An Exact Upper Limit for the Variance Bias in the Carry-over Model with Correlated Errors

Oliver Sailer *

Faculty of Statistics, TU Dortmund University, Germany

Abstract

The analysis of crossover designs assuming i.i.d. errors leads to biased variance estimates whenever the true covariance structure is not spherical. As a result, the OLS F-Test for treatment differences is not valid. Bellavance et al. (Biometrics 52:607-612, 1996) use simulations to show that a modified F-Test based on an estimate of the within subjects covariance matrix allows for nearly unbiased tests. Kunert and Utzig (JRSS B 55:919-927, 1993) propose an alternative test that does not need an estimate of the covariance matrix. However, for designs with more than three observations per subject Kunert and Utzig (1993) only give a rough upper bound for the worst-case variance bias. This may lead to overly conservative tests. In this paper we derive an exact upper limit for the variance bias due to carry-over for an arbitrary number of observations per subject. The result holds for a certain class of highly efficient carry-over balanced designs.

Key words: bias, correlated errors, crossover designs, fixed effects model, upper limit, variance estimation

1 Introduction

In a crossover design each subject receives multiple treatments. Data from crossover designs are often analyzed with a linear model that includes direct treatment effects, carry-over effects, subject effects and order effects. If we assume i.i.d. errors, in matrix notation we have the model

$$Y = 1_{np}\mu + P\alpha + U\pi + T\tau + F\rho + \epsilon,\ \mathrm{E}(\epsilon) = 0,\ \mathrm{Cov}(\epsilon) = \sigma^2 I_{np}. \quad (1)$$

*Email: sailer@statistik.uni-dortmund.de

Here, $Y = (y_{11}, \ldots, y_{np})^T$ is the vector of observations and y_{ij} the observation on subject i at period j, $i = 1, \ldots, n$, $j = 1, \ldots, p$. There are a general mean, μ, fixed effects for subjects, $\alpha = (\alpha_1, \ldots, \alpha_n)^T$ and fixed effects for periods (order effects) $\pi = (\pi_1, \ldots, \pi_p)^T$. $P = I_n \otimes 1_p$ and $U = 1_n \otimes I_p$ denote the corresponding design matrices. The vectors of direct and residual (carry-over) treatment effects are given by $\tau = (\tau_1, \ldots, \tau_t)^T$ and $\rho = (\rho_1, \ldots, \rho_t)^T$ respectively. We assume that there is no residual effect in period 1. We denote the corresponding design matrices for direct and carry-over effects by T and F. The vector of errors, $\epsilon = (\epsilon_{11}, \ldots, \epsilon_{np})^T$, follows a distribution with finite second moments. The errors are i.i.d. with variance $\sigma^2 > 0$. If we allow for correlated errors, we get

$$Y = 1_{np}\mu + P\alpha + U\pi + T\tau + F\rho + \epsilon, \; \mathrm{E}(\epsilon) = 0, \; \mathrm{Cov}(\epsilon) = \Sigma = I_n \otimes S. \quad (2)$$

Here, we assume that the within subjects covariance matrix $S \in \mathbb{R}^{p \times p}$ is the same for all subjects. So (1) is a special case of (2) where $S = \sigma^2 I_p$.

It is well known that the analysis of crossover designs assuming i.i.d. errors leads to biased variance estimates whenever the true covariance structure is not spherical. As a result of this, ordinary least squares (OLS) F-Tests for treatment differences are no longer valid. If S were known, GLS estimates could be used. Bellavance et al. (1996) compare several alternatives to the OLS F-Test based on estimates of S. Along with Correa and Bellavance (2001) and Chen and Wei (2003) they conclude from simulation studies that a modified F-Test based on an approximation by Box (1954) yields nearly unbiased and reasonably powerful tests for treatment effects, see also Jones and Kenward (2003)[p.262].

For studies with few subjects the estimates of S may be unreliable, thus leading to biased tests. Therefore Kunert and Utzig (1993) do not estimate S. They analyze the worst-case performance of treatment estimates under (1) when in fact (2) holds and then correct the corresponding test statistics for the worst-case bias. This is achieved by dividing the F-Statistic by the maximum of the ratio of the variance of a treatment contrast in (2) and the expected value of the estimated variance, where the variance estimate is computed assuming (1).

However, for designs with more than three observations per subject Kunert and Utzig (1993) do not give a sharp upper bound for the worst-case scenario. This leads to overly conservative tests whenever the covariance matrix is close to spherical.

The next section details this approach and introduces some useful notation for computing the worst-case scenario. In section 3 we derive an exact upper limit for the variance bias due to carry-over for an arbitrary number of observations per subject.

2 The upper bound for the variance quotient by (Kunert and Utzig, 1993)

A crossover design is a block design d with t treatments and n subjects as blocks. Each block is of length p. Let $\Lambda_{t,n,p}$ the set of such designs. As in Kunert and Utzig (1993) we will restrict our attention to a subset $\Lambda^*_{t,n,p}$ of designs suitable for analysis under (1). Also, as the above authors point out, it suffices to assume $p > 2$, since the variance estimates are unbiased for $p = 2$ regardless of S.

Definition 1. *A block design d is called totally balanced, if it fulfills the following conditions.*

(i) d is a balanced block design with $t \geq p$, i.e. the number of subjects that receive treatments i and j is the same for all pairs of treatments $i \neq j$ and each treatment is administered to each subject at most once.

(ii) The number of subjects that receive treatments i and j during the first $p-1$ periods is the same for all $i \neq j$.

(iii) d is uniform on the periods, i.e. each treatment appears in each period exactly n/t times.

(iv) d is neighbor balanced, i.e. each treatment is preceded by every other treatment equally often but is never preceded by itself.

(v) The number of subjects that receive treatments i during the first $p-1$ periods and that receive treatment j in the last period is the same for all $i \neq j$.

Let $\Lambda^*_{t,n,p}$ the set of totally balanced designs for given t, n, p.

Note that a totally balanced design does not exist for every t, n, p. Examples of totally balanced designs include the designs proposed by Patterson (1952) and Williams (1949).

In (1) we are interested in estimating contrasts $\psi = \ell^T \tau$ of direct treatment effects, where $\ell = (\ell_1, \ldots, \ell_t)^T \in \mathbb{R}^t$ and $\sum_i \ell_i = 0$. Without loss of generality we restrict our attention to standardized contrasts, i.e. $\sum_i \ell_i^2 = 1$. Let $\hat{\psi} = \ell^T \hat{\tau}$ an OLS estimate of $\psi = \ell^T \tau$ under (1).

Let $\omega_A = \omega(A) = A(A^T A)^- A^T$ the projection matrix on the column span of A and $\omega_A^\perp = \omega^\perp(A) = I - \omega(A)$. Here, A^- is any generalized Inverse of A. We denote a partitioned matrix by $A = [A_1, \ldots, A_n]$ and define $Q_n = \omega^\perp(1_n) = I_n - \frac{1}{n} 1_n 1_n^T$, the centering matrix of rank $n-1$.

If $d \in \Lambda^*_{t,n,p}$, then we have information matrices

$$\begin{aligned} C_d &= T^T \omega^\perp_{[P,U,F]} T = c_d Q_t, \\ C_{d11} &= T^T \omega^\perp_{[P,U]} T = c_{d11} Q_t, \\ C_{d12} &= T^T \omega^\perp_{[P,U]} F = c_{d12} Q_t, \\ C_{d22} &= F^T \omega^\perp_{[P,U]} F = c_{d22} Q_t, \end{aligned}$$

where

$$\begin{aligned} c_d &= \frac{n(p-1)}{t-1}\left(1 - \frac{t}{p(pt-t-1)}\right), \\ c_{d11} &= \frac{n(p-1)}{t-1}, \\ c_{d12} &= \frac{-n(p-1)}{p(t-1)}, \\ c_{d22} &= \frac{n(p-1)(pt-t-1)}{p(t-1)t}, \end{aligned}$$

cf. Kunert and Utzig (1993).

We denote by E_1 and E_2 expected values under (1) and (2) respectively. Analogous notation is applied for variances, estimated variances and covariances. The BLUE for ψ in (1) equals $\hat{\psi} = \ell^T C_d^- T^T \omega^\perp_{[P,U,F]} Y$. By construction $\hat{\psi}$ is unbiased in (1), i.e. $\mathrm{E}_1(\hat{\psi}) = \psi$. If (2) holds, $\hat{\psi}$ is unbiased, too, as

$$\begin{aligned} \mathrm{E}_2(\hat{\psi}) &= \mathrm{E}_2 \frac{1}{c_d} \ell^T T^T \omega^\perp_{[P,U,F]} \left([P,U,F](\alpha^T,\beta^T,\rho^T)^T + T\tau + \epsilon\right) \\ &= \frac{1}{c_d} \ell^T C_d \tau + \mathrm{E}_2\left(\frac{1}{c_d} \ell^T T^T \omega^\perp_{[P,U,F]} \epsilon\right) \\ &= \frac{c_d}{c_d} \ell^T \tau + 0 \\ &= \psi. \end{aligned}$$

In (1) an unbiased estimate of σ^2 is $\hat{\sigma}^2 = \frac{1}{c_f} Y_d^T \omega^\perp_{[P,U,F,T]} Y$, where

$$c_f = np - 2t - n - p + 3$$

is the degrees of freedom for the error term. For a standardized contrast ψ we then have $\mathrm{var}_1(\hat{\psi}) = \hat{\sigma}^2 \ell^T C_d^- \ell = \hat{\sigma}^2 / c_d$.

Kunert and Utzig (1993) require that the treatment labels be randomized. Obviously, if we randomize any starting design $d_0 \in \Lambda^*_{t,n,p}$, the randomized design d is also totally balanced. Randomization of treatment labels means that ℓ becomes random. The results above still hold for randomized designs, as they do not depend on the choice of ℓ. Under randomization, standardized contrasts have the same variance, irrespective of the choice of ℓ.

With the notation $\tilde{S} = Q_p S Q_p$ and the upper left element of $\tilde{S}$ equal to s_{11}, Kunert and Utzig (1993) get

$$\mathrm{E}_2\, \hat{\mathrm{var}}_1(\hat{\psi}) = \frac{1}{c_d c_f}\left\{(n-1)\mathrm{tr}\,(\tilde{S}) - \frac{n}{c_{d22}}\left(\mathrm{tr}\,(\tilde{S}) - (t-1)s_{11}/t\right)\right\} - \frac{t-1}{c_f}\mathrm{var}_2(\hat{\psi}),$$

where

$$\mathrm{var}_2(\hat{\psi}) = \frac{n}{(t-1)c_d^2}\mathrm{tr}\left(\tilde{S} - 2\gamma V^T\tilde{S} + \gamma^2 V^T\tilde{S}V - \frac{1}{t}\gamma^2 1_p^T V^T \tilde{S} V 1_p\right) \tag{3}$$

and $\gamma = c_{d12}/c_{d22} = \frac{-t}{pt-t-1}$.

Here,

$$V = \begin{bmatrix} 0 & 0 \\ I_{p-1} & 0 \end{bmatrix}.$$

Note that $T = [T_1^T, \ldots, T_n^T]$ and $F = [VT_1^T, \ldots, VT_n^T]$.

Definition 2. *For fixed $(t,n,p)^T \in \mathbb{N}^3$ let $d \in \Lambda^*_{t,n,p}$, the treatment labels in d randomized, $S \in \mathbb{R}^{p\times p}$ nonnegative definite (n.n.d.) and $\mathcal{S}$ the set of n.n.d. matrices in $\mathbb{R}^{p\times p}$.*

The variance quotient $k_{t,n,p}$ is defined by

$$k_{t,n,p}(S) = \frac{var_2(\hat{\psi})}{E_2\, v\hat{a}r_1(\hat{\psi})}. \tag{4}$$

The maximum $k^*_{t,n,p}$ of the variance quotient with respect to $S \in \mathcal{S}$ is called Kunert-Utzig constant, *i.e.*

$$k^*_{t,n,p} = \max_{S\in\mathcal{S}} k_{t,n,p}. \tag{5}$$

Any matrix that maximizes the variance quotient is called worst-case covariance matrix.

By construction, the variance quotient does not depend on d for fixed t, n, p, it does not depend on ℓ and equals 1 if $S = \sigma^2 I_p$. If for S the variance quotient is less than 1, we overestimate the true variance of $\hat{\tau}$. Tests based on $\hat{\tau}$ will tend to be conservative in this case. If, however, $k_{t,n,p}(S) > 1$ then we underestimate the true variance and our tests get anti-conservative.

Definition 3. *For fixed* $(t,n,p)^T \in \mathbb{N}^3$ *let*

$$k^v_{t,n,p} = \begin{cases} \left(\frac{(t-1)c_d\left(u(z^2+z+1)+v\right)}{fn(w(z^2+z+1)-\gamma z^2-r)} - \frac{t-1}{c_f}\right)^{-1}, \text{ if } p=3 \\ \left(\frac{(t-1)c_d u}{fn(w-\gamma)} - \frac{t-1}{c_f}\right)^{-1}, \text{ if } p=4 \\ \left(\frac{(t-1)c_d u}{fn(1-\gamma)^2} - \frac{t-1}{c_f}\right)^{-1}, \text{ if } p\geq 4 \end{cases}$$

We define the Kunert-Utzig bound $k^u_{t,n,p}$ *by*

$$k^u_{t,n,p} = \begin{cases} k^v_{t,n,p}, \text{ if } k^v_{t,n,p} > 0 \\ \infty, \text{ else.} \end{cases}.$$

Here $u = n-1-n/c_{d22}$, $v = \frac{n}{c_{d22}}\frac{t+1}{2t}$, $w = 1+\gamma^2$, $r = \gamma^2\frac{t+1}{2t}$ *and*

$$z = \frac{1}{\gamma u}\left(-\gamma(u+v) - ru - vw - \sqrt{(-\gamma(u+v)-ru-vw)^2 - \gamma u(ru+vw)}\right).$$

We now have

Theorem 1 (Kunert and Utzig, 1993)**.** *Whenever* $k^*_{t,n,p}$ *exists,* $k^*_{t,n,p} \leq k^u_{t,n,p}$.

Table 1 shows some values of the Kunert-Utzig bound. In the discussion, we compare those to the values derived from the exact limit.

If we want to estimate the variance of a contrast estimate in (2) we may multiply the estimate $\hat{\mathrm{var}}_1(\hat{\psi})$ by $k^u_{t,n,p}$. Then, on average we will not underestimate the true variance of $\hat{\psi}$ by wrongly assuming (1) since for any S it holds that

$$\begin{aligned} \mathrm{E}_2\left(\hat{\mathrm{var}}_1(\hat{\psi})\right)k^u_{t,n,p} &\geq \mathrm{E}_2\left(\hat{\mathrm{var}}_1(\hat{\psi})\right)k^*_{t,n,p} \\ &\geq \mathrm{E}_2\left(\hat{\mathrm{var}}_1(\hat{\psi})\right)k_{t,n,p}(S) \\ &= \mathrm{var}_2(\hat{\psi}). \end{aligned}$$

3 The maximization of the variance quotient

We start by computing the numerator and denominator of the variance quotient (4). We will then get to a representation of the maximization problem (5) as an eigenvalue problem that has a solution for every totally balanced design.

The first lemma allows us to decompose a projection matrix on the column span of a partitioned matrix. We use this lemma repeatedly in the following proofs.

$p=3$								
m	t	3	4	5	6	7	10	100
1								
2		1.80	1.77	1.75	1.74	1.73	1.71	1.68
4		1.51	1.49	1.47	1.46	1.46	1.45	1.43
6		1.48	1.45	1.44	1.43	1.43	1.42	1.40
1000000		1.44	1.41	1.40	1.39	1.39	1.38	1.36
$p=4$								
m	t	3	4	5	6	7	10	100
1			∞	∞	∞	∞	84.90	18.80
2			2.11	2.10	2.09	2.08	2.07	2.04
4			1.80	1.78	1.78	1.77	1.76	1.74
6			1.74	1.72	1.71	1.71	1.70	1.67
1000000			1.65	1.63	1.62	1.61	1.60	1.58
$p=5$								
m	t	3	4	5	6	7	10	100
1				3.37	3.29	3.24	3.16	2.99
2				1.96	1.96	1.96	1.95	1.93
4				1.79	1.78	1.78	1.77	1.76
6				1.75	1.74	1.74	1.73	1.72
1000000				1.68	1.68	1.67	1.66	1.65
$p=6$								
m	t	3	4	5	6	7	10	100
1					2.01	2.00	1.98	1.94
2					1.65	1.64	1.64	1.63
4					1.56	1.56	1.56	1.55
6					1.54	1.54	1.54	1.53
1000000					1.51	1.51	1.50	1.49
$p=7$								
m	t	3	4	5	6	7	10	100
1						1.65	1.64	1.62
2						1.49	1.48	1.48
4						1.44	1.44	1.43
6						1.43	1.42	1.42
1000000						1.40	1.40	1.40
$p=10$								
m	t	3	4	5	6	7	10	100
1							1.32	1.32
2							1.28	1.28
4							1.26	1.26
6							1.26	1.26
1000000							1.25	1.25
$p=100$								
m	t	3	4	5	6	7	10	100
1								1.02
2								1.02
4								1.02
6								1.02
1000000								1.02

Table 1: The Kunert-Utzig bound $k^u_{t,n,p,}$ for the comparison of t treatments in $n = mt$ blocks of length p.

Lemma 1. *Let $A = [A_1, A_2]$ a partitioned matrix. Then*

$$\begin{aligned} \omega_A &= \omega_{A_2} + \omega(\omega_{A_2}^{\perp} A_1) \text{ and} \\ \omega_A^{\perp} &= \omega_{A_2}^{\perp} - \omega(\omega_{A_2}^{\perp} A_1). \end{aligned}$$

Proof. Let $C = A_1^T \omega_{A_2}^{\perp} A_1$. Then

$$(A^T A)^- = \begin{bmatrix} C^- & -C^- A_1^T A_2 (A_2^T A_2)^- \\ -(A_2^T A_2)^- A_2^T A_1 C^- & (A_2^T A_2)^- + (A_2^T A_2)^- A_2^T A_1 C^- A_1^T A_2 (A_2^T A_2)^- \end{bmatrix}$$

is a generalized inverse of $A^T A$. From this it follows that $\omega_A = A(A^T A)^- A^T = \omega_{A_2} + \omega(\omega_{A_2}^{\perp} A_1)$. □

Let $Q_{p,t} = I_p - \frac{1}{t} 1_p 1_p^T$, then

Lemma 2.

$$var_2(\hat{\psi}) = \frac{n}{(t-1)c_d^2}\, tr\left(A_d \tilde{S}\right),$$

where $A_d = I_p - \gamma(V + V^T) + \gamma^2 V Q_{p,t} V^T$.

Proof. The trace of a product of matrices is invariant under cyclical permutation. Then,

$$\begin{aligned} \operatorname{tr}\left(V^T \tilde{S} V - \frac{1}{t} 1_p^T V^T \tilde{S} V 1_p\right) &= \operatorname{tr}\left(V^T Q_p S Q_p V - \frac{1}{t} 1_p 1_p^T V^T Q_p S Q_p V\right) \\ &= \operatorname{tr}(Q_p V Q_{p,t} V^T Q_p S) \end{aligned}$$

and since $\operatorname{tr} V^T \tilde{S} = \operatorname{tr} \tilde{S} V$, we can plug in (3) to get

$$\begin{aligned} \operatorname{var}_2(\hat{\psi}) &= \frac{n}{(t-1)c_d^2} \operatorname{tr}\left(Q_p Q_p S - \gamma Q_p (V + V^T) Q_p S + \gamma^2 Q_p V Q_{p,t} V^T Q_p S\right) \\ &= \frac{n}{(t-1)c_d^2} \operatorname{tr}\left(Q_p \{I - \gamma(V + V^T) + \gamma^2 V Q_{p,t} V^T\} Q_p S\right) \\ &= \frac{n}{(t-1)c_d^2} \operatorname{tr}(Q_p A_d Q_p S) \\ &= \frac{n}{(t-1)c_d^2} \operatorname{tr}(A_d \tilde{S}), \end{aligned}$$

where $A_d = I_p - \gamma(V + V^T) + \gamma^2 V Q_{p,t} V^T$. □

For the expected variance we have

Lemma 3.

$$E_2\, \hat{var}_1(\hat{\psi}) = \frac{n}{c_d^2 c_f} tr\left(B_d \tilde{S}\right),$$

where $B_d = (\frac{c_d(n-1)}{n} - 1) I_p + \gamma(V + V^T + p V Q_{p,t} V^T)$.

Proof. Note that $\hat{\sigma^2} = \frac{1}{c_f} Y_d^T \omega^{\perp}_{[P,U,F,T]} Y$, $\mathrm{E}_2 Y = 1_{np}\mu + P\alpha + U\beta + T\tau + F\rho$ and $\mathrm{Cov}_2 Y = \Sigma$. Since the column space of $[P,U,T,F]$ includes 1_{np} it holds that

$$\mathrm{E}_2\, \hat{\mathrm{var}}_1(\hat{\psi}) = \frac{1}{c_d} \mathrm{E}_2\, \hat{\sigma}^2$$

where

$$\begin{aligned} \mathrm{E}_2 \hat{\sigma}^2 &= \frac{1}{c_f}\left(\mathrm{tr}\,(\omega^{\perp}_{[P,U,F,T]}\ \Sigma) + (\mathrm{E}_2 Y)^T \omega^{\perp}_{[P,U,F,T]} (\mathrm{E}_2 Y)\right) \qquad (6) \\ &= \frac{1}{c_f} \mathrm{tr}\,(\omega^{\perp}_{[P,U,F,T]}\ \Sigma). \end{aligned}$$

We now compute $\mathrm{tr}\,(\omega^{\perp}_{P,U,F,T}\ \Sigma)$. Since

$$\omega^{\perp}_P = I_{np} - (I_n \otimes 1_p)(I_n \otimes p)^- (I_n \otimes 1_p^T) = I_n \otimes Q_p$$

we get

$$\omega^{\perp}_P U = (I_n \otimes Q_p)(1_n \otimes I_p) = 1_n \otimes Q_p.$$

With Lemma 1 it follows that

$$\omega^{\perp}_{[P,U]} = \omega^{\perp}_P - \omega(\omega^{\perp}_P U) = Q_n \otimes Q_p.$$

Again applying Lemma 1 we have

$$\begin{aligned} \omega^{\perp}_{[P,U,F]} &= \omega^{\perp}_{[P,U]} - \omega(\omega^{\perp}_{[P,U]} F) \\ &= (Q_n \otimes Q_p) - (Q_n \otimes Q_p) F \left(F^T (Q_n \otimes Q_p) F\right)^+ F^T (Q_n \otimes Q_p) \\ &= (Q_n \otimes Q_p) - \frac{1}{c_{d22}} (Q_n \otimes Q_p) F F^T (Q_n \otimes Q_p). \end{aligned}$$

This implies

$$\begin{aligned} \omega^{\perp}_{[P,U,F,T]} &= \omega^{\perp}_{[P,U,F]} - \omega(\omega^{\perp}_{[P,U,F]} T) \\ &= \omega^{\perp}_{[P,U,F]} - \omega^{\perp}_{[P,U,F]} T (T^T \omega^{\perp}_{[P,U,F]} T)^+ T^T \omega^{\perp}_{[P,U,F]} \\ &= \omega^{\perp}_{[P,U,F]} - \frac{1}{c_d} \omega^{\perp}_{[P,U,F]} T T^T \omega^{\perp}_{[P,U,F]}, \end{aligned}$$

because $(T^T \omega^{\perp}_{[P,U,F]} T)^+ = Q_t / c_d$, $1_t^T T = 1_{np}^T$ and the columns of $\omega^{\perp}_{[P,U,F]}$ sum to zero.

Now

$$\begin{aligned} \mathrm{tr}\,(\omega^{\perp}_{[P,U,F]}\ \Sigma) &= \mathrm{tr}\,((Q_n \otimes Q_p)\ \Sigma) - \frac{1}{c_{d22}} \mathrm{tr}\left((Q_n \otimes Q_p) F F^T (Q_n \otimes Q_p)\ \Sigma\right) \\ &= \mathrm{tr}\left(Q_n \otimes \tilde{S}\right) - \frac{1}{c_{d22}} \mathrm{tr}\left(F^T (Q_n \otimes \tilde{S}) F\right). \end{aligned}$$

Also, for totally balanced designs we have $\sum_{i=1}^n T_i = \frac{n}{t} 1_p 1_t^T$. Thence,

$$
\begin{aligned}
F^T(Q_n \otimes \tilde{S})F &= [T_1^T V^T, \ldots, T_n^T V^T](Q_n \otimes \tilde{S})[T_1^T V^T, \ldots, T_n^T V^T]^T \\
&= \left\{ [T_1^T V^T \tilde{S}, \ldots, T_n^T V^T \tilde{S}] - \frac{1}{n} 1_n^T \otimes \sum_{i=1}^n T_i^T V^T \tilde{S} \right\} [T_1^T V^T, \ldots, T_n^T V^T]^T \\
&= \sum_{i=1}^n \left(T_i^T V^T \tilde{S} V T_i \right) - \frac{1}{n} (\frac{n}{t} 1_t 1_p^T V^T \tilde{S} V) \frac{n}{t} 1_p 1_t^T
\end{aligned}
$$

and since $T_i T_i^T = I_p$,

$$
\begin{aligned}
\operatorname{tr}\left(F^T(Q_n \otimes \tilde{S})F \right) &= \operatorname{tr}(nV^T \tilde{S} V - \frac{n}{t} 1_p 1_p^T V^T \tilde{S} V) \\
&= n \operatorname{tr}(V Q_{p,t} V^T \tilde{S}).
\end{aligned}
$$

It follows that

$$
\operatorname{tr}(\omega_{[P,U,F]}^{\perp} \ \Sigma\!\!\!| \ ) = (n-1)\operatorname{tr}(\tilde{S}) - \frac{n}{c_{d22}} \operatorname{tr}(V Q_{p,t} V^T \tilde{S}).
$$

Similar computations show that

$$
\begin{aligned}
\operatorname{tr}(\omega_{[P,U,F]}^{\perp} T T^T \omega_{[P,U,F]}^{\perp} \ \Sigma\!\!\!| \ ) &= \operatorname{tr}(T^T \omega_{[P,U,F]}^{\perp} \ \Sigma\!\!\!| \ \omega_{[P,U,F]}^{\perp} T) \\
&= \operatorname{tr}\big((T^T - \gamma Q_t F^T)(Q_n \otimes Q_p) \ \Sigma\!\!\!| \ (Q_n \otimes Q_p)(T - \gamma F Q_t) \big) \\
&= n \operatorname{tr}(\tilde{S}) - 2n\gamma \operatorname{tr}(Q_{p,t} V^T \tilde{S}) + n\gamma^2 \operatorname{tr}(Q_{p,t} V^T \tilde{S} V).
\end{aligned}
$$

In all, we have

$$
\begin{aligned}
\operatorname{tr}(\omega_{P,U,F,T}^{\perp} \ \Sigma\!\!\!| \ ) &= \operatorname{tr}\left(\left\{ (n-1) I_p - \frac{n}{c_{d22}} (V Q_{p,t} V^T) \right\} \tilde{S} \right) \\
&\quad - \frac{n}{c_d} \operatorname{tr}\left(\left\{ I_p - 2\gamma Q_{p,t} V^T + \gamma^2 V Q_{p,t} V^T \right\} \tilde{S} \right) \\
&= \frac{n}{c_d} \operatorname{tr}\left(\tilde{B}_d \tilde{S} \right),
\end{aligned}
$$

where $\tilde{B}_d = (\frac{c_d(n-1)}{n} - 1) I_p + \gamma(V + V^T) - (\frac{c_d}{c_{d22}} + \gamma^2) V Q_{p,t} V^T$. If we plug in c_d, c_{d12} and c_{d22} we see that $p\gamma = -(\frac{c_d}{c_{d22}} + \gamma^2)$ and thus $\tilde{B}_d = B_d$. The result now follows from (6). $\square$

From Lemmas 2 and 3 we immediately get a new representation of the variance quotient.

Theorem 2. *The variance quotient (4) equals*

$$k_{t,n,p}(S) = \frac{c_f}{t-1} \frac{tr\,(Q_p A_d Q_p S)}{tr\,(Q_p B_d Q_p S)},$$

where $A_d = I_p - \gamma(V + V^T) + \gamma^2 V Q_{p,t} V^T$ *and* $B_d = (\frac{c_d(n-1)}{n} - 1)I_p + \gamma(V + V^T + pVQ_{p,t}V^T)$.

We transform the above expression by applying the spectral decomposition of S. Since $S = \sum_{i=1}^{p} \lambda_i s_i s_i^T$ it holds that

$$\begin{aligned} k_{t,n,p}(S) &= \frac{c_f}{t-1} \frac{\mathrm{tr}\,(Q_p A_d Q_p \sum_{i=1}^{p} \lambda_i s_i s_i^T)}{\mathrm{tr}\,(Q_p B_d Q_p \sum_{i=1}^{p} \lambda_i s_i s_i^T)} \\ &= \frac{c_f}{t-1} \frac{\sum_{i=1}^{p} \lambda_i s_i^T Q_p A_d Q_p s_i}{\sum_{i=1}^{p} \lambda_i s_i^T Q_p B_d Q_p s_i}. \end{aligned} \tag{7}$$

We maximize $k_{t,n,p}(S)$ by choosing the worst-case covariance matrix S. Note that we cannot simply apply the Rayleigh-Ritz theorem (see e.g. Horn and Johnson (1985)[p.176]) to solve this problem since (7) involves a quotient of sums and $Q_p B_d Q_p$ is not positive definite (*p.d.*). The next lemma shows how to compute the maximum.

Lemma 4. *Let A, B and S n.n.d., where $A1_p = B1_p = 0$ and $rg(B) = p-1$. Then*

$$\frac{tr\,(AS)}{tr\,(BS)} \le \lambda^*,$$

where λ^* is the largest eigenvalue of B^+A. Let v an eigenvector of B^+A corresponding to λ^*. Then equality holds for $S = vv^T$.

Proof. Let $U = [u_1, \ldots, u_p]$ where $u_p = 1_p/\sqrt{p}$. Then there is a spectral decomposition $U^T B U = D$, where D is a diagonal matrix with diagonal elements $\gamma_1, \ldots, \gamma_p$, where $\gamma_1 \ge \ldots \ge \gamma_{t-1} > 0$ and $\gamma_p = 0$ are the eigenvalues of B. Here, $U^T U = U U^T = I_p$. If we define

$$W = \left[\begin{array}{cccc} \frac{1}{\sqrt{\gamma_1}} & & & 0 \\ & \ddots & & \\ & & \frac{1}{\sqrt{\gamma_{p-1}}} & \\ 0 & & & 1 \end{array} \right] U^T,$$

then W^{-1} exists, the last row of W equals $1_p/\sqrt{p}$ and it holds that

$$WBW^T = \left[\begin{array}{cc} I_{p-1} & 0 \\ 0 & 0 \end{array} \right].$$

We want to compute

$$\lambda^* = \max_{S \in \mathcal{S}} \frac{\mathrm{tr}\,(AS)}{\mathrm{tr}\,(BS)},$$

where $\mathcal{S}$ is the set of *n.n.d.* matrices. Since W is invertible, $S_W = {W^T}^{-1} S W^{-1}$ is a *n.n.d.* matrix and for any *n.n.d.* matrix S_W there is an S, such that $S_W = {W^T}^{-1} S W^{-1}$, i.e.

$$\mathcal{S} = \{S_W = {W^T}^{-1} S W^{-1} : S \in \mathcal{S}\}.$$

Thence we may write $\mathrm{tr}\,(AS) = \mathrm{tr}\,(AW^T {W^T}^{-1} S W^{-1} W) = \mathrm{tr}\,(AW^T S_W W)$ and it follows that

$$\lambda^* = \max_{S_W \in \mathcal{S}} \frac{\mathrm{tr}\,(AW^T S_W W)}{\mathrm{tr}\,(BW^T S_W W)}.$$

Now

$$\mathrm{tr}\left(BW^T S_W W\right) = \mathrm{tr}\left(WBW^T S_W\right) = \mathrm{tr}\left(\left[\begin{array}{cc} I_{p-1} & 0 \\ 0 & 0 \end{array}\right] S_W\right).$$

Also, $A1_p = 0$ and

$$WAW^T = \left[\begin{array}{cc} W_1 A W_1^T & 0 \\ 0 & 0 \end{array}\right] = \left[\begin{array}{cc} I_{p-1} & 0 \\ 0 & 0 \end{array}\right] WAW^T \left[\begin{array}{cc} I_{p-1} & 0 \\ 0 & 0 \end{array}\right],$$

where $W^T [W_1^T, 1_p/\sqrt{p}]$. This implies that the maximum is achieved in a subset of the *n.n.d.* matrices, i.e.

$$\lambda^* = \max_{S \in \mathcal{S}^*} \frac{\mathrm{tr}\,(WAW^T S)}{\mathrm{tr}\,(S)},$$

where $\mathcal{S}^* = \{S \in \mathbb{R}^{p \times p} : S = \left[\begin{array}{cc} S^* & 0 \\ 0 & 0 \end{array}\right]$ and $S^* \in \mathbb{R}^{p-1 \times p-1}$ is *n.n.d.*$\}$. Now for $S \in \mathcal{S}^*$ we have a spectral decomposition $\sum_{i=1}^{p-1} \lambda_i x_i x_i^T$, where $\lambda_i \geq 0$, $x_i^T x_i = 1$, $x_i^T x_j = 0 \, \forall \, j \neq i$ and each x_i is of the form $x_i = [x_{i1}, \ldots, x_{ip-1}, 0]^T$. This implies

$$\lambda^* = \max \frac{\mathrm{tr}\,(\sum_{i=1}^p \lambda_i x_i x_i^T WAW^T)}{\sum_{i=1}^p \lambda_i} = \max \frac{\lambda_i x_i^T WAW^T x_i}{\sum_{i=1}^p \lambda_i}.$$

Let z the eigenvector corresponding to the largest eigenvalue ρ of WAW^T. Then by the theorem of Rayleigh-Ritz (see e.g. Horn and Johnson (1985)[p.176]) $\forall \, x_i : x_i^T WAW^T x_i \leq \rho$ and thus $\lambda^* \leq \rho$. There are matrices S for which equality holds because the largest eigenvector of WAW^T is equal to $[z_1, \ldots, z_{t-1}, 0]^T$ since

$$WAW^T = \left[\begin{array}{cc} W_1 A W_1^T & 0 \\ 0 & 0 \end{array}\right].$$

Note that WAW^T and W^TWA have the same eigenvalues. Therefore ρ is the largest eigenvalue of

$$\begin{aligned} W^TWA &= U \begin{bmatrix} \frac{1}{\gamma_1} & & & \\ & \ddots & & \\ & & \frac{1}{\gamma_{p-1}} & \\ & & & 1 \end{bmatrix} U^TA \\ &= U \begin{bmatrix} \frac{1}{\gamma_1} & & & \\ & \ddots & & \\ & & \frac{1}{\gamma_{p-1}} & \\ & & & 0 \end{bmatrix} U^TA \\ &= B^+A, \end{aligned}$$

as $U^T = [u_1, \ldots, u_p]^T$ with $u_p = 1_p/\sqrt{p}$, i.e. $u_p^T A = 0$ and $B^+ = U^T D^+ U$. It is easy to see that $v = W^T z$ is an eigenvector of B^+A to the eigenvalue $\rho = \lambda^*$.

□

We want to apply this lemma with $Q_pA_dQ_p$ in place of A and $Q_pB_dQ_p$ in place of B. Therefore, we must show that the assumptions in Lemma 4 hold.

Lemma 5. *Let $A = Q_pA_dQ_p$. Then A is n.n.d. and $A1_p = 0$.*

Proof. Note that Q_pAQ_p is *n.n.d.*, if there is a matrix L, such that $Q_pAQ_p = LL^T$. Let $L = Q_p(I - \gamma V)(I - (\frac{1+\sqrt{1-p/t}}{p})1_p1_p^T)$. Then $LL^T = Q_pAQ_p$. As $Q_p = \omega_{1_p}^{\perp}$, it is obvious that $A1_p = 0$.

□

One can show that $B = [I_p, 0]\omega^{\perp}_{[P,U,F,T]}[I_p, 0]^T$. This does imply B *n.n.d.* But we also need to show that $rg(B) = p - 1$ to apply Lemma 4. To achieve this, we use a theorem on *diagonally dominant* matrices.

Definition 4. *A matrix $A \in \mathbb{R}^{n\times n}$ is called strongly diagonally dominant, if*

$$a_{ii} > \sum_{\substack{j=1 \\ j\neq i}}^{n} |a_{ij}| \quad \forall\, i = 1, \ldots, n.$$

Here, a_{ij} is the element in the (i, j) position of A.

For the proof of the following lemma, we refer to Horn and Johnson (1985)[p. 349].

Lemma 6. *Let $A \in \mathbb{R}^{n\times n}$ symmetric and strongly diagonally dominant. Then A is p.d.*

Lemma 7. *The matrix B_d of Lemma 3 is p.d. for any $d \in \Lambda^*_{t,n,p}$.*

Proof. Note that

$$VQ_{p,t}V^T = \begin{bmatrix} 0 & 0 & 0 & \cdots & 0 \\ 0 & \frac{t-1}{t} & \frac{-1}{t} & \cdots & \frac{-1}{t} \\ 0 & \frac{-1}{t} & \ddots & \ddots & \vdots \\ 0 & \vdots & \ddots & \ddots & \frac{-1}{t} \\ 0 & \frac{-1}{t} & \cdots & \frac{-1}{t} & \frac{t-1}{t} \end{bmatrix}.$$

Therefore

$$B_d = \begin{bmatrix} b_{11} & \gamma & 0 & 0 & \cdots & 0 \\ \gamma & b_{22} & \gamma(1-\frac{p}{t}) & -\frac{\gamma p}{t} & \cdots & -\frac{\gamma p}{t} \\ 0 & \gamma(1-\frac{p}{t}) & \ddots & \ddots & \ddots & \vdots \\ 0 & -\frac{\gamma p}{t} & \ddots & \ddots & \ddots & -\frac{\gamma p}{t} \\ \vdots & \vdots & \ddots & \ddots & \ddots & \gamma(1-\frac{p}{t}) \\ 0 & -\frac{\gamma p}{t} & \cdots & -\frac{\gamma p}{t} & \gamma(1-\frac{p}{t}) & b_{22} \end{bmatrix}.$$

Here,

$$\begin{aligned} b_{11} &= \frac{c_d(n-1)}{n} - 1, \\ b_{22} &= \frac{c_d(n-1)}{n} - 1 + \gamma p \frac{t-1}{t} \end{aligned}$$

This leads to the following inequalities. B_d is strongly diagonally dominant, if

(a) $b_{11} > |\gamma|$ for the first row

(b) $b_{22} > |\gamma| + |\gamma(1-\frac{p}{t})| + (p-3)|\frac{-\gamma p}{t}|$ for the second row

(c) $b_{22} > 2|\gamma(1-\frac{p}{t})| + (p-4)|\frac{-\gamma p}{t}|$ for rows 3 to $(p-1)$ (if $p > 3$)

(d) $b_{22} > |\gamma(1-\frac{p}{t})| + (p-3)|\frac{-\gamma p}{t}|$ for the last row.

Since $|\gamma| > 0$, (d) holds if (b) holds. Because of $|\gamma| + |\frac{-\gamma p}{t}| = -\gamma(1+\frac{p}{t}) < -\gamma(1-\frac{p}{t}) = |\gamma(1-\frac{p}{t})|$, (c) holds, if (b) holds. Finally, as $b_{22} < b_{11}$ (a) holds, if (b) holds. Thus, it suffices to show (b), regardless of the number of periods.

Now $|\gamma| + |\gamma(1 - \frac{p}{t})| + (p-3)|\frac{-\gamma p}{t}| = -\gamma - \gamma(1-\frac{p}{t}) - (p-3)\frac{\gamma p}{t} = -\gamma\{2+(p-4)\frac{p}{t}\}$. For any totally balanced block design we have $n = mt$ and since $t \geq p$ we can substitute t by $p + r$, where $r \in \mathbb{N} \cup \{0\}$. If we now plug in γ and c_d, we may express (b) in terms of the design related parameters m, p and r. Straightforward calculations show that (b) holds, if for $f : \mathbb{R}^3 \to \mathbb{R}$

$$\begin{aligned} f(m,p,r) &= mp^5 + (2mr - 2m - 4)p^4 + (mr^2 - 4mr - 6r - m + 9)p^3 \\ &\quad +(-2mr^2 - 2r^2 - mr + 7r + 2m - 2)p^2 \\ &\quad +(-r^2 + 3mr + 2r - 3)p + mr^2 - r \\ &> 0, \end{aligned}$$

at the appropriate values of m, p, r.

For the partial derivative of f with respect to m we have

$$\begin{aligned} \frac{\partial f}{\partial m}(m,p,r) &= p^5 + (2r-2)p^4 + (r^2 - 4r - 1)p^3 + (-2r^2 - r + 2)p^2 + 3rp + r^2 \\ &= p^2\{(p-2)r^2 + (2p^2 - 4p - 1)r + (p-2)(p^2-1)\} + 3rp + r^2 \\ &\geq p^2\{r^2 + (2p-1)r + (p^2-1)\} + 3rp + r^2 \\ &> 0, \end{aligned}$$

since $p \geq 3$. Thus, whenever $f(m_0, p, r) > 0$ then $f(m_1, p, r) > 0$ for any $m_1 > m_0$.

We now differentiate between 5 distinct cases. We will either show that diagonal dominance holds or, in case it does not hold, B_d is *p.d.* nevertheless or that the case is irrelevant because there is no totally balanced design for this case.

(i) $m = 1$, $p = 3$ and $r \geq 0$

(ii) $m \geq 2$, $p = 3$ and $r \geq 0$

(iii) $m = 1$, $p = 4$ and $r \geq 0$

(iv) $m \geq 2$, $p = 4$ and $r \geq 0$

(v) $m \geq 1$, $p \geq 5$ and $r \geq 0$

Case (i). A necessary condition for the existence of a neighbor balanced design is that $(n-1)p/(t(t-1)) = 3/t$ be a natural number. This only holds for $t = 3$. However, there is no totally balanced design for $n = t = p = 3$. So this case is irrelevant for the proposition.

Case (ii). Here, $f(2,3,r) = -r^2 + 14r + 36 < 0$ für $r = 17$. However, note that if

$$B_d^* = (2r+5)(3r+6) \begin{bmatrix} 2 & 0 & 0 \\ 0 & 3 & 0 \\ 0 & 0 & 2 \end{bmatrix} B_d \begin{bmatrix} 2 & 0 & 0 \\ 0 & 3 & 0 \\ 0 & 0 & 2 \end{bmatrix}$$

is *p.d.* ist, then B_d is also *p.d.* It is easy to show that B_d^* is strongly diagonally dominant.

Case (iii). Note that $f(1,4,r) = -3r^2 - 13r - 12 < 0$ for any $r \geq 0$. A necessary condition for d to be neighbor balanced is that $(n-1)p/(t(t-1)) = 4/t$ be a natural number. This is only true for $t = 4$, i.e. $r = 0$. For $n = t = p = 4$ we see that B_d is *p.d.* by numerical computation of the eigenvalues. Other values of r are irrelevant in this case.

Case (iv). Straightforward calculations show that $f(m,4,r) \geq f(2,4,r) > 0$.

Fall (v). Again, straightforward algebra shows that in this case $f > 0$. □

Lemma 8. *Let $d \in \Lambda^*_{t,n,p}$. Then $B = Q_p B_d Q_p$ is n.n.d. with rank $p-1$ and it holds that $B1_p = 0$.*

Proof. B is *n.n.d.* since Q_p is *n.n.d.* and B_d is *p.d.*, i.e. $rk(B_d) = p$. Also, $rk(Q_p) = \operatorname{tr}(Q_p) = p - 1$. Since B_d exists, $rk(Q_p) = rk(B_d^{-1} B_d Q_p) \leq rk(B_d Q_p) \leq rk(Q_p)$, thence $rk(B_d Q_p) = rk(Q_p) = p - 1$. On the other hand there is an L, such that $B_d = LL^T$ since B_d is *p.d.* This implies that $rk(B_d Q_p) = rk(LL^T Q_p) \leq rk(L^T Q_p) = rk((L^T Q_p)^T L^T Q_p) = rk(Q_p LL^T Q_p) = rk(Q_p B_d Q_p) \leq rk(B_d Q_p)$ and therefore $rk(B) = rg(Q_p B_d Q_p) = p - 1$. Finally, $B1_p = Q_p B_d Q_p 1_p = 0$. □

We can now state our main result.

Theorem 3. *Let $d \in \Lambda^*_{t,n,p}$ and in (2) let $\Sigma = I_n \otimes S$, where S is a covariance matrix. Let $A = Q_p\{I - \gamma(V + V^T) + \gamma^2 V Q_{p,t} V^T\} Q_p$ and $B = Q_p\{(\frac{c_d(n-1)}{n} - 1) I_p + \gamma(V + V^T + pVQ_{p,t}V^T)\} Q_p$. Let v an eigenvector of B^+A with respect to the largest eigenvalue λ^* of B^+A. Then*

$$\begin{aligned} k_{t,n,p}(S) &\leq \frac{c_f}{t-1}\lambda^* \textit{ for any } S \textit{ and} \\ k_{t,n,p}(S) &= \frac{c_f}{t-1}\lambda^* \textit{ for } S = vv^T, \end{aligned}$$

i.e. the Kunert-Utzig constant of Definition 2 is given by $k^*_{t,n,p} = \frac{c_f \lambda^*}{t-1}$.

Proof. Lemmas 5 and 8 show that the prerequisites for Lemma 4 hold. We can now apply Lemma 4 to the representation of the variance quotient (4) in Theorem 2. □

We can easily compute the limit $\lim_{n\to\infty} k^*_{t,n,p}$.

Corollary 1. *In Theorem 3 let λ^*_A the largest eigenvalue of A and $S = vv^T$ the worst-case covariance matrix. Then*

$$k_{t,\infty,p}(S) = \lim_{n\to\infty} k_{t,n,p}(S) = \frac{\lambda^*_A}{1+\frac{\gamma}{p}}.$$

Proof. With λ^* the largest eigenvalue of B^+A we have that $k_{t,n,p} = \frac{c_f}{t-1}\lambda^*$ is the largest eigenvalue of $(\frac{t-1}{c_f}B)^+A$. Note that A does not depend on n and remember that $c_f = n(p-1) - 2t - p + 3$ and $\gamma = \frac{-t}{pt-t-1}$. This implies

$$\begin{aligned}
\frac{t-1}{c_f}B &= Q_p\left((t-1)\left\{\frac{c_d(n-1)}{c_f n} - \frac{1}{c_f}\right\} I_p + \frac{(t-1)\gamma}{c_f}(V + V^T + pVQ_{p,t}V^T)\right) Q_p \\
&\underset{n\to\infty}{\longrightarrow} Q_p\left(\left\{(t-1)\lim_{n\to\infty}\frac{c_d}{c_f}\right\} I_p\right) Q_p \\
&= (t-1)\lim_{n\to\infty}\frac{c_d}{c_f} Q_p.
\end{aligned}$$

Here,

$$\begin{aligned}
(t-1)\lim_{n\to\infty}\frac{c_d}{c_f} &= (t-1)\lim_{n\to\infty}\frac{n(p-1)}{n(p-1)-2t-p+3}\,\frac{1-\frac{t}{p(pt-t-1)}}{t-1} \\
&= 1+\frac{\gamma}{p},
\end{aligned}$$

thus $\lim_{n\to\infty}\frac{t-1}{c_f}B = (1+\frac{\gamma}{p})Q_p$. This implies that $\lim_{n\to\infty}(\frac{t-1}{c_f}B)^+A = Q_pA/(1+\frac{\gamma}{p}) = A/(1+\frac{\gamma}{p})$. □

If, in addition, $t\to\infty$, it is easy to see that $\gamma \to -1/(p-1)$ and $Q_{p,t} \to I_p$. This implies

$$\lim_{t\to\infty}\lim_{n\to\infty} A/(1+\frac{\gamma}{p}) = \frac{p(p-1)}{p(p-1)+1} Q_p\left(I_p + \frac{1}{p-1}(V+V^T) + \frac{1}{(p-1)^2}\begin{bmatrix} 0 & 0 \\ 0 & I_{p-1}\end{bmatrix}\right) Q_p.$$

This means that $\lim_{t\to\infty}\lim_{n\to\infty} A/(1+\frac{\gamma}{p})$ is close to Q_p for large p and therefore

$$\lim_{t\to\infty}\lim_{n\to\infty}\lim_{p\to\infty} k^*_{t,n,p} = 1.$$

Table 2 shows some values of the Kunert-Utzig limit $k^*_{t,n,p}$. Note that $k^*_{t,n,p}$ is only defined for totally balanced designs. However, we can numerically compute the eigenvalues of B^+A to get a would-be value of $k^*_{t,n,p}$, if a totally balanced design existed for a given choice of t, n, p. Such values are included in Table 2 for convenience.

m	t	3	4	5	6	7	10	100
$p = 3$								
1								
2		1.80	1.77	1.75	1.74	1.73	1.71	1.68
4		1.51	1.49	1.47	1.46	1.46	1.45	1.43
6		1.48	1.45	1.44	1.43	1.43	1.42	1.40
∞		1.44	1.41	1.40	1.39	1.39	1.38	1.36
$p = 4$								
1			5.09	4.51	4.20	4.01	3.71	N/A
2			1.61	1.61	1.60	1.60	1.59	1.58
4			1.49	1.48	1.48	1.47	1.47	1.46
6			1.47	1.46	1.45	1.45	1.44	1.43
∞			1.44	1.43	1.42	1.42	1.41	1.40
$p = 5$								
1				1.96	1.93	1.92	1.89	1.83
2				1.49	1.49	1.49	1.49	1.48
4				1.43	1.42	1.42	1.42	1.41
6				1.41	1.41	1.40	1.40	1.39
∞				1.39	1.38	1.38	1.38	1.37
$p = 6$								
1					1.61	1.60	1.59	1.56
2					1.41	1.41	1.41	1.40
4					1.37	1.37	1.36	1.36
6					1.36	1.35	1.35	1.35
∞					1.34	1.34	1.33	1.33
$p = 7$								
1						1.46	1.45	1.44
2						1.35	1.35	1.34
4						1.32	1.32	1.31
6						1.31	1.31	1.31
∞						1.30	1.30	1.29
$p = 10$								
1							1.27	1.27
2							1.24	1.23
4							1.22	1.22
6							1.22	1.22
∞							1.21	1.21
$p = 100$								
1								1.02
2								1.02
4								1.02
6								1.02
∞								1.02

Table 2: The Kunert-Utzig constant $k^*_{t,n,p,}$ for the comparison of t treatments in $n = mt$ blocks of length p.

4 Discussion

Note from Table 2 that $k^*_{t,n,p}$ is decreasing in all three design parameters. The constant converges rather rapidly with increasing n. If the number of periods is very large (e.g. $p = 100$), the constant is close to 1. That means the mean underestimation of the variance is very small even for the worst-case covariance matrix. However, crossover designs with such a large number of periods are rarely, if at all, used in practice. Applications in pharmaceutical research will often deal with 3 or 4 treatments with as few periods. In this case the correction factor for the approach by Kunert and Utzig (1993) is roughly $1.4 - 1.6$. Sensory studies in the food industry may easily have 10 treatments with blocks of length 10. Here the correction factor for the worst-case covariance matrix will still be around 1.25. If we would not correct for this bias, we might get seriously biased test results.

Inspection of Tables 1 and 2 shows that, especially for medium sized p, the exact limit $k^*_{t,n,p}$ is noticeably smaller as the upper bound $k^u_{t,n,p}$. This means that the maximum overestimation of the variance is smaller for $p > 3$ than would be expected from Kunert and Utzig (1993). For a neighbor balanced Latin Square with $t = n = p = 4$ the Kunert-Utzig bound is infinite. In fact, the upper limit $k^*_{t,n,p}$ equals 5.09. Practically more relevant crossover designs with $p = 4$ or $p = 5$ and $m > 1$ have a corresponding upper limit that is about $20 - 30\%$ lower than the upper bound. If in such a case the covariance structure were far from worst-case, application of the exact limit in the approach by Kunert and Utzig (1993) will lead to significantly less conservative tests.

In fact, it is possible to show that the variance quotient is identical to the correction factor of Box (1954) that is applied in the approach of Bellavance et al. (1996). However, Box (1954) also corrects the degrees of freedom in the F-Test. As this is not done in the approach of Kunert and Utzig (1993), their approach might even lead to anti-conservative tests if the exact Kunert-Utzig constant $k^*_{t,n,p}$ is used and if the covariance matrix is close to worst-case.

Acknowledgements

I would like to thank my adviser Prof. J. Kunert for helpful comments especially concerning the proof of Lemma 4. The financial support of the Deutsche Forschungsgemeinschaft (SFB 475, Reduction of complexity in multivariate data structures) is gratefully acknowledged.

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