Optimal Designs for Prediction in Two Treatment Groups
Random Coefficient Regression Models

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Abstract: The subject of this work is two treatment groups random coefficient regression models, in which observational units receive some group-specific treatments. We provide A- and D-optimality criteria for the estimation of the fixed parameter and the prediction of the random effects. We illustrate the behavior of optimal designs by a simple example.

Keywords: Mixed models, estimation and prediction, optimal design, cluster randomization

1 Introduction

The subject of this paper is optimal designs in two treatment groups random coefficient regression (RCR) models, in which observational units receive some group-specific kinds of treatment. These models are typically used for cluster randomized trials. For some real data examples see e.g. Piepho and Möhring (2010).

Optimal designs for fixed effects models with multiple groups are well discussed in the literature (see e.g. Bailey (2008), ch. 3). In models with random coefficients, the estimation of the population (fixed) parameters is usually of prior interest (see e.g Fedorov and Jones (2005), Kunert et al. (2010), Van Breukele and Candel (2018)). Optimal designs for the prediction of random effects in models with known population parameters have been considered in detail in Gladitz and Pilz (1982). Prus and Schwabe (2016) provide analytical results for the models with unknown population mean under the assumption of same design for all individuals. Multiple group models with fixed group sizes were briefly discussed in Prus (2015), ch. 6.

Here, we consider two groups models with unknown population parameters and group specific designs. We provide A- and D-optimality criteria for the estimation and the prediction of fixed and random effects, respectively. Our main focus is optimal designs for the prediction. As a by-product we obtain some results for the estimation of fixed effects.

The paper is structured in the following way: In Section 2 the two groups RCR model will be introduced. Section 3 presents the best linear unbiased estimator for the population parameter and the best linear unbiased predictor for individual random effects. Section 4 provides analytical results for the designs, which are optimal for the estimation and for the prediction. The paper will be concluded by a short discussion in Section 5.

2 Two Treatment Groups RCR Model

In this work we consider RCR models with two treatment groups \(G_1\) and \(G_2\), where observational units (or individuals) receive group-specific kinds of treatment, \(T_1\) and \(T_2\), respectively. The first group includes \(n_1\) individuals and the second group \(n_2\) individuals. The groups sizes \(n_1\) and \(n_2\) are to be optimized and the total number of individuals \(N = n_1 + n_2\) in the experiment is fixed. The \(k\)-th observation at the \(i\)-th individual is described for the first group by

\[
Y_{ik} = \mu_{i1} + \varepsilon_{ik}, \quad i = i_1, \ldots, i_{n_1}, \quad k = 1, \ldots, K
\]  

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and for the second group by

\[ Y_{2ik} = \mu_{2i} + \varepsilon_{2ik}, \quad i = i_{n1+1}, \ldots, i_N, \quad k = 1, \ldots, K, \]

where \( K \) is the number of observations per individual, which is assumed to be the same for both groups, \( \varepsilon_{1ik} \) and \( \varepsilon_{2ik} \) are the observational errors in the first and the second group with zero expected value and the variances \( \text{var}(\varepsilon_{1ik}) = \sigma_1^2 \) and \( \text{var}(\varepsilon_{2ik}) = \sigma_2^2 \), respectively. \( \mu_{1i} \) and \( \mu_{2i} \) are the individual response parameters.

As it has been already mentioned above, we optimize the group sizes \( n_1 \) and \( n_2 \). Therefore, we define the individual parameters for all individuals for both groups: \( \theta_i := (\mu_{1i}, \mu_{2i})^\top, \) \( i = 1, \ldots, N \). The parameters can be interpreted as follows: Let the individual \( i \) be in the second group. Then the parameter \( \mu_{1i} \) describes the response, which would be observed at individual \( i \) if the individual would receive treatment \( T_2 \). Otherwise, if individual \( i \) is in the first group, \( \mu_{1i} \) is the real response of the \( i \)-th individual.

The individual parameters are assumed to have an unknown mean \( \mathbb{E}(\theta_i) = (\mu_{1}, \mu_{2})^\top =: \theta_0 \) and a covariance matrix \( \text{Cov}(\theta_i) = \text{diag}(\sigma_1^2 u, \sigma_2^2 v) \) for given dispersions \( u > 0 \) and \( v > 0 \). All individual parameters \( \theta_i, \) \( i = 1, \ldots, N \), and all observational errors \( \varepsilon_{1i'k} \) and \( \varepsilon_{2i'k'} \), \( i' = 1, \ldots, N \), \( k, k' = 1, \ldots, K \), are assumed to be uncorrelated.

Further we focus on the following contrasts: population parameter \( \alpha_0 = \mu_{1} - \mu_{2} \) and individual random parameters \( \alpha_i = \mu_{1i} - \mu_{2i}, \) \( i = 1, \ldots, N \). \( \alpha_0 \) describes the difference between the mean parameters \( \mu_{1} \) and \( \mu_{2} \) in the first and in the second group, respectively, and \( \alpha_i \) may be interpreted as the difference for individual \( i \) between the real response and the response, which could be observed if the individual would receive another treatment. We search for the designs (group sizes), which are optimal for the estimation of \( \alpha_0 \) or for the prediction of \( \alpha_i \).

### 3 Estimation and Prediction

In this section we concentrate on the estimation of the population parameter \( \alpha_0 \) and the prediction of the individual parameters \( \alpha_i \). We use the standard notation \( \bar{Y}_i = \frac{1}{n_i} \sum_{i=n1+1}^{n_i} \frac{1}{K} \sum_{i=1}^{K} Y_{1ik} \) and \( \bar{Y}_2 = \frac{1}{n_2} \sum_{i=n1+1}^{i_N} \frac{1}{K} \sum_{i=1}^{K} Y_{2ik} \) for the mean response in the first and the second treatment group, respectively, and obtain the following best linear unbiased estimator (BLUE) for \( \alpha_0 \).

**Theorem 1.** The BLUE for the population parameter \( \alpha_0 \) is given by

\[ \hat{\alpha}_0 = \bar{Y}_1 - \bar{Y}_2. \]

The next theorem provides the variance of the BLUE \( \hat{\alpha}_0 \).

**Theorem 2.** The variance of the BLUE \( \hat{\alpha}_0 \) is given by

\[ \text{var}(\hat{\alpha}_0) = \frac{\sigma_1^2(Ku + 1)}{Kn_1} + \frac{\sigma_2^2(Kv + 1)}{Kn_2}. \]

Further we use the notation \( \bar{Y}_{1i} = \frac{1}{K} \sum_{k=1}^{K} Y_{1ik} \) and \( \bar{Y}_{2i} = \frac{1}{K} \sum_{k=1}^{K} Y_{2ik} \) for the mean individual response for individuals in the first and in the second treatment group, respectively. We obtain the next result for the best linear unbiased predictor (BLUP) for the individual response parameter \( \alpha_i \).

**Theorem 3.** The BLUP for the individual response parameter \( \alpha_i \) is given by

\[ \hat{\alpha}_i = \begin{cases} \frac{Ku}{Ku + 1} \bar{Y}_{1i} + \frac{1}{Ku + 1} \bar{Y}_1 - \bar{Y}_2, & \text{ind. } "i" \text{ in } G1 \\ \bar{Y}_1 - \frac{Kv}{Kv + 1} \bar{Y}_2 + \frac{1}{Kv + 1} \bar{Y}_2, & \text{ind. } "i" \text{ in } G2. \end{cases} \]
The next theorem presents the mean squared error (MSE) matrix for the total vector \( \hat{\alpha} := (\hat{\alpha}_1, ..., \hat{\alpha}_N) \) of all BLUPs \( \hat{\alpha}_i \) for all individuals.

**Theorem 4.** The MSE matrix of the vector \( \hat{\alpha} \) of individual predictors is given by

\[
\text{Cov}(\hat{\alpha} - \alpha) = \begin{pmatrix} A_{11} & A_{12} \\ A_{12}^\top & A_{22} \end{pmatrix}
\]

(6)

for

\[
A_{11} = \left( \frac{\sigma_1^2}{K(Ku+1)n_1} + \frac{\sigma_2^2}{Kn_2} \right) 1_{n_1} 1_{n_1}^\top + \sigma_1^2 \left( \frac{u}{Ku+1} + v \right) I_{n_1},
\]

where \( 1_m \) denotes the vector of length \( m \) with all entries equal to 1, \( I_m \) is the \( m \times m \) identity matrix and \( \otimes \) denotes the Kronecker product,

\[
A_{12} = \left( \frac{\sigma_1^2}{Kn_1} + \frac{\sigma_2^2}{Kv(Kv+1)n_2} \right) 1_{n_1} 1_{n_2}^\top
\]

and

\[
A_{22} = \left( \frac{\sigma_1^2(Ku+1)}{Kn_1} + \frac{\sigma_2^2}{K(Ku+1)n_2} \right) 1_{n_2} 1_{n_2}^\top + \sigma_2^2 \left( u + \frac{v}{Kv+1} \right) I_{n_2}.
\]

Proofs of Theorems 1-4 are deferred to Appendix A.

4 Experimental Design

We define the experimental (exact) design for the RCR model with two treatment groups \( G_1 \) and \( G_2 \) as follows:

\[
\xi := \begin{pmatrix} G_1 \\ n_1 \\ G_2 \\ n_2 \end{pmatrix}.
\]

For analytical purposes, we generalize this to the definition of an approximate design:

\[
\xi := \begin{pmatrix} G_1 \\ w \\ G_2 \\ 1-w \end{pmatrix},
\]

where \( w = \frac{n_1}{N} \) and \( 1-w = \frac{n_2}{N} \) are the allocation rates for the first and the second groups, respectively, and only the condition \( 0 \leq w \leq 1 \) has to be satisfied. Then only the optimal allocation rate \( w^* \) to the first group has to be determined for finding an optimal design.

Further we search for the allocation rates, which minimize variance (4) of the BLUE \( \hat{\alpha}_0 \) and MSE matrix (6) of the BLUP \( \hat{\alpha} \) and concentrate on the A- (average) and D- (determinant) optimality criteria.

4.1 Optimal designs for estimation of population parameter

For the estimation of the population parameter \( \alpha_0 \) both A- and D-criteria may be considered to be equal to variance (4) of the BLUE \( \hat{\alpha}_0 \). The A-criterion is initially defined as the trace of the covariance matrix of the estimator and results in the variance itself for one-dimensional parameters. The D-criterion, which is defined as the logarithm of the determinant of the covariance matrix, may be simplified to the determinant since the logarithm is a monotonic function. We rewrite the variance of the estimator in terms of the approximate design and receive the next result (neglecting the constant factor \( (KN)^{-1} \)).
Theorem 5. The A- and D-criteria for the estimation of the population parameter $\alpha_0$ are given by

$$\Phi_{A,D,\alpha_0}(w) = \frac{\sigma_1^2 (Ku + 1)}{w} + \frac{\sigma_2^2 (Kv + 1)}{1 - w}. \quad (7)$$

Criterion function (7) can be minimized directly. The optimal allocation rate is presented in the following theorem.

Theorem 6. The A- and D-optimal allocation rate for the estimation of the population parameter $\alpha_0$ is given by

$$w_{\alpha_0}^* = \frac{1}{1 + \sqrt{\frac{\sigma_2^2 (Kv + 1)}{\sigma_1^2 (Ku + 1)}}}. \quad (8)$$

Note that the optimal allocation rate $w_{\alpha_0}^*$ to the first group increases with increasing observational error variance $\sigma_1^2$ and the dispersion $u$ of random effects for the first group and decreases with variance parameters $\sigma_2^2$ and $v$ for the second group. Note also that if the observational error variance is the same for both groups ($\sigma_1^2 = \sigma_2^2$), $w_{\alpha_0}^*$ is larger than 0.5 for $u > v$ and smaller than 0.5 for $u < v$.

4.2 Optimal designs for prediction of individual response parameters

We define the A-criterion for the prediction of the individual response parameters $\alpha = (\alpha_1, ..., \alpha_N)^T$ as the trace of MSE matrix (6):

$$\Phi_{A,\alpha} := \text{tr} \left( \text{Cov} \left( \hat{\alpha} - \alpha \right) \right). \quad (9)$$

We extend this definition for approximate designs and receive the following result (neglecting the constant factor $K^{-1}$).

Theorem 7. The A-criterion for the prediction of the individual response parameters $\alpha = (\alpha_1, ..., \alpha_N)^T$ is given by

$$\Phi_{A,\alpha}(w) = c_1 + \sigma_1^2 \left( \frac{Ku + 1}{w} + Nw \left( \frac{Ku}{Ku + 1} + Kv \right) \right)$$
$$+ \sigma_2^2 \left( \frac{Kv + 1}{1 - w} + N (1 - w) \left( \frac{Kv}{Kv + 1} + Ku \right) \right), \quad (10)$$

where

$$c_1 = \sigma_1^2 \left( \frac{1}{Ku + 1} - Ku - 1 \right) + \sigma_2^2 \left( \frac{1}{Kv + 1} - Kv - 1 \right).$$

For this criterion no finite formulas for optimal allocation rates can be provided. For given dispersion matrix of random effects (given values of $u$ an $v$), the problem of optimal designs can be solved numerically. In this work we are however interested in the behavior of optimal designs with respect to the variance parameters. Therefore, we consider some special cases, which illustrate this behavior.

Special case 1: $\sigma_1^2 = \sigma_2^2$ and $u = v$

If the variances $\sigma_1^2$ and $\sigma_2^2$ of the observational errors as well as the dispersions $u$ and $v$ (and consequently the variances $\sigma_1^2 u$ and $\sigma_2^2 v$) of the random effects are the same for both groups, A-criterion (10) simplifies to

$$\Phi_{A,\alpha}(w) = c_2 + \frac{1}{w} + \frac{1}{1 - w}. \quad (11)$$
where

\[ c_2 = \frac{NKu'(Ku' + 2)}{(Ku' + 1)^2} - 2 \]

for \( u' = u = v \) (neglecting the factor \( Ku' + 1 \) and the observational errors variance). We obtain for this criterion the optimal allocation rate \( w_{A,\alpha}^* = 0.5 \), which is also optimal for estimation in the fixed-effects model \((u = v = 0)\).

**Special case 2:** \( \sigma_1^2 = \sigma_2^2 \)

If only the variances \( \sigma_1^2 \) and \( \sigma_2^2 \) of the observational errors are the same for both groups, the A-criterion for the prediction simplifies to

\[
\Phi_{A,\alpha}(w) = c_3 + \frac{Ku + 1}{w} + Nw\left(\frac{Ku}{Ku + 1} + Kv\right) + \frac{Kv + 1}{1 - w} + N(1 - w)\left(\frac{Kv}{Kv + 1} + Ku\right),
\]

(12)

where

\[
c_3 = \frac{1}{Ku + 1} + \frac{1}{Kv + 1} - K(u + v) - 2,
\]

(neglecting the observational errors variance). The behavior of the optimal allocation rate will be considered for this case in a numerical example later.

The D-criterion for the prediction of \( \alpha = (\alpha_1, ..., \alpha_N)^\top \) can be defined as the logarithm of the determinant of MSE matrix (6):

\[
\Phi_{D,\alpha} := \log \det (\text{Cov} (\hat{\alpha} - \alpha)).
\]

(13)

For approximate designs we obtain the next result.

**Theorem 8.** The D-criterion for the prediction of the individual response parameters \( \alpha = (\alpha_1, ..., \alpha_N)^\top \) is given by

\[
\Phi_{D,\alpha}(w) = b_1 + w N \log \left(\frac{\sigma_1^2(Kv + 1)}{\sigma_2^2(Ku + 1)}\right) + \log \left(\frac{\sigma_1^2(1 - w) + \sigma_2^2 w}{w(1 - w)}\right),
\]

(14)

where

\[
b_1 = \log \left(\frac{(\sigma_2^2)^{N-1}(v + u(Kv + 1))^{N-2}(Ku + 1)(K(u + v) + 1)}{\sigma_1^2 K^2 N(Kv + 1)^{N-1}}\right).
\]

Proof. We compute the determinant of MSE matrix (6) using the formula for block-matrices

\[ \det (\text{Cov} (\hat{\alpha} - \alpha)) = \det (A_{11}) \det \left( A_{22} - A_{12}A_{11}^{-1}A_{12}^\top \right). \]

Then we rewrite the result in terms of the approximate design and receive criterion (14). \( \square \)

Also for this criterion no finite analytical solutions for optimal designs can be provided. We consider the same special cases as for the A-criterion.

**Special case 1:** \( \sigma_1^2 = \sigma_2^2 \) and \( u = v \)

If the variances of the observational errors and the variances of the random effects are the same for the first and the second treatment groups, the D-criterion for the prediction is given by

\[
\Phi_{D,\alpha}(w) = b_2 - \log (w(1 - w)),
\]

(15)

where \( b_2 = b_1 + \log(\sigma^2) \) for \( \sigma^2 = \sigma_1^2 = \sigma_2^2 \). Then we obtain the optimal allocation rate \( w_{D,\alpha}^* = 0.5 = w_{A,\alpha}^* \) and formulate the next corollary.
Corollary 1. If the variances of the observational errors as well as the dispersions of the random effects are equal for both groups, the A- and D-optimal designs in the fixed-effects model are A- and D-optimal for the prediction of the individual response parameters in the two groups RCR model.

Special case 2: $\sigma_1^2 = \sigma_2^2$
If the variances of the observational errors are the same for both groups and the dispersions $u$ and $v$ of random effects may be different, we receive the following D-criterion for the prediction:

$$\Phi_{D,\alpha}(w) = b_2 + w N \log \left( \frac{K v + 1}{K u + 1} \right) - \log \left( w (1 - w) \right).$$

If we additionally assume different dispersions of random effects ($u \neq v$), we obtain the next result for the optimal designs.

Theorem 9. If the variances of the observational errors are the same and the dispersions of the random effects are different for the first and the second treatment groups, the D-optimal allocation rate for the prediction of the individual response parameters $\alpha = (\alpha_1, \ldots, \alpha_N)^\top$ is given by

$$w_{D,\alpha}^* = \frac{1}{2a} \left( a + 2 - \sqrt{a^2 + 4} \right),$$

where

$$a = N \log \left( \frac{K v + 1}{K u + 1} \right).$$

Note that the optimal allocation rate $w_{D,\alpha}^*$ to the first group increases with $u$ and decreases with $v$. It can be easily proved that $w_{D,\alpha}^*$ is larger than 0.5 if $u > v$ and smaller than 0.5 if $u < v$.

For further considerations we rewrite the optimal allocation rate (17) as a function of the ratio $q = \frac{u}{v}$ of the variances of random effects in the first and the second groups and the variance parameter $u$:

$$a = N \log \left( \frac{K u/q + 1}{K u + 1} \right).$$

Than it is easy to verify that $w_{D,\alpha}^*$ increases with $u$ for $q > 1$ ($u > v$) and decreases for $q < 1$.

4.3 Numerical example
In this section we illustrate the obtained results for the prediction of the individual response parameters by a numerical example. We consider the two groups RCR model with $N = 60$ individuals, $K = 1$ observation per individual and same variance of observational errors for both treatment groups: $\sigma_1^2 = \sigma_2^2$ (special case 2). We fix the ratio $q = \frac{u}{v}$ of the variances of random effects in the first and the second groups by $q = 3$, $q = 1$ and $q = 0.3$. Figures 1 and 2 illustrate the behavior of the optimal allocation rates for the A- and D-criteria in dependence of the rescaled random effects variance in the first group $\rho = u/(1 + u)$, which is monotonic in $u$ and has been used instead of random effects variance itself to cover all values of the variance by the finite interval $[0, 1]$.

As we can observe on the graphics, the optimal allocation rate to the first group increases with the rescaled variance $\rho$ from 0.5 for $\rho \to 0$ to 0.910 for the A-criterion and to 0.985 for the D-criterion for $\rho \to \infty$ if $q = 3$. If $q = 0.3$, the optimal allocation rate decreases from 0.5 to 0.083 and 0.015 for the A- and D-criterion, respectively. For $q = 1$ the model coincides with that considered in special case 1 and the optimal design remains the same ($w_{A,\alpha}^* = w_{D,\alpha}^* = 0.5$) for all values of $u$. 

6
Figures 1 and 2 exhibit the efficiencies of the balanced design $w = 0.5$ for the prediction in the two groups model for the A- and D-criteria. For computing the A- and D-efficiencies, we use the formulas

$$
eff_A = \frac{\Phi_{A,\alpha}(w_{A,\alpha}^*)}{\Phi_{A,\alpha}(0.5)} \tag{18}$$

and

$$
eff_D = \left( \frac{\exp(\Phi_{D,\alpha}(w_{D,\alpha}^*))}{\exp(\Phi_{D,\alpha}(0.5))} \right)^\frac{1}{N} \tag{19}$$

respectively.

As we can observe, the efficiency of the balanced design decreases with increasing values of $\rho$ from 1 for $\rho \to 0$ to 0.656 and 0.616 if $q = 3$ and to 0.618 and 0.585 if $q = 0.3$ for the A- and D-criteria, respectively. For $q = 1$ the balanced design is optimal for the prediction, which explains the efficiency equal to 1 for all values of the variance.

5 Discussion

In this work we have considered RCR models with two treatment groups. We have obtained the A- and D-optimality criteria for the estimation of the population parameter and the prediction of the individual response. For a particular case of the same observational error variance for both groups, we illustrate the behavior of the optimal designs by a numerical example. The optimal allocation rate to the first treatment group turns out to be larger than 0.5 if the variance of individual random effects in the first group is larger than in the second group. Otherwise, the optimal allocation rate is smaller than 0.5. The efficiency of the balanced design, which assigns equal group sizes, is relatively high only for small values of the variances of random effects. The efficiency decreases fast with increasing variance.
For simplicity, we have assumed a diagonal covariance matrix of random effects. For more general covariance structure further considerations are needed. We have also assumed the same number of observations for all individuals. Optimal designs for models with different numbers of observations for different individuals may be one of the next steps in the research. Moreover, optimal designs for RCR models with more than two groups can be investigated in the future.

Furthermore, some research on more robust design criteria (for example, minimax or maximin efficiency), which are not sensible with respect to variance parameters, may be an interesting extension of this work.

### A Proofs of Theorems 1-4

The two treatment groups RCR model described by formulas (1) and (2) may be recognized as a special case of the general linear mixed model

\[ Y = X\beta + Z\gamma + \varepsilon \]

with specific design matrices \( X \) and \( Z \) for fixed and random effects, respectively. \( \varepsilon \) are the observational errors, \( \beta \) denotes the fixed effects vector and \( \gamma \) are the random effects. The random effects and the observational errors are assumed to have zero mean and to be all uncorrelated with corresponding full rank covariance matrices \( \text{Cov}(\gamma) = G \) and \( \text{Cov}(\varepsilon) = R \).

In model (20) the BLUE for \( \beta \) and the BLUP for \( \gamma \) are solutions of the mixed model equations

\[
\begin{pmatrix}
\hat\beta \\
\hat\gamma
\end{pmatrix} = \begin{pmatrix}
X^\top R^{-1}X & X^\top R^{-1}Z \\
Z^\top R^{-1}X & Z^\top R^{-1}Z + G^{-1}
\end{pmatrix}^{-1} \begin{pmatrix}
X^\top R^{-1}Y \\
Z^\top R^{-1}Y
\end{pmatrix}
\]

if the fixed effects design matrix \( X \) has full column rank (see e.g. Henderson et al. (1959) and Christensen (2002)). According to Henderson (1975), the joint MSE matrix for both \( \hat\beta \) and \( \hat\gamma \) is
given by
\[
\text{Cov} \left( \begin{pmatrix} \hat{\beta} \\ \hat{\gamma} - \gamma \end{pmatrix} \right) = \left( \begin{array}{cc} X^\top R^{-1}X & X^\top R^{-1}Z \\ Z^\top R^{-1}X & Z^\top R^{-1}Z + G^{-1} \end{array} \right)^{-1}.
\]

(22)

To make use of the theoretical results available for the general linear mixed model, we rewrite the two groups RCR model in form (20):
\[
Y = \begin{pmatrix} 1_{K_{n_1}}e_1^\top \\ 1_{K_{n_2}}e_2^\top \end{pmatrix} \beta + \begin{pmatrix} I_{n_1} \otimes (1_{K_1}e_1^\top) \\ 0 \\ I_{n_2} \otimes (1_{K_2}e_2^\top) \end{pmatrix} \gamma + \varepsilon,
\]
where \( \beta = \theta_0, \gamma = \theta - (1_N \otimes 1_2) \beta, \theta = (\theta_1, \ldots, \theta_N) \) and \( e_m \) denotes the \( m \)-th unit vector. The covariance matrices of the random effects and the observational errors in model (23) are given by \( G = I_N \otimes \text{diag}(\sigma_1^2 u, \sigma_2^2 v) \) and \( R = \text{block-diag}(\sigma_1^2 I_{K_{n_1}}, \sigma_2^2 I_{K_{n_2}}) \), respectively.

Then we obtain using formula (21) the BLUEs \( \hat{\mu}_1 = \bar{Y}_1 \) and \( \hat{\mu}_2 = \bar{Y}_2 \) for the fixed effects and the BLUPs
\[
\hat{\mu}_{1i} = \begin{cases} \frac{K_u}{K_u+1} \bar{Y}_n + \frac{1}{K_u+1} \bar{Y}_j, & \text{ind. } \text{"i" in } G_1 \\ \bar{Y}_l, & \text{ind. } \text{"i" in } G_2 \end{cases}
\]
and
\[
\hat{\mu}_{2i} = \begin{cases} \frac{K_v}{K_v+1} \bar{Y}_n + \frac{1}{K_v+1} \bar{Y}_j, & \text{ind. } \text{"i" in } G_2 \\ \bar{Y}_2, & \text{ind. } \text{"i" in } G_1 \end{cases}
\]
for the random effects. Then the BLUE and the BLUP for the contrasts \( \alpha_0 \) and \( \alpha_i \) can be computed as \( \hat{\alpha}_0 = \hat{\mu}_1 - \hat{\mu}_2 \) and \( \hat{\alpha}_i = \hat{\mu}_{1i} - \hat{\mu}_{2i} \) and result to formulas (3) and (5), respectively.

Using formula (22) we obtain the following joint MSE matrix for both \( \hat{\beta} \) and \( \hat{\gamma} \):
\[
\text{Cov} \left( \begin{pmatrix} \hat{\beta} \\ \hat{\gamma} - \gamma \end{pmatrix} \right) = \left( \begin{array}{cc} C_{11} & C_{12} \\ C_{12}^\top & C_{22} \end{array} \right),
\]
where
\[
C_{11} = \begin{pmatrix} \sigma_1^2 (K_u + 1) & 0 \\ 0 & \sigma_2^2 (K_v + 1) \end{pmatrix},
\]
\[
C_{12} = \begin{pmatrix} \frac{1}{n_1} \sigma_1^2 u 1_{n_1}^\top \otimes e_1^\top & 0 \\ 0 & \frac{1}{n_2} \sigma_2^2 v 1_{n_2}^\top \otimes e_2^\top \end{pmatrix},
\]
and
\[
C_{22} = \begin{pmatrix} B_1 & 0 \\ 0 & B_2 \end{pmatrix}
\]
for
\[
B_1 = \sigma_1^2 \left( \frac{K_u^2}{n_1 (K_u + 1)} 1_{n_1} 1_{n_1}^\top \otimes (e_1 e_1^\top) + I_{n_1} \otimes \text{diag} \left( \frac{u}{K_u + 1}, v \right) \right)
\]
and
\[
B_2 = \sigma_2^2 \left( \frac{K_v^2}{n_2 (K_v + 1)} 1_{n_2} 1_{n_2}^\top \otimes (e_2 e_2^\top) + I_{n_2} \otimes \text{diag} \left( u, \frac{v}{K_v + 1} \right) \right).
\]
As we can see by formula (26), the covariance matrix of \( \hat{\beta} \) is equal to \( C_{11} \). Then we present the variance of the estimator \( \hat{\alpha}_0 \) in form
\[
\text{var}(\hat{\alpha}_0) = (1, 1) \text{Cov}(\hat{\beta}) (1, 1)^\top
\]
and obtain result (4) of Theorem 2.
The MSE matrix of the prediction \( \hat{\theta} \) can be written in terms of the joint MSE matrix (26):

\[
\text{Cov} \left( \hat{\theta} - \theta \right) = (1_N \otimes I_2) C_{11} \left( 1_N^\top \otimes I_2 \right) + (1_N \otimes I_2) C_{12} + C_{12}^\top \left( 1_N^\top \otimes I_2 \right) + C_{22}.
\]

(27)

Using this formula we obtain

\[
\text{Cov} \left( \hat{\theta} - \theta \right) = \begin{pmatrix} H_{11} & H_{12} \\ H_{12}^\top & H_{22} \end{pmatrix},
\]

where

\[
H_{11} = 1_{n_1} 1_{n_1}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2}{K(Ku+1)n_1} & 0 \\ 0 & \frac{\sigma_2^2(Kv+1)}{Kn_2} \end{pmatrix} + \sigma_1^2 1_{n_1} \otimes \begin{pmatrix} u \\ 0 \end{pmatrix},
\]

\[
H_{12} = 1_{n_1} 1_{n_2}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2}{Ku} \\ 0 \end{pmatrix} + \sigma_2^2 1_{n_2} \otimes \begin{pmatrix} 0 \\ \frac{u}{Kv+1} \end{pmatrix}
\]

and

\[
H_{22} = 1_{n_2} 1_{n_2}^\top \otimes \begin{pmatrix} \frac{\sigma_1^2(Ku+1)}{Ku} & 0 \\ 0 & \frac{\sigma_2^2(Kv+1)}{Kn_2} \end{pmatrix} + \sigma_2^2 1_{n_2} \otimes \begin{pmatrix} u \\ 0 \end{pmatrix},
\]

Then we present the MSE matrix of the predictor \( \hat{\alpha} \) in form

\[
\text{Cov} \left( \hat{\alpha} - \alpha \right) = (I_N \otimes 1_2^\top) \text{Cov} \left( \hat{\theta} - \theta \right) (I_N \otimes 1_2)
\]

and receive result (6) of Theorem 4.

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