Journal of Statistical Planning and Inference 140 (2010) 2057–2068

Contents lists available at ScienceDirect

Journal of Statistical Planning and Inference

journal homepage: www.elsevier.com/locate/jspi

An exact upper limit for the variance bias in a carry-over model with correlated errors ☆

Oliver Sailer

Fakultät Statistik, Technische Universität Dortmund, 44221 Dortmund, Germany

ARTICLE INFO

Article history:
Received 27 February 2009
Received in revised form
12 January 2010
Accepted 1 February 2010
Available online 6 February 2010

Keywords:
Bias
Correlated errors
Crossover designs
Fixed effects model
Upper limit
Variance estimation

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 the equality of the direct effects of the treatments is not valid. Bellavance et al. [1996. Biometrics 52, 607–612] 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 [1993. JRSS B 55, 919–927] propose an alternative test that does not need an estimate of the covariance matrix. Instead, they correct the *F*-statistic by multiplying by a constant based on the worst-case scenario. 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 balanced crossover designs.

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

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

Here, $\boldsymbol{Y} = (y_{11}, y_{12}, \ldots, y_{np})^T$ 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, $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_n)^T$ and fixed effects for periods (order effects) $\boldsymbol{\pi} = (\pi_1, \ldots, \pi_p)^T$. $\boldsymbol{U} = \boldsymbol{I}_n \otimes \boldsymbol{1}_p$ and $\boldsymbol{P} = \boldsymbol{1}_n \otimes \boldsymbol{I}_p$ denote the corresponding design matrices. The vectors of direct and residual (carry-over) treatment effects are given by $\boldsymbol{\tau} = (\tau_1, \ldots, \tau_t)^T$ and $\boldsymbol{\rho} = (\rho_1, \ldots, \rho_t)^T$, 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 $\boldsymbol{T}$ and $\boldsymbol{F}$. The vector of errors, $\boldsymbol{\varepsilon} = (\varepsilon_{11}, \ldots, \varepsilon_{np})^T$, 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

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

☆ The financial support of the Deutsche Forschungsgemeinschaft (SFB 475, Reduction of complexity in multivariate data structures) is gratefully acknowledged.

E-mail address: sailer@statistik.uni-dortmund.de

0378-3758/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jspi.2010.02.002

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

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 the equality of the direct effects of the treatments are no longer valid. If $\boldsymbol{S}$ were known, GLS estimates could be used. Bellavance et al. (1996) compare several alternatives to the OLS *F*-test based on estimates of $\boldsymbol{S}$. 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 $\boldsymbol{S}$ may be unreliable, thus leading to biased tests. Therefore Kunert and Utzig (1993) do not estimate $\boldsymbol{S}$. 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 $\Lambda_{t,n,p}$ be 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 $\boldsymbol{S}$.

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 treatment 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 $\Lambda^*_{t,n,p}$ be 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 $\psi = \ell^T \boldsymbol{\tau}$ 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 $\hat{\psi} = \ell^T \hat{\boldsymbol{\tau}}$ be an OLS estimate of $\psi = \ell^T \boldsymbol{\tau}$ under (1).

Let $\omega_{\boldsymbol{A}} = \omega(\boldsymbol{A}) = \boldsymbol{A}(\boldsymbol{A}^T\boldsymbol{A})^- \boldsymbol{A}^T$ be the projection matrix on the column span of $\boldsymbol{A}$ and $\omega^\perp_{\boldsymbol{A}} = \omega^\perp(\boldsymbol{A}) = \boldsymbol{I} - \omega(\boldsymbol{A})$. Here, $\boldsymbol{A}^-$ is any generalized inverse of $\boldsymbol{A}$. We denote a partitioned matrix by $\boldsymbol{A} = [\boldsymbol{A}_1, \ldots, \boldsymbol{A}_n]$ and define $\mathbf{Q}_n = \omega^\perp(\mathbf{1}_n) = \boldsymbol{I}_n - (1/n)\mathbf{1}_n\mathbf{1}_n^T$, the centering matrix of rank $n-1$.

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

$$\mathbf{C}_d = \boldsymbol{T}^T \omega^\perp_{[\mathbf{U},\boldsymbol{P},\boldsymbol{F}]} \boldsymbol{T} = c_d \mathbf{Q}_t,$$

$$\boldsymbol{T}^T \omega^\perp_{[\mathbf{U},\boldsymbol{P}]} \boldsymbol{F} = c_{d12} \mathbf{Q}_t,$$

$$\boldsymbol{F}^T \omega^\perp_{[\mathbf{U},\boldsymbol{P}]} \boldsymbol{F} = c_{d22} \mathbf{Q}_t,$$

where

$$c_d = \frac{n(p-1)}{t-1}\left(1 - \frac{t}{p(pt-t-1)}\right),$$

$$c_{d12} = \frac{-n(p-1)}{p(t-1)},$$