Approximate Dynamic Programming (ADP) Methods for Optimal Control of Cardiovascular Risk in Patients with Type 2 Diabetes

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INFORMS Annual Meeting
Charlotte, NC
November 14, 2011
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This project was funded in part by the National Science Foundation under grant CMMI-0969885.
Outline

- Diabetes Background
- Markov Decision Process (MDP) for Optimal Control
- Approximate Dynamic Programming Methods
  - Aggregate MDP
  - Basis Function Approximation
- Numerical Results and Conclusions
Chronic Disease Management

- Chronic diseases are the leading cause of death in the U.S. and other countries
- For many chronic diseases there are treatment options to manage the disease and reduce the risk of adverse events
- Optimal control of treatment can prolong lives, improve quality of life, and reduce costs
Diabetes

- 23.6 million people in the U.S. have diabetes
- Two out of three deaths are caused by stroke or coronary heart disease (CHD)
- Blood pressure and cholesterol medications are often part of treatment plans for diabetes patients
Medications

- Blood Pressure Medications
  - Beta Blockers
  - ACE Inhibitors / ARBs
  - Thiazides
  - Calcium Channel Blockers

- Cholesterol Medications
  - Statins
  - Fibrates
Current U.S. Guidelines

- **JNC 7**: Treatment Goal: SBP/DBP < 130/80 mmHg
- **ATP III**: Treatment Goal: LDL < 100 mg/dL


Bounded, Continuous State Space
Markov Decision Process (MDP)

Time Horizon

- $t = \{1, 2, \ldots, T\}$

States

- health states:
  - lipid ratio (LR): $\ell_t^{LR} \in \mathcal{L}_{LR} = [0, \text{LR}^{\text{max}}]$
  - systolic blood pressure (SBP): $\ell_t^{SBP} \in \mathcal{L}_{SBP} = [0, \text{SBP}^{\text{max}}]$

- medication states:
  - $\mathcal{M} = \{m_t = (m_{1,t}, m_{2,t}, \ldots, m_{n,t})| m_{i,t} \in \{0, 1\}\}$

Actions for medication $i$

$$A(\ell_t^{LR}, \ell_t^{SBP}, m_{i,t}) = \begin{cases} \{i, W_i\} & \text{if } m_{i,t} = 0 \\ \{W_i\} & \text{if } m_{i,t} = 1 \end{cases}$$
Rewards

Societal Perspective:

\[ r(\ell_t^{LR}, \ell_t^{SBP}, m_t) = \begin{cases} 
R \times q(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \\
- C(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \\
0 & \text{if the patient is alive} \\
0 & \text{otherwise}
\end{cases} \]

Patient Perspective:

\[ r(\ell_t^{LR}, \ell_t^{SBP}, m_t) = \begin{cases} 
q(m_t) & \text{if the patient is alive} \\
& \text{and has not had any events} \\
0 & \text{otherwise}
\end{cases} \]
Optimality Equations

∀t = 1, ... , T - 1:

\[ v_t(\ell_{t}, m_t) = \max_{a \in A(\ell_{t}, m_t)} \left\{ r(\ell_{t}, m_t) + \lambda \int \int_{\ell_{t+1}, m_{t+1}} p^a(\ell_{t+1}, m_{t+1} | \ell_{t}, m_t) v_{t+1}(\ell_{t+1}, m_{t+1}) d\ell_{t+1} d\ell_{t+1} \right\} \]

boundary condition for \( t = T \):

\[ v_T(\ell_T, m_T) = \mu(\ell_T, m_T) \]
ADP Approaches

- Uniform Aggregation
- Basis Function Approximation
ADP Approach 1: Uniform Aggregation

Fixed Finite Grid

Systolic Blood Pressure (SBP)

L Maximum SBP
M H
L

L Lipid Ratio (LR)

Maximum LR
ADP Approach 1: Uniform Aggregation

- A mean value is associated with each discrete state

- Example:

\[
g^{LR}(\ell^L_R) = \begin{cases} 
\mu(S^L_{1R}) & 0 \leq \ell^L_R \leq UB(S^L_{1R}) \\
\mu(S^L_{2R}) & UB(S^L_{1R}) < \ell^L_R \leq UB(S^L_{2R}) \\
\vdots & \\
\mu(S^L_{qR}) & UB(S^L_{q-1R}) < \ell^L_R \leq LR^{max}
\end{cases}
\]

- The approximate MDP is solved using backwards induction
ADP Approach 1: Uniform Aggregation

State Transition Diagram

No Medications

L₀ → M₀ → H₀ → V₀

Adverse Event or Death
ADP Approach 1: Uniform Aggregation

State Transition Diagram

No Medications

Statins

ACE Inhibitors

Statins + ACE Inhibitors

Adverse Event or Death
ADP Approach 2: Basis Function Approximation

\[ \tilde{v}_t(\ell_t^{LR}, \ell_t^{SBP}, m_t) = \sum_{k=1}^{K} \sum_{m_t} w_{t,k,m_t} b_{t,k}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \]

where each basis function \( b_{t,k}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \) is weighted by \( w_{t,k,m_t} \)

- \( b_{t,1}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \): the patient’s annual probability of no CHD event
- \( b_{t,2}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \): the patient’s annual probability of no stroke
ADP Approach 2: Basis Function Approximation

Annual Probability of No CHD Event

- Female, Medium SBP, Low LR
- Female, High SBP, Medium LR
- Male, Medium SBP, Low LR
- Male, High SBP, Medium LR

Patient Age:
- 40
- 41
- 42
- 43
- 44
- 45
- 46

Annual Probability of No CHD Event:
- 0.97
- 0.975
- 0.98
- 0.985
- 0.99
- 0.995
- 1
ADP Approach 2: Basis Function Approximation

Linear Program to Estimate Basis Function Weights

\[
\text{min } z = \sum_{m_t} \sum_{t=1}^{T} \sum_{k=1}^{K} \sum_{\ell_t^{LR}} \sum_{\ell_t^{SBP}} w_{t,k,m_t} \sum_{\ell_{t+1}^{LR}} \sum_{\ell_{t+1}^{SBP}} b_{t,k}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \\
\text{s.t. } \sum_{k=1}^{K} w_{t+1,k,m_{t+1}} b_{t+1,k}(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1}) \geq r(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1}), \\
\forall t = 1, \ldots, T - 1, a \in A(\ell_t^{LR}, \ell_t^{SBP}, m_t), \ell_t^{LR} \in \mathcal{L}_{LR}, \ell_t^{SBP} \in \mathcal{L}_{SBP}, m_t \in \mathcal{M}, \\
\sum_{k=1}^{K} w_{T,k,m_T} b_{T,k}(\ell_T^{LR}, \ell_T^{SBP}, m_T) \geq \mu(\ell_T^{LR}, \ell_T^{SBP}, m_T), \forall \ell_T^{LR} \in \mathcal{L}_{LR}, \ell_T^{SBP} \in \mathcal{L}_{SBP}, m_T \in \mathcal{M}, \\
w_{t,k,m_t} \geq 0, \forall k = 1, \ldots, K, t = 1, \ldots, T, \forall m_t.
\]
Numerical Experiments

- Comparison of ADP methods
- Comparison of near-optimal policies to international guidelines
## Data Sources

<table>
<thead>
<tr>
<th>Input</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitions among health states</td>
<td>Mayo Clinic EMR and DEMS</td>
</tr>
<tr>
<td>Probabilities of CHD or Stroke</td>
<td>UKPDS Risk Equations</td>
</tr>
<tr>
<td>Probability of death from other causes</td>
<td>CDC Mortality Tables</td>
</tr>
<tr>
<td>Medication Costs and QALY estimates</td>
<td>Health Services Literature</td>
</tr>
</tbody>
</table>
Simulation

- All models were coded in C/C++
- The basis function LP was solved with CPLEX using Concert Technology
- Computation time on a 2.83GHz PC with 8GB of RAM:
  - Simulation: < 10 seconds for each instance
  - Solution to MDP: < 18 minutes
### Patient Perspective: Comparison of ADP Methods

Expected QALYs before a stroke or CHD event: (N=60,000)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>QALYs</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation of Basis Function Policy</td>
<td>68.658</td>
<td>(68.559, 68.758)</td>
<td></td>
</tr>
<tr>
<td>Simulation of Aggregate MDP Policy</td>
<td>68.862</td>
<td>(68.765, 68.959)</td>
<td></td>
</tr>
<tr>
<td>Aggregate MDP Results</td>
<td>68.723</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>QALYs</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation of Basis Function Policy</td>
<td>73.161</td>
<td>(73.061, 73.261)</td>
<td></td>
</tr>
<tr>
<td>Simulation of Aggregate MDP Policy</td>
<td>73.610</td>
<td>(73.511, 73.708)</td>
<td></td>
</tr>
<tr>
<td>Aggregate MDP Results</td>
<td>72.974</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Societal Perspective: Male Results

![Graph showing Expected QALYs vs. Discounted Medication and Hospitalization Costs]

- Maximum QALYs
- Optimal Tradeoff Curve
- No Treatment
- Discounted Medication and Hospitalization Costs ($)
- Expected QALYs (yrs.)

Countries: European Union, Joint British, Australia, Canada, US I, US II.
Societal Perspective: Female Results

Expected QALYs (yrs.) vs. Discounted Medication and Hospitalization Costs ($)

- Maximum QALYs
- Optimal Tradeoff Curve
- No Treatment
- Discounts for different regions:
  - European Union
  - Joint British
  - Australia
  - Canada
  - US I
  - US II
Conclusions

- State aggregation is superior to basis function approximation of the value function
- Coordinated treatment of blood pressure and cholesterol in patients with diabetes substantially lowers costs and increases quality-adjusted lifespan
Future Work

- Further experimentation with basis functions to achieve better policies

- Identification of easy-to-implement and near-optimal heuristics
Questions?

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## Parameters

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual Cost</th>
<th>QALY Decrement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors / ARBs</td>
<td>$48</td>
<td>0.005</td>
</tr>
<tr>
<td>Thiazides</td>
<td>$48</td>
<td>0.005</td>
</tr>
<tr>
<td>β Blockers</td>
<td>$48</td>
<td>0.005</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>$866</td>
<td>0.005</td>
</tr>
<tr>
<td>Statins</td>
<td>$212</td>
<td>0.003</td>
</tr>
<tr>
<td>Fibrates</td>
<td>$652</td>
<td>0.003</td>
</tr>
</tbody>
</table>
## Parameters

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<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hospitalization for stroke ($C^S$)</td>
<td>$13,204</td>
<td>Nationwide Inpatient Sample 2006</td>
</tr>
<tr>
<td>Initial hospitalization for CHD ($C^{CHD}$)</td>
<td>$18,590</td>
<td>Nationwide Inpatient Sample 2006</td>
</tr>
<tr>
<td>Follow-up for stroke ($CF^S$)</td>
<td>$1,664</td>
<td>Thom et al. 2006</td>
</tr>
<tr>
<td>Follow-up for CHD ($CF^{CHD}$)</td>
<td>$2,576</td>
<td>Russell et al. 1998; Thom et al. 2006</td>
</tr>
<tr>
<td>Willingness-to-pay Factor ($R_0$)</td>
<td>$100,000</td>
<td>Rascati 2006</td>
</tr>
<tr>
<td>Discount Factor ($\lambda$)</td>
<td>0.97</td>
<td>Gold et al. 1996</td>
</tr>
<tr>
<td>CHD decrement ($d^{CHD}$)</td>
<td>0.07</td>
<td>Clarke et al. 2002; Tsevat et al. 1993</td>
</tr>
<tr>
<td>Stroke decrement ($d^S$)</td>
<td>0.21</td>
<td>Tengs et al. 2001; Clarke et al. 2002</td>
</tr>
</tbody>
</table>

**Source:**
- Nationwide Inpatient Sample 2006
- Thom et al. 2006
- Russell et al. 1998
- Rascati 2006
- Gold et al. 1996
- Clarke et al. 2002
- Tsevat et al. 1993
- Tengs et al. 2001
- Tengs et al. 2003