Applying Operations Research in Cancer Care

Mariel S. Lavieri
What is Cancer?

- “Uncontrolled growth and spread of abnormal cells”
  (American Cancer Society)
  - Cells of an organ or tissue **grow and divide** without respect to normal limits.
  - It can invade and destroy adjacent tissues and **spread** to other locations (metastasis).
  - Cells change their **structure** and **biological behavior**.

BCCA Stats

- In 2008 estimated (in Canada):
  - 166,400 new cases
  - 73,800 cancer deaths

- BCCA responsible for the delivery of all cancer treatment in BC

http://www.cancer.ca
Outline

- Background
  - CIHR Team
  - Literature Review
- My Research
  - Motivation
  - Our Goal
  - Model description
- Lessons learned
Background

- Lecture to investigators at BCCA
- Developed partnership with investigators at BCCA
- Talked to them about OR
- Described MDPs and medical decision making
- Sought context
- Developed grant proposal
- Obtained grant
  - CIHR Operations Research for Improved Cancer Care Grant
CIHR Team
“Develop, test, and implement modern management practices, especially from the field of Operations Research (O.R.), to increase the efficiency of the cancer system and to enhance patient outcomes”

www.chcm.ubc.ca/cihrteam
A Research Framework

Prevention → Healthy population → Risk management

Screen
- Radiology
- Labs
- GPs
- ...

Diagnosis
- Radiology
- Labs
- Oncologists
- ...

Treatment
- Radiation
- Surgery
- Chemotherapy
- ...

Monitoring
- Radiology
- Labs
- Oncologists
- ...

Population living with cancer

“Cured”

Death
Risk Management and Cancer Prevention

- **Risk:**
  - Measuring risk (Magat et al. 1996)
  - Burden of disease (Brailer et al. 1999) (Zhao et al. 2002)

- **Prevention:**
  - Measuring uncertainty in protecting the ozone layer (Greenstone, 1977)
  - Health effect of radon policies (Peterson, 1996)
  - Reducing smoking prevalence (Hall et al. 1992) (Levy et al. 2002)
Cancer Screening

- **Strategic decisions:**
  - Optimal location of screening centers (Verter et al. 2002)
  - Tradeoffs of quality, capacity and access to breast cancer screening centers (Güne et al. 2004)

- **Screening schedule:**
  - Minimize fraction of people that have an undetected tumor for longer than $T$ (Lincoln et al. 1963)
  - Minimize detection delay given number of screens (Kirch et al. 1974)
  - Maximize expected lifetime (Butler, 1979)
  - Minimize cost:
    - Value of alternative screening strategies (Schwartz, 1978) (Davies et al. 2002)
    - Loss function given screening policy (Baker, 1998)
    - Choose inspection schedule to min expected cost (Özekici et al. 1991)

- **Screening regimen:**
  - Predict screening attendance (Van der Pol et al. 2003)
Cancer Diagnosis and Prognosis

- Optimal number of fields of view to read a cytological sample (Laporte et al. 1998)
- Clinical decision making in liver disease (Sanchez de Rivera, 1980)
- Discriminate benign breast lumps based on FNA; predicting cancer recurrence (Mangasarian, 1995)
- Prognosis after surgical removal of cancer (Ryu et al. 2004)
- Disease simulation modeling (Stout et al. 2008)
- Cost prediction (Penberthy et al. 1999)
Cancer Treatment

- **Operational modeling:**
  - Simulation modeling of capacity, resource utilisation and wait times (VanBerkel and Blake 2007) (Matta et al. 2007) (Chow et al. 2008) (Werker et al. 2008)
  - Scheduling:
    - Treatment (Sauré et al. 2008)
    - Workforce (Werker et al. 2008)
  - Categorizing length of stay after surgery (Michalowski, 2006)

- **Patient specific decisions:**
  - Patient’s decision of whether and when to begin therapy (Mehrez et al. 1987) (Chirikos, 2003)
  - Selection of adjuvant therapy (Karnon et al. 1998)
  - Radiotherapy:
    - Beam and intensity selection (Sondeman et al. 1985) (Ferris et al. 2003), (Romeijn et al. 2006), (Holder, 2004)
    - Brachytherapy treatment (Lee et al. 2004)
  - Chemotherapy treatment planning (Agur et al. 2006)
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  - Model description

- Lessons learned
Motivation

- High risk prostate cancer patients might be offered neoadjuvant hormone therapy (to induce prostate cancer cell death and tumor regression) prior to their radiotherapy treatment.

- Patients are monitored periodically.

- “Maximal tumor regression probably occurs when PSA reaches its nadir level” M. S. Gleave, S. La Bianca, S. L. Goldeberg (2000)

- Not known when such level will be achieved.
Understanding PSA

- Protein produced (almost exclusively) by cells of the prostate

<table>
<thead>
<tr>
<th>Age</th>
<th>Typical PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>less than 2.5</td>
</tr>
<tr>
<td>50-59</td>
<td>less than 3.5</td>
</tr>
<tr>
<td>60-69</td>
<td>less than 4.5</td>
</tr>
<tr>
<td>70-80</td>
<td>less than 6.5</td>
</tr>
</tbody>
</table>

http://www.prostatecentre.ca/

http://www.bccancer.bc.ca
Our Goal

- Improve modeling of PSA kinetics and estimation of future PSA kinetics
- Provide a formal decision making tool to determine when a patient should begin radiation therapy treatment
Formulation

Initial Beliefs (based on Population Characteristics) → Observe PSA → Update Curve Parameters

Estimate Nadir
Initial Beliefs (based on Population Characteristics)

- Fit regression curve for each patient
- Cluster patients
- Fit regression for each cluster
- Estimate probability of a patient being in a cluster given baseline values

- Estimate expected time to reach the nadir ($t_{nadir}$)
- By minimum PSA value observed and $t_{nadir}$
- Weight regression parameters using cluster probabilities
Initial Beliefs (based on Population Characteristics)

\[
\ln(PSA_t) = \alpha_t + \beta_t t + \gamma_t t^2 + \nu_t \quad \nu_t \sim N(0, V_t)
\]

\[
\frac{d \ln(PSA_t)}{dt} = \beta_t + 2\gamma_t t = 0
\]

\[
t = -\frac{\beta_t}{2\gamma_t}
\]

Expected minimum \((t_{\text{nadir}})\)
Initial Beliefs (based on Population Characteristics)

- 3 groups:

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{nadir}$ (days)</td>
<td>171</td>
<td>242</td>
<td>&gt;&gt;240</td>
</tr>
<tr>
<td>min PSA</td>
<td>.21</td>
<td>.98</td>
<td>.26</td>
</tr>
<tr>
<td>Probability</td>
<td>72%</td>
<td>20%</td>
<td>8%</td>
</tr>
</tbody>
</table>
Initial Beliefs (based on Population Characteristics)

- Fit regression curve for each patient
- Cluster patients
- Fit regression for each cluster
- Estimate probability of a patient being in a cluster given baseline values

Graphs:
- PSA vs Time (Group 1)
- PSA vs Time (Group 2)
- PSA vs Time (Group 3)
Initial Beliefs (based on Population Characteristics)

- Probability in Group 1:
  \[
  \frac{\exp(2.3 - 0.16 \cdot \text{iPSA})}{1 + \exp(1.16 - 0.06 \cdot \text{iPSA}) + \exp(2.3 - 0.16 \cdot \text{iPSA})}
  \]

- Probability in Group 2:
  \[
  \frac{\exp(1.16 - 0.06 \cdot \text{iPSA})}{1 + \exp(1.16 - 0.06 \cdot \text{iPSA}) + \exp(2.3 - 0.16 \cdot \text{iPSA})}
  \]

- Probability in Group 3:
  \[
  1 - (\text{Probability in Group 1}) - (\text{Probability in Group 2})
  \]
Initial Beliefs (based on Population Characteristics) → Observe PSA → Update Curve Parameters → Estimate Nadir

**PSA vs time**

- **PSA**
  - Minimum

Time from NAH start (days)

- 0
- 30
- 60
- 90
- 120
- 150
- 180
- 210
- 240

- 100
- 10
- 1
- 0.1
Formulation

- Observation Equation:
  \[
  Y_t = F_t \theta_t + v_t \quad v_t \sim N(0, V_t)
  \]
  \[
  Y_t = \ln(PSA_t) = \alpha_t + \beta_t t + \gamma_t t^2 + v_t
  \]

- State Equation:
  \[
  \theta_t = \theta_{t-1} + w_t \quad w_t \sim N(0, W_t)
  \]
  \[
  W_t = 0
  \]

- Updating Equations:
  (1) \[
  \theta_t = \theta_{t-1} + R_{t-1} F_t Q_t^{-1} [Y_t - F_t' \theta_{t-1}]
  \]
  (2) \[
  R_t = R_{t-1} - R_{t-1} F_t Q_t^{-1} F_t' R_{t-1}
  \]
  (3) \[
  Q_t = F_t' R_{t-1} F_t + V_t
  \]
Initial Beliefs (based on Population Characteristics)

Observe PSA

Update Curve Parameters

Estimate Nadir

Update Cluster Probability

PSA vs Time (Group 1)

PSA vs Time (Group 2)

PSA vs Time (Group 3)

P₁ = .69

P₂ = .24

P₃ = .07

Distribution of time of nadir (Group 1)

Distribution of time of nadir (Group 2)

Distribution of time of nadir (Group 3)
Formulation (Revised)

- **Observation Equation:**
  \[ Y_t = F_t' \theta_{t,i} + v_{t,i} \quad v_{t,i} \sim N(0, V_{t,i}) \]
  \[ Y_t = \ln(PSA_t) = \alpha_{t,i} + \beta_{t,i} t + \gamma_{t,i} t^2 + v_{t,i} \]

- **State Equation:**
  \[ \theta_{t,i} = \theta_{t-1,i} + w_{t,i} \quad w_{t,i} \sim N(0, W_{t,i}); W_{t,i} = 0 \]

- **Updating Equations:**
  \[ \theta_{t,i} = \theta_{t-1,i} + R_{t-1,i} F_t Q_{t,i}^{-1} [Y_t - F_t' \theta_{t-1,i}] \]
  \[ R_{t,i} = R_{t-1,i} - R_{t-1,i} F_t Q_{t,i}^{-1} F_t' R_{t-1,i} \]
  \[ Q_{t,i} = F_t' R_{t-1,i} F_t + V_{t,i} \]

\[ P(i)_{t+1} = \frac{\sum_{k=1}^{3} P(k)_t \star \int f(F_{t+1}' \theta_{t,i}; Q_{t+1,k})dy}{\sum_{k=1}^{\ln(P(PSA_{t+1} + \varepsilon))} P(k)_t \star \int f(F_{t+1}' \theta_{t,i}; Q_{t+1,k})dy} \]

Probability function of a normal distribution
A Motivating Application

Figure 1  A Typical Viral Load Trajectory for an HIV-Infected Person on Combination Therapy

(D’Amato, D’Amato and Wein, 2000)
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Lessons learned
Lessons Learned

- Take the time to thoroughly define your problem
  - Learning what has been done by others is key to your own success!

- Find highly motivated and committed collaborators (clinicians and decision makers)

- Real problems might present interesting technical problems

- Make your work accessible:
  - “If a magic box predicts accurately under rigorous testing on new patients, who care how the prediction is actually made?” (D’ Amico et al.)

- Allow time for model validation & design of clinical study
Presentations at the ORAHS Meeting

Tue 9:30 (BA 1200)
Shechter Steven: Simulation versus Markov Decision Processes
Approaches to HIV Therapy Planning

Tue 11:30 (BA 1220)
Werker, Greg: An IP approach to strategic scheduling of radiation therapists
at the BC Cancer Agency

Tue 14:00 (BA 1170)
Lavieri, Mariel: Radiation therapy treatment decision making for prostate
cancer patients based on PSA dynamics

Thu 16:00 (BA 1180)
Santibanez, Pablo: Reducing wait times & improving utilization at the BC
Cancer Agency's ambulatory care unit

Chow, Vincent: Reducing surgical ward congestion at Vancouver Island
Health Authority through improved surgical scheduling
References

- Brailer, D. J. and Kroch E. A., “Member Risk Adjustment for Ambulatory Episodes of Care”, Health Care Management Science, 2, 125-136, 1999
- Cox, L. Jr., “A New Measure of Attributable Risk for Public Health Applications”, Management Science, 31, 7, 800-813, 1985
- Greenstone, R., “Protecting the Ozone Layer in the Face of Uncertainty”, Interfaces, 7, 4, 34-39, 1977
References

References

- Gerald F. Riley e, Thomas J. Smith a, Bruce E. Hillner b and Craig J. Newschaffer d
References

- Stout, N. K. and Goldie S. J., “Keeping the Noise Down: Common Random Numbers for Disease Simulation Modeling”, Health Care Manage Science, Published Online, 2008
Thank you

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