Cost-Effectiveness Analysis of Treatments for Chronic Disease: Using *R* to Incorporate Time Dependency of Treatment Response

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When constructing decision-analytic models to evaluate the cost-effectiveness of alternative treatments, we often need to extrapolate beyond the available experimental data, as these typically relate to a limited period starting from the initiation of a new treatment or the diagnosis of the current disease state. We may also be required to extrapolate beyond the available experimental evidence to compare potential treatment sequences. Markov models are often used for this extrapolation. These models have the defining assumption that future transition probabilities are independent of past transitions. This means that, in general, transition probabilities cannot be conditional of the time spent in a given state. Where data exist to show that the risks of transition are conditional on the time spent in the treatment state, the simplifying Markov assumption can result in a loss in the model's "face validity," and misleading results might be generated. Several methods are available to incorporate time dependency into transition probabilities based on standard methods and software. These include the inclusion of tunnel states in Markov models and patient-level simulation, where a series of individual patients are simulated. This article considers the features and limitations of these methods and also describes a novel approach to building time dependency into a Markov model by incorporating an additional time dimension resulting in a "semi-Markov" model. An example of the implementation of such a model, using the R *statistical programming language, is illustrated using a cost-effectiveness model for new epilepsy therapies.* ***Key words:*** *cost-effectiveness analysis; Markov models; time dependency* ***(Med Decis Making 2005;25:511–519)***

The continuing development of novel treatments for chronic diseases offers great potential health benefits, but these may be associated with high direct medical costs. Cost-effectiveness analysis of these treatments is becoming increasingly important in prioritizing the allocation of scarce medical resources. When constructing decision-analytic models to identify appropriate management of chronic disease, we often need to extrapolate beyond the available data, which typically relate to a limited period starting from the initiation of a new treatment or the diagnosis of the current disease state. In addition, we may also be required to extrapolate beyond the available data to model cost-effectiveness for a set of potential treatment sequences.

Markov models are often used for these extrapolations. These models represent disease progression as a series of discrete states. A vector representing the current probabilities of a patient occupying each state is repeatedly multiplied by a transition matrix representing the probabilities of each of the possible transitions between states. This generates vectors representing the patient's probability of occupying each state during each cycle. The effect of a treatment is typically incorporated into the model as an alteration in the transition probabilities. The expected costs and effects for the treatments being evaluated are then calculated based on the estimated costs and effects associated with each of the discrete states.

A defining restriction in a Markov model is that the probability of a given future transition is conditional

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only upon the current state occupied, and so it is independent of the transition history.[1–3] In general, this is likely to preclude incorporating time-dependent transition probabilities into most Markov models. Although comparative clinical trial data are often of short duration, long-term data from open-label trials or epidemiological studies may exist, which allows the form of the time dependency of treatment effect to be estimated. Consider the case in which the probability of treatment failure declines as the time on treatment increases—the longer a patient has responded to treatment, the less likely he or she is to suffer treatment failure. If we assume that treatment effects are simply maintained following the trial period—that there is no failure after the trial—we will overestimate the benefit of the more active treatment. In contrast, if we assume that failure continues at the same rate as observed during the trial, we will underestimate the benefit of more active treatment. Both assumptions will lack face validity and may lead to incorrect treatment choices. The converse will occur for treatments that can only be tolerated for a limited amount of time, and the probability of treatment failure increases with time. To ensure that appropriate choices are made regarding the structure of decision models for cost-effectiveness, state transition models that can incorporate time dependency into transition probabilities should be considered.

The purpose of this article is to consider alternative ways of introducing time dependency into Markov models. The 1st section discusses alternative methods for incorporating time dependency using standard modeling approaches and the strengths and weaknesses of each approach. We then go on to describe the implementation of semi-Markov models using the statistical programming language *R*. A case study is used to illustrate the method based on a recent cost-effectiveness analysis of new treatments for epilepsy. Finally, we compare Markov models to patient-level simulation, another modeling method that has been suggested as a means of introducing time dependency.

INCORPORATING TIME DEPENDENCY INTO MARKOV MODELS

Time Dependency as a Function of Time in the Model

Transition probabilities in state transition models may be time dependent in 2 ways. The probability may vary as a function of the time elapsed from the start of the model, in which case the model may be referred to as a Markov model.[4] Such a model would be appropriate in which the age of patients at the start of the modeled period is defined and where the probability of a transition is a function of the patient's age—for example, where the probability of death is estimated as function of age based on life tables. This sort of Markov model may be easily implemented by revising the transition matrix for each model cycle to reflect the time dependency. For instance, the probability of transitions to the "death" state can be altered according to actuarial tables to reflect the increased risk of death as the cohort of patients being modeled ages.

Time Dependency as a Function of Time in a State

A 2nd form of time dependency is where 1 or more transition probability varies as a function of the time from entry to the current state (often referred to as the "sojourn" time). Such a model may, for example, be appropriate when comparing treatments for cancer, where patients may enter a "remission" state following treatment, and the longer they stay in that state, the lower the risk of recurrence. The ease with which this form of time dependency can be implemented in a Markov model depends on where it occurs in the model.

Time Dependency with Respect to Time in the Starting State

If we are only interested in the time dependency as a function of the time in the current state for the *starting* state of a Markov model, and it is not possible to reenter this state once it has been left, this can be easily addressed because the model simplifies to a Markov model. An example of such a model was developed by Briggs and others[5] to consider the cost-effectiveness of alternative hip prostheses in primary total hip replacement (THR). In this model, all patients started in a "primary THR" state, but all patients surviving primary surgery made the transition to the "successful primary THR" state in the next cycle. Hence, all "patients" in the latter state, at any point in the model, would have been there for the same number of cycles. Two possible transitions were feasible from this state—death and the need for a repeat surgical procedure ("revision THR"). For both of these transitions, time dependency was feasible. In the case of transitions to the "death" state, these were based on age-dependent mortality risks from routine life tables. In the case of movement to the revision THR state, the transition probability was modeled as a parametric function of time in the successful primary THR state into which all surviving patients had moved after the 1st cycle.

Use of Tunnel States

Models in which "patients" enter a state at different time points, where the probability of moving from that state is time dependent, are less straightforward to implement, however. Reflecting this form of time dependency requires a relaxation of the standard Markovian assumption that transition probabilities are independent of previous states that occupied the model. Such a model has been referred to as a semi-Markov model.[4] It is possible to implement a semi-Markov model in 2 ways. One approach is to add further "tunnel" states to the model.[2] These are states that an individual can only occupy for 1 cycle and represent both the disease state the individual is in and the number of previous cycles spent in this state. An example of the use of tunnel states is shown in Figure 1 in the context of a cancer model. The model assumes that the probabilities of moving to the death or progression states from a remission state are dependent on how long a patient has been in remission. Specifically, these risks are higher in years 1 and 2 after treatment but, after that, remain stable with respect to time. To reflect this in the Markov model, we would define a series of 3 tunnel states representing remission: 1 year in remission, 2 years in remission, and more than 2 years in remission. By using "tunnel" states, we effectively rearrange the model as a Markov model.

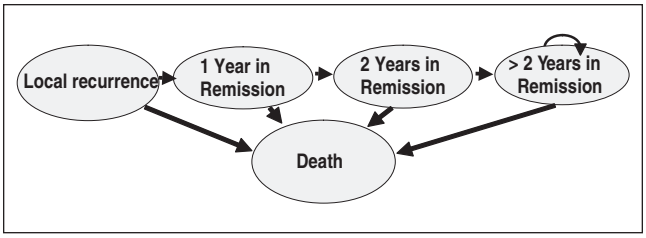

Figure 1 An example of the use of tunnel states in the context of a cancer model.

A limitation of this approach is that the transition matrix becomes large as the number of states and total number of cycles increase. Consider, for example, a semi-Markov model in which individuals may occupy n different states over a total of T cycles. This would involve a transition matrix incorporating tunnel states of $n.T$ by $n.T$ (Figure 2). Consequently, the implementation of semi-Markov models in Excel or specific decision-analytic software can be cumbersome, lack transparency, and be extremely difficult to validate.

Use of a 3-Dimensional Transition Probability Matrix

An alternative is to use a 3-dimensional matrix of transition probabilities, with dimensions for current state, future state, and time in current state (Figure 3).

		To							
		State 1 (t=2)	State 1 (t=3)	State 1 (t=4)	…	State 2 (t=2)	State 2 (t=3)…	State 2 (t=4)…	…
From	State 1 (t=1)	P[1→1]|t=1	0	0	…	P[1→2]|t=1	0	0	…
	State 1 (t=2)	0	P[1→1]|t=2	0	…	0	P[1→2]|t=2	0	…
	State 1 (t=3)	0	0	P[1→1]|t=3	…	0	0	P[1→2]|t=3	…
	…	…	…	…	…	…	…	…	…
	State 2 (t=1)	P[2→1]|t=1	0	0	…	P[2→2]|t=1	0	0	…
	State 2 (t=2)	0	P[2→1]|t=2	0	…	0	P[2→2]|t=2	0	…
	State 2 (t=3)	0	0	P[2→1]|t=3	…	0	0	P[2→2]|t=3	…
	…	…	…	…	…	…	…	…	…
	State 3 (t=1)	P[3→1]|t=1	0	0	…	P[3→2]|t=1	0	0	…
	State 3 (t=2)	0	P[3→1]|t=2	0	…	0	P[3→2]|t=2	0	…
	State 3 (t=3)	0	0	P[3→1]|t=3	…	0	0	P[3→2]|t=3	…

Figure 2 A fragment of a transition matrix for a semi-Markov model using tunnel states. t is the time spent in the current state.

The usual (2-dimensional) transition probability matrix characterizes probabilities in terms of the state in which patients start the cycle and the state in which they complete the cycle. The 3-dimensional matrix simply adds a dimension relating to how long the patients have been in the state. Although a model using a 3-dimensional transition matrix is logically equivalent to one using a series of "tunnel" states, it is more convenient than adding a large number on tunnel states. This improves the transparency of the model and simplifies its development and validation. However, it does require the use of software that supports multidimensional arrays, such as the statistical programming language *R*.[6]

The use of a multidimensional transition matrix can be extended by adding further dimensions to represent other aspects of patient history such as the cumulative number of relapses. This allows us to construct models that both appropriately represent the disease process and can be rapidly evaluated.

A CASE STUDY USING A 3-DIMENSIONAL TRANSITION MATRIX

In this section, we illustrate the implementation of a semi-Markov model using a multidimensional transition matrix with a simplified version of a model developed to assess the cost-effectiveness of alternative treatments for epilepsy.[7] A fuller description of the epilepsy model, as well as its results, is given in the accompanying article.[8]

Depending on their response to therapy, patients with epilepsy may receive treatment with a sequence of antiepileptic drugs. The available clinical trial data provided information on failure rates for specific drugs for a limited period of the time—typically 6 months—from the initiation of the study therapy. As the economic evaluation of a specific treatment required estimates of long-term costs and effects, it was necessary to extrapolate beyond the clinical trial data and to consider treatment sequences.

The model was based on 6 monthly cycles and compared different treatment sequences of up to 3 drugs and a final treatment failure state. Treatment-specific probabilities of treatment failure for the 1st cycle of a treatment were available from a meta-analysis of clinical trial data. The probabilities of treatment failure in subsequent cycles were estimated from an observational study of monotherapy and from a long-term safety study for an adjunct therapy.[9,10] The long-term observational data clearly indicated that the probability of treatment failure was time dependent, declining markedly after the first 6 months of treatment.[8] The

(t=1)

From \ To	State 1	State 2	State 3	…
State 1	P[1→1]	P[1→2]	P[1→3]	…
State 2	0	0	0	…
State 3	0	0	0	…
…	…	…	…	…

(t=2)

From \ To	State 1	State 2	State 3	…
State 1	P[1→1]	P[1→2]	P[1→3]	…
State 2	P[2→1]	P[2→2]	P[2→3]	…
State 3	P[3→1]	P[3→2]	P[3→3]	…
…	…	…	…	…

Figure 3 A 3-dimensional transition matrix for a semi-Markov model. t is the time spent in the current state.

model was implemented using the *R* statistical programming language.[6] The *R* script for the model is included in an appendix.

Figure 4 shows an example of the estimated proportion of patients in each stage of the treatment sequence as a function of time. This is shown, first, for a Markov model assuming that the probability of treatment failure is constant with time and, second, for the semi-Markov model, which includes estimates for treatment failure after 6 months based on the observational data set. The semi-Markov model produced estimates of treatment retention most similar to those seen in the observational data sets and may be considered to have the best face validity.

The 2 models produced widely differing estimates of the mean time "patients" spent in the different model states. The Markov model estimated that a cohort of "patients" would, on average, spend 16%, 10%, 11%, and 63% of the time receiving the 1st treatment, 2nd treatment, 3rd treatment, and maintenance treatment, respectively. This compared to estimates of 55%, 19%, 12%, and 13%, respectively, for the semi-Markov model. These differences may produce quite different

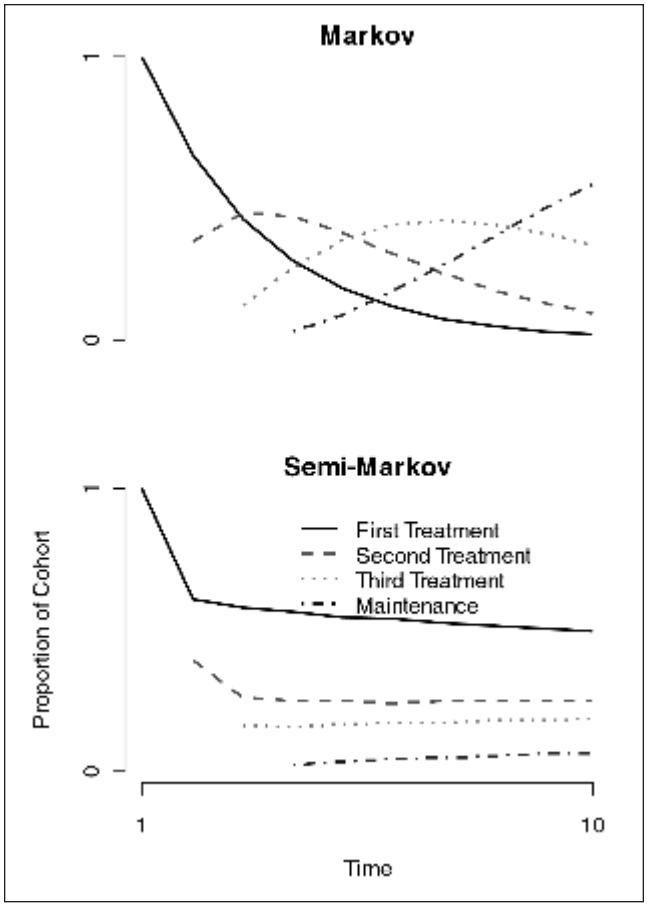

Figure 4 Example results from Markov and semi-Markov models. The graphs show the predicted proportion of patients in each state over time.

estimates for costs and effects as part of a cost-effectiveness analysis.

COMPARISON WITH PATIENT-LEVEL SIMULATION

An alternative approach to handling time dependency is to abandon cohort modeling and to use patient-level simulation (PLS). With Markov models, a notional cohort of "patients" is entered into the model and tracked over time to establish the proportion in each state during each cycle. With patient-level simulation, individual "patients" are entered into the model sequentially. Even when the model *parameters* are defined with certainty, the results for individual "patients" entering the model will vary—this has been termed 1st-order uncertainty.[11] Expected (mean) costs and effects are calculated by entering a large number of "patients" sequentially into the model and using random variables to reflect the 1st-order uncertainty. These models can incorporate time and patient history dependency in transitions, as the model can "record" the event history for each individual as he or she progresses through the model.

A limitation of PLS arises when we want to account for uncertainty in model parameters. In cohort models, parameters can be defined as random variables, and Monte Carlo simulation is used to propagate this parameter uncertainty through the model, providing estimates of the uncertainty around expected cost-effectiveness.[12] Parameter uncertainty (2nd-order uncertainty[11]) can be represented in terms of decision uncertainty using cost-effectiveness acceptability curves.[13] To reflect parameter uncertainty in PLS, however, a 2-level simulation is required: the 1st level estimates the expected costs and effects, allowing for variability between patients (1st-order uncertainty), and the 2nd reflects the uncertainty in the parameters themselves (2nd-order uncertainty). Assuming 10,000 sets of simulations in each of the 2 levels, this would require 100,000,000 simulations overall. Approaches to making these "computationally expensive" models more tractable have recently been suggested,[14] but these have yet to be used widely. In contrast, cohort models do not require the simulation of individual patients and so require 1000 to 10,000 times fewer simulations than patient-level simulation models.

CONCLUSIONS

Semi-Markov models may be useful in decision analysis involving chronic disease because, in many cases, the available experimental and observational data will correspond to this class of Markov model. Semi-Markov models may be easily implemented using multidimensional transition matrices. This form of modeling also potentially enables other aspects of patient history to be tracked and allowed for in the estimated transition probabilities, improving model "face validity."

Markov models require less time to evaluate than patient-level simulations, as expected values for a cohort of patients are estimated during each simulation. This facilitates the correct estimation of expected costs and effects for nonlinear models, the estimation of decision uncertainty arising from parameter uncertainty, and the implementation of value of information techniques.[15,16] The use of multidimensional transition matrices potentially gives cohort models the flexibility in modeling the disease process seen in microsimulations.

The use of the *R* statistical programming environment to implement decision-analytic models also offers a number of potential benefits over spreadsheets

and specific decision-analytic software. As seen in the appendix, decision models can be conveniently and transparently published as scripts. Models presented in this way can be easily inspected and assessed by a 3rd party. The availability of function calls allows the model structure to be separated from the model parameterization; this simplifies development and maintenance, as the model structure only has to be defined once rather than being repeated for each treatment pathway being considered.

APPENDIX
R Code Used in the Epilepsy Case Study

```
txModel ← function  (
                        trt1.fail=50,
                        trt1.n=50,
                        trt2.fail=60,
                        trt2.n=20,
                        trt3.fail=60,
                        trt3.n=20,
                        long.fail=numeric(),
                        long.n=numeric(),
                        xlab=" ",
                        ylab=" ",
                        main=" "
                        )
{

#number of simulations
nSims ← 5000

#number of states
nStates ← 4

#number of cycles
nCycles ← 20


#select alpha and beta parameters for probability of failure during 1st cycle


#combine short- and long-term data
trt1.fail ← c(trt1.fail,long.fail)
trt1.n ← c(trt1.n,long.n)
trt2.fail ← c(trt2.fail,long.fail)
trt2.n ← c(trt2.n,long.n)
trt3.fail ← c(trt3.fail,long.fail)
trt3.n ← c(trt3.n,long.n)
```

```
for (i in 1:nSims)
    {
      n1 ← length(trt1.n)
      n2 ← length(trt2.n)
      n3 ← length(trt3.n)

    #generate vector of probabilities
    trt1.fail.probability ← rbeta(n=n1,shape1=trt1.fail,shape2=trt1.fail+trt1.n)
    trt2.fail.probability ← rbeta(n=n2,shape1=trt2.fail,shape2=trt2.fail+trt2.n)
    trt3.fail.probability ← rbeta(n=n3,shape1=trt3.fail,shape2=trt3.fail+trt3.n)


    trt1.fail.probability ← c(trt1.fail.probability,rep(trt1.fail.probability[n1],nCycles-n1))
    trt2.fail.probability ← c(trt2.fail.probability,rep(trt2.fail.probability[n2],nCycles-n2))
    trt3.fail.probability ← c(trt3.fail.probability,rep(trt3.fail.probability[n3],nCycles-n3))


        #Set up transition matrix
        #initialize transition matrix [from state,to state, sojourn time]
        transition ← array(0,c(nStates,nStates,nCycles))

        #trt 1 to trt 1
        transition[1,1,] ← 1-trt1.fail.probability

        #trt 1 to trt 2
        transition[1,2,] ← trt1.fail.probability

        #trt 2 to trt 2
        transition[2,2,] ← 1-trt2.fail.probability

        #trt 2 to trt 3
        transition[2,3,] ← trt2.fail.probability

        #trt 3 to trt 3
        transition[3,3,] ← 1-trt3.fail.probability

        #trt 3 to fail
        transition[3,4,] ← trt3.fail.probability

    #fail to fail
    transition[4,4,] ← 1



    #Initialize population trace matrix [cycle,state,sojourn time]
        trace-array(0,c(nCycles,nStates,nCycles+1))

    trace[1,,1] ← c(1,0,0,0)


    #run model
        for (cycle in 2:nCycles)
            {
                for (sojourn in 1:cycle)
                    {
                    #determine destination states, note %*% =matrix multiplication
                    #transition matrix conditional on sojourn time
                    conditional.trans <-transition[,,sojourn]
```

```
                #get current state from previous cycle
                current.state ← trace[cycle–1,,sojourn]

                #determine transitions remaining in current states
                same.state ← current.state * diag(conditional.trans)

                #add these transitions to population matrix, increasing sojourn time by one
                trace[cycle,,sojourn+1] ← same.state

                #set diagonal to zero, as we have already counted these transitions
                diag(conditional.trans) ← 0

                #determine transitions to new states
                new.state ← current.state %*% conditional.trans

                #add these transitions to the population matrix, set sojourn time to 1
                trace[cycle,,1] ← new.state[] + trace[cycle,,1]
                }
            }
        }

    #sum population over all sojourn times
    population ← apply(trace,c(1,2),sum)


plot(x=1:nCycles,y=population[,1],bty="n",type="n",xlim=range(c(1,10)),ylim=range(c(0,1)),yaxt="n",xaxt="n",ylab=
ylab,xlab=xlab,main=main,lwd=2)
        lines(x=1:nCycles,y=population[1:nCycles,1],col=1,lty=1,lwd=2)
        lines(x=2:nCycles,y=population[2:nCycles,2],col=2,lty=2,lwd=2)
        lines(x=3:nCycles,y=population[3:nCycles,3],col=3,lty=3,lwd=2)
        lines(x=4:nCycles,y=population[4:nCycles,4],col=4,lty=4,lwd=2)

            print(apply(population,2,mean))
        }



par(mfrow=c(2,1))
par(mar=c(1,6,1,6))
txModel(main="Markov")


axis(2,c(0,1))
par(mar=c(2,6,1,6))
x ← txModel(long.fail = c(56,34,17,17,14,14,6,5),long.n = c(564,508,474,475,440,426,412,406),xlab="Cycle",ylab="Proportion
of Cohort",main="Semi-Markov"
axis(1,c(1,10))
axis(2,c(0,1))
legend(locator(1),lty=c(1,2,3,4),col=c(1,2,3,4),legend=c("First Treatment","Second Treatment","Third Treatment","Maintenance",bty="n",lwd=2)
```

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