Markov Modelling Tool: guide and tutorial with exercises

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MATCH, Multidisciplinary Assessment of Technology Centre for Healthcare
http://www.nottingham.ac.uk/match

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General introduction

Medical device companies and procurers of technology are increasingly being challenged to justify the economic value of their innovation at an early stage, in a manner that is acceptable to the health technology assessment (HTA) community. A common understanding of value between the innovator and assessors is essential to improving the efficiency of taking innovations through the HTA process and into adoption.

Amongst a range health economics methods available, decision trees and Markov models (also known as Markov chains or Markov processes) are often used to assess the potential cost-effectiveness of an innovation in comparison with an existing alternative. This is generally a comparison of 'technical efficiency' where we are interested in comparing the relative costs and the consequences of making a healthcare choice (typically involve comparison of the outcomes of an intervention or diagnostic test).

Unless they have many levels of branches, decision trees are best suited to one-off tests or treatments where there may be a number of different outcomes but where time progression or recurrence is not of major importance. This is often the case for acute diseases where there is a 'cure'. Markov models are best suited to analysis the treatment or monitoring of the progression of chronic diseases where there are several health states a patient will pass through over time or where there is the likelihood of repeated or continuous intervention.

The main steps for conducting an economic evaluation of an innovation versus an existing treatment are as follows:

- Describe the clinical pathway
- Articulate the change made by the innovation
- Construct a decision model to compare alternatives
- Gather data (costs, probabilities, utilities)
- Assign costs and benefit measures to the model based on plausible usage scenarios
- Deal with uncertainty (sensitivity of the results to model data and parameters)
- Appreciate the limitations of an early stage model

In general, a literature search is carried out to fully understand the clinical problem and to identify the key health states and transitions for the model which may include mortality rates or healing rates. It is important to convert all rates to the appropriate time period. In this tool these must be annual rates. Utilities can also be obtained from the literature. Costs may be found from databases, from manufacturers or from estimations.

Summary

This web-based tool allows the user to model the transition of a population of patients through a series of health states that are followed over time, which may include for example: living with a particular disease; having a treatment; being cured; having complications; or becoming deceased. These states are connected so that in any one time-step (typically using a cycle time of one year), there is a probability of a patient staying in their existing state or moving to a different one, and it is possible to move between specified health states in either direction. In this way it is possible to model either the progression of a chronic disease, which may includes worsening or improvement (such as the appearance or healing of a wound) or the consequences of treatment of an acute condition (such as surgery and its possible complications and follow-up). Cost and quality of life incurred in each cycle are added up incrementally as the model progresses.

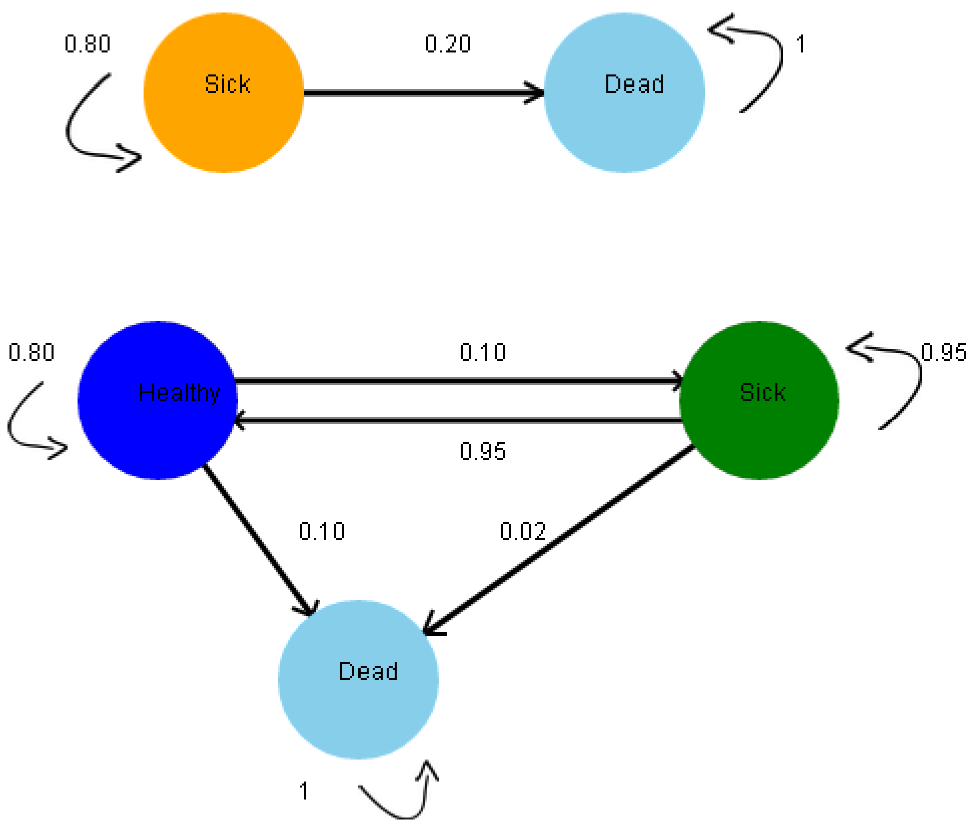

Figure 1. Two and three state Markov model diagrams with transition probabilities shown.

Features of the Markov modelling tool

- The number of states may be chosen between 2 and 4. These are shown on separate web-pages as bubble diagrams.
- States may be joined up graphically by mouse-clicking to add arrows in either direction between states. Names of states may be changed by mouse-clicking on the bubble.
- Transition probabilities between states are entered in a table.
- Relevant data are entered for each state: the annual cost of being in the state, quality of life (measured as a utility between 0.00 and 1.00) in that state. In addition, when the patient first enters the state a different cost or utility may be specified. This enables follow up costs of a treatment to be added after the treatment, whilst remaining in the state.
- The model can be run for a specified number of cycles (time step measure in years) and for a specified size of population.
- The model may be run either with a single set of data (where both tables have the same data) or as a comparison, where one model (Base case) is compared side by side with another (Innovation) with the same number of states, where any of the connections and their probabilities and state data (costs and/or utilities) may be different between the two models. This allows an innovation to be compared to the Base case (incumbent) technology.
- The model includes discounting, where the value of costs and utilities are reduced each year according to a fixed percentage, as the model proceeds into the future. A typical discounting percentage (as used by NICE) is 3.5% and so, in this case, a cost of £100 in year one is reduced to £100 divided by 1.035 in year two, by £100 divided by 1.035^2 in year three, and so on. Likewise a utility of 0.8 in year one is reduced to 0.8 divided by 1.035 in year two.
- The model may be solved in one of two ways: analytically using a Cohort method which provided a single answer, or run probabilistically using a Monte Carlo simulation method which provide a distribution of answers around a mean which is the same mean as the answer found in the Cohort method.

Outputs from the tool

After the model (or pair of models) is run for a population of patients, for example 10,000 patients for 20 cycles, it is possible to see:

- Number of patients in each final state i.e. how the patient population is distributed amongst the states after the last cycle is completed. The results are shown graphically.

- Average patient benefit accrued, calculated from the utility in each year, expressed as Quality Adjusted Life Years (QALYs). In the case of the Monte Carlo simulation, the maximum and minimum QALY of the patient population is also found.

- Average cost per patient accrued over the time of the model, calculated by adding up the costs of each patient living in each health state. In the case of the Monte Carlo simulation, the maximum and minimum costs are also found.

- In the case of comparison of two models the Incremental Cost Effectiveness Ratio (ICER), the difference in costs divided by difference in QALYs, is calculated.

Limitations

The model is aimed at early stage modelling where the level of detail is expected to be low.

- The maximum number of states has been limited to 4. Therefore it is not very feasible to model multiple risk groups where there would multiple branches for each risk group, as this would tend to increase the number of states required.
- Patients all start in one state. We do not attempt to distribute patients amongst states before running the model.
- The time-step is one year. All data must be converted to annual rates.
- Probabilities are fixed. For example it is not possible to increase mortality rate as time progresses, nor to change the probability for a patient who has entered a state twice. As such it is not possible to consider age or any increased probability of recurrence.
- Full sensitivity analysis, such as Probabilistic Sensitivity Analysis, is not included. However, the user can try running the model with different data to see the effect on the results so as to perform a sensitivity check on any of the parameters.

Tutorial

In the following tutorial, data is provided to illustrate the tool, which may be changed in the model.

The home page for the tool is:
http://www.nottingham.ac.uk/match/research/tools/markovtoolmain.html

Use Google Chrome, Mozilla Firefox, Microsoft Internet Explorer 9 or other browser that supports SVG graphics (note that older versions of IE do not).

There are three exercises in this tutorial.

Exercise 1: Gain familiarity with the main features of the tool using a two state Markov model. Learn how to change the names of the states and run a model. Change the probabilities for the innovation and see how the ICER changes. Run a Cohort analysis.

Exercise 2: Examine and run a 3-state Markov model with Well, Sick and Dead states. Compare Cohort and Monte Carlo Analyses.

Exercise 3: Populate and analyse a 4-state Markov model for a wound healing innovation. Carry out an exercise to inform pricing of the wound healing device.

Exercise 1. Gain familiarity with the main feature of the tool using a two state Markov model.

This exercise describes a simple 2 state model with a starting state and an absorbing state.

a) Go to the web page http://www.nottingham.ac.uk/match/research/tools/markovmaindemo.html

and Select the Two-State model.

Click on the button 'Two-State Markov Chain'.

You should be able to see Figure 2 and also Figure 3 when you scroll down. Success? Y / N

If you cannot see the bubble diagram in Figure 2, try installing Google Chrome, Mozilla Firefox, Microsoft Internet Explorer 9 and repeat this part of the exercise.

b) Change the names of the states

Change the name of the states so that State 1 reads 'Sick' and State 2 reads 'Dead'.

Click on text within the state circle and type in new text.

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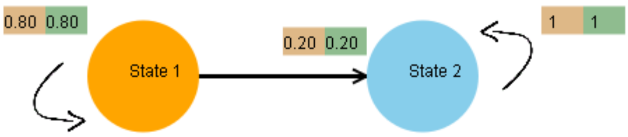
Markov Chain Simulation for Two States



Transition Matrix - Base Case		
	State 1	State 2
State 1	0.80	0.20
State 2	0	1

Transition Matrix - Innovation		
	State 1	State 2
State 1	0.80	0.20
State 2	0	1

Cost & Utilities - Base Case		
	State 1	State 2
Initial Cost	374	0
Incremental Cost	374	0
Initial Utility	0.81	0
Incremental Utility	0.81	0

Cost & Utilities - Innovation		
	State 1	State 2
Initial Cost	374	0
Incremental Cost	374	0
Initial Utility	0.81	0
Incremental Utility	0.81	0

Figure 2. Two-state model. Initial set-up of model.

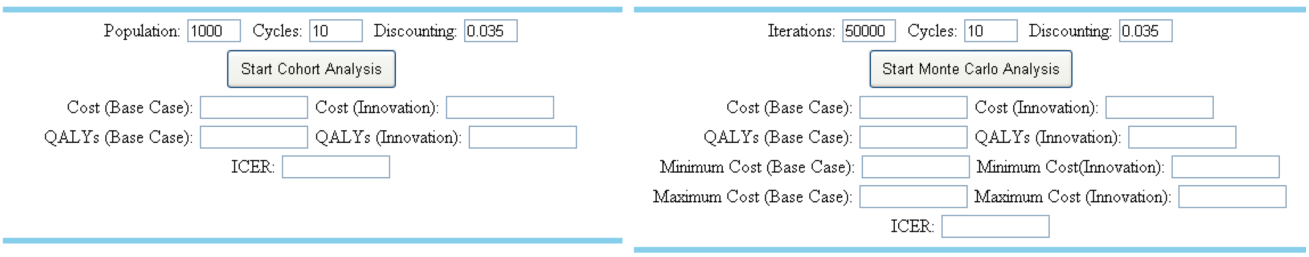


Figure 3. The two types of analysis, Cohort and Monte Carlo

c) Examine the data.

Note first that the data values in the brown and green data tables underneath are the same. We will not change these until Exercise 1e when we will compare the Base Case and Innovation models against each other with different data. Note also that the Transition Matrix boxes contain the probabilities for moving between states. The probability of staying in State 1 (Sick) is 0.80 and the probability of moving to State 2 (Dead) is 0.20. These probabilities add to 1.00. Since State 2 is an absorbing state, the probability of staying in the state is 1.00 and the probability of leaving the state is 0.00. The Transition Matrix probability values can be changed but we won't do it just yet.

Check that the Cost of being in State 1 (Sick) is £374 and the Utility is 0.81. The Initial values are those when the state is first entered and the Incremental values are those if the patient stays in the state longer than one cycle. The Cost and Utility values can be changed but we won't do it just yet.

The Cost of being in State 2 (Dead) is £0 and the Utility is 0.00

d) Run the Cohort Analysis and examine the output data

All patients start in State 1 (Sick) and after a specified period of time some will move to the absorbing state, State 2 (Dead).

To run the model click on Start Cohort Analysis. This works out the cost per patient after 10 cycles. The Incremental cost-effectiveness ration (ICER) value is not applicable here (N/A) because the Base Case and Innovation data and transition probabilities are the same in the green and blue tables.

Write down the results.

Cost (Base Case):		*Cost (Innovation):*	
QALYs (Base Case):		*QALYs (Innovation):*	

Run the analysis again a few more times and also try it with a different population size.

Do the results change on subsequent runs? Y / N

Does the size of Population affect the result? Y / N

Write down possible reasons for your answers:

e) Run the Cohort Analysis again with new probabilities and examine the output data and graphs

Change the probabilities for the Innovation (green data table) to 0.90 for State 1 (Sick) and 0.10 for State 2 (Dead). This means that patients are less likely to die.

Repeat the Cohort Analysis and write down the results from the Cohort analysis results table.

Result	*Base Case*	*Innovation*
Cost		
QALYs		
Incremental Cost-Effectiveness Ratio (ICER) $= \frac{\textit{Cost (Innovation)} - \textit{Cost (Base Case)}}{\textit{QALYs (Innovation)} - \textit{QALYs (Base Case)}}$		

f) Now examine the associated six graphs by scrolling down further.

Estimate and write down the following by reading from the graphs.

Question	*Base Case*	*Innovation*
Average annual cost of being in State 1 (Sick) at 6 years?		
Average annual cost of being in State 2 (Dead) at 10 years?		
Cumulative average cost per patient after 8 years?		
Average QALY of being in State 1 (Sick) at 6 years?		
The average QALY of being in State 2 (Dead) at 10 years:		
The cumulative average QALY per patient after 8 years:		

Exercise 2. Examine and run a 3-state Markov model with Well, Sick and Dead states.

Go to the web page http://www.nottingham.ac.uk/match/research/tools/markovmaindemo.html

and Select the Three-State model by clicking on the button 'Three-State Markov Chain'.

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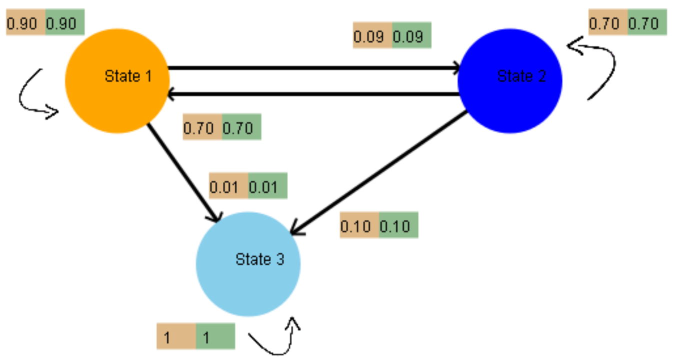
Markov Chain Simulation for Three States



Transition Matrix - Base Case			
	State 1	State 2	State 3
State 1	0.90	0.09	0.01
State 2	0.70	0.20	0.10
State 3	0	0	1

Transition Matrix - Innovation			
	State 1	State 2	State 3
State 1	0.90	0.09	0.01
State 2	0.70	0.20	0.10
State 3	0	0	1

Cost & Utilities - Base Case			
	State 1	State 2	State 3
Initial Cost	374	3153	0
Incremental Cost	374	3153	0
Initial Utility	0.81	0.70	0
Incremental Utility	0.81	0.70	0

Cost & Utilities - Innovation			
	State 1	State 2	State 3
Initial Cost	374	3153	0
Incremental Cost	374	3153	0
Initial Utility	0.81	0.70	0
Incremental Utility	0.81	0.70	0

Figure 4. 3-stage model and data tables

a) Change the names of the States 1-3 to Well, Sick and Dead.

b) Change the innovation probabilities so there is an 85% chance of healing (moving from Sick to Well). Also update the Sick->Sick transition probability to maintain consistency.

c) Perform the Cohort Analysis and write down the results from the Cohort analysis results table.

Result	*Base Case*	*Innovation*
Cost		
QALYs		
Incremental Cost-Effectiveness Ratio (ICER)		

d) Run a Monte Carlo Analysis and examine the output data

Now click on Start Monte Carlo Analysis. This works out the average cost per patient based on 50000 patients who are passed through the model with state transitions made according to random number generation e.g. if in State 1 (Well), generate a random number between 0 and 1. If it is less than 0.01, go to State 3 (Dead), otherwise if greater than 0.01 but less than 0.1 go to State 2 (Sick), otherwise stay in State 1(Well). Like the Cohort there are 10 cycles so the cost and QALYs calculated are the totals over 10 years.

Read off the Incremental Cost Effectiveness Ratio (ICER) and the Maximum & Minimum costs as well as the average Costs and QALYs.

Result	*Base Case*	*Innovation*
Cost		
QALYs		
Minimum Cost		
Maximum Cost		
ICER		

Run the model a few more time and write down the new ICER values.

ICER	
ICER	
ICER	
ICER	
ICER	
ICER	
ICER	

What do you notice about the variation of the ICER?

Run the model a few times with a different sample size of 5000 instead of 50000.

What do you notice?

e) Change the cost of the innovation

Increase the cost of the innovation (both Initial and Incremental) by £1000 to £4153. Repeat the Cohort Analysis from part c) and write down the results.

Result	*Base Case*	*Innovation*
Cost		
QALYs		
Incremental Cost-Effectiveness Ratio (ICER)		

Compare the two ICER values from c) and e). What do you notice?

f) Now find the Innovation cost to the nearest pound, at which the ICER is cost saving (this is a known as a threshold analysis). Assume initial and incremental costs are the same.

Result	*Base Case*	*Innovation*
Cost		

g) The innovation also promises to improve health after healing. Change the cost back to £1000 above the Base Case and change the innovation utilities (both initial and incremental) to obtain perfect health after healing.

What do you notice about the ICER?

h) Repeat e) to find the new cost threshold.

Result	*Base Case*	*Innovation*
Cost		

What do you notice? Write down possible reasons for your answer:

Exercise 3. Populate and analyse a 4-state Markov model for a wound healing innovation.

Go to the web page http://www.nottingham.ac.uk/match/research/tools/markovmaindemo.html and Select the Four-State model by clicking on the button 'Four-State Markov Chain'.

Problem:

An innovation has been devised to promote wound healing in patients with diabetes (poor blood glucose regulation) who may acquire Diabetic Foot Ulcer, a condition that may result in amputation and can also cause death.

From epidemiological data it is found that within any year there is a 4% chance of a diabetes patient acquiring a foot ulcer. However, it is known that 75% of cases the ulcer will heal with treatment and the wound is unlikely to recur in any one year. Other patients will not heal and 2% will have a more long-term wound, 12% will require amputation of one or more toes and unfortunately 11% will die of their wound. After an amputation there is also an 11% chance of dying.

It has been determined that a Four-state model will suffice to model the basic situation, with health states and their associated annual costs and utilities as follows: Diabetes (C=£374, U=0.81), With Ulcer (C=£3159, U=0.70), Amputee (C=£8964, U=0.59), and Dead ((C=£0, U=0.00). The costs and utilities are obtained from available NHS and health economics data. An innovation has been devised that is intended to promote wound healing by stimulating blood flow and so promises to be beneficial to patients compared to existing treatment. The cost of using this stimulation is to be added to the current cost of treatment. The National Health Service is willing to pay up to £20,000 per QALY to treat a patient using this new technique, assuming that an improved healing rate of at least 80% can be achieved. The improved healing rate means that the amputation rate is reduced accordingly. Unfortunately there is no evidence that mortality rates are reduced or that the utilities are improved in any one health state.

The product developer aims to rent the device to hospitals which will treat at least 200 patients per year so the cost is spread over this number of patient episodes. There are also consumables (electrodes) which cost £10 per patient episode and are disposable, which are also to be paid for by the hospital.

The time horizon for the analysis is ten years. Initial and incremental costs are the same.

You are asked to:

1) Determine a reasonable annual rental price for the device, and so find the unit price. This should include a sensitivity analysis based on at least two different healing rates.

2) Find how long it will take the product developer to make a profit if the manufacturing costs are 50% of the unit price, assuming a non-recoverable development expense of £1m.

To answer the question, use the Markov Tool (which is already partially populated with data, but you will need to make changes) to obtain your results and write a short report (maximum 2 pages) including a diagram of the Markov Model. The report is to be aimed at the CEO of the company manufacturing the product to help with their pricing strategy and so they can make an informed value proposition to the NHS.