An ADP Approach for Optimal Control of Cardiovascular Risk in Patients with Type 2 Diabetes

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Outline

- Diabetes Background
- Markov Decision Process (MDP) for Optimal Control
- Approximate Dynamic Programming Methods
  - Aggregate MDP
  - Basis Function Approximation
- Numerical Results and Conclusions
Chronic diseases are the leading cause of death in the U.S. and other countries, accounting for seven out of ten deaths each year.

For many chronic diseases there are treatment options to manage the disease and reduce the risk of adverse events.

Optimal control of treatment for chronic diseases 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 under Consideration for Initiation

- **Blood Pressure Medications**
  - ACE Inhibitors / ARBs
  - Thiazides
  - $\beta$ Blockers
  - Calcium Channel Blockers

- **Cholesterol Medications**
  - Statins
  - Fibrates
Current U.S. Guidelines for Diabetes Patients

- **ATP III**\(^1\):
  - Diabetes patients are now considered CHD risk equivalents
  - Treatment Goal: LDL < 100 mg/dL

- **JNC 7**\(^2\):
  - Treatment Goal: SBP/DBP < 130/80 mmHg

\(^1\): Third report on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), NIH Publication No. 01-3670, 2001

Literature Review


- Shechter et al. (2008) “The Optimal Time to Initiate HIV Therapy Under Ordered Health States”


- Denton et al. (2009) “Optimizing the Start Time of Statin Therapy for Patients with Diabetes”
Bounded, Continuous State Space

- Systolic Blood Pressure (SBP)
- Lipid Ratio (LR)
- Maximum SBP
- Maximum LR
Markov Decision Process (MDP)

Time Horizon
- \( t = \{1, 2, \ldots, T\} \)

States
- health states:
  - lipid ratio (LR): \( \ell_t^{LR} \in \mathcal{L}_{LR} = [0, LR^{\max}] \)
  - systolic blood pressure (SBP): \( \ell_t^{SBP} \in \mathcal{L}_{SBP} = [0, SBP^{\max}] \)
- 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 \( i \)
\[
A_{(\ell_t^{LR}, \ell_t^{SBP}, m_{i,t})} = \begin{cases} 
\{ l_i, W_i \} & \text{if } m_{i,t} = 0, \\
\{ W_i \} & \text{if } m_{i,t} = 1.
\end{cases}
\]
MDP

General Reward Function:

\[ r(\ell_t^{LR}, \ell_t^{SBP}, m_t) = \begin{cases} 
R \times q(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \\
- C(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \\
0 
\end{cases} \]

for the patient is alive, otherwise,

for \( t = 1, \ldots, T - 1 \), where \( R \) is the willingness-to-pay factor, \( q(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \) represents a patient’s quality-adjusted life year (QALY), and \( C(\ell_t^{\text{Stroke}}, \ell_t^{\text{CHD}}, m_t) \) represents the cost of medication and treatment for events.
Primary Prevention Reward Function from the Patient Perspective:

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

for \( t = 1, \ldots, T - 1 \).
Optimality Equations

∀t = 1, ..., T − 1:

\[ v_t(\ell_t^{LR}, \ell_t^{SBP}, m_t) = \max_{a \in A(\ell_t^{LR}, \ell_t^{SBP}, m_t)} \left\{ \begin{array}{l} \text{immediate reward} \\ r(\ell_t^{LR}, \ell_t^{SBP}, m_t) \\ + \lambda \int \int \sum_{m_{t+1}} p^a(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1} | \ell_t^{LR}, \ell_t^{SBP}, m_t) v_{t+1}(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1}) d\ell_{t+1} d\ell_{t+1} \end{array} \right\} \]

expected discounted value to go

Boundary Condition for \( t = T \):

\[ v_T(\ell_T^{LR}, \ell_T^{SBP}, m_T) = \mu(\ell_T^{LR}, \ell_T^{SBP}, m_T) \]
ADP Approaches

- Aggregation
- Basis Function Approximation
ADP Approach 1: Aggregation

Fixed Finite Grid

Systolic Blood Pressure (SBP)

L

M

H

Maximum SBP

Lipid Ratio (LR)

L

M

H

Maximum LR

An ADP Approach for Optimal Control

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ADP Approach 1: Aggregation

- A mean value is associated with each discrete state

- Example:

\[
g^{LR}(\ell_t^{LR}) = \begin{cases} 
\eta(S_{1}^{LR}) & 0 \leq \ell_t^{LR} \leq \text{UB}(S_{1}^{LR}), \\
\eta(S_{2}^{LR}) & \text{UB}(S_{1}^{LR}) < \ell_t^{LR} \leq \text{UB}(S_{2}^{LR}), \\
\vdots & \\
\eta(S_{q}^{LR}) & \text{UB}(S_{q-1}^{LR}) < \ell_t^{LR} \leq LR^{\max}.
\end{cases}
\]

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

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

![Graph showing Probability of No CHD Event vs Patient Age]

- **Female, Medium SBP, Low LR**
- **Female, High SBP, Medium LR**
- **Male, Medium SBP, Low LR**
- **Male, High SBP, Medium LR**
ADP Approach 2: Basis Function Approximation

Linear Program to Estimate Basis Function Weights

\[
\begin{align*}
\min z &= \sum_{\ell_t^{LR}} \sum_{\ell_t^{SBP}} \sum_{m_t} w_{t,k,m_t} b_{t,k}(\ell_t^{LR}, \ell_t^{SBP}, m_t) \\
\text{s.t.} \quad &\sum_{k=1}^{K} w_{t,k,m_t} b_{t,k}(\ell_t^{LR}, \ell_t^{SBP}, m_t) - \lambda \sum_{\ell_t^{LR}} \sum_{\ell_t^{SBP}} \sum_{m_{t+1}} p_a(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1} | \ell_t^{LR}, \ell_t^{SBP}, m_t) \\
&\times \sum_{k=1}^{K} w_{t+1,k,m_{t+1}} b_{t+1,k}(\ell_{t+1}^{LR}, \ell_{t+1}^{SBP}, m_{t+1}) \geq r(\ell_t^{LR}, \ell_t^{SBP}, m_t), \\
&\forall t = 1, \ldots, T - 1, a \in A(\ell_t^{LR}, \ell_t^{SBP}, m_t), \ell_t^{LR} \in \mathcal{L}_{LR}, \ell_t^{SBP} \in \mathcal{L}_{SBP}, m_t \in \mathcal{M}, \\
&\sum_{k=1}^{K} w_{T,k,m_T} b_{T,k}(\ell_T^{LR}, \ell_T^{SBP}, m_T) \geq \mu(\ell_T^{LR}, \ell_T^{SBP}, m_T), \forall \ell_T^{LR} \in \mathcal{L}_{LR}, \ell_T^{SBP} \in \mathcal{L}_{SBP}, m_T \in \mathcal{M}, \\
&w_{t,k,m_t} \geq 0, \forall k = 1, \ldots, K, t = 1, \ldots, T.
\end{align*}
\]
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>
Patient Perspective: Comparison of ADP Methods

Expected QALYs before a stroke or CHD event:

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation of Basis Function Policy</td>
<td>68.518</td>
<td>73.249</td>
</tr>
<tr>
<td>Simulation of Aggregate MDP Policy</td>
<td>68.915</td>
<td>73.685</td>
</tr>
<tr>
<td>Aggregate MDP Results</td>
<td>68.723</td>
<td>72.974</td>
</tr>
</tbody>
</table>

- All 3 models were coded in C/C++, and the basis function LP was solved with CPLEX using Concert Technology.
- Each instance of the simulation took approximately 1 second to run, and the MDP was solved in less than 18 minutes on a 2.83GHz PC with 8GB of RAM.
Societal Perspective: Male Results

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Societal Perspective: Female Results

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Conclusions from ADP Methods

- The policies found using state aggregation perform better than the policies found with the current basis functions.
- Simulation of the Aggregate MDP policy reveals greater expected QALYs before an event than estimation of expected QALYs from the MDP.
Conclusions from Comparison to Guidelines

▶ Expected QALYs could be increased and expected costs could be decreased relative to the current guidelines through the use of coordinated treatment of blood pressure and cholesterol in patients with diabetes

▶ Optimal treatment plans differentiate patients based on risk factors

▶ Low variation in optimal sequence of medication

▶ Optimal tradeoff differentiated by timing of treatment

▶ Treatment significantly influenced by gender
Future Work

- Further experimentation with basis functions to achieve better policies
- Identification of easy-to-implement guidelines that improve upon the current international guidelines
Thank You

Questions?
<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>
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<tr>
<td>Statins</td>
<td>$212</td>
<td>0.003</td>
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<tr>
<td>Fibrates</td>
<td>$652</td>
<td>0.003</td>
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## Parameters

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<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
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<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>$2,576</td>
<td>Russell et al. 1998</td>
</tr>
<tr>
<td>Willingness-to-pay Factor ($R_0$)</td>
<td>$100,000</td>
<td>Rascati 2006</td>
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<tr>
<td>Discount Factor ($\lambda$)</td>
<td>0.97</td>
<td>Gold et al. 1996</td>
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<tr>
<td>CHD decrement ($d^{CHD}$)</td>
<td>0.07</td>
<td>Clarke et al. 2002</td>
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<tr>
<td>Stroke decrement ($d^S$)</td>
<td>0.21</td>
<td>Tengs et al. 2001</td>
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<td></td>
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<td>Clarke et al. 2002</td>
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