Efficient Design and Analysis of a Two-Phase Study with Longitudinal Binary Outcomes

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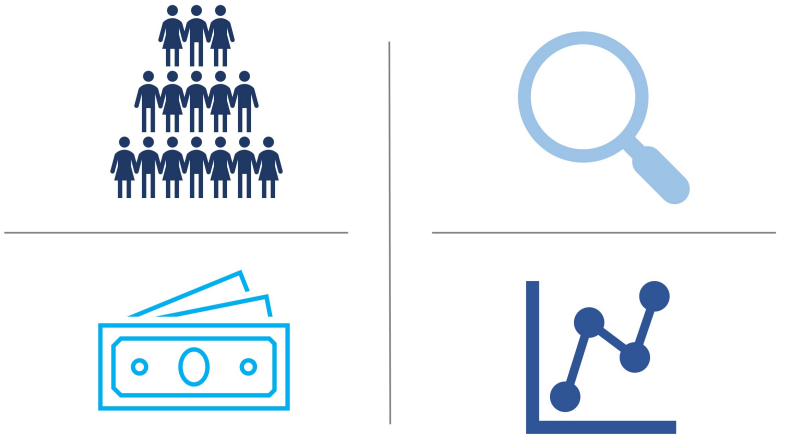
Motivation



Electronic health records and existing cohort studies provide easily accessible data on phenotype

Researchers might be interested in an exposure that is unavailable and expensive to collect

We want to use the available data to identify the most informative subjects for whom the exposure will be collected

We discuss a class of study designs for scenarios where we have a binary longitudinal outcome and baseline covariates available on all subjects, and we need to collect information on an exposure

We introduce a semi-parametric likelihood approach to estimate model's parameters

We demonstrate how the designs and estimation procedure can be used to examine genetic association with lung function

The Lung Health Study

The Lung Health Study (LHS) is a multicenter RCT of smokers with mild chronic obstructive pulmonary disease (COPD)

Hansel et al (2013) individuated SNP rs177852 to be a modifier of lung function decline in the LHS. The SNP is our expensive exposure

We define moderate lung function decline as forced expiratory volume (FEV) less than 60% at each follow-up time. We want to study the relationship between the SNP identified by Hansel et al and lung function decline

We consider a scenario where data on outcome and confounders are available on 2,563 individuals, but data on SNP can only be collected on 400 subjects

For our analysis we use a marginalized transition and latent variable model:

$$logit(\mu_{ij}^m) = \beta_0 + \beta_t \boldsymbol{T}_{ij} + \beta_x \boldsymbol{X}_i + \beta_{tx} \boldsymbol{T}_{ij} \boldsymbol{X}_i + \boldsymbol{\beta}_z^T \boldsymbol{Z}_i$$

$$logit(\mu_{ij}^c) = \Delta_{ij} + \gamma Y_{ij-1} + \sigma U_i$$

where:

- Y_{ij-1} is the FEV for subject i at visit $j-1$
- X_i is an indicator for the presence of at least one copy of the allele rs177852
- $\boldsymbol{Z}_i$ is a set of baseline covariates (age, BMI, sex, cigarettes smoked per year)
- Δ_{ij} links the marginal mean μ_{ij}^m and the conditional mean μ_{ij}^c
- $U_i \sim N(0,1)$

The NSA Design

Schildcrout et al (2008) introduced a design where informative individuals are sampled based on a summary of the outcome vector.

For each subject, compute $S_i = \sum_{j=1}^{n_i} Y_{ij}$, and classify them in one of the three strata:

- **None Stratum:** People who never experience the outcome $(S_i = 0)$
- **Some Stratum:** People who exhibit response variation $(0 < S_i < n_i)$
- **All Stratum:** People who always experience the outcome $(S_i = n_i)$

We indicate this design with the notation $D[N_n, N_s, N_a]$.

Sample from each of the three strata with different probabilities.

The Proposed Method

We introduce a full-likelihood approach that combines partial data on subjects not sampled with complete data on sampled subjects.

Let V be an indicator of whether a subject has the exposure X measured.

$$\underbrace{\sum_{i=1}^{n} V_i \left\{ log P_\beta(\boldsymbol{Y}_i | X_i, \boldsymbol{Z}_i) G(X_i | \boldsymbol{Z}_i) \right\}}_{\text{Contribution of Sampled Subjects}} + \underbrace{\sum_{i=1}^{n} (1 - V_i) \left[log \int_x P_\beta(\boldsymbol{Y}_i | x, \boldsymbol{Z}_i) G(x | \boldsymbol{Z}_i) dx \right]}_{\text{Contribution of Unsampled Subjects}}$$

We estimate $P_\beta(\boldsymbol{Y}_i | X_i, \boldsymbol{Z}_i)$ parametrically using a marginalized transition and latent variable model.

We estimate $G(X_i | \boldsymbol{Z}_i)$ by discrete probability functions $G(x_1 | \boldsymbol{Z}), \ldots, G(x_m | \boldsymbol{Z})$. For continuous $\boldsymbol{Z}$ this is challenging, so we use the method of sieves and extend the **Sieve Maximum Likelihood (SMLE)** from Tao et al (2017).

To estimate $G(X|\boldsymbol{Z})$ we use B-spline basis to construct the approximating function. If $B_j^q(\boldsymbol{Z}_i)$ is the jth B-spline of order q then:

$$logG(X_i|\boldsymbol{Z}_i) \approx \sum_{k=1}^{m} I(\boldsymbol{X}_i = x_k) \sum_{j=1}^{s_n} B_j^q(\boldsymbol{Z}_i) logp_{kj}$$

$$G(x_i|\boldsymbol{Z}_i) \approx \sum_{i=1}^{m} I(\boldsymbol{X}_i = x_k) \sum_{j=1}^{s_n} B_j^q(\boldsymbol{Z}_i) p_{kj}$$

- s_n is the total number of functions in the B-spline basis
- p_{kj} is the coefficient associated with the B-spline term $B_j^q(\boldsymbol{Z}_i)$ at $X = x_k$

The Observed Data Log-Likelihood

$$\sum_{i=1}^{n} V_i \left[log P_\beta(\boldsymbol{Y}_i | X_i, \boldsymbol{Z}_i) + \sum_{k=1}^{m} \sum_{k=1}^{m} I(\boldsymbol{X}_i = x_k) \sum_{j=1}^{s_n} B_j^q(\boldsymbol{Z}_i) log p_{kj} \right] +$$

$$\sum_{i=1}^{n} (1 - V_i) \left[log \left(\sum_{i=1}^{m} I(\boldsymbol{X}_i = x_k) P_\beta(\boldsymbol{Y}_i | x_k, \boldsymbol{Z}_i) \sum_{j=1}^{s_n} B_j^q(\boldsymbol{Z}_i) p_{kj} \right) \right]$$

Direct maximization of this likelihood is difficult.

We introduce a latent variable $W \in \{1/s_n, \ldots 1\}$ such that the second term can be interpreted as the log-likelihood of $(Y_i, \boldsymbol{Z}_i)$ assuming that the complete data consist of $(Y_i, X_i \boldsymbol{Z}_i, W_i)$ but X_i and W_i are missing.

We estimate the parameters $\boldsymbol{\beta}$ using the EM algorithm.

We estimate $Cov(\boldsymbol{\beta})$ using the profile likelihood method from Murphy et al (2000).

Simulation Study

We generate data from a marginalized transition model

$$logit(\mu_{ij}^m) = \beta_0 + \beta_t T_{ij} + \beta_x X_i + \beta_{tx} T_{ij} X_i + \beta_z Z_i$$

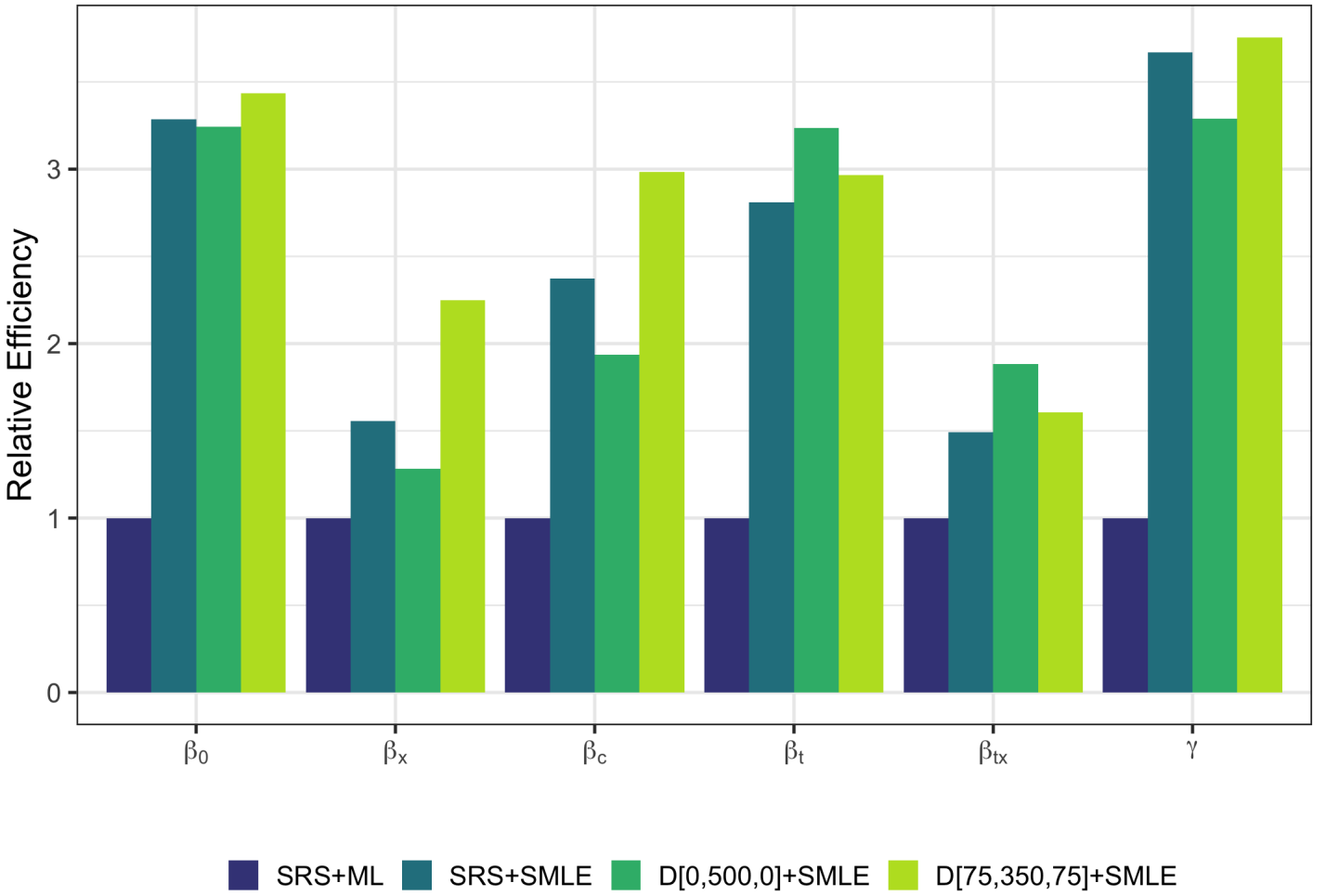
$$logit(\mu_{ij}^c) = \Delta_{ij} + \gamma Y_{ij-1}$$

Assuming that:

- each subject i $(i = 1, \ldots, 2000)$ has been observed 4 times $T_{ij} = \{0, 1, 2, 3\}$
- only one baseline confounder Z_i such that $P(Z_i = 1) = 0.3$
- one binary expensive covariate X_i such that $P(X_i = 1) = 0.1 \times I(Z = 0) + 0.5 \times I(Z = 1)$
- prevalence of the outcome across all times and subjects is 27%

We are going to sample 500 people using three different designs

- Estimated coefficients and standard errors were unbiased
- Relative efficiency compared to a simple random sample where models parameters are estimated using the sampled subject only



The Lung Health Study

During the follow-up period, 2,165 never experienced the outcome, 343 exhibited response variation and 55 always experienced the outcome. Prevalence of the outcome across all times and subjects was 9%

We sample 400 subjects and examine two designs: simple random sampling (SRS), and D[50, 300, 50]

	Full Cohort	SRS + ML	SRS + SMLE	D[50, 300, 50] + SMLE
SNP	0.02 (0.19)	0.35 (0.41)	0.06 (0.33)	-0.08 (0.22)
SNP $\times$ Visit	0.05 (0.04)	0.00 (0.09)	0.02 (0.08)	0.03 (0.04)
Visit	0.30 (0.03)	0.33 (0.06)	0.31 (0.05)	0.32 (0.03)
Sex	0.17 (0.12)	0.23 (0.27)	0.18 (0.12)	0.18 (0.12)
Age (per 10 years)	0.55 (0.10)	0.61 (0.18)	0.54 (0.14)	0.54 (0.11)
BMI (per 1 kg/m^2)	-0.01 (0.01)	0.01 (0.03)	-0.02 (0.02)	-0.02 (0.02)
Pack-Years (per 20 packs)	0.24 (0.06)	0.17 (0.14)	0.24 (0.06)	0.24 (0.06)
γ	1.15 (0.25)	0.75 (0.95)	1.17 (0.38)	1.18 (0.26)
$log(\sigma)$	1.50 (0.08)	1.76 (0.30)	1.50 (0.08)	1.49 (0.08)

Summary

We discussed a class of designs for a binary longitudinal outcome, and proposed a semi-parametric approach to estimate the parameters

We examined finite sampling operating characteristics of the proposed approach and demonstrated how the design and estimation procedure can be used to examine genetic associations with lung function

We are planning to extend the designs to account for baseline covariates available on everyone and improve efficiency

Reference

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Thank you!

Appendix: The Latent Variable W

- $W \in \{1/s_n, \ldots, 1\}$
- $B_q^j(\boldsymbol{Z}) = P(W = j/s_n|\boldsymbol{Z})$
- $p_{kj} = P(\boldsymbol{X} = \boldsymbol{x}_k|\boldsymbol{Z}, W = j/s_n) = P(\boldsymbol{X} = \boldsymbol{x}_k|W = j/s_n)$
- $P(\boldsymbol{Y}|\boldsymbol{X}, \boldsymbol{Z}, W) = P(\boldsymbol{Y}|\boldsymbol{X}, \boldsymbol{Z})$