Stepped Wedge Cluster Randomized Trials

Kenny Chiu

Supervising Faculty: John Petkau

The University of British Columbia
Department of Statistics

STAT 548 Qualifying Paper 2
Oral Presentation

December 9, 2021

Outline

Introduction

Background

Paper by Hussey and Hughes [1] can be viewed as entry point to stepped wedge cluster randomized trials (SW-CRT)

- Provides an overview of motivation, design and analysis of SW-CRTs
- Focuses on technical aspects of practical interest such as power and estimators
- Presents ideas in an accessible and succinct format

Main limitations and weaknesses from our perspective:

1. Limited breadth: discussion is restricted to primarily one SW-CRT setting
2. Minimal depth: technical details are only briefly explained or omitted entirely
3. Writing: unclear which aspects are novel; some typos and/or errors

Objective

Our main goal is to address the limitations of Hussey and Hughes [1]:

1. Address missed technical details, explanations and derivations
2. Clarify their simulation procedure and attempt to replicate their simulation results
3. Discuss extensions to their basic model for different SW-CRT settings

Analysis of stepped wedge cluster randomized trials

Assumed SW-CRT setting

Washington State Community Expedited Partner Treatment (EPT) Trial:

- Hypothesis: EPT public health programs decrease prevalence of chlamydia and incidence of gonorrhea in young women
- Method: Program implemented in 23 local health jurisdictions (LHJ) in 4 waves; primary outcomes were prevalence (incidence) of chlamydia (gonorrhea) in tested women

Primary SW-CRT setting based on EPT trial that Hussey and Hughes [1] work under:

- SW-CRT with $I = 24$ clusters and $T = 5$ measured time points
- Cross-sectional design with $N = 100$ units at each cluster-time

Statistical model

Individual-level model under assumed SW-CRT setting:

$$\begin{aligned} Y_{ijk} &= \mu + \alpha_i + \beta_j + X_{ij}\theta + e_{ijk} \\ &= \mu_{ij} + e_{ijk} \end{aligned}$$

- μ is the mean across clusters and time
- $\alpha_i \sim N(0, \tau^2)$ is a random effect for cluster $i \in \{1, \ldots, I\}$
- β_j is a fixed effect for time point $j \in \{1, \ldots, T-1\}$ ($\beta_T = 0$ for identifiability)
- X_{ij} is a treatment indicator for cluster i at time j (1 denotes intervention)
- θ is the treatment effect of interest
- $e_{ijk} \sim N(0, \sigma^2)$ are i.i.d. noise

Methods for estimating treatment effect θ [1]

1. Within-cluster estimator
   - Consistent if no time effects ($\beta_j = 0$ for all j); biased otherwise [A1]

2. Linear mixed effects model (LMM) via weighted least squares (WLS)
   - Useful if τ^2 and σ^2 known or clusters roughly equal sized; loss of power otherwise due to misspecified weights
   - More efficient than within-cluster estimator if no time effects; note Liao et al. [2] found an error in Hussey and Hughes' relative efficiency [A2]

3. Generalized linear mixed effects model (GLMM)
   - Weights are appropriately weighted even if variance components unknown
   - Link function allows choice of how expected response is modeled

4. Generalized estimating equations (GEE)
   - Consistent even if correlation structure misspecified as long as mean is correctly specified

Power calculation

Hussey and Hughes [1] prescribe using a Wald test to test $H_0 : \theta = 0$

- Power for a test of size α is approximately

$$\Phi\left(\frac{\theta_a}{\sqrt{\mathrm{Var}(\hat{\theta})}} - Z_{1-\frac{\alpha}{2}}\right)$$

  where Φ is the cumulative distribution function of a standard normal [A3]

Hussey and Hughes [1] also show that

- power is maximized when each cluster crosses over at its own time point [A4]
- delays in treatment effect decreases power [A5]

Investigation of simulation study

Procedure

Results

Extensions to basic model

Conclusion

Multiple factor analysis

- Factor analysis: estimate latent factors underlying observed data
- *Principal Component Analysis*: given data matrix $A \in \mathbb{R}^{n \times d}$, returns scaled *loadings* $V \in \mathbb{R}^{d \times d}$ and *principal components* (PCs) $S \in \mathbb{R}^{n \times d}$ s.t.

$$S = AV$$

  $\Rightarrow$ Represent and estimate factors by the leading $k \leq d$ PCs

- PCs are (orthogonal) vectors—difficult to interpret if there are many coefficients

Multiple factor analysis

- Factor analysis: estimate latent factors underlying observed data
- *Principal Component Analysis*: given data matrix $A \in \mathbb{R}^{n \times d}$, returns scaled *loadings* $V \in \mathbb{R}^{d \times d}$ and *principal components* (PCs) $S \in \mathbb{R}^{n \times d}$ s.t.

$$S = AV$$

  $\Rightarrow$ Represent and estimate factors by the leading $k \leq d$ PCs

- PCs are (orthogonal) vectors—difficult to interpret if there are many coefficients
- **?**]: rotate PCs to make coefficients as sparse as possible (i.e., ≈ 0)

References I

[1] Hussey, M. A. and Hughes, J. P. (2007). Design and analysis of stepped wedge cluster randomized trials. *Contemporary Clinical Trials*, 28(2):182–191.

[2] Liao, X., Zhou, X., and Spiegelman, D. (2015). A note on "Design and analysis of stepped wedge cluster randomized trials". *Contemporary Clinical Trials*, 45(Pt B):338.

Within-cluster estimator [S9]

Relative efficiency of within-cluster to WLS [S9]

Approximate power [S10]

Reduced time points [S10]

Delay in treatment effect [S10]