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The Effects of Misspecification of Level-I errors Structure in Multilevel Models for Longitudinal Design

Said Ali Shah [1], Amjad Ali[1], Sajjad Ahmad Khan[2]

[1]Department of Statistics
Islamia College, Peshawar,
Khyber Pakhtunkhwa, Pakistan

[2]Department of Statistics
Abdul Wali Khan University, Mardan,
Khyber Pakhtunkhwa, Pakistan

email: Saidalishah2@gmail.com, amjad@icp.edu.pk,
sajjadkhan@awkum.edu.pk

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Abstract

Multilevel models have become popular models for analyzing longitudinal data over past two decades. Longitudinal designs are common specially in medical science, where data is recorded on patients more than two times. As the data is collected on the same patients repeatedly over time, it is more likely that observations are correlated with each other. When the observations are correlated and the data have nested structure, traditional methods give biased estimates of the parameters, as they require the assumption of independence. The present study is concerned with exploring the effect of misspecification of level-I errors covariance structure in multilevel model for longitudinal data. The fixed effects were estimated with little to no bias, and accurate type-I error rates were observed under all the specifications of the covariance structure for the test of fixed effects. Random

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effects were estimated poorly for most of the conditions. Overestimated variances of the level-II random effects were accompanied by the underestimated level-I variance. The covariance between intercept and slope was underestimated in all conditions. The over specification of the covariance matrix of level-I errors gave better estimates than correct specification, under-specification and general misspecification.

1 Introduction

Longitudinal design also called repeated measurement design, has got much more attention recently in many fields, such as in medical, educational and psychological research. In clinical research, subjects forced expiratory volume may be measured at regular interval so that efficacy of treatment may be assessed in a treatment for the asthmas relief during study. Another example could be the data which is collected on body weights of the children, getting treatment with two types of anti-epileptic drugs every ten days for one year. In these examples measurements are made on the same individuals repeatedly over time, so the measurements are nested within individuals.

Methods used to analyze the longitudinal data consist of traditional methods and multilevel models. Traditional methods include univariate analysis of variance and multivariate analysis of variance. Due to nested nature of the data, observations are not independent of each other, which violate the basic assumption required for the traditional approaches. Multilevel models can be used to account for the dependency among observations. The other advantage of using multilevel models compared to traditional methods is the lack of requirement complete measurements across time points [21].

Multilevel models also known as hierarchical linear models [1] and growth curve models [2] have been widely used for analyzing longitudinal data, due to their ability to specify models at distinct levels. Level-I model is used to measure changes in the individuals over time (to see the effect of medicine on a patient). Level-II model is specified to describe how changes vary across individuals [3, 4]. The form of each person's growth trajectory and relationship between independent variables is determined in level-II models [20].

In multilevel models for repeated measures, level-I errors are assumed to be normally and independently distributed, means that within subject variance-covariance structure is of the form $\Sigma = \sigma^2 I$ [5]. Most of the times, researchers specify random effects to account for dependency among repeated measurements at individual level and retain the level-I structure as identity ($\sigma^2 I$). This structure of level-I errors is usually known as independent structure.

In longitudinal design, measurements are made on the same person repeatedly over time, they are more likely to be correlated with each other [6]. Random effects alone cannot account for the dependency among repeated measurements if they are measured close in time or the correlation among them do not decrease quickly, which leads to the development of more complex structure of Σ, within subject covariance matrix [7, 8, 9]. If correlations among within subject measurement errors are not properly modeled, it will result in bias estimates of the parameters [10, 11].
The correlation among repeated measurements and errors is common in longitudinal data [12, 13], and is often ignored in multilevel models by assuming covariance matrix as identity [10]. If within subject errors are correlated then autoregressive (AR) function of first order is the most commonly used model to account for the correlation. In general, moving average (MA) and autoregressive moving average (ARMA) are also used to model the within subject repeated measurements across time [14]. Time series data and growth curve data share the same features when the same individuals are studied over time, occasions are equally spaced in time and the numbers of repeated measurements are sufficient [12].
In growth curve analysis, these three processes are common to occur; therefore, it is necessary to investigate the effect of their misspecification when they exist. In a study by [10], it was shown that in growth curve modeling, variance-covariance estimates of both levels were biased when autoregressive process of order one was unmodeled. Biased estimates were obtained for the parameters of variance covariance when ARMA (1,1) was not modeled [12]. In a simulation study by [11], it was found that specifying AR (1) as unstructured resulted in increased type-I error rates for the fixed effect tests. Previous studies regarding misspecification of level-I covariance structure considered perfect conditions such as random effects follow normal distribution [10, 12, 15, 16]. It was shown in a study by [17] that most of the real-world data do not follow normal distribution. In a study by [18] misspecification of covariance structure with non-normal random effects and small group sizes 25 and 50 was assessed. The non-normal distributions which were considered in a study by [18] were Laplace and Chi-Square (1). The present simulation study investigated the effect of misspecification of level-I errors covariance structure with non-normally distributed random effects. The non-normal distributions such as Exponential and Lognormal were considered in this study. No previous study has examined the effect of misspecification of covariance structure with non-normal random effects and small and moderate sample sizes. Both the small and moderate sample sizes with non-normal

random effects were considered in this study and effect of misspecification of covariance structure on parameter estimates was examined.

2 Materials and Methods

2.1 The Model

For longitudinal data or repeated measurements, level-I model is given below:

$$Y_{ti} = \pi_{0i} + \pi_{1i} T_{ti} + e_{ti} \tag{2.1}$$

The intercept π_{0i} and slope π_{1i} vary across individuals. The error term e_{ti} is often assumed to be normally distributed with mean zero and variance σ^2.

Level-II model is used to explain variability in π_{0i} and π_{1i}, and is given by:

$$\pi_{0i} = \beta_{00} + \beta_{01} x_{1i} + \mu_{0i} \tag{2.2}$$

$$\pi_{1i} = \beta_{10} + \beta_{11} x_{1i} + \mu_{1i} \tag{2.3}$$

$$With \begin{bmatrix} \mu_{0i} \\ \mu_{1i} \end{bmatrix} \sim N \begin{bmatrix} \begin{bmatrix} 0 \\ 0 \end{bmatrix} & \begin{bmatrix} \tau_{00} & \tau_{01} \\ \tau_{10} & \tau_{11} \end{bmatrix} \end{bmatrix}$$

Parameters τ_{00} and τ_{11} are the variances of intercept and slope and τ_{01} is the covariance between intercept and slope. Level-II errors μ_{0i} and μ_{1i} are assumed to be uncorrelated with level-I errors.

Substituting equations 2.2 and 2.3 in equation 2.1, gives a single mixed linear model which is given below:

$$y = X\beta + Z\nu + \varepsilon \tag{2.4}$$

This is the representation of multilevel model as linear mixed model, where y is the column vector of outcome data, which contains the repeated measurements for individuals, X is model matrix which contains intercept and Time variable, β is the column vector which contains fixed effects, Z is the design matrix, ν is the column vector of random effects and ε is a column vector of within subject errors. The vector ε consists of within subject variance-covariance structure Σ, which corresponds to level-I error e_{ti}. It is commonly assumed that within subject variance-covariance matrix is of the form $\Sigma = \sigma^2 \mathrm{I}$ [5]. The column vector of random effects ν, can be thought of consisting a between subjects variance-covariance structure T, which corresponds to level-II errors, μ_{0i} and μ_{1i}. The expected value of y in the Equation 2.4 is $E(y) = X\beta$ and variance of y is

$$\begin{aligned} VAR(y) &= VAR(Z\nu + \varepsilon) \\ V &= VAR(Z\nu) + VAR(\varepsilon) \\ V &= ZTZ^T + \Sigma \end{aligned} \tag{2.5}$$

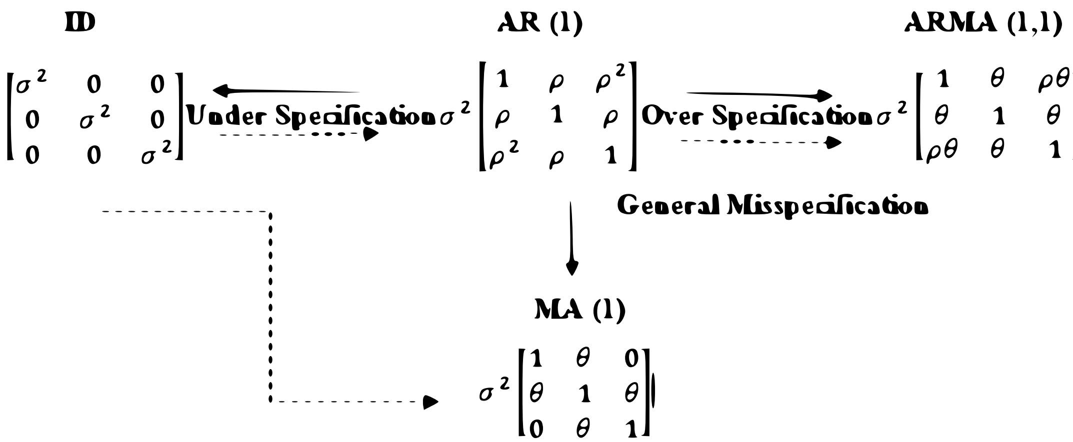
The two components ZTZ^T and Σ of total variance are due to the random effects and level-I errors respectively. Most of the times researchers assume this variance-covariance matrix of level-I errors as $\sigma^2 I$ [5], i.e., variance is homogeneous and time points are not correlated. For three time points, the underlying structure of this matrix is;

$$\Sigma = \begin{bmatrix} \sigma^2 & 0 & 0 \\ 0 & \sigma^2 & 0 \\ 0 & 0 & \sigma^2 \end{bmatrix}$$

This is called independent structure, where σ^2 is the constant variance across three time points. Response variable for the model in this paper is continuous and level-I errors are assumed to follow normal distribution.

2.2 Types of Misspecification

Earlier there was an interest in modeling the covariance structure adequately [8,9]. Recently, most of the simulations studies have been started to investigate the effect of misspecifying the level-I errors structure [10, 15, 16, 17].
Three terms which are used about the misspecification of covariance structure of level-I errors are general misspecification, under-specification and over-specification [15].
Under-specification occurs when the specified structure is nested within true structure (e.g. true structure is AR (1) and independent structure is specified). General misspecification occurs when the true and specified structures are not nested. For example, true structure is AR (1) and MA (1) is specified. Over-specification occurs when the true structure is nested within the specified structure (e.g. true covariance structure is AR (1) and ARMA (1,1) is specified) The solid lines show misspecification of covariance structure of level-I errors and dashed lines show the nested relationship between different covariance matrices.In the above figure σ^2 is the variance of level-I one errors, ρ is the coefficient of autocorrelation and θ is the moving average coefficient.



2.3 Effects of misspecification

The misspecification effect on estimation and test of significance of fixed effects was investigated by [10, 12, 15, 16, 18]. It was concluded in these simulation studies that fixed effects were estimated with small to no bias and there was some evidence of positive bias in the standard errors estimates of the fixed effects. The standard errors of random slope and random intercept were overestimated when the covariance structure was either under-specified or generally misspecified [15]. Under-specification of covariance structure as independent caused greater bias in the estimates of variance of random effects compared to other structures and variance of level-I errors was underestimated [18].
Under-specification or general misspecification can produce positively biased estimates of τ_{00} and τ_{11} [10, 15]. The variances τ_{00} and τ_{11} were underestimated when the covariance structure was over-specified [15]. There was also an evidence of bias in the variance of random effects under the correct specification [16, 18].

2.4 Proposed Method/Model and Simulation Study

In the present study two level growth curve model was examined with level-I modeling repeated measures (outcome) as a linear function of time, and level-II modeling intercept and slope as function of one predictor. In this study focus was only on linear growth curve model in which fixed effects were correctly specified and design was balance. For this simulation study, factorial type research design was used. The simulation used 4 (covariance structures: ID, MA (1), AR (1) or ARMA (1,1)) x 2 (30 and 200 individuals) x 2 (4 and 8 repeated measurements) x 3 (random effects distributions: Normal, Lognormal and Exponential) conditions for data generation. For each condition 1000 replication were generated. The number of parameters were invariant in all covariance structures for different number of time points. The four covariance structures also have non-nested and nested relationship with one another, so the effects of three types of misspecification could be investigated. Number of individuals and number of repeated measurements were based on previous simulation studies [10,12,18]. Values of the fixed effects ($\beta_{00}, \beta_{01}, \beta_{10}, \beta_{11}$) were set to zero, values of random effects (τ_{00}, τ_{11}) were taken as 1, value of the covariance between intercept and slope was zero, value of level-I errors variance (σ^2) was set to zero, coefficient of autocorrelation was equal to 0.8 and moving average parameter was set to 0.3. Parameters values selected in this study were consistent with the values used in the previous simulation studies [10,12,13, 16]. Relative and simple bias, model convergence and type-I error rates were calculated for all models. Relative bias was calculated using the formula.

$$RB = \frac{(Estimate - Parameter)}{Parameter}$$

An estimator was considered as biased if absolute value of its relative bias was greater than 0.05 [19]. When the parameter value was set to zero, relative bias for estimate could not be computed. In such circumstances, simple bias was calculated and estimate was considered biased for which absolute value of simple bias was greater than 0.05. Type-I error rates for the test of fixed effects were also computed under different covariance structures.

3 Results and Discussion

Convergence rates were calculated for all the models analyzed. When the covariance structure was specified as either MA (1) or ID, all the models were almost converged. The convergence rates were decreased for AR (1) specification but they were further decreased for ARMA (1,1) specification. Table 1 breaks the convergence percentage by the simulated and fitted specification. It can be seen in the table that convergence rate ranges from 95.18% to 100%. Over-specified structures have the lowest convergence rates compared to other specifications. Average estimates of fixed effects are given in table-2. There was no evidence of bias in the estimates as mean estimates were very close to the parameters values. Simple bias was not greater than

Table 1: Percentages of Convergence by Simulated and Fitted Specification

Simulated	Fitted	Convergence
ID	ID	99.95%
ID	AR (1)	99.76%
ID	MA (1)	99.90%
ID	ARMA (1,1)	95.18%
AR (1)	ID	99.86%
AR (1)	AR (1)	99.12%
AR (1)	MA (1)	99.88%
AR (1)	ARMA (1,1)	96.76%
MA (1)	ID	99.96%
MA (1)	AR (1)	99.26%
MA (1)	MA (1)	99.92%
MA (1)	ARMA (1,1)	96.24%
ARMA (1,1)	ID	100%
ARMA (1,1)	AR (1)	99.14%
ARMA (1,1)	MA (1)	99.87%
ARMA (1,1)	ARMA (1,1)	98.26%

0.05. Largest value for the simple bias was 0.007 when the number of measurements was 4 and the number of individuals was 200. So, the results are consistent to the previous simulation studies [10, 12, 16]. Thus, in multilevel models for longitudinal data the fixed effect estimates remain unbiased under the misspecification of the level -I errors covariance structure.

Table 2: Average Values of the Estimates of Fixed Effects for Different Covariance Specifications

Fixed Effect	ID	AR (1)	MA (1)	ARMA (1,1)
β_{00}	0.00058	0.00053	0.00051	0.00059
β_{01}	-0.00027	-0.00022	-0.00021	-0.00018
β_{10}	-0.00014	-0.00017	-0.00018	-0.00013
β_{11}	-0.00045	-0.00006	-0.00007	-0.00011

Rates of type-I error were examined for the tests of fixed effects. Table-3 shows the estimates of type-I error rates for all specifications. For all conditions examined, estimates of type-I error rates were within the range of the liberal definition of robustness. The range for the type-I error rates to be within the liberal definition of robustness is from 0.5α to 1.5α [23], where α is the nominal error rate.

Under the ARMA (1,1) specification, type-I error rates were more than nominal rate for most of the conditions. For AR (1), MA (1) and ID specifications type-I error rates were close to nominal rates in most of the conditions.

Table 3: Estimates of Type-I Error Rates for the Tests of Fixed Effects

N	L	Fixed effects	ARMA (1,1)	AR (1)	MA (1)	ID
30	4	β_{00}	0.054	0.052	0.051	0.053
		β_{01}	0.052	0.051	0.051	0.053
		β_{10}	0.060	0.058	0.059	0.058
		β_{11}	0.059	0.057	0.058	0.058
30	8	β_{00}	0.051	0.049	0.050	0.051
		β_{01}	0.050	0.048	0.049	0.051
		β_{10}	0.062	0.061	0.059	0.063
		β_{11}	0.060	0.059	0.058	0.060
200	4	β_{00}	0.050	0.049	0.048	0.050
		β_{01}	0.051	0.050	0.049	0.051
		β_{10}	0.052	0.051	0.050	0.052
		β_{11}	0.053	0.052	0.051	0.052
200	8	β_{00}	0.050	0.048	0.048	0.051
		β_{01}	0.049	0.048	0.050	0.052
		β_{10}	0.051	0.050	0.049	0.049
		β_{11}	0.052	0.051	0.050	0.050

Coefficient associated with slope equation (β_{10} and β_{11}) have liberal type-I error rates for some conditions, particularly when the number of individuals was 30 and number of repeated measurements was 4 and 8.

As for all the conditions examined, the estimates of the type-I error rates were within the liberal definition of robustness, therefore it can be said that tests of the fixed effects are not affected by the misspecification of the level -1 errors covariance structure.

Relative bias of τ_{00} and τ_{11} and simple bias of σ^2 and τ_{01} were calculated for correct specification and misspecification of covariance structure. Table 4-7 show the relative and simple bias of random components, when the covariance structure was correctly specified as ID, AR (1), MA (1) and ARMA (1,1), or misspecified as other structures (e.g. AR (1), MA (1) and ARMA (1,1)) are misspecified structures for ID structure. The estimate of intercept

Table 4: Relative and Simple Bias of Random Effects When True Covariance Structure was ID

N	L	Random Effects	ID	AR (1)	MA (1)	ARMA (1,1)
30	4	Var intercept (τ_{00})	0.5924	0.0621	0.0701	0.0547
		Var slope (τ_{11})	0.1210	0.0438	0.0419	0.0430
		Cov int and slope(τ_{01})	-0.0812	-0.0410	-0.0401	-0.0413
		Var Res (σ^2)	-0.1423	-0.0592	-0.0572	-0.0612
30	8	Var intercept (τ_{00})	0.0812	0.0395	0.0421	0.0425
		Var slope (τ_{11})	0.0030	0.0372	0.0407	0.0332
		Cov int and slope(τ_{01})	-0.0252	-0.0417	-0.0445	-0.0041
		Var Res (σ^2)	-0.0511	-0.0426	-0.0320	-0.0336
200	4	Var intercept (τ_{00})	0.0402	0.0410	0.0397	0.0361
		Var slope (τ_{11})	0.0231	0.0398	0.0404	0.0412
		Cov int and slope(τ_{01})	-0.0313	-0.0383	-0.0435	-0.0341
		Var Res (σ^2)	-0.0639	-0.0347	0.0383	-0.0399
200	8	Var intercept (τ_{00})	-0.0821	0.0385	0.0400	0.0312
		Var slope (τ_{11})	0.0027	0.0301	0.0283	0.0217
		Cov int and slope(τ_{01})	-0.0031	-0.0323	-0.0312	-0.0290
		Var Res (σ^2)	-0.0223	-0.0215	-0.0192	-0.0175

Note: Var-variance, Cov- covariance, int- intercept, Res-residual

variance was biased under the correct specification for the small number of repeated measurements and small number of individuals.

Random intercept variance was overestimated in all conditions when covariance structure was under-specified or generally misspecified. Bias was small in the estimates of the intercept variance when covariance was over-specified. There was evidence of bias in the estimates of τ_{11} under the correct specification for some conditions. The relative bias of random slope variance inflated under general misspecification and in under-specification. Under these two specifications amount of bias was greater when the small number of individuals were combined with the small number of repeated measurements. Relative bias of τ_{11} was small under over-specification of the covariance structure.

Table 5: Relative and Simple Bias of Random Effects When True Covariance Structure was AR (1)

N	L	Random Effects	ID	VAR (1)	MA (1)	ARMA (1,1)
30	4	Var intercept (τ_{00})	1.0413	0.5102	0.3616	0.0562
		Var slope (τ_{11})	0.1164	0.1621	0.0827	0.0497
		Cov int and slope(τ_{01})	-0.1212	-0.0820	-0.0507	-0.0102
		Var Res (σ^2)	-0.3216	-0.1521	-0.0725	-0.0634
30	8	Var intercept (τ_{00})	0.9924	0.0916	0.05321	0.0339
		Var slope (τ_{11})	0.0441	0.0321	0.0842	0.0394
		Cov int and slope(τ_{01})	-0.1334	-0.0173	-0.1226	-0.0022
		Var Res (σ^2)	-0.2437	-0.0622	-0.2310	-0.0231
200	4	Var intercept (τ_{00})	1.0314	-0.0220	0.6913	0.0323
		Var slope (τ_{11})	0.0823	0.0127	0.0713	0.0312
		Cov int and slope(τ_{01})	-0.1257	-0.0210	-0.1024	-0.0149
		Var Res (σ^2)	-0.3326	-0.0828	0.3016	-0.0412
200	8	Var intercept (τ_{00})	0.9523	-0.1372	0.4233	0.0162
		Var slope (τ_{11})	0.0251	0.0031	0.0134	0.0133
		Cov int and slope(τ_{01})	-0.1102	-0.0043	-0.0417	-0.0011
		Var Res (σ^2	-0.2387	-0.0239	-0.1012	-0.0172

Note: Var-variance, Cov- covariance, int- intercept, Res-residual

Under the correct specification the estimates of covariance between intercept and slope were unbiased for most of the conditions. The bias was severe under the general misspecification and in under-specification for all conditions. Evidence of small bias was also found under the over-specification of covariance structure. In all conditions the covariance of intercept and slope was estimated negatively.

Variance of level-I errors was estimated to be negative for all conditions under the correct specification. The relative bias was more substantial for the small number of individuals and small number of repeated measurements in both correct specification and in over-specification of covariance structure.

The amount of bias was larger when covariance was either under-specified or correctly specified. The underestimation of level-I variance was severe for correct specification and in under-specification.

Table 6: Relative and Simple Bias of Random Effects When True Covariance Structure was MA (1)

N	L	Random Effects	ID	VAR (1)	MA (1)	ARMA (1,1)
30	4	Var intercept (τ_{00})	0.9523	0.7516	0.4321	0.0921
		Var slope (τ_{11})	0.1034	0.0816	0.1354	0.0412
		Cov int and slope(τ_{01})	-0.1070	-0.0931	-0.0522	-0.0216
		Var Res (σ^2)	-0.2981	-0.1523	-0.0562	-0.0724
30	8	Var intercept (τ_{00})	0.8816	0.5432	-0.1260	0.0421
		Var slope (τ_{11})	0.0436	0.0356	0.0832	0.0287
		Cov int and slope(τ_{01})	-0.0812	-0.0742	-0.0243	-0.0036
		Var Res (σ^2)	-0.2312	-0.1768	-0.0420	-0.0312
200	4	Var intercept (τ_{00})	0.9613	0.6681	-0.0314	0.0454
		Var slope (τ_{11})	0.0721	0.0619	0.0232	0.0462
		Cov int and slope(τ_{01})	-0.0902	-0.0824	-0.0345	-0.0221
		Var Res (σ^2)	-0.3126	-0.2802	-0.0731	-0.0316
200	8	Var intercept (τ_{00})	0.7574	0.4011	-0.1038	0.0261
		Var slope (τ_{11})	0.0221	0.0141	0.0041	0.0316
		Cov int and slope(τ_{01})	-0.0623	-0.0503	-0.0041	-0.0031
		Var Res (σ^2)	-0.2132	-0.1817	-0.0413	-0.0132

Note: Var-variance, Cov- covariance, int- intercept, Res-residual

Table 7: Relative and Simple Bias of R.Effects When True Covariance Structure was ARMA (1,1)

N	L	Random Effects	ID	VAR (1)	MA (1)	ARMA (1,1)
30	4	Var intercept (τ_{00})	1.1201	0.6213	0.6832	0.5915
		Var slope (τ_{11})	0.0847	0.0227	0.0313	0.1623
		Cov int and slope(τ_{01})	-0.1435	-0.0448	-0.0453	-0.0827
		Var Res (σ^2)	-0.3126	-0.1927	-0.1726	-0.1629
30	8	Var intercept (τ_{00})	1.1642	0.7826	0.8216	0.0624
		Var slope (τ_{11})	0.0452	0.0135	0.0214	0.0032
		Cov int and slope(τ_{01})	-0.1190	-0.0554	-0.0493	-0.0124
		Var Res (σ^2)	-0.1923	-0.1443	-0.1123	-0.0639
200	4	Var intercept (τ_{00})	1.1052	0.8514	0.8323	-0.0214
		Var slope (τ_{11})	0.0727	0.0423	0.0442	0.0201
		Cov int and slope(τ_{01})	-0.1413	-0.0621	-0.0587	-0.0317
		Var Res (σ^2)	-0.3214	-0.2204	0.1924	-0.0673
200	8	Var intercept (τ_{00})	1.0972	0.8135	0.7926	-0.0549
		Var slope (τ_{11})	0.0352	0.0117	0.0104	0.0013
		Cov int and slope(τ_{01})	-0.1252	-0.0697	-0.0603	-0.0034
		Var Res (σ^2)	-0.2243	-0.1642	-0.1427	-0.0328

Note: Var-variance, Cov- covariance, int- intercept, Res-residual

4 Conclusion

The focus of this paper was to examine the effects of misspecifications of covariance matrix of level-I errors on the estimates of fixed effects, random effects and type-I errors rates. The estimates of fixed effects were found to be unbiased. Type-I errors rates for the tests of fixed effects were within the liberal definition of robustness under the different specifications and they were close to the nominal level. Inflated type-I errors rates were found for the combination of small number of individuals and small number of repeated measurements. The estimates of the random effects were found to be biased in some conditions. Variance of random intercept was overestimated in all conditions. The bias was severe under the general misspecification, correct specification and in under-specification. Random slope variance was overestimated under the correct specification and in under-specification. The over specification produced better estimates for the random slope variance. Covariance between intercept and slope was underestimated in all conditions. Similarly, the variance of the level-I errors was also underestimated in all specifications. The underestimation was severe in general misspecification, correct specification and in under-specification. The overestimation of the variances of second level model was accompanied by the underestimation of the variance of level-I model. Over-specification of the covariance structure produced better estimates of the variances of random effects compared with other specifications. In some conditions, correct specification also produced biased estimates for the variances of random slopes. The random effect distribution did not explain any significant variation in the bias of the estimates of fixed effects and random effects. As a future research, the performance of different estimation methods can be compared under the misspecification of level-I errors covariance structure and non-normal random effects.

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