Misspecifying within-cluster correlation structure in stepped wedge trials

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The usual stepped wedge

	Period 1	Period 2	Period 3	Period 4
Cluster 1	0	1	1	1
Cluster 2	0	0	1	1
Cluster 3	0	0	0	1

Can extend this to have more clusters and more periods: just retain the “stepped wedge” structure!

A model for continuous outcomes

Need a model for the outcome that allows for the similarity of outcomes measured on subjects *from within the same cluster*.

General model:

$$\begin{aligned}\text{Outcome} = &\ \text{Period effect} \ + \ \text{treatment effect} \\ &+ \ \textbf{random effects} \ + \ \text{errors}, \quad \text{errors} \ \sim N(0, \sigma^2_\epsilon)\end{aligned}$$

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- 2. A more complex model: for subjects in the same cluster

  Correlation b/w any two subjects **in the same period** $= \rho$

  Correlation b/w any two subjects **in different periods** $= r \times \rho$

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  Correlation b/w any two subjects **in different periods** $= r \times \rho$

- 3. Allowing for a decay in the correlation over time: (same cluster!)

  Correlation between subject **in period** t and **period** $s = r^{|t-s|}\rho$

Within-period and between-period ICCs (intra-cluster correlations)

Model	Within-period ICC Same Period	Between-period ICC Periods s and t, $s \neq t$
1	ρ	ρ
2	ρ	$r \times \rho$
3	ρ	$r^{\lvert t-s \rvert} \times \rho$

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BUT what about the confidence interval?

- Confidence interval width depends on estimates of the within-cluster correlation structure.
- ANOVA estimators available for Models 1 and 2.
  - Model 3: no such estimators available.
  - What happens if Model 1 or 2 used when Model 3 should be used?

What if a decay in correlation is omitted?

Consider confidence interval width for each model:

- V_3: the CI width under the “true” decay model
- $\hat{V}_1$: CI width when Model 1 used to estimate variance components
- $\hat{V}_2$: CI width when Model 2 used to estimate variance components

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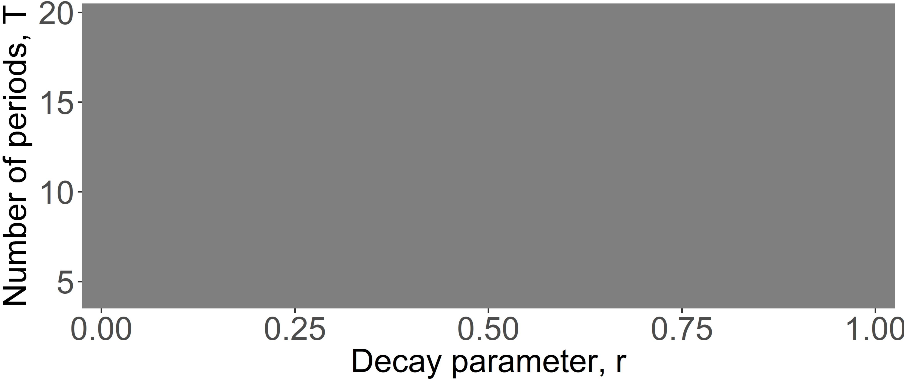
Consider $\hat{V}_1/V_3$ and $\hat{V}_2/V_3$ for stepped wedge designs for each combination of:

- $4, 5, \ldots, 20$ periods;
- decay in correlations $r = 0, 0.05, 0.1, \ldots, 0.95, 1$;
- ICC $\rho = 0.05$;
- 100 subjects in each cluster in each period.

Using Model 1 instead of Model 3 ($\hat{V}_1 / V_3$)



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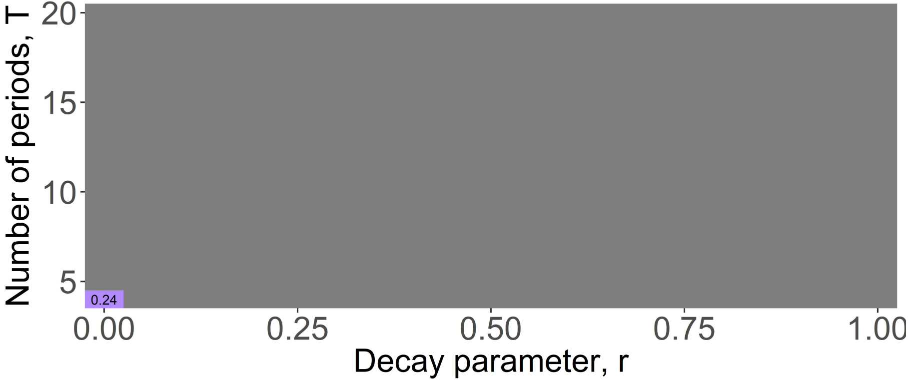

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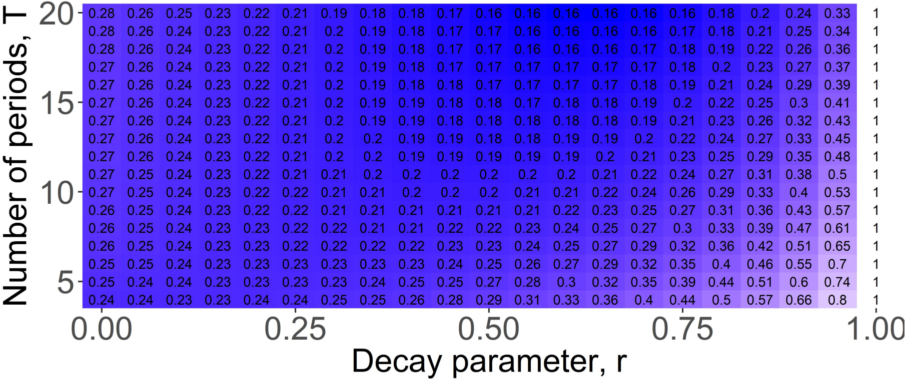
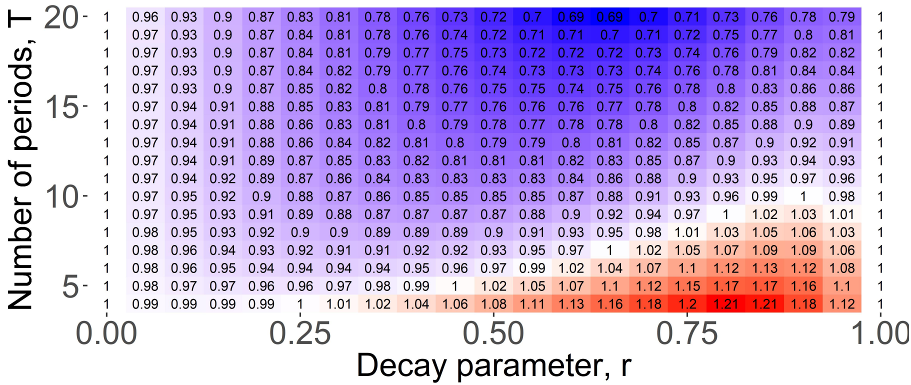


Using Model 2 instead of Model 3 ($\hat{V}_2 / V_3$)



Take-home messages

Failure to incorporate decaying within-cluster correlations leads to problems!

Model 1: Within period ICC = between period ICC

- Confidence intervals too narrow
- Type I error rate inflated.

Model 2: Within period ICC $\neq$ between period ICC, but no decay

- Confidence intervals too narrow OR too wide!
- Depends on the design (number of periods, subjects in each cluster in each period, ICC).

Check out the implications for yourself:

`https://monash-biostat.shinyapps.io/MisspecCorrStruct`

Three possible models

Y_{kti}: outcome for subject i, in cluster k, during period t

- 1. A simple model: (Hussey and Hughes)

$$Y_{kti} = \beta_t + \theta X_{kt} + \alpha_k + \epsilon_{kti}, \quad \epsilon_{kti} \sim N(0, \sigma^2_\epsilon), \quad \alpha_k \sim N(0, \sigma^2_\alpha),$$

- 2. A more complex model:

$$Y_{kti} = \beta_t + \theta X_{kt} + \alpha_k + \gamma_{kt} + \epsilon_{kti}, \quad \epsilon_{kti} \sim N(0, \sigma^2_\epsilon)$$

$$\alpha_k \sim N(0, r \times \sigma^2_\alpha), \quad \gamma_{kt} \sim N(0, (1-r) \times \sigma^2_\alpha)$$

- 3. More complex still:

$$Y_{kti} = \beta_t + \theta X_{kt} + \gamma_{kt} + \epsilon_{kti}, \quad \epsilon_{kti} \sim N(0, \sigma^2_\epsilon)$$

$$\gamma_k = (\gamma_{k1}, \ldots, \gamma_{kT})' \sim N(0, \Sigma), \quad cov(\gamma_{kt}, \gamma_{ks}) = \sigma^2_\alpha r^{|t-s|}$$

Table: Mean squares and ANOVA estimators for the variance components of the two-way crossed classification models with and without interactions.

Model 1	Mean Square	ANOVA estimators
Cluster	$MSK(1) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k\bullet\bullet} - \overline{Y}_{\bullet\bullet\bullet}\right)^2$	$\hat{\sigma}^2_{1\alpha} = \frac{MSK(1)-MSE(1)}{Tm}$
Residual	$MSE(1) = \frac{1}{KTm-K-T+1} \sum_k \sum_t \sum_i$ $\left(\overline{Y}_{kti} - \overline{Y}_{k\bullet\bullet} - \overline{Y}_{\bullet t\bullet} + \overline{Y}_{\bullet\bullet\bullet}\right)^2$	$\hat{\sigma}^2_{1\epsilon} = MSE(1)$
Model 2		
Cluster	$MSK(2) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k\bullet\bullet} - \overline{Y}_{\bullet\bullet\bullet}\right)^2$	$\hat{\sigma}^2_{2\alpha} = \frac{MSK(2)-MSKT(2}{Tm}$
Period $\times$ Cluster	$MSKT(2) = \frac{1}{(K-1)(T-1)} \sum_k \sum_t m$ $\left(\overline{Y}_{kt\bullet} - \overline{Y}_{k\bullet\bullet} - \overline{Y}_{\bullet t\bullet} + \overline{Y}_{\bullet\bullet\bullet}\right)^2$	$\hat{\sigma}^2_{\gamma} = \frac{MSKT(2)-MSE(2)}{m}$
Residual	$MSE(2) = \frac{1}{KT(m-1)} \sum_k \sum_t \sum_i \left(\overline{Y}_{kti} - \overline{Y}_{kt\bullet}\right)^2$	$\hat{\sigma}^2_{2\epsilon} = MSE(2)$

$$\overline{Y}_{kt\bullet} = \frac{1}{m} \sum_{i=1}^{m} Y_{kti}, \quad \overline{Y}_{k\bullet\bullet} = \frac{1}{mT} \sum_{t=1}^{T} \sum_{i=1}^{m} Y_{kti},$$

$$\overline{Y}_{\bullet t\bullet} = \frac{1}{mK} \sum_{k=1}^{K} \sum_{i=1}^{m} Y_{kti}, \quad \overline{Y}_{\bullet\bullet\bullet} = \frac{1}{mTK} \sum_{k=1}^{K} \sum_{t=1}^{T} \sum_{i=1}^{m} Y_{kti}.$$

Table: Expected values of variance component estimators in Table 1 for outcomes distributed according to the two-way crossed classification model without and with an interaction between cluster and period, and correlation decay models.

Fitted Model	True Model Model 3: Correlation decay
Model 1	
$E\left[\hat{\sigma}^2_{1\alpha}\right]$	$\sigma^2_{3\alpha}\left[\frac{Km-1}{T(KTm-K-T+1)}\sum_{t=1}^{T}\sum_{s=1}^{T} r^{\lvert t-s\rvert} - \frac{K-1}{KTm-K-T+1}\right]$
$E\left[\hat{\sigma}^2_{1\epsilon}\right]$	$\sigma^2_{3\epsilon} + \sigma^2_{3\alpha}\left[\frac{(K-1)Tm}{KTm-K-T+1} - \frac{m(K-1)}{T(KTm-K-T+1)}\sum_{t=1}^{T}\sum_{s=1}^{T} r^{\lvert t-s\rvert}\right]$
Model 2	
$E\left[\hat{\sigma}^2_{2\epsilon}\right]$	$\sigma^2_{3\epsilon}$
$E\left[\hat{\sigma}^2_{\gamma}\right]$	$\sigma^2_{3\alpha}\left(\frac{T}{T-1} - \frac{1}{T(T-1)}\sum_{t=1}^{T}\sum_{s=1}^{T} r^{\lvert t-s\rvert}\right)$
$E\left[\hat{\sigma}^2_{2\alpha}\right]$	$\sigma^2_{3\alpha}\left(\frac{1}{T(T-1)}\sum_{t=1}^{T}\sum_{s=1}^{T} r^{\lvert t-s\rvert} - \frac{1}{T-1}\right)$

Table: Expected values of variance component estimators in Table 1 for outcomes distributed according to the two-way crossed classification model without and with an interaction between cluster and period, and correlation decay models.

Fitted Model	True Model: Model 1: No interaction	True Model: Model 2: Interaction
Model 1		
$E\left[\hat{\sigma}^2_{1\alpha}\right]$	$\sigma^2_{1\alpha}$	$\sigma^2_{2\alpha} + \frac{K(m-1)}{KTm-T-K+1}\sigma^2_{\gamma}$
$E\left[\hat{\sigma}^2_{1\epsilon}\right]$	$\sigma^2_{1\epsilon}$	$\sigma^2_{2\epsilon} + \frac{(KT-K-T+1)m}{KTm-K-T+1}\sigma^2_{\gamma}$
Model 2		
$E\left[\hat{\sigma}^2_{2\epsilon}\right]$	$\sigma^2_{1\epsilon}$	$\sigma^2_{2\epsilon}$
$E\left[\hat{\sigma}^2_{\gamma}\right]$	0	σ^2_{γ}
$E\left[\hat{\sigma}^2_{2\alpha}\right]$	$\sigma^2_{1\alpha}$	$\sigma^2_{2\alpha}$

Within- and between-period ICCs, 4-period design

Model 1:
no decay over time

	1	2	3	4
1				
2				
3				
4				

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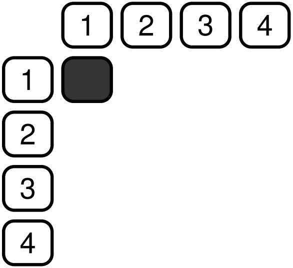
no decay over time



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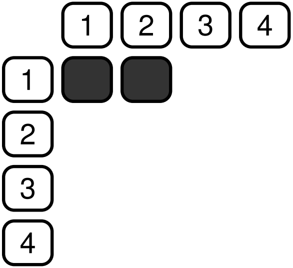

Within- and between-period ICCs, 4-period design

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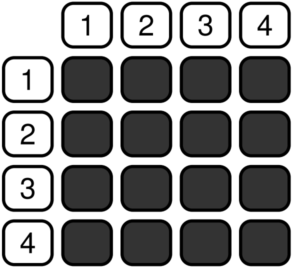

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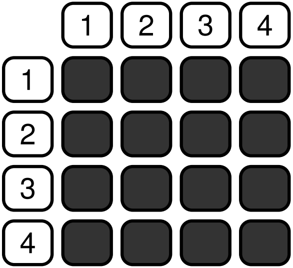
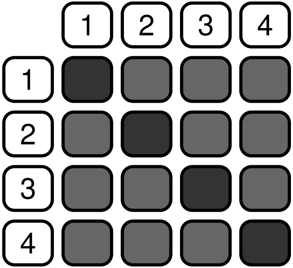


Model 2: within ICC
$\neq$ between ICC



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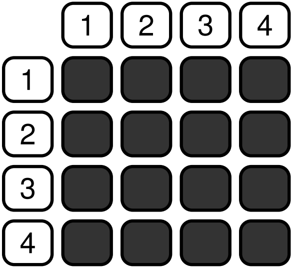

Model 2: within ICC
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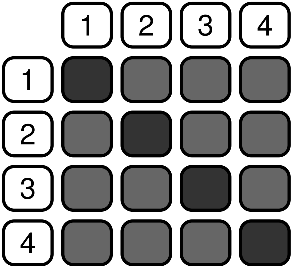

Model 3: ICC that
decays over time