Evaluating dynamic treatment strategies

Barbra Dickerman
Department of Epidemiology

Objectives

• Define dynamic treatment strategies
• Describe when g-methods are needed
• Review an application of the parametric g-formula to cancer research
  • Causal inference perspective
• Discuss the AI Clinician
  • Reinforcement learning perspective
WHAT ARE DYNAMIC TREATMENT STRATEGIES?

Treatment strategies

<table>
<thead>
<tr>
<th>Point interventions</th>
<th>Sustained strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Static</td>
</tr>
<tr>
<td></td>
<td>1. Initiate treatment at baseline</td>
</tr>
<tr>
<td></td>
<td>2. Do not initiate treatment at baseline</td>
</tr>
</tbody>
</table>
Dynamic treatment strategies

- Take into consideration a patient’s evolving characteristics before making a decision
  - Decisions about prevention, screening, or treatment interventions over time may depend on evolving comorbidities, screening results, or treatment toxicity
- Strategies in clinical guidelines and practice are often dynamic
- The optimal strategies will be dynamic

WHEN ARE G-METHODS NEEDED?
Conventional statistical methods cannot appropriately compare dynamic strategies with treatment-confounder feedback

\[ A_0 \rightarrow L_1 \rightarrow A_1 \rightarrow Y \]

- \( A_t \): Vasopressors
- \( L_1 \): Systolic blood pressure
- \( Y \): Survival
- \( U \): Disease severity

G-methods

- Parametric g-formula
- G-estimation of structural nested models
- Inverse probability weighting of marginal structural models
Case study: Physical activity and survival among men with prostate cancer

Question
- What is the effect of adhering to guideline-based physical activity strategies on survival among men with nonmetastatic prostate cancer?

Data
- Health Professionals Follow-up Study (HPFS)
### Physical activity and survival among men with prostate cancer

| Eligibility criteria | • Diagnosed with nonmetastatic prostate cancer at age 50-80 between 1998-2010  
|                      | • No cardiovascular/neurological condition limiting physical ability  
|                      | • Data on all potential confounders measured in the past 2 years |
| Treatment strategies | Initiate 1 of 6 physical activity strategies at diagnosis and continue it over follow-up until the development of a condition limiting physical ability |
| Follow-up            | Starts at diagnosis and ends at death, loss to follow-up, 10 years after diagnosis, or administrative end of follow-up (June 2014), whichever happens first |
| Outcome              | All-cause mortality within 10 years of diagnosis |
| Causal contrast      | Per-protocol effect |
| Statistical analysis | Parametric g-formula |

### Parametric g-formula

- Generalization of standardization to time-varying exposures and confounders
- Conceptually, the g-formula risk is a **weighted average of risks** conditional on a specified intervention history and observed confounder history
  - The **weights** are the probability density functions of the time-varying confounders, estimated using parametric regression models
  - The weighted average is approximated using Monte Carlo simulation
Steps of the parametric g-formula

1. **Fit parametric regression models** for treatment, confounders, and death at each follow-up time $t$ as a function of treatment and covariate history among those under follow-up at time $t$

2. **Monte Carlo simulation** to generate a 10,000-person population under each strategy by sampling with replacement from the original study population (to estimate the standardized cumulative risk under a given strategy)

3. **Repeat in 500 bootstrap samples** to obtain 95% confidence intervals (CIs)

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Estimated risk of all-cause mortality under several physical activity strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>10-year risk (%)</th>
<th>95% CI</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No intervention</td>
<td>15.4</td>
<td>(13.3, 17.7)</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td><strong>Vigorous activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1.25 h/week</td>
<td>13.0</td>
<td>(10.9, 15.4)</td>
<td>0.84</td>
<td>(0.75, 0.94)</td>
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<tr>
<td>≥2.5 h/week</td>
<td>11.1</td>
<td>(8.7, 14.1)</td>
<td>0.72</td>
<td>(0.58, 0.88)</td>
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<tr>
<td>≥3.75 h/week</td>
<td>10.5</td>
<td>(8.0, 13.5)</td>
<td>0.68</td>
<td>(0.53, 0.85)</td>
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<td><strong>Moderate activity</strong></td>
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<td>≥5 h/week</td>
<td>12.6</td>
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<td>0.81</td>
<td>(0.73, 0.88)</td>
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<tr>
<td>≥7.5 h/week</td>
<td>12.2</td>
<td>(10.3, 14.4)</td>
<td>0.79</td>
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All strategies excuse men from following the recommended physical activity levels after development of metastasis, MI, stroke, CHF, ALS, or functional impairment.
Potential unmeasured confounding by chronic disease (i.e. reverse causation)

- Severe enough to affect both physical activity and risk of death
- G-formula provides a natural way to partly address this
  - By estimating risk under physical activity interventions that are only applied at each time point to those who are sufficiently healthy at that time
  - Main analysis: excused men from following the intervention after developing metastasis, MI, stroke, CHF, ALS, or functional impairment

Sensitivity analyses for unmeasured confounding: Expanded definition of “serious condition”

All strategies excuse men from following the recommended physical activity levels after development of metastasis, MI, stroke, CHF, ALS, or functional impairment, angina pectoris, pulmonary embolism, heart rhythm disturbance, diabetes, chronic renal failure, rheumatoid arthritis, gout, ulcerative colitis or Crohn's disease, emphysema, Parkinson's disease, and multiple sclerosis

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Sensitivity analyses for unmeasured confounding: Lag and negative outcome control

- **Lagged** physical activity and covariate data by two years
- **Negative outcome control** to detect potential unmeasured confounding by clinical disease
  - Questionnaire non-response

![Diagram of original analysis and negative outcome control](image)

G-methods let us validly estimate the effect of pre-specified dynamic strategies

- And estimate adjusted absolute risks
  - Appropriately adjusted survival curves
  - Not only hazard ratios
  - Even in the presence of treatment-confounder feedback
- Under the assumptions of exchangeability, consistency, positivity, no measurement error, no model misspecification
- Powerful approach to estimate the effects of currently recommended or proposed strategies
- But, these pre-specified strategies may not be the optimal strategies
DISCUSSION: THE AI CLINICIAN

Figure 1 Data flow of the AI Clinician

Komoroski et al. Nat Med 2018
Figure 2b Distribution of the estimated value of the clinicians’ actual treatments, the AI policy, a random policy and a zero-drug policy across the 500 models in the MIMIC-III test set ($n = 500$ models in each boxplot).

Discussion

- Study overview
- System representation
- Policy evaluation
- Interpretability
- Future directions