Constructing Dynamic Treatment Regimes

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Title: Constructing Dynamic Treatment Regimes

We are using a different data set from star*d/catie

Abstract

Both STARD and CATIE are large clinical trials in mental health in which patients are randomized and then rerandomized each time the patient shows insufficient response to treatment. One of the objectives of the trials is to formulate best sequences of treatment. In this talk we discuss how Q-learning can be used to construct more deeply tailored sequences of treatment, sometimes called adaptive treatment strategies or dynamic treatment regimes or policies. We discuss how one can provide measures of confidence as well.

Dynamic treatment regimes are individually tailored treatments, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

k Stages for one individual

$$X_1,\ a_1,\ X_2,\ a_2, ...,\ a_k, X_{k+1}$$

X_j: Observation available at j[th] stage

a_j : Action at j[th] stage (usually a treatment)

X: subject outcomes such as test results, adherence, preferences, response to past treatment, self management skill, side effects, co-occurring problems

a: whether to treat, which treatment to use, dose of treatment, whether to change treatment, whether to stop treatment, ... The term action is more common in the field of decision theory.

k=2 Stages

Goal: Construct decision rules that input information available at each stage and output a recommended decision; these decision rules should lead to a maximal mean Y where Y is a function of

$$X_1,\ a_1,\ X_2,\ a_2, X_3$$

The *dynamic treatment regime* is the sequence of two decision rules:

$$d_1(X_1),\ d_2(X_1, a_2, X_2)$$

Y might be a measure of symptoms or functionality or a composite

Note that mean Y is maximized if the decision rule selects each person's maximal potential (counterfactual) Y

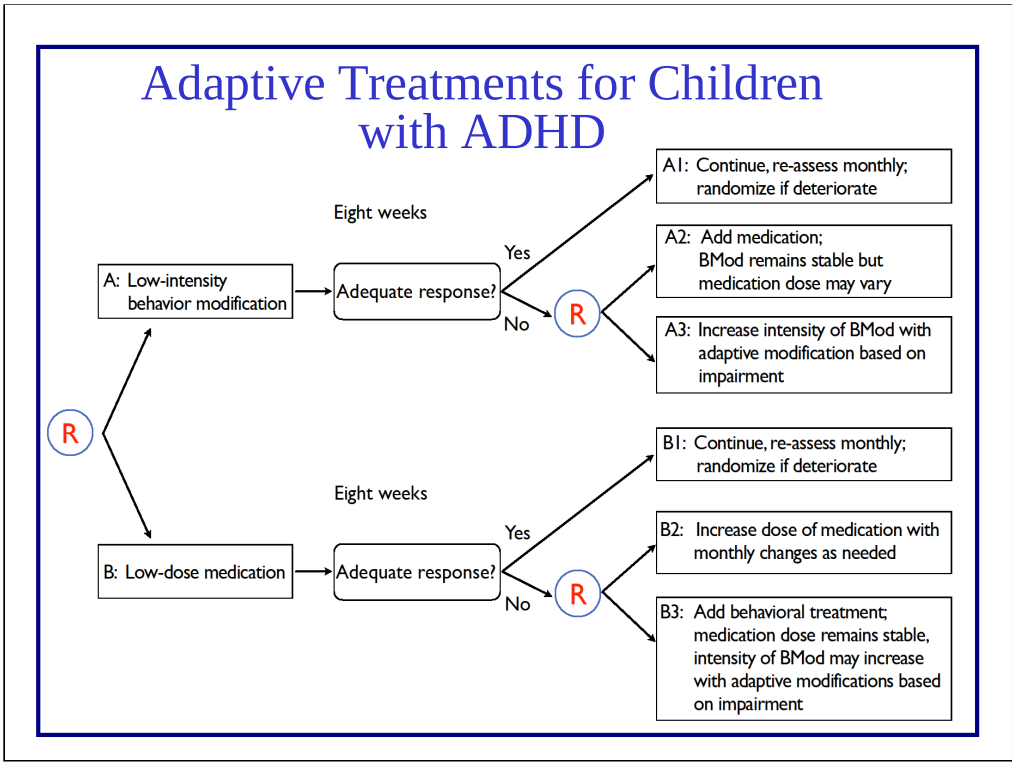
Data for Constructing the Dynamic Treatment Regime:

Subject data from sequential, multiple assignment, randomized trials. At each stage subjects are randomized among alternative options.

$$X_1,\ A_1,\ X_2,\ A_2,\ X_3$$

A_j is a randomized action with known randomization probability.

binary actions with $P[A_j=1]=P[A_j=-1]=.5$



Adaptive Pharmacological and Behavioral Treatments for Children with ADHD: Sequencing, Combining, and Escalating Doses

(1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND (2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

Our outcome will be a teacher rated classroom performance recorded at 8 months. N=149

Secondary Analysis: regression-based methods for constructing decision rules

- Q-Learning (Watkins, 1989; Murphy, 2005) (a popular method from computer science)
- Optimal nested structural mean model (Murphy, 2003; Robins, 2004)
  - The first method is an inefficient version of the second method when linear models are used in which each stages' covariates include the prior stages' covariates and the actions are centered to have conditional mean zero.

Focus on Q-learning—use a setting in which these methods are equivalent (each stage's covariates include the prior stage's covariates and the actions are

Centered to have conditional mean zero)—this is for finite horizon problems.

A-learning/ optimal nested structural mean model was developed to accommodate the presence of unknown causes; a more important property is that it assists in dimension reduction.

Other methods

Likelihood methods (Thall) Likelihood-based (Thall et al. 2000, 2002; POMDP's in medical decision making and in reinforcement learning; vast literature)

POMDP's requires assumptions on the data structure with regards to unobserved causes POMDP's are used with great utility in pharmacokinetics –regulating the administration of chemo according to ongoing measures of the active chemical in blood stream.

Weighting (Murphy, et al., 2002, Robins et al., 2008 related to policy search in reinforcement learning)

Need to mention work in econometrics here

Michael Lechner (sequences of treatments --inference about a regime does not incorporate tailoring variables)

http://www.siaw.unisg.ch/org/siaw/web.nsf/wwwPubPublikationEng/AD87C4EBE2CF65EBC1256A4F004C5913

Jaap Abbring's work is very nice –see http://www.xs4all.nl/~jabbring/papers.htm

A Simple Version of Q-Learning – $a_j \in \{-1, 1\}$

There is a regression for each stage.

- Stage 2 regression: Regress Y on S_2', $S_2 A_2$ to obtain $\widehat{\alpha}_2^T S_2' + \widehat{\beta}_2 S_2 A_2$

- Stage 1 regression: Regress $\widehat{Y}$ on S_1', $S_1 A_1$ to obtain $\widehat{\alpha}_1^T S_1' + \widehat{\beta}_1^T S_1 A_1$

S_2' and S_2 are summaries of X_1, A_1, X_2
S_1' and S_1 are summaries of X_1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S_1, S_1', S_2, S_2' include a constant
  indicator to pick up the intercept  (or
  main effect of A_1, A_2).
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$\hat{Y}$ for subjects entering stage 2:

$$\hat{Y} = \hat{\alpha}_2^T S_2' + \max_{a_2} \hat{\beta}_2^T S_2 a_2$$

- $\hat{Y}$ is the estimated mean response in stage 2 as a function of variables that may include or be affected by stage 1 treatment.
- $\hat{Y}$ is the estimated mean response setting the stage 2 treatment equal to the "best" treatment (note *max* in formula).
- $\hat{Y}$ will be the dependent variable in the stage 1 regression for patients moving to stage 2

Patients who remain responding get a Yhat=Y

Patients who do not respond as some time after 2 months get a Yhat.

You could pool over time, use more flexible models and use penalization etc…… one could use log linear regression.

Yhat is a pseudo-outcome

Because because S2' contains all covariates for the step 1 regression this is a good Yhat. Otherwise you would want to use a

Yhat as in Murphy (2003) or Robins (2004). This Yhat is

Yhat= Y –beta2*S2*A2 + max_{a2} beta2*S2*a2

A Simple Version of Q-Learning – $a_j \in \{-1, 1\}$

- Stage 2 regression, (using Y as dependent variable) yields

$$\hat{\alpha}_2^T S_2' + \hat{\beta}_2^T S_2 a_2$$

- Stage 1 regression, (using $\hat{Y}$ as dependent variable) yields

$$\hat{\alpha}_1^T S_1' + \hat{\beta}_1^T S_1 a_1$$

If S_2′ contains (S_1A_1, S_1′) and actions are centered to have mean zero then Q-learning = opt. nested structural mean model(not doubly robust version of robins).

You could pool over time, use more flexible models and use penalization etc……

Yhat is a pseudo-outcome

Decision Rules:

$$\hat{d}_2(x_1, a_1, x_2) = \begin{cases} 1 & \text{for } \hat{\beta}_2^T s_2 > 0 \\ -1 & \text{for } \hat{\beta}_2^T s_2 \leq 0 \end{cases}$$

and

$$\hat{d}_1(x_1) = \begin{cases} 1 & \text{for } \hat{\beta}_1^T s_1 > 0 \\ -1 & \text{for } \hat{\beta}_1^T s_1 \leq 0 \end{cases}$$

where s_j is a vector summary of the observations (x's, a's) available at stage j.


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The \hat\beta2^TS_2 is like a decision
  boundary.
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Non-regularity

We'd like to conduct hypothesis tests concerning the parameters in β_1, e.g. $H_0 : c^T \beta_1 = 0$.

$\hat{Y}$ is non-differentiable in the estimators from the stage 2 regression–due to *max*.

$$\begin{aligned} \hat{Y} &= \hat{\alpha}_2^T S_2' + \max_{a_2} \hat{\beta}_2^T S_2 a_2 \\ &= \hat{\alpha}_2^T S_2' + |\hat{\beta}_2^T S_2| \qquad \text{if } a_2 \in \{-1, 1\} \end{aligned}$$

Why hypothesis tests? Reduce the variety of information that needs to be collected in clinical practice;

Would like to know when decision rules should allow clinical expertise

Standard errors derived by usual means are inconsistent except in unrealistic settings. (e.g. bootstrap, Taylor series etc)

Non-regularity

The distribution of $\widehat{\beta}_1$ is approximately normal in large samples if $P[\beta_2^T S_2 = 0] = 0$.

If $P[\beta_2^T S_2 = 0] > 0$ then the large sample distribution of $\widehat{\beta}_1$ is nonnormal.

(Usual bootstrap may not work: usual estimators of standard errors based on Taylor series may not work.....)

Practical implications: If beta_2^TS_2 is close to zero with non-zero probability (e.g. if the best treatments perform very similarly at stage 2) then in finite samples a standard use of the bootstrap can perform poorly.

It is not the non-normality that is the problem—it is the abrupt change from a normal to a nonnormal distribution that is problematic.

If things are even close get odd results

Robins, 2004 has a detailed discussion of this nonregularity.

Non-regularity –

Potentially problematic term in $c^T\sqrt{n}(\hat{\beta}_1 - \beta_1^*)$ is

$$c^T\hat{\Sigma}_1^{-1}\sqrt{n}P_n\left[S_1A_1\left(|S_2^T\hat{\beta}_2| - |S_2^T\beta_2^*|\right)\right]$$

- Not a problem if $|S_2^T\beta_2^*| >> 0$ with high probability
- We will want to form an *adaptive* confidence interval.

P_n means take average over sample

Adaptation is achieved via the use of a pretest –

We form an adaptive CI by combining a pretest of

$$H_0 : s_2^T \beta_2^* = 0$$

for each s_2 with the bootstrap.

Reject and conclude that $s_2^T \beta_2^* \neq 0$

if $t_n(s_2^T \hat{\beta}_2) > \sqrt{\log n}$

$$t_n(s_2^T \hat{\beta}_2) = \frac{\sqrt{n}|s_2^T \hat{\beta}_2|}{\sqrt{s_2^T \hat{\Sigma}_2 s_2}}$$

We eliminate Type I error by using sqrt(log n) as cutoff.

Pretests have been used by others to deal with non-regularity points in parameter space:

INFERENCE FOR PARAMETERS DEFINED BY MOMENT INEQUALITIES USING GENERALIZED MOMENT SELECTION

By

Donald W.K. Andrews and Gustavo Soares

October 2007

COWLES FOUNDATION DISCUSSION PAPER NO. 1631

Also

Robust Confidence Intervals in Nonlinear Regression under

Weak Identification

Xu Cheng

Department of Economics

Yale University

JOB MARKET PAPER

November 14, 2008

Non-regularity – We bootstrap an upper/lower bound for

$$c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) \right]$$

$$= c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) > \lambda_n} \right]$$

$$+ c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n} \right]$$

to form the limits of the adaptive CI. $\lambda_n = \sqrt{\log n}$

Discuss the problem of local alternatives and Type II error. We eliminate Type I error by using sqrt(log n) as cutoff.

See slides at end of talk for details of upper bound.

Non-regularity – We bootstrap an upper/lower bound of

$$c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) > \lambda_n} \right]$$

$$+ c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2 - S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n,\ S_2^T \beta_2^* = 0} \right]$$

$$+ c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n,\ S_2^T \beta_2^* \neq 0} \right]$$

to form the limits of the ACI.

$$\lambda_n = \sqrt{\log n}$$

Discuss the problem of local alternatives.

Overall Simulation Results

- Two stages, two treatments at each stage
  - Projection method is problematic
  - The ACI, Bootstrap and Soft-Thresholding perform well and approximately the same (the latter two can be shown to be inconsistent).
- Three stages, two treatments at each stage
  - Often the ACI, Bootstrap and Soft-Thresholding perform well and approximately the same.
  - In settings inducing anti-conservatism, the ACI performs better.

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projection CI proposed in Robins' (2004) (with estimated variance-covariance matrix);

soft-threshold method with percentile bootstrap proposed in Chakraborty and Murphy (2009) that is a generalization of work by Moodie and Richardson 2007

Centered percentile bootstrap (i.e. bootstrap $C^T\sqrt n(\boldsymbol{\hat\beta}_1-\boldsymbol{\beta}^*_1)$)

Samworth, Biometrika 2003 points out that the inconsistent bootstrap can often perform better and no worse than the m out of n bootstrap in these types of examples (even when sample is large).

Example –Three Stages, two treatments per stage (non-regular)

N	ACI	Bootstrap	Soft-Threshold	Projection Interval
150	91.5(.51)	90.3(.48)	86.9(.5)	---
300	94.4(.35)	93.0(.34)	88.1(.35)	100(1.1)
500	94.3(.27)	92.5(.27)	86.5(.27)	100(.8)

Coverage (length) 5000 data sets

Conf. Intervals for the regression coefficient of A_1 in stage 1

projection CI proposed in Robins' (2004) (with estimated variance-covariance matrix);

soft-threshold method with percentile bootstrap proposed in Chakraborty and Murphy (2009)

Centered percentile bootstrap (i.e. bootstrap $C^T\sqrt n(\boldsymbol{\hat\beta}_1-\boldsymbol{\beta}^*_1)$)

Simulation design:

S_1, S_2, S_3 are normal with variance 1 and conditional means (given prior observations) markovian,

e.g. E[S_3|S_1,S_2, A_1,A_2]=is a linear function of S_2, A_2, S_2A_2 (all coefficients are equal to .5)

Y is normal with variance 1 and conditional mean (given all prior observations) equal to

.25 +.25S_1 + (.25 +.25S_1)A_1 +.25 S_2 + .25A_1A_2 + (.25 +.25A_2)A_3

Analysis model is correct –with interactions: A_j (1, A_{j-1}, S_j)

P[(1, A_{j-1}, S_j) \beta_j^*=0]=.5

Example –Three Stages, two treatments per stage (regular but close to non-regular)

N	ACI	Bootstrap	Soft-Threshold
150	92.4(.51)	90.7(.48)	89.1(.5)
300	94.6(.35)	93.5(.34)	90.8(.35)
500	94.6(.27)	94.0(.27)	91.9(.27)

Coverage (length) 5000 data sets

Conf. Intervals for the regression coefficient of A_1 in stage 1

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Centered percentile bootstrap (i.e. bootstrap $C^T\sqrt n(\boldsymbol{\hat\beta}_1-\boldsymbol{\beta}^*_1)$)

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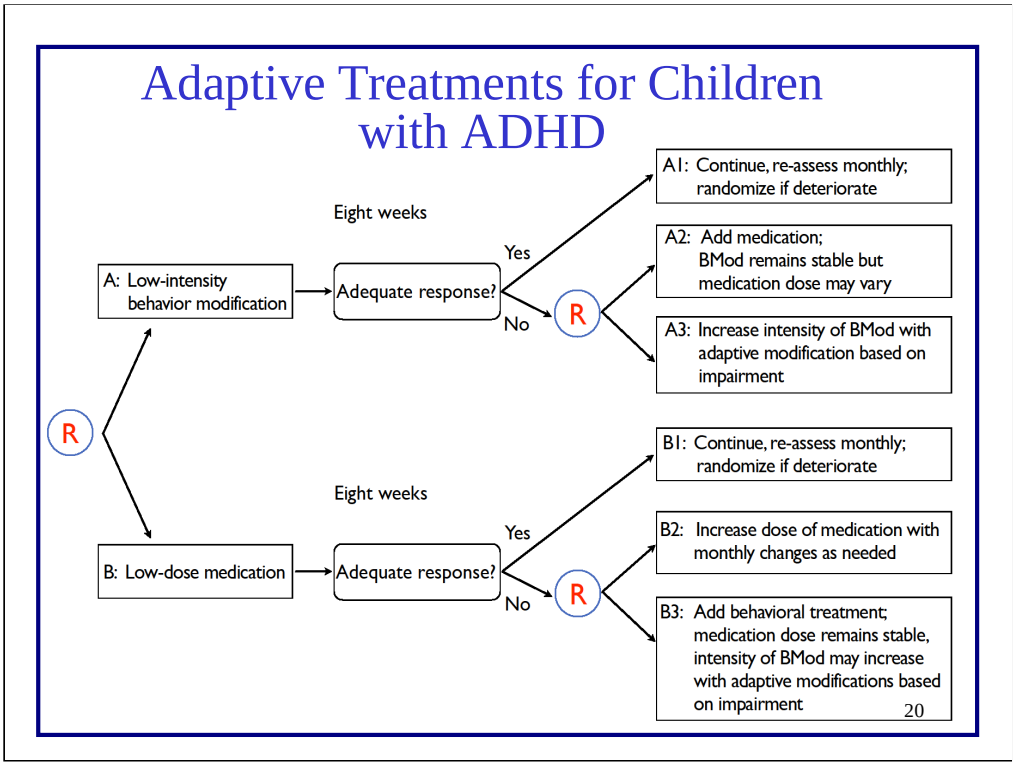
e.g. E[S_3|S_1,S_2, A_1,A_2]=is a linear function of S_2, A_2, S_2A_2 (all coefficients are equal to .5)

Y is normal with variance 1 and conditional mean (given all prior observations) equal to

.25 +.25S_1 + (.25 +.25S_1)A_1 +.25 S_2 + .25A_1A_2 + (.25 +.23A_2)A_3

Analysis model is correct –with interactions: A_j (1, A_{j-1}, S_j)

P[(1, A_{j-1}, S_j) \beta_j^*=.02]=.5



Adaptive Pharmacological and Behavioral Treatments for Children with ADHD: Sequencing, Combining, and Escalating Doses

(1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND (2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

Our outcome will be a teacher rated classroom performance recorded at 8 months. N=149 in original study

Adaptive Treatments for Children with ADHD

- $(X_1, A_1, R_1, X_2, A_2, Y)$
  - Y = end of year school performance
  - $R_1=1$ if responder; $=0$ if non-responder
  - X_2 includes the month of non-response, M_2, and a measure of adherence in stage 1 (S_2)
  - $S_2 =1$ if adherent in stage 1; $=0$, if non-adherent
  - X_1 includes baseline school performance, Y_0 and a measure of acceptability of medication (S_1)
  - $S_1 =1$ if medication known to be acceptable; $=0$, if this is unknown.

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2.

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

Adaptive Treatments for Children with ADHD

- Stage 2 regression for *Y*:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_1\beta_{23})$$

- Stage 1 outcome: $R_1 Y + (1 - R_1)\hat{Y}$

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_1\hat{\beta}_{23}|$$

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2.

Adaptive Treatments for Children with ADHD

- Stage 2 regression for Y :

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_1\beta_{23})$$

- Stage 1 regression for $\widehat{Y}$:

$$(1, Y_0, S_1)\alpha_1 + A_1(\beta_{11} + S_1\beta_{12})$$

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2.

Adaptive Treatments for Children with ADHD

- Stage 1 regression for $\hat{Y}$:

$$(1, Y_0, S_1)\alpha_1 + A_1(\beta_{11} + S_1\beta_{12})$$

- Interesting stage 1 contrast: should the knowledge that medication is highly acceptable, determine the best initial treatment in the sequence?

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2.

S1=1 if med is highly acceptable, =0 otherwise

Adaptive Treatments for Children with ADHD

ALTERED DATA!

- Contrast between stage 1 treatments for $S_1=1$

$$2(\beta_{11}+\beta_{12})$$

- Contrast between stage 1 treatments for $S_1=0$

$$2\beta_{11}$$

	Est.	95% ACI
$2(\beta_{11}+\beta_{12})$	-.40	(-1.13, 0.27)
$2\beta_{11}$	.49	(0.08, 0.90)

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2. S1=0 if no indication that med is highly acceptable S1=1 if we know that medication is highly acceptable by family/child.

A1=1 if BMOD, -1 if MED

Adaptive Treatments for Children with ADHD

Dynamic Treatment Regime Proposal:

- If there is no evidence that medication is highly acceptable begin with BMOD; otherwise select either BMOD or MED.
- If the child is nonresponse and was non-adherent, augment present treatment; if the child is nonresponse and was adherent, select either augmentation or intensification of current treatment.

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Since the primary analyses are being written up at this time we use altered data and do not disclose the precise measures of Y, S1,S2.

S1=1 if med is highly acceptable, =0 otherwise

Discussion

- There are multiple ways to form $\hat{Y}$
- Improving robustness of the adaptive CI by coding of A_j
- Confidence bands for the decision rules.
- Time-varying Y
- Improve adaptation by a pretest of

$$H_0: \ E[A_1|S_1, \ S_2] = 0?$$

This seminar can be found at:
http://www.stat.lsa.umich.edu/~samurphy/seminars/ICHPS01.22.10.ppt

Email Eric Laber or me for questions:
laber@umich.edu or samurphy@umich.edu

Non-regularity – We bootstrap an upper/lower bound on third term in

$$c^T\hat{\Sigma}_1^{-1}\sqrt{n}P_n\left[S_1A_1\left(|S_2^T\hat{\beta}_2| - |S_2^T\beta_2^*|\right)1_{t_n(S_2^T\hat{\beta}_2)>\lambda_n}\right]$$
$$+c^T\hat{\Sigma}_1^{-1}\sqrt{n}P_n\left[S_1A_1\left(|S_2^T\hat{\beta}_2 - S_2^T\beta_2^*|\right)1_{t_n(S_2^T\hat{\beta}_2)\leq\lambda_n,\ S_2^T\beta_2^*=0}\right]$$
$$+c^T\hat{\Sigma}_1^{-1}\sqrt{n}P_n\left[S_1A_1\left(|S_2^T\hat{\beta}_2| - |S_2^T\beta_2^*|\right)1_{t_n(S_2^T\hat{\beta}_2)\leq\lambda_n,\ S_2^T\beta_2^*\neq 0}\right]$$

to form the limits of the CI.

$$\lambda_n = \sqrt{\log n}$$

Discuss the problem of local alternatives.

Upper Bound on Third term --

$$c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n,\ S_2^T \beta_2^* \neq 0} \right]$$

$$\leq \max \left\{ c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \left(\hat{\beta}_2 - \beta_2^* \right)| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n,\ S_2^T \beta_2^* \neq 0} \right], \right.$$

$$\left. c^T \hat{\Sigma}_1^{-1} \sqrt{n} P_n \left[S_1 A_1 \left(|S_2^T \hat{\beta}_2| - |S_2^T \beta_2^*| \right) 1_{t_n(S_2^T \hat{\beta}_2) \leq \lambda_n,\ S_2^T \beta_2^* \neq 0} \right] \right\}$$

$$\lambda_n = \sqrt{\log n}$$

Discuss the problem of local alternatives.

Bootstrap Upper Bound

$$c^T\left(\hat{\Sigma}_1^{(b)}\right)^{-1}\sqrt{n}P_n^{(b)}\left[S_1A_1\left(\left|S_2^T\hat{\beta}_2^{(b)}\right|-\left|S_2^T\hat{\beta}_2\right|\right)1_{t_n(S_2^T\hat{\beta}_2^{(b)})>\lambda_n}\right]$$

$$+c^T\left(\hat{\Sigma}_1^{(b)}\right)^{-1}\sqrt{n}P_n^{(b)}\left[S_1A_1\left|S_2^T\left(\hat{\beta}_2^{(b)}-\hat{\beta}_2\right)\right|1_{t_n(S_2^T\hat{\beta}_2^{(b)})\le\lambda_n,\ t_n(S_2^T\hat{\beta}_2)\le\lambda_n}\right]$$

$$+\max\left\{c^T\left(\hat{\Sigma}_1^{(b)}\right)^{-1}\sqrt{n}P_n^{(b)}\left[S_1A_1\left|S_2^T\left(\hat{\beta}_2^{(b)}-\hat{\beta}_2\right)\right|1_{t_n(S_2^T\hat{\beta}_2^{(b)})\le\lambda_n,\ \ t_n(S_2^T\hat{\beta}_2)>\lambda_n}\right],\right.$$

$$\left.c^T\left(\hat{\Sigma}_1^{(b)}\right)^{-1}\sqrt{n}P_n^{(b)}\left[S_1A_1\left(\left|S_2^T\hat{\beta}_2^{(b)}\right|-\left|S_2^T\hat{\beta}_2\right|\right)1_{t_n(S_2^T\hat{\beta}_2^{(b)})\le\lambda_n,\ t_n(S_2^T\hat{\beta}_2)>\lambda_n}\right]\right\}$$

$$\lambda_n=\sqrt{\log n}$$

```
\begin{eqnarray*}
c^T\left(\hat{\Sigma}_{1}^{(b)}\right)^{-
  1}\sqrt{n}P_n^{(b)}\left[ S_1A_1
\left(|S_{2}^T\hat{\beta}_{2}^{(b)}| -
  |S_{2}^T\hat\beta_{2}|\right)
1_{t_n(S_{2}^T\hat\beta_{2}^{(b)})
>\lambda_n}
\right]\\
+c^T\left(\hat{\Sigma}_{1}^{(b)}\right)^{-
  1}\sqrt{n}P_n^{(b)}\left[ S_1A_1
\left|S_{2}^T\left(\hat{\beta}_{2}^{(b)} -
  \hat\beta_{2}\right)\right|
1_{t_n(S_{2}^T\hat\beta_{2}^{(b)})
\le\lambda_n,\ t_n(S_{2}^T\hat\beta_{2})
\le\lambda_n}
\right]
\end{eqnarray*}
\begin{eqnarray*}
+\max\left\{c^T\left(\hat{\Sigma}_{1}^{(b)}\ri
  ght)^{-1}\sqrt{n}P_n^{(b)}\left[ S_1A_1
\left|S_{2}^T\left(\hat{\beta}_{2}^{(b)}-
  \hat\beta_{2}\right)\right|
1_{t_n(S_{2}^T\hat\beta_{2}^{(b)})
```