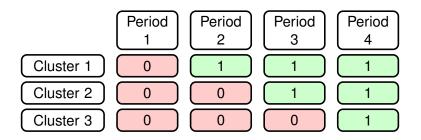
# Misspecifying within-cluster correlation structure in stepped wedge trials

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

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

General model:

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

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   Correlation b/w any two subjects in the same period = ρ
   Correlation b/w any two subjects in different periods = r × ρ
- 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	Between-period ICC
	Same Period	Periods <i>s</i> and <i>t</i> , $s \neq t$
1	ρ	ρ
2	ho	r  imes  ho
3	ρ	$\frac{\textbf{r} \times \rho}{\textbf{r}^{ t-s } \times \rho}$

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• Even if a decay in correlation is incorrectly omitted, estimate for treatment effect unbiased!

**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<sub>3</sub>: 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

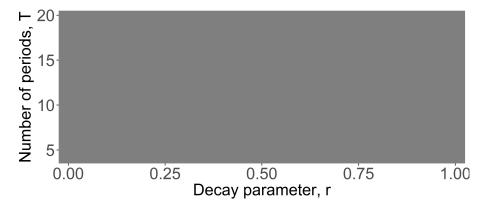
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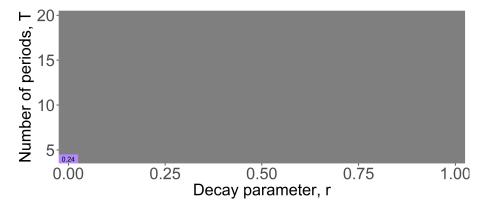
# Consider $\hat{V}_1/V_3$ and $\hat{V}_2/V_3$ for stepped wedge designs for each combination of:

- 4, 5, ..., 20 periods;
- decay in correlations *r* = 0, 0.05, 0.1, ..., 0.95, 1;
- ICC ρ = 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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F	20-	0.28	0.26	0.25	0.23	0.22	0.21	0.19	0.18	0.18	0.17	0.16	0.16	0.16	0.16	0.16	0.16	0.18	0.2	0.24	0.33	1
· .	20	0.28	0.26	0.24	0.23	0.22	0.21	0.2	0.19									0.18	0.21	0.25	0.34	1
Ś		0.28	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17							0.19	0.22	0.26	0.36	1
periods		0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.17					0.17	0.18	0.2	0.23	0.27	0.37	1
0	4 -	0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.18	0.18					0.18	0.19	0.21	0.24	0.29	0.39	1
. <u> </u>	15	0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.19						0.19	0.2	0.22	0.25	0.3	0.41	1
Q		0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.19	0.19						0.19	0.21	0.23	0.26	0.32	0.43	1
		0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.2	0.19	0.19	0.18	0.18	0.19	0.19	0.2	0.22	0.24	0.27	0.33	0.45	1
of		0.27	0.26	0.24	0.23	0.22	0.21	0.2	0.2	0.19	0.19	0.19	0.19	0.19	0.2	0.21	0.23	0.25	0.29	0.35	0.48	1
0	10	0.27	0.25	0.24	0.23	0.22	0.21	0.21	0.2 0.21	0.2 0.2	0.2 0.2	0.2 0.2	0.2 0.21	0.2 0.21	0.21	0.22	0.24	0.27	0.31	0.38	0.5	1
5	10	0.27	0.25	0.24	0.23	0.22	0.22	0.21	0.21	0.2	0.2	0.2	0.21	0.21	0.22	0.24	0.20	0.29	0.35	0.4	0.53	1
Number		0.20	0.25	0.24	0.23	0.22	0.22	0.21	0.21	0.21	0.21	0.21	0.21	0.22	0.25	0.23	0.27	0.33	0.30	0.43	0.61	1
¥		0.26	0.25	0.24	0.23	0.23	0.22	0.22	0.22	0.22	0.23	0.23	0.24	0.25	0.27	0.29	0.32	0.36	0.42	0.51	0.65	1
Ľ		0.25	0.25	0.24	0.23	0.23	0.23	0.23	0.23	0.23	0.24	0.25	0.26	0.27	0.29	0.32	0.35	0.4	0.46	0.55	0.7	1
	5	0.25	0.24	0.24	0.23	0.23	0.23	0.23	0.24	0.25	0.25	0.27	0.28	0.3	0.32	0.35	0.39	0.44	0.51	0.6	0.74	1
Z	0	0.24	0.24	0.23	0.23	0.24	0.24	0.25	0.25	0.26	0.28	0.29	0.31	0.33	0.36	0.4	0.44	0.5	0.57	0.66	0.8	1
	0		٦ ٦			0	).2	E			C	).50	0			0	).7	E			4	'n
	U	0.00	J			U	).Z	C			U	J.50	U			U	)./;	C			1	.00
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										υa,	γP	uic			<b>,</b> ,,							

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

F	20-	1	0.96	0.93	0.9	0.87	0.83	0.81	0.78	0.76	0.73	0.72	0.7	0.69	0.69	0.7	0.71	0.73	0.76	0.78	0.79	1
		1	0.97	0.93	0.9	0.87	0.84	0.81	0.78	0.76	0.74	0.72	0.71	0.71	0.7	0.71	0.72	0.75	0.77	0.8	0.81	1
periods,		1	0.97	0.93	0.9	0.87	0.84	0.81	0.79	0.77	0.75	0.73	0.72	0.72	0.72	0.73	0.74	0.76	0.79	0.82	0.82	1
σ		1	0.97	0.93	0.9	0.87	0.84	0.82	0.79	0.77	0.76	0.74	0.73	0.73	0.73	0.74	0.76	0.78	0.81	0.84	0.84	1
0		1	0.97	0.93	0.9	0.87	0.85	0.82	0.8	0.78	0.76	0.75	0.75	0.74	0.75	0.76	0.78	0.8	0.83	0.86	0.86	1
. C	15-	1	0.97	0.94	0.91	0.88	0.85	0.83	0.81	0.79	0.77	0.76	0.76	0.76	0.77	0.78	0.8	0.82	0.85	0.88	0.87	1
Ð	. •	1	0.97	0.94	0.91	0.88	0.86	0.83	0.81	0.8	0.79	0.78	0.77	0.78	0.78	0.8	0.82	0.85	0.88	0.9	0.89	1
		1	0.97	0.94	0.91	0.88	0.86	0.84	0.82	0.81	0.8	0.79	0.79	0.8	0.81	0.82	0.85	0.87	0.9	0.92	0.91	1
of		1	0.97	0.94	0.91	0.89	0.87	0.85	0.83	0.82	0.81	0.81	0.81	0.82	0.83	0.85	0.87	0.9	0.93	0.94	0.93	1
0	4.0	1	0.97	0.94	0.92	0.89	0.87	0.86	0.84	0.83	0.83	0.83	0.83	0.84	0.86	0.88	0.9	0.93	0.95	0.97	0.96	1
<u>ب</u>	10-	1	0.97	0.95	0.92	0.9	0.88	0.87	0.86	0.85	0.85	0.85	0.85	0.87	0.88	0.91	0.93	0.96	0.99	1	0.98	1
Number		1	0.97	0.95	0.93	0.91	0.89	0.88	0.87	0.87	0.87	0.87	0.88	0.9	0.92	0.94	0.97	1	1.02	1.03	1.01	1
9		1	0.98	0.95	0.93	0.92	0.9	0.9	0.89	0.89	0.89	0.9	0.91	0.93	0.95	0.98	1.01	1.03	1.05	1.06	1.03	1
3		1	0.98	0.96	0.94	0.93	0.92	0.91	0.91	0.92	0.92	0.93	0.95	0.97	1	1.02	1.05	1.07	1.09	1.09	1.06	1
5	E	1	0.98	0.96	0.95	0.94	0.94	0.94	0.94	0.95	0.96	0.97	0.99	1.02	1.04	1.07	1.1	1.12	1.13	1.12	1.08	1
Ē	5-	1	0.98	0.97	0.97	0.96	0.96	0.97	0.98	0.99	1	1.02	1.05	1.07	1.1	1.12	1.15	1.17	1.17	1.16	1.1	1
~		1	0.99	0.99	0.99	0.99	1	1.01	1.02	1.04	1.06	1.08	1.11	1.13	1.16	1.18	1.2	1.21	1.21	1.18	1.12	1
	0	.0	0			C	).2	5			C	).5(	)			С	).7!	5			1	.00
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# 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

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

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

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

• 2. A more complex model:

$$\begin{aligned} Y_{kti} &= \beta_t + \theta X_{kt} + \alpha_k + \gamma_{kt} + \epsilon_{kti}, \quad \epsilon_{kti} \sim \mathcal{N}(0, \sigma_{\epsilon}^2) \\ \alpha_k &\sim \mathcal{N}(0, r \times \sigma_{\alpha}^2), \quad \gamma_{kt} \sim \mathcal{N}(0, (1 - r) \times \sigma_{\alpha}^2) \end{aligned}$$

• 3. More complex still:

$$\begin{aligned} \mathbf{Y}_{kti} &= \beta_t + \theta \mathbf{X}_{kt} + \gamma_{kt} + \epsilon_{kti}, \quad \epsilon_{kti} \sim \mathbf{N}(\mathbf{0}, \sigma_{\epsilon}^2) \\ \gamma_k &= (\gamma_{k1}, \dots, \gamma_{kT})' \sim \mathbf{N}(\mathbf{0}, \Sigma), \quad \mathbf{cov}(\gamma_{kt}, \gamma_{ks}) = \sigma_{\alpha}^2 \mathbf{r}^{|t-s|} \end{aligned}$$

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

Mean Square	ANOVA estimators
$MSK(1) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$	$\hat{\sigma}_{1\alpha}^2 = \frac{MSK(1) - MSE(1)}{Tm}$
$MSE(1) = \frac{1}{KTm-K-T+1}\sum_{k}\sum_{t}\sum_{i}$	$\hat{\sigma}_{1\epsilon}^2 = MSE(1)$
$\left(\overline{Y}_{kti} - \overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet t \bullet} + \overline{Y}_{\bullet \bullet \bullet}\right)^2$	
$MSK(2) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$	$\hat{\sigma}_{2\alpha}^2 = \frac{MSK(2) - MSKT(2)}{Tm}$
	$\hat{\sigma}_{\gamma}^2 = \frac{MSKT(2) - MSE(2)}{m}$
$MSE(2) = \frac{1}{KT(m-1)} \sum_{k} \sum_{t} \sum_{i} \left(\overline{Y}_{kti} - \overline{Y}_{kt\bullet}\right)^2$	$\hat{\sigma}^2_{2\epsilon} = MSE(2)$
$\overline{Y}_{kt\bullet} = \frac{1}{m} \sum_{i=1}^{m} Y_{kti},  \overline{Y}_{k\bullet\bullet} = \frac{1}{mT} \sum_{t=1}^{T} \sum_{i=1}^{m} Y_{kti}$	Y <sub>kti</sub> ,
$= \frac{1}{mK} \sum_{k=1}^{K} \sum_{i=1}^{m} Y_{kti},  \overline{Y}_{\bullet\bullet\bullet} = \frac{1}{mTK} \sum_{k=1}^{K} \sum_{t=1}^{T} \overline{Y}_{ti}$	$\sum_{i=1}^{m} Y_{kti}$ .
-	$MSK(1) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$ $MSE(1) = \frac{1}{KTm-K-T+1} \sum_{k} \sum_{t} \sum_{t} \sum_{i}$ $\left(\overline{Y}_{kti} - \overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet t \bullet} + \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$ $MSK(2) = \frac{1}{K-1} \sum_{k=1}^{K} Tm \left(\overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$ $MSKT(2) = \frac{1}{(K-1)(T-1)} \sum_{k} \sum_{t} m$ $\left(\overline{Y}_{kt \bullet} - \overline{Y}_{k \bullet \bullet} - \overline{Y}_{\bullet t \bullet} + \overline{Y}_{\bullet \bullet \bullet}\right)^{2}$ $MSE(2) = \frac{1}{KT(m-1)} \sum_{k} \sum_{t} \sum_{i} \left(\overline{Y}_{kti} - \overline{Y}_{kt \bullet}\right)^{2}$ $\overline{Y}_{kt \bullet} = \frac{1}{m} \sum_{i=1}^{m} Y_{kti},  \overline{Y}_{k \bullet \bullet} = \frac{1}{mT} \sum_{t=1}^{T} \sum_{i=1}^{m}$

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.

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

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.

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

Model 1: no decay over time 1234 1 2 3 4 Model 1: no decay over time 1 2 3 4 1 2 3 4

Model 1: no decay over time 3 3

