Designing individually randomized group treatment trials with repeated outcome measurements using generalized estimating equations

Xueqi Wang
Yale University

Joint work with:
Elizabeth L. Turner, Duke University
Fan Li, Yale University

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Section

1. Introduction
2. Statistical Model
3. Power and Sample Size Considerations
4. Simulation Study
5. Application to the SYV Trial
6. Summary

Introduction

Individually randomized group treatment (IRGT) trials

- Randomization level: individual
- Post-randomization clustering in one or both conditions
  - treatment being group-based
    (e.g. a group-based psychological treatment)
  - treatment delivered to multiple participants by the same individual
    (e.g. surgeon)
- Differential clustering in different trial arms

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Individually randomized group treatment (IRGT) trials

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- Post-randomization clustering in one or both conditions
  - treatment being group-based
    (e.g. a group-based psychological treatment)
  - treatment delivered to multiple participants by the same individual
    (e.g. surgeon)
- Differential clustering in different trial arms
- Different from individually randomized controlled trials (RCTs)
  - outcomes of individuals assumed independent
- Different from cluster randomized trials (CRTs)
  - randomization level: a pre-existing cluster of individuals
  - usually same clustering of outcomes in both arm

Introduction

Longitudinal IRGT trials

- Repeated outcome measurements for each individual
- Additional level of nesting in each arm

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Longitudinal IRGT trials

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Motivating example

- Sauti ya Vijana (SYV, The Voice of Youth) trial
- Randomization level: individual
- Comparison
  - treatment: a series of group-based mental health sessions
  - control: routine care as usual delivered individually
- Outcome: log viral load assessed at 3 follow-up time points

Introduction

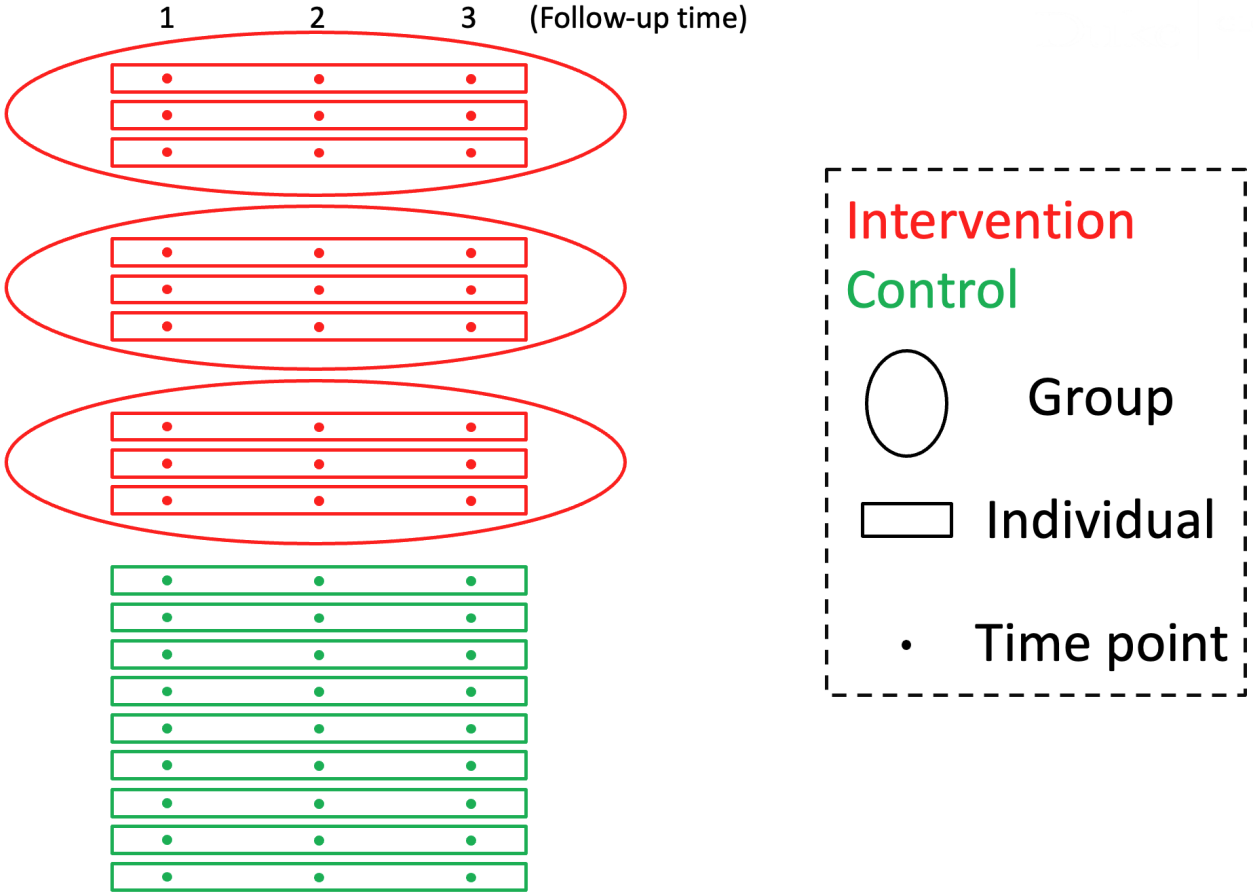

Figure 1: An illustration of the SYV trial, a longitudinal IRGT trial with 9 individuals per arm, 3 individuals per group in the treatment arm, no treatment-induced clustering of individuals in the control arm, and 3 follow-up time points per individual. A motivating design question is to determine the number of individuals in a given setting.

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Statistical Model

Notation

- Y_{ijk}: continuous or binary outcome for individual $k = 1, \ldots, K_i$ in cluster (i.e. group) $i = 1, \ldots, I_t, I_t + 1, \ldots, I_t + I_c$ at follow-up time point $j = 1, \ldots, T$

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  - $i = 1, \ldots, I_t$: treatment arm
    $K_i = K_t$: cluster size in the treatment arm
    $N_t = I_t \times K_t$: total number of individuals in the treatment arm

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  - $i = I_t + 1, \ldots, I_t + I_c$: control arm
    $K_i = K_c$: cluster size in the control arm
    $N_c = I_c \times K_c$: total number of individuals in the control arm

Statistical Model

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  - $i = I_t + 1, \ldots, I_t + I_c$: control arm
    $K_i = K_c$: cluster size in the control arm
    $N_c = I_c \times K_c$: total number of individuals in the control arm
- $I = I_t + I_c$: total number of clusters
- $N = N_t + N_c$: total number of individuals
- $\pi_c = N_c/N$: proportion of individuals in the control arm
- $q_c = I_c/I$: proportion of clusters in the control arm
- $N = I \times \{q_c K_c + (1 - q_c) K_t\}$

Statistical Model

Generalized linear model

- $\boldsymbol{X}_{ijk} = (X_{ijk1}, \ldots, X_{ijkp})'$: p covariates
  - X_i: binary treatment indicator

Statistical Model

Generalized linear model

- $\boldsymbol{X}_{ijk} = (X_{ijk1}, \ldots, X_{ijkp})'$: p covariates
  - X_i: binary treatment indicator
- $\mu_{ijk} = \mathrm{E}(Y_{ijk}|\boldsymbol{X}_{ijk})$: marginal mean outcome given $\boldsymbol{X}_{ijk}$, specified by

$$g(\mu_{ijk}) = \boldsymbol{X}'_{ijk}\boldsymbol{\beta} \tag{1}$$

  - g: link function
  - $\boldsymbol{\beta}$: $p \times 1$ vector of regression parameters

Statistical Model

Generalized linear model

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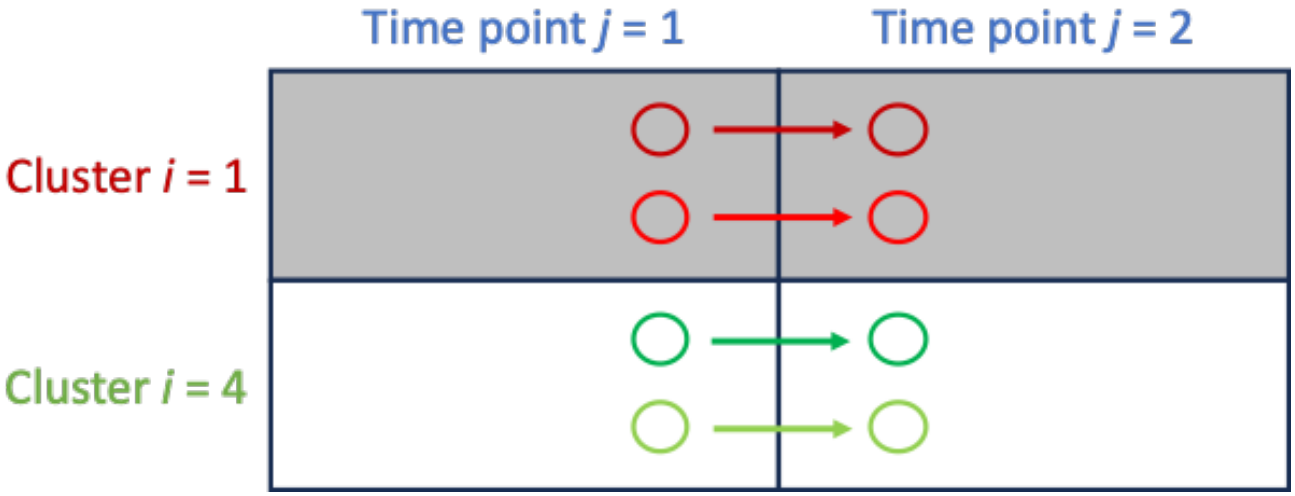
$$g(\mu_{ijk}) = \boldsymbol{X}'_{ijk}\boldsymbol{\beta} \tag{1}$$

  - g: link function
  - $\boldsymbol{\beta}$: $p \times 1$ vector of regression parameters
- $\mathrm{Var}(Y_{ijk}|\boldsymbol{X}_{ijk}) = \phi_i \nu_{ijk}$: marginal variance function
  - $\phi_i = \phi_t$ for i in the treatment arm
  - $\phi_i = \phi_c$ for i in the control arm
  - ν_{ijk}: variance function

Statistical Model

Three-parameter correlation model for each arm

- Simplified example



Statistical Model

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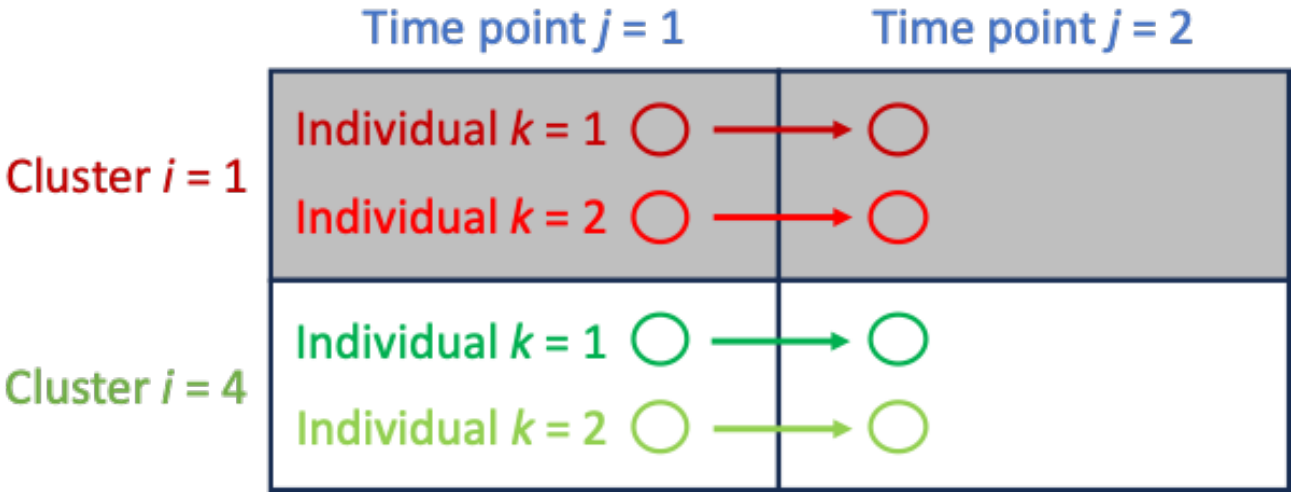

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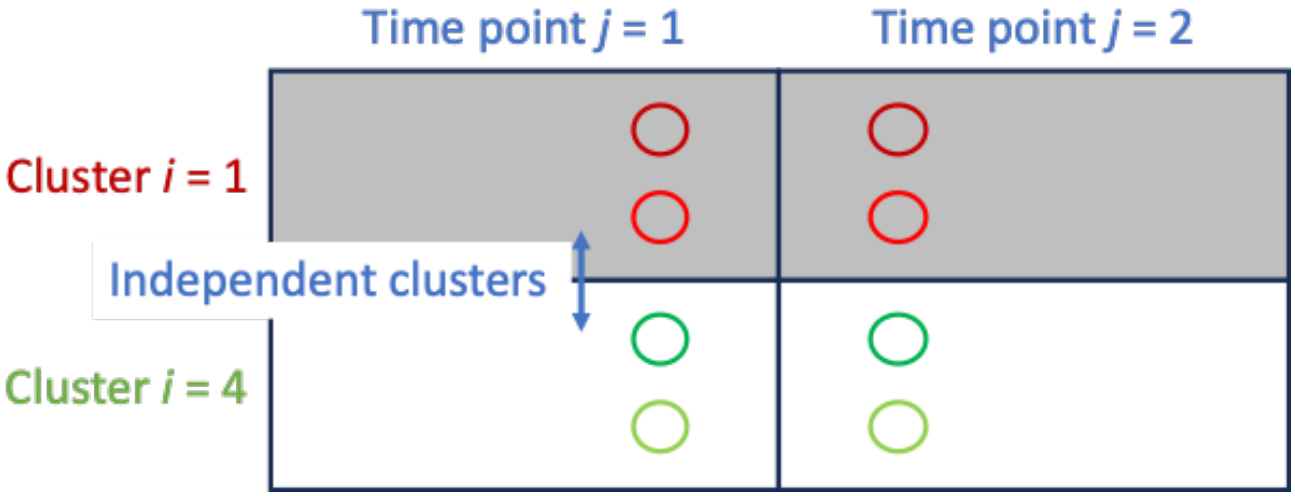

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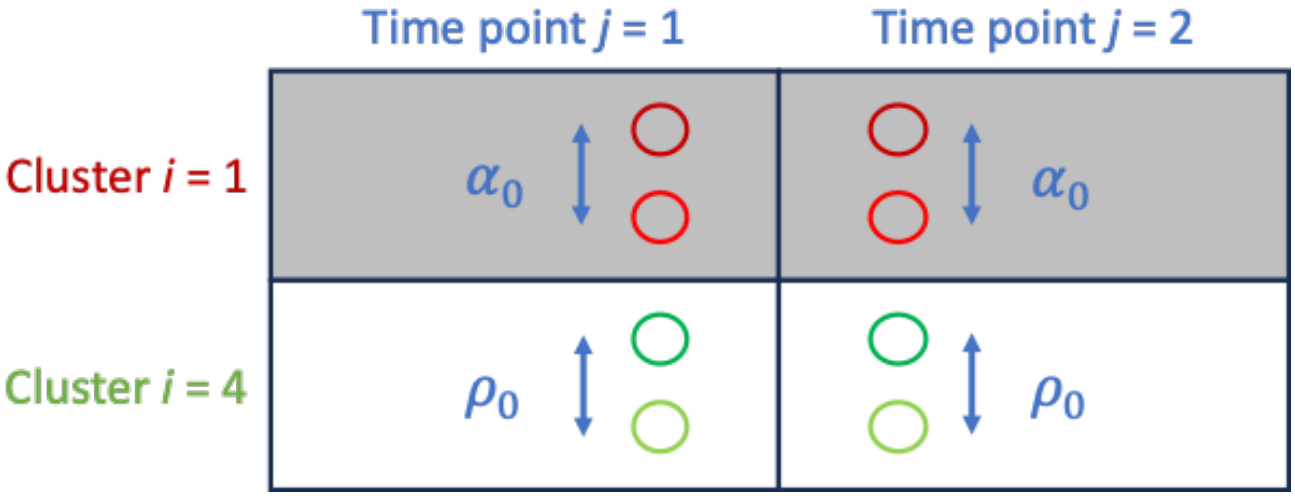
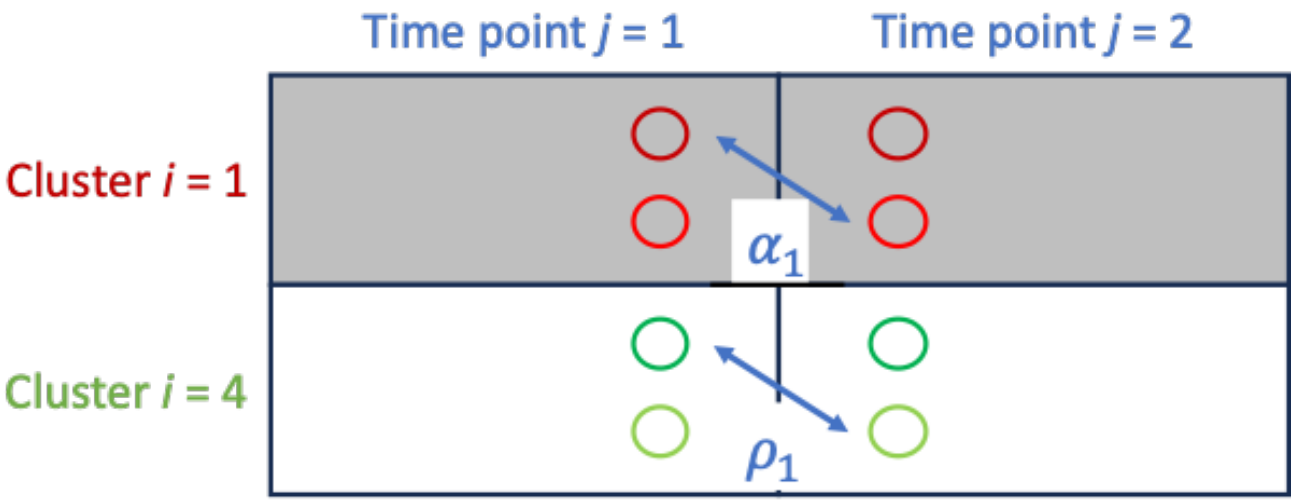


- (i) Within-time correlation for two different individuals
  - treatment arm: $\text{corr}\,(Y_{ijk}, Y_{ijk'}) = \alpha_0 \quad \text{for } k \neq k'$
  - control arm: $\text{corr}\,(Y_{ijk}, Y_{ijk'}) = \rho_0 \quad \text{for } k \neq k'$

Statistical Model

Three-parameter correlation model for each arm

- Simplified example

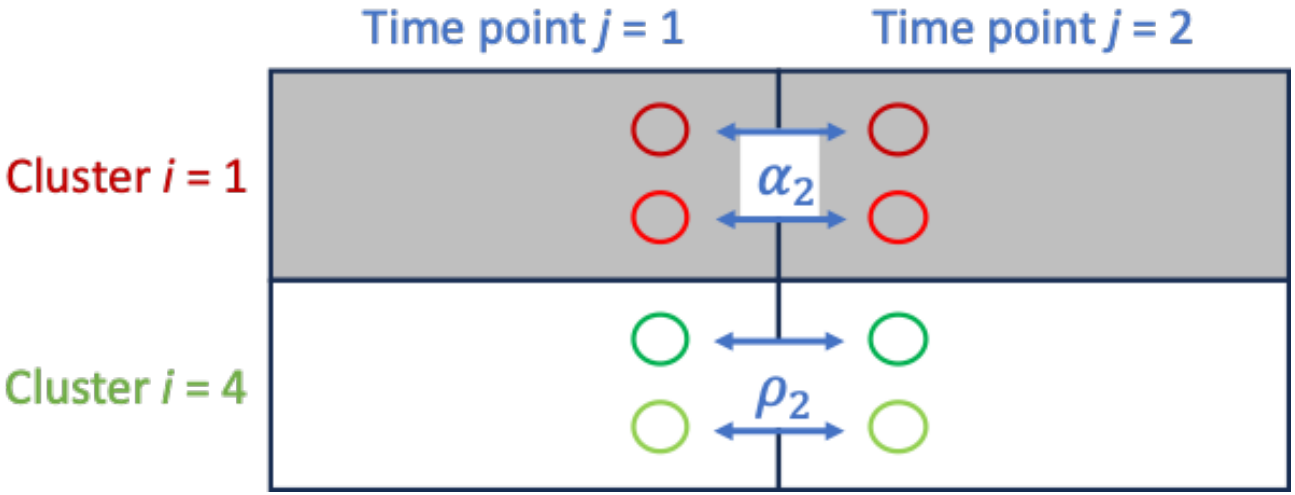


- (ii) Between-time correlation for two different individuals
  - treatment arm: $\text{corr}\left(Y_{ijk}, Y_{ij'k'}\right) = \alpha_1$ for $j \neq j'$ and $k \neq k'$
  - control arm: $\text{corr}\left(Y_{ijk}, Y_{ij'k'}\right) = \rho_1$ for $j \neq j'$ and $k \neq k'$

Statistical Model

Three-parameter correlation model for each arm

- Simplified example

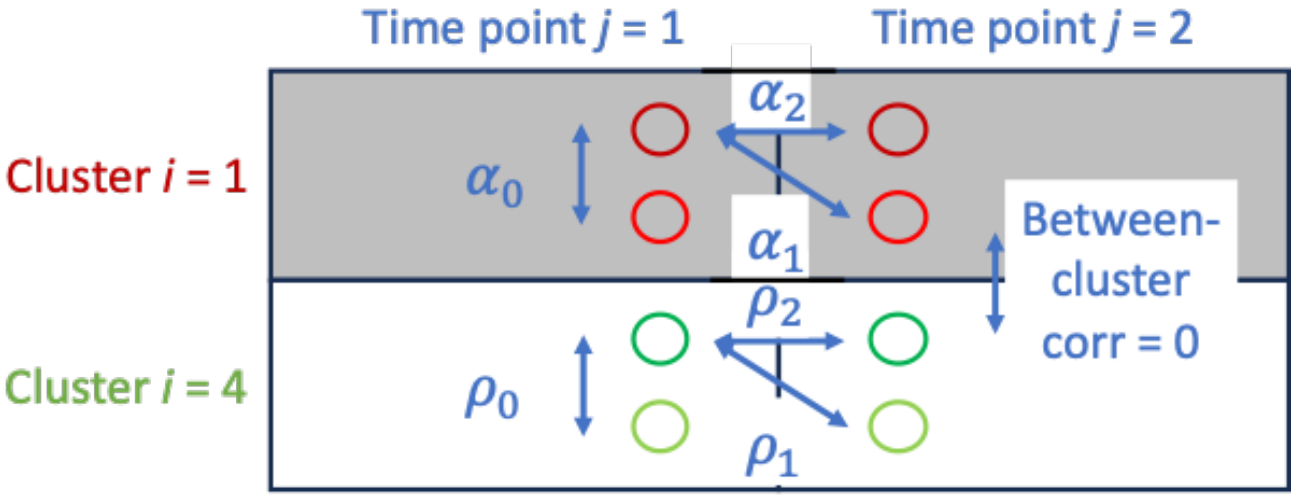


- (iii) Within-individual correlation over time
  - treatment arm: $\text{corr}\left(Y_{ijk}, Y_{ij'k}\right) = \alpha_2 \quad \text{for } j \neq j'$
  - control arm: $\text{corr}\left(Y_{ijk}, Y_{ij'k}\right) = \rho_2 \quad \text{for } j \neq j'$

Statistical Model

Three-parameter correlation model for each arm

- Simplified example



- Intraclass correlation coefficient (ICC) vector
  - treatment arm: $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \alpha_2)'$
  - control arm: $\boldsymbol{\rho} = (\rho_0, \rho_1, \rho_2)'$

Statistical Model

Block exchangeable correlation structure (Li et al., 2018) for the treatment arm

- Matrix notation

$$\begin{aligned}\boldsymbol{R}_t = &(1-\alpha_0+\alpha_1-\alpha_2)\,\boldsymbol{I}_{TK_t} + (\alpha_2-\alpha_1)\,\boldsymbol{J}_T \otimes \boldsymbol{I}_{K_t} \\ &+ (\alpha_0-\alpha_1)\,\boldsymbol{I}_T \otimes \boldsymbol{J}_{K_t} + \alpha_1 \boldsymbol{J}_{TK_t}\end{aligned}$$

  - $\otimes$: Kronecker product
  - $\boldsymbol{I}_s$: $s \times s$ identity matrix
  - $\boldsymbol{J}_s$: $s \times s$ matrix of ones

Statistical Model

Block exchangeable correlation structure (Li et al., 2018) for the treatment arm

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$$\boldsymbol{R}_t = (1 - \alpha_0 + \alpha_1 - \alpha_2)\, \boldsymbol{I}_{TK_t} + (\alpha_2 - \alpha_1)\, \boldsymbol{J}_T \otimes \boldsymbol{I}_{K_t} + (\alpha_0 - \alpha_1)\, \boldsymbol{I}_T \otimes \boldsymbol{J}_{K_t} + \alpha_1 \boldsymbol{J}_{TK_t}$$

  - $\otimes$: Kronecker product
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- Four distinct eigenvalues:

$$\lambda_{t1} = 1 - \alpha_0 + \alpha_1 - \alpha_2$$
$$\lambda_{t2} = 1 - \alpha_0 - (T - 1)(\alpha_1 - \alpha_2)$$
$$\lambda_{t3} = 1 + (K_t - 1)(\alpha_0 - \alpha_1) - \alpha_2$$
$$\lambda_{t4} = 1 + (K_t - 1)\alpha_0 + (T - 1)(K_t - 1)\alpha_1 + (T - 1)\alpha_2$$

Statistical Model

Block exchangeable correlation structure (Li et al., 2018) for the control arm

- Matrix notation

$$\boldsymbol{R}_c = (1 - \rho_0 + \rho_1 - \rho_2)\, \boldsymbol{I}_{TK_c} + (\rho_2 - \rho_1)\, \boldsymbol{J}_T \otimes \boldsymbol{I}_{K_c} + (\rho_0 - \rho_1)\, \boldsymbol{I}_T \otimes \boldsymbol{J}_{K_c} + \rho_1 \boldsymbol{J}_{TK_c}$$

  - $\otimes$: Kronecker product
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Statistical Model

Block exchangeable correlation structure (Li et al., 2018) for the control arm

- Matrix notation

$$\boldsymbol{R}_c = (1 - \rho_0 + \rho_1 - \rho_2)\, \boldsymbol{I}_{TK_c} + (\rho_2 - \rho_1)\, \boldsymbol{J}_T \otimes \boldsymbol{I}_{K_c} + (\rho_0 - \rho_1)\, \boldsymbol{I}_T \otimes \boldsymbol{J}_{K_c} + \rho_1 \boldsymbol{J}_{TK_c}$$

  - $\otimes$: Kronecker product
  - $\boldsymbol{I}_s$: $s \times s$ identity matrix
  - $\boldsymbol{J}_s$: $s \times s$ matrix of ones

- Four distinct eigenvalues:

$$\lambda_{c1} = 1 - \rho_0 + \rho_1 - \rho_2$$
$$\lambda_{c2} = 1 - \rho_0 - (T - 1)(\rho_1 - \rho_2)$$
$$\lambda_{c3} = 1 + (K_c - 1)(\rho_0 - \rho_1) - \rho_2$$
$$\lambda_{c4} = 1 + (K_c - 1)\rho_0 + (T - 1)(K_c - 1)\rho_1 + (T - 1)\rho_2$$

Statistical Model

Notes for ICCs

- Allow for differential clustering in the two arms
  - example: treatment leads to greater consistency of outcomes within an individual over time
- Special case: $\rho_0 = \rho_1 = 0$
  - treatment-induced clustering only in the treatment arm but none in the control arm
  - longitudinal generalization of the partially nested design

Statistical Model

Notes for ICCs

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- Special case: $\rho_0 = \rho_1 = 0$
  - treatment-induced clustering only in the treatment arm but none in the control arm
  - longitudinal generalization of the partially nested design
- Value choice for $\boldsymbol{\alpha}$ (similarly for $\boldsymbol{\rho}$)
  - pilot study
  - α_0 often reported in parallel-arm CRTs
  - $\alpha_1 = \alpha_0/2$
  - $\alpha_2 > \alpha_0 > \alpha_1$

Statistical Model

Generalized estimating equations (GEE) approach (Liang and Zeger, 1986)

- Mean model: estimating equations
- Two variance (of estimated mean) estimation approaches
  - model-based variance
  - robust sandwich variance
- Finite-sample adjustments: consider 2 approaches
  - KC bias correction (Kauermann and Carroll, 2001)
  - MD bias correction (Mancl and DeRouen, 2001)

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GEE/MAEE (Preisser et al., 2008)

- Correlation estimation via matrix-adjusted estimating equations (MAEE)
- GEE/MAEE with robust preferred
  - ICC estimates can inform future trial designs (Preisser et al., 2008)
  - good practice per the CONSORT extension (Campbell et al., 2012)

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Power and Sample Size Considerations

Power and sample size considerations

- Test for the global treatment effect
  - under t-test for a single parameter
  - under F-test for multiple parameters
- Assume the true correlation matrix is block exchangeable for each arm (with different correlation parameters)
- Survey five mean models

Power and Sample Size Considerations

Five mean models

- Model 1: No-time constant treatment effect (NT-CTE)

$$g(\mu_{ijk}) = \beta_1 + \beta_2 X_i$$

  - $H_0 : \beta_2 = 0$, with $df = I - 2$
  - simplified example of model parameters

	Time point 1 $\rightarrow$	Time point 2 $\rightarrow$	Time point 3
Secular trend	β_1	β_1	β_1
Treatment effect	β_2	β_2	β_2

Power and Sample Size Considerations

Five mean models

- Model 2: Linear-time constant treatment effect (LT-CTE)

$$g(\mu_{ijk}) = \beta_1 + \beta_2 t_j + \beta_3 X_i$$

  - $H_0 : \beta_3 = 0$ with $df = I - 3$
  - simplified example of model parameters

	Time point 1 $\rightarrow$	Time point 2 $\rightarrow$	Time point 3
Secular trend	$\beta_1 + \beta_2$	$\beta_1 + 2\beta_2$	$\beta_1 + 3\beta_2$
Treatment effect	β_3	β_3	β_3

Power and Sample Size Considerations

Five mean models

- Model 3: Categorical-time constant treatment effect (CT-CTE)

$$g(\mu_{ijk}) = \beta_j + \beta_{T+1} X_i$$

  - $H_0 : \beta_{T+1} = 0$ with $df = I - 2$
  - simplified example of model parameters

	Time point 1 $\rightarrow$	Time point 2 $\rightarrow$	Time point 3
Secular trend	β_1	β_2	β_3
Treatment effect	β_4	β_4	β_4

Power and Sample Size Considerations

Five mean models

- Model 4: Linear time by treatment interaction (LT-TI)

$$g(\mu_{ijk}) = \beta_1 + \beta_2 t_j + \beta_3 X_i + \beta_4 t_j X_i$$

  - $\boldsymbol{H}_0 : \boldsymbol{\beta}_{sub} = \boldsymbol{h}_0$, where $\boldsymbol{\beta}_{sub} = (\beta_3, \beta_4)'$ and $\boldsymbol{h}_0 = (0, 0)'$
  - simplified example of model parameters

	Time point 1 $\rightarrow$	Time point 2 $\rightarrow$	Time point 3
Secular trend	$\beta_1 + \beta_2$	$\beta_1 + 2\beta_2$	$\beta_1 + 3\beta_2$
Treatment effect	$\beta_3 + \beta_4$	$\beta_3 + 2\beta_4$	$\beta_3 + 3\beta_4$

Power and Sample Size Considerations

Five mean models

- Model 5: Categorical time by treatment interaction (CT-TI)

$$g(\mu_{ijk}) = \beta_{1j} + \beta_{2j} X_i$$

  - $\boldsymbol{H}_0 : \boldsymbol{\beta}_{sub} = \boldsymbol{h}_0$, where $\boldsymbol{\beta}_{sub} = (\beta_{21}, \ldots, \beta_{2T})'$ and $\boldsymbol{h}_0 = (0, \ldots, 0)'$
  - simplified example of model parameters

	Time point 1 $\rightarrow$	Time point 2 $\rightarrow$	Time point 3
Secular trend	β_{11}	β_{12}	β_{13}
Treatment effect	β_{21}	β_{22}	β_{23}

Power and Sample Size Considerations

Sample size calculations

- Closed-form sample size expressions for a continuous outcome, through two methods
  - model-based variance with the true working correlation
  - robust variance with an independence working correlation

Power and Sample Size Considerations

Sample size calculations

- Closed-form sample size expressions for a continuous outcome, through two methods
  - model-based variance with the true working correlation
  - robust variance with an independence working correlation
- Numerical sample size procedures for a binary outcome

Power and Sample Size Considerations

Table 1: A brief summary of variance estimators under different models for longitudinal IRGT trials with a continuous outcome.

Model	$\boldsymbol{H}_0$	Variance
1. NT-CTE	$\beta_2 = 0$	$\sigma^2_\beta = \frac{1}{T}\left\{\frac{\phi_c\lambda_{c4}}{q_cK_c} + \frac{\phi_t\lambda_{t4}}{(1-q_c)K_t}\right\}$
2. LT-CTE	$\beta_3 = 0$	
3. CT-CTE	$\beta_{T+1} = 0$	
4. LT-TI	$(\beta_3, \beta_4)' = (0, 0)'$	$\boldsymbol{V}_{sub} = \frac{1}{T}\left[\left\{\frac{\phi_c\lambda_{c3}}{q_cK_c} + \frac{\phi_t\lambda_{t3}}{(1-q_c)K_t}\right\}\frac{12}{T^2-1}\begin{pmatrix}\frac{(T+1)^2}{4} & -\frac{T+1}{2}\\ -\frac{T+1}{2} & 1\end{pmatrix} + \left\{\frac{\phi_c\lambda_{c4}}{q_cK_c} + \frac{\phi_t\lambda_{t4}}{(1-q_c)K_t}\right\}\begin{pmatrix}1 & 0\\ 0 & 0\end{pmatrix}\right]$
5. CT-TI	$(\beta_{21}, \ldots, \beta_{2T})' = (0, \ldots, 0)'$	$\boldsymbol{V}_{sub} = \left\{\frac{\phi_c\lambda_{c3}}{q_cK_c} + \frac{\phi_t\lambda_{t3}}{(1-q_c)K_t}\right\}\boldsymbol{I}_T + \frac{1}{T}\left\{\frac{\phi_c(\lambda_{c4}-\lambda_{c3})}{q_cK_c} + \frac{\phi_t(\lambda_{t4}-\lambda_{t3})}{(1-q_c)K_t}\right\}\boldsymbol{J}_T$

Power and Sample Size Considerations

Analytical insights for a continuous outcome

- Same variance formula[1] under Models 1-3
  - $\sigma_\beta^2 = \frac{1}{T}\left\{\frac{\phi_c \lambda_{c\mathbf{4}}}{q_c K_c} + \frac{\phi_t \lambda_{t\mathbf{4}}}{(1-q_c)K_t}\right\}$
  - no interaction between treatment and time
  - possible minor difference in sample size due to change in *df*
  - more efficient than the model for a singe time point

[1] $\lambda_{c\mathbf{4}} = \mathbf{1}+(K_c-\mathbf{1})\,\rho_{\mathbf{0}}+(T-\mathbf{1})\,(K_c-\mathbf{1})\,\rho_{\mathbf{1}}+(T-\mathbf{1})\rho_{\mathbf{2}}$, $\lambda_{t\mathbf{4}} = \mathbf{1}+(K_t-\mathbf{1})\,\alpha_{\mathbf{0}}+(T-\mathbf{1})\,(K_t-\mathbf{1})\,\alpha_{\mathbf{1}}+(T-\mathbf{1})\alpha_{\mathbf{2}}$.

Power and Sample Size Considerations

Theorem 1

Consider a longitudinal IRGT trial where the true correlation structure is block exchangeable with arm-specific correlation parameters. We further allow for arm-specific group sizes (K_t, K_c) and dispersion parameters (ϕ_t, ϕ_c). For a continuous outcome, using the sandwich variance expression under working independence results in the same value for σ^2_β or $\boldsymbol{V}_{sub}$ in each model (Models 1-5) as we obtain using the model-based variance expression in Table 1.

Power and Sample Size Considerations

Mean model choice

- Depend on the context of the trial and research objective
- Underlying time effects or secular trend
  - duration of the trial
- Plausibility of time-dependent treatment effect
  - immediate and constant effect
  - delayed effect or learning effect over time
- Based on content knowledge or pilot data

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Simulation Study

Simulation study

- For both continuous and binary outcomes
- Longitudinal IRGT trial with equal allocation $\pi_c = 1/2$
- $\rho_0 = \rho_1 = 0$ and $\rho_2 = \alpha_2$
  - control arm only has a within-individual correlation
  - same within-individual correlation in the two arms
  - mimic the SYV trial in practice
- $K_t = 10$, $K_c = 1$, $q_c = 10/11$

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  - control arm only has a within-individual correlation
  - same within-individual correlation in the two arms
  - mimic the SYV trial in practice
- $K_t = 10$, $K_c = 1$, $q_c = 10/11$
- 6 scenarios with different parameters for each of the 5 models
  - calculate the smallest sample size for predicted power $\geq 85\%$
  - I_t ranges from 8 to 23

Simulation Study

Simulation study

- 1000 data replications for each scenario
- Two GEE analyses with bias-corrected sandwich variance estimators
  - GEE/MAEE with the true working correlation
  - GEE with an independence working correlation
- Four variance estimators
  - Model-based variance estimator (MB)
  - Uncorrected robust sandwich variance estimator (ROB)
  - KC-bias corrected sandwich variance estimator (KC)
  - MD-bias corrected sandwich variance estimator (MD)

Simulation Study

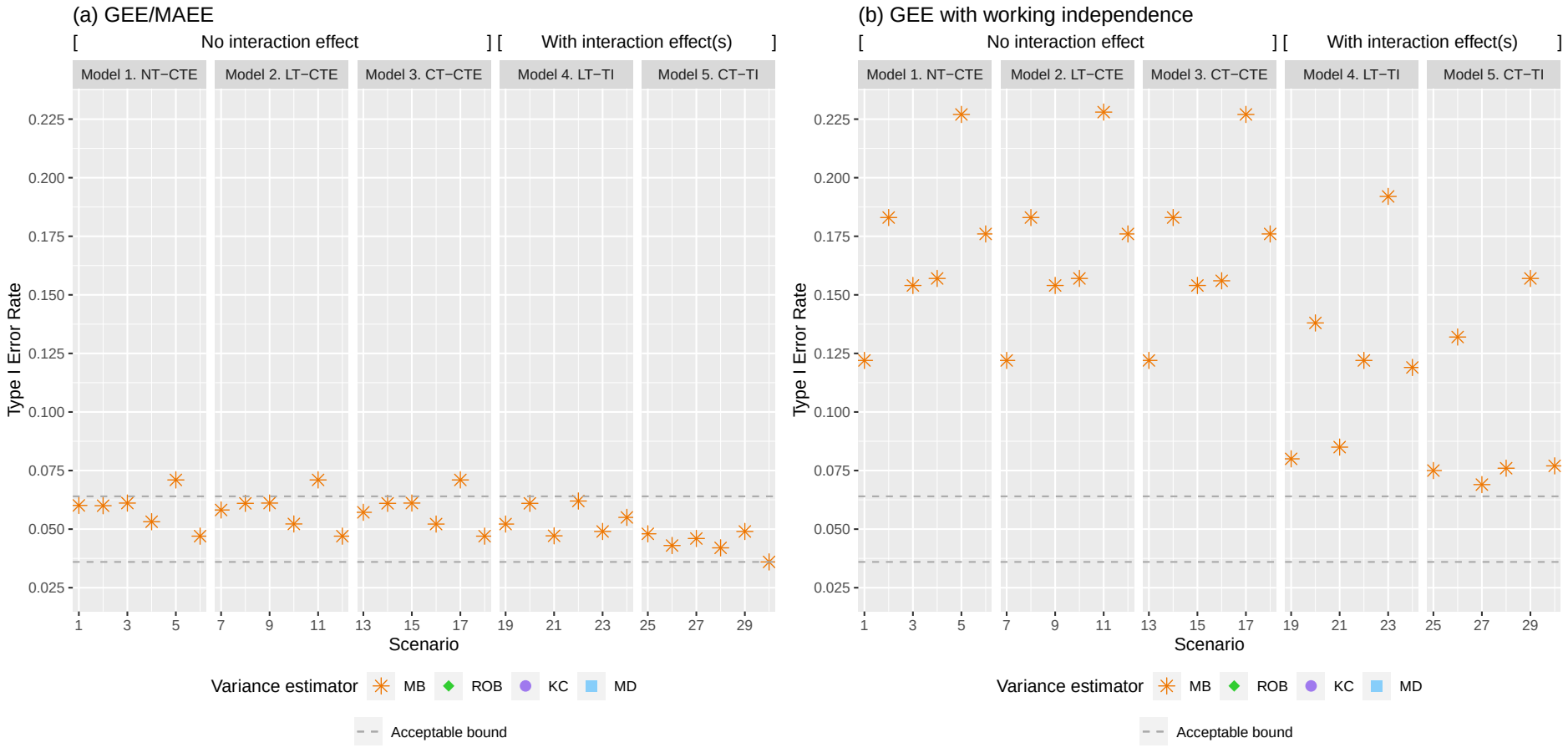

Figure 2: Empirical type I error rates of analyses for continuous outcomes using (a) GEE/MAEE with the true working correlation structures and (b) GEE with an independence working correlation structure, based on different variance estimators. NT-CTE: No-time constant treatment effect; LT-CTE: Linear-time constant treatment effect; CT-CTE: Categorical-time constant treatment effect; LT-TI: Linear time by treatment interaction; CT-TI: Categorical time by treatment interaction.

Simulation Study

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Simulation Study

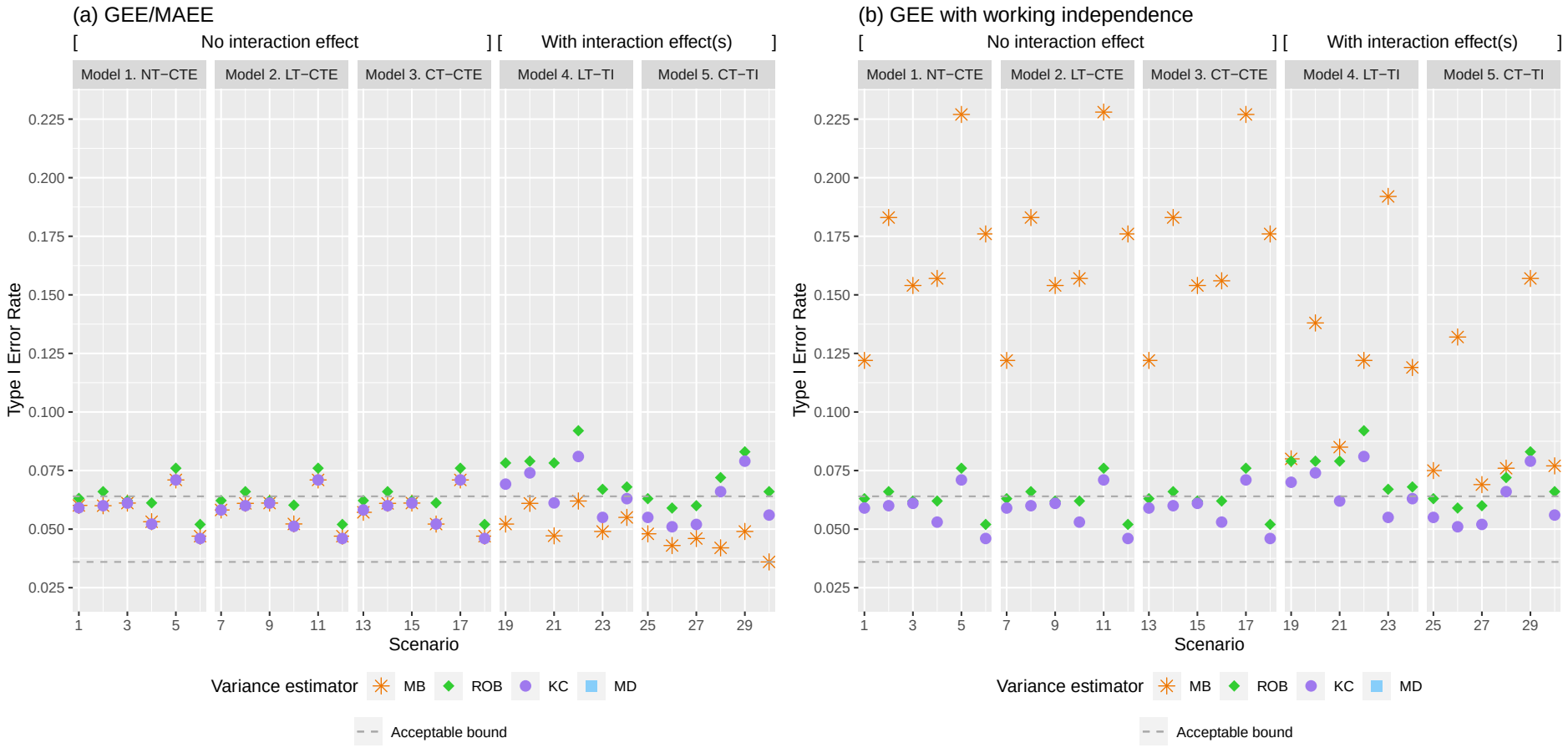

Figure 2: Empirical type I error rates of analyses for continuous outcomes using (a) GEE/MAEE with the true working correlation structures and (b) GEE with an independence working correlation structure, based on different variance estimators. NT-CTE: No-time constant treatment effect; LT-CTE: Linear-time constant treatment effect; CT-CTE: Categorical-time constant treatment effect; LT-TI: Linear time by treatment interaction; CT-TI: Categorical time by treatment interaction.

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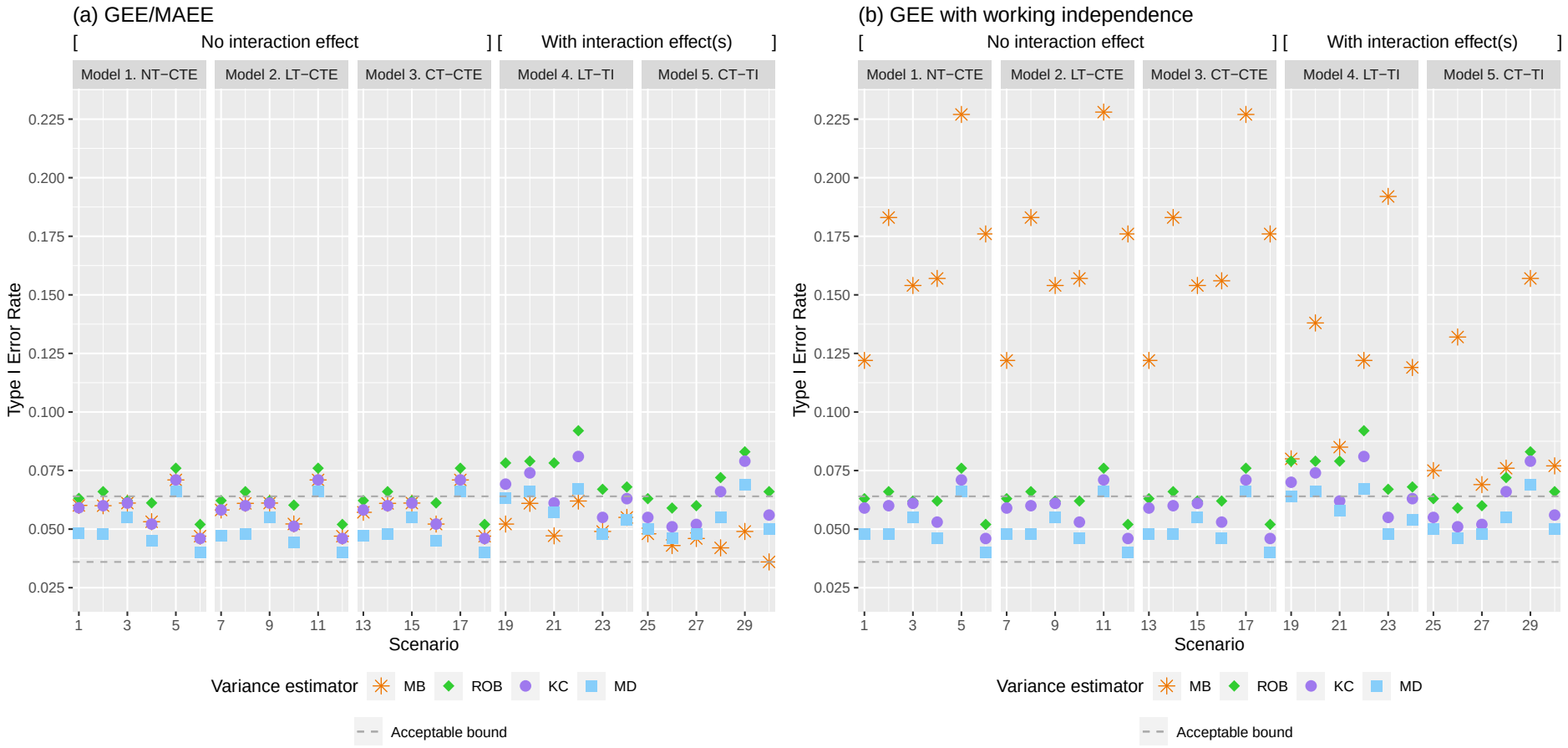

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Simulation Study

Figure 3: Differences between the empirical power and the predicted power of analyses for continuous outcomes using (a) GEE/MAEE with the true working correlation structures and (b) GEE with an independence working correlation structure, based on different variance estimators. NT-CTE: No-time constant treatment effect; LT-CTE: Linear-time constant treatment effect; CT-CTE: Categorical-time constant treatment effect; LT-TI: Linear time by treatment interaction; CT-TI: Categorical time by treatment interaction.

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Section

1 Introduction

2 Statistical Model

3 Power and Sample Size Considerations

4 Simulation Study

5 Application to the SYV Trial

6 Summary

Application to the SYV Trial

SYV trial

- Longitudinal IRGT trial
- Randomization level: individual
- Equal allocation to the two arms
- Comparison
  - treatment: a series of group-based mental health sessions
  - control: routine care as usual delivered individually
- 8 individuals per treatment group
- Outcome: log viral load assessed at 3 follow-up time points

Application to the SYV Trial

Sample size calculation

- No assumed treatment-by-time interactions
- Correlation assumption[1]
  - $\rho_0 = \rho_1 = 0$
  - $\rho_2 = \alpha_2$
  - $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \alpha_2) = (0.04, 0.03, 0.8)$
- Assumed standardized effect size $= 0.3$
- Target a minimum of 85% power

[1] $\alpha_{\mathbf{0}}$ = within-time correlation for two different individuals in the same treatment group, $\alpha_{\mathbf{1}}$ = between-time correlation for two different individuals in the same treatment group, $\alpha_{\mathbf{2}}$ = within-individual correlation in both arms.

Application to the SYV Trial

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- Assumed standardized effect size $= 0.3$
- Target a minimum of 85% power
- The proposed sample size formula suggested that the required number of individuals is 400 with power of 85.4%
  - 25 groups for a total of 200 individuals in the treatment arm
  - 200 individuals in the control arm

[1] α_0 = within-time correlation for two different individuals in the same treatment group, α_1 = between-time correlation for two different individuals in the same treatment group, α_2 = within-individual correlation in both arms.

Application to the SYV Trial

Sensitivity analysis

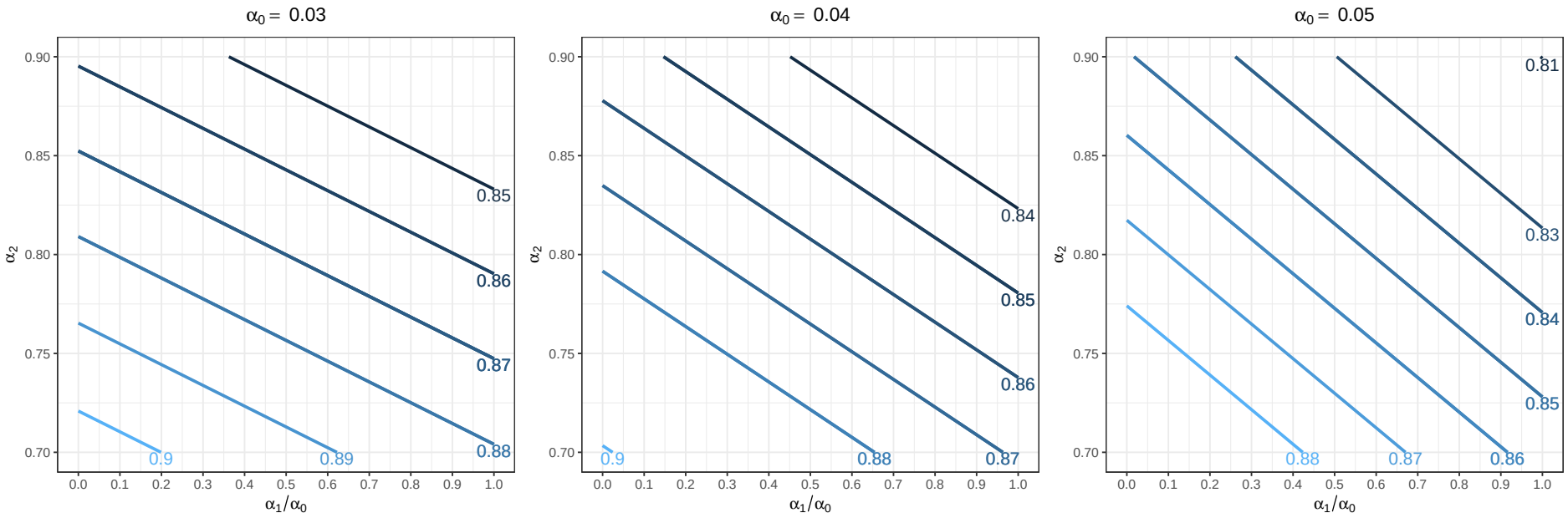

Figure 4: Predicted power contours as a function of α_1/α_0 and α_2 at $\alpha_0 = \{0.03, 0.04, 0.05\}$, with $N = 400$, $I = 225$, $K_t = 8$, $K_c = 1$, $T = 3$, $b = 0.3\sqrt{\phi}$ for the SYV trial[1].

[1] α_0 = within-time correlation for two different individuals in the same treatment group, α_1 = between-time correlation for two different individuals in the same treatment group, α_2 = within-individual correlation in both arms.

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Summary

Summary

- Developed sample size methodology for longitudinal IRGT trials
  - block exchangeable correlation structures with different correlation parameters for the two arms
  - survey 5 marginal mean models
  - closed-form sample size expressions for a continuous outcome
  - numerical sample size procedures for a binary outcome
- Demonstrated proposed methods work well for as few as 8 groups formed in the treatment arm
  - GEE analysis with a bias-corrected sandwich variance estimator
- Simulation code openly available in GitHub at `https://github.com/XueqiWang/Longitudinal_IRGT`

Summary

Paper published

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RESEARCH ARTICLE

Statistics in Medicine WILEY

Designing individually randomized group treatment trials with repeated outcome measurements using generalized estimating equations

Xueqi Wang[1,2] | Elizabeth L. Turner[1,3] | Fan Li[2,4]

Thank You
Any questions?

References I

Campbell, M. K., Piaggio, G., Elbourne, D. R., and Altman, D. G. (2012). Consort 2010 statement: extension to cluster randomised trials. *Bmj* **345,** e5661.

Kauermann, G. and Carroll, R. J. (2001). A note on the efficiency of sandwich covariance matrix estimation. *Journal of the American Statistical Association* **96,** 1387–1396.

Li, F., Turner, E. L., and Preisser, J. S. (2018). Sample size determination for gee analyses of stepped wedge cluster randomized trials. *Biometrics* **74,** 1450–1458.

Liang, K.-Y. and Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73,** 13–22.

Mancl, L. A. and DeRouen, T. A. (2001). A covariance estimator for gee with improved small-sample properties. *Biometrics* **57,** 126–134.

Preisser, J. S., Lu, B., and Qaqish, B. F. (2008). Finite sample adjustments in estimating equations and covariance estimators for intracluster correlations. *Statistics in Medicine* **27,** 5764–5785.