Advanced Decision Analysis: Markov Models
Reasons to understand Markov models

• It’s the standard in academia

• Very powerful/flexible tool
  – simple decision trees
    • relatively inflexible
      – limited time frame
      – hard to model recurring risks
  – Markov models:
    • allow you to model anything (well, almost anything)
Challenges of Markov models

- More difficult conceptually than simple decision tree models
- Trickier math
  - rates vs. probabilities
Overview

• Introduction to Markov models
  – Problems with simple decision trees
  – Markov models
    • general structure
    • how they run
    • rates & probabilities
    • how they keep score (expected value)
Should patients with Björk-Shiley valves undergo prophylactic replacement?

JOHN D. BIRKMeyer  CHARLES A. S. MARRIN  GERALD T. O'CONNOR

About 85 000 patients have undergone replacement of diseased heart valves with prosthetic Björk-Shiley convexo-concave (CC) valves. These valves are prone to fracture of the outlet strut, which leads to acute valve failure that is usually fatal. Should patients with these valves undergo prophylactic replacement to avoid fracture? The incidence of strut fracture varies between 0% and 1.5% per year, depending on valve opening angle (60° or 70°), diameter (< 29 mm or ≥ 29 mm), and location (aortic or mitral). Other factors include the patient's life expectancy and the expected morbidity and mortality associated with reoperation. We have used decision analysis to identify the patients most likely to benefit from prophylactic reoperation.

The incidence of outlet strut fracture was estimated from the data of three large studies on CC valves, and stratified by opening angle and diameter. The risk of outlet strut fracture is higher for valves with a diameter ≥ 29 mm than for valves with a diameter < 29 mm, and higher for valves with an opening angle of 70° than for valves with an opening angle of 60°. The risk of outlet strut fracture is also higher for aortic valves than for mitral valves. The risk of outlet strut fracture is higher for valves that were implanted in the USA than for valves that were implanted in Europe.

Introduction

Several large cohort studies have assessed the risk of outlet strut fractures in Björk-Shiley convexo-concave (CC) prosthetic heart valves. The CC valve, introduced in 1976, features a tilting disc that swivels between inlet and outlet struts. Difficulties with strut fractures were identified in several models, and all models of the CC valves were withdrawn from the market in 1986, by which time CC valves had been implanted in about 85 000 patients. Because strut fracture results in acute valve failure that is usually fatal, prophylactic valve replacement has lately received much attention in the lay press.

The risk of outlet strut fracture depends on both valve characteristics and location. The 70° CC valve (opening angle 70°) has a substantially higher risk of strut fracture than the 60° CC valve. The 70° CC valve was never approved for use in the USA, but it was implanted in about 4000 patients in Europe. There is a higher risk of strut fracture for large valves (> 29 mm) than for small valves (< 29 mm).
Risk of strut fracture of Björk-Shiley valves

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Lex A. van Herwerden  Jo Defauw
Should patients with Bjork-Shiley valves undergo prophylactic replacement?

Risks of Outlet Strut Fracture (and its consequences) vs. Risks with reoperation
Clinical Scenario

- 65 year man with prosthetic valve in 1986
  - otherwise healthy
    - predicted operative risk 3%
  - 29mm, 70° Björk-Shiley valve
    - strut fracture risk 10.5% at 8 years
    - 63% case-fatality
Decision Analysis

Four Basic Steps

1. structure competing strategies and clinical outcomes in a decision model
2. estimate probabilities for clinical outcomes
3. assign values for clinical outcomes (utility)
4. analysis
   - calculate expected values of strategies
   - assess stability of results (sensitivity analysis)
1. Structure model (simple tree)

- **Choose**
  - **Watchful waiting**
    - **Strut fracture**
      - Die
      - Survive/well
  - **No fracture/well**
  - **Prophylactic reop**
    - Die
    - Survive
2. Assign probabilities

- **Choose**
  - **Watchful waiting**
    - **Strut fracture**
      - **Die**
        - Probability: 0.63
      - **Survive/well**
        - Probability: 0.105
    - **No fracture/well**
      - **Die**
        - Probability: 0.03
      - **Survive**
        - Probability: 0.97
  - **Prophylactic reop**
    - **Die**
      - Probability: 0.37
    - **Survive/well**
      - Probability: 0.895
3. Assign values (e.g. in QALYs)

- **Watchful Waiting**
  - **Strut Fracture**
    - Die: 0.63
    - Survive/Well: 0.37
  - **No Fracture/Well**
    - Die: 0.03
    - Survive: 0.97

- **Prophylactic Reop**
  - Die: 0
  - Survive: 17.9
4(a). Baseline analysis

- **Choose**
  - **Watch wait**
    - **No fracture**
      - **Die**
        - $U^*P$: 0
        - **Survive**: 0.37
        - **Expected Value (EV)**: 17.9
      - **Survive**: 0.895
      - **EV**: 17.9
    - **Die**: 0.105
    - **Survive**: 0.97
    - **EV**: 17.9
  - **Proph reop**
    - **Die**: 0.03
    - **Survive**: 0.97
    - **EV**: 17.4
    - **EV**: 17.4 QALYS

- **U*P**
  - **Die**: 0
  - **Survive**: 0.7
  - **EV**: 16.7 QALYS
4(b). Sensitivity analysis

Expected Value (QALYs)

Operative Mortality Risk (%)
Limitations of simple decision trees

• Don’t account for timing of events
  – Roll the dice once, at time zero

• Problems with parameter estimates (time)
  – probabilities, dealing with competing risks over time
  – values applied to future outcomes may be underestimated (all bad events considered to be happening immediately)
Problems with simple trees

What if the person lived 20 good years before dying from strut fracture? EV=0???
Markov models to the rescue …

• Definition:
  – iterative model in which hypothetical patients make transitions between health states over time, accumulating QALYs along the way

• 2 main types:
  – Cohort simulation (large pop of identical patients)
  – Monte Carlo simulation (one pt at a time)
Decision analysis with Markov models

• Same four basic steps as simple trees
  – structuring the model
  – probabilities
  – assigning values to outcomes
  – baseline and sensitivity analysis

• But a little more complex …
Model structures viewed left to right

• Simple trees
  – specify alternatives (decision node)
  – chance events (chance nodes)
  – final health states (terminal nodes)

• Markov models
  – specify alternatives (decision node)
  – parse to health states (intermediate and final)
  – chance events move hypothetical patients between health states
Specifying alternatives

choose

- watchful waiting
- prophylactic reop
Health states

choose

watchful waiting

well

well, postop

dead

prophylactic reop

well, postop

dead
Whole model

1. Alternatives
2. Health states
3. Cycle trees (end with a health state assignment)
How the model “runs”

• Markov cohort simulation
  – hypothetically large cohort
  – start in distribution of health states at time zero
  – some members make transitions between health states with each cycle
    (Cycle = “stage” in TreeAge)
  – keep cycling until everyone (or nearly everyone) absorbed into the state “dead”
Folding back: Time zero

- Choose
  - Watchful waiting
    - Well, postop
      - Well
      - Dead
        - Dead
          - Dead

Cycle length = 1 year
Folding back: Cycle 1

choose

watchful waiting

well

well, postop

937 pts

4 pts

59 pts

prophylactic reop

well, postop

923 pts

77 pts

cycle length = 1 year
Folding back: Cycle 10

- **choose**
  - watchful waiting
    - well
      - well, postop
        - dead
          - 448 pts
  - prophylactic reop
    - well, postop
      - dead
        - 444 pts

- 540 pts
- 12 pts
- 556 pts

**cycle length = 1 year**
Folding back: Cycle 50

choose

watchful waiting

well, postop

well

0 pts

well, postop

0 pts

dead

1000 pts

prophylactic reop

well, postop

0 pts

dead

1000 pts

cycle length = 1 year
Decision analysis with Markov models

• Four components
  – structuring the model (and how it runs)
  – probabilities
  – assigning values to outcomes
  – analysis
Probabilities

- Events with short time horizons (e.g., op risk)
- Events that occur over time (e.g., valve-failure)
  - Constant
  - Changing

Simple trees

Markov models
Events with short time horizons (easy)

1. Alternatives  
2. Health states  
3. Cycle trees
Events occurring over time (harder)

1. Alternatives  
2. Health states  
3. Cycle trees
What you need:

Probabilities of events occurring during each cycle of the model (aka transition probabilities)
Problem:

Published studies don’t give you cycle-specific probabilities
What do you get from literature?

• Cumulative incidence
  – (e.g., “stroke incidence at 5 years was 24%…”)
• Kaplan-Meier plots
  – proportion of population free of event
• Number of events, size of population
Deriving transition probabilities

Data from source studies

Step 1

Annual rates

Step 2

Cycle-specific probabilities
## Step 1. Deriving rates

<table>
<thead>
<tr>
<th>Source Data</th>
<th>Rate Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>x-year probability</td>
<td>$\ln (1 - p)$</td>
</tr>
<tr>
<td>(% pts with event at x years)</td>
<td>$t$</td>
</tr>
<tr>
<td>survival / event-free curve</td>
<td>$\ln (f)$</td>
</tr>
<tr>
<td>(% pts [f] without event)</td>
<td>$t$</td>
</tr>
<tr>
<td># events</td>
<td># events/pt-yrs follow-up</td>
</tr>
</tbody>
</table>
Deriving rates: Example

- Kaplan-meier plot
- 89.5% free of OSF at 8 years
- \( \text{rate} = - \frac{\ln (f)}{t} \)
  \[= - \frac{\ln 0.895}{8} \]
  \[= 0.0139 \, \text{yr}^{-1} \]
  \[= 1.39\% \, \text{yr}^{-1} \]
Deriving transition probabilities

Data from source studies

Step 1

Rates

Step 2

Cycle-specific probabilities
Step 2. Converting rates to transition probabilities

- Transition probability \( p \) = \( 1 - e^{-r \cdot t} \)
  - \( r \) = rate, \( t \) = cycle length

- Example:
  - Strut Fx rate = 0.0139; 3 month cycle length
  - \( p \) = \( 1 - e^{-0.0139 \cdot 0.25} \)
  - = 0.00347

- TreeAge function: “RateToProb”
Should patients undergo proph reop?

cyclelength=0.5
muASR=0.06
muOSF=0.015
pDieASR=RateToProb(muASR, cyclelength)
pDieOSF=0.03
pDieSurg=0.05
pOSF=RateToProb(muOSF, cyclelength)
pStrokeSurg=0.10
tStroke=0.03
qStroke=0.5
well

1

survive

**B-S Lab.00: Define Variable "pDieASR"**

At node: (none) Default Definition for Document

Operators: ▼ Functions: ▼ Variables: ▼

**pDieASR =**

RateToProb(muASR, cyclelength)

Show Nodes

Distribution...

Help

OK

Cancel
Decision analysis with Markov models

• Four components
  – structuring the model (and how it runs)
  – probabilities
  – assigning values to outcomes
  – analysis
Assigning values (rewards)

- **Simple trees:**
  - one value assigned each terminal node

- **Markov:**
  - assigned at each health state
  - can be credited multiple times (with each cycle of the model)
Assigning values to health states ("rewards")

• Measures of expected value
  – Costs ($), years of life, QALYs
Accumulating rewards: Cycle 0 to 1

Incremental reward = cycle length = 1 year
Accumulating rewards: Cycle 1 to 2

Incremental reward = cycle length = 1 year
Accumulating reward: Cycle 10 to 11

Incremental reward = cycle length = 1 year

choose

watchful waiting

well

well, postop

dead

prophylactic reop

well, postop

dead

540 pts

12 pts

448 pts

556 pts

444 pts

Cycle

552

Cum

7822

Cycle

556

Cum

7810

Incremental reward = cycle length = 1 year
Accumulating reward: Cycle 50

Incremental reward = cycle length = 1 year
## Baseline analysis

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<tr>
<th>Strategy</th>
<th>Cumulative reward</th>
<th>Expected Value</th>
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<tbody>
<tr>
<td>Watchful Waiting</td>
<td>17,145</td>
<td></td>
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<tr>
<td>Prophylactic Reoperation</td>
<td>17,411</td>
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## Baseline analysis

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How do you incorporate utilities?
Accumulating rewards: Cycle 0 to 1

Incremental reward = 0.5 * 1 year
Building a Decision Model

Your patient is a 65 year old white male with a large abdominal aortic aneurysm. Although asymptomatic, the aneurysm has grown substantially over the last year, from 4.6cm to 6.0cm. You have decided that the aneurysm needs repair. However, the patient also has severe angina and a positive stress test, and cardiac catheterization reveals good ventricular function, but severe coronary disease that is not amenable to PTCA or stenting.

Question: Should this patient undergo AAA repair only, AAA repair followed by CABG, or CABG prior to AAA repair?
Basic Steps

1. Structure a decision model
2. Enter probabilities, life expectancy and utility values
3. Perform a baseline analysis
4. Perform sensitivity analysis