

# Optimal Two-Stage Adaptive Enrichment Designs, using Sparse Linear Programming

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Working paper giving full results available here:  
<http://biostats.bepress.com/jhubiostat/paper273/>

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# Problem Motivation

Goal: Testing Treatment Effects in Two Subpopulations and the Overall Population in Adaptive Enrichment Designs

Example:

- Treating resistant HIV. Recent HIV drugs (maraviroc, raltegravir) have shown stronger benefit in those with lower phenotypic sensitivity to background therapy.

We assume two, predefined, subpopulations that partition the overall population.

# Multiple Testing Problem: Null Hypotheses Definition

Define three treatment effects of interest:

- $\Delta_1$ : Mean Treatment Effect for Subpopulation 1  
(i.e., difference between population mean of the primary outcome under treatment and under control)
- $\Delta_2$ : Mean Treatment Effect for Subpopulation 2
- $\Delta_C = p_1\Delta_1 + (1 - p_1)\Delta_2$ :  
Mean Treatment Effect for Combined Population

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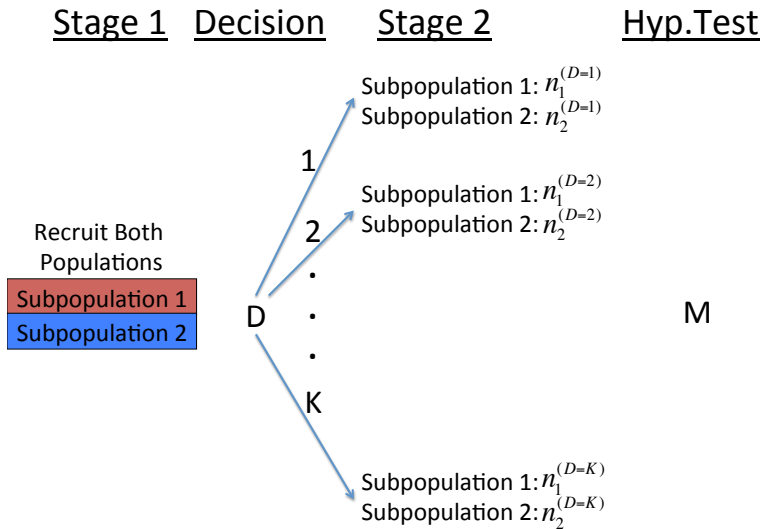
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**Goal: construct adaptive enrichment design  $D$  and multiple testing procedure  $M$  for:**

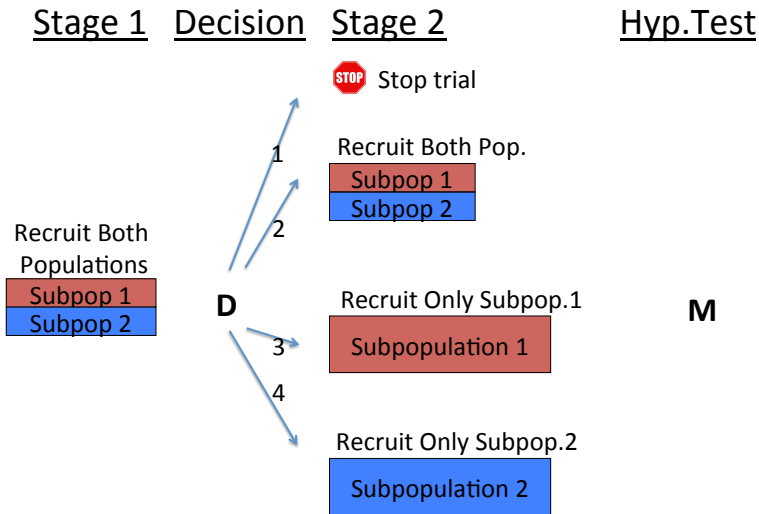
- $H_{01} : \Delta_1 \leq 0$ ,
- $H_{02} : \Delta_2 \leq 0$ ,
- $H_{0C} : p_1\Delta_1 + (1 - p_1)\Delta_2 \leq 0$ ,

that strongly controls familywise Type I error rate, and is optimal in sense defined below.

# General Two-Stage Adaptive Enrichment Design

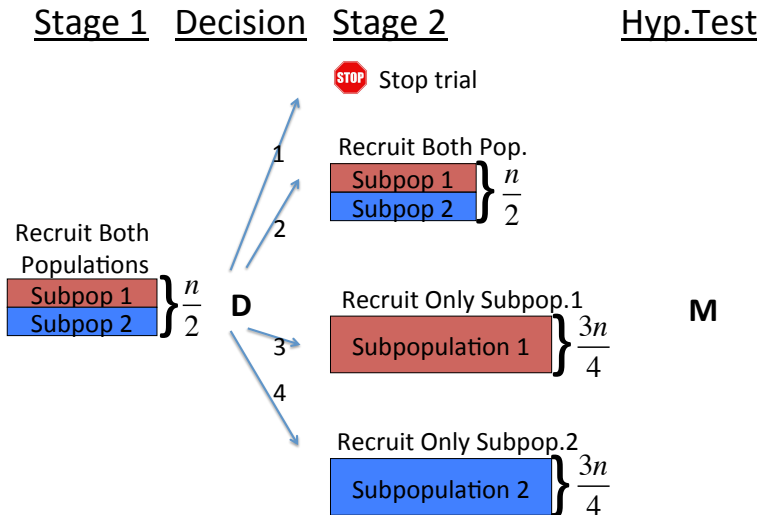


# Example Two-Stage Adaptive Enrichment Design



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$n$  = total sample size if both subpopulations enrolled in stage 2.



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Assume known variances and normally distributed outcomes; subpopulation cumulative sample sizes and z-statistics and are then sufficient statistics for  $\Delta_1, \Delta_2, \Delta_C$ .



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Decision rule  $D$  is map from  $\mathbf{Z}^{(1)} = (Z_1^{(1)}, Z_2^{(1)})$  to possible decisions  $\mathcal{D}$ .

Multiple testing procedure  $M$  is map from  $\mathbf{Z}^{(F)} = (Z_1^{(F)}, Z_2^{(F)})$  and decision  $D$  to set of null hypotheses rejected (if any).

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Power at alternative  $\Delta_1, \Delta_2$  to reject  $H_{01}$  is

$$\Pr_{(\Delta_1, \Delta_2)}[M(\mathbf{Z}^{(F)}, D(\mathbf{Z}^{(1)})) \text{ rejects } H_{01}].$$

User specifies: (i) loss function  $L(D, M; \Delta_1, \Delta_2)$ , e.g., total sample size; and (ii) distribution  $\Lambda$  on alternatives  $(\Delta_1, \Delta_2)$ .

# Constrained Bayes Optimization Problem

**Problem inputs:**  $p_1$ ; set of possible stage 2 decisions;  $\sigma_1^2, \sigma_2^2$ ; clinically meaningful min. treatment effect  $\Delta^{\min}$ ; loss function  $L$ ; distribution  $\Lambda$  on alternatives  $(\Delta_1, \Delta_2)$ ;  $\alpha, \beta_1, \beta_2, \beta_C$ .

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**Constrained Bayes Opt. Problem:** Find pair  $(D, M)$  minimizing:

$$\int E_{(\Delta_1, \Delta_2)}[L(D, M; \Delta_1, \Delta_2)] d\Lambda(\Delta_1, \Delta_2),$$

under **familywise Type I error constraints:**

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and **power constraints:**

$$\Pr_{(\Delta^{\min}, 0)}[M \text{ rejects } H_{01}] \geq 1 - \beta_1.$$

$$\Pr_{(0, \Delta^{\min})}[M \text{ rejects } H_{02}] \geq 1 - \beta_2.$$

$$\Pr_{(\Delta^{\min}, \Delta^{\min})}[M \text{ rejects } H_{0C}] \geq 1 - \beta_C.$$

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- 2 For each decision  $d \in \{1, \dots, K\}$ , discretize rejection regions  $\mathbb{R}^2$  into small rectangles  $\mathcal{R}'_d$ ; for any  $r' \in \mathcal{R}'_d$ , enforce that if  $D = d$ , multiple testing procedure  $M$  rejects same set of hypotheses for any  $(Z_1^{(F)}, Z_2^{(F)}) \in r'$ .
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Discretized opt. problem is not convex. However, we construct reparametrization that is sparse, linear program:

$$\max_{\mathbf{x}} \mathbf{c}^T \mathbf{x} \quad \text{s.t.} \quad \mathbf{A} \mathbf{x} \leq \mathbf{b}.$$

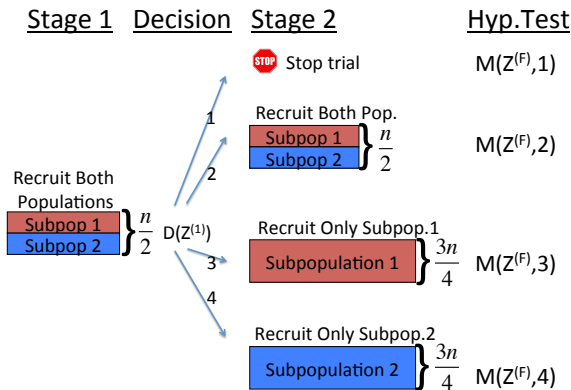
We apply advanced optimization methods to solve this.

# Example

$p_1 = 1/2$ ,  $\alpha = 0.05$ ,  $\sigma_1^2 = \sigma_2^2$ .  $L$  = total sample size. Prior  $\Lambda$  equally weighted pt. masses at  $(\Delta_1, \Delta_2)$  equal to  $(0, 0)$ ,  $(\Delta^{\min}, 0)$ ,  $(0, \Delta^{\min})$ ,  $(\Delta^{\min}, \Delta^{\min})$ .

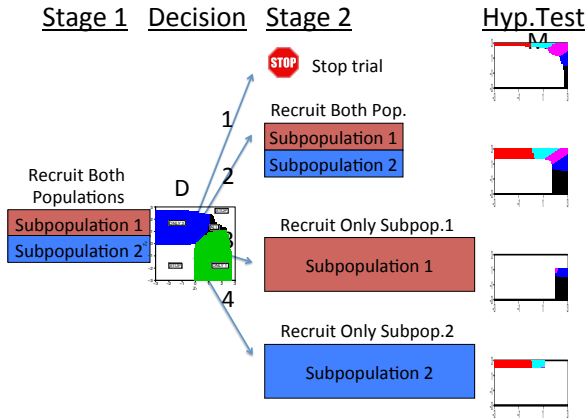
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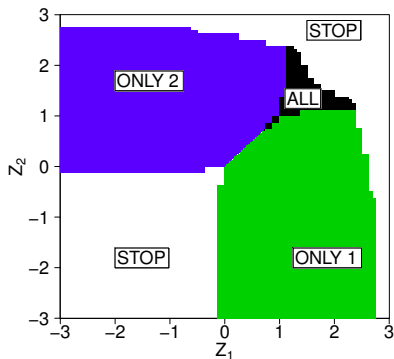
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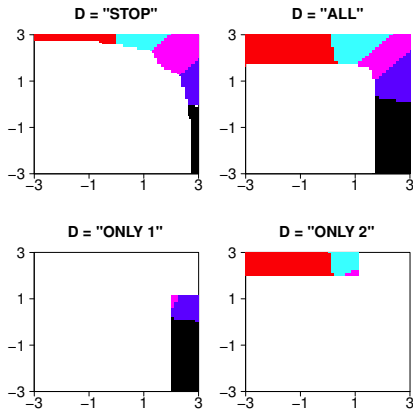


# Approximately Optimal Solution

Decision Rule for Stage 2 Enrollment:

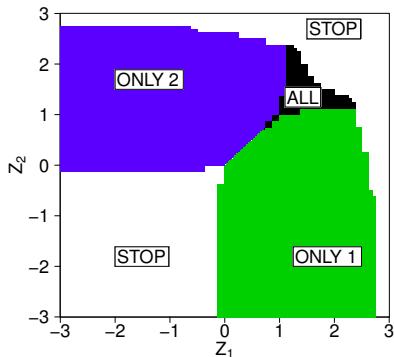


Rejection Regions under Each Decision: (in terms of  $Z_1^{(F)}$ ,  $Z_2^{(F)}$ )

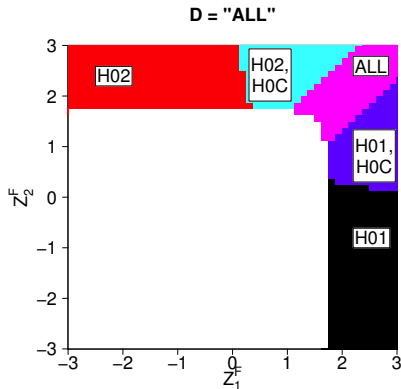


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Decision Rule to Enroll Stage 2:

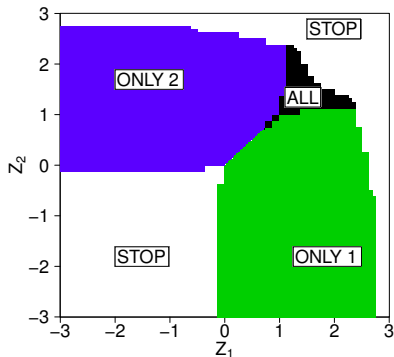


Rejection Regions for Decision:

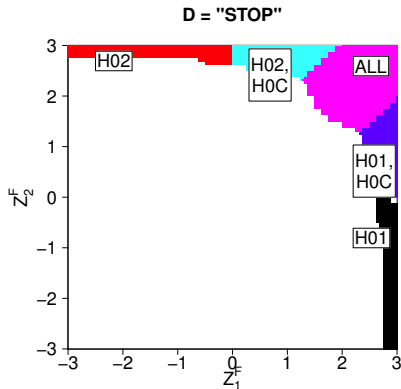


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Decision Rule to Enroll Stage 2:

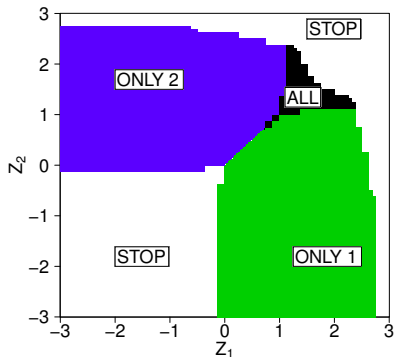


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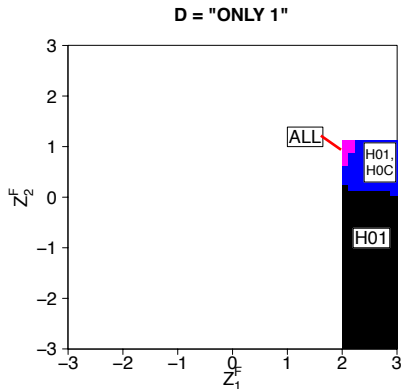


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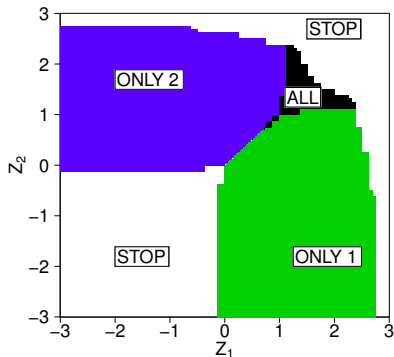
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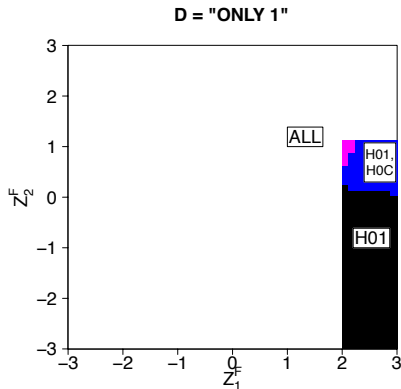


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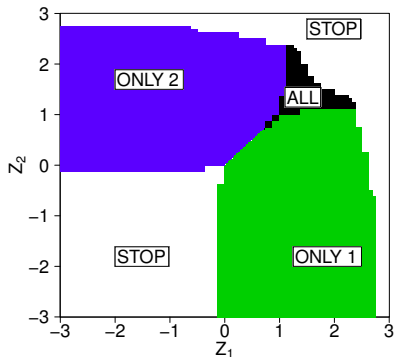


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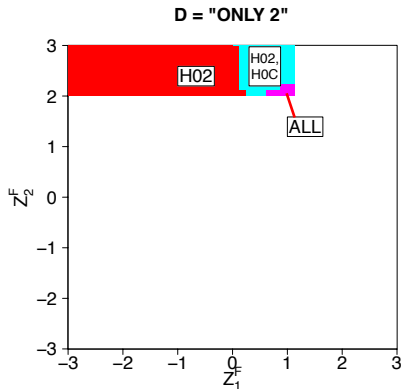


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Decision Rule to Enroll Stage 2:



Rejection Regions for Decision:



# Power Comparison

Compare to adaptive enrichment design using p-value combination approach (Bauer and Köhne, 1994), with Dunnett intersection test and inverse-normal combination function. Early stopping is incorporated using O'Brien-Fleming boundaries for each intersection null hypothesis. Decision rule for stage 2:

- if combined population statistic  $(Z_1^{(1)} + Z_2^{(1)})/\sqrt{2} > t_c$ , enroll both subpop.
- else, enroll from each subpopulation  $s$  for which  $Z_s^{(1)} > t$ .

Consider  $\beta = \beta_1 = \beta_2 = \beta_C$ . For each power threshold  $1 - \beta$ , we optimized over  $t, t_c$  to minimize expected sample size under the power constraints.  $n$  = total sample size if both enrolled stage 2.

**Table:** Minimum of  $\int ESS d\Lambda$ , as power constraint  $1 - \beta$  varied.

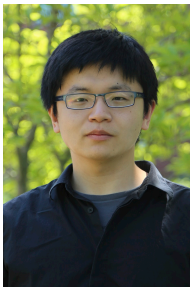
Required Power $1 - \beta$ :	70%	74%	78%	82%
Comparator	$0.96n$	$1.02n$	infeasible	infeasible
Optimal	$0.79n$	$0.84n$	$0.92n$	$1.03n$

Rosenblum, M., Fang, X., and Liu, H., Optimal, Two Stage, Adaptive Enrichment Designs for Randomized Trials Using Sparse Linear Programming (2014). Johns Hopkins University, Dept. of Biostatistics Working Papers. Working Paper 273.  
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Rosenblum, M., Liu, H., and Yen, E.-H. (2014), Optimal Tests of Treatment Effects for the Overall Population and Two Subpopulations in Randomized Trials, using Sparse Linear Programming, *Journal of American Statistical Association, Theory and Methods Section*, Volume 109. Issue 507. 1216-1228.

Rosenblum, M. (In Press), Adaptive Randomized Trial Designs that Cannot be Dominated by Any Standard Design at the Same Total Sample Size. *Biometrika*.

## Collaborators



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