Stepped wedge cluster randomized controlled trials with two layers of clustering: Designs and comparisons of power

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Stepped Wedge Design

- The intervention is given sequentially to the clusters whose orders are randomly determined.

	Time						
Pattern	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	0	1	1	1	1	1	1
2	0	0	1	1	1	1	1
3	0	0	0	1	1	1	1
4	0	0	0	0	1	1	1
5	0	0	0	0	0	1	1
6	0	0	0	0	0	0	1

Aims

- Introduce a well-defined set of novel stepped wedge designs for data with two layers of clustering (e.g., wards within a hospital).
- Compare the efficiency of detecting the treatment effect under different designs.
- Find a class of optimal designs yielding the highest estimation efficiency across all values of considered data features.

Motivating Example

- A study was conducted to find the association of an adult tele-intensive care unit (ICU) intervention (the delivery of care to critically ill patients by remote health care professionals) with hospital mortality, length of stay, and other relevant outcomes.
- The researchers performed a stepped wedge design under which the tele-ICU intervention was rolled out sequentially to 14 adult ICUs from 3 medical centers.
- In this case, we have a three-level data structure: patients, ICUs (units), and medical centers (clusters).

Proposed designs for complete SW-CRTs with multiple layers of clustering

Proposed Designs

- For the data structure "units within clusters", we proposed a set of stepped wedge designs.
- Four example designs are given here.
- 6 independent clusters, numbered from 1 to 6.
- 6 units in each cluster, numbered from 1 to 6.
- Use (cluster, unit) to indicate which unit from which cluster. E.g., (1, 3) means unit 3 from cluster 1.

Example Designs – Design 1
(All units transfer at a single step)

		Time						
Pattern	**(Cluster, Units)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	**(1, 1-6)**	0	1	1	1	1	1	1
2	**(2, 1-6)**	0	0	1	1	1	1	1
3	**(3, 1-6)**	0	0	0	1	1	1	1
4	**(4, 1-6)**	0	0	0	0	1	1	1
5	**(5, 1-6)**	0	0	0	0	0	1	1
6	**(6, 1-6)**	0	0	0	0	0	0	1

- As proposed by Hemming et al. (2015), all units in a cluster complete the transition from the control arm to the intervention arm in one step.
- May be suitable for those who plan to roll out the intervention at one place at a time due to labor or some other constraints.

Example Designs – Design 4 (Units transfer at all of the steps)

		Time						
Pattern	(Cluster, Units)	1	2	3	4	5	6	7
1	(1-6, 1)	0	1	1	1	1	1	1
2	(1-6, 2)	0	0	1	1	1	1	1
3	(1-6, 3)	0	0	0	1	1	1	1
4	(1-6, 4)	0	0	0	0	1	1	1
5	(1-6, 5)	0	0	0	0	0	1	1
6	(1-6, 6)	0	0	0	0	0	0	1

- Units from the same cluster are randomly assigned to transfer at different points.
- Given adequate labor, researchers can be divided into six groups, each of which works with a cluster until the end of the study.
- Advantage is that these research groups do not need to travel among clusters, especially when traveling is difficult or expensive.

Example Designs – Design 2 (Units transfer within two adjacent steps)

		Time						
Pattern	(Cluster, Units)	1	2	3	4	5	6	7
1	(1, 1-3); (2, 1-3)	0	1	1	1	1	1	1
2	(1, 4-6); (2, 4-6)	0	0	1	1	1	1	1
3	(3, 1-3); (4, 1-3)	0	0	0	1	1	1	1
4	(3, 4-6); (4, 4-6)	0	0	0	0	1	1	1
5	(5, 1-3); (6, 1-3)	0	0	0	0	0	1	1
6	(5, 4-6); (6, 4-6)	0	0	0	0	0	0	1

- Units within the same cluster transfer to the intervention arm at separate and adjacent steps.
- Half of the cluster receives the intervention first. Then the other half goes through the transition one period after the first half completes the transition.

Example Designs – Design 3
(Units transfer in two nonadjacent steps)

		Time						
Pattern	**(Cluster, Units)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	(1, 1-3); (2, 1-3)	0	1	1	1	1	1	1
2	(3, 1-3); (4, 1-3)	0	0	1	1	1	1	1
3	(5, 1-3); (6, 1-3)	0	0	0	1	1	1	1
4	(1, 4-6); (2, 4-6)	0	0	0	0	1	1	1
5	(3, 4-6); (4, 4-6)	0	0	0	0	0	1	1
6	(5, 4-6); (6, 4-6)	0	0	0	0	0	0	1

- Units from the same cluster complete the transition from the control to the intervention in two separate and nonadjacent steps.
- The first three steps constitute a mini stepped wedge design among the first halves of clusters 1–6.

Evaluation of the Designs

Model

Proposed in Hemming et al. (2015), the following mixed model is used to analyze multi-level data:

$$Y_{ijkl} = \mu + \alpha_i + \beta_{ij} + \delta_k + X_{ijk}\theta + \epsilon_{ijkl}. \quad (1)$$

- $i = 1, \ldots, I$, I being the number of clusters; $j = 1, \ldots, G$, G being the number of units within each cluster; $k = 2, \ldots, T$, T being the number of time points; and $l = 1, \ldots, N$, N being the cell size, i.e., the number of individuals in each unit within a cluster measured at each time point.
- The fixed effects of time and treatment are δ_k and θ, respectively. X_{ijk} is the indicator for receiving the intervention (1 if the intervention is received; 0 otherwise).
- $\alpha_i \sim N(0, \sigma_a^2)$, $\beta_{ij} \sim N(0, \sigma_b^2)$, and $\epsilon_{ijkl} \sim N(0, \sigma_e^2)$. α_i, β_{ij}, and ϵ_{ijkl} are mutually independent.

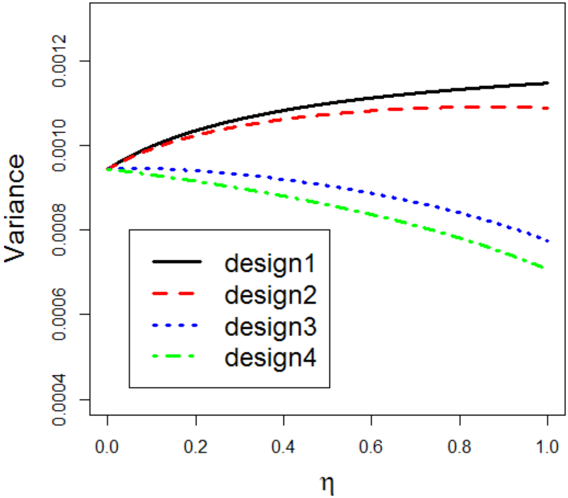
Two Relevant Quantities

- The **intra-cluster correlation (ICC)** among individuals within the same unit of a cluster, $\rho = \frac{\sigma_a^2 + \sigma_b^2}{\sigma_a^2 + \sigma_b^2 + \sigma_e^2}$.
- The **proportion of correlation due to the first layer clustering**, defined to be $\eta = \frac{\sigma_a^2}{\sigma_a^2 + \sigma_b^2}$.

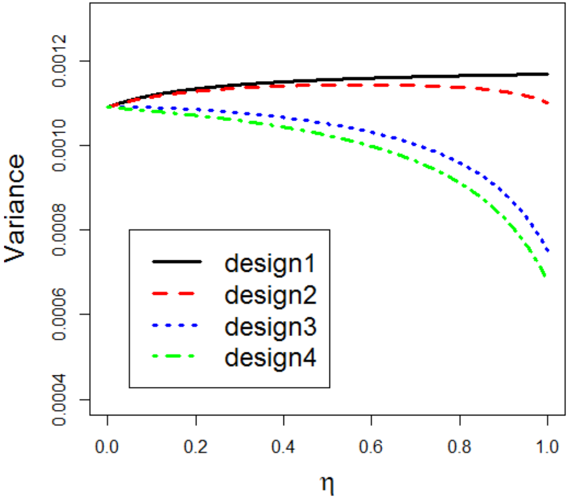
Study Setup

- The number of clusters $I = 12$; the number of units within each cluster $G = 6$; within each combination of units and time points (cells), the number of participants $N = 20$.
- The number of time periods $T = 7$.
- The total variance of the response Y_{ijkl} is fixed at 1.
- The fixed effects are set to be $\psi = (\mu, \theta, \delta_2, ..., \delta_T)^T = (0.3, 0.1, 0, \ldots, 0)^T$.
- Study 1: Vary η for fixed ρ (0.01, 0.05, 0.2, 0.4).
- Study 2: Vary ρ for fixed η (0, 0.3, 0.7, 1).

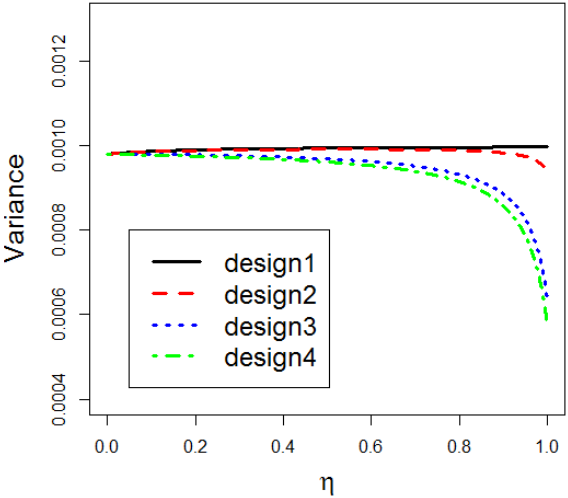
Results – Study 1 ($\rho = 0.01$)



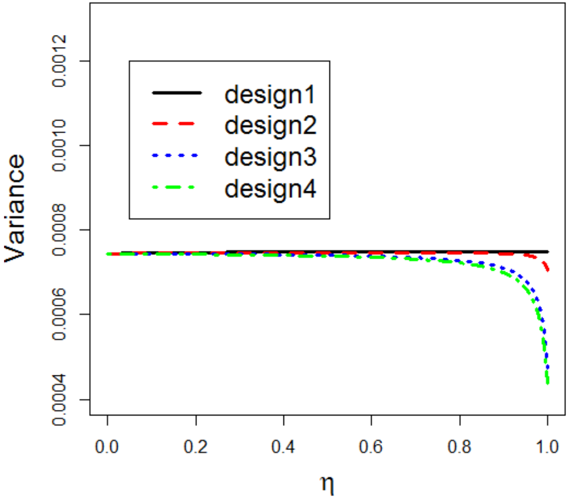
Results – Study 1 ($\rho = 0.05$)



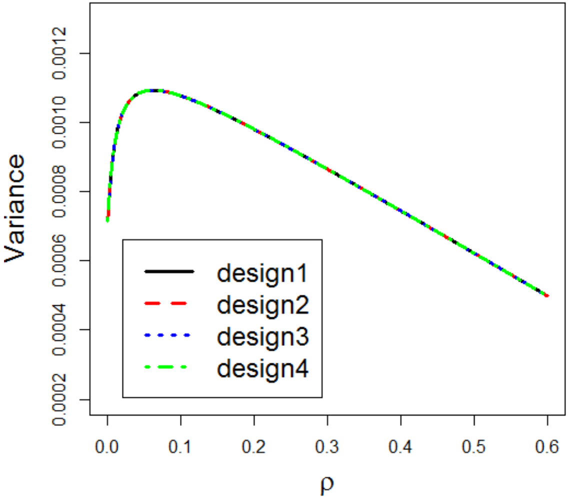
Results – Study 1 ($\rho = 0.2$)



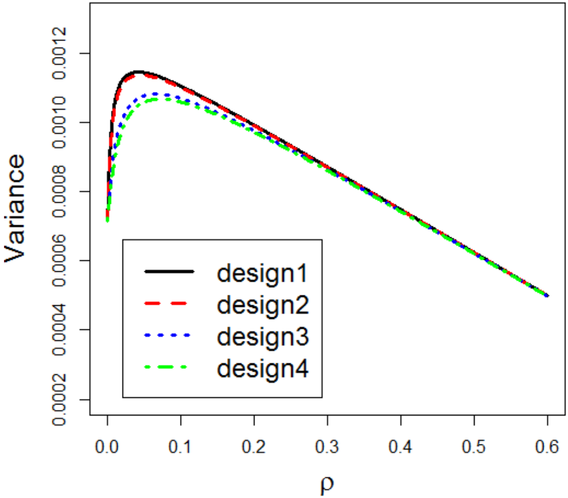
Results – Study 1 ($\rho = 0.4$)



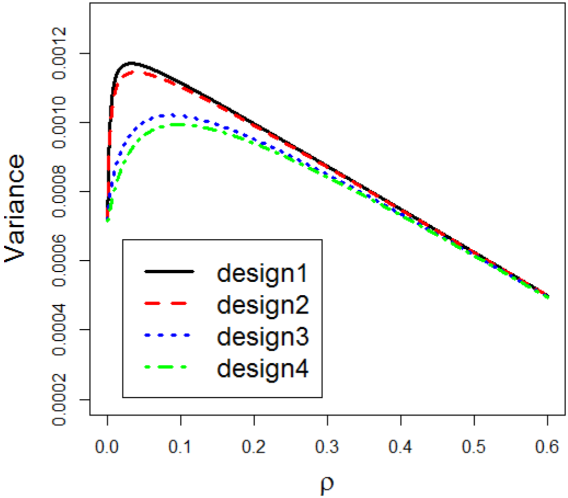
Results – Study 2 ($\eta = 0$)



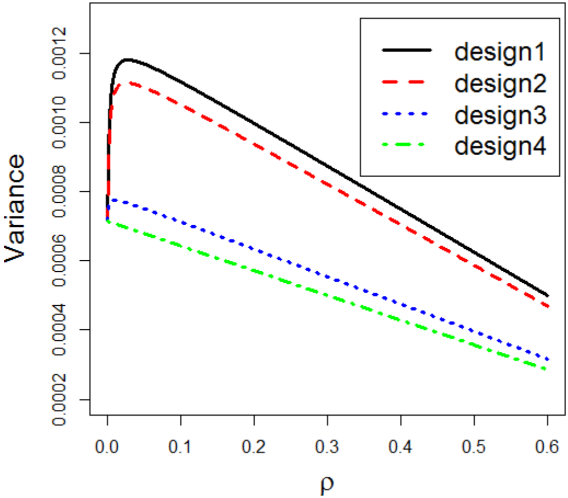
Results – Study 2 ($\eta = 0.3$)



Results – Study 2 ($\eta = 0.7$)



Results – Study 2 ($\eta = 1$)



Discussion

- Design 1 is least efficient. Design 4 is most efficient.
- Designs that maximize the number of within-cluster between-unit comparisons are optimal among the designs with the same design features (number of patterns, cluster/unit number, cluster/unit size).
- Several directions for future research: Change of correlation structures; Characterize the robustness of our designs to misspecification of the covariance matrix of outcomes and contamination.

References

- Brown, C. A. and Lilford, R. (2006). The stepped wedge trial design: a systematic review. *BMC Medical Research Methodology*, 6.
- Hemming, K., Haines, T. P., Chilton, P. J., Girling, A. J., and Lilford, R. J. (2015a). The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *British Medical Journal*, 350.
- Hemming, K., Lilford, R., and Girling, A. J. (2015b). Stepped-wedge cluster randomized controlled trials: a generic framework including parallel and multiple-level designs. *Statistics in Medicine*, 34:181-196.
- Hussey, M. A. and Hughes, J. P. (2007). Design and analysis of stepped wedge cluster randomized trials. *Contemporary Clinical Trials*, 28:182-191.

Thank you!

Proposed Designs

For data with the structure "units within clusters", we propose a set of stepped wedge design and impose a list of restrictions on the designs:

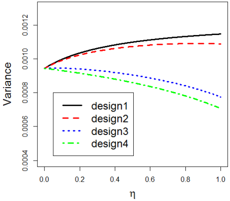
- The design is fully balanced. First, the numbers of clusters in different steps are equal. Second, the number of units within a cluster is fixed. Third, within each combination (cell) of different units and time periods, the number of participants remains the same.
- The number of clusters I is a multiple of the number of steps S.
- The number of units G in each cluster is a multiple of the number of steps S.

Example Designs – Design 2 (Unbalanced)

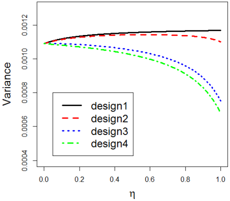
		Time							
Pattern	**(Cluster, Units)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	(1, 1-3)	0	1	1	1	1	1	1	1
2	(1, 4-6); (2, 1-3)	0	0	1	1	1	1	1	1
3	(2, 4-6); (3, 1-3)	0	0	0	1	1	1	1	1
4	(3, 4-6); (4, 1-3)	0	0	0	0	1	1	1	1
5	(4, 4-6); (5, 1-3)	0	0	0	0	0	1	1	1
6	(5, 4-6); (6, 1-3)	0	0	0	0	0	0	1	1
7	(6, 4-6)	0	0	0	0	0	0	0	1

May be especially useful when researchers prefer allocating the intervention to fewer participants at the initial step as a trial.

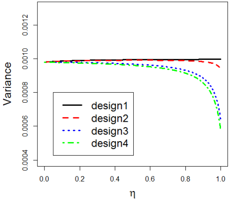
Results – Study 1 (Fixed ρ)



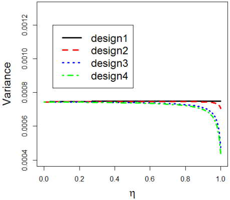
(a) $\rho = 0.01$



(b) $\rho = 0.05$

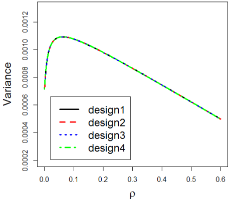


(c) $\rho = 0.2$

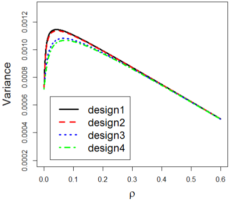


(d) $\rho = 0.4$

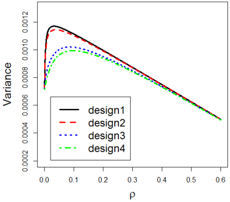
Results – Study 2 (Fixed η)



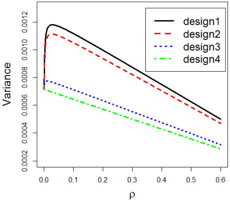
(e) $\eta = 0$



(f) $\eta = 0.3$



(g) $\eta = 0.7$



(h) $\eta = 1$