Robust Optimal Control for Medical Treatment Decisions—An Application to Type 2 Diabetes

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Type 2 Diabetes

Prevalence

- Approximately 29 million people had diabetes in U.S. ¹
- Approximately 9.3% of the population
- 90-95% have type 2 diabetes

¹ Data from the 2012 National Diabetes Fact Sheet
Type 2 Diabetes

Prevalence

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- Approximately 9.3% of the population
- 90-95% have type 2 diabetes

Glycemic Control

- The focus of managing type 2 diabetes
- Clinically measured by glycated haemoglobin (HbA1c)

\[
\text{Glucose} + \frac{\text{Haemoglobin molecules (Hb)}}{\text{Total Hb concentration}} = \text{HbA1c}
\]

\[
\text{HbA1c level (\%)} = \frac{\text{HbA1c concentration}}{\text{Total Hb concentration}}
\]

¹ Data from the 2012 National Diabetes Fact Sheet
Importance of Glycemic Control

High blood sugar causes damage throughout the body

- Daily symptoms
  - Thirst
  - Fatigue
  - Blurred vision
- Microvascular events:
  - Kidney Disease
  - Blindness
  - Amputation
- Macrovascular events:
  - Heart Attack
  - Stroke
Challenges in Glycemic Control

1: A patient’s HbA1c level changes stochastically over time
2: Treatment guidelines are not consistent and are “one size fits all”

Why not keep HbA1c as low as possible?

The Action to Control Cardiovascular Risk in Diabetes trial was halted in February, 2008 because of high mortality rate in intensive control arm.
1: A patient’s HbA1c level changes stochastically over time
2: Treatment guidelines are not consistent and are “one size fits all”

Why not keep HbA1c as low as possible?

The Action to Control Cardiovascular Risk in Diabetes trial was halted in February, 2008 because of high mortality rate in intensive control arm.
Challenges in Glycemic Control (cont’d)

3: Many glycemic control medications are available with differences in treatment effects, side effects and costs

Oral medications:
- Metformin (met)
- Sulfonylurea (sulf)
- DPP-4 inhibitor (DPP-4)

Injectable medications:
- Insulin
- GLP-1 agonist (GLP-1)

DPP-4 inhibitor: Dipeptidyl peptidase-4 inhibitor
GLP-1 agonist: Glucagon-like peptide-1 receptor agonists
**Glycemic control goal**

Varies from HbA1c ≤ 6.5% to HbA1c ≤ 8%

**Treatment Regimens**

- met+sulf+insulin
- met+DPP-4+insulin
- met+GLP-1+insulin
- met+insulin
Markov Decision Process Model Components

Time horizon: \( t = \{1, 2, \ldots, T\} \)
- 1: age at diagnosis
- \( T \): age 100 years
- Discretized into 3-month time intervals

States: \( s_t \in \{\mathcal{L} \times \mathcal{M}\} \cup \mathcal{D} \)
- HbA1c states: \( \ell_t \in \mathcal{L} = \{\ell(1), \ell(2), \ldots, \ell(k)\} \)
- Medication states: \( m_t \in \mathcal{M} = \{(m_{1,t}, m_{2,t}, \ldots, m_{n,t}) | m_{i,t} \in \{0, 1\}\} \)
- Absorbing states: \( \mathcal{D} = \{E^{\text{macro}}, E^{\text{micro}}, D^0\} \)

Actions: \( \alpha_t \)
The selection of medication(s) to initiate at each time epoch
Probabilities of transitioning into absorbing states: $p_t^D(s_t, \alpha_t)$

HbA1c state transition probabilities: $q_t,\ell_t(\ell_{t+1})$
One-period Rewards

Quality-adjusted life-years (QALYs)

\[ r^Q_t(s_t, \alpha_t) = \begin{cases} 
0.25 (1 - D^{\text{hyper}}(s_t, \alpha_t))(1 - D^{\text{med}}(\alpha_t)), & \forall s_t \in \mathcal{L} \times \mathcal{M}, \\
0, & \text{otherwise.} \end{cases} \]

- \( D^{\text{hyper}}(s_t, \alpha_t) \): disutility of daily symptoms
- \( D^{\text{med}}(\alpha_t) \): disutility of using medications

Medication costs

\[ r^C_t(s_t, \alpha_t) = \begin{cases} 
\sum_{i=1}^{n} c_i \alpha_{i,t}, & \forall s_t \in \mathcal{L} \times \mathcal{M}, \\
0, & \text{otherwise.} \end{cases} \]

- \( c_i \): the quarterly cost of using medication \( i \)
Outcome measures:

- Expected QALYs prior to the first event
- Expected total medication costs

\[ V(\pi) = \sum_{i=1}^{k} p(i) \mathbb{E}_{\ell(i)}^{\pi} \left[ \sum_{t=1}^{T-1} \lambda^{t-1} r_t(s_t, \alpha_t) + \lambda^{T-1} r_T(s_T) \right] \]

- \( \pi \): a treatment policy
- \( p(i) \): the probability of being in HbA1c state \( \ell(i) \) at diagnosis
Data Sources

<table>
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<th>Source</th>
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<td>Ingenix dataset</td>
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<tr>
<td>Medication effects on HbA1c</td>
<td>Ingenix dataset</td>
</tr>
<tr>
<td>Probabilities of micro- and macro-vascular events</td>
<td>UKPDS outcomes model&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Probability of death from other causes</td>
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<tr>
<td>Disutility of medications</td>
<td>Sinha et al. 2010&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td>Disutility of hyperglycemia</td>
<td>Kahn et al. 2010&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quarterly cost of medications</td>
<td>Bennett et al. 2011&lt;sup&gt;4&lt;/sup&gt;,Yeaw et al. 2012&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Ingenix dataset**

- An administrative claims data set with linked laboratory data
- ~37,000 patients diagnosed with type 2 diabetes

<sup>1</sup> Clarke et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes, 2006
<sup>2</sup> Sinha et al., Cost and consequences associated with newer medications for glycemic control in T2DM, 2010
<sup>3</sup> Kahn et al., Age at initiation and frequency of screening to detect type 2 diabetes, 2010
<sup>4</sup> Bennett et al., Comparative effectiveness and safety of medications for type 2 diabetes, 2011
<sup>5</sup> Yeaw et al., Cost of self-monitoring of blood glucose in US among patients on an insulin regimen for diabetes, 2012
Method for Estimating HbA1c Transition Probabilities

1: Extract all patients’ HbA1c records and pharmacy records
2: Pick HbA1c records at 3 month intervals (∼ 30,000 pairs)
3: Adjust HbA1c values for the effects of medication
4: Discretize natural HbA1c values into 10 HbA1c states
5: Estimate the maximum likelihood estimate for the transition probabilities

Validation

- Cross validation
- Test set: all two consecutive HbA1c records if the period between the tests was over 3 months (∼ 97,000 pairs)
Main Results

Expected QALYs prior to the First Event vs. Expected Medication Cost per QALY ($/QALY)

- met+sulf+insulin
- met+DPP-IV+insulin
- met+GLP-1+insulin
- met+insulin

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Robust Medical Treatment Decisions
Sensitivity Analysis on HbA1c Transition Probabilities

The solid bar represents males, and the hatched bar represents females. TPM: transition probability matrix

Medication Disutility

TPM (Method 2)

TPM (Method 1)

Medication Effect on HbA1c

Medication Cost

Absolute changes in the Expected QALYs (QALYs)
### TPM Sampling Algorithm

<table>
<thead>
<tr>
<th>Basic idea: Hit-and-Run (Smith, 1984)</th>
</tr>
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<tbody>
<tr>
<td>- Random-direction algorithm for sampling random vectors over convex region</td>
</tr>
<tr>
<td>- Sample each row of the TPM independently</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure</th>
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<tbody>
<tr>
<td>- Start with a point in the uncertainty set (e.g. MLE)</td>
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<tr>
<td>- Sample a random direction in the uncertainty set</td>
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<tr>
<td>- Determine the bounds so that the all points along the random direction fall in the standard simplex</td>
</tr>
<tr>
<td>- Reduce the line segment iteratively until finding a point in the uncertainty set</td>
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</table>

Conclusions

- Treatment effects of medications are over-estimated by randomized trials

- Use of sulfonylurea as the second-line medication dominates other treatment regimens

- The ADA’s glycemic control threshold of HbA1c $\leq 7\%$ results in higher QALYs than other published thresholds

- Results are sensitive to uncertainty in transition probability matrices

Extensions to Treatment Optimization

A robust Markov decision process model (RMDP) that assumes an adversarial context:

- Address uncertainty in transition probabilities by using an uncertainty set and uncertainty budget.

- Generate policies that perform well with respect to maximum likelihood estimates of transition probabilities and are insensitive to uncertainty.
Decision Process

Action: 
Medication 
State: 
Decision 
Epoch: 
HbA1c 
State:
Absorbing 
State:

$\mathbf{m}_0$

$0$

$\ell_0$
Decision Process

Action: Medication
State: Decision
Epoch: HbA1c
State: Absorbing
State: m0
Decision Process
Decision Process

- **Action:** Medication
- **Medication State:**
- **Decision Epoch:** HbA1c
- **HbA1c State:**
- **Absorbing State:**

Diagram:
- Transition from \( m_0 \) to \( m_1 \) to \( m_2 \) to \( m_3 \) to \( m_{T-1} \) to \( m_T \) to \( \emptyset \)
- Decision Horizon: \( R_T(\ell_T, m_T) \)
- Post Decision Horizon: \( r_{T-1}(\ell_{T-1}, m_{T-1}) \)
- Absorbing States: \( \mathbb{D} \)
- Decision Horizon: \( \ell_0 \) to \( \ell_1 \) to \( \ell_2 \) to \( \ell_{T-1} \) to \( \ell_T \)
RMDP vs TI-RMDP

The optimal value function of the RMDP-TM

\[ \nu^{\text{RMDP-TM}}_t(s_t) = \begin{cases} \max_{\pi \in \Pi} \min_{\theta_t \in \Theta_t} \mathbb{E}_{s_t} \left[ \sum_{k=t}^{T-1} \lambda^{k-t} r_k(s_k, \alpha_k(s_k)) + \lambda^{T-t} r_T(s_T) \right], & \forall s_t \in \mathcal{L} \times \mathcal{M}, \\ 0, & \text{otherwise.} \end{cases} \]

The optimal value function of the time-invariant RMDP

\[ \nu^{\text{TI-RMDP-TM}}_t(s_t) = \begin{cases} \max_{\pi \in \Pi} \min_{\theta \in \Theta} \mathbb{E}_{s_t} \left[ \sum_{k=t}^{T-1} \lambda^{k-t} r_k(s_k, \alpha_k(s_k)) + \lambda^{T-t} r_T(s_T) \right], & \forall s_t \in \mathcal{L} \times \mathcal{M}, \\ 0, & \text{otherwise.} \end{cases} \]
Uncertainty Set

Uncertainty Set of TPM:

\[ Q_t \triangleq [q_{t,\ell_t}(\ell_{t+1})] \in Q_t \]

Interval Model with Uncertainty Budget (IMUB)

\[ Q_{t,\ell_t}^{\text{IMUB}}(\Gamma) = \prod_{\ell_t \in \mathcal{L}} Q_{t,\ell_t}^{\text{IMUB}}(\Gamma) \]

Constraints for \( Q_{t,\ell_t}^{\text{IMUB}}(\Gamma) \)

- The row vector is in the standard simplex
- Each element lies in its statistical confidence interval
- The total variation from MLE can not exceed the uncertainty budget, \( \Gamma \)

\[
\sum_{i \in \mathcal{L}} (z_{t,\ell_t}^l(i) + z_{t,\ell_t}^u(i)) \leq \Gamma, \quad z_{t,\ell_t}^l(\ell_{t+1}) \cdot z_{t,\ell_t}^u(\ell_{t+1}) = 0
\]
Optimality Equations of the RMDP with IMUB

\[

\nu_t^{\text{RMDP}}(\ell_t, m_t) = \max_{\alpha_t(s_t) \in A_t} \left\{ r_t(s_t, \alpha_t(s_t)) + (1 - p_t^E(s_t, \alpha_t(s_t))) \lambda \right\} \min_{q_{t, \ell_t} \in Q_{t, \ell_t}(\Gamma)} \sum_{\ell_{t+1} \in \mathcal{L}} q_{t, \ell_t}(\ell_{t+1}) \nu_{t+1}^{\text{RMDP}}(\ell_{t+1}, m_{t+1}) \right\}

\]

inner problem

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**Robust Dynamic Programming (RDP) Algorithm**

- A backward-induction based algorithm
- The inner problem, a nonlinear program, needs to be solved $|\mathcal{L}| \cdot |\mathcal{M}| \cdot (T - 1)$ times

---

\[ ^2 \text{Nilim et al. Robust control of markov decision processes with uncertain transition matrices, } \textit{Operations Research}, \text{2005} \]
Inner Problem: IMUB-NLP

\[
\begin{align*}
\text{min} & \quad \sum_{\ell_{t+1} \in \mathcal{L}} q_{t,\ell_t}(\ell_{t+1}) v_{t+1}^{\text{RMDP-TM}}(\ell_{t+1}, m_{t+1}) \\
\text{s.t.} & \quad q_{t,\ell_t}(\ell_{t+1}) = \hat{q}_{t,\ell}(\ell_{t+1}) - \delta^l_{t,\ell}(\ell_{t+1}) z^l_{t,\ell}(\ell_{t+1}) + \delta^u_{t,\ell}(\ell_{t+1}) z^u_{t,\ell}(\ell_{t+1}), \\ & \quad \forall \ell_{t+1} \in \mathcal{L}, \\
& \quad \sum_{\ell_{t+1} \in \mathcal{L}} q_{t,\ell_t}(\ell_{t+1}) = 1, \\
& \quad \sum_{\ell_{t+1} \in \mathcal{L}} (z^l_{t,\ell_t}(\ell_{t+1}) + z^u_{t,\ell_t}(\ell_{t+1})) \leq \Gamma_{t,\ell}, \\
& \quad z^l_{t,\ell_t}(\ell_{t+1}) \cdot z^u_{t,\ell_t}(\ell_{t+1}) = 0, \\ & \quad 0 \leq z^l_{t,\ell_t}(\ell_{t+1}), z^u_{t,\ell_t}(\ell_{t+1}) \leq 1, \\ & \quad 0 \leq q_{t,\ell_t}(\ell_{t+1}) \leq 1, \\
& \quad \forall \ell_{t+1} \in \mathcal{L},
\end{align*}
\]
**Proposition**

The following linear reformulation of the inner problem, called IMUB-LP, is equivalent to IMUB-NLP

\[
\begin{align*}
\min & \quad \sigma_t^{IMUB-LP}(s_t, \alpha_t(s_t), \Gamma_t, \ell_t) = \sum_{\ell_{t+1} \in \mathcal{L}} q_{t, \ell_t}(\ell_{t+1}) v_{t+1}^{RMDP}(\ell_{t+1}, m_{t+1}) \\
\text{s.t.} & \quad \sum_{\ell_{t+1} \in \mathcal{L}} q_{t, \ell_t}(\ell_{t+1}) = 1, \\
& \quad \sum_{\ell_{t+1} \in \mathcal{L}} [x_{t, \ell_t}^l(\ell_{t+1}) + x_{t, \ell_t}^u(\ell_{t+1})] \leq \Gamma_t, \\
& \quad x_{t, \ell_t}^u(\ell_{t+1}) \geq \frac{q_{t, \ell_t}(\ell_{t+1}) - \hat{q}_{t, \ell_t}(\ell_{t+1})}{\delta_{t, \ell_t}(\ell_{t+1})}, \quad \forall \ell_{t+1} \in \mathcal{L} \\
& \quad x_{t, \ell_t}^l(\ell_{t+1}) \geq \frac{\hat{q}_{t, \ell_t}(\ell_{t+1}) - q_{t, \ell_t}(\ell_{t+1})}{\delta_{t, \ell_t}(\ell_{t+1})}, \quad \forall \ell_{t+1} \in \mathcal{L}, \\
& \quad 0 \leq x_{t, \ell_t}^l(\ell_{t+1}), x_{t, \ell_t}^u(\ell_{t+1}) \leq 1, \\
& \quad 0 \leq q_{t, \ell_t}(\ell_{t+1}) \leq 1, \quad \forall \ell_{t+1} \in \mathcal{L}.
\end{align*}
\]
An optimal solution to the inner problem with $\Gamma = |\mathcal{L}|$ can be found using an algorithm with complexity, $O(|\mathcal{L}|)$.

A fast algorithm to solve the inner problem with $\Gamma = |\mathcal{L}|$

1: For all $\ell(i)$, Set $y^l_i \leftarrow q^l_{t,\ell}(\ell(i))$, $y^u_i \leftarrow q^u_{t,\ell}(\ell(i))$, $c_i \leftarrow v^{\text{RMDP-TM}}_{t+1}(\ell(i), m_{t+1}(\alpha_t(s_t)))$

2: for $\tau = 1 \rightarrow |\mathcal{L}|$ do

3: $\sigma \leftarrow (1 - \sum_{i=1}^{|\mathcal{L}|} y^l_i) c_\tau + \sum_{i=1}^{|\mathcal{L}|} (y^u_i - y^l_i) \min\{c_i - c_\tau, 0\} + \sum_{i=1}^{|\mathcal{L}|} c_i y^l_i$

4: if ($\tau == 1$) or ($\tau > 1$ and $\sigma > \sigma^{\text{IMUB-LP}}_t(s_t, \alpha_t(s_t))$) then

5: $\sigma^{\text{IMUB-LP}}_t(s_t, \alpha_t(s_t)) \leftarrow \sigma$

6: else

7: Next $\tau$

8: end if

9: end for

10: Return $\sigma^{\text{IMUB-LP}}_t(s_t, \alpha_t(s_t))$
Proposition

For RMDP with IM model, if the following conditions hold:

(I): \(Q^\text{IM}_t = Q^\text{IM}_{t'}, \forall t, t' \in \mathcal{T}\backslash\{T\}\),

(II): \(r_t(\ell_t, m_t, \alpha_t(s_t))\) is nonincreasing in \(\ell_t\), \(\forall m_t \in \mathcal{M}, \alpha_t(s_t) \in \mathcal{A}_t\), and \(t \in \mathcal{T}\backslash\{T\}\), and \(r_T(\ell_T, m_T)\) is nonincreasing in \(\ell_T\), \(\forall m_T \in \mathcal{M}\),

(III): \(p^E_t(\ell_t, m_t, \alpha_t(s_t))\) is nondecreasing in \(\ell_t\), \(\forall m_t \in \mathcal{M}, \alpha_t(s_t) \in \mathcal{A}_t\), and \(t \in \mathcal{T}\backslash\{T\}\), and

(IV): \(Q^\text{WC,|L|}_{T-1}\), has the increasing failure rate (IFR) property

then

(a): \(v^\text{RMDP}_t(\ell_t, m_t)\) is nonincreasing in \(\ell_t\), \(\forall m_t \in \mathcal{M}, t \in \mathcal{T}\backslash\{T\}\), and

(b): the optimal policy of nature is stationary.
Numerical Experiments

Research questions

- Can the RMDP be solved for the diabetes treatment problem?
- What are the benefits of using robust optimal solutions?
<table>
<thead>
<tr>
<th>Solution methods</th>
<th>0 (= MDP)</th>
<th>1</th>
<th>2</th>
<th>...</th>
<th>9</th>
<th>10</th>
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<tr>
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<td>1129</td>
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Computation time (in seconds) are presented in terms of central processing unit (CPU) time.

- Linear reformulation of the inner problem can significantly reduce the CPU for solving the RMDP.
- The RMDP with $\Gamma = 10$ can be solved as efficiently as solving MDP using the backward induction algorithm.
Treatment Policy Performance Measures

Nominal Performance
The expected total discounted reward under MLE

Wost-case Performance
The expected total discounted reward under the worst-case criterion when the TPM can vary over the entire uncertainty set
Treatment Policy Performance Comparison

Treatment guideline: ADA’s consensus algorithm with the glycemic control goal of HbA1c \( \leq 7\% \).
Conclusions

- RMDP with IMUB provides a new approach for controlling robustness of medical treatment decisions with respect to uncertainty in transition probability matrices.

- The RMDP with IMUB can be solved efficiently with the proposed solution methods.

- RMDP-based optimal policy could provide guidance for clinicians and policy makers when making treatment policies.

Zhang, Y., Denton, B.T., “Robust Markov Decision Processes for Medical Treatment Decisions” under review, 2015 (available at Optimization Online)
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Interval Matrix (IM) Model

\[ Q_{t, \ell_t}^{\text{IM}} = \left\{ q_{t, \ell_t} \in \mathbb{R}_+^{L} \left| \begin{array}{l} \sum_{\ell_{t+1} \in L} q_{t, \ell_t}(\ell_{t+1}) = 1, \\
q^l_{t, \ell_t}(\ell_{t+1}) \leq q_{t, \ell_t}(\ell_{t+1}) \leq q^u_{t, \ell_t}(\ell_{t+1}),
\forall \ell_{t+1} \in L, \\
0 \leq q_{t, \ell_t}(\ell_{t+1}) \leq 1,
\forall \ell_{t+1} \in L, \\
N_{\ell_t} \end{array} \right. \right\} \]

- \( q^l_{t, \ell_t}(\ell_{t+1}) = \bar{q}_{\ell_t}(\ell_{t+1}) - \left[ \chi^2_{|L|-1, \alpha/(2|L|)} \frac{\bar{q}_{\ell_t}(\ell_{t+1})(1-\bar{q}_{\ell_t}(\ell_{t+1}))}{N_{\ell_t}} \right]^{\frac{1}{2}} \)

- \( q^u_{t, \ell_t}(\ell_{t+1}) = \bar{q}_{\ell_t}(\ell_{t+1}) + \left[ \chi^2_{|L|-1, 1-\alpha/(2|L|)} \frac{\bar{q}_{\ell_t}(\ell_{t+1})(1-\bar{q}_{\ell_t}(\ell_{t+1}))}{N_{\ell_t}} \right]^{\frac{1}{2}} \)

- \( \bar{q}_{\ell_t}(\ell_{t+1}) \): maximum likelihood estimate (MLE) of \( q_{\ell_t}(\ell_{t+1}) \)

- \( N_{\ell_t} \): total number of patients in state \( \ell_t \)
Robust Dynamic Programming (RDP) Algorithm (Nilim et al. 2005)

1: \( v^{\text{RMDP-TM}}_T(\ell_T, m_T) \leftarrow r_T(\ell_T, m_T), \forall \ell_T \in \mathcal{L}, m_T \in \mathcal{M} \)
2: for \( t = T - 1 \rightarrow 0, \ell_t \in \mathcal{L}, \text{and } m_t \in \mathcal{M} \) do
3: for \( \alpha_t \in A_t(\ell_t, m_t) \) do
4: Solve the inner problem and calculate
   \[ w_t(\ell_t, m_t, \alpha_t) = r_t(\ell_t, m_t, \alpha_t) + \lambda[1 - p^E_t(\ell_t, m_t, \alpha_t)]\sigma_t^*(\ell_t, m_t, \alpha_t, \Gamma_t, \ell_t) \]
5: end for
6: Update Value Function: \( v^{\text{RMDP-TM}}_t(\ell_t, m_t) \leftarrow \max_{\alpha_t \in A_t(\ell_t, m_t)} \{ w_t(\ell_t, m_t, \alpha_t) \} \)
7: Update Optimal Action Set: \( A_t^*(\ell_t, m_t) \leftarrow \arg\max_{\alpha_t \in A_t(\ell_t, m_t)} \{ w_t(\ell_t, m_t, \alpha_t) \} \)
8: end for
Interval Model with Uncertainty Budget (IMUB)

\[ Q_{t, \ell_t}^{\text{IMUB}}(\Gamma_{t, \ell_t}) = \left\{ q_{t, \ell_t} \in \mathbb{R}_+^{\mathcal{L}} \mid \begin{align*}
q_{t, \ell_t}(\ell_{t+1}) &= \hat{q}_{t, \ell}(\ell_{t+1}) - \delta^l_{t, \ell}(\ell_{t+1}) z^l_{t, \ell}(\ell_{t+1}) + \delta^u_{t, \ell}(\ell_{t+1}) z^u_{t, \ell}(\ell_{t+1}), \\
\sum_{\ell_{t+1} \in \mathcal{L}} q_{t, \ell_t}(\ell_{t+1}) &= 1, \\
\sum_{\ell_{t+1} \in \mathcal{L}} \left( z^l_{t, \ell_t}(\ell_{t+1}) + z^u_{t, \ell_t}(\ell_{t+1}) \right) &\leq \Gamma_{t, \ell_t}, \\
z^l_{t, \ell_t}(\ell_{t+1}) \cdot z^u_{t, \ell_t}(\ell_{t+1}) &= 0, \\
0 &\leq z^l_{t, \ell_t}(\ell_{t+1}), z^u_{t, \ell_t}(\ell_{t+1}) \leq 1, \\
0 &\leq q_{t, \ell_t}(\ell_{t+1}) \leq 1,
\end{align*} \right\} \]

- \( \hat{q}_{t, \ell}(\ell_{t+1}) \): nominal value (the point estimate)
- \( \delta^l_{t, \ell}(\ell_{t+1}) \): maximum left(right)-hand side variation
- \( z^l_{t, \ell_t}(\ell_{t+1}) \): proportion of variation
- \( \Gamma_{t, \ell_t} \): the total uncertainty budget on row \( \ell_t \) of \( Q_t \)
Simulation-based Analyses on Life Years Gained from Selected Population-based Prevention Programs

Steele et al. 2004¹ (colorectal cancer screening)

100% reduction in indoor tanning

Ekwueme et al. 2014² (cervical cancer screening)

80% reduction in indoor tanning

Wright et al. 1998³ (cervical cancer screening)

Maciosek et al. 2010⁴ (breast cancer screening)

Maciosek et al. 2010⁴ (colorectal cancer screening)

50% reduction in indoor tanning

Maciosek et al. 2010⁴ (cholesterol screening)

Maciosek et al. 2010⁴ (influenza immunization)

Under 18 age restriction on indoor tanning

20% reduction in indoor tanning

Maciosek et al. 2010⁴ (hypertension screening)


Optimal Value Functions of the RMDP

\[ v_{t}^{\text{RMDP}}(s_{t}) = \begin{cases} 
\max_{\pi \in \Pi} \min_{\theta_{t} \in \Theta_{t}} \mathbb{E}_{s_{t}}^{t} \left[ \sum_{k=t}^{T-1} \lambda^{k-t} r_{k}(s_{k}, \alpha_{k}(s_{k})) + \lambda^{T-t} r_{T}(s_{T}) \right], \\
0, & \forall s_{t} \in \mathcal{L} \times \mathcal{M}, \text{ otherwise.}
\end{cases} \]

- **Treatment policy:** \( \pi \)
- **All admissible treatment policies:** \( \Pi \)
- **Adversaries policy:** \( \theta_{t} \triangleq (Q_{t}, Q_{t+1}, \ldots, Q_{T-1}) \)
- **All admissible adversary policies:** \( \Theta_{t} \triangleq \prod_{\tau=t}^{T-1} Q_{\tau} \)