Markov Models, part II

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Outline

- Examples of Markov models in cost effectiveness
- Markov model extensions
    1. Incorporating time dependency
    2. Relaxing the Markov assumption (memoryless property)
    3. Patient-level simulation (microsimulations)
    4. Static and dynamic models
- Summary

Big picture

- In the last two classes we incorporated **uncertainty** into cost-effectiveness using decision analysis and Markov models
- We use these models to go from the **short run to the long run**
- We essentially model **disease progression**
- Good setting for calculating life expectancy and costs
- Today we will see more examples and talk about extensions
- In some circumstances Markov models have limitations. We will discuss other alternatives

Review

- Remember, we needed few elements to build a Markov model
  1. Health states
  2. Cycles
  3. Transition probabilities
  4. Rewards (costs, utilities, life years)
- Even though there are few elements, Markov models can be fairly complex (in a good way, mostly)
- We will review actual applications. After today's class, **you have the tools to replicate all the examples**

Example 1: description

- Cost-effectiveness of options for the diagnosis of high blood pressure in primary care, *Lovibond et al (2011), Lancet; 378:1219-30*
- **Which diagnosis strategy is more cost effective?** Further blood pressure measurement 1) in clinic, 2) at home, 3) ambulatory monitor
- **Hypothetical** primary care population 40 or older with a screening blood-pressure greater than 140/90 and risk-factor prevalence of the general population (UK)
- Cycle: 3 months; time-horizon: 60 years
- Rewards: costs and QALYs
- **Stratified** by age (that is, separate models by age category)
- Data: meta-analyses, risk of events using Framingham risk equations

Example 1: Model
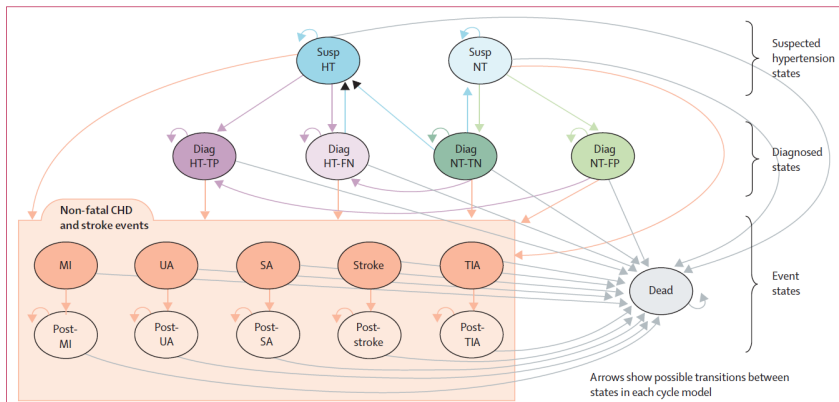
Figure 1: Markov model, a simplified transition-state diagram
Susp HT=suspected of having hypertension with true raise blood pressure (truly hypertensive). Susp NT=suspected of having hypertension with falsely raised blood pressure (truly normotensive). Diag HT-TP=diagnosed as hypertensive—true positive (truly hypertensive). Diag HT-FN=diagnosed as normotensive—false negative (truly hypertensive). Diag NT-TN=diagnosed as normotensive—true negative (truly normotensive). Diag NT-FP=diagnosed as hypertensive—false positive (truly normotensive). CHD=coronary heart disease. MI=myocardial infarction. UA=unstable angina. SA=stable angina. TIA=transient ischemic attack.

Example 1: Model

- The cohort starts at the point of first diagnosis: hypertension (HT) is either suspected or not
- In either case, there could false positives (FP), false negatives (FN), true positives (TP), true negatives (TN)
- Possible to go back to suspected hypertension in some cases
- There is of course a cost due to mistakes. If a person is deemed not to have HT but has it, then that person doesn't receive treatment and has a higher risk of a bad event. But getting unnecessary treatment is also costly
- Certain events last only one cycle (MI, angina, stroke, TIA) (**tunnel states**; more on this shortly)
- Even though patients stay in that state for one cycle, this cycle is expensive and lowers QALY (and it changes the probability of death). Note that if they have the bad event, they are stuck there until death
- One Markov model by intervention; used Excel, stratified by sex and age group. Transition probabilities were not fixed (were changed later at later cycles)

Example 1: Conclusions

- Ambulatory monitoring most cost effective
- After an initial raised reading, it reduces the misdiagnosis and thus saves costs
- Additional costs of monitoring are compensated by cost savings from targeted treatment
- Recommended monitoring *before* starting antihypertensive drugs
- Note that there was no intervention; used other data for evidence
- **All based on a simulation**

Example 2: description

- Objective: to estimate the cost effectiveness of herpes zoster (shingles) vaccine versus no vaccination
- Herpes zoster: a reactivation of the chickenpox virus in the body (causes a painful rash)
- Cohort entered the model healthy at 50 y/o
- **Rewards**: costs and QALYs
- **Time horizon**: 70 years (lifelong)
- **Cycle**: 1 year

Example 2: Model
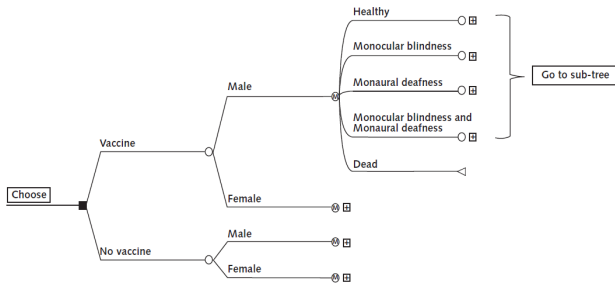
The model begins with a decision node representing the choice between the vaccine or no vaccination. The cohort then moves to a chance node (*open circle*) of male or female, depending on the sex distribution of the general population, and then enters the Markov node (*letter "M" inside circle*). For the first cycle, the entire cohort enters the "healthy" state, then moves between Markov health states depending on transition probabilities in subsequent cycles until everyone is subsumed by the "dead" state, at which point the model terminates.

Example 2: Model
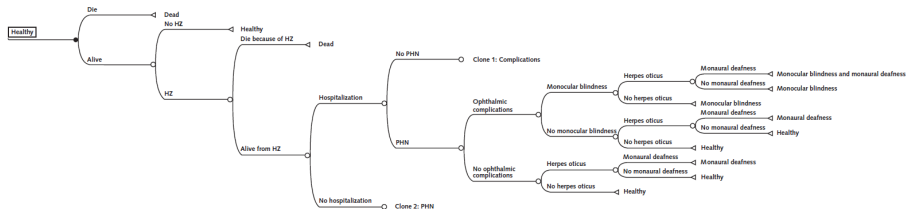
The chance of events occurring within each annual cycle for persons starting at the "healthy" state. For subsequent cycles beginning in the "monocular blindness," "monaural deafness," or "monocular blindness and monaural deafness" states, the tree is identical, but cohort members return to the corresponding initial states instead of "healthy" after recovering from HZ and any short-term complications (hospitalization and PHN). Those who acquire a second disability move to the combined disability state. Bilateral blindness and deafness are extremely rare and are not considered. HZ = herpes zoster; PHN = postherpetic neuralgia.

Example 2: features

- Model showed as decision tree with Markov models inside the tree
- The decision node shows the options: vaccine or no vaccine
- Sex is a chance node (no pun intended); similar to stratification in the hypertension example. It's a way of including data for male and females because the probabilities of events are different
- The probability of being male or female in the sex chance node is just the proportion of males/females in the population
- **Their model is not very clear**. It is easier to understand Markov models using transition diagrams, but it could be that the transition diagram was too messy

Example 2: Conclusions

- Vaccination is not cost effective: ICER = $500,754 per QALY
- The vaccine is expensive and the incidence of shingles is **low at that age**
- Efficacy of vaccine is very low after 10 to 12 years
- It's cost effective to use the vaccine in older patients
- "Herpes zoster vaccine for persons aged 50 years does not seem to represent good value according to generally accepted standards. Our findings support the decision of the Advisory Committee on Immunization Practices not to recommend the vaccine for adults in this age group."

Example 2: Conclusions

- **Back to policy**: note that the vaccine **IS** effective. We are talking about value
- If some people 50-59 do not get the vaccine they will suffer from shingles. What the study found is that for this group the additional costs of the vaccine are not justified the additional gains in QALYs
- We are not maximizing QALYs
- Also, we are not considering whether, say, Medicaid could afford the vaccines
- For the final, you need to understand the difference between the cost-effectiveness notion of "value", affordability, and clinical effectiveness (or maximizing health)

Example 3: description

- Cost effectiveness of alternative treatments for breast cancer
- One-year adjuvant trastuzumab (AT) therapy, with or without anthracyclines
- Evidence comes from clinical trial data; they wanted to model lifespan outcomes. The most typical case of CEA modeling: going from clinical trial evidence (short-run) to the long run (lifespan)
- "Markov modeling allowed extension of the time horizon of the model beyond the 2-year median follow-up available from randomized clinical trials."
- **Cohort**: 49 y/o women with early-stage breast cancer
- **Cycle**: 1 month
- **Time-horizon**: could not find it in paper, probably around 40 to 50 years
- Note, once in recurrence they can't get back to well. Not sure why

Example 3: Model
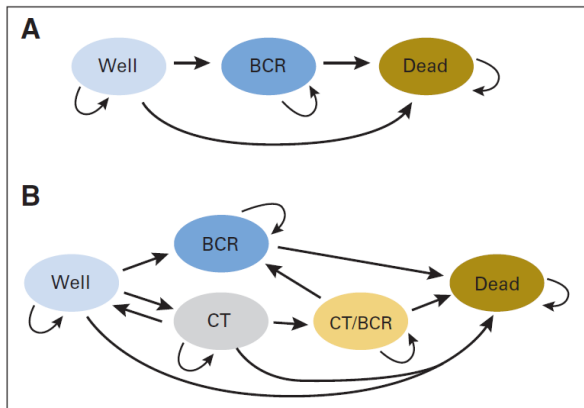
Fig 1. (A) Model schema for no trastuzumab and nonanthracycline trastuzumab arms: transitions between well, breast cancer recurrence (BCR), and dead states. (B) Model schema for anthracycline-based trastuzumab arm: transitions between well, BCR, cardiac toxicity (CT), simultaneous CT and BCR, and dead states.

Example 3: Conclusions

- The ICER is $39,982 per QALY: cost effective by any standard
- Of course, results very sensitive to medication costs (always the case in CEA of new medications)
- A straightforward model but lots of assumptions about parameter inputs
- In particular, they had to make assumptions about long-term outcomes because clinical trials are short term
- **The Special Assignment II is based on this paper**

Extending Markov models: time-dependency

- So far we have only dealt with Markov models that have the **same transitions probabilities each cycle**
- The transition probabilities did not depend on the **time spent in one state** or **just time** (i.e. cycle)
- Patients getting older would not have an accompanying increase in the probability of dying (but this doesn't mean that it matters; remember, always a comparison...)
- (By the way, this is often called **competing risk**)
- Making probabilities vary by cycle is easier than modeling time spent in a state because of the **memoryless property**

Probabilities vary according to **time in model**

- Some transition probabilities change as people get old
- In other words, **transition probabilities can be a function of cycle**
- In the HIV example, the probability of state D (death) should be higher as time passes because people are getting older
- In the homework, that created a somewhat unrealistic situation. If the medication was like a cure, nobody was dying in the combination group. That meant that people were "stuck" in the expensive states
- It's straightforward to implement competing risks: we just add another state

Probabilities vary according to **time in model**

Table 3.1 Revised transition probability matrix for the HIV case study where transitions to a dead state vary with the age of the cohort. See Table 2.2 for initial transitions

	State A	State B	State C	State D	State E
State A	$1 - 0.202 - 0.067 - 0.010 - P(age)$	0.202	0.067	0.010	P(age)
State B	0.000	$1 - 0.407 - 0.012 - P(age)$	0.407	0.012	P(age)
State C	0.000	0.000	$1 - 0.250 - P(age)$	0.250	P(age)
State D	0.000	0.000	0.000	1.0	0.000
State E	0.000	0.000	0.000	0.000	1.0

P(age1)	P(age2)	P(age3)	P(age4)	P(age5)	P(age6)	P(age7)	P(age8)	P(age9)	P(age10)
0.001	0.001	0.002	0.003	0.003	0.005	0.005	0.006	0.006	0.007

States A, B and C are as defined in Fig. 2.3. State D is HIV/AIDS-specific mortality and State E is other-case mortality. The numbers in the table below the main transition probability matrix are the age-dependent probabilities of other-cause mortality over a 10-year period.

- Two absorbing states: death due to HIV and death due to aging (non-HIV)
- Could have kept one death state while increasing the probability of dying

Probabilities vary according to **time in a state**

- Different situation: transition probabilities depend on **time in state**
- Example: Probability of dying increases according to how long a person has had AIDS
- This is a harder situation to handle with the type of Markov models we have covered
- We do not have a way to keep track of people moving from state to state
- I the HIV example, we can only keep track of people in state A because there is only one way to be in state A (previously being in state A)
- We **need to relax the Markov assumption** (memoryless property), which is possible, but cumbersome

Adding some "memory" to memoryless Markov models

- I'll use an example from Briggs et al. (2006) (Chapter 2): probability of dying of cancer after a cancer recurrence
- Patients can have a local or regional recurrence and then remission
- But after remission, the probability of death should depend on **time in remission** and also on whether the recurrence was regional or local
- More time in remission is better. Local recurrece is better than regional recurrence
- We need to incorporate different type of remission and keep track of **time in remission**

Partial transition diagram
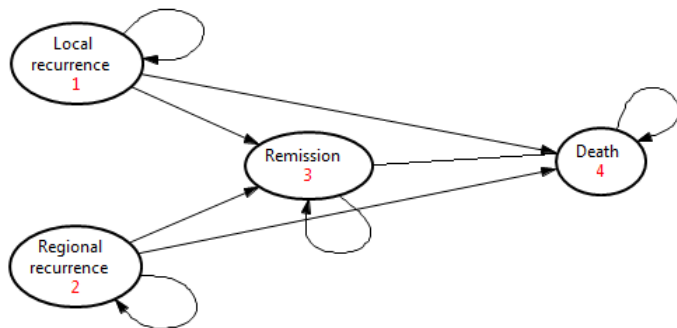
- Initial transition diagram. We can't keep track of time in remission once in remission

Add different types of remission first

- We can follow the **most common trick** in Markov models: adding states
- Remember that we "store" costs and benefits in health states and we can add as many states as we want (although it increases the complexity of the model)
- Instead of one remission state, we want two remission states, one for local and one for regional
- At any point in the simulation, we can still keep track of all remissions
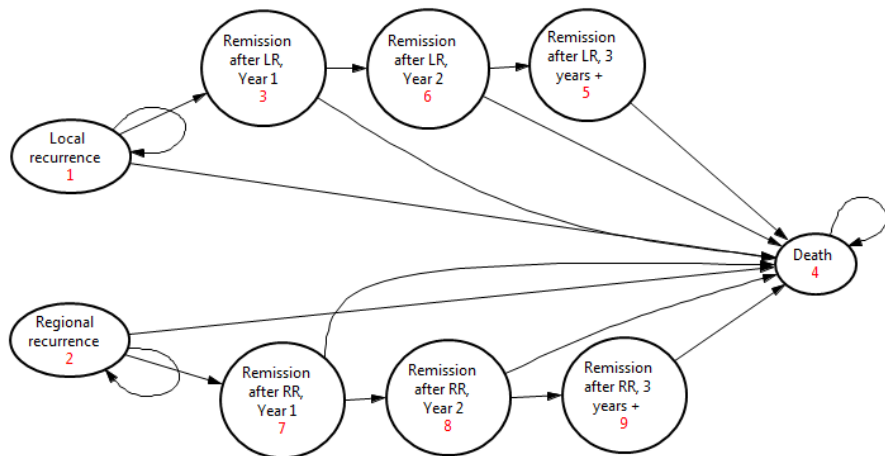
Adding remission states
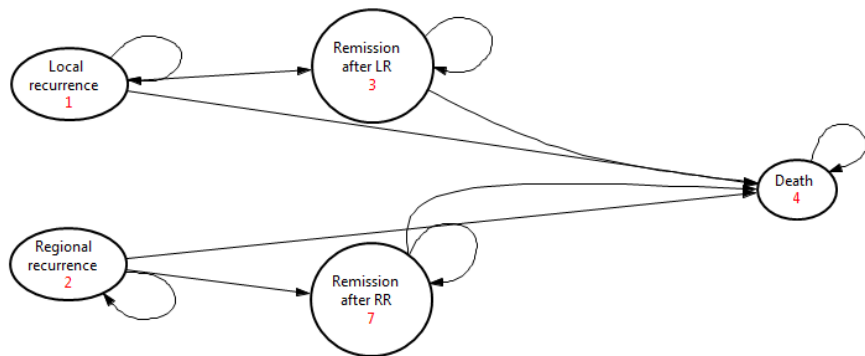
- Now the transition probability from remission to death could be different depending on the type of recurrence
- Costs and benefits can also be different; we have divided the remission state into two different remissions

We now need to solve the time issue

- We have made remission dependent of the type of recurrence
- We also wanted to consider the **time** in remission because it affects the probability of dying
- We'll follow the same trick of adding more states, but with one key variation: **people cannot stay in that state for more than 1 cycle**
- This type of state is called a **tunnel state**

Health states that reflect time

Why does it work?

- Patients cannot stay in the new remission states for more than one cycle (no arrow to the same health state)
- **We have added memory** to the Markov model. We now know that patients in, say, "Remission after LR, Year 2" have been cancer free for two years (no other way to get to this state)
- We now can make the probability of death different for each tunnel state, which means making the probability different **according to time in state**
- Of course we could add more tunnel states. **The cost is the added complexity of the model**
- **Note that the time in a tunnel state is guided by cycle length**

Tunnel states

- Tunnel states have a very good name; think of them as **tunnels will tolls**
- A tunnel is the only way to go from state A to B
- They impose costs and benefits (life years) that last only one cycle
- If you are in B, that means that you came from A one cycle ago
- Markov models with some sort of memory are sometimes called **semi-Markov processes** or models

Big picture

- The extensions we have covered could be called "games you can play by adding health states"
- They are relatively easy ways to make Markov models more realistic
- The methods we have covered so far are extensively used
- But for many types of problems, we still need different tools
- There are things that we can't model with Markov models