Using Genetic Algorithms in the Design of Two-phase Studies

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Outline

Background

Given typically modest genetic effect sizes, large-scale population studies are necessary

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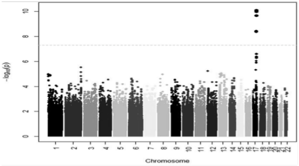
Costs of next-generation sequencing remain prohibitively expensive for large studies

Motivation: Two-phase Fine-mapping Studies

GWAS

$$Y = \gamma_0 + \gamma_Z Z$$

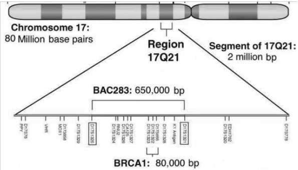
Phase 1 (N)



Fine-mapping

$$Y = \beta_0 + \beta_G G$$

Phase 2, S_2 (n)



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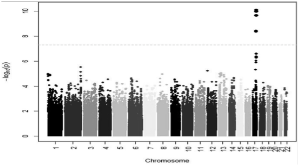

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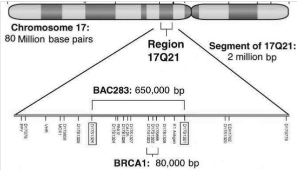

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Aim: Identify designs that select informative individuals for S_2 data collection

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Regression via Maximum Likelihood Methods

The observed data likelihood is defined as:

$$L(\boldsymbol{\beta}, \boldsymbol{p}) \propto \prod_{i=1}^{N} \left[f_\beta(y_i | g_i, z_i) p(g_i, z_i) \right]^{R_i} \left[\sum_{g \in \mathcal{G}} f_\beta(y_i | g, z_i) p(g, z_i) \right]^{(1-R_i)} \tag{1}$$

$$= \prod_{i \in S_2} f_\beta(y_i | g_i, z_i) p_{g_i, z_i} \prod_{i \in \bar{S}_2} \sum_{g \in \mathcal{G}} f_\beta(y_i | g, z_i) p_{g, z_i} \tag{2}$$

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where

- $R_i = \mathbb{1}\{i \in S_2\}$ with $\mathbb{P}(R_i = 1|y_i, z_i) = \pi(y_i, z_i; \psi)$, $\boldsymbol{R} = (R_1, \ldots, R_N)'$, and $\sum_{i=1}^{N} R_i = n$.
- $f_\beta(y|g, z)$ is a member of the exponential family, focus on $Y|G = g, Z = z \sim \mathcal{N}(\beta_0 + \beta_1 g + \beta_2 z, \sigma^2)$ with $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)$.
- $p_{g,z}$ is the joint probability of $G = g$ and $Z = z$, $\boldsymbol{p} = \{p_{g,z}\}_{g \in \mathcal{G}, z \in \mathcal{Z}}$.
- $\mathcal{G}$, $\mathcal{Z}$ are sets of uniquely observed values of G (in S_2) and Z (in $S_2 \cup \bar{S}_2$).
- $\bar{S}_2$ is the set of $N - n$ unselected subjects.

Remarks on Statistical Analysis

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- Maximum likelihood estimates are obtained via the EM algorithm.
- The variance-covariance matrix (VCM) is computed via the Louis' method (1982).
- Main interest lies in testing for $\mathrm{H}_0 : \beta_1 = 0$ vs $\mathrm{H}_A : \beta_1 \neq 0$.

Outline

Outcome/Covariate - Dependent Sampling

Let $R_i = \mathbb{1}\{i \in S_2\}$ and

$$\mathbb{P}(R_i = 1|Z_i, Y_i, G_i) = \mathbb{P}(R_i = 1|Z_i, Y_i) = \pi_i, \ i = 1, \ldots, N \quad \text{(Missing at random)}$$

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Marginal sampling:

$$\mathbb{P}(R_i = 1|Z_i, Y_i) = \begin{cases} \pi(Z_i) & \text{covariate-dependent} \\ \pi(Y_i) & \text{outcome-dependent} \end{cases}$$

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Joint sampling:

$$\mathbb{P}(R_i = 1 | Z_i, Y_i) = \pi(Z_i, Y_i)$$

For the lead SNP (Z) sampling, strata are naturally defined by the number of copies of the minor allele.

To operationalize the outcome sampling, we discretize Y into a K strata variable Y_{st}, ($T_1, \dots, T_K$) using pre-specified cut-offs $(C_1, \dots, C_{K-1})$.

A First Approach

Let N be the phase 1 sample size and n be the phase 2 sample size ($N > n$)

$Z \backslash Y_{st}$	**Phase 1 data** $\mathbf{T}_1$	$\ldots$	$\mathbf{T}_K$	$\mathbf{M}_Z$	**Phase 2 design** $\mathbf{T}_1$	$\ldots$	$\mathbf{T}_K$	$\mathbf{M}_Z$
0	N_{01}	$\ldots$	N_{0K}	$N_{0\cdot}$	n_{01}	$\ldots$	n_{0K}	$n_{0\cdot}$
1	N_{11}	$\ldots$	N_{1K}	$N_{1\cdot}$	n_{11}	$\ldots$	n_{1K}	$n_{1\cdot}$
2	N_{21}	$\ldots$	N_{2K}	$N_{2\cdot}$	n_{21}	$\ldots$	n_{2K}	$n_{2\cdot}$
$\mathbf{M}_Y$	$N_{\cdot 1}$	$\ldots$	$N_{\cdot K}$	N	$n_{\cdot 1}$	$\ldots$	$n_{\cdot K}$	n

where

$$n_{I_z,I_y} = \#\{i : Z_i \in I_z, Y_i \in I_y\}$$

is the number of subjects to be allocated in each stratum for the joint sampling design.

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$\mathbf{T}_1$	$\dots$	$\mathbf{T}_K$	$\mathbf{M}_Z$
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$N_{\cdot 1}$	$\dots$	$N_{\cdot K}$	N

Phase 2 design			
$\mathbf{T}_1$	$\dots$	$\mathbf{T}_K$	$\mathbf{M}_Z$
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Q: How to allocate samples for the phase 2 design?

Heuristic designs

Strata are defined using Y and Z (observed at phase 1)

- Y, the QT, is discretized into a $K = 3$ strata variable Y_{st} (T_1, T_2, T_3)
- Z, the lead SNP, is defined by the number of copies of the minor allele $(0, 1, 2)$

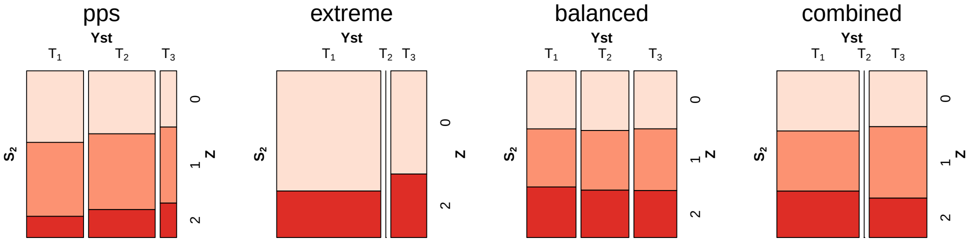

Figure: Heuristic designs when $n \approx N/2$, $Y \sim \mathcal{N}(2, 2.25)$, minor allele frequency (MAF) for Z, $q_Z = 0.3$

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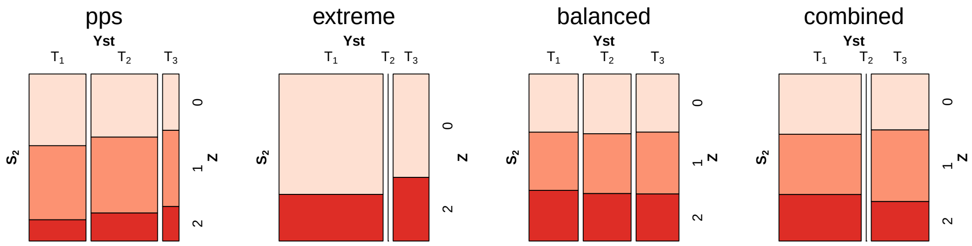

Figure: Heuristic designs when $n \approx N/2$, $Y \sim \mathcal{N}(2, 2.25)$, minor allele frequency (MAF) for Z, $q_Z = 0.3$

Q: Is there a better way to find phase 2 designs given a fixed n?

Optimality in Two-Phase Studies

Let $\theta = (\beta^t, \boldsymbol{p}^t)^t$, under regularity conditions, the limiting distribution of $\hat{\theta}$ follows asymptotically:

$$\sqrt{N}(\hat{\theta} - \theta) \sim \mathcal{N}(0, \mathbb{J}(\Phi)^{-1}),$$

where $\Phi = (\theta^t, \psi^t)^t$, and

- ψ is a parameter determining $\pi(y_i, z_i; \psi) = \mathbb{P}(R_i = 1 | y_i, z_i; \psi)$, and
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Following experimental design literature, different optimality criteria, $\Lambda(\cdot)$, can be investigated:

A-optimality: minimizes trace of VCM, i.e. $\Lambda\left[\mathbb{J}(\Phi)\right] = \sum \text{diag}(\mathbb{J}(\Phi)^{-1})$

D-optimality: minimizes determinant of VCM, i.e. $\Lambda\left[\mathbb{J}(\Phi)\right] = \det(\mathbb{J}(\Phi)^{-1})$

Parameter-specific: minimizes the entry of the VCM corresponding to β_1, i.e. $\Lambda\left[\mathbb{J}(\Phi)\right] = \left[\mathbb{J}(\Phi)^{-1}\right]_{\beta_1,\beta_1}$

The Optimization Problem

We want to identify a design that satisfies the following optimization problem:

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or similarly

$$\min\ \Lambda\left[\mathbb{J}(\Phi)\right] \text{ subject to } \mathbb{P}(\boldsymbol{R} = 1|\boldsymbol{Y},\boldsymbol{Z}) = \frac{n}{N}.$$

Designs via Lagrange Multipliers

Aims to optimize the stratum-specific selection probabilities by minimizing the following expression

$$\Lambda\left[\mathbb{J}(\Phi)\right] + \lambda N^{-1}\left(\sum_{k,j \in Y_{st},Z} \pi_{kj}(\psi) N_{kj} - n\right)$$

where λ is a Lagrange multiplier (LM) that accounts for the budget constraint and N_{kj} is the phase 1 stratum size.

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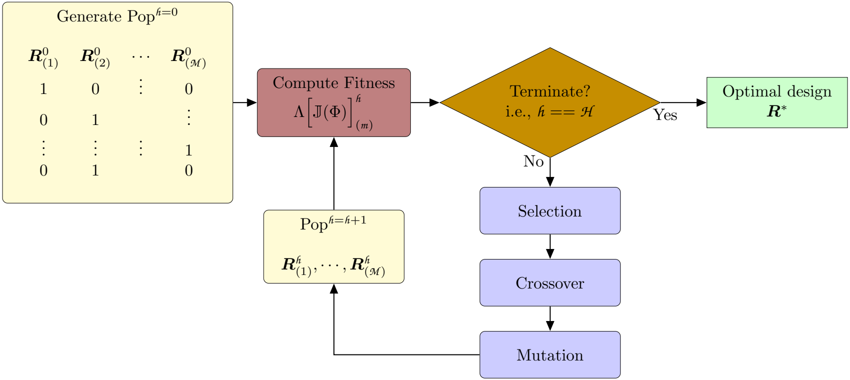
Notes:

- $\theta = (\boldsymbol{\beta}^t, \boldsymbol{p}^t)^t$ are design quantities, i.e. need to be specified a priori
- Provides a set of optimal sampling fractions π^*_{kj} for each stratum
- A phase 2 subsample is drawn given $\boldsymbol{\pi}^* = (\pi^*_{10}, \ldots, \pi^*_{K2})$

Designs via Genetic Algorithms

Aims to identify an "optimal" phase 2 subsample design ($\boldsymbol{R}^*$).



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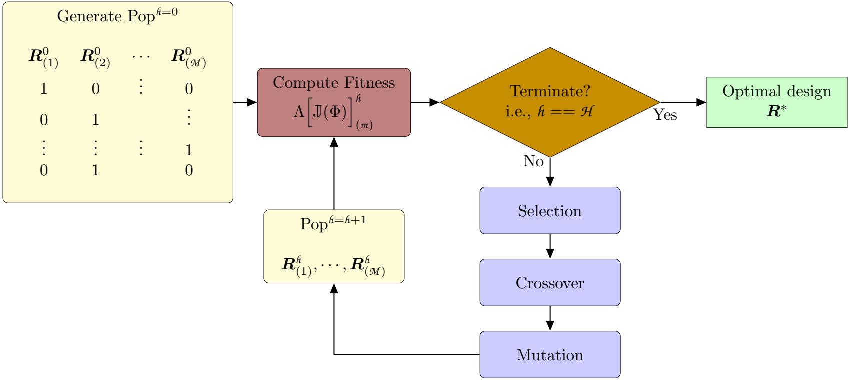

Notes:

- Suitable for discrete optimization in large search spaces (2^N).
- The budget constraint is accounted for via fixed-size subset selection.
- Hyper-parameter tuning is needed.

Rank-based Designs

Grounded in theoretical findings, these designs achieve a phase 2 sample size by selecting an equal number of subjects from each of the top and bottom rankings of the following quantities:

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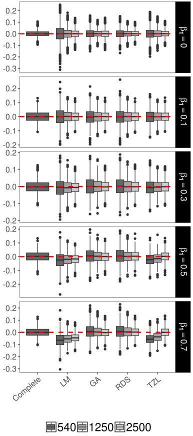
TZL: Tao-Zeng-Lin's scaled residuals design. Tao et al. (2020) showed that scaling the residuals by $\mathrm{Var}(G|Z)^{1/2}$ (unknown at design stage) yields a design with minimum variance under the score test, i.e. $\beta_1 = o(1)$.

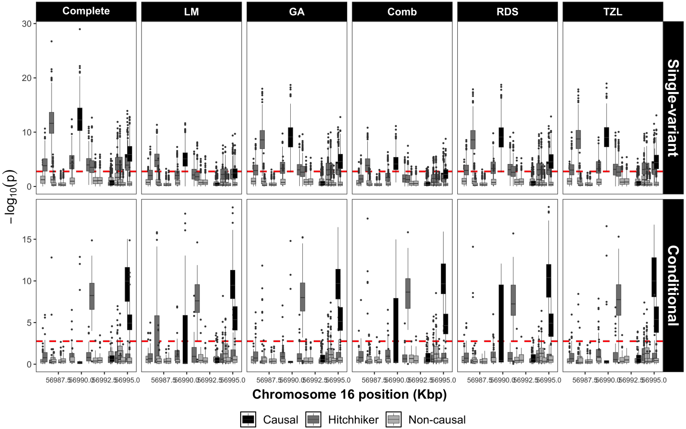
Characteristics of the Studied Designs

Feature	Design				
	Heuristic	LM	GA	ODS/RDS	TZL
Design quantities β, p need to be specified	$\times$	$\surd$	$\surd$	$\times$	$\surd$
Subject to sampling variability	$\surd$	$\surd$	$\times$	$\times$	$\times$
Computationally intensive	$\times$	$\times$	$\surd$	$\times$	$\times$
Depends on strata definition	$\surd$	$\surd$	$\times$	$\times$	$\times$

Simulation results in realistic scenario

- GA demonstrates less estimation bias compared to TZL.
- GA shows comparable power to TZL when $\mathrm{Var}(G|Z)$ is misspecified.





Summary

- The proposed GA designs can be more powerful than heuristic designs and comparable to rank-based designs.
- Similar results for GA over different MAFs, LDs and sample sizes (N,n).
- GA achieves power similar to complete data with half sequencing info.
- GA can be implemented across a variety of models.
- Implementation available at `github.com/egosv/twoPhaseGAS`.

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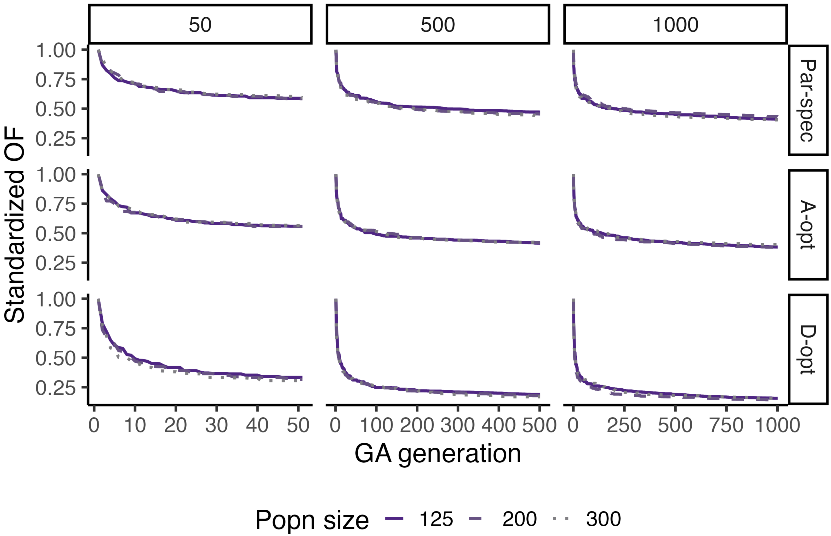
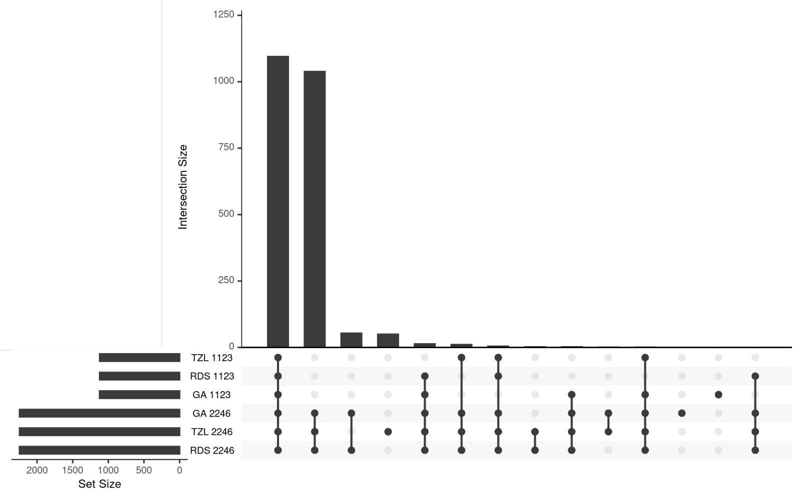
Convergence



Solution Uniqueness



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High-dimensional Covariate Settings

Let $\boldsymbol{Z} \in \mathbb{R}^p$ be a high-dimensional covariate vector, with observed likelihood:

$$L(\boldsymbol{\beta}, \gamma) = \prod_{i=1}^{N} \left\{ f_\beta(Y_i|G_i, \mathbf{Z}_i) h_\gamma(G_i, \mathbf{Z}_i) \right\}^{R_i} \times \left\{ \int f_\beta(Y_i|g, \mathbf{Z}_i) h_\gamma(g, \mathbf{Z}_i) \mathrm{d}g \right\}^{1-R_i},$$

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the optimization problem becomes:

$$\begin{aligned} \text{min} \quad & -\log L(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{R}) + \Lambda\left[\mathbb{J}(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{R})^{-1} \right] \\ \text{subject to} \quad & \sum_{i=1}^{N} R_i = n, \ \sum_{j=2}^{p+2} c_{1j} \mathbb{1}(\beta_j) \leq C_1, \ \sum_{j=2}^{p+2} c_{2j} \mathbb{1}(\gamma_j) \leq C_2, \end{aligned}$$

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here

- $\mathbb{1}(\cdot)$ is the indicator function denoting whether the jth parameter is to be selected,
- c_{kj}, $k = 1, 2; j = 2, \ldots, p+2$ represent covariate-specific costs, and
- C_k, $k = 1, 2$, are budget constraints for the parameters in f and h.

Alternative Optimization Methods

- Dynamic Programming (knapsack problem)
- Simulated Annealing
- Estimation of Distribution Algorithms

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Guan Wang (Master’s student, DLSPH, U of T)

OICR Ontario Institute for Cancer Research

CIHR IRSC Canadian Institutes of Health Research Instituts de recherche en santé du Canada

CANSSI INCASS ONTARIO

STAGE Strategic Training for Advanced Genetic Epidemiology

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Thank you for listening!

Questions?