LEADING ARTICLE

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An Introduction to Markov Modelling for Economic Evaluation

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Summary

Markov models are often employed to represent stochastic processes, that is, random processes that evolve over time. In a healthcare context, Markov models are particularly suited to modelling chronic disease. In this article, we describe the use of Markov models for economic evaluation of healthcare interventions. The intuitive way in which Markov models can handle both costs and outcomes make them a powerful tool for economic evaluation modelling. The time component of Markov models can offer advantages of standard decision tree models, particularly with respect to discounting. This paper gives a comprehensive description of Markov modelling for economic evaluation, including a discussion of the assumptions on which the type of model is based, most notably the memoryless quality of Markov models often termed the 'Markovian assumption'. A hypothetical example of a drug intervention to slow the progression of a chronic disease is employed to demonstrate the modelling technique and the possible methods of analysing Markov models are explored. Analysts should be aware of the limitations of Markov models, particularly the Markovian assumption, although the adept modeller will often find ways around this problem.

The use of decision-analytical modelling to estimate the cost effectiveness of healthcare interventions is becoming widespread.[1,2] Models have a range of uses including the synthesis of data from various sources and extrapolation from primary data sources. Hence, a sound knowledge of modelling can be an important and powerful tool for economic evaluation.

A particular type of model that is now used frequently in economic evaluation is the Markov model. Markov models have a long history of use in health service decision-making, including clinical and epidemiological applications.[3,4] Health economists are also beginning to use Markov models widely in economic-evaluation studies.[5-8] The fundamental difference between economic and other applications of Markov modelling in medical decision-making is that economists are interested in both the resource and health outcome consequences of healthcare interventions. The way in which Markov models simply and intuitively handle both costs and outcomes simultaneously is one of their strengths.

The aim of this article is to provide an introduction to the use of Markov models for performing economic evaluation. An excellent and comprehensive introduction to Markov modelling has been provided by Sonnenberg and Beck,[9] which we strongly recommend to interested readers. We hope that our article will add additional insight to the use of Markov modelling in economic evaluation. The paper is divided into 3 main sections. The

first section considers some of the advantages of using decision-analytical models as part of economic evaluation. The second section describes the process of constructing Markov models and the assumptions underlying their use. An illustrative example of a Markov model of disease progression is also developed. The third section is concerned with the analysis of Markov models and uses the illustrative example to demonstrate the different options available to the analyst.

1. The Advantages of Decision-Analytical Models

It is becoming recognised that economic evaluation should ideally be undertaken early in the development of a new healthcare technology.[10] However, the evaluative process is not a single event, rather economic analysis should be regarded as iterative. Sculpher et al.[11] have described 4 stages of economic evaluation, and decision-analytical modelling has an important role to play at each stage. Stage I economic analysis is the earliest assessment of the economic characteristics of a new technology and is undertaken when basic scientific investigation has been completed. The focus of analysis at this stage tends to be in defining the scope that exists for the new intervention to be cost effective by estimating the cost and effectiveness of the existing form(s) of management against which the new technology will ultimately compete, and hence, the costs and/or effectiveness the new technology must attain to supplant the existing intervention(s).

Modelling has a major role at stage I, which is characterised by significant uncertainty about particular variables, most notably about the cost and effectiveness of the new intervention. Models provide a way of systematically managing the uncertainty using sensitivity and threshold analysis. Currently, few stage I assessments are being undertaken and even fewer are published. Pharmaceutical companies are beginning to use this form of analysis prior to large investment in phase II and III trials in order to begin to understand the likelihood of a new drug being cost effective at particular price levels.[12]

Stage II economic evaluation is required on all technologies which, on the basis of analysis undertaken at Stage I, were considered to offer some scope for being more cost effective than existing interventions. This stage of analysis is usually undertaken when the intervention is being used on patients in a few specialist centres which produce data in the form of case series and small randomised trials. Again, modelling is crucial to this stage of analysis. One major role of the model is to assist in the design of the trial-based economic evaluation that tends to be undertaken subsequently. For example, models can identify particular parameters to which the cost effectiveness of the new intervention is likely to be sensitive, and this will help in decisions regarding data collection and sample size determination in later trials. Indeed, stage II models can be used formally to evaluate the cost effectiveness of proposed trials by assessing the value for money of the additional information they provide.[13,14]

Stage III economic evaluation is probably the most prevalent in terms of publications. Although the randomised trial is widely seen as the ideal data collection vehicle for this stage of analysis, the model still has a major role. Often stage III analysis is based on the synthesis of data from various sources. For example, although randomised trials had been undertaken to assess the clinical effectiveness of *H. pylori* eradication therapy for ulcer-related dyspepsia, in order to assess the potential cost effectiveness of a strategy of screening all patients with dyspepsia and providing eradication therapy to those with confirmed ulcer, it was necessary to synthesise a range of trial, observational and epidemiological data using a modelling framework.[8] Indeed, given the desire not to overload trials with enormous amounts of data collection and to increase the generalisability of the analysis, trials may not be the ideal vehicle for the collection of all data for economic analysis.

Models are also an important element of stage III analysis when trial data are only concerned with

an intermediate measure of outcome. In these circumstances, models can estimate the effects of changes in this clinical outcome on the long term costs, morbidity and mortality of the disease. For example, whereas most clinical trials of drug therapies to reduce serum cholesterol levels assessed effectiveness in terms of percentage changes in cholesterol levels, estimates of cost effectiveness required the development of models to link this reduction to changes in life expectancy.[15] Even where such trials do continue for long enough to have mortality as a major outcome measure,[16,17] economic evaluations will most likely be concerned with lifetime costs and effectiveness, and hence will have to use modelling techniques to extrapolate the observed results.[18]

Of course, many stage III evaluations are based on much shorter time horizons, usually mirroring the clinical data collection in the trials, which might only have a follow-up of 1 or 2 years. Again, in this situation, modelling can be used to extrapolate cost and effectiveness estimates over a longer time horizon using available epidemiological and natural history data. For example, in an economic evaluation of 2 thrombolytic therapies for acute myocardial infarction, a clinical trial provided 1-year survival data but long term survival was modelled using data from an observational database.[19]

Stage IV analysis is concerned with evaluating the cost effectiveness of interventions when they are used in routine clinical practice. Many stage III analyses are based on trials undertaken in artificial clinical contexts involving unrepresentative patients which may generate inappropriate estimates of the cost effectiveness of interventions when they diffuse widely into clinical practice. In this situation, models can be used as a framework to synthesise data to explore how routine data collected from a range of centres subsequent to the trial might alter the results of the stage III analysis.[20]

Decision-analytical models, therefore, have an important role to play at each stage of the economic evaluation process. Ideally, modelling should be initiated at stage I of the evaluative process and the economic model should be dynamically updated as the analysis proceeds through each evaluative stage.

2. Markov Models of Medical Prognosis

Markov models are generally used to represent stochastic processes, that is random processes which evolve over time. In the field of medical decision analysis, they are particularly suited to modelling the progression of chronic disease. The disease in question is divided into distinct states and transitions probabilities are assigned for movement between these states over a discrete time period known as a 'Markov cycle'. By attaching estimates of resource use and health outcome consequence to the states and transitions in the model, and then running the model over a large number of cycles, it is possible to estimate the long term costs and outcomes associated with a disease and a particular healthcare intervention. The types of Markov states, the setting of transition probabilities and the attaching of cost and outcome data are described in detail below.

2.1 Markov States

When constructing a Markov model of disease progression, the first task is to define the disease in terms of different states. These states should be chosen to represent, clinically and economically, important events in the disease process that is to be modelled. The states should also be mutually exclusive since one of the requirements of a Markov model is that a patient cannot be in more than 1 state at any one time.

A simple illustrative Markov model of disease progression is presented in figure 1. The model consists of just 3 states to characterise a chronic disease. These states are represented by the ovals and possible transitions between these states are shown by the arrows joining the states. This form of state transition diagram is a simple and convenient method to illustrate Markov models. The first state of the disease process in figure 1 is defined as an 'asymptomatic' disease state, indicating that a patient has acquired a disease, but is not experiencing any ill consequences of the disease nor is the

patient at any greater risk of death than an equivalent individual without the disease. From this disease state, patients can move to either the 'dead' state (with transition probability equal to the all-cause mortality excluding the disease in question) or to the 'progressive' disease state. It is this disease state which characterises the more unpleasant aspects of the disease, with the patient experiencing the symptoms of the disease and experiencing an increased risk of death as a direct result of the disease over and above the all-cause mortality risk. States of Markov models from which it is impossible to leave are known as 'absorbing states', the most common example of an absorbing state is death (fig. 1). Also, notice that the backward bending arrows returning to the state that they left in figure 1 show that it is possible for patients to remain in the states they were in during the previous cycle. Although not illustrated in figure 1, some models might allow for improvement in the clinical condition. For example, patients with progressive disease might move back to an asymptomatic disease state if their disease goes into remission.

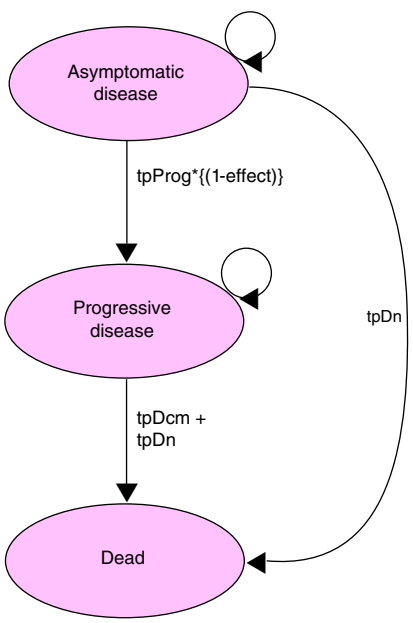

Fig. 1. Illustrative Markov model of disease progression. Disease states are represented by ovals and possible transitions between those states are shown by arrows. Variable names adjacent to the arrows are the transition probabilities for the model. *Abbreviations:* effect = effectiveness of drug in terms of reducing disease progression; tpDcm = transition probability to the death state caused as a direct result of the disease; tpDn = transition probability to natural death; tpProg = transition probability to progression.

2.2 Transition Probabilities

Transitions are assumed to take place for each cycle of the model. In a model comprising k states, all possible transitions between those states are given by a k k transition matrix. Of course in practice, many of these may be set to 0, hence, reducing the number of transition probabilities to be estimated. For example, in our model illustrated in figure 1, there are 3 states and 9 possible transitions between those states. However, it is assumed that patients do not recover from their progressive disease, hence, transitions from dead to progressive disease, progressive to asymptomatic disease or dead to asymptomatic disease are ruled out. Also, since the probability of moving to states in each cycle must sum to 1 (since patients must be in 1 and only 1 state at any given time), the probability of staying in the same state in a given cycle is simply 1 minus the probability of leaving that state. Therefore, of the 9 possible transitions in our model, we have only to estimate 3 transition probabilities: (i) moving from the asymptomatic to the progressive disease state (tpProg); (ii) dying when in the asymptomatic state from a condition other than the disease in question (tpDn); and (iii) dying when in the progressive disease state [from either the disease itself (tpDcm) or from an unrelated condition (tpDn)]. Table I shows the transition matrix for the model in figure 1 using the variable names set out above. Note that each row of the matrix sums to 1.

An important limitation of the Markov model is that the probability of moving out of a state is not dependent on the states a patient may have experienced before entering that state. This is the 'memoryless' feature of Markov models which is often referred to as the 'Markovian assumption'. It

is important for analysts to be aware of this assumption when constructing models since it may be seen to be limiting in some cases. However, the adept modeller will often find ways to get around the more constraining aspects of the Markovian assumption by using a combination of distinct states to model particular patient histories and the use of time-dependent transition probabilities. For example, in a coronary heart disease (CHD) model, once a CHD event has occurred, the patient could be modelled as entering a disease state which specifically represents the experience of patients with a history of CHD events, with correspondingly altered transition probabilities.

Two different types of Markov model can be characterised by the form of the transition probabilities. In Markov chains, all the transition probabilities are assumed to be constant over time. This has distinct analytical advantages since the probability of being in a particular state at a particular point in time can be calculated simply by raising the transition matrix to the power of the appropriate cycle. It is clear, however, that an assumption of constant transition probabilities may be too restrictive for many potential applications in the health field. Consider a very simple Markov model characterised by just 2 states: alive and dead. For all but the shortest of time periods, it would be fallacious to assume that the risk of death was constant. In fact, the risk of all-cause mortality for adults can be approximated quite accurately using an exponential function.[21,22] The more general Markov models, where transition probabilities can vary over time, are known as time-dependent Markov processes. These are less convenient to represent in terms of matrix algebra, but are much more flexible with regard to the modelling of chronic disease.

In terms of figure 1, the transition probability of moving from the asymptomatic to the progressive state of the disease is assumed to be an increasing function of the time (i.e. the cycle of the model). Similarly, the risk of death from all causes is assumed to be time-dependent. By contrast, the risk of death from the disease itself is assumed to be constant. This is mainly due to the desire to keep this illustrative example simple. However, suppose we felt that this assumption did not adequately characterise the disease process, perhaps because the chance of dying from the progressive form of the disease is thought to increase with time. Notice that we cannot make the transition probability tpDcm ('progressive disease' to 'dead') in figure 1 dependent on the time patients have spent in the progressive disease state since the Markov model treats all patients in the progressive disease state the same, although they may have entered that state at different cycles of the model (hence, we have a problem with the Markovian assumption of no memory). It may be possible to get around this problem by characterising the progressive part of the disease as tunnel states (tunnel states are a series of temporary states that must be visited in a fixed sequence[9]). Consider figure 2 as an alternative formulation of the model in figure 1. We still have a Markov model since the 2 requirements of patients only being in 1 state at any one time and state transition probabilities independent of previous states of the model apply. However, in this model, tunnel states are employed to define the experience of patients through (3) progressive stages of disease leading ultimately to death (the absorbing state).

A final word of caution is appropriate when calculating transition probabilities for Markov models. The terms rates and probabilities are often used interchangeably in the literature, although a rate is in fact an instantaneous likelihood of transition at any point in time, whereas a probability is the proportion

Table I. Transition matrix for the illustrative model

Transition from	To			Total
	asymptomatic	progressive	death	
Asymptomatic	1 – tpProg – tpDn	tpProg	tpDn	1
Progressive	0	1 –tpDcm	tpDcm	1
Dead	0	0	1	1

Abbreviations: tpDcm = transition probability to the death state caused as a direct result of the disease; tpDn = natural death rate (i.e. death as a result of other causes not directly as a result of the disease in question); tpProg = transition probability to progression.

of a population at risk that makes a transition over a specified period of time. A detailed discussion of the distinction between rates and probabilities can be found in Miller and Homan.[23] Since Markov models concern transitions over specified time periods, it is transition probabilities that are appropriate to Markov modelling (even if incorrectly referred to as rates in the literature). The problem is that probabilities available in the literature may not refer to the same period of time as the chosen Markov cycle. Suppose we wish to use a published probability of death over 5 years as the basis for a death transition probability estimate in a Markov model based on a yearly cycle. We cannot simply estimate the yearly transition probability by dividing the 5-yearly probability by 5 since this will overestimate the 5-year probability of a transition due to the effect of compounding. Instead we can use the following formula:

$$tp_1 = 1 - (1 - tp_t)^{1/t}$$

where tp_1 is the yearly transition probability we wish to estimate and tp_t is the overall probability over time period t.

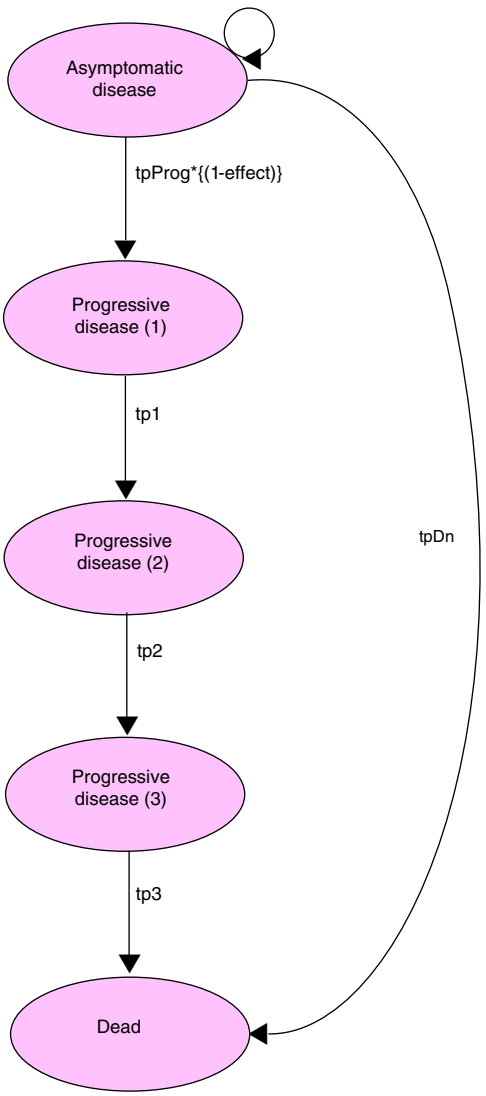

Fig. 2. Possible alternative formulation of the illustrative model which defines the experience of progressive disease. *Abbreviations:* effect = effectiveness of drug in terms of reducing disease progression; tp = transition probability; tpDn = transition probability to natural death; tpProg = transition probability to progression.

2.3 Attaching Weights to the Markov Model

In order to complete the Markov model, it is necessary to attach weights to the model for the cost and health outcome quantities to be estimated. The easiest way to see this is in terms of predicting life expectancy from the model. A weight of 1 is attached to each state of the model in which the patient is alive and a weight of 0 is attached to the dead state. Running the model over a large number of cycles and summing the weights across those cycles gives an estimate of the average life expectancy of the patient in terms of the model cycle length. This can then be multiplied by the length of the cycle in years to give life expectancy in years. In economic evaluation, analysts are often interested not only in life expectancy but also in quality-adjusted life-years (QALYs). Since the construction of QALYs involves weighting the length of time spent in a particular state of health by a value representing quality of life experienced in that state of health, Markov models are particularly suited to the calculation of QALYs. Attaching weights to the Markov states that represent quality of life on a standard 0 to 1 scale will generate a

QALY score when summed over a large number of model cycles.

The calculation of costs over the lifetime of the model follows the same method. The costs of spending 1 cycle in each of the states of the model are attached to that state, the model is run over a large number of cycles and the total cost obtained by summing across those cycles. However, when calculating costs it is often useful to attach costs not only to the states of the model themselves, but also to transitions between states, which might represent single treatment events. For example, in terms of the model in figure 1, while there is clearly no cost associated with spending a cycle in the dead state, there may be important costs associated with the process of dying itself, particularly since the most intensive care a patient receives may be in the last few days of life. Hence, it may be appropriate to attach a 'cost of dying' to the transition between the progressive disease state and death, as well as the state costs associated with the asymptomatic and progressive disease states of the model.

2.4 Adjustments to the Cost and Outcome Quantities

There are two types of adjustments to costs and outcomes that analysts will want to consider when constructing a Markov model. The first involves discounting adjustments for differential timing and the second is the principle of half-cycle correction.

2.4.1 Discounting

It is standard practice in economic evaluation to adjust costs and outcomes for differential timing by applying a rate of discount which allows comparison of costs and outcomes in terms of a net present value (NPV). The standard discounting formula is given by:

$$V_0 = \frac{V_t}{(1+r)^t}$$

where V_0 is the equivalent current value at time zero (or NPV), V_t is the value at time t and r is the rate of discount. In a standard decision tree type of decision-analytical model, costs and outcomes may be specified which span a considerable time frame, e.g. 20 years. The analyst then has to make a difficult judgement – how should these costs and outcomes be discounted? The most common approach is to discount all costs and outcomes as if they had occurred at the midpoint of the time scale, e.g. 10 years, although different approaches are possible, all of which may produce different results.[24] In contrast to standard decision trees, Markov models, since they deal explicitly with the dimension of time, allow discounting of costs and outcomes at the point in time that they occur in the model. Hence, providing the model is appropriately constructed, Markov models will automatically discount both costs and outcomes correctly, with the cycle number (in years) feeding in directly to the formula above.

Given the recent controversy surrounding whether it is appropriate to discount costs at the same rate as health outcomes,[25,26] it is advisable that Markov models are constructed with separate discount rate variables for costs and outcomes such that the analyst can explore the potential importance of differential discounting in their sensitivity analysis.

2.4.2 Half-Cycle Corrections

Markov models assume that transitions occur between cycles and that the patient membership of each of the states of the model is constant for the duration of the cycle. In reality of course, patients will be moving between the different phases of their disease continuously, not at discrete points in time. Rather than assume that patients move between states at the beginning or the end of a cycle, a half-cycle correction can be employed, which is equivalent to an assumption that, on average, patients will move between states half way through the cycle. Such half-cycle corrections will be most important for the health outcome predictions of the model, particularly life expectancy, since without a half-cycle correction Markov models will either consistently overestimate or underestimate life expectancy.[9] However, the extent to which this is a significant problem will depend on the cycle length chosen for the model. The longer the cycle length,

Table II. Parameter values for the illustrative Markov model of disease progression

Name	Value	Description
Transition probabilities		
tpProg	0.01	Coefficient of increase for probability of entering the progressive disease state
tpDcm	0.15	Probability of dying from the disease in a single cycle
tpDn	0.0138	Other cause mortality for age 55 to 64
	0.0379	Other cause mortality for age 65 to 74
	0.0912	Other cause mortality for age 75 to 84
	0.1958	Other cause mortality for age 85 and over
Costs (£)		
cAsymp	500	Cost of 1 cycle in the asymptomatic disease state
cProg	3000	Cost of 1 cycle in the progressive disease state
cDrug	1000	Cost of drug for 1 cycle
cDeath	1000	Cost associated with transition to the dead state
Quality-of-life adjustments		
uAsymp	0.95	Quality-of-life weight for 1 cycle in the asymptomatic disease state
uProg	0.75	Quality-of-life weight for 1 cycle in the progressive disease state
Other parameters		
Cycle	1	Length in years of 1 cycle
Effect (%)	50	Effectiveness of drug in terms of reducing disease progression
Initial age	55	The initial age (in years) at which patients are deemed to start the model
oDR (%)	6	Discount rate for outcomes
cDR (%)	6	Discount rate for costs

Abbreviation: £ = pounds sterling.

the more important it will be to include a half-cycle correction.

For economic evaluation, however, the importance of the half-cycle correction is less clear. In an economic analysis, the outcomes of interest are the additional costs of one therapy over another compared with the additional health benefits. Therefore, although the magnitude of the costs and health outcomes of an economic analysis may be significantly affected by a half-cycle correction, the differences are not likely to be affected. If the analysts are intending to report the magnitude of the costs and outcomes in the analysis or, for example, estimates of life expectancy, then half-cycle corrections will most likely be required. If, however, only an incremental analysis is to be reported, then half-cycle corrections are unlikely to affect the results and can be omitted.

3. Analysis and Presentation of Markov Models

Markov models have a long history of use in many areas of mathematical science predating the use of computers. One of the traditional advantages of Markov chain models, which have constant transition probabilities, is that they can be solved using simple matrix algebra from the transition matrix to yield a matrix solution showing the time spent in each state and the overall expected value of each outcome. This matrix solution is simple to execute and provides an exact solution. However, the main limitation with this approach is that it is limited to models with constant transition probabilities. Such models rarely characterise disease processes, as argued in section 2.2. Furthermore, matrix algebra solutions cannot incorporate discounting formulae into the model.

The increasing application of Markov models in medical decision-making and, more specifically, economic evaluation of healthcare interventions, is most likely due to the increasing use of personal computers. Spreadsheet packages and, more recently, dedicated decision-analysis software allow iterative solutions to Markov models which are not associated with the technical complexity of a matrix algebra solution, and which more importantly are not limited to the special case of constant transition probabilities. Hence, below we describe 2 solutions to the more general Markov process type model: cohort simulation and individual simulation.

These solutions are not necessarily alternatives. Depending on the application, the results provided by these models may prove complementary and we focus on how the results of these solutions may be presented using the illustrative model introduced previously (fig. 1).

Before describing these techniques, however, the illustrative example is defined in full. Table II gives full details of all the transition probabilities, costs, quality-of-life adjustments, discount rates and treatment effectiveness required to operationalise the Markov model of disease progression from figure 1. In terms of the economic evaluation itself, the decision problem is whether to implement a new drug therapy that can reduce the rate of disease progression. Hence, the relevant comparison is the Markov model of disease progression without drug therapy (equivalent to a current practice scenario) with the Markov model including drug therapy (equivalent to the new scenario if drug treatment is implemented). This comparison is illustrated as a decision tree in figure 3. The square decision node indicates that a choice has to be made. The 2 arms emanating from this node lead to 2 Markov models of disease progression: one including drug therapy and one without. The efficacy of the drug therapy from table I is assumed to reduce the rate of progression from the asymptomatic disease state in figure 1, for the patients receiving the drug. Hence, in an economic analysis, we are interested in the incremental costs and the incremental effectiveness of the drug therapy compared with no drug treatment. Where one arm does not dominate (i.e. is not both more effective and less costly) then an incremental cost-effectiveness ratio (ICER) can be calculated from the following formula:

$$\text{ICER} = \frac{C_T \quad C_C}{E_T \quad E_C} = \frac{C}{E}$$

where C_T and E_T are the costs and effects associated with the drug therapy (or treatment) arm and C_C and E_C are the costs and effects associated with the no drug therapy (or control) arm. It is these quantities which we are seeking to estimate from the Markov model.

3.1 Cohort Simulation

The cohort simulation approach to solving the Markov model is straightforward. A hypothetical cohort of, for example, 1000 patients serves to illustrate the experience of patients as predicted by the model. The usual assumption is that the whole cohort begins the model at time 0 in the initial disease state (asymptomatic disease in our model), although if necessary, the cohort can be distributed between all the model states. At each cycle of the model the appropriate transition probabilities are applied and the distribution of patients in each state of the Markov model is adjusted. Running this analysis for many cycles builds up a 'profile' of how many patients are in each state of the model over time. Table III presents the results of this cohort simulation for the disease progression model in figure 1 (in the absence of drug therapy) for the first 10 cycles of the model. The middle 3 columns show the number of patients in each state of the

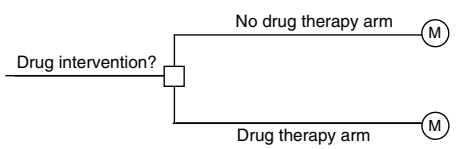

Fig. 3. The economic evaluation decision: should drug therapy be implemented? *Abbreviation:* M = Markov model of disease progression (not shown).

Table III. Cohort simulation for the illustrative model (no drug therapy)

Cycle	Disease state			Total
	asymptomatic	progressive	death	
0	1000	0	0	1000
1	976	10	14	1000
2	943	28	29	1000
3	902	52	46	1000
4	854	79	67	1000
5	799	109	92	1000
6	740	139	121	1000
7	678	168	154	1000
8	614	195	191	1000
9	551	218	231	1000
10	488	237	275	1000

model. At the start of the model, the whole cohort (1000 patients) begins the model in the asymptomatic disease state. The last column shows that the sum of the patients in each state of the model adds up to the original number of patients: i.e. each patient must be in one and only one disease state at any given time.

An alternative presentation is given in figure 4 for the cohort simulation. The cohort is presented as a cumulative proportion chart showing exactly what proportion of the cohort is in which state at a given time (or model cycle). Furthermore, the reduction and delay of disease progression induced by the drug therapy is shown as the difference between the no drug therapy chart (fig. 4a) and the drug therapy chart (fig. 4b). For example, after 15 cycles the model predicts that, in the absence of drug therapy, just 20% of the original cohort will remain asymptomatic while a further 22% will be in the progressive stage of the disease and 58% of the original cohort will have died. By contrast, the model predicts that with drug therapy, 38% of patients will still be asymptomatic after 15 cycles, 16% will be in the progressive stage of the disease and 46% of the cohort will have died.

Such graphical presentations of the Markov model can be useful for validating the model with clinical experts, as well as conducting economic analysis, since it is clear from these diagrams what underlying predictions of disease progression are being generated by the Markov model. Analysts may want to consider presenting these sorts of figures as a means of making the modelling process and disease progression predictions of the model explicit, before going on to consider the economic predictions of the model.

Notice from the representation in figure 4 that the upper bound of the shaded area representing the progressive phase of the disease is equivalent to the survival curve for the cohort predicted by the model. Again, for the purposes of validating the model, this predicted survival curve could be compared with observed data on survival. Of course, in an economic analysis we are most often interested in QALYs. By weighting the quality of life of the state by the length of time in the state and the number of patients from the cohort in the state, an estimate of the number of QALYs experienced by the cohort is obtained for each cycle. Summing across

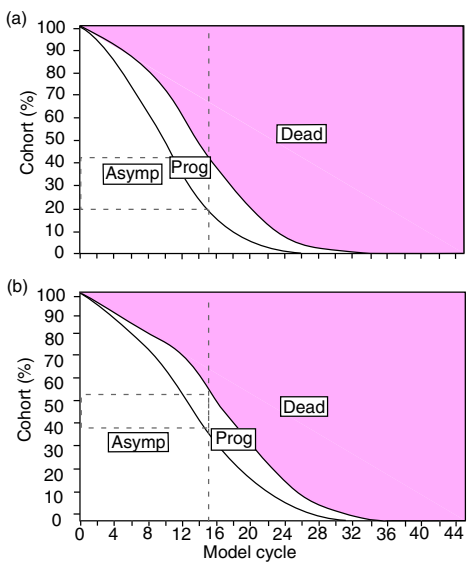

Fig. 4. Results of a cohort simulation for the illustrative model without drug therapy (a) or with drug therapy (b) presented as a cumulative proportion of the cohort by disease state over time. *Abbreviations:* Asymp = asymptomatic; Prog = progressive stage of disease.

all cycles of each model generates the QALY estimates for each arm.

Cost estimates for the overall cohort of patients are generated in the same way by summing the costs for patients across the different states for each cycle then summing the cycle costs across all cycles of the model. In addition, costs associated with transition between states (in this model, the cost of the transition between 'progression' and 'dead') are added in to the total costs. The results of the illustrative model presented above for a cohort simulation of 1000 patients are given in table IV. The model clearly predicts that the implementation of a new drug will be both more effective and more expensive than the existing profile of care. Hence an ICER of 7931 pounds sterling (£) per QALY is calculated as the summary value for money measure of the drug intervention.

Table IV. Results of a 1000-patient cohort simulation for the illustrative model

Strategy	Cost (£)	QALYs
No drug	9 264 897	7756
Drug	16 155 440	8625
Difference	6 890 544	869
ICER	7931 per QALY	

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years; £ = pounds sterling.

3.2 Individual Simulation

The other method for evaluation of Markov models is individual (or Monte Carlo) simulation. Rather than start a whole cohort of patients through the model together, a large number of patients are followed through the model individually. The difference between these 2 methods is that although individual patients are subjected to the same probabilities of transition as the cohort of patients above, since an individual patient can only be in 1 state at a given time, they may or may not transit between states in any given cycle. Hence the path followed by different patients will differ due to random variation. Following the patient through the model allows an overall profile of costs and outcomes to be generated for that patient according to the path that they follow through the model. For example, the first patient through our model may live for 15 years in the asymptomatic phase of the disease and a further 5 years in the progressive disease state before dying. Thus, as an individual, they are predicted to cost £10 423 while they accrue 10.5 QALYs. By contrast, the second patient through the model may live for only 5 years in the asymptomatic phase of disease and for only 1 year in the progressive disease state before dying. This patient will therefore have a predicted cost of £4886 and will have accrued 4.5 QALYs. Averaging these costs and effects over a large number of patients gives the overall estimate of the average costs and effects in each arm.

The results of 10 000 simulations of individual patients through each arm of the model are given in table V. It is clear that the (per-patient) estimates of the average costs and effects for each arm of the model are very similar between tables IV and V. In fact, the cohort simulation method is more precise than the individual simulation method since it gives an exact solution for the chosen cycle length. By contrast, the individual simulation method will not give the same results on any 2 occasions due to the random nature of the simulation. Providing the number of simulations over which the results are averaged is very large, the differences between the 2 methods are likely to be small and insignificant. The advantage of the individual simulation method is that it gives an estimate of the likely variance associated with the parameters estimated by the model – note the estimated standard deviations in parentheses in table V. This representation of uncertainty in the estimated cost and effects relates simply to the inherent uncertainty of the probabilistic structure of the model and is often termed a 'first order' Monte Carlo simulation. Second order Monte Carlo simulations, which in addition allow the parameters of the model to vary over a given range with a given distribution can also be conducted. However, they are deemed to be beyond the scope of this introductory paper.

Table V. Results of 10 000 simulations of individual patients for the illustrative model

Strategy	Cost (SD) [£]	QALYs (SD)
No drug	9258 (5658)	7.74 (2.89)
Drug	16 108 (5977)	8.59 (3.09)
Difference	6850	0.85
ICER	8059 per QALY	

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life-years; SD = standard deviation; £ = pounds sterling.

4. Conclusion

Although economic analysis is increasingly being conducted alongside clinical trials, it is clear that economic-evaluation modelling will be important for 2 reasons. First, for various reasons including scarce evaluative resources, clinical trials cannot be undertaken for all interventions.[27] Economic modelling is a relatively cheap and effective way of synthesising existing data and evidence available on the costs and outcomes of alternative interventions. Economic evaluation by decision-analytical modelling is an important preliminary to the design of a prospective economic evaluation alongside a clinical trial since modelling can identify critical variables appropriate to the economic analysis. In addition, economic models may obviate the need for a trial if the synthesis of existing evidence suggests that scarce evaluative resources would be better employed elsewhere. Second, even where economic analysis is undertaken alongside a clinical trial, for many interventions, the necessity to extrapolate beyond the follow-up of a trial or from an intermediate to a final health outcome will mean that some form of modelling will be required.

Markov models are particularly suited to the modelling of disease progression over time. In particular, the intuitive way in which Markov models can simultaneously handle both the costs and effects (and therefore the covariance between them) means that they are likely to prove an invaluable addition to the economic analyst's toolbox. Although, some of the assumptions on which Markov models are based may be restrictive in some circumstances (particularly their memoryless quality), the adept modeller will often find ways around these limitations using a combination of time-dependent transition probabilities and distinct disease states to model particular patient histories.

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