Optimal Tests of Treatment Effects for the Overall Population and Two Subpopulations in Randomized Trials, using Sparse Linear Programming

Michael Rosenblum
Johns Hopkins Bloomberg School of Public Health

Joint work with:
Han Liu and Xingyuan (Ethan) Fang at Princeton University,
En-Hsu Yen at University of Texas, Austin

June 13, 2017

Outline

Part I: **Standard (Non-adaptive) Randomized Trial**; Goal is to Optimize Multiple Testing Procedure

Outline

Part I: **Standard (Non-adaptive) Randomized Trial**; Goal is to Optimize Multiple Testing Procedure

Part II: **Adaptive Enrichment Designs**; Goal is to Simultaneously Optimize Decision Rule and Multiple Testing Procedure

Part I: **Standard (Non-adaptive) Randomized Trial**
Problem Motivation

Goal: Testing Treatment Effects in Two Subpopulations and the Overall Population in Randomized Trials

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.
We optimize analysis at end of randomized trial.

Multiple Testing Problem: Null Hypotheses Definition

Define three treatment effects of interest:

- Δ_1: Mean Treatment Effect for Subpopulation 1
  (i.e., difference between population mean of the primary outcome under treatment and under control)
- Δ_2: Mean Treatment Effect for Subpopulation 2
- $\Delta_C = p_1\Delta_1 + (1 - p_1)\Delta_2$:
  Mean Treatment Effect for Combined Population

Multiple Testing Problem: Null Hypotheses Definition

Define three treatment effects of interest:

- Δ_1: Mean Treatment Effect for Subpopulation 1
  (i.e., difference between population mean of the primary outcome under treatment and under control)
- Δ_2: Mean Treatment Effect for Subpopulation 2
- $\Delta_C = p_1\Delta_1 + (1 - p_1)\Delta_2$:
  Mean Treatment Effect for Combined Population

Goal: construct multiple testing procedure M for null hypotheses:

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

that strongly controls familywise Type I error rate,
and optimizes power in sense described below.

Multiple Testing Problem: Optimization Criteria

Goal: multiple testing procedure for:

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

Assume known variances σ_1^2, σ_2^2 and normally distributed outcomes; subpopulation z-statistics Z_1, Z_2 are then sufficient statistics.

Let $\Delta^{\min} > 0$ denote minimum, clinically meaningful treatment benefit. Let L denote loss function and Λ denote prior on (Δ_1, Δ_2).

Constrained Bayes Optimization Problem

For loss function L and prior Λ on parameters (Δ_1, Δ_2),

find multiple testing procedure M minimizing Bayes criterion:

$$\int E_{\Delta_1,\Delta_2} L[M(Z_1, Z_2); \Delta_1, \Delta_2] d\Lambda(\Delta_1, \Delta_2),$$

Constrained Bayes Optimization Problem

For loss function L and prior Λ on parameters (Δ_1, Δ_2),

find multiple testing procedure M minimizing Bayes criterion:

$$\int E_{\Delta_1,\Delta_2} L[M(Z_1, Z_2); \Delta_1, \Delta_2] d\Lambda(\Delta_1, \Delta_2),$$

under **familywise Type I error constraints**:

$$\sup_{(\Delta_1,\Delta_2)\in\mathbb{R}^2} P_{\Delta_1,\Delta_2}[M \text{ rejects any true null hypothesis}] \leq \alpha,$$

Constrained Bayes Optimization Problem

For loss function L and prior Λ on parameters (Δ_1, Δ_2),

find multiple testing procedure M minimizing Bayes criterion:

$$\int E_{\Delta_1,\Delta_2} L[M(Z_1, Z_2); \Delta_1, \Delta_2] d\Lambda(\Delta_1, \Delta_2),$$

under **familywise Type I error constraints**:

$$\sup_{(\Delta_1,\Delta_2)\in\mathbb{R}^2} P_{\Delta_1,\Delta_2}[M \text{ rejects any true null hypothesis}] \leq \alpha,$$

and **power constraint for combined population**:

$$P_{\Delta^{\min},\Delta^{\min}}[M \text{ rejects } H_{0C}] \geq 1 - \beta.$$

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our solution:

1. Discretize decision region $\mathbb{R}^2$ into small rectangles $\mathcal{R}$; for any $r \in \mathcal{R}$, enforce test procedure M rejects same set of hypotheses for any $(Z_1, Z_2) \in r$.
2. Discretize constraints into fine grid on boundaries of null spaces.

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our solution:

1. Discretize decision region $\mathbb{R}^2$ into small rectangles $\mathcal{R}$; for any $r \in \mathcal{R}$, enforce test procedure M rejects same set of hypotheses for any $(Z_1, Z_2) \in r$.
2. Discretize constraints into fine grid on boundaries of null spaces.

Discretized, constrained Bayes opt. problem can be represented as sparse, linear program:

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

Even in simple example below, $\mathbf{A}$ is 1,757,113 $\times$ 1,506,006 matrix. We solve this by tailoring advanced optimization methods to the structure of this problem (and leveraging sparseness of $\mathbf{A}$).

Optimal Procedures at $\alpha = 0.05$; $1 - \beta = 0.9$ and 0.88

Example: $p_1 = 1/2$; $\sigma_1^2 = \sigma_2^2$. **Loss function** penalizes 1 unit for failure to reject H_{0k} at $\Delta_k \geq \Delta^{\min}$. **Prior**: equally weighted pt. masses at $(0, 0), (\Delta^{\min}, 0), (0, \Delta^{\min}), (\Delta^{\min}, \Delta^{\min})$. **Sample size** is min s.t. UMP test of H_{0C} has 90% power at $(\Delta^{\min}, \Delta^{\min})$.

Optimal Procedures at $\alpha = 0.05$; $1 - \beta = 0.9$ and 0.88

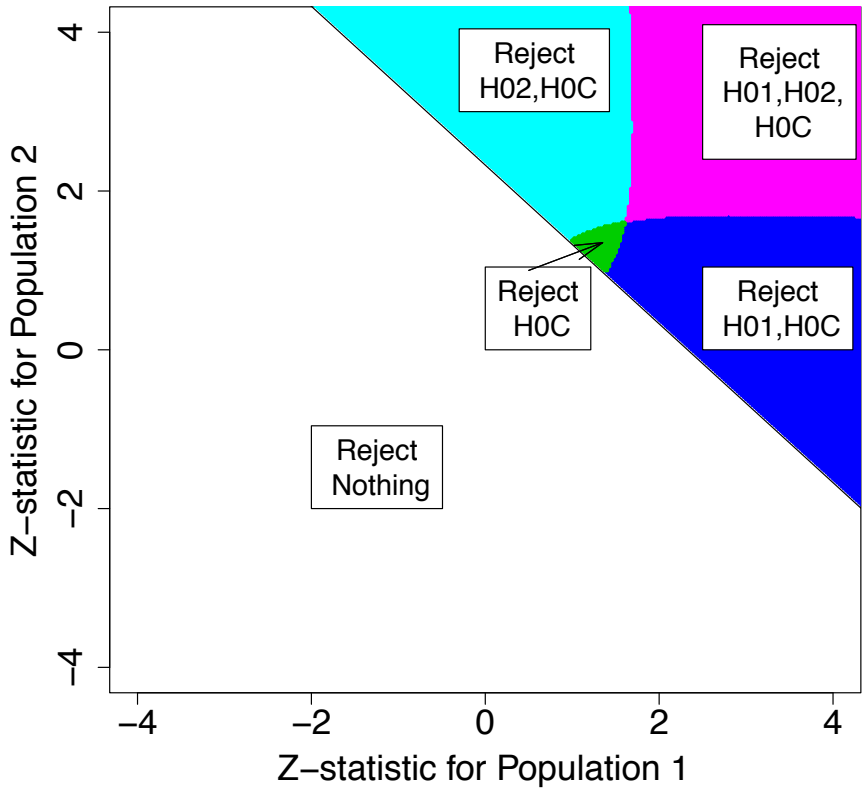
Example: $p_1 = 1/2$; $\sigma_1^2 = \sigma_2^2$. **Loss function** penalizes 1 unit for failure to reject H_{0k} at $\Delta_k \geq \Delta^{\min}$. **Prior**: equally weighted pt. masses at $(0, 0), (\Delta^{\min}, 0), (0, \Delta^{\min}), (\Delta^{\min}, \Delta^{\min})$. **Sample size** is min s.t. UMP test of H_{0C} has 90% power at $(\Delta^{\min}, \Delta^{\min})$.

H_{0C} Power Constr. $1 - \beta = 0.90$

Optimal Procedures at $\alpha = 0.05$; $1 - \beta = 0.9$ and 0.88

Example: $p_1 = 1/2$; $\sigma_1^2 = \sigma_2^2$. **Loss function** penalizes 1 unit for failure to reject H_{0k} at $\Delta_k \geq \Delta^{\min}$. **Prior**: equally weighted pt. masses at $(0, 0), (\Delta^{\min}, 0), (0, \Delta^{\min}), (\Delta^{\min}, \Delta^{\min})$. **Sample size** is min s.t. UMP test of H_{0C} has 90% power at $(\Delta^{\min}, \Delta^{\min})$.

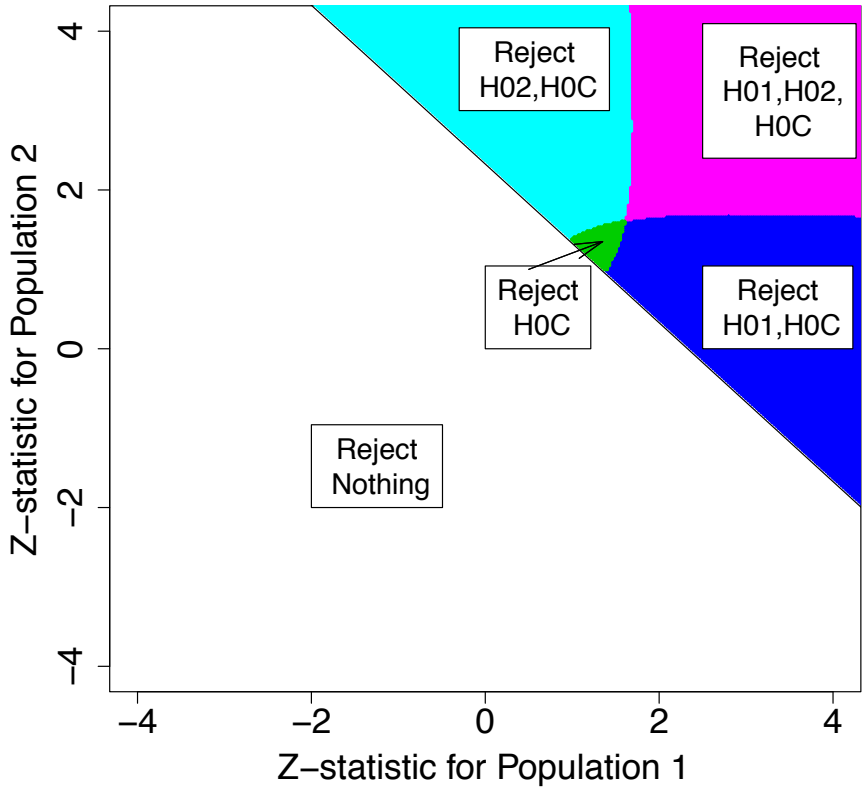
H_{0C} Power Constr. $1 - \beta = 0.90$



Optimal Procedures at $\alpha = 0.05$; $1 - \beta = 0.9$ and 0.88

Example: $p_1 = 1/2$; $\sigma_1^2 = \sigma_2^2$. **Loss function** penalizes 1 unit for failure to reject H_{0k} at $\Delta_k \geq \Delta^{\min}$. **Prior**: equally weighted pt. masses at $(0,0), (\Delta^{\min}, 0), (0, \Delta^{\min}), (\Delta^{\min}, \Delta^{\min})$. **Sample size** is min s.t. UMP test of H_{0C} has 90% power at $(\Delta^{\min}, \Delta^{\min})$.

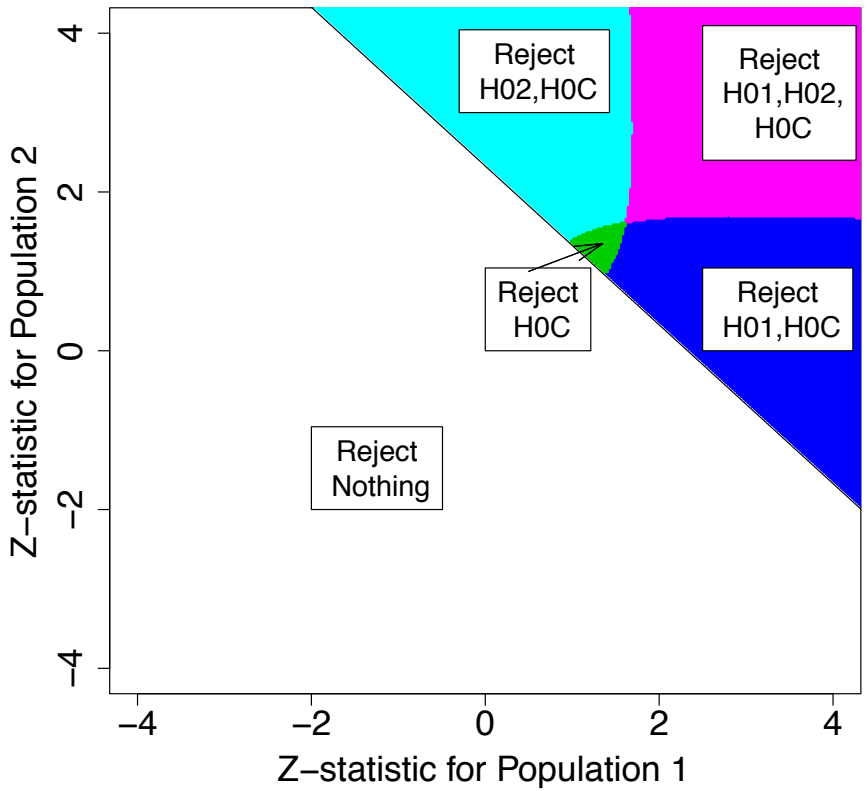
H_{0C} Power Constr. $1-\beta = 0.90$ H_{0C} Power Constr. $1-\beta = 0.88$



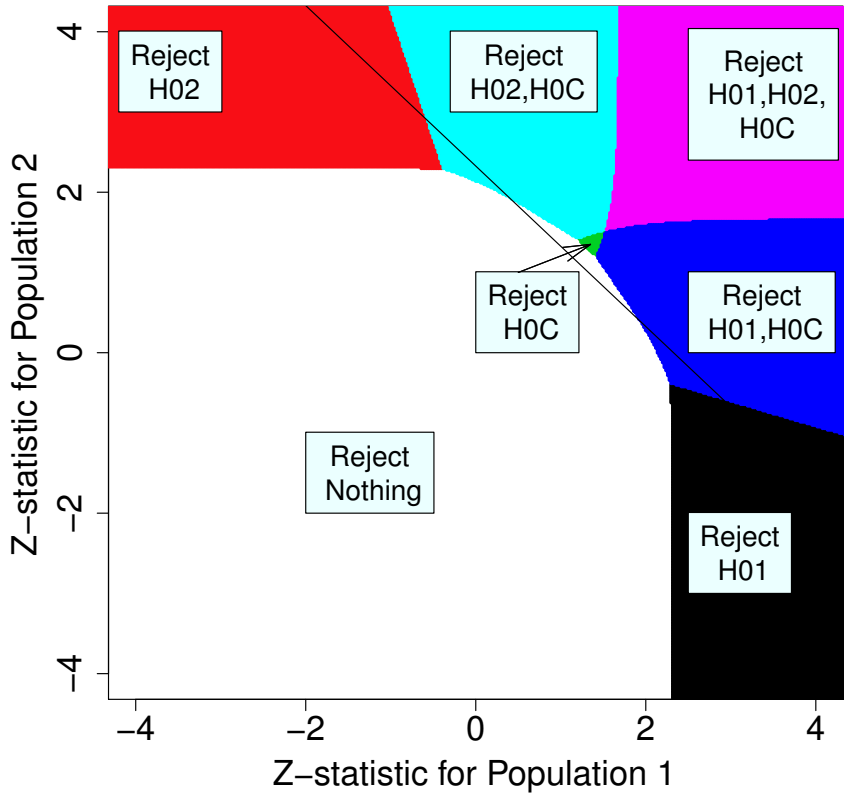
Optimal Procedures at $\alpha = 0.05$; $1 - \beta = 0.9$ and 0.88

Example: $p_1 = 1/2$; $\sigma_1^2 = \sigma_2^2$. **Loss function** penalizes 1 unit for failure to reject H_{0k} at $\Delta_k \geq \Delta^{\min}$. **Prior**: equally weighted pt. masses at $(0,0), (\Delta^{\min}, 0), (0, \Delta^{\min}), (\Delta^{\min}, \Delta^{\min})$. **Sample size** is min s.t. UMP test of H_{0C} has 90% power at $(\Delta^{\min}, \Delta^{\min})$.

H_{0C} Power Constr. $1-\beta = 0.90$



H_{0C} Power Constr. $1-\beta = 0.88$



Power for optimal multiple testing procedures at $1-\beta = 0.9$ and $1-\beta = 0.88$.

Let $m^*(1-\beta)$ denote optimal procedure having power $1-\beta$ for H_{0C} at alternative $(\Delta^{\min}, \Delta^{\min})$.

Power Comparison of Two Optimal Procedures

	Procedure: $m^*(0.9)$	$m^*(0.88)$
Power for H_{01} at $(\Delta^{\min}, 0)$:	0.39	0.51
Power for H_{02} at $(0, \Delta^{\min})$:	0.39	0.51
Power for H_{0C} at $(\Delta^{\min}, \Delta^{\min})$:	0.90	0.88

Part II: **Adaptive Enrichment Designs**:

Part II: **Adaptive Enrichment Designs**; Goal is to Simultaneously Optimize Decision Rule and Multiple Testing Procedure

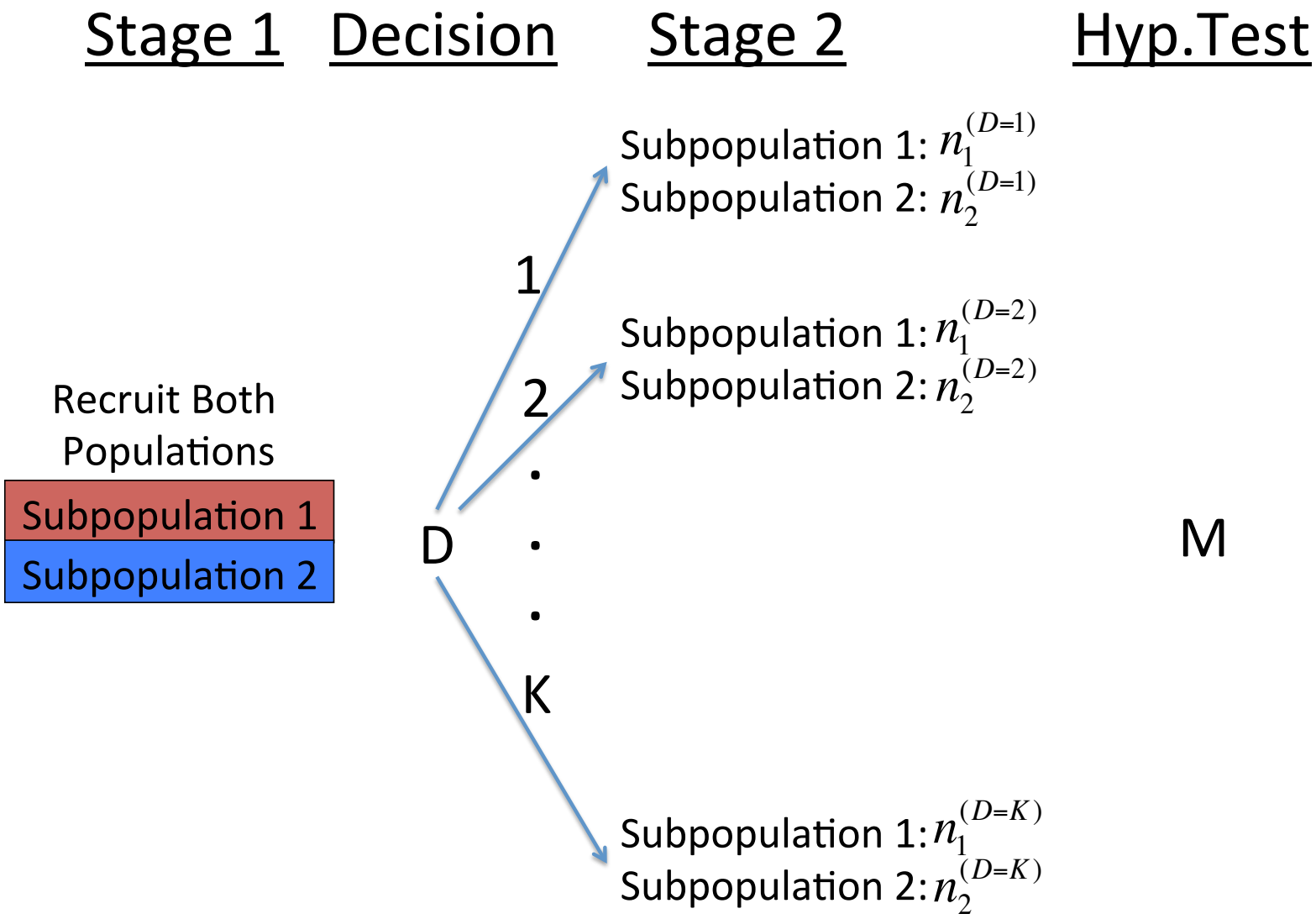
Part II: **Adaptive Enrichment Designs**; Goal is to Simultaneously Optimize Decision Rule and Multiple Testing Procedure

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

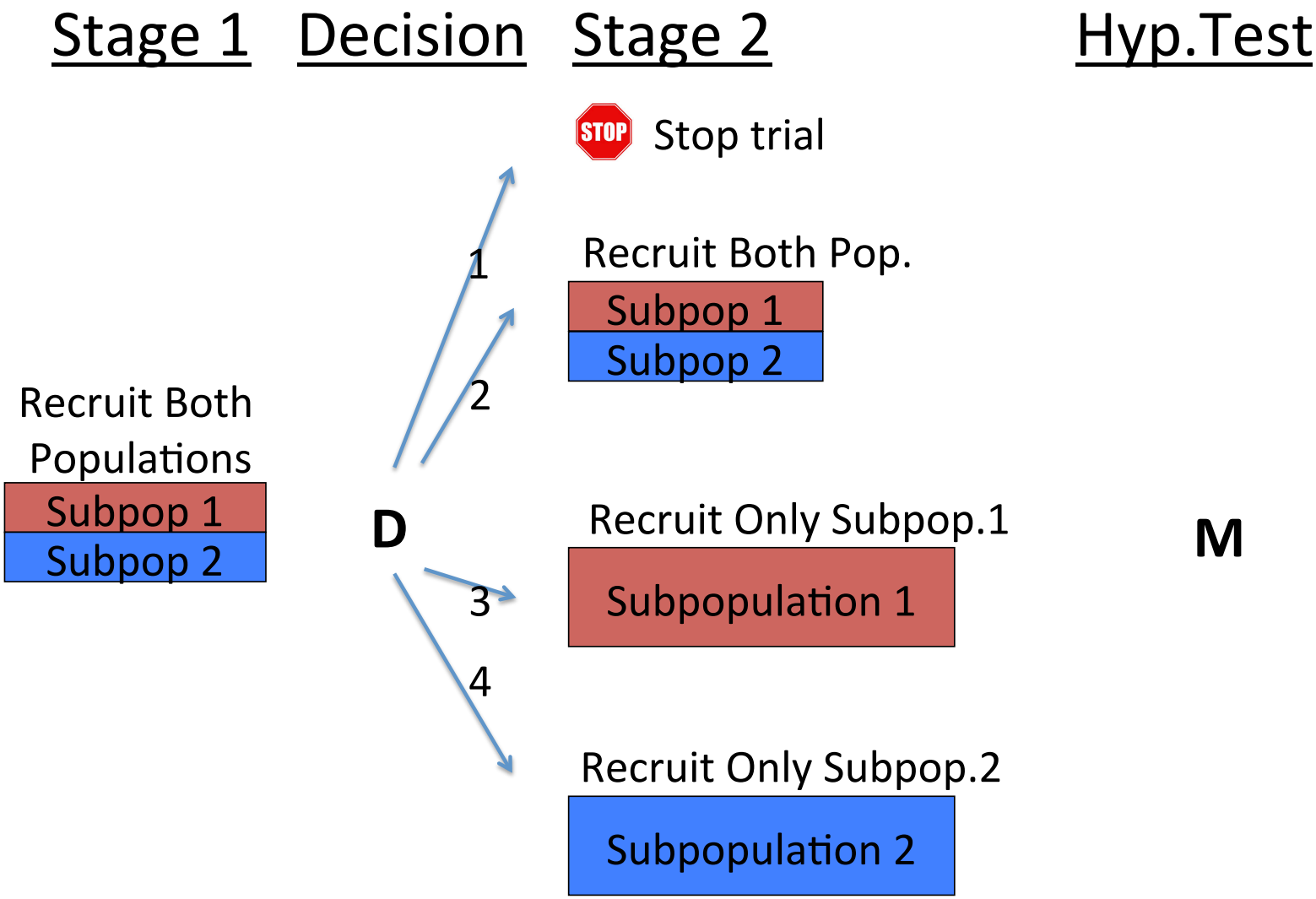
- $H_{01} : \Delta_1 \leq 0,$
- $H_{02} : \Delta_2 \leq 0,$
- $H_{0C} : p_1\Delta_1 + (1 - p_1)\Delta_2 \leq 0,$

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

General Two-Stage Adaptive Enrichment Design

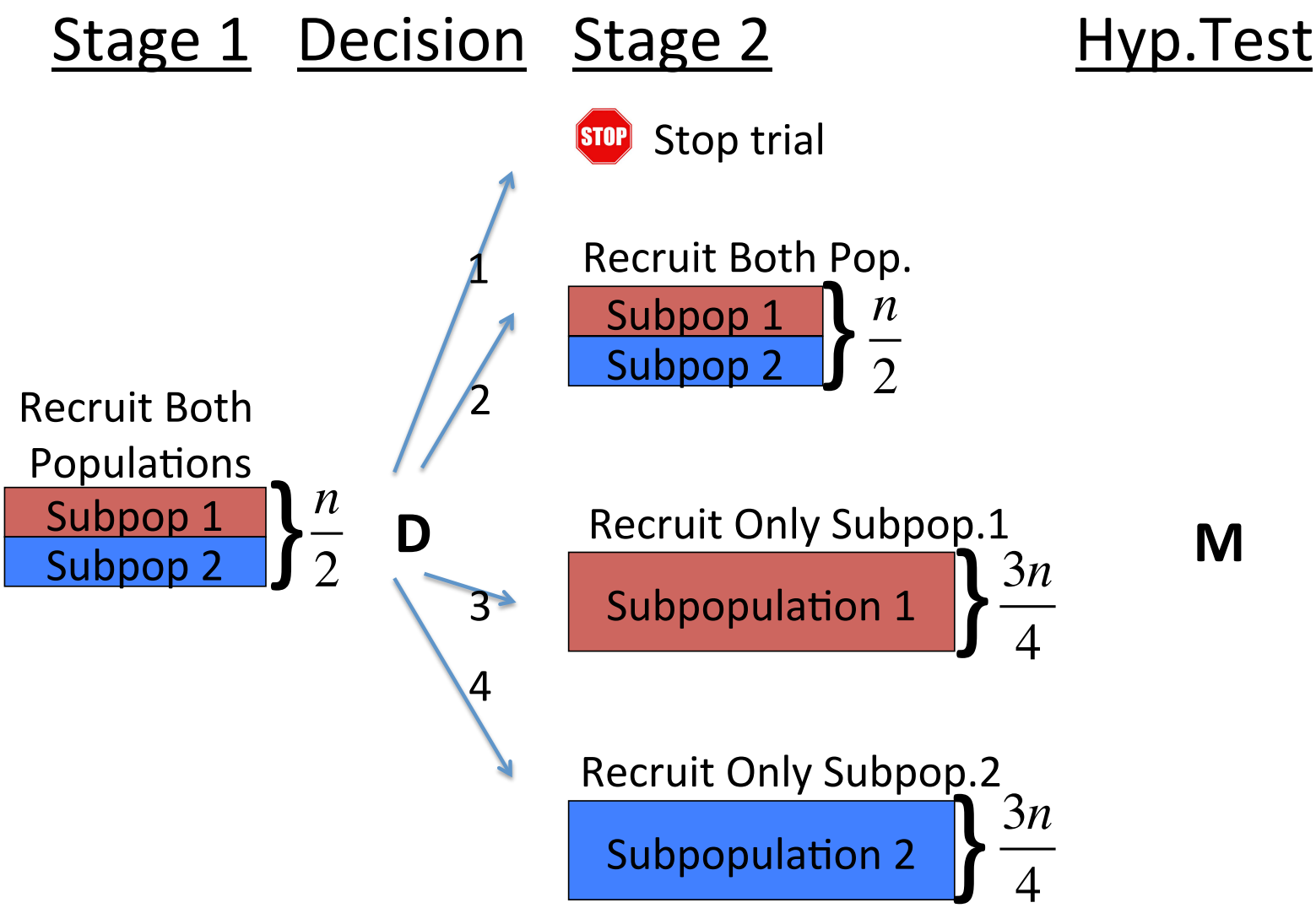


Example Two-Stage Adaptive Enrichment Design



Example Two-Stage Adaptive Enrichment Design

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



Two-Stage Adaptive Enrichment Design

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

Two-Stage Adaptive Enrichment Design

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

- $Z_s^{(1)}$: z-statistic for subpopulation s at end of stage 1;
- $Z_s^{(F)}$: Final, cumulative z-statistic for subpop. s at end of stage 2.

Two-Stage Adaptive Enrichment Design

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

- $Z_s^{(1)}$: z-statistic for subpopulation s at end of stage 1;
- $Z_s^{(F)}$: Final, cumulative z-statistic for subpop. s at end of stage 2.

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

Two-Stage Adaptive Enrichment Design

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

- $Z_s^{(1)}$: z-statistic for subpopulation s at end of stage 1;
- $Z_s^{(F)}$: Final, cumulative z-statistic for subpop. s at end of stage 2.

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

User specifies: (i) loss function $L(D, M; \Delta_1, \Delta_2)$, e.g., total sample size; and (ii) distribution Λ on alternatives (Δ_1, Δ_2).

Constrained Bayes Optimization Problem

Problem inputs: p_1; set of possible stage 2 decisions; σ_1^2, σ_2^2; clinically meaningful min. treatment effect $\Delta^{\min}$; loss function L; distribution Λ on alternatives (Δ_1, Δ_2); $\alpha, \beta_1, \beta_2, \beta_C$.

Recall $D = D(\mathbf{Z}^{(1)})$ and $M = M(\mathbf{Z}^{(F)}, D(\mathbf{Z}^{(1)}))$.

Constrained Bayes Optimization Problem

Problem inputs: p_1; set of possible stage 2 decisions; σ_1^2, σ_2^2; clinically meaningful min. treatment effect $\Delta^{\min}$; loss function L; distribution Λ on alternatives (Δ_1, Δ_2); $\alpha, \beta_1, \beta_2, \beta_C$.

Recall $D = D(\mathbf{Z}^{(1)})$ and $M = M(\mathbf{Z}^{(F)}, D(\mathbf{Z}^{(1)}))$.

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**:

$$\sup_{(\Delta_1,\Delta_2)\in\mathbb{R}^2} \Pr_{\Delta_1,\Delta_2}[M \text{ rejects any true null hypothesis}] \leq \alpha,$$

Constrained Bayes Optimization Problem

Problem inputs: p_1; set of possible stage 2 decisions; σ_1^2, σ_2^2; clinically meaningful min. treatment effect $\Delta^{\min}$; loss function L; distribution Λ on alternatives (Δ_1, Δ_2); $\alpha, \beta_1, \beta_2, \beta_C$.

Recall $D = D(\mathbf{Z}^{(1)})$ and $M = M(\mathbf{Z}^{(F)}, D(\mathbf{Z}^{(1)}))$.

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**:

$$\sup_{(\Delta_1,\Delta_2)\in\mathbb{R}^2} \Pr_{\Delta_1,\Delta_2}[M \text{ rejects any true null hypothesis}] \leq \alpha,$$

and **power constraints**:

$$\begin{aligned} \Pr_{\Delta^{\min},0}[M \text{ rejects } H_{01}] &\geq 1-\beta_1. \\ \Pr_{0,\Delta^{\min}}[M \text{ rejects } H_{02}] &\geq 1-\beta_2. \\ \Pr_{\Delta^{\min},\Delta^{\min}}[M \text{ rejects } H_{0C}] &\geq 1-\beta_C. \end{aligned}$$

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our solution:

1. Discretize decision region $\mathbb{R}^2$ into small rectangles $\mathcal{R}$; for any $r \in \mathcal{R}$, enforce decision rule D makes same decision for any $(Z_1^{(1)}, Z_2^{(1)}) \in r$.
2. For each decision $d \in \{1, \ldots, K\}$, 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 $(Z_1^{(F)}, Z_2^{(F)}) \in r'$.
3. Discretize Type I error constraints into fine grid on boundaries of null spaces.

Our Method to Solve Optimization Problem

Computational challenge: continuum of Type I error constraints. (It's not enough to satisfy only at global null $(\Delta_1, \Delta_2) = (0, 0)$.)

Our solution:

1. Discretize decision region $\mathbb{R}^2$ into small rectangles $\mathcal{R}$; for any $r \in \mathcal{R}$, enforce decision rule D makes same decision for any $(Z_1^{(1)}, Z_2^{(1)}) \in r$.
2. For each decision $d \in \{1, \ldots, K\}$, 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 $(Z_1^{(F)}, Z_2^{(F)}) \in r'$.
3. Discretize Type I error constraints into fine grid on boundaries of null spaces.

Discretized opt. problem is not convex. However, we construct reparametrization that is sparse, linear program:

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

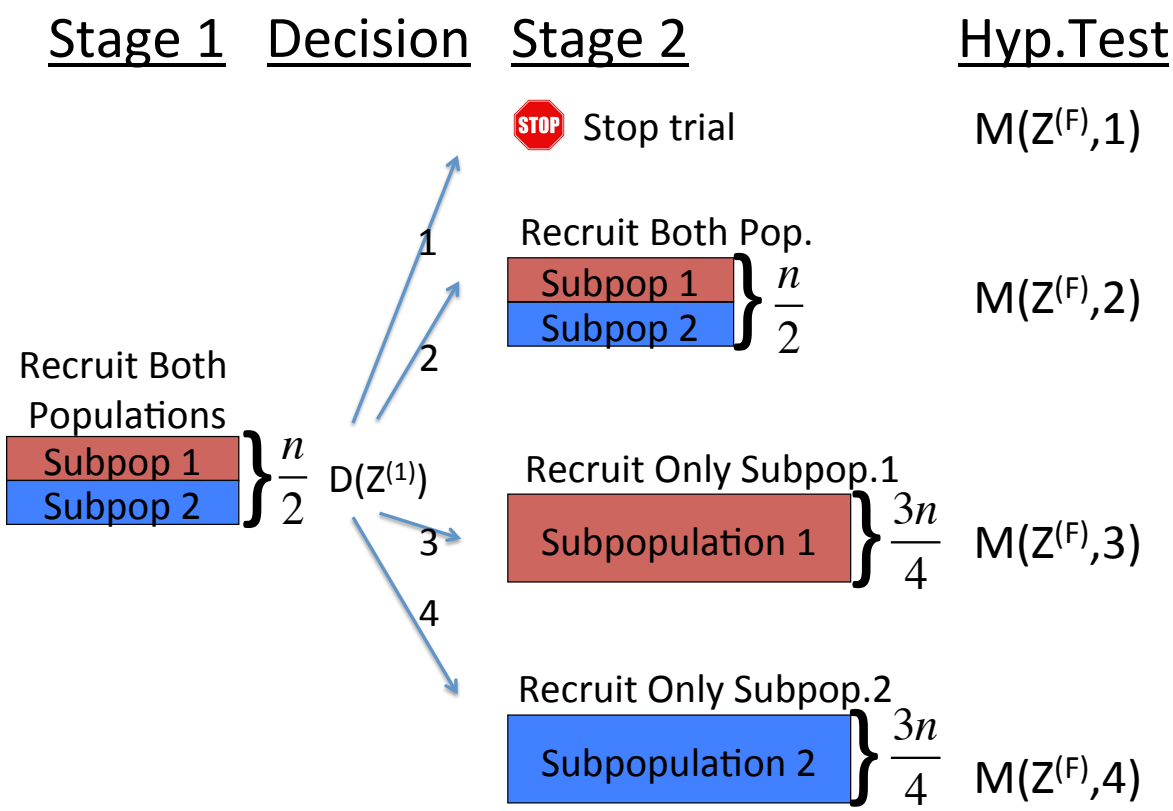
We apply advanced optimization methods to solve this.

Example

$p_1 = 1/2$, $\alpha = 0.05$, $\sigma_1^2 = \sigma_2^2$. L =total sample size. Prior Λ equally weighted pt. masses at (Δ_1, Δ_2) equal to $(0, 0), (\Delta^{\min}, 0)$, $(0, \Delta^{\min})$, $(\Delta^{\min}, \Delta^{\min})$.

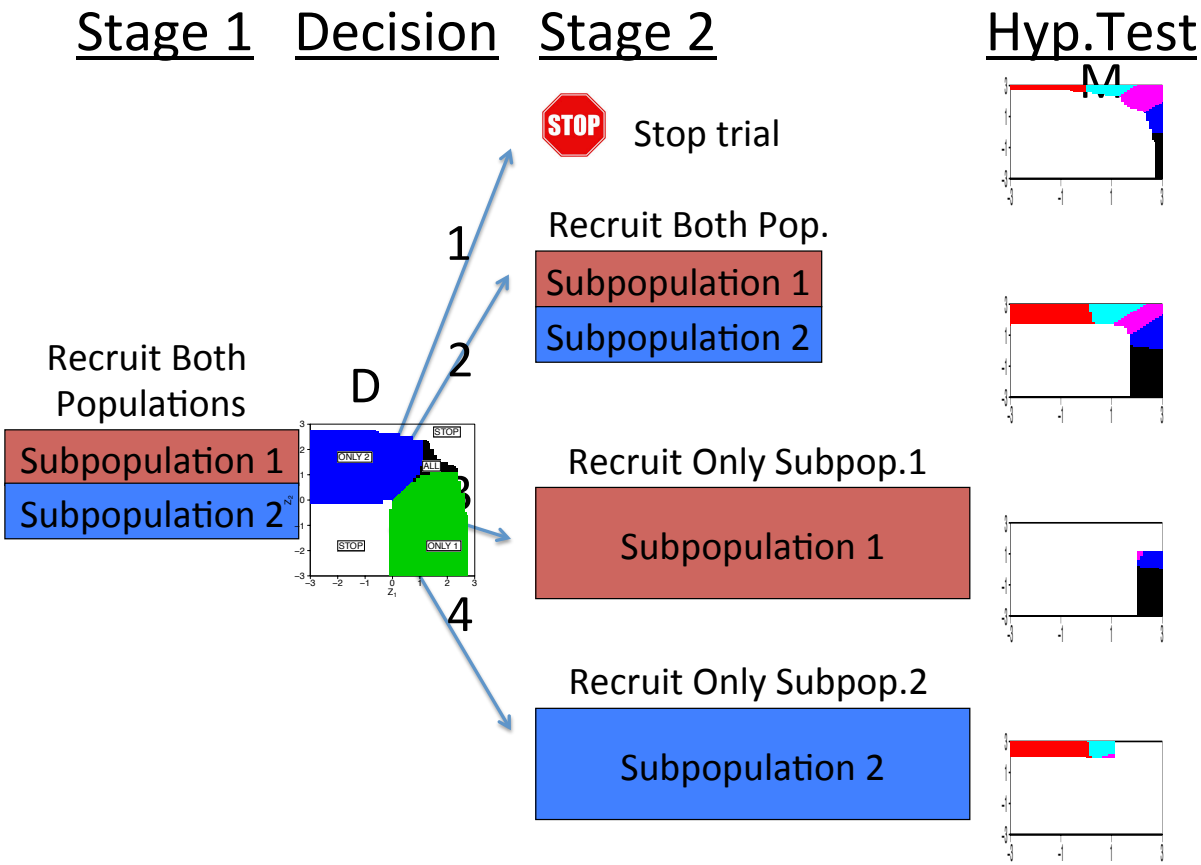
Example

$p_1 = 1/2$, $\alpha = 0.05$, $\sigma_1^2 = \sigma_2^2$. L =total sample size. Prior Λ equally weighted pt. masses at (Δ_1, Δ_2) equal to $(0,0)$, $(\Delta^{\min}, 0)$, $(0, \Delta^{\min})$, $(\Delta^{\min}, \Delta^{\min})$. Sample size n is min s.t. standard design satisfies each power constraint at $1 - \beta_j = 0.64$ for $j \in \{1, 2, C\}$. Set each $1 - \beta_j = 0.82$.



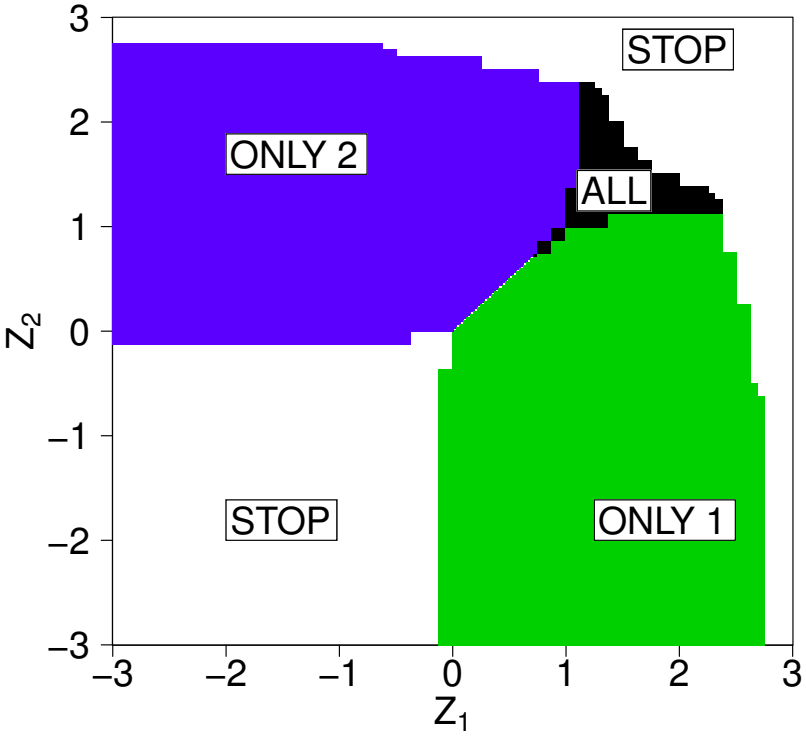
Example

$p_1 = 1/2$, $\alpha = 0.05$, $\sigma_1^2 = \sigma_2^2$. L =total sample size. Prior Λ equally weighted pt. masses at (Δ_1, Δ_2) equal to $(0,0)$, $(\Delta^{\min}, 0)$, $(0, \Delta^{\min})$, $(\Delta^{\min}, \Delta^{\min})$. Sample size n is min s.t. standard design satisfies each power constraint at $1 - \beta_j = 0.64$ for $j \in \{1, 2, C\}$. Set each $1 - \beta_j = 0.82$.

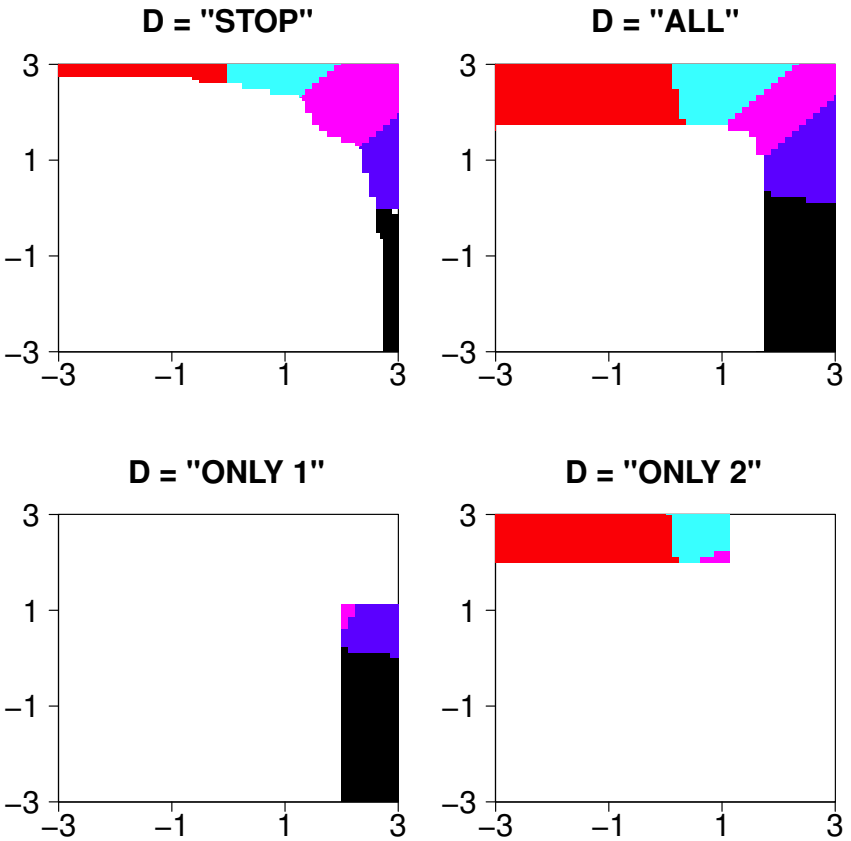


Approximately Optimal Solution

Decision Rule for Stage 2 Enrollment:

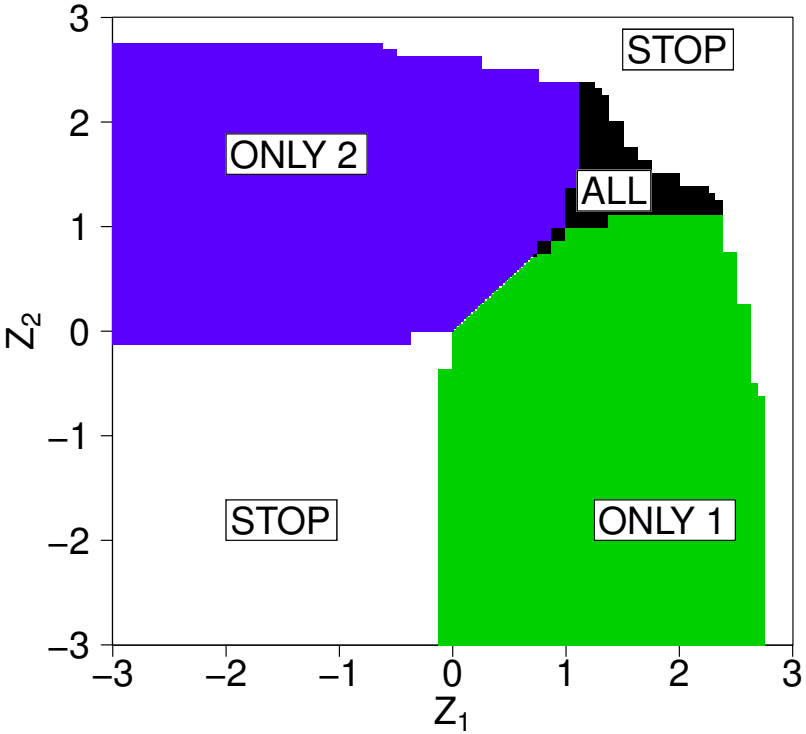


Rejection Regions under Each Decision: (in terms of $Z_1^{(F)}, Z_2^{(F)}$)

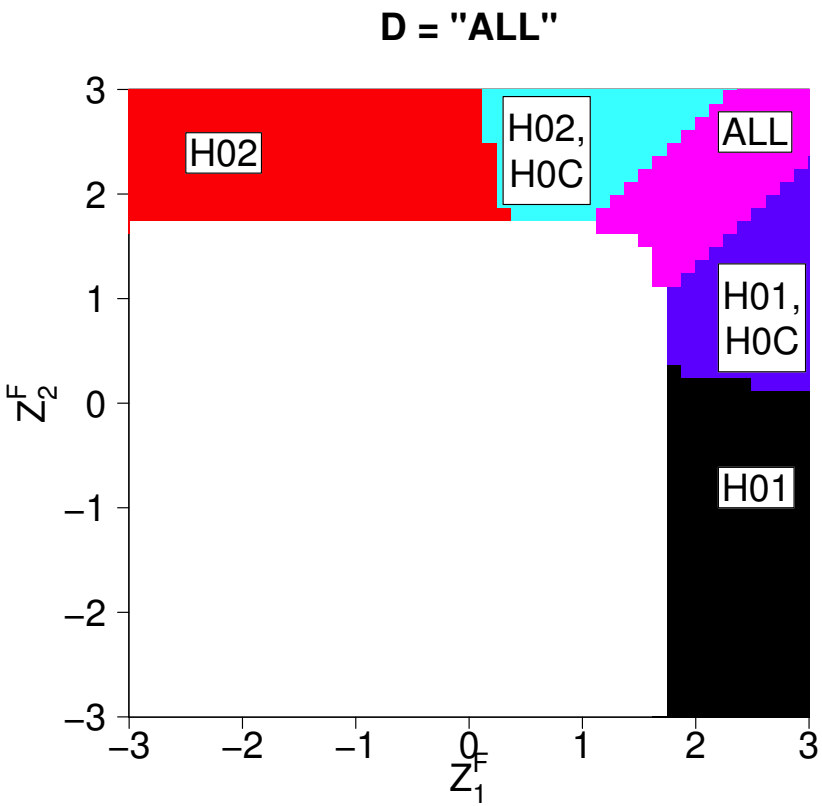


Approximately Optimal Solution

Decision Rule to Enroll Stage 2:

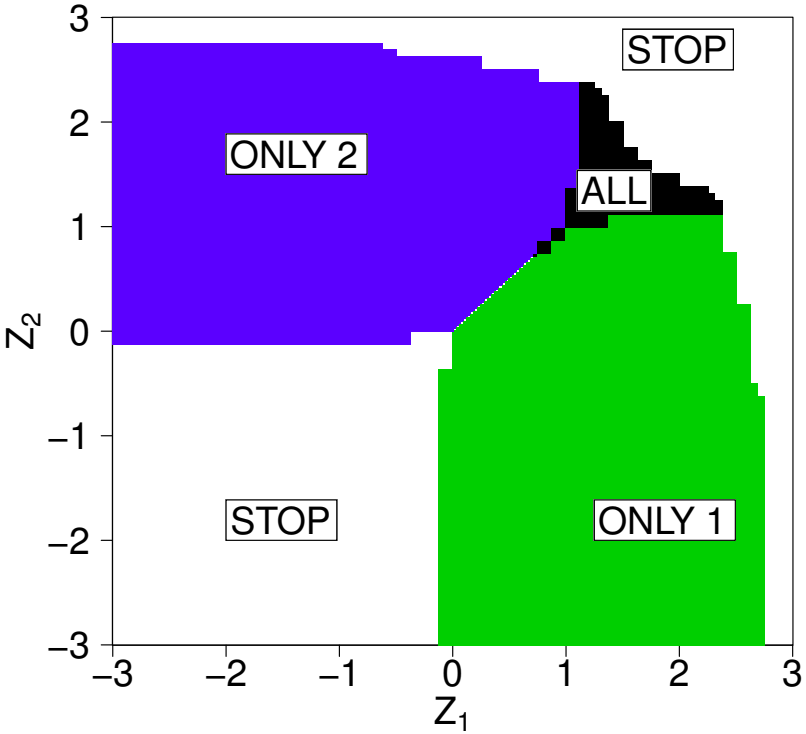


Rejection Regions for Decision:

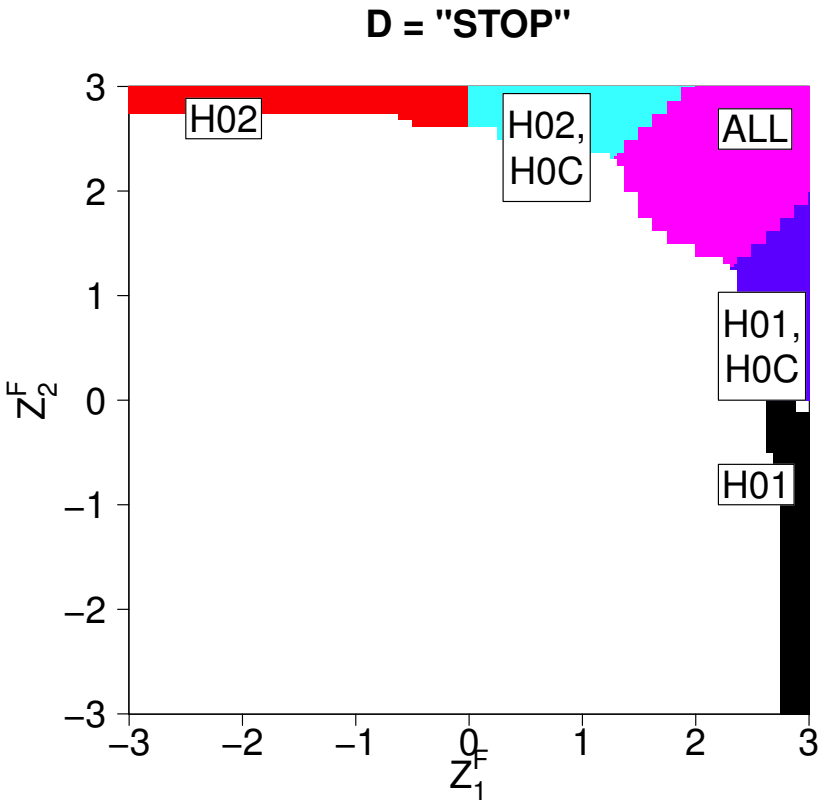


Approximately Optimal Solution

Decision Rule to Enroll Stage 2:

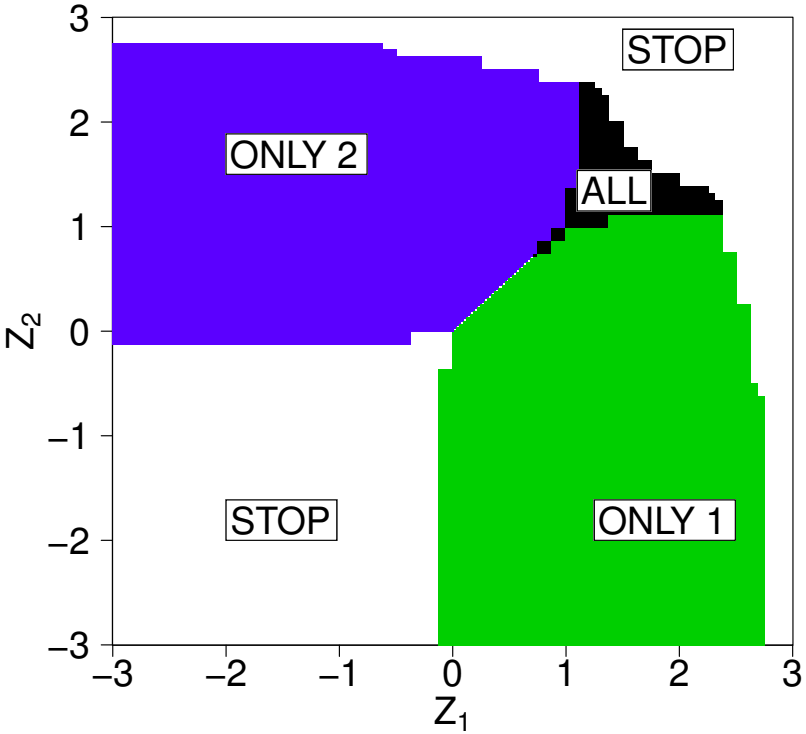


Rejection Regions for Decision:

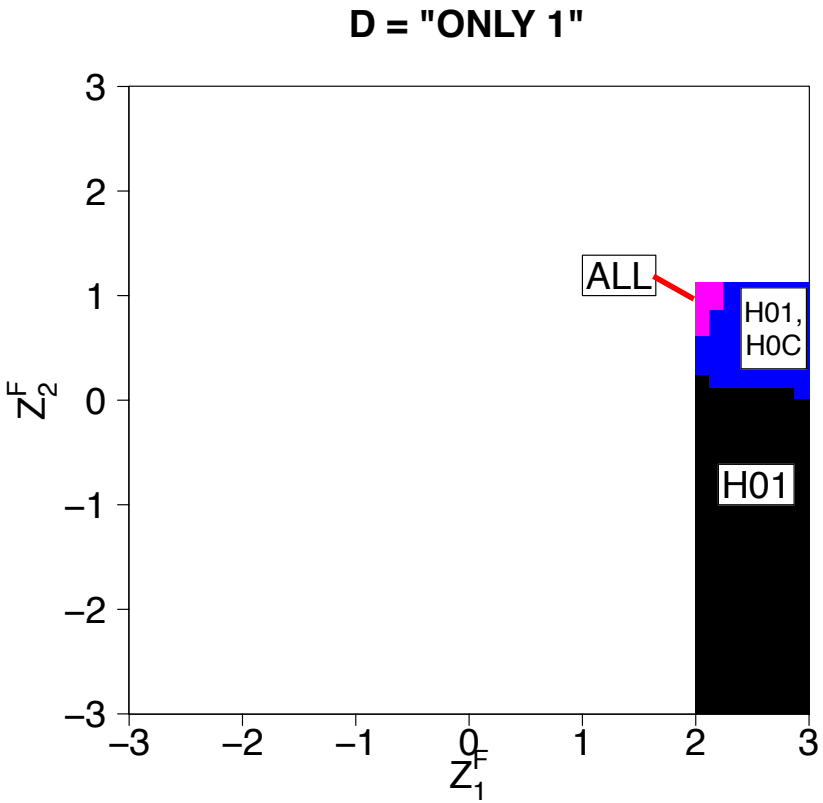


Approximately Optimal Solution

Decision Rule to Enroll Stage 2:

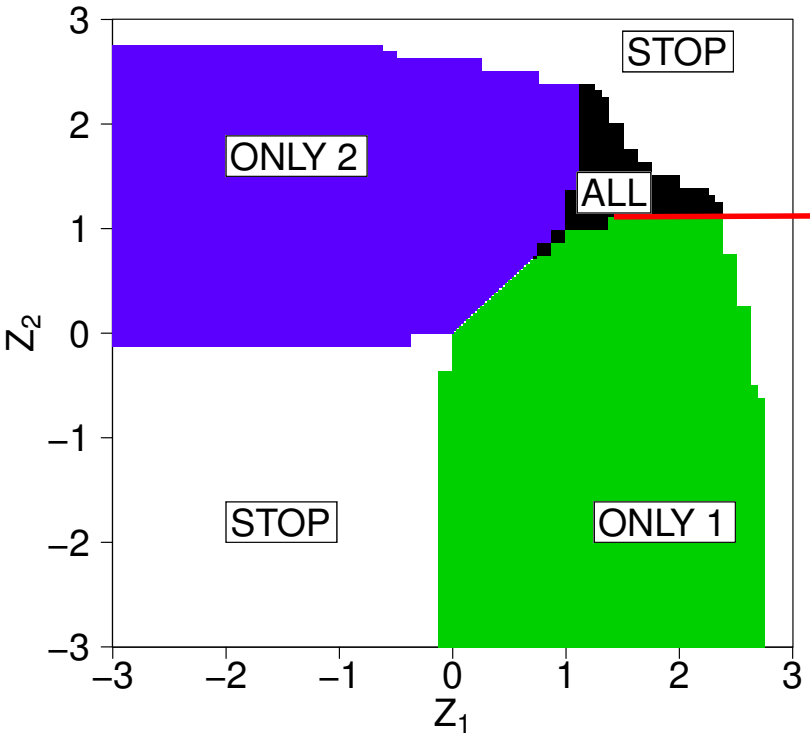


Rejection Regions for Decision:

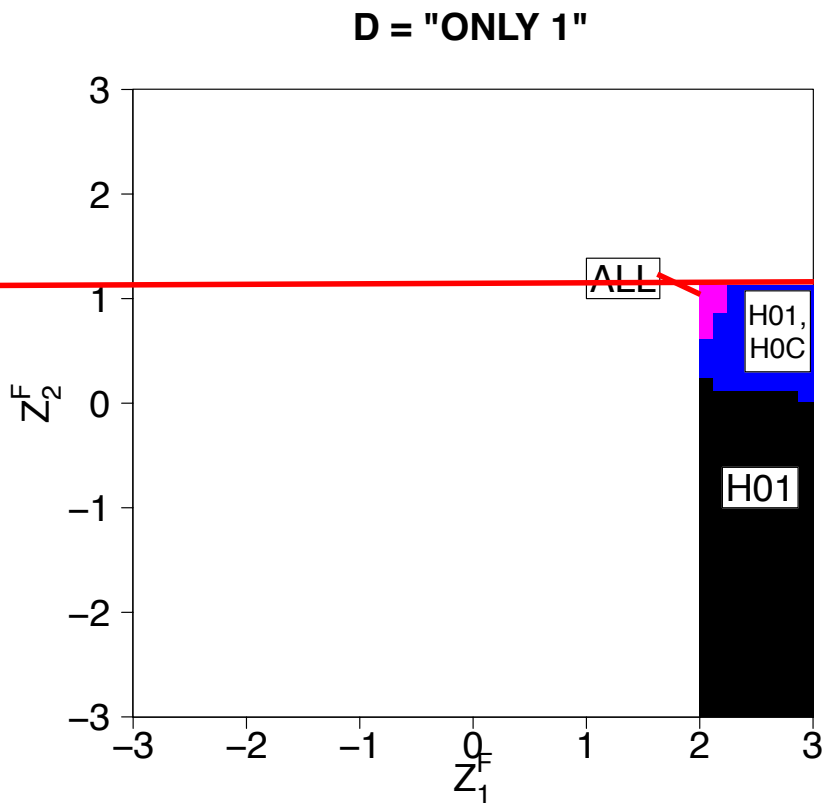


Approximately Optimal Solution

Decision Rule to Enroll Stage 2:

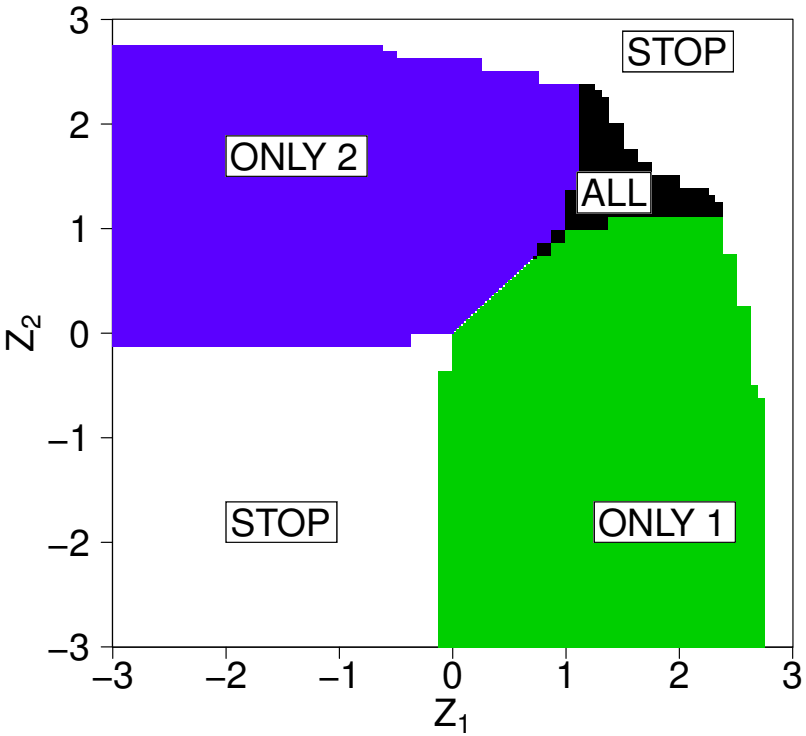


Rejection Regions for Decision:

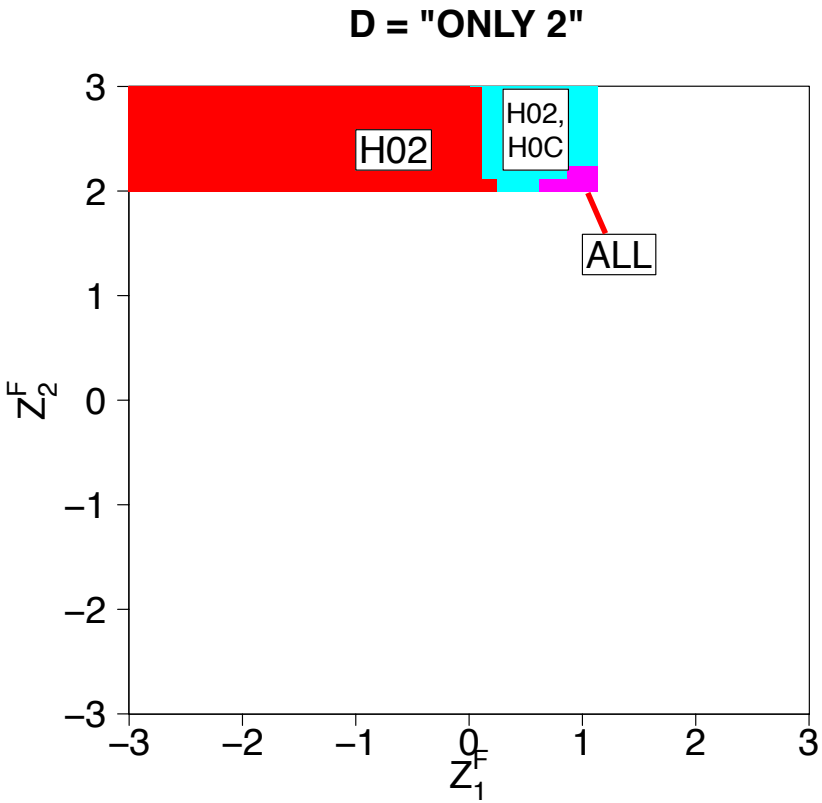


Approximately Optimal Solution

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	$0.97n$	$1.01n$	infeasible	infeasible
Optimal	$0.79n$	$0.84n$	$0.92n$	$1.03n$

References

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. http://biostats.bepress.com/jhubiostat/paper273

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*.

Optimal Tradeoff Curve: Power for Subpop. vs. Power for Combined Pop.

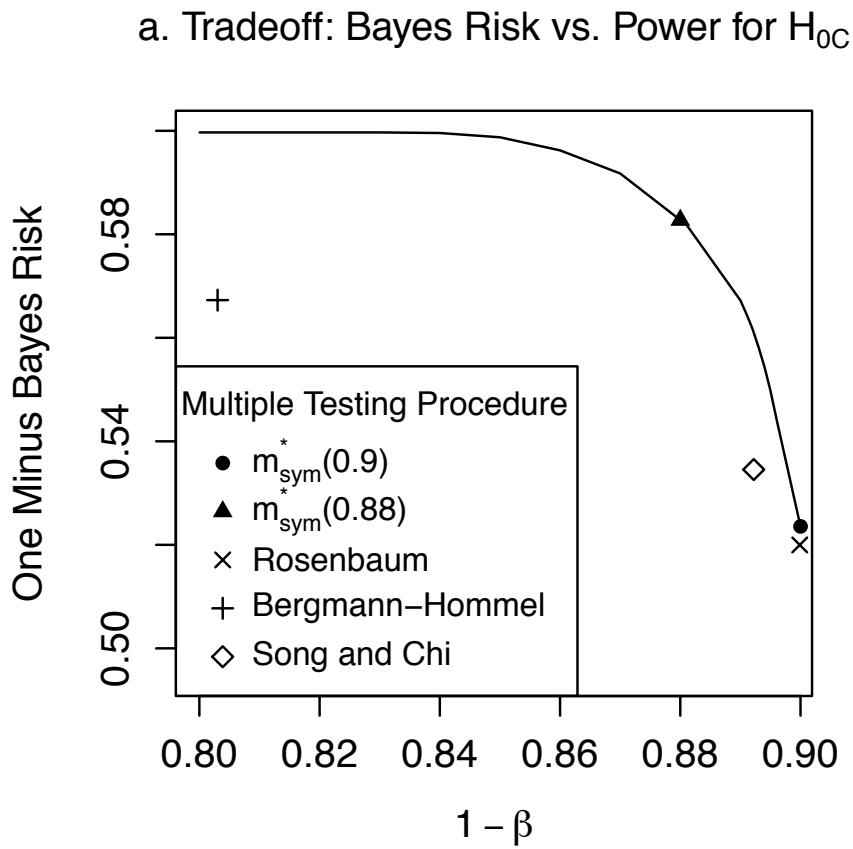
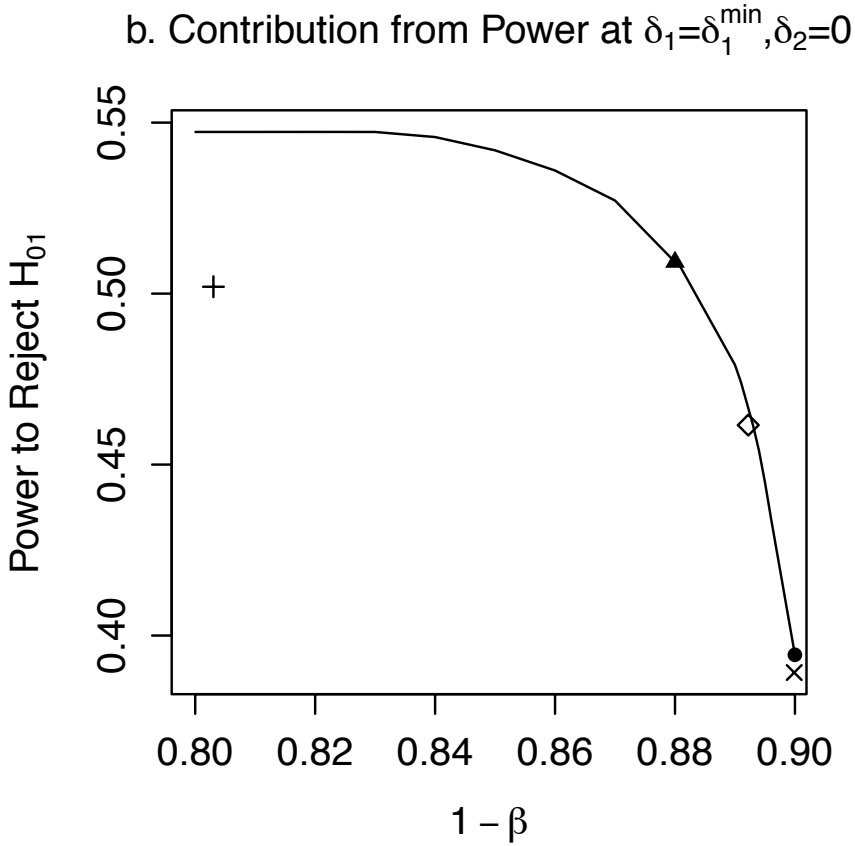
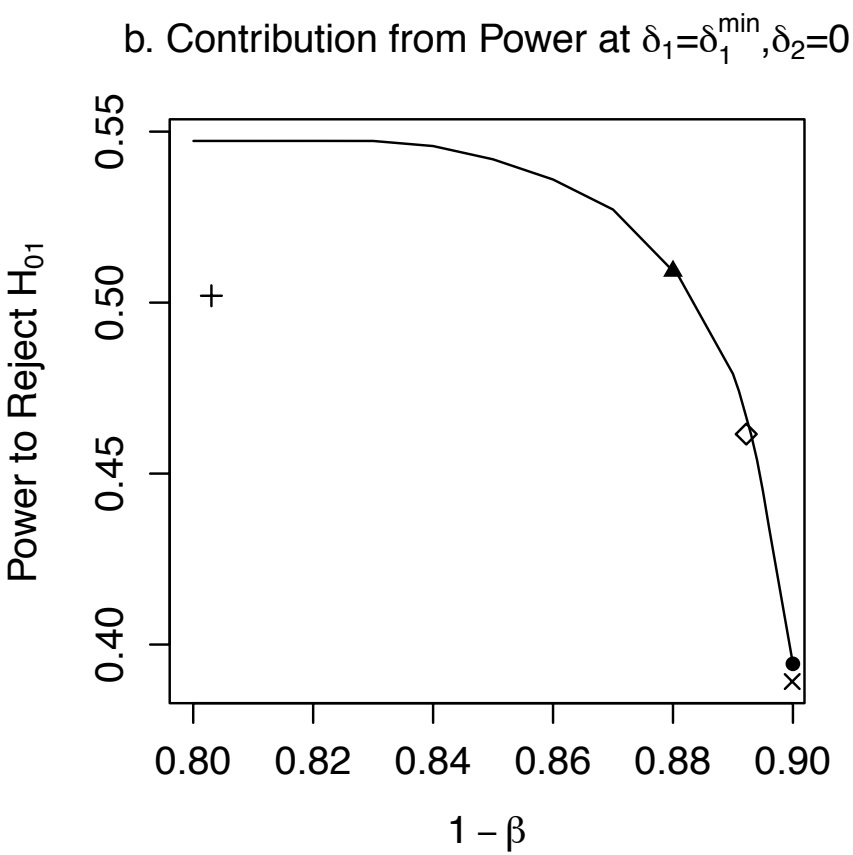


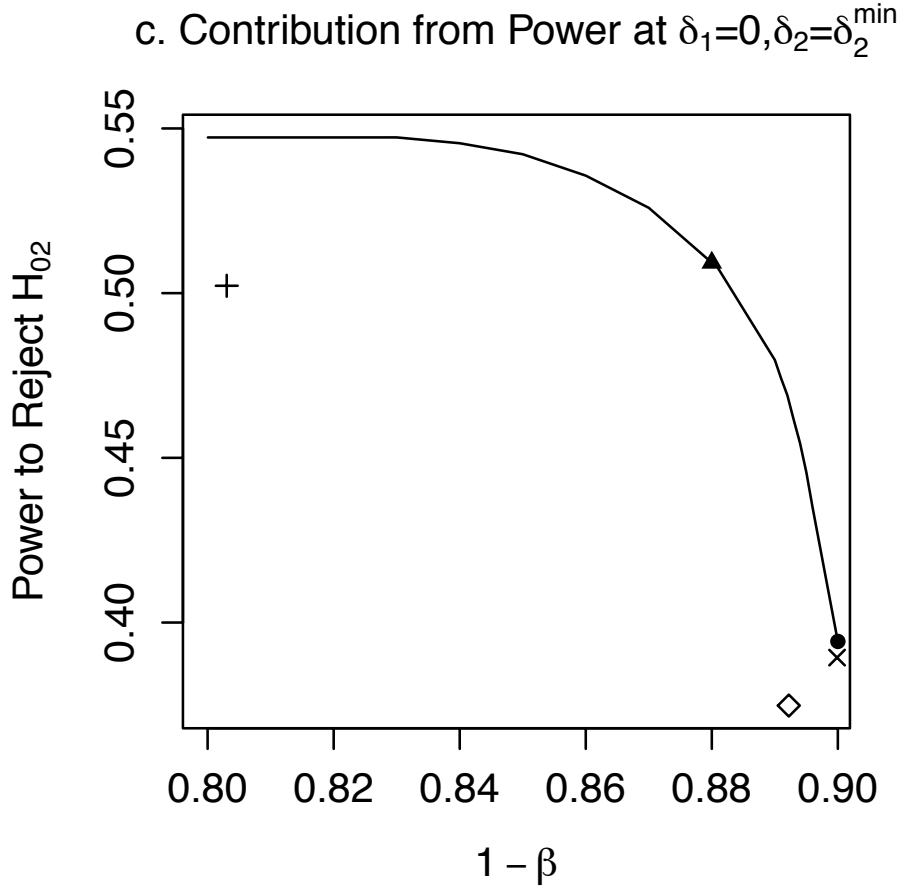
Figure: Optimal tradeoff between one minus Bayes risk and power constraint $1 - \beta$ on H_{0C}. One minus Bayes risk is weighted combination of power at different alternatives.

Optimal Tradeoff Curve: Contributions from Power at Different Alternatives

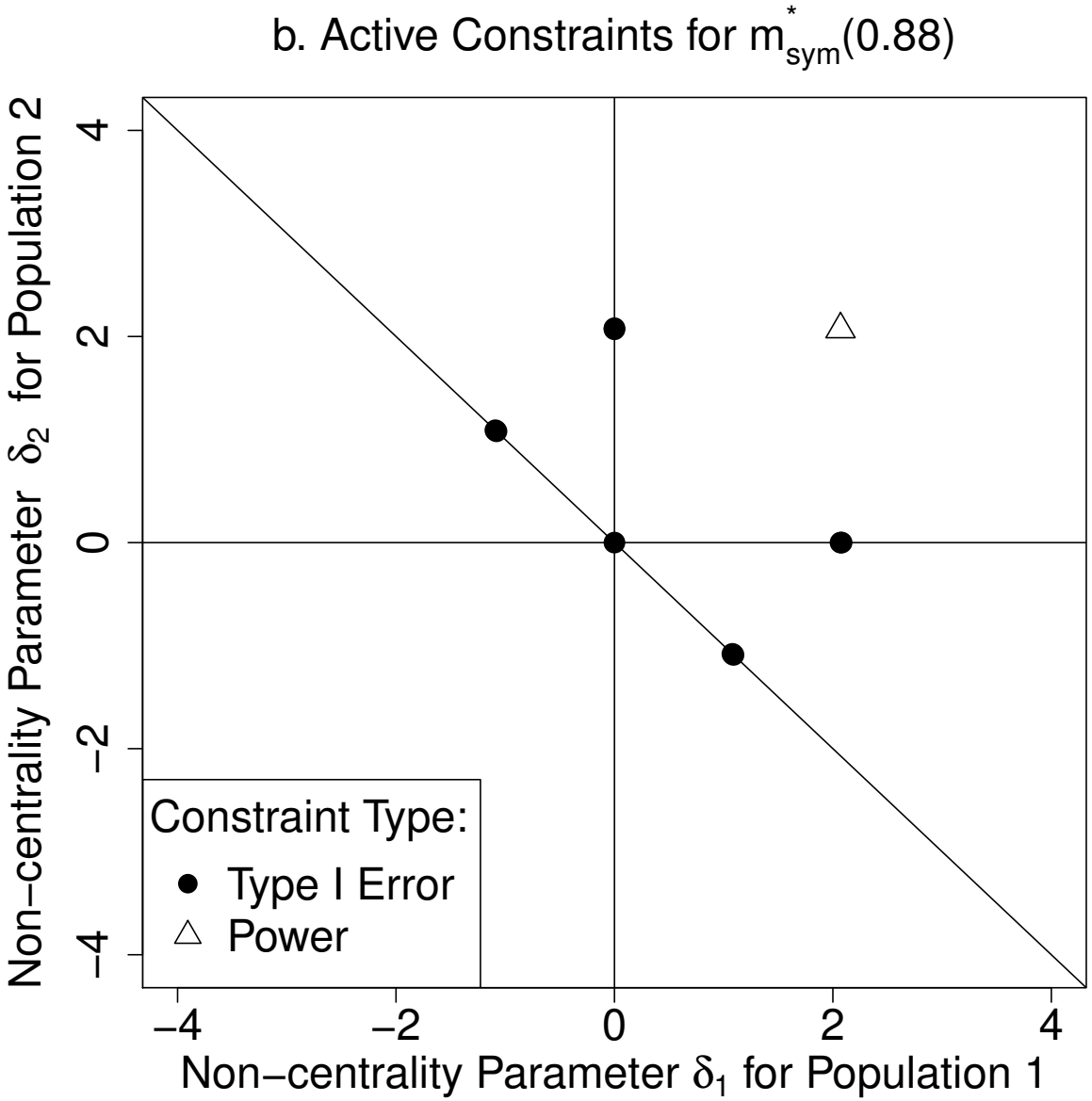


Optimal Tradeoff Curve: Contributions from Power at Different Alternatives





Active Constraints



More Diffuse Prior: Mixture of Bivariate Normal Distributions Centered at Four Points in Λ

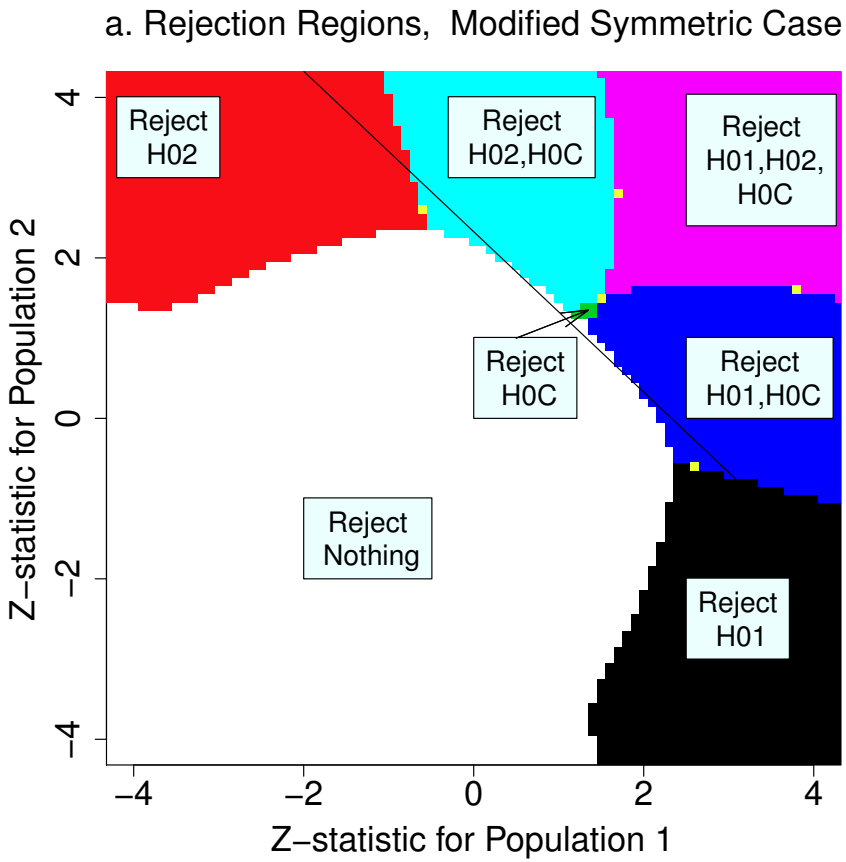


Figure: Optimal multiple testing procedures under more diffuse prior at coarser discretization. Yellow dots: optimal procedure is a randomized procedure.

Why Discretized Problem is Linear Program

Partition $\mathbb{R}^2$ into a set of rectangles $\mathcal{R}$. Let $\mathcal{M}_{\mathcal{R}}$ denote all randomized mult. testing procedures M such that for any $r \in \mathcal{R}$, $(z_1, z_2) \in r$, $(z_1', z_2') \in r$, we have $M(z_1, z_2) = M(z_1', z_2')$.

Why Discretized Problem is Linear Program

Partition $\mathbb{R}^2$ into a set of rectangles $\mathcal{R}$. Let $\mathcal{M}_{\mathcal{R}}$ denote all randomized mult. testing procedures M such that for any $r \in \mathcal{R}$, $(z_1, z_2) \in r$, $(z_1', z_2') \in r$, we have $M(z_1, z_2) = M(z_1', z_2')$.
For any $M \in \mathcal{M}_{\mathcal{R}}$, its behavior is completely characterized by $\{x_{rs}\}$, where for each rectangle r and $s \subseteq \{H_{01}, H_{02}, H_{0C}\} \equiv \mathcal{H}$:

$$x_{rs} = P\left[M(Z_1, Z_2) \text{ rejects s } \mid (Z_1, Z_2) \in r\right].$$

Why Discretized Problem is Linear Program

Partition $\mathbb{R}^2$ into a set of rectangles $\mathcal{R}$. Let $\mathcal{M}_{\mathcal{R}}$ denote all randomized mult. testing procedures M such that for any $r \in \mathcal{R}$, $(z_1, z_2) \in r$, $(z_1', z_2') \in r$, we have $M(z_1, z_2) = M(z_1', z_2')$.
For any $M \in \mathcal{M}_{\mathcal{R}}$, its behavior is completely characterized by $\{x_{rs}\}$, where for each rectangle r and $s \subseteq \{H_{01}, H_{02}, H_{0C}\} \equiv \mathcal{H}$:

$$x_{rs} = P\left[M(Z_1, Z_2) \text{ rejects s } \mid (Z_1, Z_2) \in r\right].$$

To show objective function
$\int E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2) d\Lambda(\Delta_1, \Delta_2)$ is linear in $\{x_{rs}\}$, consider term inside the integral:

$$E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2)$$

Why Discretized Problem is Linear Program

Partition $\mathbb{R}^2$ into a set of rectangles $\mathcal{R}$. Let $\mathcal{M}_{\mathcal{R}}$ denote all randomized mult. testing procedures M such that for any $r \in \mathcal{R}$, $(z_1, z_2) \in r$, $(z_1', z_2') \in r$, we have $M(z_1, z_2) = M(z_1', z_2')$.
For any $M \in \mathcal{M}_{\mathcal{R}}$, its behavior is completely characterized by $\{x_{rs}\}$, where for each rectangle r and $s \subseteq \{H_{01}, H_{02}, H_{0C}\} \equiv \mathcal{H}$:

$$x_{rs} = P\left[M(Z_1, Z_2) \text{ rejects s } \mid (Z_1, Z_2) \in r\right].$$

To show objective function
$\int E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2) d\Lambda(\Delta_1, \Delta_2)$ is linear in $\{x_{rs}\}$, consider term inside the integral:

$$\begin{aligned} & E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2) \\ = & \sum_{r \in \mathcal{R}, s \subseteq \mathcal{H}} E_{\Delta_1,\Delta_2}[L(M(Z_1, Z_2); \Delta_1, \Delta_2) \mid M(Z_1, Z_2) = s, (Z_1, Z_2) \in r \\ & \times P_{\Delta_1,\Delta_2}[M(Z_1, Z_2) = s | (Z_1, Z_2) \in r] P_{\Delta_1,\Delta_2}[(Z_1, Z_2) \in r] \end{aligned}$$

Why Discretized Problem is Linear Program

Partition $\mathbb{R}^2$ into a set of rectangles $\mathcal{R}$. Let $\mathcal{M}_{\mathcal{R}}$ denote all randomized mult. testing procedures M such that for any $r \in \mathcal{R}$, $(z_1, z_2) \in r$, $(z_1', z_2') \in r$, we have $M(z_1, z_2) = M(z_1', z_2')$.
For any $M \in \mathcal{M}_{\mathcal{R}}$, its behavior is completely characterized by $\{x_{rs}\}$, where for each rectangle r and $s \subseteq \{H_{01}, H_{02}, H_{0C}\} \equiv \mathcal{H}$:

$$x_{rs} = P\left[M(Z_1, Z_2) \text{ rejects s } \mid (Z_1, Z_2) \in r\right].$$

To show objective function
$\int E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2) d\Lambda(\Delta_1, \Delta_2)$ is linear in $\{x_{rs}\}$, consider term inside the integral:

$$\begin{aligned}
& E_{\Delta_1,\Delta_2} L(M(Z_1, Z_2); \Delta_1, \Delta_2) \\
= & \sum_{r \in \mathcal{R}, s \subseteq \mathcal{H}} E_{\Delta_1,\Delta_2}[L(M(Z_1, Z_2); \Delta_1, \Delta_2) \mid M(Z_1, Z_2) = s, (Z_1, Z_2) \in r] \\
& \quad \times P_{\Delta_1,\Delta_2}[M(Z_1, Z_2) = s | (Z_1, Z_2) \in r] P_{\Delta_1,\Delta_2}[(Z_1, Z_2) \in r] \\
= & \sum_{r \in \mathcal{R}, s \subseteq \mathcal{H}} L(s; \Delta_1, \Delta_2) P_{\Delta_1,\Delta_2}[(Z_1, Z_2) \in r] x_{rs}.
\end{aligned}$$

Idea for Solving Large, Sparse Linear Program

The discretized problem can be expressed in the canonical form:

$$\max_{x \in \mathbb{R}^{n_v}} \quad \mathbf{c}^{\mathbf{T}}\mathbf{x} \qquad \text{s.t.} \quad \mathbf{A}\mathbf{x} \leq \mathbf{b}. \tag{1}$$

Constraint matrix $\mathbf{A}$ has $\approx 2.6 \times 10^{12}$ entries. We use a projected subgradient descent method, at iteration $k+1$:

$$\mathbf{x}^{(k+1)} = P_s\left(\mathbf{x}^{(k)} - \delta_k \mathbf{g}^{(k)}\right), \tag{2}$$

where $P_s(.)$ means projection onto the feasible region determined by the sparse constraints, δ_k is a step size, and $\mathbf{g}^{(k)}$ is the subgradient of $\mathbf{x}_k$, defined as

$$\mathbf{g}^{(k)} = \begin{cases} \mathbf{c}, & \text{if for all} \quad i = 1, \ldots, n_d,\ \mathbf{a}_i^T \mathbf{x}^{(k)} \leq b_i, \\ -\mathbf{a}_{i'}, & \text{otherwise, where } i' \in \{i : \mathbf{a}_i^T \mathbf{x}^{(k)} > b_i\}. \end{cases} \tag{3}$$

Open Problems

- construct optimal testing procedures for comparing multiple treatments
- optimizing group sequential designs, seamless Phase II/Phase III designs, and adaptive enrichment designs
- more than 2 subpopulations
- optimizing power in adaptive designs

References

Rosenblum, M., Liu, H., and Yen, E.-H., (2013) Optimal Tests of Treatment Effects for the Overall Population and Two Subpopulations in Randomized Trials, using Sparse Linear Programming. JASA (In Press)

Rosenblum, M. Adaptive Randomized Trial Designs that Cannot be Dominated by Any Standard Design at the Same Total Sample Size. Under review at Biometrika.

Idea for Solving Large, Sparse Linear Program

Solver leverages structure of constraint matrix $\mathbf{A}$, which is a $1{,}757{,}113 \times 1{,}506{,}006$ matrix with structure:

$$\mathbf{A} = \left[\begin{array}{c} \text{106 rows in which most elements are non-zero} \\ \hline \text{251,001 rows of the form:} \left\{\begin{array}{l} 11111100000000000000\ldots \\ 00000011111100000000\ldots \\ 00000000000111111000\ldots \\ \vdots \end{array}\right. \\ \hline -\mathbf{I}_{1,506,006}\text{ , that is, the negative identity matrix} \end{array}\right]$$

Decision Theory Problem

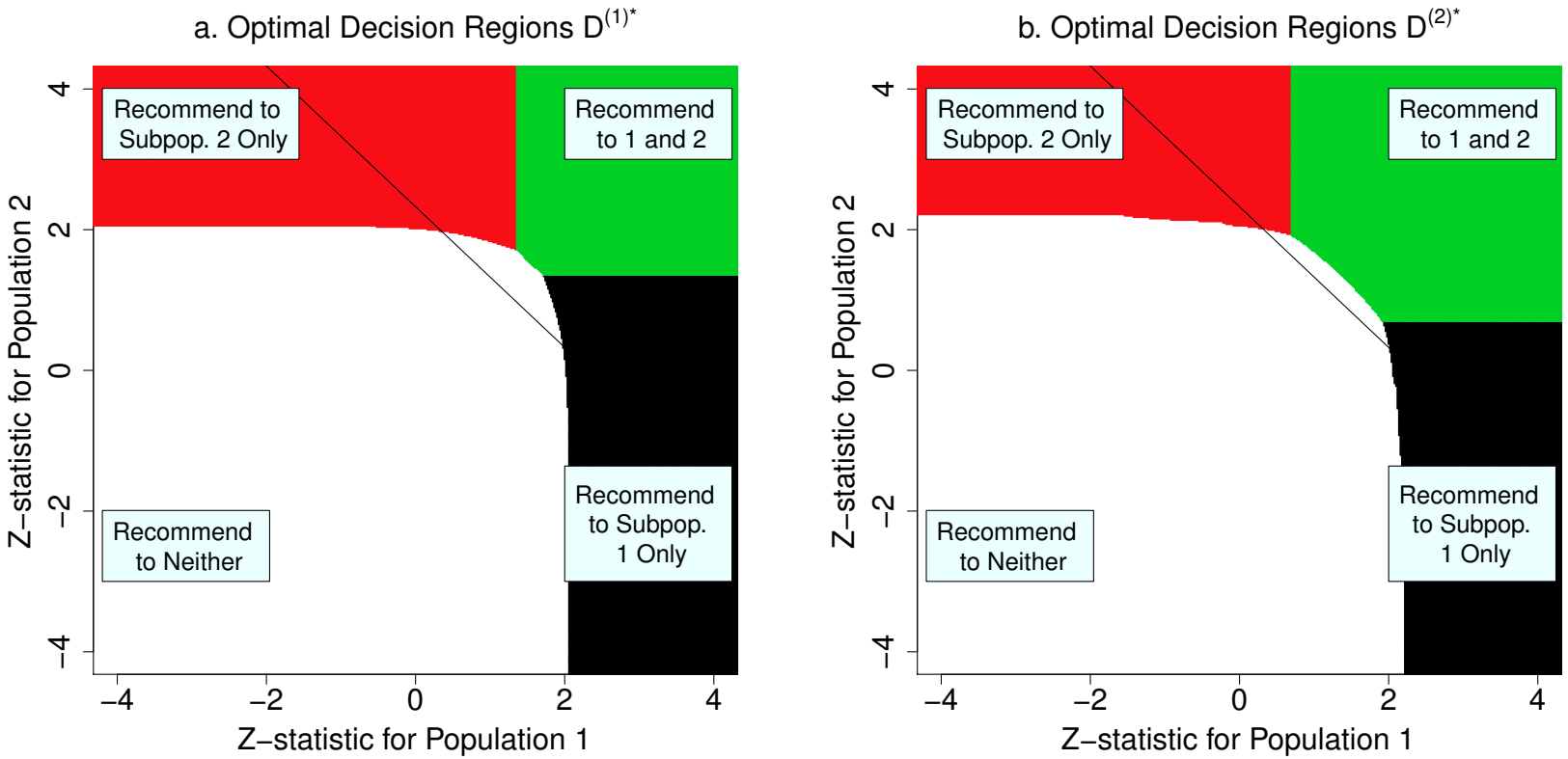


Figure: Optimal decision regions using loss function with: (a) higher penalty for false positives; (b) higher penalty for false negatives.

Minimum Sample Size Required to Achieve a Desired Subpop. Power under Constraint: Combined Pop. Power ≥ 0.9

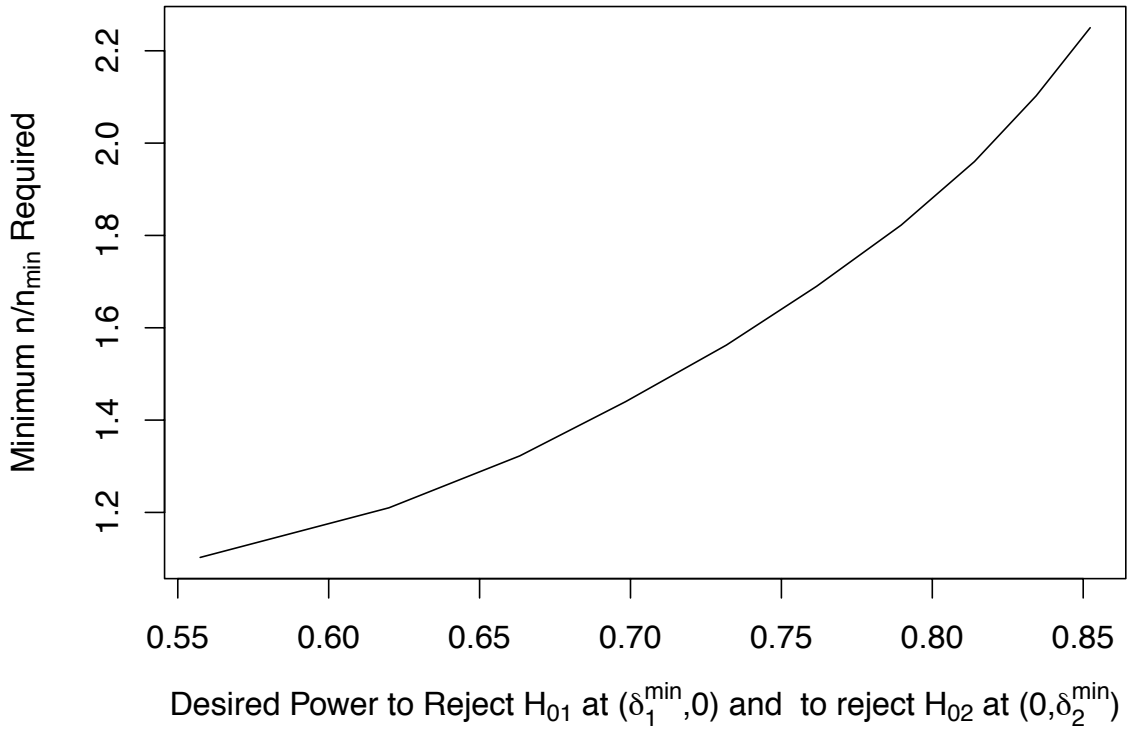
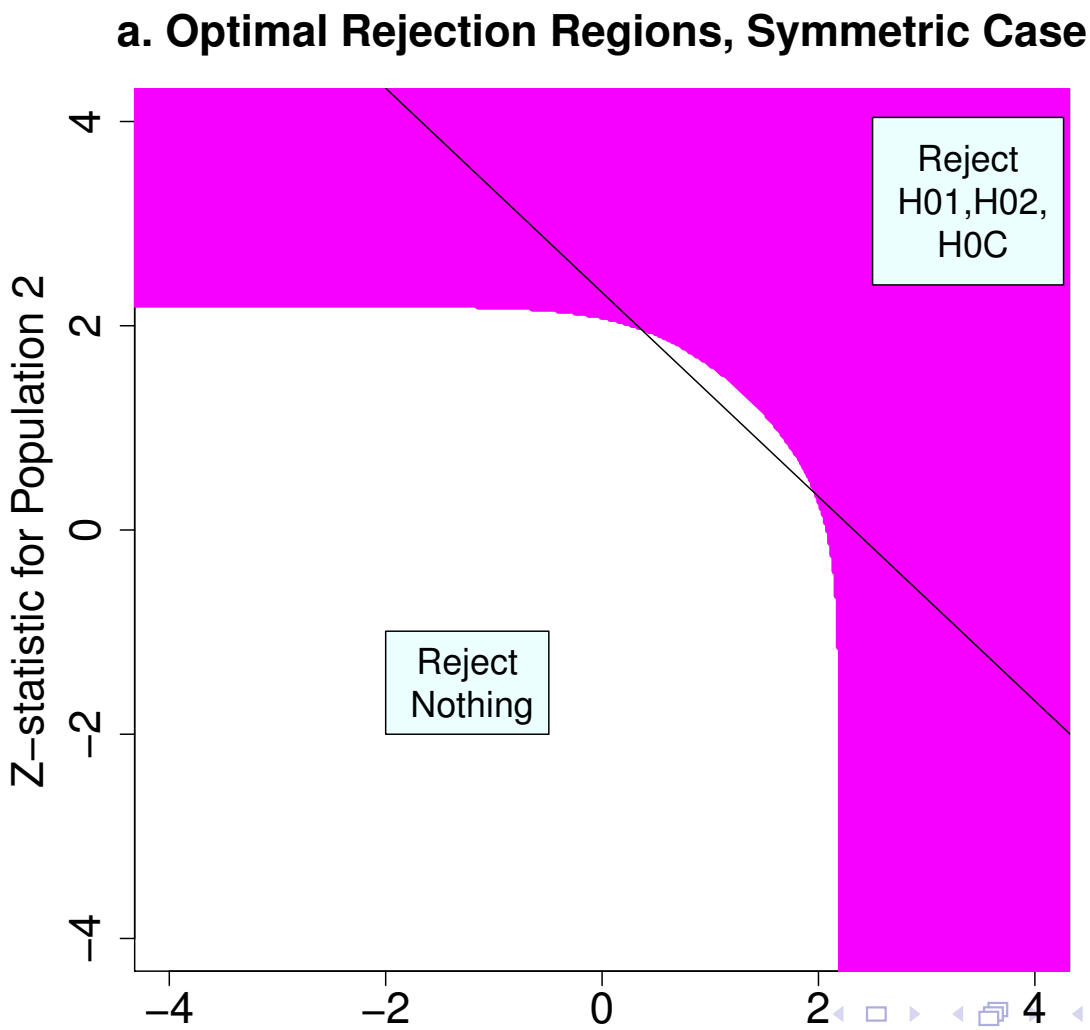


Figure: Minimum value of $n/n_{\min}$ to achieve a desired power for both H_{01} and H_{02}, under H_{0C} power constraint $1 - \beta = 0.9$.

Optimal Solution When Only Impose Type I Error Constraint at Global Null Hypothesis, and H_{0C} Power Constraint $1 - \beta = 0.88$



A Different Problem

Uniformly Most Powerful Tests for Overall Population and at Least One Subpopulation

- Three Null Hypotheses:
  H_{0C}: Mean Effect in Combined Population is ≤ 0.
  H_{01}: Mean Effect in Subpopulation 1 is ≤ 0.
  H_{02}: Mean Effect in Subpopulation 2 is ≤ 0.

We give the first procedures that are Uniformly Most Powerful for:

$$P(\text{Reject } H_{0C} \text{ and at least one of } H_{01}, H_{02})$$

over all multiple testing procedures that strongly control familywise Type I error rate at level 0.05.