Introduction to Decision Analysis and Markov Modeling

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Outline

• Decision analysis and simple trees
• Modeling concepts
• Use of modeling in economic evaluations
• Introduction to Markov models
• Importance of modeling in cost-effectiveness analyses
• Modeling mortality
Decision Analysis

- Decision analysis is a quantitative, probabilistic way of modeling problems under situations of uncertainty.
Elements of Decision Analysis

- Structuring the problem
- Assigning probabilities to all chance events
- Assigning utility, or value, to all outcomes
- Evaluating the expected utility of each strategy
- Performing sensitivity analyses
Structuring the Problem

- Decision model (usually decision tree) is chosen to represent the clinical problem
- Model needs to be simple enough to be understood, but complex enough to capture the essentials of the problem
- Many simplifying assumptions are needed for modeling
Structuring the Problem: Decision Nodes

- Decision nodes are the choices being considered for a problem -- these choices are under the control of the decision maker
  - To perform a test (or tests)
  - To treat medically or surgically
  - To do something now or later
  - To do nothing at all
Structuring the Problem: Chance Nodes

- Chance nodes are the temporal sequence of possible events which follow a decision node.
- Chance events are out of the control of the decision maker — they’re based on probability or outcome data.
- Chance events at a particular node need to add up to 100%.
Chance Nodes

- Objective data -- based on hard data from the literature (randomized controlled trials)
- Subjective data -- softer data based on expert opinion
- Bayes’ Rule applied to test results
  - predictive value of positive/negative tests
Structuring the Problem: Terminal Nodes

- Terminal nodes are the final outcome state associated with each possible pathway.
- Some measure of value or worth needs to be applied to the terminal nodes.
- Whose values: patient’s, society, hospital, etc.
- Outcome measure needs to be consistent:
  - life expectancy, 0 to 100 scale, dollars, etc.
Example: Boy with abdominal pain

12 yo boy with 8 hrs of abdominal pain and nausea, who vomited once. He ate at a restaurant earlier in the day. There is no significant past history, no meds.

Exam: scared boy with diffuse abdominal pain, but only mild guarding in the periumbilical area. CBC is only mildly elevated. He is being considered for admission for “R/O Appendicitis”
Decision Elements

- Choices are to admit and observe for the next 6 hrs, or take to the OR now.
- Probability data (surgeon guestimates):
  - appendicitis: 50%
  - rupture of observed for 6 hrs: 20%
  - operative mortality with immediate surgery: 1%
  - operative mortality after rupture: 4%
  - operative mortality with stabilization: 0.02%
  - surgical morbidity 5 time greater after rupture
  - Morbidity=1 day lost
Surgery

Survive Surgery

Die from Surgery

Wait and See
Surgery
  - Die from Surgery
  - Survive Surgery
    - Appdx
      - Wait and See
        - Non-specific Abdominal Pain
Surgery

- Die from Surgery
  - Survive Surgery
    - Ruptures
      - Appdx
        - Remains Same
      - Non-specific Abdominal Pain
    - Wait and See
Surgery

Wait and See

Die from Surgery

Survive Surgery

Go to Surgery (worse results)

Go to Surgery (better results)

Appdx

Ruptures

Remains Same

Non-specific Abdominal Pain
Surgery

- Die from Surgery
  - Dead
- Survive Surgery
  - Alive, surgery
    - Ruptures
      - Go to Surgery (worse results)
    - Remains Same
      - Go to Surgery (better results)
- Wait and See
  - Non-specific Abdominal Pain
    - Alive, no surgery
Evaluating the Decision Tree

Decision tree is “folded back” from right to left by determining the product sum of the series of chance/terminal nodes.
Expected value of “Option A” is the product sum of the outcomes of “Better” and “Worse”

\[ 0.8 \times 100 + 0.2 \times 50 = 90 \]
Go to surgery—worse results

Expected value is the product sum of the outcomes of: \[ 0.96 \times (100-5) + 0.04 \times 0 = 91.2 \]
Die from Surgery

Survive Surgery

Surgery

Go to Surgery (worse results)

Go to Surgery (better results)

Wait and See

Non-specific Abdominal Pain

Ruptures

Remains Same

p = .01

p = .99

p = .2

p = .5

p = .5

p = .99

p = .5

p = .8

p = .2

p = .5

p = .8

p = .99

p = .5

p = .8

p = .5

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8

p = .8
Sensitivity Analysis

• Systematically asking “what if” questions to see how the decision result changes.
• Determines how “robust” is the decision.
• Threshold analysis: one parameter varied.
• Multiway analysis: multiple parameters systematically varied.
Probability of Appendicitis

Expected Utility

One-Way Sensitivity Analysis

Surgery

Wait and See

baseline --> threshold = 0.77

Probability of Appendicitis
Two-Way Sensitivity Analysis

Probability of Appendicitis

Probability of Rupture

Wait and See

Surgery

baseline-- *
Three-Way Sensitivity Analysis

P(Rupture)

Surgery

op mort = 5%

op mort = 0

Wait and See

Probability of Appendicitis
Treat

Test

positive

disease

no disease

disease

no disease

no disease, treated

disease, treated

disease, untreated

negative

disease

no disease

disease

no disease

no disease, treated

disease, treated

disease, untreated

No Test or Rx

no disease

no disease

no disease, untreated

disease, untreated

no disease, untreated
## Balance Sheet for Decision Analysis

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Explicit</td>
<td>• Explicit</td>
</tr>
<tr>
<td>• Provides structure</td>
<td>• Encourages oversimplification</td>
</tr>
<tr>
<td>• Allows diverse data to be combined</td>
<td>• Requires data</td>
</tr>
<tr>
<td>• Allows explicit use of patient preferences</td>
<td>• Unfamiliar</td>
</tr>
<tr>
<td>• Allows examination of soft data</td>
<td>• Time consuming</td>
</tr>
<tr>
<td>• Separates a large problem into smaller, manageable ones</td>
<td>• Demystifies medicine</td>
</tr>
<tr>
<td>• Provides documentation of clinical reasoning</td>
<td>• Provides documentation of clinical reasoning</td>
</tr>
</tbody>
</table>
Economic Evaluations

• Trial-based analysis
  – costs and effectiveness measure estimated simultaneously from clinical trial cohort

• Model-based analysis
  – integrates a variety of data sources on the costs and outcomes of alternative clinical strategies

• “Hybrid” analysis
  – incorporation of a modeling effort in a trial-based analysis
Randomized Clinical Trials

- New Treatment
- Alternative Treatment

Primary Endpoint:
- Intermediate
- Combined
Cost-Effectiveness Analysis

Test Strategies

New Rx

Comparator.

Endpoint

Natural History

- LE
- Events
  - cost
  - qol
- QALYs
Acceptance of Modeling (US)

“... models to provide estimates of pharmacoeconomic parameters should only be used when it is impractical or impossible to gather data using adequate and well-controlled studies.”

Acceptance of Modeling (Canada)

“Because effectiveness data are generally not available, appropriate modeling techniques based on sound pharmaco-epidemiology are permissible.”

Markov Models in CEA

- Analytical structures that represent key elements of a disease
- Useful for diseases in which events may occur repeatedly over time
- Synthesizes data on costs, effects, and HRQOL life of alternative clinical strategies
- Calculates life expectancy or quality-adjusted life expectancy
Principle Elements

- Set of mutually exclusive health states
  - transient, temporary, absorbing
- Set of transition probabilities among states
  - constant, time-dependent
- Cycle length
- Utility value and/or cost per health state
Markovian Assumption

• Probability of transition depends only on current health state residence and not on past health states (memoryless property)
• Health state definitions should include all relevant history
  – history of precancerous lesion
  – history of acute myocardial infarction
  – time since HIV seroconversion
Simple Markov Model

Time

\[ t \]

\[ t+1 \]

Well \rightarrow Sick \rightarrow Dead
Well \rightarrow Sick \rightarrow Dead
Well \rightarrow Sick \rightarrow Dead

Well \rightarrow Sick \rightarrow Dead
Well \rightarrow Sick \rightarrow Dead
Well \rightarrow Sick \rightarrow Dead
Transition Probability Matrix:

<table>
<thead>
<tr>
<th></th>
<th>Well</th>
<th>Sick</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well</td>
<td>0.75</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>Sick</td>
<td>0</td>
<td>0.70</td>
<td>0.30</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Starting Probability Vector: [ 1 0 0 ]
In DATA

Markov

Well
1

Sick
0

Dead
0

Well
0.75
Sick
0.20
Dead
0.05
Sick
0.70
Dead
0.30
Alternative Structure

Markov

Well
1
Survive
0.95
Dead
0.05
Sick
0.70
Dead
0.30

Sick
0
Well
0.79
Sick
0.21
Quality-of-Life Adjustments

Well: 1.0
Sick: 0.5
Dead: 0.0
## Running the Model

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Well</th>
<th>Sick</th>
<th>Dead</th>
<th>Cycle Reward</th>
<th>Total Reward</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1</td>
<td>0.75</td>
<td>0.20</td>
<td>0.05</td>
<td>0.85</td>
<td>1.35</td>
</tr>
<tr>
<td>2</td>
<td>0.56</td>
<td>0.29</td>
<td>0.15</td>
<td>0.71</td>
<td>2.06</td>
</tr>
<tr>
<td>3</td>
<td>0.42</td>
<td>0.32</td>
<td>0.26</td>
<td>0.58</td>
<td>2.64</td>
</tr>
<tr>
<td>4</td>
<td>0.32</td>
<td>0.31</td>
<td>0.38</td>
<td>0.47</td>
<td>3.11</td>
</tr>
</tbody>
</table>
Markov Approximation to LE

Life Expectancy = Area Under the Survival Curve
Common Methods of Evaluation

• Cohort simulation
  – hypothetical cohort of patients transition through the model simultaneously

• Monte Carlo simulation
  – first order simulation randomly selects a patient from the hypothetical cohort and they transition through the model one at a time
Monte Carlo Simulation

Well → Sick → Dead
Well → Sick → Dead
Well → Sick → Dead
Well → Sick → Dead
Well → Sick → Dead
Probabilistic Sensitivity Analysis
(2nd order Monte Carlo)

- Decision tree estimates of probabilities and utilities are replaced with probability distributions (logistic-normal)
- The tree is evaluated many times with random values selected from each distribution
- Results include means and standard deviations of the expected values of each strategy
Markov Tools

• Markov tunnels
  – useful when transition probabilities are a function of how long a person has been in the state

• Markov tolls (transition rewards)
  – assigns a value (toll/reward) for going down a branch in the Markov subtree
Benefits of a Model in CEA

- Incorporates the benefits and costs beyond time horizon of existing data
- Considers all relevant clinical strategies
- Incorporate data from multiple sources
- Evaluates “what if” scenarios
Example: DCCT

Patients with IDDM → Retinopathy • Nephropathy • Neuropathy

Clinical Trial Data

Model

• Blindness
• ESRD
• Amputation

Five-Year Trial Data

**Survival Probability**

- **Control** (solid line)
- **Treatment** (dotted line)

**Time (years)**

What next?
Consider All Relevant Strategies

- Comparison of interventions often not compared head-to-head in a trial
  - pharmaceutical vs. educational interventions
- Clinical trials do not always consider those strategies which would be most relevant in a cost-effectiveness analysis
- Too many plausible strategies to be feasible for a clinical trial
“What If” Scenarios

• How great would the diagnostic accuracy of a noninvasive imaging test for coronary arteries have to be to replace the tests used in current practice?
• How effective does a treatment need to be, and at what duration of treatment effect, to replace current therapy?
• Identifies important gaps in our knowledge
Some Take-Home Messages

• Use of models are appropriate in a number of situations
• Model assumptions and input variables should be as transparent as possible
• Adequate sensitivity analysis should be performed
• Modeling as well as clinical expertise should be consulted
G.I.G.O.
References

Books:
- Sox HC: *Medical Decision Making*, Butterworths, Boston, 1988

Articles:
- Pauker SG, Kassirer JP: Threshold approach to clinical decision making, NEJM, 302:1109, 1980

Software:
- DATA
- Decision Maker, by Steve Pauker, MD, New England Medical Center, Boston