Markov Modelling for Health Technology Assessment

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Synopsis

- What is Markov modelling?
- How is it used in health technology assessment (HTA)?
- 2-state models
  - inputs & outputs
- 3-state models
  - quality of life and sensitivity analysis
- Multi-state models
- Demo: modelling software (*TreeAge Pro*)
What is Markov modelling?

- A **Markov model** is a stochastic **model** used to model randomly changing systems where it is assumed that future states depend only on the current state not on the events that occurred before it (that is, it assumes the **Markov** property of **historical independence**)

- Developed in nuclear physics to describe the random motion of nuclear particles

- In healthcare: usually follows one or more hypothetical cohorts of people
  - e.g. compare vaccinated vs unvaccinated birth cohorts over their lifetime

- Non linear, e.g. doubling an input won’t double the output
Markov models in health technology assessment

- Used to predict future costs and benefits of interventions
  - Compares an intervention with ‘usual care’ or another intervention
    - In 2+ identical cohorts
  - Extends the results of clinical trial(s) to the patient’s lifetime or another time horizon
  - Calculates the cost per event prevented or cost per QALY gained (ICER)
- Can include competing risks
  - E.g. Death from CVD or other causes
- Can have time varying inputs
  - E.g. costs or mortality rates that change over time
Markov models are used for prediction:

- “it is very difficult to predict anything—especially the future.”

  Neils Bohr, 1956
The 2-state Markov model

- Based on local mortality tables (life tables)
  - These reflect recent mortality, not future mortality
- 2 states:
  - Alive
  - Dead
- Considers how a cohort of individuals progresses over its lifetime
  - OR how discrete individuals progress over time
- Compares life expectancy under 2 or more different circumstances
- Can calculate life years gained by an intervention
- Can run sensitivity analyses (‘alternative facts?’)
The ‘Markov trace’ for a 2-state model
The 3-state Markov model

- Based on disease progression, quality of life and mortality
- Only 3 states:
  - Well
  - Unwell
  - Dead
- Compares \textit{quality-adjusted} life expectancy under different circumstances
- Can calculate \textit{lifetime} costs and QALYs gained by an intervention
- Requires sensitivity analyses on uncertain parameters (e.g. risk of an event)
- Easily expanded to a multi-state model
3-state Markov model
3-state Markov model, corrected

Well

Unwell

Dead
Example

- A new intervention is available for reducing cardiovascular risk
- Is it likely to be cost effective compared to ‘usual care?’
Information required:

Epidemiology
- Baseline risk of specified target group, for men and women age 60+ (= annual prob. of CVD event)
- Case fatality of CVD events (age/sex dependent)
- Effectiveness of the new programme (includes efficacy and adherence)
- CVD risk after first CVD event
- Mortality from other causes

Costs
- Annual cost of novel programme or medicine
- Cost of healthcare for a CVD event (stroke or AMI)
- Annual costs of maintenance therapy after CVD event

Quality of life
- Mean quality of life (utility) of target group
- Mean quality of life post-CVD event (stroke or AMI)
3 state model of cardiovascular disease

- Event free
  - Well
  - Alive after 1 y
  - Post CVD event
- CVD event
  - RR_event*pEvent
  - CVD death
  - Post CVD event
- Die of other causes
  - mort2014[stage + _stage;Sex]
  - CVD death
- Intervention
  - Post CVD event
  - CVD death
  - Death from other causes
- Usual care
  - Clone 1: Tree

Parameters:
- CF = 0.3
- dinc = 790
- Cost_cvd_dih = 0.2*1000
- Cost_cvd_diah = 5000
- Cost_size = 4*GP+2*dinc
- Cost_mud = 5.5
- Cost_mudmed = 500
- Cost_prog = GP+4*Cost_med
- Cost_program = -4*Cost_med
- D = 0.005
- Eff = 0.25
- GP = 50
- pDih_cvd = 0.05
- RR_event = 1
- RR_event = 1
- Event = 1
- Term = 60
- Usual = 100-startage
- U = 1
- Ucvd = 0.9
## A 3-state CVD Markov model

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Root Definition</th>
<th>Low</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Cost_GP</td>
<td>Annual cost of GP visits</td>
<td>200</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CF</td>
<td>CVD case fatality</td>
<td>0.3</td>
<td>0.2</td>
<td>0.6</td>
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<td>clinic</td>
<td>Cost of CV clinic</td>
<td>500</td>
<td>300</td>
<td>500</td>
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<tr>
<td>Cost_cvd_dth</td>
<td>Cost of CVD death</td>
<td>1000</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Cost_med</td>
<td>Annual cost of new medicine</td>
<td>200</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cost_nonfatal</td>
<td>Cost of non fatal CVD event</td>
<td>Cost_cvd_gamma</td>
<td>4000</td>
<td>8000</td>
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<tr>
<td>Cost_post_cvd</td>
<td>Annual cost after CVD event</td>
<td>750</td>
<td>0</td>
<td>0</td>
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<tr>
<td>D</td>
<td>Discount rate</td>
<td>0.035</td>
<td>0</td>
<td>0.05</td>
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<tr>
<td>Efficacy</td>
<td>Efficacy of novel therapy</td>
<td>Efficacy_normal</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Event</td>
<td>CVD event</td>
<td>discount(1;D;_stage)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP</td>
<td>Annual cost of GP (quarterly)</td>
<td>200</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pDth_cvd</td>
<td>Prob of cvd death</td>
<td>0.01</td>
<td>0.005</td>
<td>0.015</td>
</tr>
<tr>
<td>pEvent</td>
<td>Annual prob of CVD event</td>
<td>prob_event_beta</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td>RR_event</td>
<td>Relative risk of CVD event</td>
<td>1-Efficacy</td>
<td>0.75</td>
<td>1</td>
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<tr>
<td>Sex</td>
<td>Male=1, Female=2</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>startage</td>
<td>Age at start</td>
<td>60</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Term</td>
<td>Time horizon</td>
<td>100-startage</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Ucvd</td>
<td>QoL post CVD</td>
<td>0.9</td>
<td>0.8</td>
<td>1</td>
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<tr>
<td>X</td>
<td></td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
3-state Markov model trace

Markov Probability Analysis

- CVD death
- Death from other causes
- Post CVD event
- Well

Stage

Probability

Age 60 y

Age 100 y
The multi-state model

- Useful when chronic disease progression is well characterised clinically
  - e.g. CVD, cancer, respiratory disease, rheumatic heart disease
- One disease with several disease states:
  - Well
  - Disease State 1, Disease State 2, Disease State 3, etc.
  - Dead
- Based on mortality, disease progression & quality of life in each health state
- Compares quality-adjusted life years (QALYs) under many different circumstances
- Calculates lifetime cost and QALYs gained by an intervention
- Calculates the cost per QALY gained (ICER= incremental cost effectiveness ratio)
- Requires sensitivity analyses on uncertain parameters
- Powerful, flexible, useful
Monotherapy

Ditherapy

AMI

AP

HF

Stroke

Two or more complications

Tritherapy

Death
Progression from well to: acute rheumatic fever; rheumatic heart disease; valve surgery; surgical revision; death from RHD or other

School intervention

Never ARF

ARF

RHD, some with surgery

Valve surgery

Surgical revision

Death

No school intervention
ICER = slope of line = $3800/0.62 = $6000 per QALY

ICER = $4000/0.25 = $16,000 per QALY
Analysis of Markov models

- Base case analysis uses the most probable value of each variable
  - Cost per clinical outcome averted (e.g. cost per premature death prevented)
  - Cost per life year gained
  - Cost per QALY gained
- Sensitivity analyses
  - One-way, e.g. vary the cost of the intervention or baseline risk
  - Two-way, e.g. vary the cost and the baseline risk
  - Multi-variate, vary all important variables (Tornado diagram)
  - Probabilistic, present in a Cost Effectiveness Acceptability Curve (CEAC)
    - Run the model many times, sampling from distributions of variables
Populating the Markov model

- Costs
  - MoH (admissions)
  - PHARMAC dispensing (medicines)
  - Suppliers (medicines, medical devices)
  - DHBs

- Incidence rates and efficacy
  - Pivotal RCTs and meta-analyses

- Adherence/uptake
  - Publications or naturalistic trials

- Quality of life
  - RCTs or specific QoL publications

- Mortality
  - Statistics NZ

- Many of the above
  - IDI
TreeAge Pro modelling software

- Has been available since about 1995
- Continually upgraded (for a price!)
- Visual, flexible, dynamic, powerful
- Can be linked to a spreadsheet for inputs and outputs
- Can be converted to a spreadsheet model
- Requires multiple inputs
- Used by Industry and PHARMAC
- Moderately good ‘Help’ file and YouTube training
- Remote support via email or phone
- Moderately expensive

Disclaimer: I have no commercial interest in this or any other modelling software
Supplementary Notes

- QALYs
- Discounting
Health related quality of life

- Patient reported outcomes (PROs):
  - Patient satisfaction surveys
  - Health related-quality of life (HRQoL or QoL)
    - Disease-specific questionnaire (e.g. St. Georges asthma QoL scale)
    - Generic questionnaire (e.g. Short Form 36)
    - Health state index: EQ-5D, HUI3, Visual analogue scale (VAS)
    - Range: full health = 1 to death = 0
Quality of Life (QoL) – EuroQol EQ-5D

- **Mobility**
  - 1. No problems walking around
  - 2. Some problems walking around
  - 3. Confined to bed

- **Self-Care**
  - 1. No problems with self care
  - 2. Some problems with self care
  - 3. Unable to wash or dress

- **Usual activities**
  - 1. No problems with performing usual activities
  - 2. Some problems with performing usual activities
  - 3. Unable to perform usual activities

- **Pain/Discomfort**
  - 1. No pain or discomfort
  - 2. Moderate pain or discomfort
  - 3. Extreme pain or discomfort

- **Anxiety/Depression**
  - 1. Not anxious or depressed
  - 2. Moderately anxious or depressed
  - 3. Extremely anxious or depressed

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Ordinary health
Health State: 11111
Utility: 1.000

Severe Bipolar Disorder
Health State: 11212
Utility: 0.690

Moderate Arthritis
Health State: 2(1-2)221
Utility: 0.592
Defining a Quality Adjusted Life Year (QALY)

- The quality-adjusted life-year (QALY) is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value for money of medical interventions.

- One QALY equates to one year in perfect health.
- 0.5 QALYs =
  - 6 mths in perfect health
  - 12 mths in 50% health (health state index 0 to 1)

Discounting of future costs and benefits

- Expenditure in the future is valued lower than current expenditure
- Distant health benefits are valued less highly than immediate benefits
- *Future costs should always be reduced* = ‘discounted to present value’
  - And the rate justified
- *Future health outcomes* may also be discounted
  - Debated by economists, who often do it both ways
- Discount rates are country-specific
  - US: 3% pa, UK 6%, NZ 3.5% (PHARMAC)
  - Often use 5% pa and vary in a sensitivity analysis