Figure 3 is the distribution of costs for a particular person. With this strategy, all patients are charged for an angiography, some may have bypass surgery and some may have a second infarction or other cardiac event. For a particular patient a different outcome measure, such as life years, may be more important, but knowing the risk of a cost exceeding $25,000 may also influence the decision.

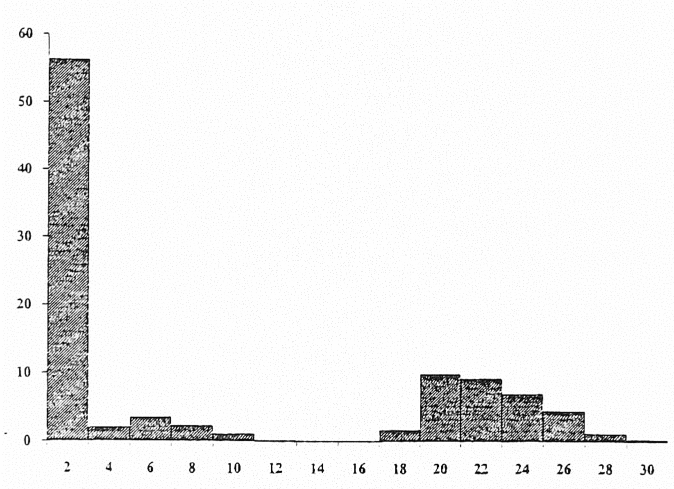

Figure 3: Distribution for any one Transaction

Finally, Figure 4 is the distribution of the average cost per patient of groups of 50 patients. For a hospital that sees 50 such patients per month, this distribution and those for alternative strategies, can be invaluable to the administration for planning, budgeting and setting policy.

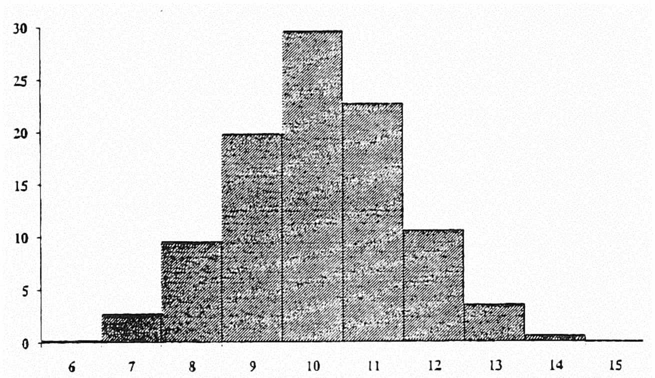

Figure 4: Distribution of Groups of 50

4.4 Future Enhancements

Percutaneous transluminal coronary angioplasty (PTCA) has become such a common treatment alternative (Ryan et al. 1988), that a credible model of coronary care must include strategies in which PTCA is used for appropriate patient subgroups. Thus, work to determine appropriate input data for a model including this treatment option is underway. Also, chemical stressing as an alternative to exercise testing for patients unable to exercise is being examined. Finally, because of the wealth of data and the financial magnitude of the question, this clinical problem remains an excellent vehicle for comparing the different tools available to analyze trees with random variable parameters.

5 CONCLUSION

Many decision analysis packages restrict random variables to only branches or only clinical outcome or cost expressions, although uncertainty is often inherent in both. Furthermore, many packages only allow outcomes to be assigned at terminal (leaf) nodes so obtaining a distribution for a cost that is really the cost of three or more procedures can be burdensome. SLN, TreeModeler, and a spreadsheet with @RISK all allow distributions on any number of branching probabilities and/or node costs or utilities, so they are more suitable for evaluating trees with random variable parameters.

Traditional decision analysis uses probability point estimates to represent the uncertainty of a future event. Uncertainty is often disquieting for a decision maker because it usually means there is a chance of a bad outcome. Moreover, even the best decision can result in a bad outcome. However, by quantifying the uncertainty surrounding a decision, it is possible to have the highest expected outcome value, minimize the chance of the worst outcome, or maximize the chance of the best outcome. Now, decision analysis can go further. By representing the uncertainty as a distribution and simultaneously incorporating uncertainty in the assessment of outcomes or costs, the decision maker has access to the likelihoods for the whole range of outcomes for each alternative. Thus decisions can be made based on all available information and judgments can be made as to what additional information would reduce the risk of a decision.

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