Providing a R-package for sampling data of cluster randomized trials to show the impact of implementation errors on effect estimation within stepped wedge design studies

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R package

Aim

In the past years multilevel designs, which collect additional units nested within the original sampling units, become very popular. The complete data of such examples is then multivariate distributed. The aim of the package *samplingDataCRT* is to provide an easy implementation of sampling multivariate normal distributed data for further investigations. Data of cluster randomized trials within different study designs types, namely parallel, cross-over and stepped wedge design (SWD), can be sampled.

Study design & multidimensional normal distribution

For the situation of a cluster-randomized trial with T number of time points, C number of clusters and N number of subjects within a cluster (and time point, when it is a cross-sectional) the complete data set can be written as the vector of responses $\overrightarrow{Y} = \{Y_{ijk}\}$ of length $T \times C \times N$. This response vector $\overrightarrow{Y}$ can be sampled from a multidimensional normal distribution:

$$\overrightarrow{Y} \sim N(Zb, V),$$

The form of the mean vector Zb (fixed part) depends on the type of **study design**, namely parallel, cross-over or SWD, whereas the form of the covariance-variance-matrix V (random part) depends on the sampling of either a cross-sectional or a longitudinal.

A **parallel design** is present, when for two groups of randomly selected clusters and one treatment one group receives only the treatment while the other group receives this not.

In a **cross-over design** trial each cluster (randomly allocated to one arm) receives a sequence of different treatments over time, whereby the clusters in different arms receive at one time point different treatments.

SWD is a type of cross-over design: clusters in different arms cross-over step-wise from control to treatment, each at a randomly determined time point.

	T_1	T_2	T_3	T_4
C_1	0	0	0	0
C_2	0	0	0	0
C_3	0	0	0	0
C_4	1	1	1	1
C_5	1	1	1	1
C_6	1	1	1	1

	T_1	T_2	T_3	T_4
C_1	0	0	1	1
C_2	0	0	1	1
C_3	0	0	1	1
C_4	1	1	0	0
C_5	1	1	0	0
C_6	1	1	0	0

	T_1	T_2	T_3	T_4
C_1	0	1	1	1
C_2	0	1	1	1
C_3	0	0	1	1
C_4	0	0	1	1
C_5	0	0	0	1
C_6	0	0	0	1

In such trials two kinds of data collection with a different number of included subjects in total (n) are possible :

For **cross-sectional** data, within a cluster the measurement units (subjects) are different at each time point ($n = C \times T \times N$).

For **longitudinal** data, within a cluster the measurement units (subjects) are the same at all time points, known as repeated measurements ($n = C \times N$).

Functions of the R package

The `designMatrix` and `completeDataDesignMatrix` create the design matrix or the complete data design matrix, which is required for specifying (internally) the mean vector Zb of the normal distribution.

With `implemMatrix.SWD` it is possible to specify the grade of intervention implementation pattern into the design matrix.

`CovMat.Design` perform the covariance-variance-matrix V for the normal distribution depending on type of sampling.

`sampleData` can be used to sample responses for a given numbers of individuals by given a model depending on specified design.

Package can be downloaded:

From the website of Comprehensive R Archive Network (CRAN) under `https://cran.r-project.org/web/packages/samplingDataCRT/index.html`

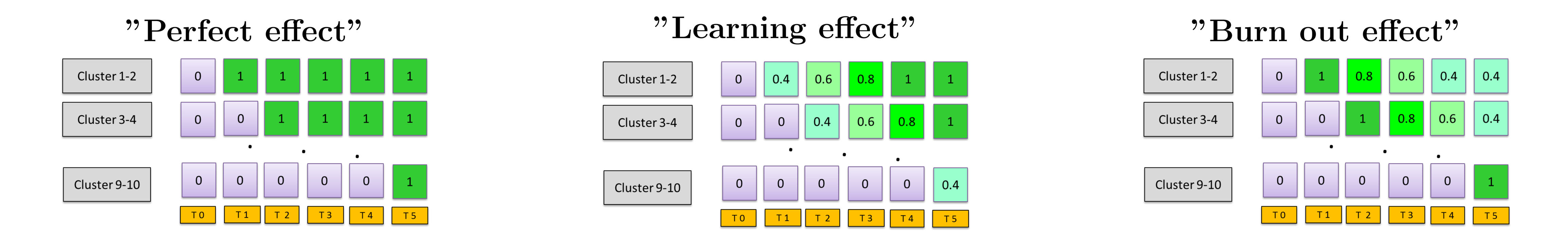
Application of the R package: A simulation study

Introduction

A simulation can be a tool to explore methodological challenges of common study designs or data analysis methods. Motivated by an ongoing trial we use a simulation to illustrate how sensitive a study is against some common scenarios in research practice. Here, the provided R-package is used to sample multidimensional distributed data within cluster randomized trials of one study design - the Stepped Wedge Design (SWD).

In practice the assumed situation in trials is often violated. Some deviations within SWD trials, for example learning intervention effect or cluster heterogeneity, are already described by [1], but not well investigated. Other deviations, which have a practical interest, are also possible in health care research. For example a decreasing intervention effect over time or cluster loss at different time points are possible. The aim is to investigate the effect of different scenarios on the intervention effect estimation for typical SWD trials using a simulation study. The results of the simulation can support the interpretation of a real SWD trial.

Identified different intervention implementation patterns in time course



Method: Simulation study on the basis of the R package

We use a simulation experiment to evaluate how much effect estimates within a SWD deviates from the given effect, if deviations from the perfect situation exists. Three **categories** are investigated:

A = Degree of intervention implementation (Perfect, learning, burnout effect of the intervention)

B = Number of missing individuals or clusters (0%,10%,30%)

C = Time point at which clusters get lost (at the end, at random, at the beginning)

This results in **27** different scenarios, where the reference is the perfect-world scenario (A = 'perfect', B = 0%). For each of the possible scenarios the following **simulation steps** are replicated $S = 100000$ times:

1) Construct a SWD model for a given scenario, which is defined by the design matrices of implementation pattern X_A, and the following SWD setup parameters:

   Design: 10 cluster, 6 time points, 2 cluster switch each time point, 10 individuals within each cluster and time point

   Model: baseline-mean $\mu = 10$, intervention effect $\Theta = 1$, no possible time effects ($\forall \beta_j = 0$), between cluster variability $\sigma_\alpha = 2$, within cluster variability $\sigma_\epsilon = 2$,

2) Sample continuous outcomes for individual level responses Y_{ijk} from the constructed SWD model by using the R package:

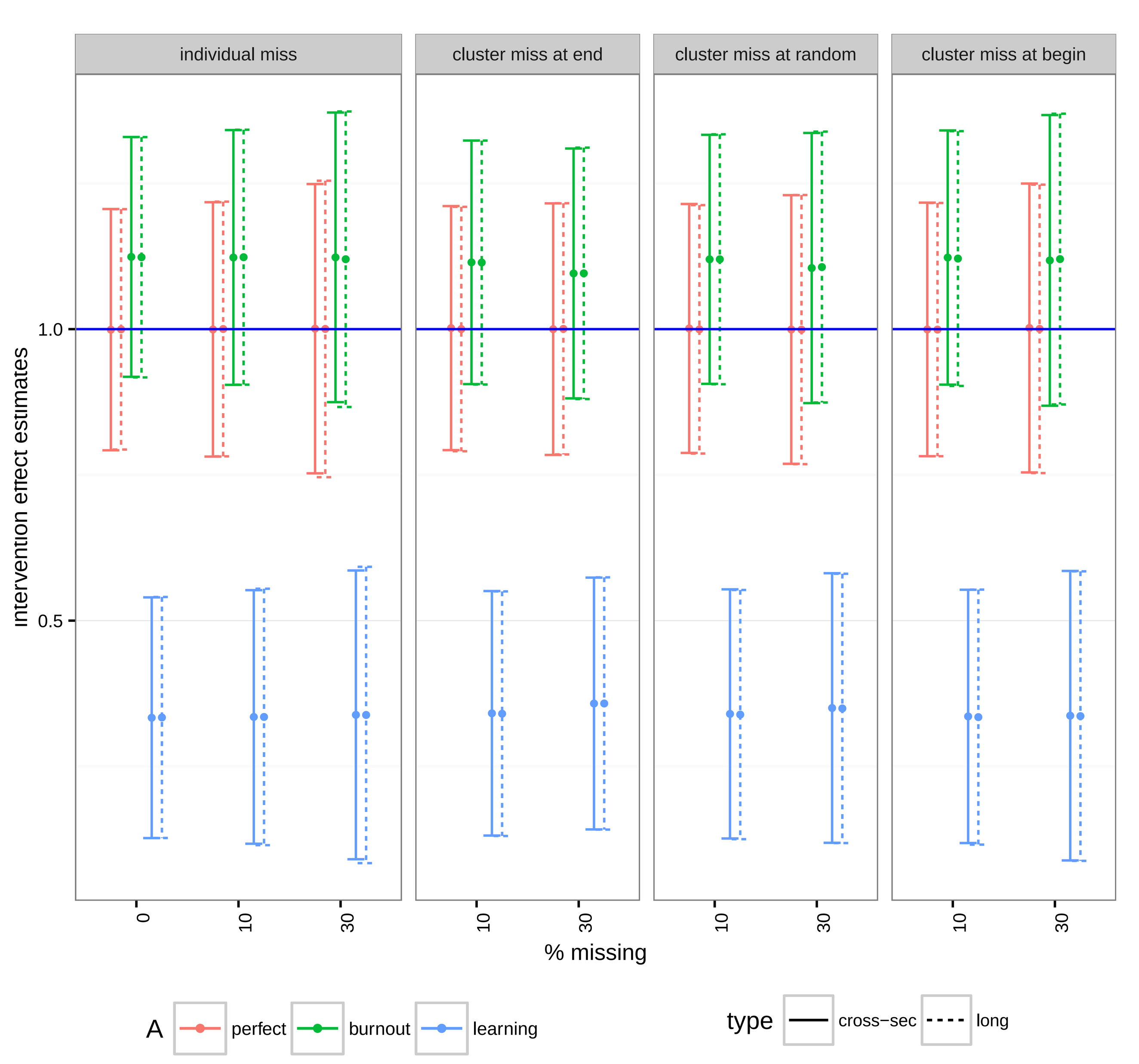
   i) For a **cross-sectional design** a linear mixed model (lmm) based on [2] with fixed intervention and time effects θ, β_j, random cluster and individual effects $\alpha_i \sim N(0, \sigma^2_\alpha)$, $\epsilon_{ijk} \sim N(0, \sigma^2_\epsilon)$ (ϵ_{ij} independent of α_i) and the design matrix X_A for the intervention effect (corresponds to factor A) with

$$Y_{ijk} = \mu + \alpha_i + \beta_j + X_A\theta + \epsilon_{ijk}, \qquad i = 1,...,10; j = 1,...,6; k = 1,...,10$$

   ii) For a **longitudinal design** the same model with an additional additive term of random subject effects $\gamma_{ij} \sim N(0, \sigma^2_\gamma)$

3) Estimation of intervention effect $\hat{\theta}$ from simulated data with the same linear mixed model, but for assumed perfect intervention effect (corresponds to a design matrix X with only (0,1)).

Results of the simulation study



The estimates for each scenario are summarized by the average $\bar{\hat{\Theta}}$ (eq. 1) and the empirical standard error $SE\left(\hat{\Theta}\right)$ (eq. 2) as suggested by [3].

$$\bar{\hat{\Theta}} = \frac{1}{S}\sum_{s=1}^{S}\hat{\Theta}_s, \qquad s = 1, \ldots, S \quad (1)$$

$$SE\left(\hat{\Theta}\right) = \frac{1}{S-1}\sum_{s=1}^{S}\left(\hat{\Theta}_s - \bar{\hat{\Theta}}\right)^2 \quad (2)$$

If deviations from the assumed perfect situation in SWD trial exists, under-/overestimation of intervention effect is possible.

Different patterns of unfulfilled implementations influence the mean of effect estimates. The 'learning' effect had the largest effect compared to the 'perfect' reference scenario with a reduction of more than a half.

Variation of effect estimates increases with the number of individuals or cluster loss and most, if cluster get loss at the beginning. The impact of cross-sectional or longitudinal data is barely visibly.

[1] J. P. Hughes, T. S. Granston, and P. J. Heagerty, "Current issues in the design and analysis of stepped wedge trials," *Contemporary Clinical Trials*, 2015.

[2] M. A. Hussey and J. P. Hughes, "Design and analysis of stepped wedge cluster randomized trials," *Contemp Clin Trials*, vol. 28, no. 2, pp. 182–91, 2007.

[3] A. Burton, D. G. Altman, P. Royston, and R. L. Holder, "The design of simulation studies in medical statistics," *Statistics in Medicine*, vol. 25, pp. 4279–4292, 2006.