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The Markov Process in Medical Prognosis

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The physician's estimate of prognosis under alternative treatment plans is a principal factor in therapeutic decision making. Current methods of reporting prognosis, which include five-year survivals, survival curves, and quality-adjusted life expectancy, are crude estimates of natural history. In this paper we describe a general-purpose model of medical prognosis based on the Markov process and show how this simple mathematical tool may be used to generate detailed and accurate assessments of life expectancy and health status. (Med Decis Making 3:419–458, 1983)

Controversies about therapy are often rooted in the assessment of prognosis. One sometimes undertakes a risky therapeutic procedure hoping that it will reduce or eliminate the mortality or morbidity of an underlying condition. Faced with a choice of therapies for a particular medical problem, physicians often muse, "What effects will the various options have on the natural history of this patient's disease?"

Clinical decision analysis can provide formal answers to such questions. Its conceptual framework, the "decision tree," permits a therapeutic management problem to be separated into discrete, manageable units. The overall structure of the problem, including all reasonable choices and their effects, form the central portion of the decision tree. Events that may sometimes occur, depending on choices made and the effects of chance, are represented as probabilities. As each potential outcome is described in the

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tree structure, a utility value is assigned to represent the relative worth of the outcome [1]. Recent work in clinical decision analysis has focused on the establishment of "natural" utility systems for medical problems; many current applications of clinical decision analysis utilize quality-adjusted life expectancies as relevant outcome measures [2,3].

The decision-analytic formalism works well for problems involving chance events that occur once over a short time horizon (e.g., the results of a surgical procedure). When the natural history of disease involves either events that may occur repeatedly (such as episodic hemorrhage with anticoagulation) or over prolonged time (such as myocardial infarctions after coronary artery bypass surgery), the decision tree becomes "bushy" and the approach becomes cumbersome. The utility structure also becomes unmanageable, because utility must depend on *when* each good and each deleterious clinical event occurs.

In this paper we explicate the *Markov model of prognosis* as an alternative to standard decision-analytic formalisms. The Markov model can replace a decision tree outright or can be grafted onto standard decision analysis as an equivalent to the utility structure. Of several mathematical models that could serve as adjuncts to the clinical decision making process, the Markov model is distinguished by its simplicity, its ease of use in calculating prognosis, and its faithful representation of many clinical problems. In this study we describe the design and implementation of a general Markov prognostic model, and illustrate its application in a clinical decision analysis with complex utility features.

The Markov Model

The general problem considered here is the natural history of a chronic disease, which can be viewed for an individual patient as a sequence of particular *states* of health. Figure 1 illustrates this model. In this example a patient may be classified into one of three categories: WELL, ILL, and DEAD. At any time i, he or she resides in just one of the states. In Figure 1 this is represented as a patient being in one of the three ovals in the upper row (labeled TIME i). The possible changes of state, or *transitions*, that occur over the fixed time interval from i to $i+1$ are illustrated in Figure 1 as arrows. At TIME $i+1$ the patient resides in one of the ovals in the bottom row. In the Markov model the passage of time is represented by cycles (or "ticks") on an implicit "clock," where i denotes the cycle count. Transitions among states occur instantaneously at each clock tick.

Note that it is possible to get to the DEAD state from either of the other states, and there is of course no possible transition from the DEAD state. On the other hand, it is possible to leave WELL or ILL via a transition. In the language of mathematical modeling, WELL and ILL are termed "Nonabsorbing" states, and DEAD is an "absorbing" state. Once all patients are in the DEAD state, no further transitions are possible and the process is said to have been absorbed [4].

Figure 1 illustrates another feature of a Markov model of prognosis. Each change of state is represented by a single transition from one status to another. Implied in this picture is the property that the process has no memory of prior states; knowing that the current status is WELL is sufficient to predict what the next state will be. This is shown on Figure 1 as specific single-step probabilities associated with the arrows. For example, the probability of changing in one step from ILL to DEAD is depicted as P_{id}. It does not matter whether the patient has always been in the ILL state or whether the two states prior to the current ILL one were WELL. This no-memory feature of the model categorizes it as a *Markov process.* Furthermore, because this example has an absorbing state (DEAD), it is an absorbing Markov process. The absence of memory in the Markov process is known in mathematics as the *Markovian assumption* [4,5]. The assumption is quite strong: knowing only the present state of health of a patient is sufficient to project the entire trajectory of future states. In other words, all patients in a given state at a given time have the same prognosis, no matter how they got to the present state. There are few biological systems that obey the Markovian assumption strictly, yet its simplicity and approximate correctness make the Markov model very attractive.

MARKOV PROCESSES AND CHAINS. Two types of Markov models are used in medical decision making—those in which the state transition probabilities are constant, and those in which the transition probabilities vary over time according to preset regular rules. The first class of models are *Markov chains.* These models are a subset of the more general *Markov processes,* in which transition probabilities are time-dependent.

In terms of the calculational burden they impose, Markov chains are quite easy to use. We shall illustrate this feature of Markov chains in the clinical case example. On the other hand, Markov chains may be applied to medical problems only if the chances of moving among clinical states can be assumed to be constant. Constant transition probabilities are realistic only for diseases with a short time horizon. In more chronic conditions there is

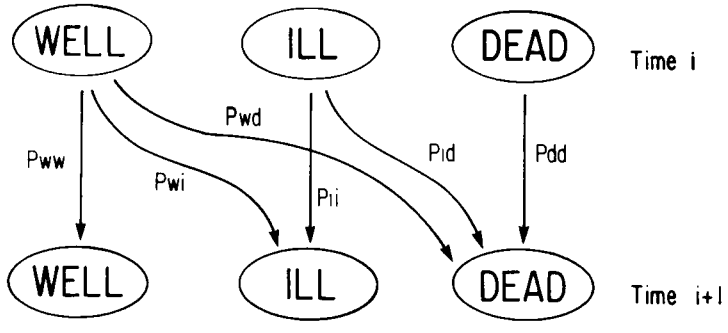

Figure 1. Three-state Markov Model.

usually the inescapable factor of increasing age. The annual mortality of the healthy population increases exponentially with age [6,7]. Inasmuch as clinical Markov models use death as an absorbing state, the population mortality must be built into the model. For problems with short time horizons an appropriate average annual mortality rate may be used as an approximation. If the disease-specific probabilities of mortality and morbidity are likewise approximately constant, the entire problem may be modeled as a Markov chain.

Longer-term or complex problems may be handled in two ways. The more general *Markov process* formulation may be used, with each transition probability being a function not only of the state of health but also of the time (or, equivalently, of the number of cycles the process has undergone). Conversely, an approximation may be made of the mean transition probability over the lifetime of the process, a procedure analogous to using the declining exponential approximation of life expectancy (DEALE) in classical clinical decision analysis [3]. The averaged transition probabilities may then be used in a Markov chain. The effects of using DEALE transformations on mortality probabilities will be discussed in Appendix A.

CONSTRUCTION OF THE MODEL. The first step in building a Markov model of prognosis is the enumeration of all distinct states of health. These are shown simplistically in Figure 1 as WELL, ILL, and DEAD. These clinical states should be clearly defined. Importantly, they should enable estimation or abstraction from the literature of specific transition probabilities per unit time among the various states. An example of a poorly formulated process would be the application of a simple three-state model (such as Figure 1) to polymyalgia rheumatica. In such a simple model a variety of clinical conditions would be lumped into the ILL category. Is the patient ill due to steroid toxicity, or due to the onset of temporal arteritis, or is he or she recovering from a temporal artery biopsy? Each of these conditions would merit its own state, inasmuch as the transition probabilities would differ among them and each would engender a different quality of life when a patient is in the state. Thus states must (1) be distinguished by their prognoses or transition probabilities, (2) be defined to correspond to standard or literature-based notions of disease, and (3) be capable of being placed in a continuous scale of relative values (see below).

Having listed the possible states of health, the next step in the construction of a Markov model is the definition of allowable state transitions. Figure 1 shows the allowable state changes for the sample model, drawn as arrows between possible states of health. From WELL it is possible to move to each of the other states or to remain WELL. Transitions from ILL to WELL are not allowed in this particular example but may, in general, be permitted in a Markov model. We presume then that the clinical process modeled in Figure 1 proceeds inexorably from WELL, perhaps through

ILL, to DEAD. Of course there are no possible transitions from DEAD—once dead, the patient remains dead.

For Markov medical decision making we have found it useful to consider two types of states: long-term and temporary. Long-term states, such as those shown in Figure 1, are states in which it is possible to remain from cycle to cycle. That is, a transition from a long-term state to itself is allowable. Temporary states reflect short-term events that force transition to another state in the model in the next cycle. For example, we could add a state to the model in Figure 1 labeled HOSPITALIZED, to reflect one cycle spent in the hospital. If all transitions from HOSPITALIZED were to other states, then this new addition would be a temporary state.

Note that in our temporary state the probability of remaining in that state is set to zero. A less rigid effect could be achieved by setting the probability of remaining in the state to a low but nonzero number (e.g., 0.2). Obviously the mean duration of time in a state (expressed as cycles), once the state is reached, equals the reciprocal of one minus the residual probability. Thus, if the state represented hospitalization, then a residual probability of 0.2 would imply a mean duration of 1.25 cycles, whereas a residual probability of 0.5 would imply a mean hospital stay of two cycles. A similar effect can be achieved by constructing a chain of temporary states, one leading to the next with high probability and with no transitions allowed to earlier states in the chain, and with zero residual probabilities. For example, three such states might be HOSPITALIZATION, MONTH 1, HOSPITALIZATION, MONTH 2, and HOSPITALIZATION, MONTH 3. The length of such a temporary chain would be a measure of the duration of hospitalization.

Next, probabilities must be associated with the state transitions. In Figure 1 these are given alongside the arrows that represent the allowable transitions: P_{ww}, P_{wi}, P_{wd}, P_{ii}, P_{id}, P_{dd}. These probabilities are abstracted from the clinical literature, or may represent experts' assessments. In the clinical literature, state transitions are commonly expressed as *rates*. Rates can range from zero to infinity and are expressed per unit time (e.g., "The mortality rate with disease X is two percent per year."). Probabilities, on the other hand, vary from zero to one and have time built into them implicitly. For any rate r, the probability of an event occurring over a time interval of t time units is [8]

$$P[t] = 1 - e^{-rt}.$$

To illustrate: Imagine that, in a published study of the clinical problem modeled in Figure 1, 100 well patients were followed for three years, and 70 became ill over that period. This data may be summarized as 70 transitions from WELL to ILL per 100 patients per three years, or 0.233 transitions per patient-year (70/100/3). This value is the annual rate associated with the transition WELL to ILL. If the cycle length chosen for the Markov model is

one year, the transition probability P_{wi} would be $1-e^{-0.233}$, or 0.208. If the cycle length is one month, P_{wi} would be $1-e^{(-0.233/12)}$, or 0.019. Thus the rate, while unchanged on an annual basis, leads to very different transition probabilities with differing cycle lengths for the Markov model. (Note that this decrease in transition probabilities, as the cycle length shortens, applies only to transitions to a different state. The residual probability of remaining in a given state *increases* with decreasing cycle length, and must be calculated as one minus the sum of the transition probabilities.) The cycle length chosen for a Markov model should closely approximate clinical follow-up, to eliminate biases in data introduced by vagaries in patient evaluation.

The choice of cycle length produces other effects on the Markov model. In the Markov process formulations the accuracy of the results and the time required for calculation varies inversely with the cycle length. These problems vanish in the Markov chain, where the calculation is performed using matrix algebra (see below).

Some transitions in the Markov model may reflect two or more independent forces. In Figure 1, we may suppose that the transition from WELL to DEAD (probability P_{wd}) reflects both the force of mortality in the general population and disease-specific effects. Methods for assessing disease-specific mortality rates have been reported elsewhere [3]. If, in our example problem, the disease-specific excess mortality rate (i.e., the rate of transition from WELL to DEAD without intervening ILL) is 0.1 per patient-year, and the average general population mortality rate is 0.05 per patient-year, corresponding to age 56 [9], then the transition probability P_{wd} for a cycle length of one year would be $1-e^{-(0.1+0.05)}$, or 0.139. (Note that 0.05/year is the average death rate [3,10] over the lifetime of a 56-year-old man. The rate in his 56th year alone would be far lower (0.012), but that instantaneous annual rate would increase yearly, reaching 0.098 at age 80.)

If the process depicted in Figure 1 were modeled as a Markov process (with time-dependent transition probabilities), instead of a Markov chain, then specific functions or tables would be needed for the various transitions. Consider the example just reported for P_{wd}. The disease-specific mortality rate is 0.1 per patient-year, a constant. The instantaneous general population mortality rate could be modeled by the Gompertz function

$$\mu_{\text{ASR (age)}} = 0.000185\, e^{(0.071\text{age})},$$

where (age) is the patient age, a variable. This function produces an exponentially increasing mortality rate that corresponds to the mortality experience of white males. The transition probability associated with the variable population mortality rate and the constant disease-specific mortality rate would also be a function of age:

$$1-e^{-(0.1+0.000185\, e^{(0.071\text{age})})}.$$

All of the transition probabilities in the Markov model need to be enu-

merated or expressed as functions of time. In the calculation shown above, patient age can be translated easily to the equivalent clock time or cycle count.

In additon to the exponential increase in annual mortality rates, we can model temporary increases or decreases in other transition probabilities by specifying a window of time (in terms of the clock cycle count) during which the temporary changes hold. For example, certain tumors might have an excess mortality of μ_{t1} (e.g., 0.2/year) for the first three years (or 36 monthly cycles), μ_{t2} (e.g., 0.05/year) for the next 12 years (cycles 37–180), and zero thereafter (i.e., long-term cure).

CALCULATION OF LIFE EXPECTANCY WITH THE MARKOV MODEL. Life expectancy, a commonly employed outcome measure for clinical decision making problems [2,3], is defined as the average future lifetime of a cohort of patients with identical clinical features [11]. The enumeration of states and the assignment of transition probabilities is sufficient to calculate life expectancy with the Markov model. Before describing the three methods by which this calculation can be made, we need to establish how the model can be used to estimate life expectancy. It is intuitive that for any Markov process with an absorbing state (e.g., DEAD) that can be reached from every other state, the probability of eventual absorption (or death) is unity. In other words, everyone dies eventually. This is proved elsewhere [4, cf. Isaiah 40:6–8]. A corollary is that the expected time before absorption of a Markov process is finite and can be calculated. Inasmuch as "absorption" in a clinical Markov process is death, the expected time before absorption is the life expectancy of the cohort of patients modeled by the process.

The expected time before absorption can be calculated in three ways: a Monte Carlo simulation of a large series of individual patients, a probabilistic simulation of a cohort of patients, and, for a Markov chain only, a matrix algebraic solution.

Individual Monte Carlo Simulation. In this approach, patients traverse a Markov process one by one, with a random number generator determining what happens to the individual at each cycle of the process. Each patient begins in the initial state or in one of a limited distribution of states of health (e.g., WELL in Figure 1). At each cycle the patient changes state according to the laws of chance, as dictated by the transition probabilities. Inasmuch as the underlying transition probabilities are point estimates derived from the literature, the type of random number generator used is immaterial. In practice, a function that generates uniform numbers on the interval [0,1] is optimal. A clock cycle length is defined, and a cycle counter increments with each transition. When the patient enters the absorbing DEAD state, the current cycle count represents the length of his or her individual life time (Figure 2). While the patient is traversing the temporary

states of the model, the length of time in each nonabsorbing state is recorded. Finally, in clinical problems with long clock cycles, it may be necessary to reduce the total time before absorption by one-half cycle, because the patient dies, on average, halfway through that final cycle. (The same correction might be made whenever moving between states with different incremental utilities. In practice, this is only important if the difference in utilities is large.)

After the first person has completed the simulation (i.e., has died), another patient begins in one of the initial states and a new simulation is performed. After a large number (on the order of 10^4) of identical patients have been simulated, with each individual's trajectory through the Markov process governed by the laws of chance, the averaged number of cycles before absorption (death) is equivalent to life expectancy. Similarly, the averaged or expected number of cycles in each nonabsorbing state may be calculated. Of course, because we know for each simulated patient not only how long is spent in each nonabsorbing state but also when these nonabsorbing cycles occur, we could simulate the effect of changes in the utility of each state over time (e.g., discounting or decreasing marginal value).

Every patient need not begin the simulation in the same state. Sometimes the clinical problem is such that the patient may initially be in one of several different states of health. In such cases we distribute the initial states of the simulated patients so as to correspond to our best knowledge about the probability density distribution of the patient's initial state of health.

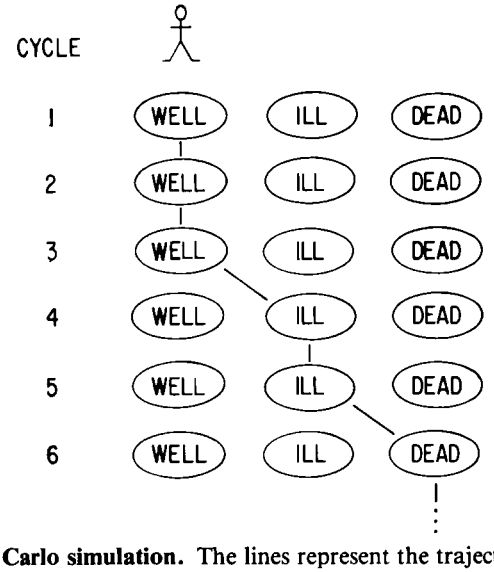

Figure 2. Monte Carlo simulation. The lines represent the trajectory of an individual patient through the Markov model. This patient is WELL for three cycles, becomes ILL in the fourth cycle, and dies in the sixth cycle.

This approach, termed a Monte Carlo simulation, is equivalent to the performance of a large number of experiments with the Markov model. Its accuracy is as good as the number of patients simulated, the quality of the random number generator used, and our knowledge about the initial state and transition probability distributions. Because each patient must be simulated individually, the approach is time-consuming. On the other hand, because the process is a simulation the probabilities and utilities can easily change as functions of time. Thus Markov process models with time-dependent probabilities may be studied with the Monte Carlo approach. Because patients are simulated as individuals this approach provides the greatest flexibility and detail. In particular, measures of variability around life expectancies are easy to calculate.

Markov Cohort. In this method, a large number of patients are followed as a cohort. The cohort begins in an initial distribution of states, and at each cycle of the process the entire cohort is reallocated to states according to the transition probabilites. Table 1 shows the first few transitions of a Markov Cohort analysis of the simple three-state model we have been using as an example. In the cohort analysis two values are kept for each state at each cycle: the number of patients currently in the state and the total number of patient-cycles in the state. For example, at Cycle 2 the WELL state includes 9000 patients; the cumulative number of WELL patient-months is 100 000 + 30 000 + 9000, or 139 000. After a sufficient number of cycles almost everyone will be DEAD. The few remaining patients (the "tail" of the survival curve) can be treated in one of two ways: a small arbitrary amount of life expectancy can be added to each state that has remaining cohort members or the life expectancy can be truncated. The Markov cohort simulation is stopped when the remaining cohort has diminished to the point where any error introduced by summing up the experience of the remainder (dealing with the tail) is small compared to the total patient-cycles accumulated during the analysis.

When a Markov cohort analysis is terminated, the total number of patient-cycles for each state is divided by the size of the original cohort, yielding the expected time that each individual member will spend in each state. Life expectancy is the sum of these expected values (see Table 1, bottom), possibly adjusted for differences in the utilities associated with the states. A half-cycle correction should be made for the final (i.e., tail) state if the cycle length is relatively long. The Markov cohort analysis is a simulation, although it does not follow patients as individuals. Time-dependent probabilities and utilities may be easily incorporated into the analysis. If the quality adjustment is done as the cohort moves through the model (and not at the end), then discounting and risk aversion can be accommodated by this technique. It cannot, however, provide information on the distribution or variance of expected values, as can the Monte Carlo technique.

Table 1. Markov Cohort Simulation

Time	State WELL	ILL	DEAD
0	100 000	0	0
1	30 000	50 000	20 000
2	9 000	40 000	51 000
3	2 700	24 500	72 800
•	•	•	•
•	•	•	•
•	•	•	•
Sum	142 860	142 860	----
Average Cycles (Sum/100,000)	1.43	1.43	
Life Expectancy	1.43 + 1.43 = 2.86 cycles		

Fundamental Matrix Solution. This approach requires constant transition probabilities and thus is appropriate only for Markov chains. As shown in Figure 3, in this formulation a matrix P of single-step transition probabilities is constructed. The states are listed along the left and top margins of the matrix; for each cycle, the left (row) margin denotes the starting states and the top (column) margin denotes the finishing states. The appropriate transition probabilities fill the cells of the matrix; P_{ij} is the probability of going from state i to state j in any given cycle of the chain.

This matrix formulation has many useful properties [4]. Of special interest is the portion of the matrix containing the transition probabilities among nonabsorbing states. This section, labeled Q in the upper left of Figure 3, reflects the probability of not being absorbed, depending on the starting state of the cycle. Figure 4 illustrates a sample Markov matrix. The upper left section (Q) has four elements: 0.3, 0.5, 0, and 0.5. If an individual is in the WELL state, the probability of not being absorbed (i.e., staying alive) in one cycle is 0.3 + 0.5, or 0.8. The probability of not dying in one cycle for an individual in the ILL state is simply 0 + 0.5, or 0.5. Section Q may be manipulated in a special way: Each element is subtracted from a corresponding element in another 2×2 matrix (Figure 5) composed of ones on the diagonal and zeroes elsewhere (called an identity or I matrix). By a technique of linear algebra known as matrix inversion a new matrix

$$N = (I - Q)^{-1}$$

is constructed (Figure 6). This process is the matrix algebraic equivalent of taking the reciprocal of a transition probability, and thus bears an interesting analogy to the DEALE technique described elsewhere [10]. Matrix N, known as the fundamental matrix of an absorbing Markov chain, has as its elements by column the expected time in each state before absorption, given

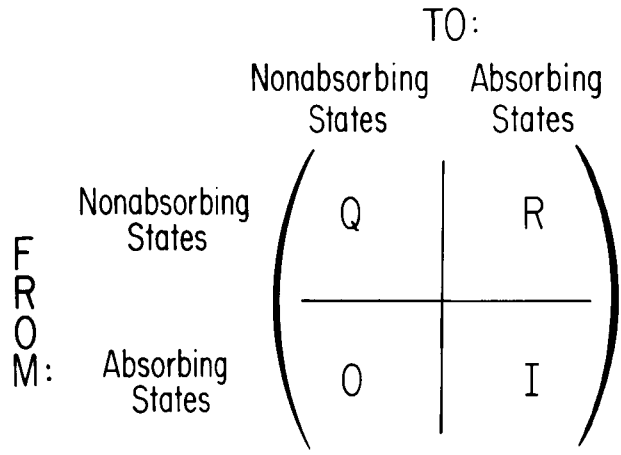

Figure 3. Transition probability matrix (P). The four cells reflect single-step transitions between and within absorbing and transient states. See the text for details.

the starting state corresponding to the row of the N matrix. For example, if a patient began in the state WELL, he can expect to spend 1.43 cycles WELL and 1.43 cycles ILL before dying; if a patient began in the ILL state, he can expect to spend 2.00 cycles in that state before dying. A proof of this relationship is given in Appendix B. The N matrix, then, contains the same values as the totals in the Markov cohort analysis, with one important difference. The fundamental matrix is equivalent to running the cohort simulation for an infinite time with an infinitesimally short clock cycle. The proof of the relationship between the Q and N matrices demonstrates that the model will converge for all sets of probabilities, because everyone in the

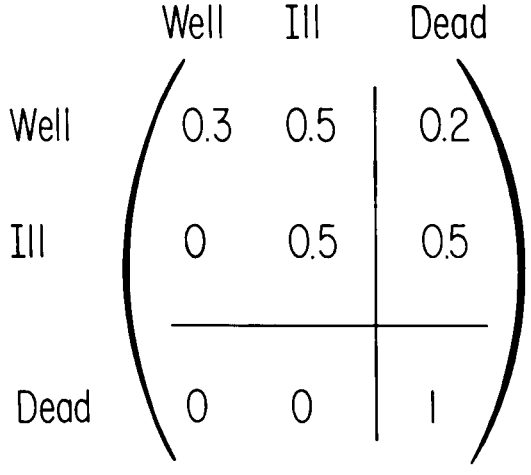

Figure 4. Example matrix.

$$I = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$$

Figure 5. Identity (*I*) matrix.

cohort will eventually die in the Markov chain formulation. A sum of the row elements in the N matrix, then, gives the total life expectancy for the initial state represented by that row. For example, beginning WELL, life expectancy (unadjusted) is 2.86 cycles.

Although the fundamental matrix approach is conceptually difficult, it has some powerful advantages over the other two methods. It does not require simulation, and therefore it is very quick to perform. Algorithms exist for handheld programmable calculators that will invert matrices with up to five rows. Microcomputers permit the fast inversion of larger matrices. Also, the N matrix is an exact solution. The problems of deciding how many patients to simulate in a Monte Carlo analysis and deciding when to terminate a Markov cohort model do not occur in the fundamental matrix solution. Furthermore, there is an exact solution to the problem of finding the variance of each expectation in matrix N. The variance matrix V is

$$N(2N' - I) - N^2,$$

where N' is a copy of the N matrix with only the diagonal entries preserved (and zeroes elsewhere) and N^2 is a matrix with each entry of the N matrix squared (not $N^{(2)}$, a product matrix used in Appendix B) [4]. The variance matrix from the example problem is shown in Figure 7.

Table 2 describes the comparative advantages and limitations of the three formulations of Markov analysis.

INCORPORATION OF QUALITY-OF-LIFE AND UTILITY ADJUSTMENT INTO A MARKOV MODEL. Each of the three methods of Markov analysis yields a set of expected survivals in the nonabsorbing states of the Markov process. The simple sum of these survival values is the patient's life expectancy. We may take advantage of the state model, however, and assign different quality-of-life measurements to each clinical classification. This differential assignment introduces the concept of incremental utility. In standard decision theory, the utility associated with a given length of survival is represented by a function of time. In the Markov formulation, we assess a state-dependent

$$I - Q = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} - \begin{pmatrix} 0.3 & 0.5 \\ 0 & 0.5 \end{pmatrix}$$

$$= \begin{pmatrix} 0.7 & -0.5 \\ 0 & 0.5 \end{pmatrix}$$

$$(I - Q)^{-1} = N = \begin{pmatrix} 1.43 & 1.43 \\ 0 & 2.00 \end{pmatrix}$$

Figure 6. Construction of a fundamental (*N*) matrix. The cells of this matrix represent expected time spent in each nonabsorbing state, given the starting state shown in the corresponding row label of Figure 4. See the text for details.

increment of utility for each cycle through which the patient remains in that state, i.e., dU/dt. In most applications, one full unit of utility is given to a cycle in the best possible state of health (WELL in Figure 1). Fractional units are given to cycles in which the state of health is suboptimal. These units may be further adjusted for attitudes towards risk, as functions of

$$V = N(2N' - I) - N^2$$

$$V = \begin{pmatrix} 1.43 & 1.43 \\ 0 & 2.00 \end{pmatrix} \left(2 \begin{pmatrix} 1.43 & 0 \\ 0 & 2.00 \end{pmatrix} - \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \right) - \begin{pmatrix} 1.43^2 & 1.43^2 \\ 0 & 2.00^2 \end{pmatrix}$$

$$= \begin{pmatrix} 1.43 & 1.43 \\ 0 & 2.00 \end{pmatrix} \begin{pmatrix} 1.86 & 0 \\ 0 & 3.00 \end{pmatrix} - \begin{pmatrix} 2.04 & 2.04 \\ 0 & 4.00 \end{pmatrix}$$

$$= \begin{pmatrix} 2.66 & 4.29 \\ 0 & 6.00 \end{pmatrix} - \begin{pmatrix} 2.04 & 2.04 \\ 0 & 4.00 \end{pmatrix}$$

$$= \begin{pmatrix} 0.62 & 2.25 \\ 0 & 2.00 \end{pmatrix}$$

Figure 7. Variance matrix for the example problem.

time. If risk aversion or discounting is used, then not only are the state dependent incremental utilities different, but each dU/dt diminishes fo later clock cycles.

Figure 8 illustrates the concept of incremental utility, using the Mont Carlo simulation from Figure 2. The utility increment per cycle for WEL] is defined as 1.0. Let us assume that the quality increment for ILL is 0.' units per cycle. For simplicity, let us not address the question of risk aver sion. The patient is WELL for three cycles, accumulating one unit of incre mental utility per cycle, then in the fourth cycle becomes ILL. For two IL] cycles the patient accumulates 0.7 units each, then dies. The total survival i five cycles; the total utility is $(3\times1.0)+(2\times0.7)$, or 4.4 quality-adjuste cycles.

The Markov model can keep track of incremental utility in two ways. I quality adjustments are the only utility factor of interest, then the expecte time a patient spends in each state of the Markov process may be multiplie by its corresponding fractional utility; these *adjusted survivals* are the added to yield quality-adjusted life expectancy. If time-dependent adjust ments to utility, such as risk aversion and discounting, are important, the at each cycle the overall state-specific utility is increased by the product c the current state membership, the quality increment (from zero to one), an the current value of the utility adjustment function (i.e., the current dis count factor). Thus, the product is really quality- and risk-adjusted patien cycles. The fundamental matrix approach may be treated analogously—th survival values in the N matrix may be multiplied by the quality adjustment to obtain the state-specific adjusted utility. If incremental utility value change over time (as in risk aversion or discounting), then the fundamenta matrix approach cannot be used explicitly.

Table 2. Characteristics of Markov Approaches

Feature	Monte Carlo	Markov Cohort	Fundamental Matri
TRANSITION PROBABILITIES	Time dependent	Time dependent	Constant
INCREMENTAL UTILITIES	Time dependent	Time dependent	Constant
ACCURACY	Cycle dependent	Cycle dependent	Invariant
COMPUTATION REQUIRED	Most	Moderate	Least
CALCULATES			
EXPECTED UTILITY	Yes	Yes	Yes
VARIABILITY MEASURES	Yes	No	Yes
SENSITIVITY ANALYSIS	Yes	Yes	Yes

USE OF THE MARKOV MODEL IN MEDICAL DECISION MAKING. Markov models, in their several formulations, yield risk- and quality-adjusted life expectancies. Such measures may be used in two general ways. The Markov process can be the entire analysis, if different management choices are reflected solely as different sets of transition probabilities [12] or possibly different incremental utilities. Alternatively, the results of a Markov process may provide utilities for "tree-based" clinical decision analyses. A decision tree is constructed that has "natural history" as its terminal nodes or outcome states. Different pathways in the tree might imply using Markov models with different transition probabilities. Of course the entire Markov analysis can be represented equivalently as a very deep decision tree.

The choice between a Markov analysis, a standard decision tree, and a combined analysis is made on the basis of ease of representation and requirements for relevant sensitivity analysis. The Markov model is conceptually attractive (viz. Figure 1), but the transition probabilities are hidden from view. Although sensitivity analyses are possible on the parameters of the Markov process, the calculations are more straightforward and the results easier to understand if the probability is in plain view, as in a decision tree.

On the other hand, the Markov model is preferable for problems with repetitive chances that would require very deep and broad decision trees.

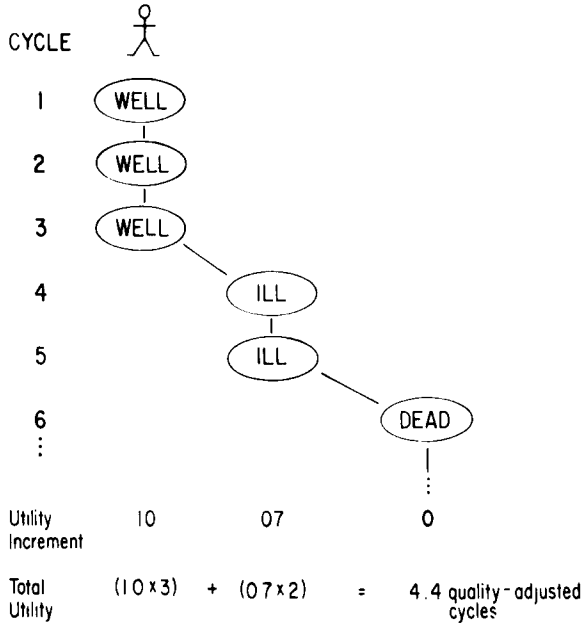

Figure 8. Monte Carlo simulation with the addition of state-dependent incremental utility. The example patient survives five cycles, but quality-adjusted survival is 4.4 cycles. See the text for details.

Case Example: Should anticoagulation be withheld in a patient with an artifical heart valve and recent hemorrhagic cerebral infarction?

A 59-year-old white female with chronic rheumatic heart disease and atrial fibrillation underwent a mitral valve replacement (Starr-Edwards, bare metal cage) seven years ago. She experienced no further mitral dysfunction and was maintained on warfarin anticoagulation since surgery without sequelae. She remained in atrial fibrillation. Her course was complicated by severe tricuspid insufficiency and chronic congestive heart failure. She had good left ventricular function but a markedly enlarged left atrium. She was admitted to another hospital with a large hemorrhagic infarction involving the right cerebral hemisphere. Anticoagulation was discontinued, and a consultation was requested to clarify the risks and benefits of continued anticoagulation.

The central question was: Should anticoagulation be resumed in the setting of a recent cerebral hemorrhage that might be primary or might represent secondary bleeding into an embolic infarct? The patient was at risk for two potentially catastrophic events, cerebral embolization and recurrent cerebral hemorrhage. Complicating the decision was uncertainty regarding the etiology of the hemorrhagic event. Computed tomography of the head was interpreted as "90 percent probability of primary cerebral hemorrhage," but the clinical story favored an embolic episode, and therefore secondary hemorrhage.

THE DECISION TREE. We approached this problem with decision analysis, using a Markov model of prognosis to measure outcomes of treatment. The decision tree in Figure 9 summarizes the model we developed. The square node at the left of Figure 9 shows the decision faced in this case: withhold anticoagulation or resume warfarin therapy. Whether or not anticoagulation is resumed, the patient's prognosis depends on the etiology of her stroke. Thus the decision tree shows a circular chance node on each branch of the central decision, the chances being PRIMARY or SECONDARY cerebral hemorrhage. The probability of primary hemorrhage p was estimated at 0.9 by the neuroradiologists at the outside hospital. A panel of radiologists suggested that the likelihood of primary cerebral infarction in this setting, with this patient's CT scan, would range from 0.8 to 0.95.

At the right of Figure 9, on each of the four terminal branches of the decision tree, is a rectangular box labeled Markov Model. We need to develop four outcome assessments, corresponding to the various combinations of therapeutic decision and etiology of hemorrhage.

MARKOV MODELS OF PROGNOSIS. Figure 10 shows the state model constructed for this analysis. This model is similar to the one we used in an analysis of the anticoagulation decision in the bradycardia-tachycardia syndrome [12]. There are three major states of health, WELL, DISABLED, and DEAD. There is in addition one temporary state of health, MINOR

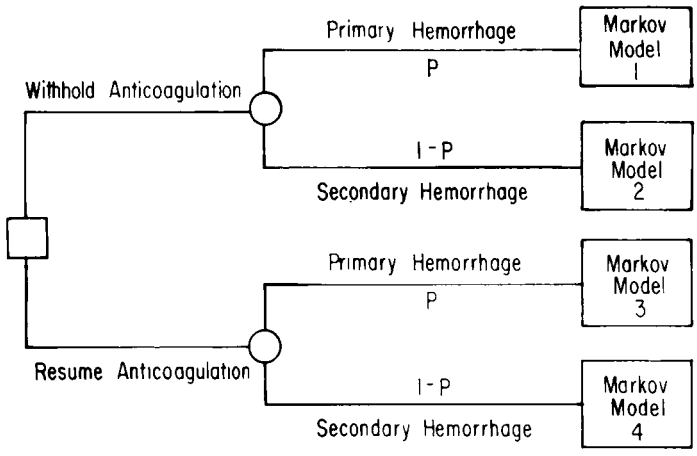

Figure 9. Decision tree for the case example. Markov models will be used to calculate quality-adjusted life expectancies as utility measures.

EVENT. This state occurs when the patient suffers a small, nondisabling stroke or hemorrhage that leads to medical attention but not to permanent disability. DISABLED is reserved for events that produce permanent incapacitation. The creation of a state MINOR EVENT allows two things: A catalogue of minor strokes and hemorrhages may be kept, and a short-term utility adjustment may be made when a patient suffers a minor event. Death may occur from four causes: catastrophic stroke, catastrophic hemorrhage, underlying cardiac disease, or other causes. The latter two causes of death do not depend on the therapeutic decision made; they are constant across the four Markov models of prognosis. The chances of stroke, hemorrhage, and event-related morbidity do depend on the choice of therapy and on the etiology of the patient's initial hemorrhage.

ASSUMPTIONS. In addition to the standard Markovian assumption of no memory of prior states of health, we shall make several simplifying assumptions in this case. First, we assume that embolization and hemorrhagic events occur randomly in time and at a constant rate. This allows us to exploit all possible constructions of the Markov model.

Second, we assume that fatal hemorrhage and fatal stroke are equally undesirable and indistinguishable from death occurring at the same time due to underlying cardiac disease or old age. This analysis therefore uses a single DEAD state and does not distinguish the relative undesirability of different etiologies of death, but considers only when death occurs.

Third, hemorrhages are either minor or fatal. This is substantiated by the current literature [13,14]. On the other hand, embolic events may be minor, permanently disabling, or fatal. A disabling embolus diminishes the quality of a patient's remaining life, but does not affect the likelihood of future events.

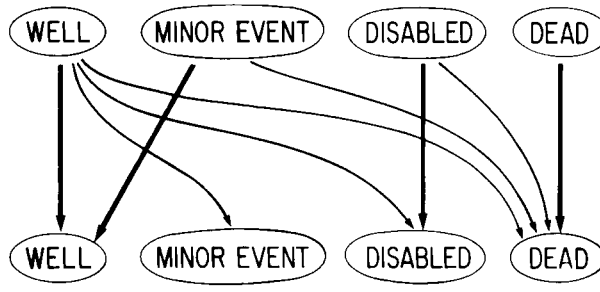

Figure 10. Markov state model for the case example. See the text for details.

Fourth, the major morbidity of anticoagulation is hemorrhage. Inasmuch as the patient has been maintained on warfarin for several years, this assumption appears warranted.

Fifth, if the patient suffers systemic embolization, we assume that anticoagulation is resumed immediately and the probability of re-embolization is not increased in the periembolic period. The literature suggests that the risk of a second embolus is increased for a short time after an event [15], but it does not indicate how efficacious immediate anticoagulation can be in the prevention of such re-embolization.

Sixth, we assume that there is no increased risk of hemorrhage without anticoagulation. Spontaneous cerebral hemorrhage is exceedingly rare in the absence of predispositions such as anticoagulant therapy, severe hypertension or arteriovenous malformation [16]. Although common sense would suggest that one primary cerebral hemorrhage is a risk factor for a second, no data has been collected to verify this belief. Furlan's large population study does not mention recurrent cerebral hemorrhage when other risk factors are absent [16]. This patient was on warfarin when the first hemorrhage occurred. We assume that regardless of the etiology of the first bleeding event, cessation of anticoagulant therapy will prevent recurrent hemorrhage, but we examine the effects of this assumption with sensitivity analysis.

Eighth, we shall analyze the decision using the Monte Carlo, Markov cohort and fundamental matrix approaches. For the third analysis, we use the DEALE assumption of constant population mortality rates [3]. For all analyses we assume that the mortality rate of underlying cardiac disease is constant [17].

Data Used in the Analysis. In this Markov model the transition probabilities govern the likelihood of embolization, hemorrhage, and death due to cardiac disease or other causes.

Wolf and his colleagues used data from the Framingham cardiovascular disease study to obtain a rate of cerebral embolization in the setting of mitral valve replacement and atrial fibrillation [18]. Assuming no anticoagulation, the rate of cerebral embolization in a patient with a cage-type

artificial valve was 82 events per 1000 patients per year. Embolization in patients with primary atrial fibrillation unassociated with mitral disease was 41 events per 1000 patients per year. A maximum value for the chance of cerebral embolization in a patient suffering from both conditions would be the sum of these numbers, or 123 events per 1000 patient-years (unless the diseases were synergistic and exacerbating, which is unlikely on pathophysiologic grounds). According to a recent review by Levine [19], two-thirds of clinically detected systemic emboli are cerebral. Thus a maximum of 123 / (2/3), or 184 embolic events would be expected in 1000 patient-years of follow-up without anticoagulation. Levine also suggests that ten percent of systemic emboli are fatal and 20 percent are permanently disabling [19].

The efficacy of warfarin in systemic embolization is widely recognized, although there are no controlled studies proving its worth. Uncontrolled studies and clinical experience suggest that the rate of systemic embolization on warfarin is decreased by two-thirds. Thus a maximum of 62 embolic events per 1000 patient-years of follow-up would be expected on warfarin therapy.

In the case under analysis, the hazards of warfarin are related primarily to cerebral hemorrhage. The rate of cerebral bleeding depends on whether the previous hemorrhage was a primary or secondary event. If it was secondary, then we may use the literature and expert assessments of 30 to 50 cerebral hemorrhages per 1000 patient-years of anticoagulant therapy, with a fatality rate of four percent [12,13]. If the initial event was a primary hemorrhage, we need to adjust that value upward. There are no large reported series of patients receiving long-term anticoagulation after intracerebral hemorrhage, but Lieberman and other neurologists, based on their experience, suggest a rate of 500 hemorrhages per 1000 patient-years, with a case fatality rate of 15 percent to 20 percent [14]. In selecting maximum estimates for embolic rate we have chosen to bias the analysis in favor of resuming anticoagulation. Maintaining this bias, we selected the lower value of $4\% \times 30$, or 1.2 fatal hemorrhages per 1000 patients per year, under the assumption of secondary hemorrhage, and likewise used a cerebral hemorrhagic mortality of $15\% \times 500$, or 75 per 1000 patient-years, along the PRIMARY hemorrhage branch.

The contribution of severe tricuspid regurgitation and congestive heart failure to mortality is taken from the Framingham study [17]. The annual mortality rate due to such cardiac disease alone is in excess of ten percent. This "added load" to the patient's baseline risk has the effect of decreasing the patient's life expectancy in all Markov process models, but the effect is constant across them. Thus this excess risk decreases the *absolute difference* between the results of different management strategies, but does not influence the decision whether or not to anticoagulate.

Finally, the patient's risk due to age, sex, and race may be incorporated in two ways. Tables of vital statistics provide the increasing annual mortality rate of the healthy population [9]; for a 59-year-old female it is approxi-

mately 9.4 per 1000 per year (0.0094) and increases exponentially with age to become 0.062/year by age 80. Either mortality rate tables or a mathematical model (e.g., Gompertz) may be used in a Markov cohort or Monte Carlo analysis. For the Markov chain matrix solution, the average mortality rate, calculated using the DEALE, is used [10]. This is the reciprocal of the life expectancy of a 59-year-old female (22.6 years), or 0.044/year. Note that this value is much higher than the instantaneous age-specific mortality rate of 0.0094/year found in vital statistics tables for women of age 59, but less than that of women of age 80, because it is applied as a *constant* force of mortality. The exponentially increasing rate of mortality found in the tables eventually reaches and exceeds the constant mortality rate (at about age 70 for females), so that the life expectancy in both formulations is the same. This comparison is discussed briefly in Appendix A and more extensively elsewhere [10].

Transition Probabilities of a Markov Process. The data just summarized are incorporated into the four Markov models, as shown in Table 3. In the upper section of the table we display the data assuming increasing age-specific death rates, modeled by the Gompertz function [6]. These models will drive the Monte Carlo and cohort analyses. In the lower section of Table 3 we display the data assuming constant risk of death due to age, race, and sex. These values will be incorporated directly into the fundamental matrix approach.

There are four possible transitions from the WELL state: to WELL, MINOR EVENT, DISABLED, and DEAD. The residual "transition" from WELL to WELL represents no event of interest over one clock cycle. It is calculated by subtracting the sum of all risk probabilities from unity. The transition probability from WELL to MINOR EVENT is derived from two independent risks—that of a small stroke and that of a minor hemorrhage. The overall risk is the sum of the rates of each event. For example, given the decision to RESUME ANTICOAGULATION and the PRIMARY hemorrhagic etiology (Markov Model 3, Figure 9), the risk of embolus is 62/1000 patient-years. Of these 70 percent will be minor events (ten percent are fatal and 20 percent disabling). The risk of minor stroke is thus 43/1000 patient-years. The risk of hemorrhage is 500/1000 patient years; 85 percent will be minor. The overall risk of a minor event, then, is (43 + 425)/1000/year.

We chose a clock cycle of one month for the Markov process (a reasonable choice—larger cycles are insensitive to the small transition probabilities in the model, smaller cycles do not accurately reflect the duration and frequency of clinical observation in this disorder). The risk of a minor event is 468/1000/12, or 0.0390/patient-month. The probability corresponding to this rate is the exponential transform, $1 - e^{-0.0390}$, or 0.0382. If the decision is to withhold anticoagulation (Markov Models 1 and 2, Figure 9), the risk of hemorrhage becomes very small (Assumption 6). The rate of embolization increases to 184/1000 patient-years. Inasmuch as 70 percent of emboli

Table 3. Monthly Transition Probabilities for the Case Example

MARKOV PROCESS WITH INCREASING AGE-RELATED MORTALITY

Starting state			Withhold anticoagulation		Resume anticoagulation	
			Primary hemorrhage (Model 1)	Secondary hemorrhage (Model 2)	Primary hemorrhage (Model 3)	Secondary hemorrhage (Model 4)
WELL	→	WELL	*	*	*	*
		MINOR EVENT	0.0106	0.0106	0.0382	0.0060
		DISABLED	0.0031	0.0031	0.0010	0.0010
		DEAD	$f(0.0099)$	$f(0.0099)$	$f(0.0151)$	$f(0.0089)$
MINOR EVENT	→	WELL	*	*	*	*
		DEAD	$f(0.0099)$	$f(0.0099)$	$f(0.0151)$	$f(0.0089)$
DISABLED	→	DISABLED	*	*	*	*
		DEAD	$f(0.0099)$	$f(0.0099)$	$f(0.0151)$	$f(0.0089)$
DEAD	→	DEAD	1	1	1	1

$f(m) = 1 - e^{-(m + 4.33 \times 10^{-6} \times e^{(0.088 \times [\text{age}])})}$

m is the monthly mortality rate attributable to emboli, hemorrhages, and underlying cardiac disease

* represents 1 – (the sum of the other transition probabilities from a particular state): the residual probability

MARKOV CHAIN WITH CONSTANT TRANSITION PROBABILITIES

Starting state			Withhold anticoagulation		Resume anticoagulation	
			Primary hemorrhage (Model 1)	Secondary hemorrhage (Model 2)	Primary hemorrhage (Model 3)	Secondary hemorrhage (Model 4)
WELL	→	WELL	0.9729	0.9729	0.9422	0.9805
		MINOR EVENT	0.0106	0.0106	0.0382	0.0060
		DISABLED	0.0031	0.0031	0.0010	0.0010
		DEAD	0.0134	0.0134	0.0186	0.0125
MINOR EVENT	→	WELL	0.9866	0.9866	0.9814	0.9875
		DEAD	0.0134	0.0134	0.0186	0.0125
DISABLED	→	DISABLED	0.9866	0.9866	0.9814	0.9875
		DEAD	0.0134	0.0134	0.0186	0.0125
DEAD	→	DEAD	1	1	1	1

are minor, the monthly transition probability from WELL to MINOR EVENT would be

$$1 - e^{-(184 \times 70\%/1000/12)},$$

or 0.0106. Similar calculations give the monthly transition probabilities under the assumption that the cerebral hemorrhage is secondary.

Within the upper section of Table 3 are several occurrences of a function, $f(m)$. Because the Markov process model allows for increasing age-related mortality, we cannot give a constant value for the transition rate to DEAD. This rate, which changes with every clock cycle, has two components. The variable component is monthly age-specific mortality, which is modeled by the Gompertz mortality function. For a white female, this is shown in the center of Table 3 as $4.33 \times 10^{-6} \times e^{0.088 \times [\text{age}]}$. The constant component m is the monthly mortality due to underlying cardiac disease (the load), fatal embolus, or fatal hemorrhage. The variable and constant components are combined as $f(m)$, shown also in the center of Table 3.

As an example, consider the transition from WELL to DEAD, under the decision to RESUME ANTICOAGULATION, with a secondary etiology of hemorrhage (Markov Model 4, Figure 9). The constant component of the transition rate is calculated as follows: The death rate due to underlying disease is 1/12 of ten percent per patient-year, or 0.0083/patient-month. The death rate due to fatal embolus is 1/12 of 62/1000 patient-years $\times$ 0.1 (the stroke rate while on anticoagulation multiplied by the likelihood of case fatality), or 0.0005/patient-month. The death rate due to fatal hemorrhage is 1/12 of 30/1000 patient-years $\times$ 0.04, or 0.0001/patient-month. The constant component m is the sum of these rates, or 0.0089/patient-month. This value is inserted in Table 3 as $f(0.0089)$, as shown.

For the decision to withhold anticoagulation, the etiology of hemorrhage is immaterial to the baseline analysis. The decision tree in Figure 9 reflects the question of etiology, and it will come into play in structural sensitivity analyses. Table 3 thus shows identical values in the primary hemorrhage and secondary hemorrhage columns under the decision to withhold anticoagulation.

State-Dependent Utilities. As a starting point, inasmuch as the patient was hospitalized in another city, we have abstracted quality values for the states WELL, MINOR EVENT, and DISABLED from a related case [12]. DEAD, of course, accumulates no incremental utility. WELL is defined as 1/month. In the related case, ten months with discomfort due to a minor stroke or hemorrhage were equated with eight months well; the incremental utility associated with MINOR EVENT, then, is 0.8/month. Ten months with permanent disability were equated with three months well. The utility assigned to the state DISABLED, then, is 0.3/month. These values will be subjected to sensitivity analyses.

CALCULATION OF QUALITY-ADJUSTED LIFE EXPECTANCY

Monte Carlo Approach. Table 4 contains the expected months in each major and temporary state, calculated using the Gompertz model of exponentially increasing mortality rates according to a Monte Carlo simulation. These expected values are listed for each combination of decision and etiology of the initial hemorrhagic event. Ten thousand simulations were performed using a mainframe digital computer, whereupon the averaged number of months in each state converged toward a limit. The standard deviation of the number of months in each state, as well as the life expectancy for each branch of the decision tree shown in Figure 9, are also shown in the table. The greatest life expectancy, not surprisingly, occurs in the setting of a secondary hemorrhage with anticoagulation resumed (Model 4). The least life expectancy occurs in the setting of primary hemorrhage with anticoagulation resumed (Model 3). Quality-adjusted life expectancy, the rightmost column of Table 4, is calculated for each combination of management plan and hemorrhagic etiology by multiplying the expected months in each state by the state-specific quality factor, and then adding.

The standard deviations of the expected survivals are quite large. This is true for Markov processes in general [4]; the implications of the high variability will be explored in the discussion below.

Markov Cohort Approach. Table 5 contains the expected survivals (in months) in each major and temporary state, calculated using the Gompertz model of life expectancy according to a cohort analysis; the results are similar to those in the Monte Carlo approach. The life expectancies calculated in Table 5 are more exact than the simulated values but do not contain any measures of variation.

Markov Chain Approach. Table 6 contains the expected months in each major and temporary state, calculated by representing the data in Table 3 as Markov canonical matrices and calculating the fundamental or N matrices by inversion. Compared to the cohort formulation, the Markov chain analysis shows approximately 13 percent fewer months spent in the WELL state and 20 percent fewer months spent in the DISABLED state for each set of parameters. This occurs because the probability of death due to causes unrelated to cardiac disease in the Gompertz model is small in the early months of the simulation. The Gompertz model does not "catch up" to the DEALE approach until age 67. Thus the summed mortality rates due to congestive heart failure, population mortality, and catastrophic events extract more penalty early in the matrix approach [10]. The fundamental matrix thus underestimates life expectancy, as calculated using the more accurate Markov cohort analysis.

Although not identical, the life expectancies and quality-adjusted life expectancies for the fundamental matrix and cohort analyses are on the

Table 4. Expected Survivals, Monte Carlo Approach

Decision	Etiology of Hemorrhage	Survival (months in):			Life expectancy (months)	Quality-adjusted life expectancy (months)
		WELL	MINOR EVENT	DISABLED		
WITHHOLD ANTICOAGULATION	Primary Mean:	69.51	0.75	17.72	87.98	75.43
	(Model 1) SD:	65.30	1.10	47.50	80.76	70.30
	Secondary Mean:	69.51	0.75	17.72	87.98	75.43
	(Model 2) SD:	65.30	1.10	47.50	80.76	70.30
RESUME ANTICOAGULATION	Primary Mean:	55.60	2.11	3.16	60.87	58.24
	(Model 3) SD:	52.82	2.43	17.68	55.75	53.74
	Secondary Mean:	87.01	0.52	7.40	94.93	89.65
	(Model 4) SD:	78.30	0.87	33.15	85.03	80.38

Table 5. Expected Survivals, Markov Cohort Approach

Decision	Etiology of Hemorrhage	Survival (months in): WELL	MINOR EVENT	DISABLED	Life expectancy (months)	Quality-adjusted life expectancy (months)
WITHHOLD ANTICOAGULATION	Primary Mean: (Model 1)	69.20	0.74	17.37	87.31	75.00
	Secondary Mean: (Model 2)	69.20	0.74	17.37	87.31	75.00
RESUME ANTICOAGULATION	Primary Mean: (Model 3)	55.97	2.14	3.42	61.41	58.67
	Secondary Mean: (Model 4)	86.23	0.52	7.33	94.08	88.85

Table 6. Expected Survivals, Markov Chain Approach

Decision	Etiology of Hemorrhage	Survival (months in):			Life expectancy (months)	Quality-adjusted life expectancy (months)
		WELL	MINOR EVENT	DISABLED		
WITHHOLD ANTICOAGULATION	Primary Mean:	60.09	0.64	13.90	74.63	64.77
	(Model 1) SD:	59.59	1.02	43.22	73.62	64.12
	Secondary Mean:	60.09	0.64	13.90	74.63	64.77
	(Model 2) SD:	59.59	1.02	43.22	73.62	64.12
RESUME ANTICOAGULATION	Primary Mean:	49.24	1.88	2.65	53.77	51.54
	(Model 3) SD:	48.74	2.30	16.59	51.54	49.62
	Secondary Mean:	73.66	0.44	5.93	79.99	75.78
	(Model 4) SD:	73.16	0.79	30.03	79.09	74.99

same order. This patient, who if well would enjoy a life expectancy of 22.9 years, can, in the best possible setting, expect only 7.8 years of life with her multiple medical problems (the N matrix calculates this as 6.7 years, a 15 percent apparent reduction). With adjustments for morbidity, this is decreased further to 7.4 quality-adjusted years (6.3 years in the matrix analysis).

The standard deviations calculated by the matrix approach, also listed in Table 6, are comparable to those calculated by the Monte Carlo simulation (Table 4).

CALCULATION OF EXPECTED UTILITY. The values of quality-adjusted life expectancy are used as utility asessments in the decision tree shown in Figure 9, and the expected quality-adjusted survival is calculated by multiplying the utility values by their associated probabilities of occurrence, and then adding. Using the values from the Monte Carlo analysis for the decision to withhold anticoagulation, the expected utility is thus 75.43 quality-adjusted months. For the decision to resume anticoagulation, the expected utility is $(89.65 \times 0.1 + 58.24 \times 0.9)$, or 61.38 quality-adjusted months. Table 7 summarizes the expected utilities for each management approach, according to the three illustrated methods of Markov analysis. Although the matrix approach underestimates life expectancy as calculated by the simulation, the decision analysis reaches the same conclusion as in the Monte Carlo and cohort models; in the baseline analysis, withholding anticoagulation provides a real quality-adjusted life expectancy benefit of 17 percent to 19 percent.

SENSITIVITY ANALYSIS. A number of variables in the case may be examined systematically using techniques of sensitivity analysis. Of greatest interest is the etiology of the presenting cerebral hemorrhage. Because of its intrinsic interest we kept this chance event in the decision tree proper, outside of the Markov utility structure, to facilitate sensitivity analysis. We varied the likelihood of primary cerebral hemorrhage over the range from 0.8 to 0.95, corresponding to the range suggested by the panel of radiologists. At all values over this interval the preferred decision is to withhold anticoagulation. Figure 11 expands this sensitivity analysis to all conceivable likelihoods of primary hemorrhage; the threshold probability of primary hemorrhage below which anticoagulation is preferred is 46 percent using utility values from the cohort analysis (45 percent in the Markov chain formulation).

Within the Markov model of prognosis, several variables may be examined. The embolic rate, 184 events/1000 patient-years without anticoagulation, was taken as a maximum value. Any lesser value further favors withholding anticoagulation at this time. Similarly, the values pertaining to the risks of anticoagulation were taken at their minima. Any increase in these would favor withholding anticoagulation.

Table 7. Expected Utilities for the Case Example

Decision	Expected utility (quality-adjusted months)		
	Monte Carlo	Markov cohort	Markov chain
Withhold anticoagulation	75.43	75.00	64.77
Resume anticoagulation	61.38	61.69	53.96
Difference	14.05 (18.6%)	13.31 (17.7%)	10.81 (16.7%)

One variable that was unbiased in the baseline analysis is the efficacy of anticoagulation (two-thirds reduction of embolic frequency in the baseline case). Figure 12 shows the effect of varying this value across its full range, from worthless (efficacy zero) to completely eradicating embolic strokes (efficacy 100 percent), in a Markov cohort analysis. Even if anticoagulation is 100 percent effective, the hemorrhagic risk in the setting of primary etiology reduces the quality-adjusted life expectancy below that of WITHHOLD ANTICOAGULATION. The same result is obtained by Monte Carlo or matrix analysis.

The sixth assumption, that the risk of repeated hemorrhage is negligible if anticoagulation is withheld, regardless of its etiology, was examined in a matrix analysis. In this sensitivity analysis, the transition probabilities to MINOR EVENT and DEAD were modified in Markov Model 1 (Figure 9). Even if the rate of recurrent hemorrhage were 1.1 per 100 patient-months, with a case fatality rate of 15 percent (as in the RESUME ANTICOAGULATION, PRIMARY HEMORRHAGE scenario, Model 3), the expected utility of the decision to WITHHOLD ANTICOAGULATION decreases from 64.77 to 58.36 quality-adjusted months. This is still eight percent higher than the expected utility associated with RESUME ANTICOAGULATION (53.96 quality-adjusted months).

The Markov model itself can be subjected to a structural sensitivity analysis. The baseline analysis assumed that a decision is reached (resume or withhold anticoagulation) and that the decision remains in force for the patient's lifetime. Another approach would be to make an initial decision, but allow a change in therapy every time an event occurs. If the patient suffers a systemic embolus, for example, anticoagulation will be instituted if not already in force; if the patient suffers a hemorrhagic complication, anticoagulation will be withheld unless the patient is already severely disabled and the hemorrhage is minor (Figure 13). The effect of this assumption is shown in Table 8 for Markov chain model. In effect, this formulation adds two states to the Markov model, because we now need to differentiate the states WELL and MINOR EVENT on the basis of anticoagulation status (Figure 13). Furthermore, just two Markov models suffice for this analysis. Each initial treatment decision is reflected in a row of the Markov matrix. The upper section of Table 8 contains the single-step transition probabilities in the six-state Markov chain, given primary etiology of hemorrhage. The lower section of Table 8 is the probability matrix for the secondary hemor-

rhagic etiology. Table 9 shows the expected number of months in each major and temporary state, for various combinations of hemorrhagic etiology and starting state. These are simply the N or fundamental matrices of these six-state absorbing Markov chains. The top row lists the expected natural history, beginning without anticoagulation. The decision to resume anticoagulation is reflected in the second row of the table. The upper section of Table 9 contains the fundamental matrix assuming a primary etiology of the presenting hemorrhage. The secondary etiology of hemorrhage results in the N matrix displayed in the lower section of Table 9.

Multiplying the respective expected lengths of stay in each state by an

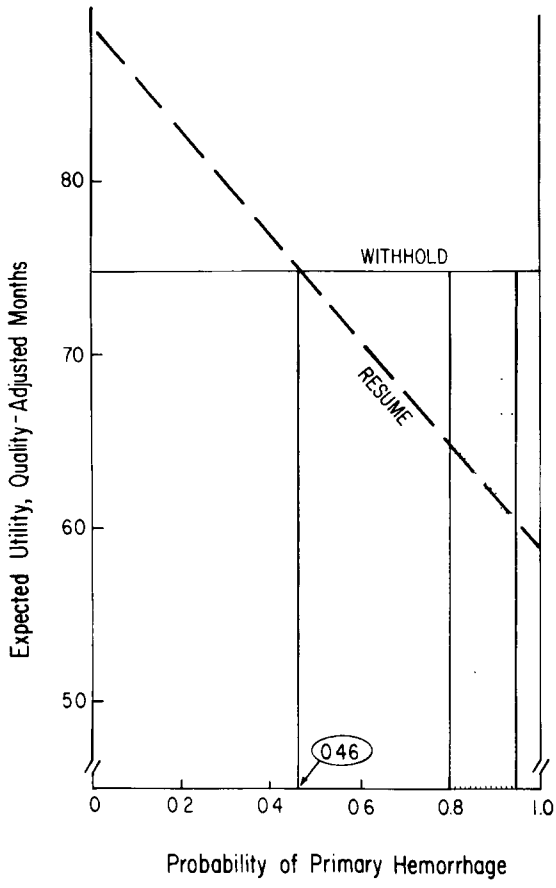

Figure 11. One-way sensitivity analysis of the probability of primary hemorrhagic etiology. A Markov cohort model was used to generate this graph. The shaded area depicts the range of likelihood of primary hemorrhage as given by the panel of neuroradiologists (0.80–0.95). The threshold probability, below which resumption of anticoagulation is indicated, is well below this range (0.46).

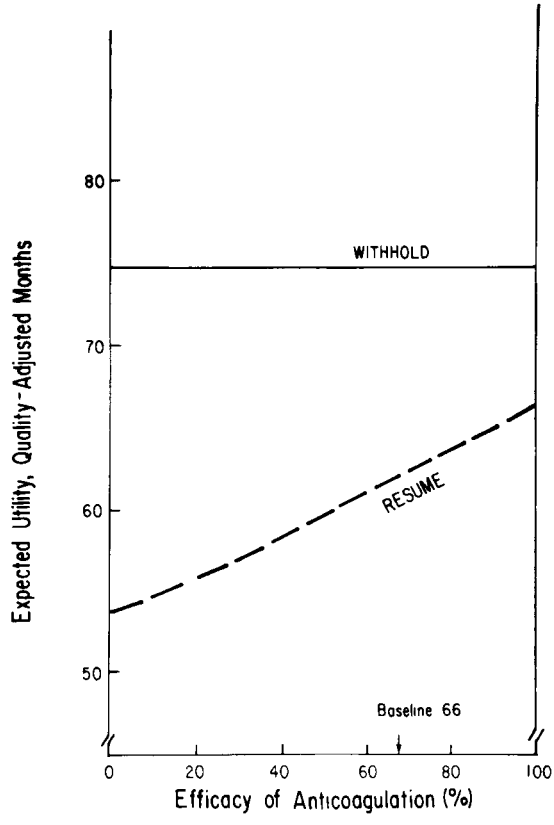

Figure 12. One-way sensitivity analysis of the efficacy of anticoagulation. A Markov cohort analysis was used to generate this graph. Efficacy is defined as the fractional reduction in embolic rate due to anticoagulation. Over all possible values of efficacy, WITHHOLD ANTICOAGULATION is the preferable strategy.

appropriate state-dependent quality adjustment leads to a quality-adjusted life expectancy of 62.01 months for the decision to withhold anticoagulation. An initial decision to resume anticoagulation yields 59.53 quality-adjusted months. Compared with the Markov chain results in the baseline case (Table 7), these strategies yield intermediate expected quality-adjusted survivals. Withholding anticoagulation initially still offers the better prognosis.

Finally, we subjected the incremental utility values to sensitivity analysis. Figure 14 shows a two-way sensitivity analysis of the probability of primary cerebral hemorrhage as a function of the incremental utility assigned to permanent disability (0.3 in the baseline case). As can be seen from Tables 4 through 6, withholding anticoagulation produces more months with disability. Thus a higher utility value assigned to DISABLED tends to further favor withholding treatment. Interpreted another way, if the patient can tolerate permanent disability, he or she would tend to favor the therapy that minimizes fatal hemorrhages, even at a cost of more serious embolizations.

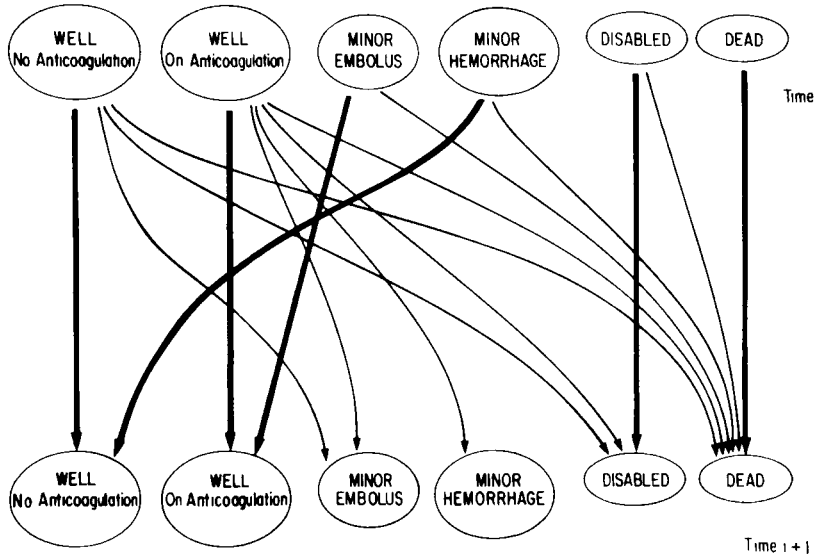

Figure 13. Six-State Markov model. This model incorporates changing therapy as a result of nonfatal embolic or hemorrhagic events. Anticoagulation status and type of minor event are specified in this amended model.

In another sensitivity analysis of the utility structure we examined the seventh assumption, that once permanently disabled, subsequent MINOR EVENTS generate no additional disutility. If we set the utility associated with future minor events to zero, the net effect on quality-adjusted life expectancy is less than 0.5 percent in all Markov models. This effect changes no decisions and affects the decision to withhold or resume anticoagulation equivalently.

Discussion

The Markov model of prognosis is an alternative to traditional concepts of multiattribute utility. It can be developed using data from the clinical literature and can be solved in various ways using a calculator or microcomputer. The Markov model generates quality-adjusted life expectancy values in a fashion similar to the declining exponential approximation of life expectancy (DEALE) [10]. Both techniques employ real-life units and values from the literature, a major advantage over arbitrary utility scales. Furthermore, because the expected durations of survival in transient states are explicitly calculated in the Markov model, quality adjustment is easier than in the DEALE.

The Markov model introduces the concept of incremental utility, in which a patient is observed in a particular state of health over a discrete time interval (the clock cycle), and a quality or utility score is assigned to that interval. As a patient's clinical status waxes and wanes, utility is accumu-

Table 8. Six-State Amended Markov Chain Model

Primary Hemorrhagic Etiology						
	Ending state					
Starting state	WNAC	WAC	ME	MH	DIS	DEAD
Well-no anticoagulation (WNAC)	0.9729	0.0000	0.0106	0.0000	0.0031	0.0134
Well-on anticoagulation (WAC)	0.0000	0.9422	0.0035	0.0347	0.0010	0.0186
Minor embolus (ME)	0.0000	0.9814	0.0000	0.0000	0.0000	0.0186
Minor hemorrhage (MH)	0.9866	0.0000	0.0000	0.0000	0.0000	0.0134
Disabled (DIS)	0.0000	0.0000	0.0000	0.0000	0.9814	0.0186
Dead (DEAD)	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000
Secondary Hemorrhagic Etiology						
	Ending state					
Starting state	WNAC	WAC	ME	MH	DIS	DEAD
Well-no anticoagulation (WNAC)	0.9729	0.0000	0.0106	0.0000	0.0031	0.0134
Well-on anticoagulation (WAC)	0.0000	0.9805	0.0035	0.0025	0.0010	0.0125
Minor embolus (ME)	0.0000	0.9875	0.0000	0.0000	0.0010	0.0125
Minor hemorrhage (MH)	0.9866	0.0000	0.0000	0.0000	0.0000	0.0134
Disabled (DIS)	0.0000	0.0000	0.0000	0.0000	0.9875	0.0125
Dead (DEAD)	0.0000	0.0000	0.0000	0.0000	0.0000	1.0000

Table 9. Fundamental Matrices for the Modified Markov Chain

Primary Hemorrhagic Etiology					
Initial State	**Months in:**				
	WNAC	WAC	ME	MH	DIS
Well-no anticoagulation (WNAC)	48.66	9.31	0.55	0.32	8.61
Well-on anticoagulation (WAC)	30.64	24.25	0.41	0.84	6.41
Minor embolus (ME)	30.07	23.81	1.40	0.83	6.29
Minor hemorrhage (MH)	48.01	9.18	0.54	1.32	8.50
Disabled (DIS)	0	0	0	0	53.76
Secondary Hemorrhagic Etiology					
Initial state	**Months in:**				
	WNAC	WAC	ME	MH	DIS
Well-no anticoagulation (WNAC)	39.23	25.59	0.51	0.06	11.78
Well-on anticoagulation (WAC)	6.03	66.26	0.30	0.17	6.80
Minor embolus (ME)	5.96	65.44	1.29	0.16	6.71
Minor hemorrhage (MH)	38.70	25.25	0.50	1.06	11.62
Disabled (DIS)	0	0	0	0	80.00

lated, rather than being assessed at the termination of the strategy or path, as in standard clinical decision analysis. This incremental utility can be modified using any of the methods available for decision making (risk adjustment, discounting).

Leviton and his colleagues developed a Markov model of headache recurrence for patients with chronic daily headache [20]. They were able to

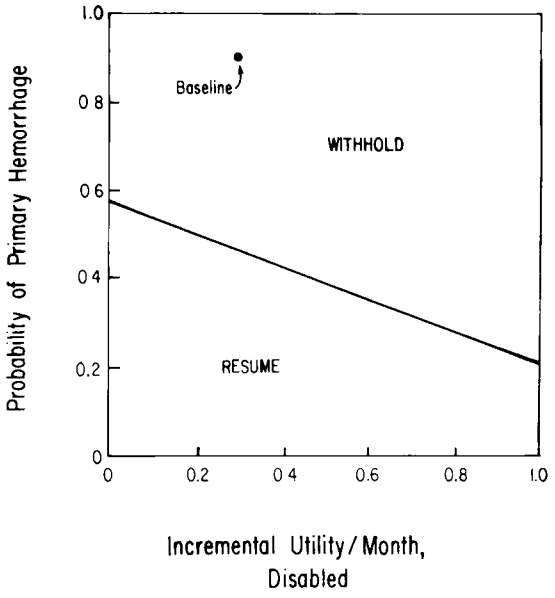

Figure 14. Two-way sensitivity analysis of the probability of primary hemorrhage and state-dependent incremental utility associated with disability. The threshold line separates the regions in which WITHHOLD and RESUME ANTICOAGULATION are preferable. The solid circle denotes the baseline conditions in the case example.

fit experimental data closely to a Markov chain with four nonabsorbing states. There are, however, several limitations to Markov modeling. The natural history of prostatic cancer has been modeled using Markov chains, but with several forced assumptions about disease status [21]. In order to invoke the Markovian assumption, the authors permitted transitions between clinical states defined by alkaline phosphatase and acid phosphatase levels. They assumed that sequential determinations of these enzymes gave results independent of both prior testing and clinical remission status. In most malignancies, the full prior history is incorporated in decision making: "Is this the first, second, or later relapse?" Such data invalidate the central assumption of the Markov process, because they imply some memory of prior states of health. Some simple oncologic problems may however be modeled using Markov processes that distinguish among time-related events: WELL, FIRST RELAPSE, REMISSION, LATER RELAPSE, LATE REMISSION, DEAD.

It is always possible to expand a problem with finite memory into a Markov process by increasing the number of states, creating a so-called semi-Markov process. In the example case, we did just this when we considered the effects of switching therapies in the case of nonfatal embolic or hemorrhagic events. Here the "memory" was whether or not the patient was anticoagulated at the time of the event—the issue was handled by adding two states that reflected event type and anticoagulant status. There is a

practical limit to this tactic, however—the advantage of the Markov model is its simplicity, and this advantage can be eroded by a complex state model formulation. That is, as the number of states increases, the number of transition probabilities that must be assessed grows exponentially.

Another limitation to Markov modeling is the variability of a multiple parameter model. As shown in the case example, while imposing little calculational burden, the matrix formulation underestimates life expectancy. This is explored further in Appendix A, where it is shown that this underestimation does not lead to incorrect therapeutic decision making. Furthermore, the standard deviations of the expected months in each nonabsorbing state are large. This implies that if the Markov model were rewritten as a deep decision tree, a huge number of pathways with different survivals would result. To worry about large variability in Markov analyses, then, is to admit that any large decision tree has numerous pathways. If we adhere to the central tenet of decision making by maximizing expected utility, than Markov analysis assists us in providing expected utilities as well as explicit measures of variability in the Monte Carlo and matrix formulations.

For bedside application of Markov modeling—in a clinical decision analysis—the fundamental matrix will arrive at a decision quickly. This is especially true if only a few states are involved and if a calculator capable of matrix inversion is available. We have written a program for one calculator that permits matrix operations (the HP-15C, Hewlett-Packard, Portland Oregon). If the variance matrix V is required, this calculator will handle Markov models with up to five clinical states. If only expected survivals are of interest, this machine will calculate the fundamental matrix of an eight-state model.

In cases when the actual number of months lived becomes important, the time horizon must be short for the matrix model to closely approximate the Gompertz simulation or cohort models of life expectancy.

We recommend the development of Markov models of prognosis in clinical situations involving decision making about chronic disease. For prompt, bedside analyses the matrix formulation of the Markov model, employing constant transition probabilities abstracted from the literature using the DEALE, provides correct decisions in all cases and accurate values of life expectancy in problems having short time horizons. With access to a microcomputer [22] or at the leisure of the decision analyst, Markov cohort analyses or Monte Carlo simulations provide more exact calculations of quality-adjusted life expectancy. The availability of a simple formulation for prognostic modeling should be another solid step in the practical application of utility theory to medical decision making.

Appendix A

ANALYSIS OF DISCREPANCIES BETWEEN MARKOV MATRIX AND COHORT FORMULATIONS. The differences between the fundamental matrix solution

of a Markov chain and the cohort analysis using exponentially increasing population mortality rates are analogous to the discrepancies between the DEALE and Gompertz models of life expectancy reported previously [10]. In fact, the DEALE itself describes a two-state Markov model with a 1×1 fundamental matrix whose inverse is simply its reciprocal. The constant probabilities used in the Markov matrix are taken from averaged rates using the DEALE method [3]. To assess the relative and absolute accuracy of constant transition probabilities in Markov medical decision making, two experiments were conducted. The first was designed to test the absolute differences between matrix and cohort formulations of Markov processes. The second experiment was designed to assess whether the optimal choices in quantitative decisions analyzed with the convenient matrix formulation differed notably from repeat analyses using the exponentially increasing population mortality approach.

Design of Experiment 1. In this experiment Markov models with from two to five nonabsorbing states were constructed, and life expectancies were calculated using both matrix and cohort formulations. The cohort model was taken as the "gold standard." Calculations were made for patient ages ranging between 20 and 80, and for diseases with transition probabilities between nonabsorbing states and to the DEAD state from 0 to 0.05/month. In all, 313 488 analyses were performed.

The Markov matrices were developed as follows. One absorbing state (death) was defined. For each of the nonabsorbing states, transition probabilities to death and to any other nonabsorbing state were varied from zero to 0.05, in increments of 0.01, Thus the probability of remaining in the starting state was the greatest single value in every analysis (generally 0.90/month or greater). This general model was developed to reflect clinical examples of Markov processes, in which the greatest single probability is often remaining in one's present state.

Design of Experiment 2. This experiment utilized the results of the first experiment as outcome measures in a prototypical clinical decision. We used the same decision tree as reported previously [10], wherein a hypothetical clinical problem was constructed that contained branches describing immediate mortality (e.g., surgical death) and therapeutic efficacy. Figure 15 shows the two Markov matrices for the problem. The chronic disease has nonabsorbing states WELL and ILL. Constant transition probabilities P_{wi}, P_{wd}, and P_{id} define state transitions. Additionally, there is the risk of death due to other causes and general population mortality (P_g). In the cohort formulation, P_g is calculated by the Gompertz model of exponentially increasing mortality rate. In the matrix analysis, P_g is calculated using the DEALE. If surgery is selected (upper matrix). then there is a risk of operative death, denoted as M. For the purpose of this experiment, we can call "surgery" a state in the Markov model, with two possible transitions, to DEAD or to

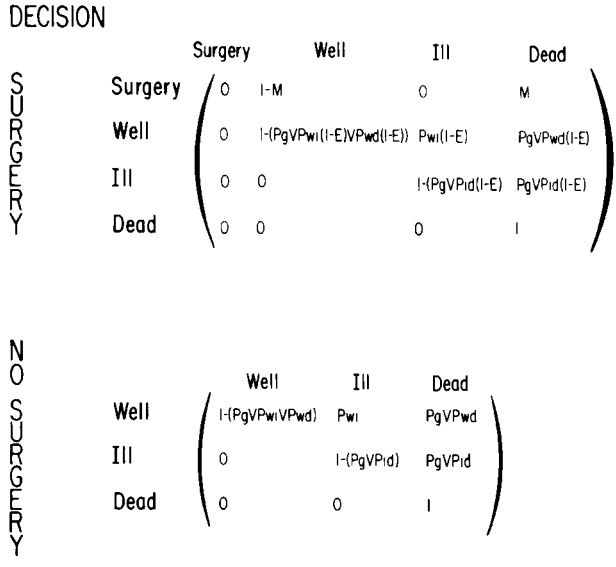

Figure 15. Transition probability matrices for Experiment 2. These matrices represent a Markov decision analysis of surgical versus medical therapy for a hypothetical condition. In the upper matrix, SURGERY is a temporary state leading either to WELL or DEAD. WELL and ILL are clinical states in both models, with DEAD a common absorbing state. Transition probabilities include mortality related to age, sex, and race (general factors, P_g), as well as state transitions related to the hypothetical disease (P_{wi}, P_{wd}, P_{id}). Operative efficacy is denoted by E. The symbol V represents the probability of two independent events occurring together (A V B: A or B occurs). In algebraic terms the probability of A V B (Pr[AVB]) is (Pr[A] + Pr[B] – Pr[A]Pr[B]).

WELL. If surgery is survived, an operative efficacy E reduces the transition probabilities from WELL to ILL and to DEAD as shown. Operative efficacy was varied from 20 percent to 100 percent. In addition, the quality of life associated with the ILL state was varied from 0.1 to 0.9. In all, 22 680 analyses were performed.

Results. Both experiments confirmed the prior experience with the DEALE. For small values of disease-specific mortality, the matrix formulation underestimates life expectancy relative to the cohort formulation. The magnitude of the underestimation does not depend on the number of states directly, but on the magnitude of the excess risk of death relative to the annual mortality rate of the healthy population. Differences between the models are greatest for young patients with small disease-specific excess mortalities; when the monthly excess mortality rate is one percent or

greater, even for a 20-year-old patient the absolute difference in life expectancy between the cohort and matrix formulations is no greater than 14 months. Comprehensive data are available from the authors but are not presented here due to space limitations.

The results of the second experiment indicate that the matrix and cohort models do not lead to different therapeutic decisions, for reasonable combinations of operative risk and efficacy. In over 97 percent of the analyses the two models yielded the same therapeutic decision. For virtually all of the remaining situations, the discrepancy amounted to less than one percent of life expectancy. Only in cases where high operative mortality was coupled with high surgical efficacy were discrepancies greater than one year of life.

The results indicate that the differences between the constant mortality approximation using the DEALE and the exact Markov cohort analysis are analogous to the simple DEALE modeling problem reported previously [10]. The addition of temporary states does not affect the performance of the model, as long as disease-specific transition probabilities remain constant.

Appendix B

DEMONSTRATION OF THE ANALOGY BETWEEN THE FUNDAMENTAL MATRIX OF A MARKOV CHAIN AND LIFE EXPECTANCY. The canonical form of a Markov matrix has four sections (Figure 3). Two sections, labeled I and O, signify that it is impossible to leave an absorbing state. The R section contains the single-step transition probabilities between intermediate or nonabsorbing states and the absorbing state (or states). The Q section is a matrix of single-step transition probabilities among the nonabsorbing states.

The Q matrix has information necessary and sufficient to predict the behavior of a patient entering the Markov process in one of the nonabsorbing states. What follows is a demonstration of the properties of the Q matrix. Interested readers are referred to Kemeny and Snell [4] for a formal proof of these properties.

Matrix multiplication is illustrated in Figure 16. Rows of the multiplicand are projected across columns of the multiplier, so that the product matrix contains elements that reflect the weighted product of the elements of the original two matrices. In effect, this weighted multiplication is analogous to moving forward long a path in a decision tree. The Markov matrix is essentially a "shorthand" representation of an arbitrarily deep tree, with repetitive probabilities at each level of the tree. In the case of the Q matrix, the elements signify the likelihood of a patient being in each nonabsorbing state after a single cycle of the process. When the Q matrix is multiplied by itself,

$$Q \times Q = Q^{(2)},$$

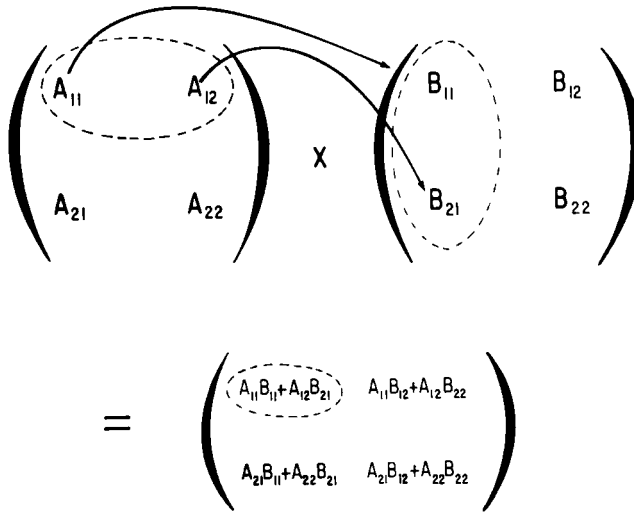

Figure 16. Demonstration of matrix multiplication. An element of the product matrix is formed by multiplying each element of the corresponding row in the multiplicand (first) matrix by its relative element in the corresponding column of the multiplier (second) matrix, and then adding.

the product matrix is composed of elements that reflect the likelihood of the patient being in each nonabsorbing state in two cycles. When this matrix is multiplied again by Q,

$$Q^{(2)} \times Q = Q^{(3)},$$

the elements denote three-step likelihoods of the process being in specific nonabsorbing states. This process can, of course, be repeated indefinitely. With each step, the absolute values of the entries in the Q matrix decreases, because the Markov process has an absorbing state; eventually, everyone will die. Thus

$$Q^{(n)} \to 0,$$

as n gets very large. Eventually, no one will be in a nonabsorbing state.

Because the limit of $Q^{(n)}$ approaches a zero matrix, the sequence

$$I + Q + Q^{(2)} + Q^{(3)} + \cdots$$

is bounded [4] and, upon inspection, represents a matrix of life expectancies. The I matrix is analogous to giving a patient one unit of incremental utility for starting in a particular nonabsorbing state. Q represents that fraction of the cohort not absorbed (i.e., alive) after one cycle, $Q^{(2)}$ that fraction still in nonabsorbing states after two cycles, and so forth. This procedure is identical to summing the surviving cohort in the Markov cohort analysis, as depicted in Table 1.

The sum (let us call it S) is itself a matrix of the same dimensions as Q. If we multiply S by a matrix created by subtracting the transition probabilities Q from an identity matrix I, we have

$$\begin{aligned} S(I-Q) &= (I+Q+Q^{(2)}+\cdots+Q^{(n-1)})(I-Q) \\ &= (I+Q+Q^{(2)}+\cdots+Q^{(n-1)})-(Q+Q^{(2)}+Q^{(3)}+\cdots+Q^{(n)}) \\ &= (I-Q^{(n)}), \end{aligned}$$

letting n be arbitrarily large. But $Q^{(n)}$ approaches zero, so

$$S(I-Q) = I.$$

Because the inverse of $(I-Q)$, $(I-Q)^{-1}$, exists (as is proven in [4]), multiplying both sides by the inverse is a legal matrix algebraic manipulation, and we find a new equation,

$$S(I-Q)(I-Q)^{-1} = I(I-Q)^{-1},$$

or

$$S = (I-Q)^{-1},$$

because multiplying a matrix by an identity matrix is analogous to multiplying a number by 1. Thus S, the sum of the sequence of powers of Q, is equal to the inverse of $I-Q$, or N, the fundamental matrix of a Markov chain. The elements of N are easily seen as expected lengths of time before absorption, or life expectancies, given starting the process in the row state of N.

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Note Added in Proof

While this manuscript was in press, David F. Ransohoff, MD, and his colleagues published a decision analysis in which a Markov process was utilized to calculate survivals. An analysis of their article indicates that they considered three clinical states; "silent," "pain," and "complication." The last two of these states are temporary. State dependent quality adjustments were not made.
(Ransohoff DF, Gracie WA, Wolfenson LB, Neuhauser D: Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. Ann Intern Med 99:199-204, 1983)