Markov Models, part I

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Outline

- Elements of Markov models
- An extended example: HIV transitions
- State transition diagrams
- Adding costs and benefits
- Simulating the transitions of a cohort
- Half-cycle correction
- The memoryless property of cohort models
- Markov models as “trees”
- When should we use Markov models?
Last week we covered decision trees as they apply to CEA

The key new element was the introduction of **uncertainty** into the calculation of ICERs

The ICER is an **expected value**

We also saw that decision models are not explicit about time and that they get **too complicated if events are recurrent**

Markov models solve these problems

**Confusion alert**: Markov models can be illustrated using (sort of) trees and decision trees and Markov models are often combined
We will define **transitions** from **health states** (well, ill, dead, relief, no relief)

Markov models are sometimes called **transition models**

Each transition has a probability (**transition probability**)

We need to add **time**: transitions happen over a period of time (called a **cycle**)

Each health state can have a **cost** and/or **benefit** associated to it (called **rewards** in Markov models; just like payoffs in decision models)
We will use an example from your textbook and Briggs et al (2006)

Two therapeutical strategies for HIV: zidovudine monotherapy and zidovudine in combination with lamivudine (for simplicity, “monotherapy” versus “combination” therapy)

Four possible health states, some of them depending on CD4 counts:

1. State A: CD4 from 200 to 500 (best)
2. State B: CD4 less than 200 (not so good)
3. State C: AIDS (bad)
4. State D: Death (very bad)

Cycle is one year

We can illustrate possible transitions with a state transition diagram
HIV state transition diagram

- All paths lead to death and death leads to... nowhere (aka absorbing state)
- Note that in this example there is no way to get better (no longer true for HIV)
- Possible to remain in same state after a cycle
Note that combo therapy has better outcomes. To be precise, combo therapy’s risk is reduced by about half (0.509) (See Excel file for actual probabilities)
Where do probabilities come from?

- As with decision models, probabilities come from clinical trials, observational data, meta-analyses, expert panels, surveys...
- Note that we could have used a decision tree instead.
- More precisely, a recursive decision tree with one tree per year but it would be too complicated.
- Now we need to add rewards (payoffs).
Costs

- We will do a cost analysis (we will add life years later)
- The HIV study collected health care, community, and medication costs
- Drug costs: zidovudine (£2,278); lamivudine (£2,086); combination (£4364)
- Cost per state (health care and community): A: £2756; B: £3052 C: £9007; D: £0
- Costs are per cycle (i.e. year)
“Solving” Markov models

- We now have all ingredients: **health states**, **transition probabilities**, and **rewards** for each cycle.
- “Solving” the Markov model means that we will simulate what would happen to a group (cohort) of people over time (that’s why they are called **cohort models** sometimes).
- We will then calculate **expected costs**.
- In this example, we will simulate the transitions of 1,000 patients in each type of therapy over **20 years**.
- **Pay attention!** It’s actually **very easy** but it’s also very easy to get confused.
Monotherapy: we start with 1000 patients in the healthy state A
After 1 cycle, what will happen?
We know that the probability of staying in state A is 0.721, so after one year, 721 will remain in state A \(1000 \times 0.721\)
Same logic for all other states 202 in B, 67 in C, and 10 in D
See, super easy! We are just “allocating” the 1,000 people into the four possible states
Now we need to repeat the process for the next cycle

Of the 721 in state A, how many will stay in A? **520** \((0.721 \times 721)\)

How many in B? We need to take into account that some will move from A to B but also that some in B will stay in B:

\[
721 \times 0.202 + 202 \times 0.581 = 263
\]

Easier to see it graphically
Transition probabilities

Cycle number | State A | State B | State C | State D
--- | --- | --- | --- | ---
0 | 1000 | 0 | 0 | 0
1 | 721 | 202 | 67 | 10
2 | 520 | 263 | 181 | 36
After the second year, copy-pasting formula in Excel will do it.

Just be careful and make sure some of the cells’ references are “fixed” (press F4 or double $ sign).

See Excel file for this lecture.
Big picture

- We start with a group of patients (the number doesn’t matter, we could use 1 person)
- Cycle by cycle, we transition them to different health states
- That’s it
- We have simulated a disease progression
- Note that we are transitioning a group of patients. We are not following each patient (more on this later)
Now we know what will happen to our cohort over time. What about expected costs?

We just need to multiply the number of people in each health state by the corresponding cost (in each cycle)

For example, in cycle 2:

\[520 \times (2756 + 2278) + 263 \times (3052 + 2278) + 181 \times (9007 \times 2278) + 36 \times 0 = 6,056,510.75\]

Per person: £6060
Life years

- We are simulating 20 years of life for these patients
- Some of them die
- We can therefore calculate life years (or life expectancy)
- In the first cycle, 10 people died but 990 were alive so these “alive” people accumulated 990 life years in the first cycle
- In the second cycle, $520 + 263 + 181 = 964$ were alive, so they accumulated another 964 years of life
- We do the same for each cycle
- At the end of the 20 cycles, we add up all the years of life over the 20 years
Survival curve

Survival Curve

% Surviving

Stage

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Survival
Half-cycle correction

- Why didn’t we give any life years “credit” to those who died during each cycle?
- Because we essentially assumed that people died at the start of the cycle
- But we should take into account that patients die at different times; otherwise, we underestimate costs and benefits
- Not a big problem if we do the same in both treatments (the shorter the cycles the less of a problem)
- The best solution (the unbiased solution) is to assume that patients die in the middle of the cycle
- This is a result of assuming that patients die randomly (uniformly) during the year
We now have the expected costs and benefits

We need to repeat the same simulation for another cohort for the combination group

The way I worked out this example, we need to simulate 1,000 patients in the combination group

Not really necessary. We could calculate costs and benefits per person

After calculating costs and benefits for both groups, we can obtain the ICER
What about QALYs and other features of CEAs?

- Note that **adjusting for quality** (i.e. preferences) is straightforward.
- Each health state would have a preference score (typically between 0 and 1) associated with it.
- We just multiply the score by the time spent in each year.
- **Discounting** is easy too: we have costs and benefits per cycle so we just need the discount rate per cycle.
- Note too that with Markov models we can go from **intermediate** to **final** outcomes.
Markov models as trees
Some parts of a decision tree could be calculated using Markov models.
Markov models and decision models are not that different

We have changed the language because decision trees and Markov models have different origins

Health states could be represented by a branch in a decision tree

In the migraine example, health states could be relief, no relief, no recurrence, recurrence, hospitalization...

The main difference is the introduction of time in the form of cycles and that recurrent events are easily modeled

In the migraine example, an appropriate cycle could be a day or a week
The **memoryless** property or the **Markov assumption**

- One limiting assumption of cohort Markov models is that transitions to a state **do not depend on the past** or the **time a patient has been** in a state.
- In other words, once in a cycle, there is no “memory” of the past.
- In many cases, how long a patient stays in a state affects the chances of an outcome.
- For example, a person experiencing his third bout of depression has higher chances of worse outcomes.
- There are ways to fix this limitation: adding additional transition states (second, third depression episode) and/or making transition probabilities conditional on past events.
When should we use Markov models?

- When events are **recurrent**
- When we want to model the “**natural history**” of the disease
- Long time horizon: we want to go for intermediate outcomes to final outcomes
- When life years or QALYs are outcomes of interest
- **Important**: We haven’t talked much about this but **choosing a valid cycle length matters**
- Ideally we want a cycle length in which two events usually do not happen
- Cohort Markov models are not good for modeling infectious diseases: the probability of infection depends on the number of people infected (**herd immunity**)
Markov models allow us to model complex diseases.

Markov models better incorporate time and disease progression.

Simulating cohort models is easy.

As with decision analysis, the hard part is to come up with a model that isolates the key elements that need to be considered – that’s not easy.

There are extensions to Markov models that are better for some problems (next week).