Inference for Dynamic Treatment Regimens

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Definition of a Dynamic Treatment Regimen

A dynamic treatment regimen is a sequence of decision rules that specify whether, how, and when to alter the intensity, type, dosage, or delivery of treatment at critical decision points.

- Dynamic treatment regimens (DTRs)
  - Operationalize sequential, clinical decision making via a sequence of decision rules
    - One decision rule for each stage (e.g. critical decision point)
    - A decision rule inputs patient history and outputs a recommended treatment
Why Dynamic Treatment Regimens?
Necessary because...

- Disorder is chronic
  - Waxing and waning course (multiple relapse, recurrence)
  - Co-occurring disorders may arise
  - Maintaining adherence is difficult

- High heterogeneity in response to treatment
  - Between person differential response to treatment
  - Within person (over time) differential response to treatment

- The effect of each treatment in the regimen should be considered as part of a sequence of treatments in addition to considering the effect of each treatment in isolation.
An Example DTR for ADHD

Stage 1
Prior medication?

Yes → Low dose MEDS
No → Low dose BMOD

Stage 2
Adequate response?

Yes → Continue MEDS
No → High adherence?

No → Intensify MEDS
Yes → High adherence?

No → Add BMOD
Yes → Add MEDS
Constructing a DTR: The Data

Sequential, Multiple Assignment, Randomized Trial

- Each patient participates in multiple stages of treatment
- At each stage, patients are randomized among a set of treatment options
- Treatment options for a patient may be restricted (depending on response to prior stages and prior treatment)
ADHD Trial (Pelham, PI)

Treatment A
Low Intensity BMOD → Response?

Yes → Treatment AA
Augment with MEDS

No → Treatment AB
Intensify BMOD

Treatment B
Low Intensity MEDS → Response?

Yes → Treatment BA
Augment with BMOD

No → Treatment BB
Intensify MEDS
Data and Goal

- Goal of trial is to inform the construction of a DTR.
  - Primary Analysis Goal: Compare embedded –simple– DTRs
  - Secondary Analysis Goal: develop a high quality proposal for a more individualized DTR
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  - Primary Analysis Goal: Compare embedded –simple– DTRs
  - Secondary Analysis Goal: develop a high quality proposal for a more individualized DTR

- \((X_1, A_1, X_2, A_2, Y)\) for each individual
  - \(X_j\): Observations available at stage \(j\)
  - \(A_j\): Treatment at stage \(j\)
  - \(Y\): Primary outcome (larger is better)
  - \(H_j\): History at stage \(j\), \(H_1 = X_1, H_2 = (X_1, A_1, X_2)\)
    - Known randomization probability at stage \(j\) (usually uniform)

- The proposed DTR, \(\pi = \{\pi_1, \pi_2\}\), \(\pi_j : H_2 \rightarrow A_2\), should have high Value: \(V^\pi = E^\pi (Y)\)
Constructing a DTR: Q-Learning

- Generalization of regression to multiple treatment stages
- Backwards induction like dynamic programming
- Approximate conditional expectation with regression
- Watkins (1989), Ernst et al. (2005); in Statistics: Murphy (2005), Zhao et al. (2009)
Constructing a DTR: Q-Learning

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- In computer science there are many variations; almost always presented as part of a stochastic approximation algorithm for solving an infinite number of stages (infinite horizon) Sutton & Barto (1998)

- In statistics there are a few variations, with a finite number of stages, appearing in Murphy (2003), Robins (2004), Henderson et al. (2009) + more
Idea behind Q-Learning

In two stages, the optimized Value can be written as

\[ V^{opt} = E \left[ \max_{a_1} E \left[ \max_{a_2} E \left[ Y \mid H_2, A_2 = a_2 \right] \mid H_1, A_1 = a_1 \right] \right] \]

- Stage 2 Q-function \( Q_2(H_2, A_2) = E \left[ Y \mid H_2, A_2 \right] \)

\[ V^{opt} = E \left[ \max_{a_1} E \left[ \max_{a_2} Q_2(H_2, a_2) \mid H_1, A_1 = a_1 \right] \right] \]

- Stage 1 Q-function \( Q_1(H_1, A_1) = E \left[ \max_{a_2} Q_2(H_2, a_2) \mid H_1, A_1 \right] \)

\[ V^{opt} = E \left[ \max_{a_1} Q_1(H_1, a_1) \right] \]
Simple Version of Q-Learning

Two stages; linear regressions; \( A_j \in \{0, 1\} \), \( H_{j1}, H_{j2} \) features of patient history, \( H_j \):

- **Stage 2 regression**: Regress \( Y \) on \( H_{21}, H_{22} \) to obtain
  \[
  \hat{Q}_2(H_2, A_2) = \hat{\beta}_{21}^T H_{21} + \hat{\beta}_{22}^T H_{22} A_2
  \]
- \( \hat{\pi}_2(H_2) = \arg \max_{a_2} \hat{Q}_2(H_2, a_2) = \arg \max_{a_2} \hat{\beta}_{22}^T H_{22} a_2 \)
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- Form $\tilde{Y}$, a predictor of $\max_{a_2} Q_2(H_2, a_2)$; $\tilde{Y}$ is the dependent variable in the stage 1 regression
Simple Version of Q-Learning

Recall $\hat{Q}_2(H_2, A_2) = \hat{\beta}_{21}^T H_{21} + \hat{\beta}_{22}^T H_{22} A_2$

- Form $\tilde{Y}$, a predictor of $\max_{a_2} Q_2(H_2, a_2)$; $\tilde{Y}$ is the dependent variable in the stage 1 regression

- Many options for constructing $\tilde{Y}$
  - $\tilde{Y} = \hat{\beta}_{21}^T H_{21} + \max_{a_2} \hat{\beta}_{22}^T H_{22} a_2$
  - $\tilde{Y} = Y - \hat{\beta}_{22}^T H_{22} A_2 + \max_{a_2} \hat{\beta}_{22}^T H_{22} a_2$
  - $\tilde{Y} = Y \frac{1_{A_2 = \arg \max_a \beta_{22}^T H_{22} a_2}}{p_2(A_2 | H_2)}$ (\(p_2\) is known randomization probability)
Simple Version of Q-Learning

- We formed $\tilde{Y}$, the dependent variable for the stage 1 regression ($\tilde{Y}$ is a predictor of $\max_{a_2} Q_2(H_2, a_2)$)

- Stage 1 regression: Regress $\tilde{Y}$ on $H_{11}, H_{12}$ to obtain
  $\hat{Q}_1(H_1, A_1) = \hat{\beta}_{11} H_{11} + \hat{\beta}_{12} H_{12} A_1$
  
  $\hat{\pi}_1(H_{12}) = \arg \max_{a_1} \hat{Q}_1(H_1, a_1) = \arg \max_{a_1} \hat{\beta}_{12}^T H_{12} a_1$
Review of Q-Learning

Two stages; linear regressions; $A_j \in \{0, 1\}, H_{j1}, H_{j2}$ features of $H_j$:

- **Stage 2 regression:** Regress $Y$ on $H_{21}, H_{22}$ to obtain
  \[ \hat{Q}_2(H_2, A_2) = \hat{\beta}_{21}^T H_{21} + \hat{\beta}_{22}^T H_{22} A_2 \]
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Inference for DTRs

- Goal: confidence interval for $c^T \beta^*_1$ for fixed contrast, $c$
  1. For a fixed patient history, is there strong evidence that the first stage treatment recommended by the constructed DTR is really the unique best treatment?
  2. Should a particular patient characteristic or patient outcome be used to recommend treatment?
  3. Is a particular patient characteristic or patient outcome useful in predicting the primary outcome?
Challenge: Non-regularity

- Non-differentiable max operator used in Q-learning; recall
  \[ \hat{Y} = \hat{\beta}_{21}^T H_{21} + \max_{a_2} \hat{\beta}_{22}^T H_{22} a_2 \]

- Limiting distribution of \( c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*) \) is non-regular

- Standard asymptotic approaches invalid without modification (see Shao, 1994; Andrews, 2000)
  - In this setting the centered percentile bootstrap can be anticonservative, (95% confidence interval covers 90%-93% in two stages, each with two treatments; 84%-93% for two stages, each with three treatments)
Limiting Distribution of $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$

- Local Alternative:
  - $\beta_{n,22}^* = \beta_{22}^* + b/\sqrt{n}$
  - The limiting distribution of $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ is the distribution of
    $$c^T \Sigma_1^{-1} (W_\infty + f(V_\infty, b))$$

where

$$f(v, b) = E \left[ B_1^T \left( [H_{22}^TV + H_{22}^Tb]^+ - [H_{22}^Tb]^+ \right) 1_{H_{22}^T\beta_{22}^* = 0} \right]$$

and $B_1 = (H_{11}^T, H_{12}^TA_1)$ (e.g. row of the design matrix) and $W_\infty, V_\infty$ are jointly normal vectors

- The fact that the limiting distribution depends on $b$ means that $\hat{\beta}_1$ is a nonregular estimator (unless $P [H_{22}^T\beta_{22}^* = 0] = 0$)
Some Consequences

- Bootstrap distribution is inconsistent when the true parameters are equal to the “bad” parameter values.
- Bootstrap distribution can behave poorly in small samples even when the true parameters are close to the “bad” parameter values.

- Straightforward generalizations of the bootstrap assume $b = 0$ in $\beta^* n$, $\beta^* 2^2 = \beta^* 2^2 + b/\sqrt{n}$ (e.g. consider only fixed alternatives; A. Chatterjee and S.N. Lahiri, 2009)
- The small sample frequentist properties of the confidence interval can be poor if your method assumes $b = 0$ (Andrews, 2000; Cheng, 2010; Laber & Murphy, 2010).
Some Consequences

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► The small sample frequentist properties of the confidence interval can be poor if your method assumes $b = 0$ (Andrews, 2000; Cheng, 2010; Laber & Murphy, 2010).
An Idea from Econometrics

- Many natural problems occurring in Economics are nonregular: weakly identified parameters, weak instruments, unit root problems
- In these settings there are a fixed number of easily identified “bad” parameter values at which you have nonregular behavior of the estimator

(Rough) Idea is to use a pretest (e.g. an hypothesis test) to test if you are near a “bad” parameter value; if the pretest rejects, use standard critical values to form confidence interval; if the pretest accepts, use the maximal critical value over all possible local alternatives. (Andrews & Soares, 2007; Andrews & Guggenberger, 2009)
An Idea from Econometrics

Many natural problems occurring in Economics are nonregular: weakly identified parameters, weak instruments, unit root problems.

In these settings there are a fixed number of easily identified “bad” parameter values at which you have nonregular behavior of the estimator.

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Recall that under the local alternative, $\beta_{n,22}^* = \beta_{22}^* + b/\sqrt{n}$:

The limiting distribution of $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ is the distribution of

$$c^T \Sigma_1^{-1} (W_\infty + f(V_\infty, b))$$

where

$$f(v, b) = E \left[ B_1^T ([H_{22}^T v + H_{22}^T b]^+ - [H_{22}^T b]^+) 1_{H_{22}^T \beta_{22}^*=0} \right]$$

and $B_1 = (H_{11}^T, H_{12}^T A_1)$ (e.g. row of the design matrix) and $W_\infty, V_\infty$ are jointly normal vectors.

“Bad” parameter values are any combination of the distribution of $H_{22}$ and values of $\beta_{22}^*$ for which

$$P [H_{22}^T \beta_{22}^* = 0] > 0$$
Our Approach (Conceptually)

Idea: construct smooth upper and lower bounds on $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ with the following property:

- The upper bound $U(c)$ is bigger than $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$. Similarly for the lower bound $L(c)$.

- The first step is to embed in the formula for $\sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ a pretest based on the test statistic, $T_n(h_{22}) = \frac{n \left( h_{22}^T \hat{\beta}_{22} \right)^2}{h_{22}^T \Sigma_2 h_{22}}$.

- Note it is easy to derive an explicit formula for $\sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ since we are using linear regression.
Our Approach (Algebraically)

- Construct smooth upper and lower bounds on $c^T \sqrt{n}(\hat{\beta}_1 - \beta_1^*)$
- Bounds formed in three steps
  1. Replace $1\{H_{22}^T \beta_{22}^* = 0\}$ by $1\{T_n(H_{22}) < \lambda_n\}$ in the formula for $\sqrt{n}(\hat{\beta}_1 - \beta_1^*)$
  2. Replace $\sqrt{n} \beta_{22}^*$ by $b$ and
  3. Take supremum over $b$
- Bootstrap the resulting bounds to form a confidence set

Notes on upper bound, $U(c)$ and lower bound, $L(c)$
- Selecting $\lambda_n$ to increase with sample size controls Type I error of pretest
- Use of bounds controls Type II error of pretest
Our Approach (Algebraically)

The upper bound adds to $c^T \sqrt{n} (\hat{\beta}_1 - \beta_1^*)$:

$$
-c^T \hat{\Sigma}_{11}^{-1} \mathbb{P}_n B_1^T \left( U_{n,b} - [H_{22}^T \mathbb{V}_n]_+ \right) 1_{T_n(H_{22},b) \leq \lambda_n} \bigg|_{b=\sqrt{n} \beta_1^*} \\
\sup_{b} c^T \hat{\Sigma}_{11}^{-1} \mathbb{P}_n B_1^T \left( U_{n,b} - [H_{22}^T \mathbb{V}_n]_+ \right) 1_{T_n(H_{22},b) \leq \lambda_n}
$$

- $B_1 = (H_{11}^T, H_{12}^T A_1)$
- $\mathbb{V}_n = \sqrt{n} (\hat{\beta}_1 - \beta_1^*)$
- $U_{n,b} = \left( [H_{22}^T \mathbb{V}_n + H_{22}^T b]_+ - [H_{22}^T b]_+ \right)$
- $T_n(h_{22}, b) = \frac{(h_{22}^T \mathbb{V}_n + h_{22}^T b)^2}{h_{22}^T \hat{\Sigma}_2 h_{22}}$
**Assumptions**

(A1) The histories \( H_j \) with \( B_j = (H^T_{j1}, H^T_{j2}A_j) \), \( j = 1, 2 \) and primary outcome \( Y \), satisfy the moment inequalities
\[
P||H_2||^2 ||B_1||^2 < \infty \text{ and } PY^2||B_j||^2 < \infty.
\]

(A2) Define:
1. \( \Sigma_j \triangleq PB_j^T B_j \) for \( j = 1, 2; \)
2. \( g_2(B_2, Y_2; \beta_2^*) \triangleq B_2^T (Y_2 - B_2 \beta_2^*); \)
3. \( g_1(B_1, Y_1, H_2; \beta_1^*, \beta_2^*) \triangleq B_1^T (H^T_{21} \beta_{21}^* + |H^T_{22} \beta_{22}^*| - B_1 \beta_1^*); \)
assume the matrices \( \Sigma_j \) and \( \Omega \triangleq \text{Var-cov}(g_1, g_2) \) are strictly positive definite.

(A3) The sequence \( \lambda_n \) tends to infinity and satisfies \( \lambda_n = o(n) \). We use \( \lambda_n = \log \log n \)
Adaptive Confidence Interval

- Let $\mathcal{U}^{(b)}(c)$ and $\mathcal{L}^{(b)}(c)$ be the bootstrap analogues of $\mathcal{U}(c)$ and $\mathcal{L}(c)$.
- Define $P_M$ to be probability with respect to bootstrap weights.
Adaptive Confidence Interval

Let $U^{(b)}(c)$ and $L^{(b)}(c)$ be the bootstrap analogues of $U(c)$ and $L(c)$.

Define $P_M$ to be probability with respect to bootstrap weights.

Theorem (Validity of the bootstrap confidence interval)

Assume (A1)-(A3), fix $c \in \mathbb{R}^{\dim(\beta_1^*)}$, and fix a level $\delta \in (0, 1)$. Define $\hat{l}$ to be the $\delta/2$ quantile of $L^{(b)}(c)$ and $\hat{u}$ to be the $1 - \delta/2$ quantile of $U^{(b)}(c)$. Then:

$$P_M \left( c^T \hat{\beta}_1 - \hat{u}/\sqrt{n} \leq c^T \beta_1^* \leq c^T \hat{\beta}_1 - \hat{l}/\sqrt{n} \right)$$

is bounded below by $1 - \delta + o_P(1)$. 
Special Cases

- Adaptation: When there is a second stage treatment effect for all, e.g. \( P [H_{22}^T \beta_{22}^* \neq 0] = 1 \) then the ACI delivers exact asymptotic coverage.

- Methodology and theory extend to greater than two treatments and greater than two stages
Empirical study

- Competing methods
  - Soft-thresholding (ST) (Chakraborty, Murphy, and Strecher 2009)
  - Centered percentile bootstrap (CPB)
  - Plug-in pretesting estimator (PPE)

- Generative models from Chakraborty et al. (2009)
  - Each model is classified as
    1. Non-regular (NR): $P(H_{22}^T \beta_{22}^* = 0) > 0$
    2. Nearly non-regular (NNR): $P(H_{22}^T \beta_{22}^* \approx 0) > 0$
    3. Regular (R): $P(H_{22}^T \beta_{22}^* \approx 0) = 0$

- Monte Carlo evaluation of interval coverage and width
  - 1000 Monte Carlo replications; each data set is of size 150.
  - 1000 bootstrap resamples within each replication
  - Target coverage 95%
Coverage for Stage 1 Treatment Effect When $X_1 = 1$

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## Interval Diameters

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<td>0.7491</td>
<td>0.7332</td>
</tr>
</tbody>
</table>
Empirical Study: Remarks

- $ACI$ achieved nominal coverage on all examples
- $ACI$ is conservative when there is no stage 2 treatment effect.
- Relative performance of ACE improves on examples with increasing numbers of stages and/or treatments
ADHD Trial (Pelham, PI)

Treatment A
Low Intensity BMOD

Response?

Yes
- Treatment AA
  - Augment with MEDS

No
- Treatment AB
  - Intensify BMOD

Treatment B
Low Intensity MEDS

Response?

Yes
- Treatment BA
  - Augment with BMOD

No
- Treatment BB
  - Intensify MEDS
ADHD Dynamic Treatment Regime

**Stage 1**
Prior medication?  
- Yes: Low dose MEDS  
  - Yes: High adherence?  
    - Yes: Intensify MEDS  
    - No: Add BMOD  
  - No: Intensify MEDS  
- No: Low dose BMOD

**Stage 2**
Adequate response?  
- Yes: Continue MEDS  
  - No: High adherence?  
    - Yes: Intensify BMOD  
    - No: Add MEDS  
- No: Add BMOD
## Inference for ADHD Treatment Effects

<table>
<thead>
<tr>
<th>Stage</th>
<th>History</th>
<th>Lower (2.5%)</th>
<th>Upper (97.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Had prior med.</td>
<td>-0.55</td>
<td>0.19</td>
</tr>
<tr>
<td>1</td>
<td>No prior med.</td>
<td>-0.09</td>
<td>0.41</td>
</tr>
<tr>
<td>2</td>
<td>High adherence and BMOD</td>
<td>-0.16</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>Low adherence and BMOD</td>
<td>-1.19</td>
<td>-0.21</td>
</tr>
<tr>
<td>2</td>
<td>High adherence and MEDS</td>
<td>-0.26</td>
<td>0.70</td>
</tr>
<tr>
<td>2</td>
<td>Low adherence and MEDS</td>
<td>-1.34</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

- Positive stage 1 effect favors BMOD ($A_1 = 1$ if BMOD; $A_1 = -1$ if MED)
- Positive stage 2 effect favors Intensify ($A_2 = 1$ if Intensify; $A_2 = -1$ if Augment)
ADHD Dynamic Treatment Regime

Prior medication?

Yes

Adequate response?

Yes

Continue SAME

No

Low dose MEDS ~OR~ BMOD

No

High adherence?

Yes

Add OTHER ~OR~ Intensify SAME

No

Adequate response?

Yes

Continue BMOD

No

High adherence?

No

Add MEDS

Yes

Add MEDS ~OR~ Intensify BMOD
Many modern statistical problems involve nonregular estimators. Most frequently these occur in $p$ large($p < n$) or $p >> n$ problems. Examples:

- Estimators that involve the estimation of a matrix with eigenvalues that may be near zero,
- Prediction intervals after using lasso or other variable selection methods,
- Evaluation of the misclassification rate of a learned classifier
- Constrained estimation

Principled approaches to forming confidence intervals and hypothesis tests are currently lacking.
Questions: laber@umich.edu, samurphy@umich.edu
A copy of this talk can found at:
www.stat.lsa.umich.edu/~samurphy

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