Modeling in Medical Decision Analysis

Jeremy D. Goldhaber-Fiebert, PhD

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Agenda

• Decision analysis
• Cost-effectiveness analysis
• Decision trees
• Sensitivity analysis
• Markov models
• Microsimulations
WHAT IS A DECISION ANALYSIS?
What is a decision analysis?

• A quantitative method for evaluating decisions between multiple alternatives in situations of uncertainty
What is a decision analysis?

• A quantitative method for evaluating decisions between multiple alternatives in situations of uncertainty

Decisions between multiple alternatives:
• Allocate resources to one alternative (and not the others)
• There is no decision without alternatives => making a choice
What is a decision analysis?

• A quantitative method for evaluating decisions between multiple alternatives in situations of uncertainty

Quantitative method for evaluating decisions:
• Gather information
• Assess the consequences of each alternative
• Clarify the dynamics and trade-offs involved in selecting each
• Select an action to take that gives us the best expected outcome

We employ probabilistic models to do this
The steps of a decision analysis

1. Enumerate all relevant alternatives
2. Identify important outcomes
3. Determine relevant uncertain factors
4. Encode probabilities for uncertain factors
5. Specify the value of each outcome
6. Combine these elements to analyze the decision

Decision trees and related models important for this
What is a decision analysis called when its important outcomes include costs?

1. Enumerate all relevant alternatives
2. Identify important outcomes
3. Determine relevant uncertain factors
4. Encode probabilities for uncertain factors
5. Specify the value of each outcome
6. Combine these elements to analyze the decision

Cost-effectiveness analysis a type of decision analysis that includes costs as one of its outcomes
WHAT IS A COST-EFFECTIVENESS ANALYSIS?
What is a cost-effectiveness analysis?

• In the context of health and medicine, a **cost-effectiveness analysis (CEA)** is a method for evaluating tradeoffs between health benefits and costs resulting from alternative courses of action.

• CEA supports decision makers; it is not a complete resource allocation procedure.
Cost-Effectiveness Ratio (CER): How to compare two strategies in CEA

- **Numerator**: Difference between costs of the intervention (strategy) and costs of the alternative under study
- **Denominator**: Difference between health outcomes (effectiveness) of the intervention and health outcomes of the alternative

\[
CER = \frac{C_i - C_{alt}}{E_i - E_{alt}}
\]
Models for decision analysis and CEAs

- **Decision model**: a *schematic* representation of all of the clinically and policy relevant features of the decision problem
  - Includes the following in its structure:
    - Decision alternatives
    - Clinical and policy-relevant outcomes
    - Sequences of events
  - Enables us to integrate knowledge about the decision problem from many sources (i.e., probabilities, values)
  - Computes expected outcomes (i.e., averaging across uncertainties) for each decision alternative
Building decision-analytic model

1. Define the model’s structure
2. Assign probabilities to all chance events in the structure
3. Assign values (i.e., utilities) to all outcomes encoded in the structure
4. Evaluate the expected utility of each decision alternative
5. Perform sensitivity analyses

Simple enough to be understood; complex enough to capture problem’s elements convincingly (assumptions)
"All models are wrong; but some models are useful"

-- George Box and Norman Draper, 1987
Building decision-analytic model

1. Define the model’s structure
2. Assign probabilities to all chance events in the structure
3. Assign values (i.e., utilities) to all outcomes encoded in the structure
4. Evaluate the expected utility of each decision alternative
5. Perform sensitivity analyses
WHAT ARE THE ELEMENTS OF A DECISION TREE’S STRUCTURE?
Decision node

A place in the decision tree at which there is a choice between several alternatives

The example shows a choice between 2 alternatives, but a decision node can accommodate a choice between more alternatives ... provided alternatives are mutually exclusive.
Chance node

A place in the decision tree at which chance determines the outcome based on probability.

The example shows only 2 outcomes, but a chance node can accommodate more outcomes ... provided they are mutually exclusive AND collectively exhaustive.
What do mutually exclusive and collectively exhaustive mean?

- **Mutually exclusive**
  - Only one alternative can be chosen
  - Only one event can occur

- **Collectively exhaustive**
  - At least one event must occur
  - One of the possibilities must happen
  - Taken together, the possibilities make up the entire range of outcomes
Terminal node

Final outcome associated with each pathway of choices and chances

Final outcomes must be valued in relevant terms (cases of disease, Life years, Quality-adjusted life years, costs) so that they can be used for comparisons
Summary

• **Decision nodes**: enumerate a choice between alternatives for the decision maker

• **Chance nodes**: enumerate possible events determined by chance/probability

• **Terminal nodes**: describe outcomes associated with a given pathway (of choices and chances)

The entire structure of the decision tree can be described with only these elements
Example: decision tree

• Patient presents with symptoms
• Likely serious disease; unknown w/o treatment
• Two treatment alternative:
  – Surgery, which is potentially risky
  – Medical management, which has a low success rate
• With surgery, one must assess the extent of disease and decide between curative and palliative surgery
• **Goal: maximize life expectancy for the patient**
The initial decision is between surgery and medical management.
Treatment is initiated on patients w/ symptoms; some w/o disease
Those with disease have a chance to benefit from treatment.
Likewise with surgery
Surgery is risky even for those with no disease.
For disease, try cure vs. palliate?

- Disease Present → Live → Cure
- Disease Absent → Surg → Dth
- Medical Mgmt → Disease Present → No Cure
- Surgery → Palliate
- Cure → Palliate
Surgical risks here too

Disease Present 

Disease Absent 

Surgery 

Medical Mgmt 

Cure 

No Cure 

Live 

Surg Dth 

Palliate 

Try Cure 

Live 

Surg Dth 

Live
1. Surgery
2. in a patient with disease
3. where curative surgery chosen
4. and patient survives
5. and is cured
Disease Present
10%
90%
Disease Absent
1%

Surgery
10%
90%
Medical Mgmt
10%
90%

Disease Present
10%
90%
Disease Absent
1%

Surg
Dth
Cure
Palliate

Add probabilities (studies, experts)
Now add outcomes
Death yields 0 years of additional life
Uncured disease confers 2 years of additional life
Surgery

Disease Present
- 10% Cure
- 90% Disease Absent

Disease Absent

Medical Mgmt
- 10% Cure
- 90% Disease Absent

Cure yields 20 years of additional life
Now average out & fold back

10% * 20 + 90% * 2 = 3.8 years (expected)
Now average out & fold back

Surgery

- Disease Present
  - 10% Cure
  - 90% Live

- Disease Absent
  - 1% Cure
  - 99% Live

Medical Mgmt

- Disease Present
  - 10% Cure
  - 90% Live

- Disease Absent
  - 20 Y

Same calculation here
10% * 20 + 90% * 2 = 3.8 years (expected)
Now average out & fold back

Since disease presence unknown, we do this again
Now average out & fold back

Surgery
- Disease Present
  - 10% Cure, 90% Live
- Disease Absent
  - 1% Cure, 99% Live

Medical Mgmt: 18.38 Y

10%*3.8 + 90%*20 = 18.38 years
Now average out & fold back

Surgery

Disease
- Present
  - 10%
  - 90%
- Absent

Live
- 99%

Try
- Cure
  - Cure
    - 10%
    - 90%
    - 90%

Surg
- Dth
  - 10%
  - 90%
  - 90%

Palliate
- Surg
  - Dth
    - 2%
    - 98%

Medical Mgmt
- 18.38 Y

Try
- Cure
  - 0 Y

Surg
- 20 Y

Now average out & fold back
Now average out & fold back

Surgery
- Disease Present
  - 10% Cure
  - 90% Palliate
- Disease Absent
  - 99% Palliate
  - 1% Live
  - 0 Y Palliate

Medical Mgmt
- 18.38 Y Palliate

Try Cure
- 10% Cure
- 90% Palliate
- 20 Y Palliate

Surg Dth
- 10% Cure
- 90% Palliate
- 2 Y Palliate

Palliate
- 3.72 Y Palliate
Now average out & fold back

- **Surgery**
  - Disease Present: 10%
    - Live: 99%
    - Death: 1%
  - Disease Absent: 90%
    - Live: 20 Y
    - Death: 0 Y

- **Medical Mgmt**
  - Average Out: 18.38 Y

- **Try Cure**
  - Live: 18.2 Y

- **Palliate**
  - Average Out: 3.72 Y

**Surgical**
- Cure: 10%
- Death: 90%
Now average out & fold back

- Surgery
  - Disease Present: 10% Live, 90% Dth
  - Disease Absent: 1% Live, 99% Dth
- Medical Mgmt: 18.38 Y
- Try Cure: 10% Cure, 90% Palliate, 1% Dth
- Palliate: 3.72 Y
- Live: 20 Y
Now average out & fold back

Surgery

Disease Present
10% Cure 16.38 Y
90%

Disease Absent
1%

Live 99%

Surg 0 Y

Dth

Medical Mgmt 18.38 Y

Palliate 3.72 Y
This one is different:
Decision node:
Surgeon picks option with greatest expected benefit:
Try Cure (16.38 years) preferred (called “folding back”)

10% Disease Present
90% Disease Absent
10% Medical Mgmt
18.38 Y
90% Live
99% Palliate
1% Surger Dth
20 Y
16.38 Y
3.72 Y
Now average out & fold back

- Disease Present: 10% Cure, 90% Live
- Disease Absent: 1% Surg, 99% Live

Surgery: 10% Cure, 90% Live
Medical Mgmt: 18.38 Y
Try Cure: 16.38 Y
Now average out & fold back

Surgery

Disease

Present
10%

90%

Disease
Absent

Live

20 Y

Try Cure
16.38 Y

Medical Mgmt
18.38 Y
Now average out & fold back

Surgery
  Disease
    Present
      10%
    Absent
      90%
  Medical Mgmt
      18.38 Y

Try Cure
  16.38 Y

Disease
  19.8 Y
Decision node again (overall) Surgery is preferred to Medical Management because the incremental benefit of surgery is:

\[ 19.46 - 18.38 = 1.08 \text{ years} \]

Recommendation: Choose surgery (with “try cure” surgical option)
Use same approach for CEA but now with second set of outcomes:

19.46 – 18.38 = 1.08 years

$10,000 – $100 = $9,900

$9,900 / 1.08 = $9,167 per life year gained

Surgery if willing to pay at least $9,167 per life year gained, otherwise medical management.
SENSITIVITY ANALYSIS
But probabilities and outcome values uncertain...
Sensitivity Analysis

• Systematically asking “what if” questions to see how the decision result changes
• Determines how “robust” the decision is
  – **Threshold analysis:** one parameter varied
  – **Multi-way analysis:** multiple parameters systematically varied
If probability of surgical death with curative surgery uncertain.
1-way sensitivity analysis: Curative Surgical Death

Base Case

Threshold

Expected Life Years

Probability of Curative Surgical Death

Surgery - Curative
Med Mgmt
Advanced: Probabilistic Sensitivity Analysis (2nd order Monte Carlo)

- Decision tree estimates of probabilities and utilities are replaced with probability distributions (e.g. 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 MODELS VS. DECISION TREES
WHAT TO DO WHEN THERE IS A POSSIBILITY OF REPEATED EVENTS AND/OR DECISIONS?
Decision about one-time, immediate action
Decision about one-time, immediate action
Decisions: repeated actions and/or with time-dependent events
Repeated in what sense?
Disease process involves events occurring at multiple time points
Intervention (can) be delivered repeatedly too

- Repeated events can occur throughout an individual’s life.
- Interventions delivered at multiple time points. Subsequent transitions depend on prior intervention outcomes.
What is a Markov Model?

• **Markov Model**: Mathematical modeling technique, derived from matrix algebra, that describes the transitions a cohort of patients make among a number of mutually exclusive and exhaustive health states during a series of short intervals or cycles.
Properties of a Markov Model

• Individuals are always in one of a finite number of health states
• Events are modeled as transitions from one state to another
• Time spent in each health state determines overall expected outcome
  – Living longer without disease yields higher life expectancy and quality adjusted life expectancy
• During each cycle of the model, individuals may make a transition from one state to another
Constructing a Markov Model

• Define mutually exclusive health states
• Determine possible transitions between these health states
  – State transitions
  – Transition probabilities
• Determine clinically valid cycle length
Cycle Length

• Short enough that for a given disease being modeled the chance of two events/transitions occurring in one cycle is essentially 0
  – Many applications: weekly or monthly
  – Some (e.g., ICU) may hourly or daily
Natural history disease model: health states

- Mutually exclusive and collectively exhaustive health states
- Best defined by actual biology/pathophysiology
- Markovian assumptions:
  - Homogeneity: All individuals in the same state have the same costs, quality of life, risks of transition
  - Memorilessness: The current state determines future risks
  - Note: Stratification and tunnel states used to ensure Markov assumptions hold (advanced topic)
Natural history disease model: transitions

- Transitions between health states (arrows)
- The proportion that do not transition stay in current state
- Risk of death at all times and from all states!
- If no transition out of a state = absorbing state (i.e., death)
Natural history disease model: time and matrix representation

For example, $p_{SH}$ is the probability of going from Sick to Healthy.

States:
- HEALTHY
- SICK
- DEAD

Transition Probabilities:

- $p_{HH} \quad p_{SH} \quad 0$
- $p_{HS} \quad p_{SS} \quad 0$
- $p_{HD} \quad p_{SD} \quad 1$
Natural history disease model: time and matrix representation

At time $t$, cohort has proportions in various states (Sum to 1!)

- $p_{HH}$, $p_{SH}$, $0$
- $p_{HS}$, $p_{SS}$, $0$
- $p_{HD}$, $p_{SD}$, $1$

propH, propS, propD

time=$t$
Natural history disease model: time and matrix representation

HEALTHY  SICK  DEAD

\[
\begin{pmatrix}
    \text{pHH} & \text{pSH} & 0 \\
    \text{pHS} & \text{pSS} & 0 \\
    \text{pHD} & \text{pSD} & 1
\end{pmatrix}
\]

\[
\begin{pmatrix}
    \text{propH} \\
    \text{propS} \\
    \text{propD}
\end{pmatrix}
\]

\[
= \\
\begin{pmatrix}
    \text{propH} \\
    \text{propS} \\
    \text{propD}
\end{pmatrix}_{\text{time=t+1}}
\]

NOTE: transition probabilities can be time dependent as well
Natural history disease model: time and matrix representation

\[
\begin{align*}
\text{HEALTHY} & \quad \rightarrow \quad \text{SICK} & \quad \rightarrow \quad \text{DEAD} \\
\begin{pmatrix}
pHH & pSH & 0 \\
pHS & pSS & 0 \\
pHD & pSD & 1
\end{pmatrix} & \quad = \quad \\
& \quad \text{propH} \quad \text{propS} \quad \text{propD}
\end{align*}
\]
Natural history disease model: time and matrix representation

\[ \begin{align*}
\text{HEALTHY} & \quad \rightarrow \quad \text{SICK} \\
\text{SICK} & \quad \rightarrow \quad \text{DEAD}
\end{align*} \]

\[ \begin{align*}
pHH & \quad pSH & \quad 0 & \quad \text{propH} \\
pHS & \quad pSS & \quad 0 & \quad \text{propS} \\
pHD & \quad pSD & \quad 1 & \quad \text{propD}
\end{align*} \]

\[ \text{time}=t \quad \rightarrow \quad \text{time}=t+1 \]

\[ \text{propH} = \text{propS} \quad \text{propD} \]

\[ \text{HEALTHY} \quad \rightarrow \quad \text{SICK} \quad \rightarrow \quad \text{DEAD} \]
• Is proportion the prevalence?
• Is model time the age?
Underlying the trace

<table>
<thead>
<tr>
<th>Stage</th>
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Quality Adjusted Life Years (QALYS) & quality-of-life weights

HEALTHY: 1.0
SICK: 0.6
DEAD: 0.0
Valuing outcomes

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\[
QALYs = \sum_{t=0}^{T} \left[ (propH_t \times qH) + (propS_t \times qS) + (propD_t \times 0) \right]
\]

\[
COSTs = \sum_{t=0}^{T} \left[ (propH_t \times cH) + (propS_t \times cS) + (propD_t \times 0) \right]
\]
Interventions?

HEALTHY → SICK → DEAD

\[ \begin{align*}
\text{pHH} & \quad \text{pSH} & \quad 0 \\
\text{pHS} & \quad \text{pSS} & \quad 0 \\
\text{pHD} & \quad \text{pSD} & \quad 1
\end{align*} \]

\[ \text{propH} = \text{propS} \quad \text{time=t} \]

\[ \text{propH} = \text{propS} \quad \text{time=t+1} \]
Screening before treatment

• Screening 70% sensitivity, 100% specific
• Treatment 90% effective
• Intervention occurs after natural hx transitions every cycle

• Calculations
  – $p_{HS\_i} = p_{HS} \times (0.3) + p_{HS} \times (0.7 \times 0.1)$
  – $p_{SS\_i} = p_{SS} \times (0.3) + p_{SS} \times (0.7 \times 0.1)$
  – $p_{SH\_i} = p_{SH} + p_{SS} \times (0.7 \times 0.9)$
  – $p_{HH\_i} = p_{HH} + p_{HS} \times (0.7 \times 0.9)$
Natural History

\[
\begin{pmatrix}
0.5 & 0.2 & 0 \\
0.4 & 0.6 & 0 \\
0.1 & 0.2 & 1
\end{pmatrix}
\]
Screening before treatment

\[
\begin{align*}
\text{pHH}_i & \quad \text{pSH}_i & \quad 0 \\
\text{pHS}_i & \quad \text{pSS}_i & \quad 0 \\
\text{pHD} & \quad \text{pSD} & \quad 1
\end{align*}
\]
Screening before treatment

0.752   0.222   0
0.148   0.578   0
0.100   0.200   1
With and w/o intervention
The additional area represents the gain in life expectancy and/or QALYs from the intervention.
Intervention

Healthy

To Sick

T- => No Tx =>

To Healthy

T+

Tx Effective - To Healthy

Tx Ineffective - To Sick

T- => No Tx =>

To Sick

To Dead
Intervention

M To Healthy

Sick To Sick

T- => No Tx => To Healthy

T+ Tx Effective - To Healthy

Tx Ineffective - To Sick

T- => No Tx => To Sick

To Dead
Cohorts vs. individuals
Deterministic vs. stochastic

• Markov cohort model (i.e., the matrix version) is smooth model (infinite population size) of the proportion of a cohort in each state at each time
• Can use same structure to simulate many individuals (first-order Monte Carlo) (simple microsimulation)
• The matrix becomes the probability of an individual transition from one state to another instead of the % of those in a given state who deterministically flow into another state
Microsimulation

Healthy | Sick | Dead

0

1

2

3

4

5
Microsimulation

Healthy

0

1

2

3

4

5

Sick

pHS

pSS

pSH

pHS

pSD

Dead
Microsimulation

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Microsimulation

Healthy | Sick | Dead

0 | 1 | 2 |

3 |

4 |

5 |
Recall the trace and calculation of outcomes from it

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Microsimulation

• Run with many individuals
• Calculate proportions in each state at each time (just like in our Markov cohort table)
  – Stage 2: 5100 sick / 100,000 people = 5.1%
• Approximates the “smooth” cohort version
  – 5.1% [CI] is ~= 5.0% in “smooth” cohort
  – **Advanced**
    • Larger the number of individuals the closer to the smooth cohort (tighter the CI)
    • See Kuntz/Weinstein chapter of Michael Drummond’s book on Economic Evaluation for more on this for more on this
Why consider microsimulation?

• It requires longer simulation times
• It is more complex
• Fewer people are familiar with it
• There is “Monte Carlo” noise (random error) even with simulating fairly large groups of individuals (at least for rare events)
State explosion!

- Suppose you want to use a Markov model of a disease with 2 states and death (H,S,D)
- Suppose you need it stratified by sex and smoking status (3 levels), BMI (4 levels), hypertension (4 levels)
- Now you need 2x3x4x4x2 states (death is not stratified = 192 states)
- What if you need to stratify states by past history? (previous high hypertension, used to be obese) or Tx history (has a stent)?
Microsimulation as alternative

- Simulate 1 individual at a time
- Assign a set of attributes to the individual
  - Sex=M, Smoking=Y, BMI=Overweight, HT=Y
- Define a function for the probability of transitioning from H to S
  - \( P(H \text{ to } S \mid \text{Sex, Smoking, BMI, HT}) \)
- Have functions for changing attributes
  - \( P(\text{BMI=Obese} \mid \text{Sex, BMI}) \)
- Track previous health states
  - \( P(H \text{ to } S \mid \text{Sex, Smoking, BMI, HT, S in the past}) \)

**Note:** Could estimate these functions from logistic regressions
Sage advice I have heard

• Know what information your consumers need
• Pick a model that is as simple as possible ... but no simpler
• Know the limits of what your model does and make statements within those limits – All research studies have limitations
Summary: Medical Decision Analysis

- Clearly defines alternatives, events, and outcomes
- Formal method to combine evidence
- Can prioritize information acquisition
- Can help healthcare providers to make medical decisions under uncertainty
Classic sources on about decision analysis and modeling


• Society for Medical Decision Making (http://www.smdm.org)
THANK YOU
Jeremy Goldhaber-Fiebert
(jeremygf@stanford.edu)