An Adaptive Enrollment Strategy for the Identification of Maximum Treatment Effect Regions

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Outline of the talk

Motivation

- classic methods focus on estimation of population-level effects of treatments
- possible heterogeneity in treatment effect in the patient population calls for targeted therapeutics
- ethical issues may arise with adaptive randomization
- how to individuate baseline covariates of patients who would benefit most from a treatment?

In this talk

Main points we cover:

- a sequential-adaptive algorithm for patients enrollment in a randomized study
- identification of Maximum Treatment Effect Regions (MTER), building on related work (STEPP)
- research perspectives

Framework

- possibly large patient population, covariates available
- sampling approach: patients are invited to enroll
- two-arm randomized trial, fair coin toss randomization
- outcome is available quickly after randomization

Notation

Let

- U be the population
- $Y \in \mathbb{R}$ be the outcome of interest
- $Z \in \mathbb{R}^p$ be a covariate matrix
- n be the desired sample size

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- R be the number of steps (waves) of the algorithm
- $n_i, \sum_i n_i = n$ be the desired sample size at step $i = 1, .., R$
- $\Delta^{(i)}(Z)$ be the i-th step treatment effect
- $\pi^{(i)}(Z)$ be the inclusion probabilities at step i (summing to n_i)
- $\mathbf{s}^{(i)}$ denote the sample at step i and $\mathbf{s}_i = \bigcup_{m=1}^{i} \mathbf{s}^{(m)}$

The algorithm

$i = 1$ select a WOR sample $\mathbf{s}^{(1)}$ from $U^{(1)} = U$ with probabilities $\pi^{(1)}(Z)$ and randomize to treatment A or B

- estimate treatment effect for units in $U^{(2)} = U \setminus \mathbf{s}^{(1)}$ based on $\mathbf{s}^{(1)}$
- set $\pi^{(2)}(Z) \propto \hat{\Delta}^{(1)}(Z)$

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$i > 1$ select a WOR sample $\mathbf{s}^{(i)}$ from $U^{(i)} = U \setminus \mathbf{s}_{i-1}$ with probabilities $\pi^{(i)}(Z)$ and randomize to treatment A or B

- estimate treatment effect for units in $U^{(i+1)} = U \setminus \mathbf{s}_i$ based on $\mathbf{s}_i$
- set $\pi^{(i+1)}(Z) \propto \hat{\Delta}^{(i)}(Z)$

iterate until $i = R$ or some other stopping rule has been satisfied.

Estimation

Step	$U^{(i)}$	$\Delta^{(i)}(Z)$
1	U	$\Delta^{(1)}(Z) \equiv \Delta(Z)$
2	$U \setminus \mathbf{s}_1$	$\Delta^{(2)}(Z)$
3	$U \setminus \mathbf{s}_2$	$\Delta^{(3)}(Z)$
$\vdots$	$\vdots$	$\vdots$
R	$U \setminus \mathbf{s}_{R-1}$	$\Delta^{(R)}(Z)$

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R	$U \setminus \mathbf{s}_{R-1}$	$\Delta^{(R)}(Z)$

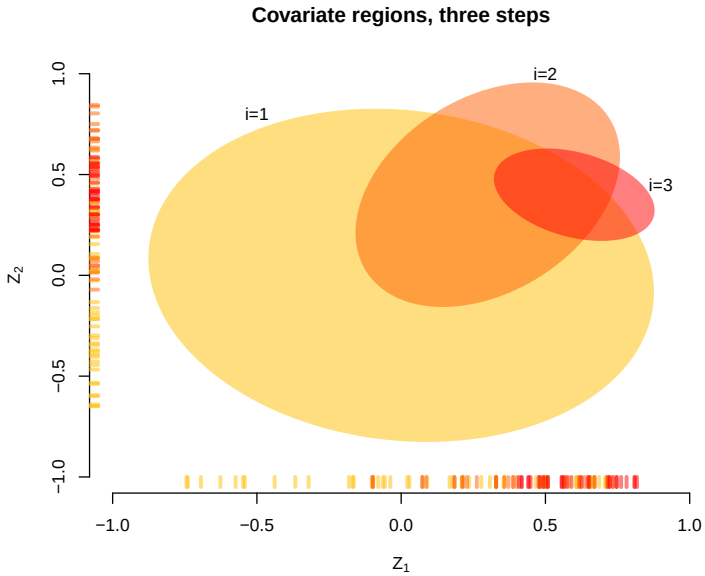
$$\hat{\Delta}(Z) = \sum_{i=1}^{R} w_i \hat{\Delta}^{(i)}(Z)$$

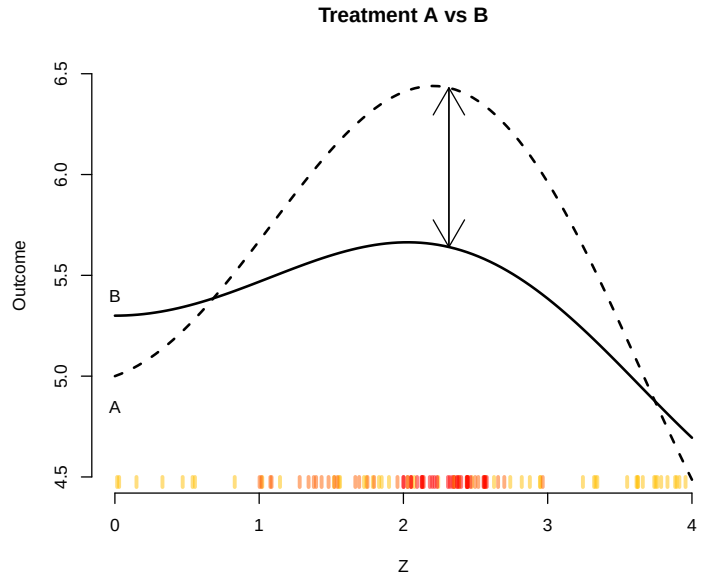
$$E\left[\hat{\Delta}^{(i)}(Z)\right] = \Delta^{(i)}(Z), \quad w_i : E\left[\hat{\Delta}(Z)\right] = \Delta(Z) \tag{1}$$

MTER identification

- the last sample likely contains individuals for which $P(Z \subseteq \text{MTER})$ is high
- inspection of the path in Z might give some useful insight
- non-trivial boundaries for MTER are possible
- confidence bands for treatment effect narrower for $Z \subseteq \text{MTER}$

Visual depiction

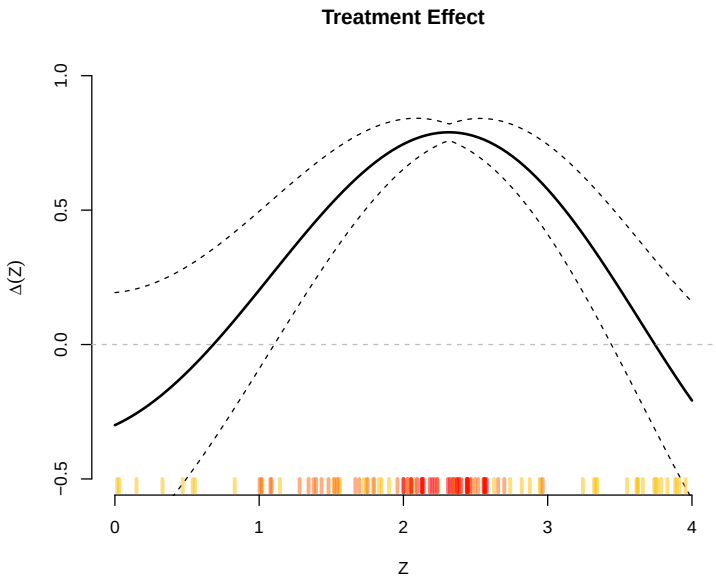




Z_1, Z_2 are covariates

Z is some covariates synthesis

$\Delta(Z)$ is the treatment effect



Conclusions and research perspectives I

- while oversampling a specific subgroup, inference is still possible w.r.t. the whole patient population
- by targeting individuals most likely to benefit and keeping randomization probabilities equal, typical ethical issues are avoided
- constraints can be added to the $\pi^{(i)}$s to focus on subjects with a minimum guaranteed positive outcome probability under both treatments $\rightarrow$ potential increase in recruitment rates
- MTER can be non-trivial regions of the covariate space
- sequential monitoring can lead to early conclusion of the trial when treatment effect is deemed either too large or too small

Conclusions and research perspectives II

- not suitable for survival data
- developments to determine properties of related estimators for treatment effect and for MTER (e.g., confidence regions)
- potentially high-dimensional and time-varying Z
- validation of the method on data from already concluded trials
- high flexibility of the algorithm, numerous potential applications

We're open to suggestions!

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....thank you!