

Methods: Mind the Gap

Webinar Series

Does it Decay? Decaying Correlations in the Design and Analysis of Stepped Wedge Trials

Presented by:

Jessica Kasza, Ph.D.

School of Public Health and Preventative Medicine
Monash University, Melbourne



National Institutes of Health
Office of Disease Prevention



Office of Disease Prevention
Putting Prevention Research First

Does it decay?

Decaying correlations in the design and analysis of stepped wedge trials.

Jessica Kasza

`jessica.kasza@monash.edu`

School of Public Health and Preventive Medicine
Monash University



MONASH University

The Cluster Cluster at Monash



Andrew Forbes



Kelsey Grantham



Ehsan Rezaei



Stephane Heritier



Jess Kasza



Rhys Bowden



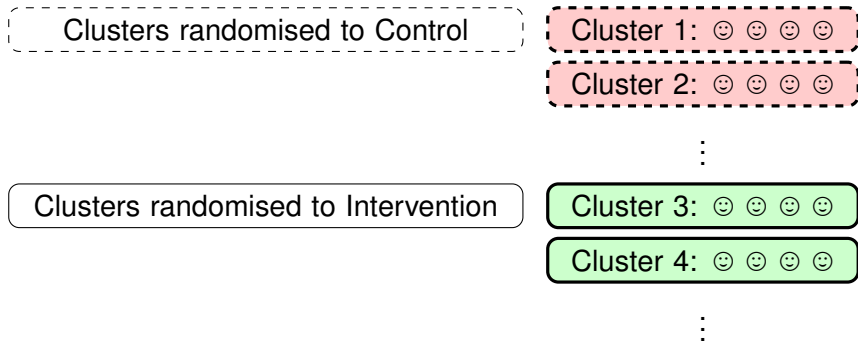
Lizzie Korevaar

Outline

1. What are cluster randomised trials?
2. What is a “decaying correlation”?
3. Where can I get estimates of the decay?
4. How do I account for a decay when designing a study?
5. How do I know if I should include a decay?
6. What if I omit a decay when analysing a study?

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The standard cluster randomised trial



- *Clusters (groups)* of participants assigned to treatments.
 - Necessary when treatment applied at the group level.
- Clusters could be hospitals, ICUs, schools, neighbourhoods...
 - The **intracluster correlation (ICC)**, ρ describes the similarity of outcomes from participants in the same cluster.

Extending cluster randomised trials over time

Cluster randomised trials not always feasible:

- What if more clusters are required than are available?

Longitudinal cluster randomised trials can help!

- Clusters are followed over time and measured repeatedly.
 - Participants within clusters may be measured only once (in one period), or contribute measurements in more than one study period.
- Clusters may switch between control and intervention conditions.

Extending cluster randomised trials over time

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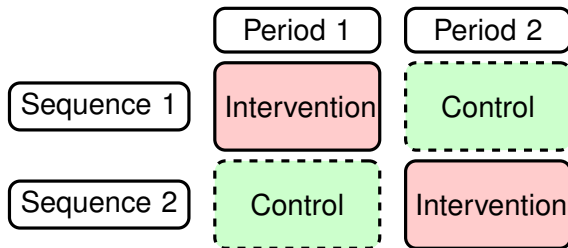
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- Clusters may switch between control and intervention conditions.

Switching between control and intervention conditions is really useful!

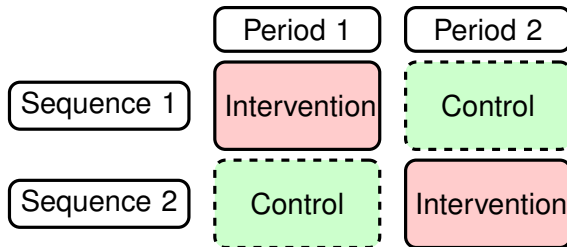
- Allows comparisons not only between clusters, but also within clusters
- ... which can lead to increases in power!

The cluster randomised cross over trial: CRXO



- Each cluster switches: treatment effect is now estimated using **BOTH** within-cluster and between-cluster comparisons.

The cluster randomised cross over trial: CRXO

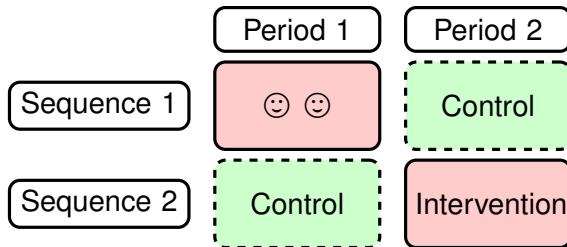


Consider two participants from the same cluster: 😊 and 😊.

- They could provide measurements in the same period.
- They could provide measurements in different periods.

Do we expect the ICC to be the same for both pairs of participants?

The cluster randomised cross over trial: CRXO

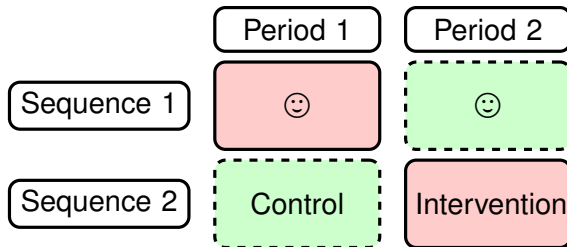


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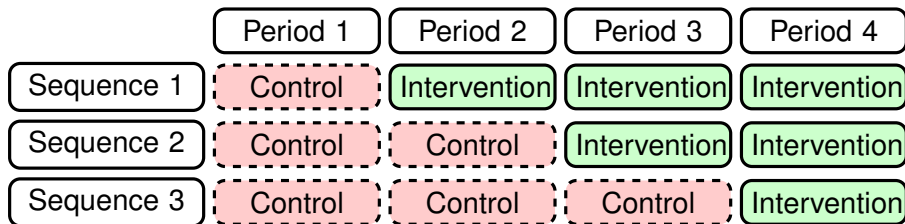


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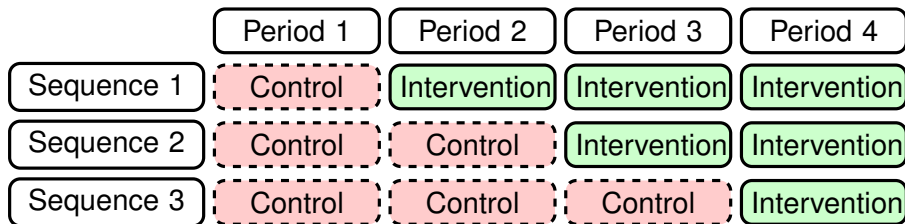
The stepped wedge cluster randomised trial design



Stepped wedge designs are wonderful!

- Useful in situations where we cannot switch back and forth between treatments.
- All clusters know they will receive the intervention (eventually...);
- Useful when interventions cannot be undone or will be rolled out anyway.

The stepped wedge cluster randomised trial design



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- All clusters know they will receive the intervention (eventually...);
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BUT... now that we're following clusters up over time, need to think more about the ICC

Changing correlations?

	Period 1	Period 2	Period 3	Period 4
Sequence 1	Control	Intervention	Intervention	Intervention
Sequence 2	Control	Control	Intervention	Intervention
Sequence 3	Control	Control	Control	Intervention

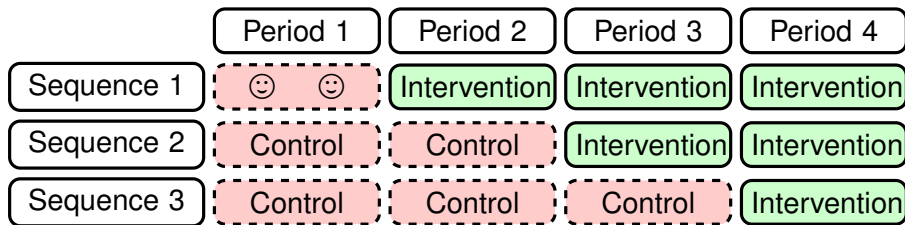
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- Could it *decay over time*?

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Within-cluster correlation structures

A simple model for continuous outcomes:

$$\text{Outcome} = \text{Period effect} + \text{Treatment effect} \\ + \textbf{random effects} + \text{error}$$

Random effects:

- Encode the similarity of participants from the same cluster.
 - Intra-Cluster Correlations (**ICCs**) describe this similarity.
 - Within-cluster correlation structure is the collection of ICCs for a cluster
- Many different assumptions about these random effects can be made!
- Different models imply different “within cluster correlation structures”

Statistical models for Y_{kti} : subject i ; period t ; cluster k .

- Model 1: constant correlation/exchangeable

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

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- Model 2: block exchangeable

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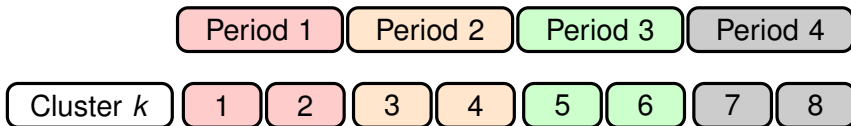
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- Model 3: discrete-time decay

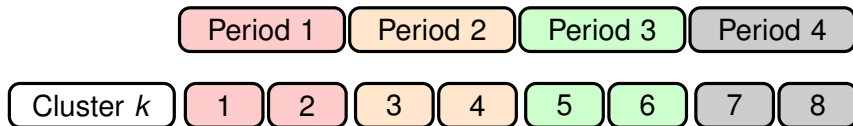
$$Y_{kti} = \beta_t + \theta X_{kt} + C_{kt} + \epsilon_{kti}, \quad \epsilon_{kti} \sim N(0, \sigma_\epsilon^2)$$

$$C_k = (C_{k1}, \dots, C_{kT}) \sim N(\mathbf{0}, \sigma_C^2 \Sigma), \quad \Sigma[t, s] = r^{|t-s|}$$

Four periods, 2 participants in each cluster in each period



Four periods, 2 participants in each cluster in each period



- **Within-period ICC:** correlation between a pair of participants in the same period;
- **Between-period ICC:** correlation between a pair of participants in different periods.

Consider the correlation between participant 1 and each other participant in cluster k .

Within-cluster correlation structure: Model 1

Period	1	1	2	2	3	3	4	4
Cluster k	1	2	3	4	5	6	7	8
Correlation	1	ρ	ρ	ρ	ρ	ρ	ρ	ρ

Model 1: Constant correlation. Within-period ICC = between-period ICC

- Correlation between the outcomes of any pair of participants is identical.
 - Correlation between participant 1 and 2 = correlation between 1 and 8.
 - This requires specifying one correlation only: convenient!
...but is it realistic?

NOTE: Shading indicates the degree of correlation between participant 1 and other participants. The correlation of participant 1 with themselves is 1.

Within-cluster correlation structure: Model 2

Period	1	1	2	2	3	3	4	4
Cluster k	1	2	3	4	5	6	7	8
Correlation	1	ρ_1	ρ_2	ρ_2	ρ_2	ρ_2	ρ_2	ρ_2

Model 2: “Block-exchangeable”. Separate within- and between-period ICCs

- Participants in the *same* treatment period have more highly correlated outcomes than participants in different treatment periods.
 - Frequently applied assumption.
 - Again: may not always be realistic.

NOTE: Shading indicates the degree of correlation between participant 1 and other participants. The correlation of participant 1 with themselves is 1.

Within-cluster correlation structure: Model 3

Period	1	1	2	2	3	3	4	4
Cluster k	1	2	3	4	5	6	7	8
Correlation	1	ρ	ρr	ρr	ρr^2	ρr^2	ρr^3	ρr^3

Model 3: Discrete-time decay

- The correlation between participant outcomes depends on their periods.
 - The correlation between a pair of participants decreases the further their measurement periods are apart in time.

NOTE: Shading indicates the degree of correlation between participant 1 and other participants. The correlation of participant 1 with themselves is 1.

Within-period and between-period ICCs

Model	Within-period ICC $\text{corr}(Y_{kti}, Y_{ktj})$	Between-period ICC $\text{corr}(Y_{kti}, Y_{ksj}), s \neq t$
1	ρ	ρ
2	ρ	$r \times \rho$
3	ρ	$r^{ t-s } \times \rho$

r is the CAC= “Cluster AutoCorrelation”.

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r is the CAC= “Cluster AutoCorrelation”.

For Model 3:

- Intraclass correlation: $\rho = 0.035$
- Decay per period: 5% $\Rightarrow$ Cluster AutoCorrelation $r = 0.95$
 - Correlation b/w two participants in the same cluster
in the same period: 0.035
in periods 1 and 2: $0.035 \times 0.95 = 0.033$
in periods 1 and 3: $0.035 \times 0.95^2 = 0.031$
in periods 1 and 4: $0.035 \times 0.95^3 = 0.030$

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Where can I get estimates of the decay?

- You could analyse data that you already have.
- You could use estimates from previously-published studies.

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- You could analyse data that you already have.
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- Or you could use the CLOUD Bank repository:
 - CLustered OUtcome Dataset bank
 - A repository of correlation parameter estimates from 44 continuous outcomes collected in 29 longitudinal cluster datasets

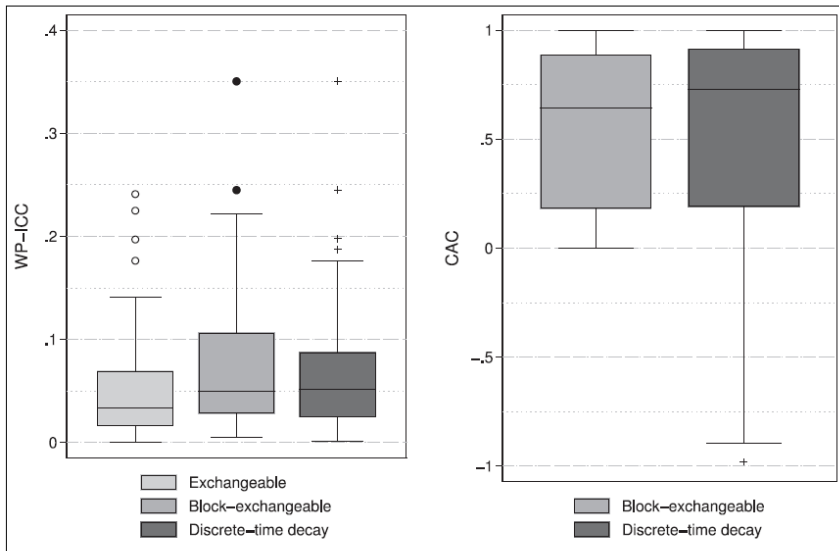
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- Or you could use the CLOUD Bank repository:
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 - A repository of correlation parameter estimates from 44 continuous outcomes collected in 29 longitudinal cluster datasets
- Our three models were fit to each dataset:
 - Model 1: within period ICC = between period ICC
 - Model 2: within period ICC $\neq$ between period ICC, but no decay
 - Model 3: discrete-time decay model

CLOUD Bank dataset characteristics: median (IQR)

Design Characteristics	Parallel with baseline	Stepped wedge	Observational
	19 studies	6 studies	4 studies
No. of periods	2 (2-3)	7.5 (5-9)	6.5 (5-10.5)
Period length (months)	12 (6-18)	2 (1-6)	2.5 (1.5-7.5)
No. of clusters	30 (20-41)	11.5 (6-12)	74 (14-278)
Cluster-period size	23.7 (12.6-36.5)	43 (20-133)	89.5 (34-146)

Results: Boxplots of ICCs and CACs



Using the CLOUD Bank for sample size calculations

① Consider the characteristics of your planned study:

- period length;
- cluster-period size;
- cluster type...

② Obtain estimates of correlation parameters from the CLOUD Bank

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

③ Plug those estimates into your sample size calculator of choice...

- such as the Shiny Cluster app.

Using the CLOUD Bank for sample size calculations

I want to design a stepped wedge trial with the following characteristics:

- Eight periods, each of length 6 months (i.e. a 7-sequence stepped wedge)
- 20 participants in each cluster in each period
- Effect size 0.2, power 80%, 2-sided significance level of 0.05.

Using the CLOUD Bank for sample size calculations

← → ↻ 🏠

monash-biostat.shinyapps.io/CLOUDbank/

CLOUD bank

☰

Welcome!

Table

Characteristic boxplots

About

Select the characteristics to the CLOUD bank by:

Period length:

☐ All

☐ >=12 months

☒ <12 months

Type of cluster:

☒ All

☐ Community

☐ Primary care

☐ School

☐ Secondary care

Study design:

☒ All

☐ Parallel with baseline

☐ Observational

☐ Stepped-wedge

Cluster-period size:

☐ All

☒ <24 per cluster

☐ >=24 per cluster

I want to view

☒ One row per outcome

☐ Three rows per outcome, one row per correlation structure

Country income status:

☒ All

☐ LMIC

☐ HIC

Results Summary - based on your selections above:

The correlation coefficients, median (IQR) for a subset of outcomes for each model:



EXCHANGEABLE: (BASED ON 9 OUTCOMES)

ICC: 0.013 (0.005 - 0.079)

BLOCK-EXCHANGEABLE: (BASED ON 9 OUTCOMES)

WP-ICC: 0.111 (0.048 - 0.162)

CAC: 0.223 (0.08 - 0.47)

DISCRETE-TIME DECAY: (BASED ON 9 OUTCOMES)

WP-ICC: 0.053 (0.031 - 0.113)

DECAYING CAC: 0.258 (0 - 0.689)

Which columns would you like in your table below:

☒ Dataset details

☒ Exchangeable results

☒ Block-exchangeable results

☒ Discrete-time decay results

Using the CLOUD Bank for sample size calculations

From the CLOUD Bank, for studies with periods less than 12 months long, fewer than 24 participants per cluster-period:

- Within-period ICC: median 0.053, IQR 0.031 to 0.113.
- Cluster autocorrelation: median 0.258, IQR 0 to 0.689.

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How to account for decaying correlations when designing studies?

The Shiny CRT Calculator allows for decaying correlations

`https://clusterrcts.shinyapps.io/rshinyapp/`

Always a good idea to assess the robustness of your study power to decays in within-cluster correlations!

The Shiny CRT Calculator: Power and Sample size for Cluster Randomised Trials

Trial Design

- ☐ Parallel
- ☐ Parallel with baseline measure
- ☐ Two-period cross-over
- ☒ Stepped-wedge
- ☐ Multiple-period cross-over
- ☐ Upload own design

A non standard design can be accommodated by uploading the design as a CSV file (click on the up-load option for more details).

Sampling Structure

- ☒ Cross-sectional sample
- ☐ Cohort

In a cross-sectional design at each measurement occasion a different sample of participants is measured. In a cohort design, participants are repeatedly measured at each measurement occasion.

Correlation Structure

- ☐ Exchangeable
- ☐ Two-period decay
- ☒ Discrete time decay

Two-period decay allows for a correlation within the same measurement period to differ to that from a different measurement period. The discrete time decay allows for correlations to decay with each measurement period.

Plot set-up

- ☐ Cluster size vs. Power
- ☒ Number of clusters vs. Power
- ☐ Number of clusters vs. Cluster size

X-axis range: Number of clusters (per sequence)

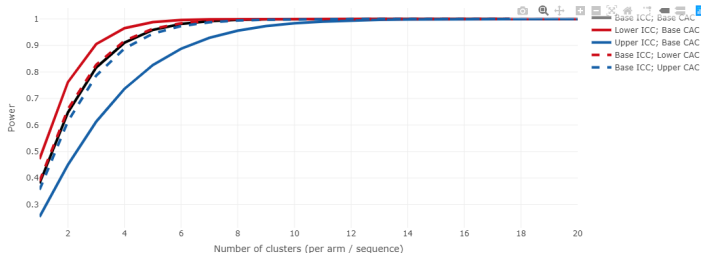


Power

Precision

Design matrix

References and Contacts



Curve shows the increase in power as the number of clusters increases (for a fixed cluster-period size). Hover cursor over curve to see actual power values

Warning: caution is needed with CRTs with a small number of clusters due to risk of lack of internal and external validity; and appropriateness of calculations used particularly for binary and count outcomes

Parameters

Mean difference: 0.2 standard deviation: 1

Significance level: 0.05

Number of sequences: 7

Cluster size per period: 20

WP-ICC: 0.053 WP-ICC (lower): 0.031 WP-ICC (upper): 0.113 CAC: 0.258

☐ Yes

Number of sequences (i.e. steps)

7

Within-period ICC

0.053

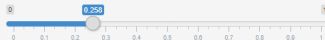
Within-period ICC lower extreme

0.031

Within-period ICC upper extreme

0.113

Cluster auto-correlation (CAC)



The Cluster Auto Correlation (CAC) is the correlation between two population means from the same cluster at different times. The lower and upper bounds for the CAC values plotted on the curve are 80% and 120% (or 1) of the base case value inputted here.

Outcome type

- ☒ Continuous
☐ Binary
☐ Count

Mean Difference

0.2

Standard Deviation

1

Significance level

0.05

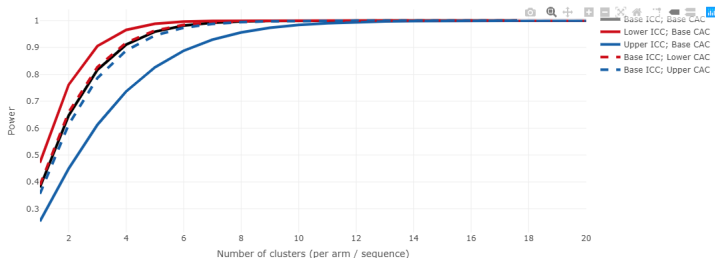
Download plot data

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- 20 participants in each cluster in each period
- Effect size 0.2, power 80%, 2-sided significance level of 0.05.

Total number of clusters required for our planned study:

Within-period ICC	Decaying CAC		
	0.00	0.258	0.689
0.031	14	21	21
0.053	21	21	28
0.113	28	35	35

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How do we know which within-cluster correlation structure is best?

- When writing your statistical analysis plan, you will pre-specify your primary analysis
 - Including your assumed within-cluster correlation structure!
- But what about for secondary analyses? Or analyses of other datasets?
 - It isn't always obvious what the best within-cluster correlation structure is!

Can we use tools like the Akaike and Bayesian Information Criteria (AIC and BIC) to select a within-cluster correlation structure?

Simulation study design

Parameter	Meaning	Values
T	Number of periods	3, 4, 5, 6, 10
K	Total number of clusters	20, 50, 100
m	Number of participants	10, 50, 100
ρ	Intra-cluster correlation	0.01, 0.05, 0.1, 0.2
r, r_d	Cluster autocorrelation	1 (exchangeable) $r = 0.95, 0.8, 0.5$ (block exchangeable) $r_d = 0.95, 0.8, 0.5$ (discrete time decay)

- Simulate each combination of parameters 1000 times.
- Each of the three models fitted to each simulated dataset
- Model with the smallest AIC and BIC recorded.

What are the AIC and BIC?

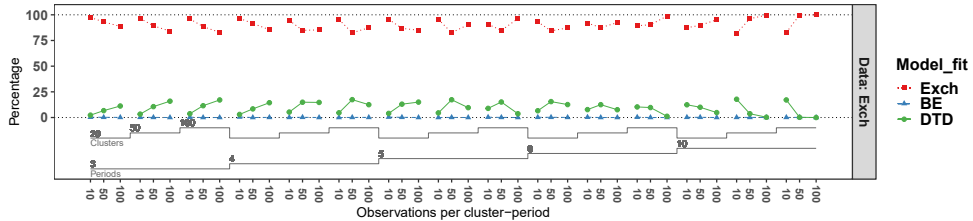
We use the definitions in ASReml-R (an R package that can fit each of our three models):

$$\text{AIC} = -2\ell + 2t$$

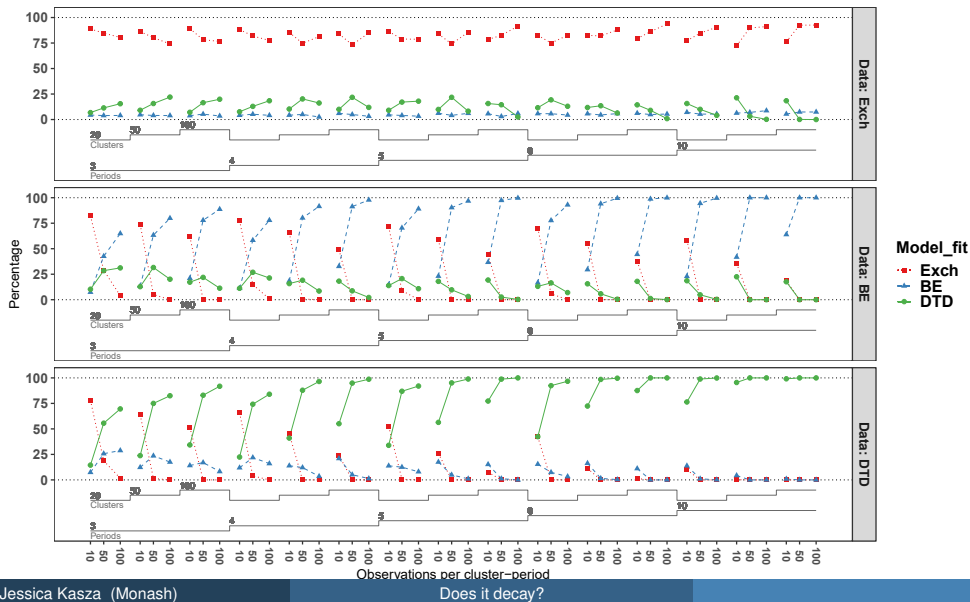
$$\text{BIC} = -2\ell + (\log(n - p))t$$

- ℓ : REML log-likelihood of the model
- t : number of covariance parameters
- n : total sample size
- p : total number of fixed effects in the model

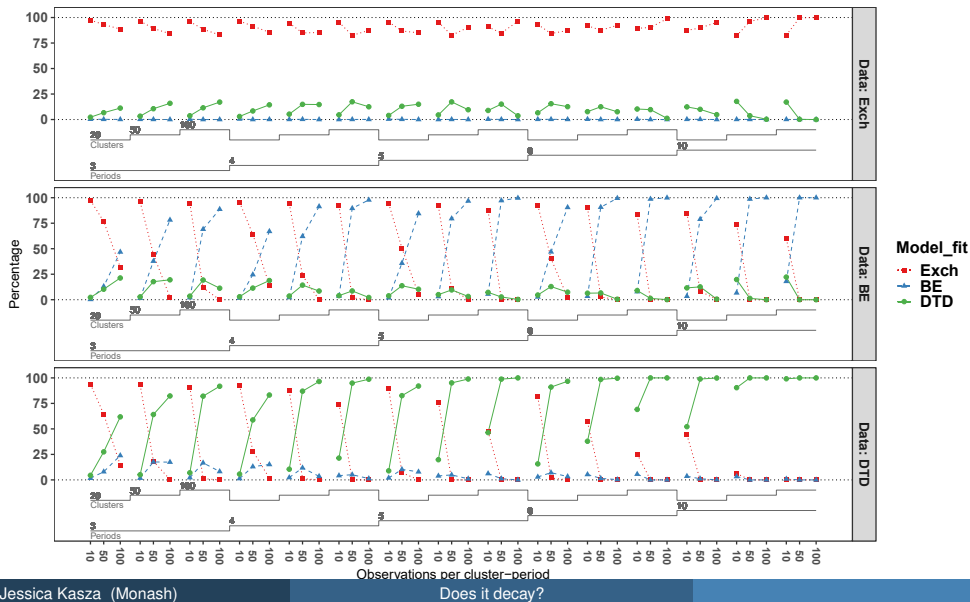
Results - AIC. $\rho = 0.05$



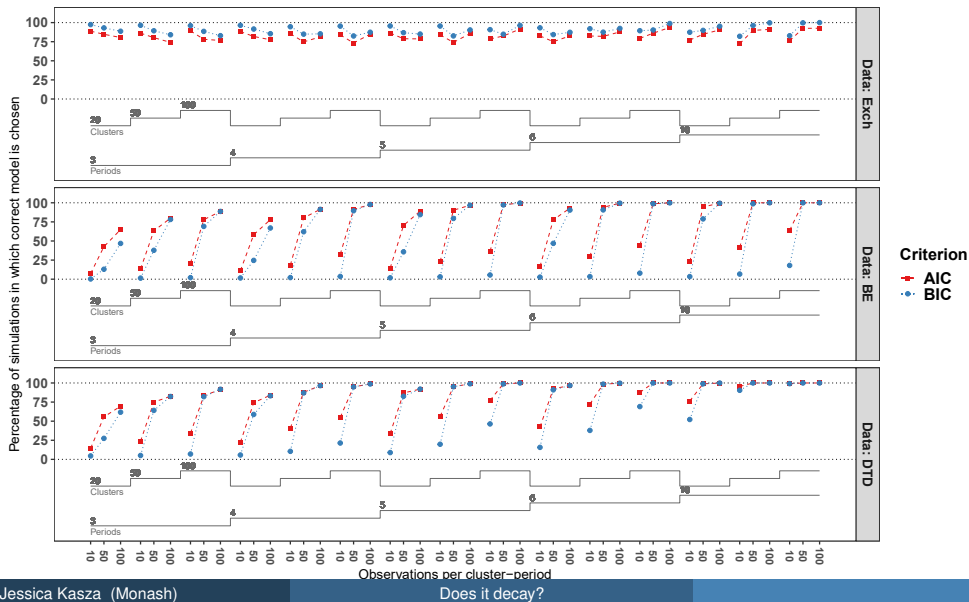
Results - AIC. $r_B = 0.8$, $r = 0.8$, $\rho = 0.05$



Results - BIC. $r_B = 0.8$, $r = 0.8$, $\rho = 0.05$



Results - AIC vs BIC



Choosing a correlation structure

- For increasing amounts of data, AIC and BIC increasingly likely to pick correct structure.
- BIC more likely to pick exchangeable structure.
- Recommend using AIC and BIC as a guide in supplementary analysis of trial data.

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Omitting a decay when estimating the treatment effect

Interest is in estimating the treatment effect

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

BUT what about the confidence interval?

Omitting a decay when estimating the treatment effect

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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_3 : the CI width under the “true” decay model
- $\hat{V}_1$: CI width when Model 1 used to estimate variance components

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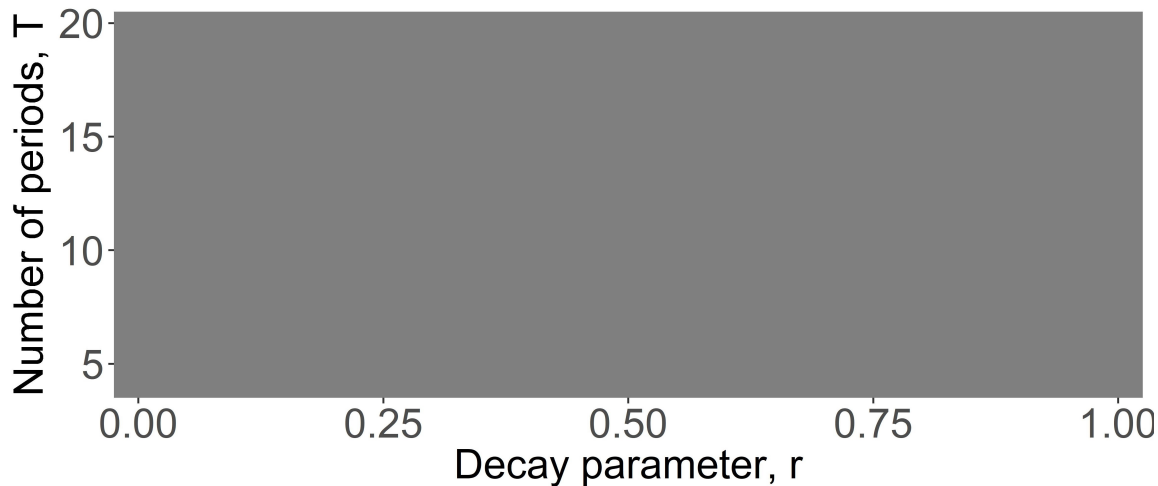
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Consider $\hat{V}_1 / V_3$ for stepped wedge designs for each combination of:

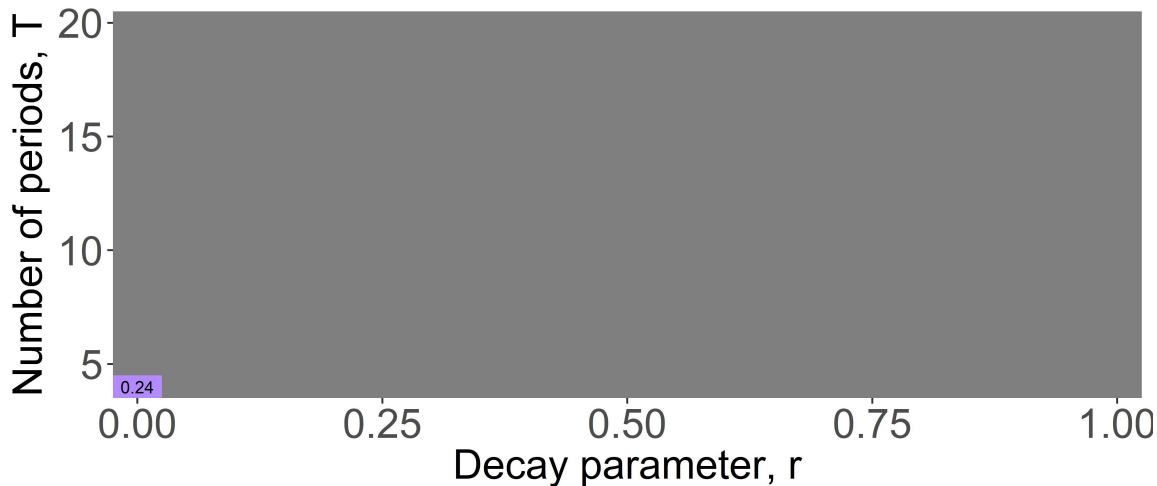
- 4, 5, ..., 20 periods;
- Cluster autocorrelations (decay parameter) $r = 0, 0.05, 0.1, \dots, 0.95, 1$;

Set ICC $\rho = 0.05$ and 100 subjects in each cluster in each period.

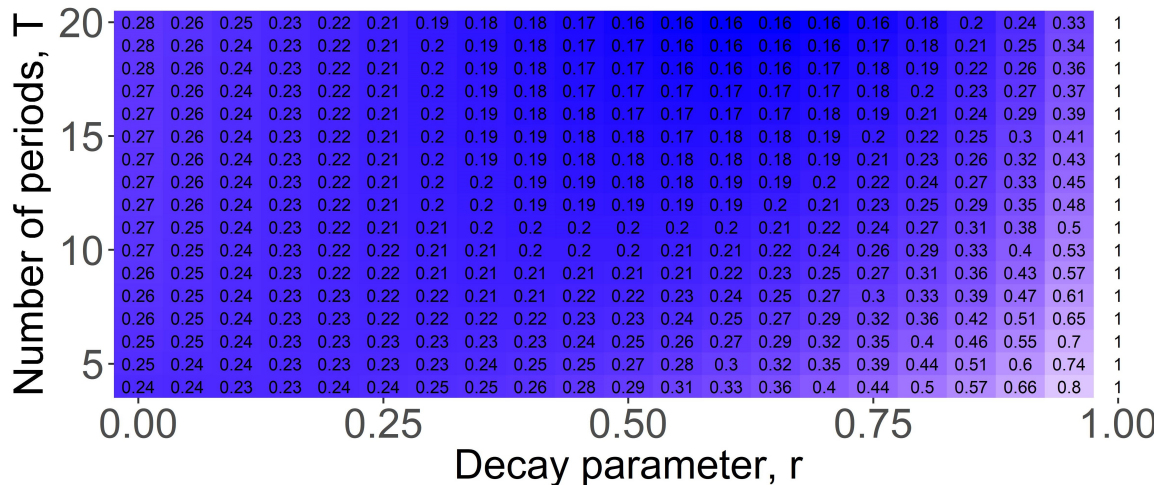
Using Model 1 instead of Model 3 ($\hat{V}_1/V_3$)



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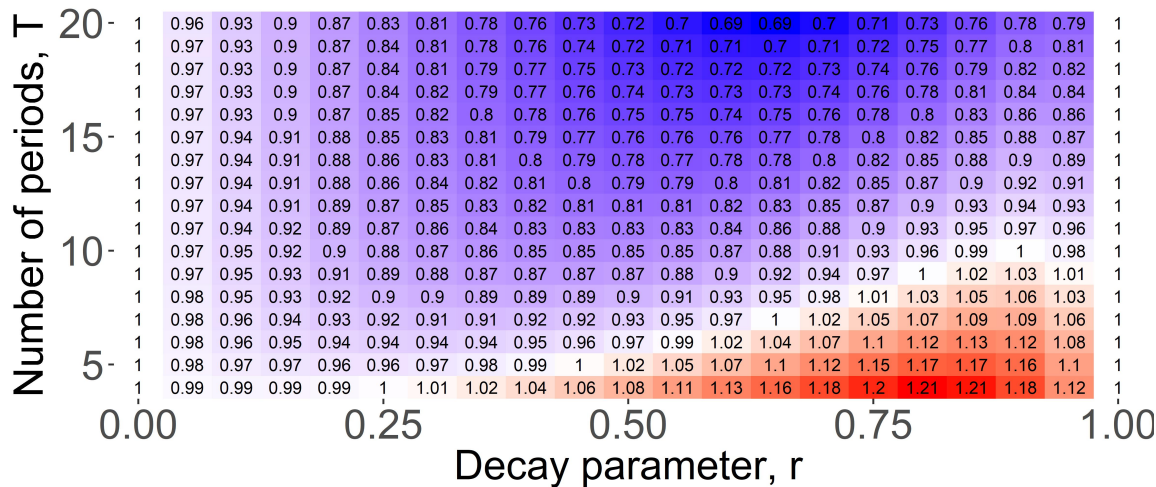


Using Model 1 instead of Model 3 ($\hat{V}_1/V_3$)



$\hat{V}_1/V_3 < 1$: confidence intervals are *too narrow*.

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



$\hat{V}_2/V_3 < 1$: confidence intervals are *too narrow*.

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).

Take home messages

- Over the past few years an enhanced understanding of within-cluster correlation structures for longitudinal cluster randomised trials has emerged.
- We have:
 - models that allow for correlations to decay over time;
 - a repository of estimates of correlation parameters;
 - sample size calculators that allow for decaying correlations;
 - some ideas about how to choose the best within-cluster correlation structure;
 - an understanding of what happens if we ignore decays at the analysis stage.

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 - Not all outcomes are continuous!
 - Time is not really discrete!
 - How can we help researchers plan the most efficient design for their setting?

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Questions? Ask now, or get in touch:

`jessica.kasza@monash.edu`

Binary outcomes

- Binary outcomes are common in longitudinal cluster randomised trials.
- Various options for design and analysis:
 - Assume a linear model for binary outcomes;
 - Generalized linear mixed models approach;
 - Generalized estimating equations approach.
- CLOUD Bank estimates of correlation parameters for binary outcomes are forthcoming.
- Watch this space: the next few years will see a wealth of work on binary outcomes.

Time isn't really discrete

- We've assumed distinct treatment periods.
- But in many situations this is a simplification!
 - Participants may be arriving at clusters and providing outcomes in continuous time.

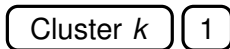
Arrival of participants within a cluster

Assume that patients arrive at each cluster at a constant rate:

Cluster k

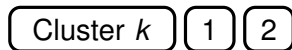
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There is another option for the within-cluster correlation structure.

Within-cluster correlation structure

Cluster k	1	2	3	4	5	6	7	8
Correlation	1	ρr	ρr^2	ρr^3	ρr^4	ρr^5	ρr^6	ρr^7

Smoothly decaying correlation

- The correlation between patient outcomes depends on the time between them
 - The correlation between a pair of patients decreases the further apart in time they are measured.
- If patient i arrives at time t and patient j at time s , $\text{corr}(Y_{kti}, Y_{ksj}) = r^{|s-t|}$

NOTE: Shading indicates the degree of correlation between patient 1 and other patients. The correlation of patient 1 with themselves is 1.

Statistical Models: Discrete vs. Continuous time

- Discrete-time decay model: Y_{kti} : subject i ; period t ; cluster k .

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

$$\text{Cov}(Y_{ksi}, Y_{ktj}) = \sigma_C^2 r^{|s-t|}$$

- Continuous-time decay model: Y_{kt} : **subject at time s** ; cluster k .

$$Y_{ks} = \sum_{j=1}^T (\beta_j + \theta X_{kj}) I(s \in [j, j+1)) + C_{ks} + \epsilon_{ks}, \quad \epsilon \sim N(0, \sigma_\epsilon^2)$$

$$\text{Cov}(Y_{ks}, Y_{kt}) = \sigma_C^2 r^{|s-t|}$$

- R: ASReml-R (paid R package)
 - Used for the AIC/BIC simulation study
- SAS
 - Used for the CLOUD Bank analyses
- Stata: can't fit these models in Stata.