Markov Decision Processes for Chronic Diseases

Lessons learned from modeling type 2 diabetes

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Department of Industrial and Operations Engineering
University of Michigan
Agenda

• Models for study of diabetes treatment decisions

• Methods for sensitivity analysis

• Examples:
  • HbA1C control
  • Cholesterol and blood pressure control
Industrial and Operations Engineering

IOE Department Statistics:

Awarded over 6,500 bachelor's degrees
Awarded more than 2,577 master's degrees
Awarded 476 doctoral degrees
528 undergraduates
208 graduate students
31 faculty members (many interested in healthcare)
Department ranked #2 in US News
My Research Interests

• Development and validation of quantitative models for comparative effectiveness

• Cost-Effectiveness of new technologies

• Predictive models for medical decision making
Why resort to models?

Privacy, Ethics, and Cost

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell
What is a Markov Decision Process?

- Starts with a Markov model for a disease (states, transition probabilities, rewards)

- Overlays a decision process on the model that:
  - Defines allowable “actions” at each time period and each state
  - Goal is to find the optimal action in each state at each period to maximize “rewards”
Health States before an event has occurred.

State Transition Diagram

Non-Fatal Events

On Treatment

Health States

L

M

H

V

Death

r(E,I)
r(L,W)
r(M,W)
r(H,W)
r(V,W)
r(S,I)
r(D,D)
Optimality Equations

- Health status: \( s_t \in S = \{1, 2, 3, \ldots, L\} \)
- Treatment Status (on or off medication): \( m \in \{0, 1\} \)
- Action:
  \[
  a(s_t, m) = \begin{cases} 
  I, W & \text{if } m = 0 \\
  W & \text{if } m = 1 
  \end{cases}
  \]

Optimal Reward to Go

\[
v_t(s_t, m) = \max \left[ R(s_t, I), r(s_t, W) + \lambda \sum_{s_{t+1}} p(s_t' \mid s_t, W) v_t(s_t', m) \right]
\]

1 Period Reward

Discounted future rewards on treatment starting at age \( t \)

Expected Future Reward

Transition probabilities

IOE512 Dynamic Programming offered every Fall Semester
Decision Process

Choose the best action each year to achieve a goal such as the following:

\[(\text{Willingness to Pay}) \cdot (\text{Life Years}) – \text{Costs}\]
States for Diabetes

- HbA1c

- Cholesterol:
  - Total Cholesterol
  - HDL
  - Triglycerides
  - LDL

- Blood Pressure

- Health History

- Medication History
Example: Cholesterol States

TC and HDL have four possible levels each, so there are 16 states in total.

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>M</th>
<th>H</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;160</td>
<td>160-200</td>
<td>200-240</td>
<td>&gt;240</td>
</tr>
<tr>
<td>HDL</td>
<td>&lt; 40</td>
<td>40-50</td>
<td>50-60</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>
Example: Total Cholesterol
Computing Treatment Effects

Treatment options:

- Statins
- Fibrates
- Ace Inhibitors
- ARBs
- Calcium Channel Blockers
- Thiazide
Computing Treatment Effects

- Electronic medical record data
  - Selection bias

- Published randomized trials
  - Adherence bias
Decision Maker Perspectives

- **Patient**
  - Maximize expected quality adjusted life years (QALYs)

- **Third-party Payer**
  - Minimize expected costs of treatment and health services

- **Society**
  - Maximize a weighted combination of expected patient rewards for QALYs minus costs of treatment and health services
Societal Perspective

- Objective function includes rewards for quality adjusted life years (QALYs) and costs

\[ r(s_t, a_t) = R(s_t, a_t) - (C^S(s_t) + C^{CHD}(s_t)) - (CF^S(s_t) + CF^{CHD}(s_t)) - mc^{ST} \]

One-time Costs

Follow-up Costs

Weighted Benefit

Statin Cost
Weighted Annual Benefit to the Patient

\[ R(s_t, a_t) = R_0 (1 - d^S(s_t))(1 - d^{CHD}(s_t))(1 - d^{ST}(a_t)) \]

- Stroke Decrement Factor
- CHD Decrement Factor
- Medication Decrement Factor

Reward in Dollars, i.e. “Willingness to Pay”
Reward Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C^S$</td>
<td>Initial hospitalization cost for a stroke.</td>
<td>$11,161</td>
</tr>
<tr>
<td>$C^{CHD}$</td>
<td>Initial hospitalization cost for a CHD event.</td>
<td>$16,085</td>
</tr>
<tr>
<td>$CF^S$</td>
<td>Yearly follow-up cost for a stroke.</td>
<td>$1,664</td>
</tr>
<tr>
<td>$CF^{CHD}$</td>
<td>Yearly follow-up cost for a CHD event.</td>
<td>$2,576</td>
</tr>
<tr>
<td>$C^{ST}$</td>
<td>Cost of statin treatment.</td>
<td>$360</td>
</tr>
<tr>
<td>$R_0$</td>
<td>Patient reward for a year of quality life.</td>
<td>$100,000</td>
</tr>
<tr>
<td>$d^S$</td>
<td>Stroke utility decrement.</td>
<td>0.21</td>
</tr>
<tr>
<td>$d^{CHD}$</td>
<td>CHD utility decrement.</td>
<td>0.07</td>
</tr>
<tr>
<td>$d^{ST}$</td>
<td>Statins utility decrement.</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- Systematic review of the literature via Pubmed
- Insurance claims data
- Pharmacy Redbook drug costs
- Cost Effectiveness Registry: [https://research.tufts-nemc.org/cear4/Home.aspx](https://research.tufts-nemc.org/cear4/Home.aspx)
Study Cohort

• **Practice setting:**
Type 2 diabetes patients seen in 6 primary care sites at Mayo Clinic Rochester

• **Sample definition:**
663 patients with:
  – Research authorization
  – No prior hx: stroke-CHD
  – 10+ years of follow-up

<table>
<thead>
<tr>
<th>Patient Attribute</th>
<th>Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.46 (8.83)</td>
</tr>
<tr>
<td>Diagnosis, years</td>
<td>3.24 (5.33)</td>
</tr>
<tr>
<td>% Female</td>
<td>39.67</td>
</tr>
<tr>
<td>Total Chol mgm%</td>
<td>216.27 (51.61)</td>
</tr>
<tr>
<td>HDL mgm%</td>
<td>43.65 (11.58)</td>
</tr>
<tr>
<td>LDL mgm%</td>
<td>126.98 (37.31)</td>
</tr>
<tr>
<td>SBP mm Hg</td>
<td>139.11 (19.75)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.01 (2.38)</td>
</tr>
</tbody>
</table>
## Treatment Effect

- Mean treatment effects for study cohort
- Costs based on 2010 Redbook

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Metabolic Factors</th>
<th>SBP</th>
<th>DBP</th>
<th>Tot Chol</th>
<th>HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ARB</td>
<td></td>
<td>-3.72</td>
<td>-5.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide</td>
<td></td>
<td>-4.97</td>
<td>-3.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β Blocker</td>
<td></td>
<td>-4.64</td>
<td>-4.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB Blocker</td>
<td></td>
<td>-2.49</td>
<td>-4.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
<td>-13.97</td>
<td>7.28</td>
</tr>
<tr>
<td>Fibrate</td>
<td></td>
<td></td>
<td></td>
<td>-3.91</td>
<td>4.73</td>
</tr>
</tbody>
</table>
Diabetes is a “CHD risk equivalent”

- **U.S. ATP III Guideline**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL (100-129 mg/dL: drug optional)*</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≤20%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>10-year risk 10-20%: ≥130 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factor¹</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

U.S. JNC 7

Lifestyle Modifications

Not at Goal Blood Pressure (<140/90 mmHg)
(<130/80 mmHg for patients with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications
- Stage 1 Hypertension (SBP 140–159 or DBP 90–99 mmHg)
  Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.

With Compelling Indications
- Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mmHg)
  Two-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).
- Drug(s) for the compelling indications (See table 8)
  Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.

Policy Evaluation

Males

Life Years to Event (yrs.) vs. Cost ($) chart showing the cost-effectiveness of different treatment options for males. The options include No Treatment, U.S. (ATPIII*), U.S., European, Canadian, and Australian, with each point on the graph representing a different treatment strategy and its associated life years to event and cost.
Optimal policy for varying willingness to pay

MDP Optimal Tradeoff Curve

Males

Life Years to Event (yrs.)

Medication Costs ($)

Canadian

European

Australian

U.S.

U.S. (ATPIII*)

Maximum LYs

No Treatment
Optimal policy for varying willingness to pay

MDP Optimal Tradeoff Curve

Females

Life Years to Event (yrs.)

Medication Costs ($)
Innovative Applications of O.R.

Optimizing the simultaneous management of blood pressure and cholesterol for type 2 diabetes patients

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ABSTRACT

We present a Markov decision process (MDP) model to determine the optimal timing of blood pressure and cholesterol medications. We study the use of our model for a high-risk population of patients with type 2 diabetes; however, the model and methods we present are applicable to the general population. We compare the optimal policies based on our MDP to published guidelines for initiation of blood pressure and cholesterol medications over the course of a patient’s lifetime. We also present a bicriteria analysis that illustrates the trade off between quality-adjusted life years and costs of treatment.

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Are Newer Drugs Better?

Second-line Agents for Glycemic Control for Type 2 Diabetes: Are Newer Agents Better?

DOI: 10.2337/dc13-1901

OBJECTIVE

While metformin is generally accepted as the first-line agent in treatment of type 2 diabetes, there are insufficient evidence and extensive debate about the best second-line agent. We aimed to assess the benefits and harms of four commonly used antihyperglycemia treatment regimens considering clinical effectiveness, quality of life, and cost.
Are Newer Drugs Better?

Men

Women
TPM Sampling Method

Basic idea:

• Random-direction algorithm\(^1\) for sampling random vectors over convex region

• Sample each row of the TPM independently from intersection of uncertainty set, \(U\), and standard simplex, \(\Delta\)

\(^1\): Smith, R.L, Efficient Monte Carlo procedures for generating points uniformly distributed over bounded regions, Operations Research, 32(6) p 1296-1308, 1984
Algorithm

Choose initial point $X_0$ in the uncertainty set, $\mathcal{U}$
For $j = 1, \ldots, W + M$ samples
  Sample $d$ such that $X_{j-1} + \lambda d \in \Delta$
  Find $\lambda$ and $\bar{\lambda}$ such that $X_{j-1} + \lambda d \in \mathcal{U}$
  Sample $\lambda$ uniformly in interval $[\underline{\lambda}, \bar{\lambda}]$
While $(X_{j-1} + \lambda d \not\in \mathcal{U})$
  if $\lambda \geq 0$ then $\bar{\lambda} \leftarrow \lambda$
  else $\underline{\lambda} \leftarrow \lambda$
  Sample $\lambda$ uniformly in interval $[\underline{\lambda}, \bar{\lambda}]$
End While
$X_j \leftarrow X_{j-1} + \lambda d$; $j \leftarrow j + 1$
End For
Sensitivity Analysis TPM for Glycemic Control

Working paper and Matlab code available for use upon request
Sensitivity Analysis

Medication Disutility

HbA1c TPM

Medication Effect on HbA1c

Absolute changes in the Expected QALYs (QALYs)
Conclusions

- Treating risk instead of risk factors has the potential for better health outcomes.

- Low variation in optimal sequence of medication; optimal tradeoff differentiated by timing of treatment for men and women.

- Treatment significantly influenced by individual risk factors.
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Slides posted on my website:

http://umich.edu/~btdenton


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Recent Work


