Design Workshop Lecture Notes
ISI, Kolkata, November, 25-29, 2002, pp. 183-192

Crossover Designs: Analysis and Optimality Using the Calculus for Factorial Arrangements

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In what follows, Section A is based on Bose and Mukherjee(2001) and Section B is reproduced from Bose and Dey(2001).

A. Cross-over designs

Crossover designs are used in experimental situations where a number of experimental subjects are exposed to the treatments under study applied sequentially over a number of time periods. They are used in a broad spectrum of research areas, some early examples being agriculture (Cochran, 1939), dairy husbandry (Cochran et. al, 1941), bioassay procedures (Finny, 1965), clinical trials (Grizzle, 1965), psychological experiments (Keppel, 1973), weather modification experiments (Mielke, 1974), tea-tasting experiments and other areas of research.

The advantage of the crossover design is the cost and the interunit variability elimination while computing treatment effects. These designs have been shown to be cost efficient as compared to completely randomized designs or parallel designs, except in a few extreme cases. However, since each subject is receiving a sequence of treaments over time, in addition to the 'direct' effect of a treatment in the period in which it is applied, a treatment may also have 'carryover' effects in one more subsequent periods. The possible presence of these 'carryover' effects complicates the analysis of data from these designs.

In recent years, crossover designs have been frequently used in clinical trials (for studying chronic ailments) because fewer subjects are needed than comparable parallel study experiments and the estimators of direct treatment effects can be efficiently obtained as between-subject variations can be eliminated.

Reserchers have considered various models for fitting repeated measures data from cross-over designs. Williams(1949) advocated the use of 'wash-out' periods between successive applications of treatments to the same experimental unit and introduced a model that does not include 'carry-over' effects, assuming that the wash-out period will help to eliminate the treatment effects left over from the previous period. However, this assumption was felt to be over-simplistic for many experimental situations and later, Patterson and others introduced a one-step carry-over in the model, assuming that the carryover effect only persisted for one subsequent period.

However, Fleiss(1989) and Senn(1993) stated that in the context of experiments where these designs are recently being used, a model with one-step carry-over is not realistic.

The optimality properties of cross-over designs have been extensively studied in the literature. We refer to Stufken(1996) for a review of these results. Some researchers used the 'circular' model where treatments were applied in a pre-period before observations were taken, in order to generate carry-over effects for the first period. This greatly simplified the analysis. However, this was felt to be somewhat wasteful and so, later this model was replaced by the 'non-circular' model where the first period had no carry-overs.

Most of the optimality results available in the literature are based on a model of Cheng and Wu(1980) which makes several assumptions. The principal assumptions of this model are:

1. Carry-over effects stop after the first period.
2. There is no interaction between the treatments applied in successive periods to the same subject.
3. The subject effects are fixed effects.
4. The errors are independent with mean zero and constant variance.

Clearly, in situations where these designs are used, specially in the recent applications of these designs, one or more of these assumptions are likely to be violated. The first assumption is untenable in situations where the effect of a treatment does not die out abruptly after one period, which is often the case when the interval between successive time periods is small. Regarding assumption 2, it is known that in many situations the successive treatments do interact and possibly the earliest data set reflecting this is in John and Quenouille (1977, pp 211-213). In experiments where the subjects are a random sample of possible subjects, assumption 3 will be invalid. Finally, since the same subject is giving rise to a set of observations over time, it is unlikely that all these observations will be uncorrelated.

Under various model assumptions, many researchers have studied the optimality pf these deisgns and the optimal designs are highly dependent on the model assumptions. Some have used random subject effects and an independent error assumption or fixed subject effects with an autoregressive error assumption. Mukhopadhyay and Saha(1983) considered optimality of some cross-over designs under a mixed effects model .

The study of cross-over designs can be considerably simplified when one has recourse to the calculus for factorial experiments. Using this approach, optimal designs for direct and carry-over effects have been obtained in Sen and Mukerjee(1986) for models where assumption 2 has been relaxed. Bose and Mukherjee(2000) obtained optimal designs for direct and carry-over effects under models which do not assume conditions 1 and 2 and Bose and Mukherjee(2001) have optimal designs for a model where all 4 of the above conditions are removed. Bose and Dey(2001) obtained designs of small sizes which are optimal for carry-over effects and highly efficient for direct effects. In this context Bose(1996, 1999) are also relevant. Bose and Dey(2002) considered general expressions for information matrices for direct and carry-over effects under a random-subject effect model with serially correlated errors in the presence of direct versus carry-over interactions and have proved several optimality results under this model.

Since we cannot discuss all the above work in detail here we only include here the work by Bose and Dey(2001). This is chosen because this study clearly illustrates how the calculus for factorial arrangements may be effectively used to obtain optimal cross-over designs. Moreover, this study leads to efficient/optimal designs which are small in size and so these designs will be useful to the practitioner.

B. Some small and efficient cross-over designs under a non-additive model

(Bose and Dey(2001))

Under a general non-circular, non-additive model which allows for the possible presence of interactions among treatments applied at successive periods, small cross-over designs are proposed. The proposed designs are shown to be optimal for the estimation of carry-over effects while being highly efficient for the direct effects under the stated model. The results are shown to be robust under a random-subject-effect model. These designs had been shown to be optimal for both direct and carry-over effects under an additive model by Cheng & Wu(1980). Our results show that their result for carry-over effects remain robust under non-additive models and also under random-subject effects.

1. Introduction

Cross-over designs are used for experiments in which each of the experimental subjects or, units receive different treatments successively over a number of time periods. These designs are widely used in clinical trials, learning experiments, animal feeding experiments, agricultural field trials and in several other areas of experimental research.

A distinctive feature of cross-over experiments is that, an observation is affected not only by the direct effect of a treatment in the period in which it is applied, but also by the effect of a treatment applied in an earlier period. That is, the effect of a treatment might also carry over to one or more of the subsequent time periods following the time of its application. The possible presence of this carry-over effect complicates the designing and analysis of such experiments. Considerable literature on the subject is already available and for an excellent review of the literature, a reference may be made to Stufken (1996).

The study of optimality aspects of cross-over designs was initiated by Hedayat & Afsarinejad (1978). Cheng & Wu (1980), Magda (1980), Kunert (1984 a,b), Stufken (1991) and others studied the optimality properties of these designs under simple additive models, with no possible interactions among the treatments applied in successive periods.

The available cross-over designs which are optimal over a wide class of competing designs, are often quite large in size. However, in most experimental situations, notably in clinical trials, the number of available experimental subjects is usually quite small and the experiment cannot be continued for a large number of periods. To overcome this problem, in this paper we study efficient designs that are quite small in size. To compare t treatments, these designs require only t subjects if t is even and t or $2t$ subjects if t is odd and further, require only $t + 1$ periods. Under a model that incorporates interaction effects among direct and carry-over effects, apart from the individual direct and carry-over effects, these designs are shown to be universally optimal and hence, A-, D- and E-optimal for the carry-over effects. Under the same model, these designs are highly efficient for the direct effects as well. Consideration of a non-additive model is motivated from practical considerations as in many experimental situations, the interaction effects may also affect the response. Examples of data sets are given in John & Quenouille (1977, p. 213) and Patterson (1970), where such interaction effects are found to be statistically significant. In such situations, the assumption of absence of interaction may not be justified and a non-additive model seems more suitable.

The existence of these efficient designs is also discussed. Finally, we prove that all the above mentioned results are robust under a random-subject non-additive model. The proofs of the results rest heavily on the use of the Kronecker calculus, introduced by Kurkjian & Zelen (1962). For a review of the calculus in the context of complete and fractional factorials, see Gupta & Mukerjee (1989) and Dey & Mukerjee (1999) respectively.

It is interesting to note that Cheng & Wu(1980) had shown these designs to be universally optimal for the estimation of both direct and carry-over effects. Our results demonstrate that their result for the carry-over effects remain robust under the presence of interactions and also under random subject effects.

2. Model and Analysis

Let $\Omega_{t,n,p}$ be the class of all cross-over designs with t treatments applied to n units over p periods. We introduce the following model by incorporating interactions among direct effects and carry-over effects of the successive treatments applied to the same subject, into the usual model in the literature; see for example, Cheng & Wu (1980).

Consider a cross-over experiment with t treatmnts applied to n experimental units over p time periods and let $d(i,j)$ denote the treatment applied to the jth unit at the ith period, $i = 0, 1, \ldots, p-1;\ j = 1, 2 \ldots, n$. Then the non-additive model is given by :

$$E(Y_{0j}) = \mu + \alpha_0 + \beta_j + \tau_{d(0,j)}, \quad 1 \le j \le n,$$

and

$$E(Y_{ij}) = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)}, \quad 1 \le i \le p-1,\ 1 \le j \le n \ \ (1),$$

where $\mu, \alpha_i, \beta_j, \tau_{d(i,j)}, \rho_{d(i-1,j)}, \gamma_{d(i,j),d(i-1,j)}$ are respectively the general mean, the ith period effect, the jth unit effect, the direct effect due to treatment $d(i,j)$, the carry-over effect due to treatment $d(i-1,j)$ and the interaction effect between $d(i,j)$ and $d(i-1,j)$, $i = 0, 1, \ldots, p-1,\ j = 1, 2, \ldots, n$, where we define $\rho_{d(0,j)} = \gamma_{d(1,j),d(0,j)} = 0$.

Under model (1), a direct extension of the usual method of analysis and proof as given in Cheng & Wu (1980) becomes intractable. Instead, model (2) given below, can be conveniently studied by noting that cross-over designs may be looked upon as a t^2 factorial experiment with two factors, F_1, F_2, where the direct effects correspond to the main effect F_1, the carry-over effects correspond to the main effect F_2 and the direct versus carry-over interaction effect corresponds to the usual factorial interaction, F_1F_2. The advantage of this formulation is that now these designs may be analysed under model (2) by applying the calculus for factorial arrangements introduced by Kurkjian and Zelen (1962).

Model (1) may be rewritten in the following equivalent form:

$$E(Y_{ij}) = \mu + \alpha_i + \beta_j + \lambda'_{ij}\xi, \quad 0 \le i \le p-1, \quad 1 \le j \le n, \tag{2}$$

where, the $t^2 \times 1$ vector

$$\xi = (\xi_{00}, \xi_{01}, \ldots, \xi_{t-1,t-1})'$$

is the vector of the effects of t^2 factorial treatment combinations;

$$\lambda_{ij} = e_{d(i,j)} \otimes e_{d(i-1,j)}, \quad 1 \le i \le p-1;\ 1 \le j \le n, \tag{3}$$

$$\lambda_{0j} = e_{d(0,j)} \otimes t^{-1}1_t, \quad 1 \le j \le n, \tag{4}$$

where for a pair of matrices $A,\ B,\ A \otimes B$ denotes their Kronecker product; $e_{d(i,j)}$ is a $t \times 1$ vector with 1 in the position corresponding to the treatment $d(i,j)$ and zero elsewhere and 1_t is a $t \times 1$ vector with all elements unity.

Let X_d denote the design matrix for a design d in $\Omega_{t,n,p}$ under model (2). Then, it can be shown from model (2) that

$$X_d{}'X_d = \begin{bmatrix} np & n1'_p & p1'_n & \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda'_{ij} \\ n1_p & nI_p & 1_p1'_n & N'_d \\ p1_n & 1_n1'_p & pI_n & M'_d \\ \sum_{i=0}^{p-1}\sum_{j=1}^{n}\lambda_{ij} & N_d & M_d & V_d \end{bmatrix}, \tag{5}$$

where

$$V_d = \sum_{i=0}^{p-1}\sum_{j=1}^{n} \lambda_{ij}\lambda'_{ij},\ N_d = (\sum_{j=1}^{n}\lambda_{0j}, \sum_{j=1}^{n}\lambda_{1j}, \ldots, \sum_{j=1}^{n}\lambda_{p-1j}) \tag{6}$$

$$M_d = (\sum_{i=0}^{p-1}\lambda_{i1}, \sum_{i=0}^{p-1}\lambda_{i2}, \ldots \sum_{i=0}^{p-1}\lambda_{in}). \tag{7}$$

The matrices N_d and M_d in (5) are the treatment versus period and the treatment versus unit incidence matrices respectively, where the treatments are actually the t^2 treatment combinations in ξ.

¿From (5) it follows that the coefficient matrix of the reduced normal equations for estimating ξ from a design d in $\Omega_{t,n,p}$ is given by

$$C_d = V_d - \frac{1}{n}N_dN'_d - \frac{1}{p}M_dM'_d + \frac{1}{np}(N_d1_p)(N_d1_p)'. \tag{8}$$

Let P_t be a $(t-1)\times t$ matrix such that $(t^{-\frac{1}{2}}1_t,\ P'_t)$ is orthogonal. Define

$$P^{01} = (t^{-\frac{1}{2}}1_t{}') \otimes P_t,\ P^{10} = P_t \otimes (t^{-\frac{1}{2}}1_t{}'),\ P^{11} = P_t \otimes P_t. \tag{9}$$

Note that $P^{01}\xi,\ P^{10}\xi$ and $P^{11}\xi$ together represent a complete set of orthonormal treatment contrasts.

Following Mukerjee (1980), it can be shown that for a design d in $\Omega_{t,n,p}$, the coefficient matrix of the reduced normal equations for estimating the carry-over effects is given by

$$A_d = P^{01}C_d\ (P^{01})' - (P^{01}\ C_d(P^{10})',\ P^{01}C_d(P^{11})')G^{-}\begin{pmatrix} P^{10}C_d(P^{01})' \\ P^{11}C_d(P^{01})' \end{pmatrix}, \tag{10}$$

where A^{-} denotes a generalized inverse of a matrix A, C_d is as in (8) and

$$G = \begin{bmatrix} P^{10}C_d(P^{10})' & P^{10}C_d(P^{11})' \\ P^{11}C_d(P^{10})' & P^{11}C_d(P^{11})' \end{bmatrix}.$$

3. Optimality Results

We need the following definitions in the sequel.

Definition 3.1.*A design in $\Omega_{t,n,p}$ is called uniform if the treatments occur equally often in each period and also equally often in each unit.*

Definition 3.2.*Under model (1), a design d in $\Omega_{t,n,p}$ is called balanced if in the order of application, no treatment is preceded by itself and each treatment is preceded by all other treatments equally often.*

Let d_1 be a design obtained by repeating the last row of a balanced uniform design. Thus, d_1 is an extra-period balanced design as defined in Lucas(1957) and Patterson & Lucas (1962). The following theorem gives the optimality properties of d_1 under model (1).

Theorem 3.1. *Under model (1), a design d_1 in $\Omega_{t,n,p}$ is universally optimal for the separate estimation of residual effects in the class of all designs in $\Omega_{t,n,p}$.*

Proof: The proof of the theorem rests on the following two lemmas, the proofs of which are given in the Appendix.

LEMMA 3.1. *For the design d_1, A_{d_1} is completely symmetric, where A_{d_1} is given by (10) with d replaced by d_1.*

LEMMA 3.2. *The design d_1 maximises the trace of A_d among all designs d in $\Omega_{t,n,p}$.*

¿From Lemmas 3.1 and 3.2, it is clear that d_1 satisfies the sufficient conditions for universal optimality of a design as given by Kiefer (1975), for the estimation of complete sets of orthonormal contrasts belonging to the carry-over effects. Hence the theorem is proved.

REMARK 3.1. It may be recalled that a design that is universally optimal over a class of competing designs is also in particular, A-, D- and E-optimal over the same class of competing designs. Thus, the design d_1 is, in particular A-, D- and E-optimal for carry-over effects in the class $\Omega_{t,n,p}$.

REMARK 3.2. Cheng & Wu (1980) have shown that the designs d_1 are universally optimal for both carry-over and direct effects under an additive model. Theorem 3.1 shows that their result is robust for carry-over effects under the non-additive model as well. One can show however that under model (1), though d_1, remains universally optimal for the carry-over effects, it does not necessarily remain universally optimal for the estimation of the direct or the interaction effects. It can be shown using a necessary and sufficient condition for inter-effect orthogonality in Mukerjee(1980) that while under a model with no interactions, the design d_1 permits the estimation of direct and carry-over effects orthogonally in the sense that the best linear unbiased estimator of a contrast among direct effects is uncorrelated with the best linear unbiased estimator of a contrast among carry over effects, this orthogonality does not hold under a model with interactions.

REMARK 3.3. To evaluate the performance of d_1 for the separate estimation of direct effects, we compute the relative efficiency of estimation of the direct effects relative to the carry-over effects, based on the A-efficiency or the average variance criterion. Clearly, the upper bound of these efficiencies is unity. Table 1 lists the A-efficiencies of d_1 for some small values of t. From this table it is seen that the efficiency of d_1 for the estimation of direct effects is quite high. It follows then that the design d_1 is useful in the sense that, using this design one can estimate the carry-over effects optimally and also estimate the direct effects with high efficiency, even under the presence of interactions.

REMARK 3.4. The optimality result in Theorem 3.1 is quite general since the competing class, $\Omega_{t,n,p}$, is the class of all designs with t treatments, n units and p periods. As stated earlier, d_1 is also optimal under the weaker and more commonly used A-,D- and E-optimality criteria.

Table 1. *Relative A-efficiencies of direct effects*

No. of treatments	3	4	5	6
A-efficiency of direct effects	0.8136	0.9259	0.8771	0.9625
No. of treatments	7	8	9	10
A-efficiency of direct effects	0.9058	0.9783	0.9232	0.9847

4. EXISTENCE OF THE OPTIMAL DESIGNS

AND SOME EXAMPLES

For any t, the minimum value of n and p for which a design d_1 may exist are t and $t+1$ respectively. This is because, for a balanced uniform design to exist, it is necssary that

$$(i)\ p \equiv 0 (\text{mod } t);\ (ii)\ n \equiv 0 (\text{mod } t) \text{ and } (iii)\ n(p-1) = \mu t(t-1),$$

where μ is a positive integer. The question of constructing uniform balanced designs in $\Omega_{t,t,t}$ is completely settled for t even, and is given by the $t \times t$ Williams' square (Williams, 1949). Thus, repeating the last row of a Williams' square once, one can construct a design d_1 in $\Omega_{t,t,t+1}$, whenever t is an even integer.

When t is odd, no general result on the existence of a balanced uniform design in $\Omega_{t,t,t}$ is known. No such design exists for $t = 3, 5, 7$. Such designs for $t = 9, 15, 21$ and 27 have been presented by Archdeacon, Dinitz, Stinson and Tillson (1980), who call these squares as row complete Latin squares. Such squares can be constructed for $t = 39, 55, 57$ by methods described in Mendelsohn (1968), Denes & Keedwell (1974) and Wang (1973). However, for all odd t it is known that a uniform balanced design exists in $2t$ units and t periods (Williams, 1949). It follows that for all odd t, d_1 exists in $\Omega_{t,2t,t+1}$ and for some specific odd values of t, d_1 exists in $\Omega_{t,t,t+1}$.

In Example 4.1, designs d_1 for some values of t are shown. The periods are given by the rows and the subjects by the columns.

Example 4.1.

$t = 3$

1	2	3	1	2	3
3	1	2	2	3	1
2	3	1	3	1	2
2	3	1	3	1	2

$t = 4$

1	2	3	4
4	1	2	3
2	3	4	1
3	4	1	2
3	4	1	2

$t = 5$

1	2	3	4	5	3	4	5	1	2
5	1	2	3	4	4	5	1	2	3
2	3	4	5	1	2	3	4	5	1
4	5	1	2	3	5	1	2	3	4
3	4	5	1	2	1	2	3	4	5
3	4	5	1	2	1	2	3	4	5

5. Robustness of the results under the random-subject-effect model

In analyzing data from cross-over experiments used in clinical trials, it is often desirable to assume the subject or the patient effect to be a random variable. Under such an assumption, the non-additive random-subject-effect model is:

$$Y_{0j} = \mu + \alpha_0 + \beta_j + \tau_{d(0,j)} + \text{ error, for } 1 \le j \le n,$$

and

$$Y_{ij} = \mu + \alpha_i + \beta_j + \tau_{d(i,j)} + \rho_{d(i-1,j)} + \gamma_{d(i,j),d(i-1,j)} + \text{ error, } 1 \le i \le p-1,\ 1 \le j \le n \quad (11),$$

where $\mu, \alpha_i, \beta_j, \tau_{d(i,j)}, \rho_{d(i-1,j)}, \gamma_{d(i,j),d(i-1,j)}$ are as in (1); and the vector of subject effects $\beta = (\beta_1, \beta_2, \ldots, \beta_n)'$ has the normal distribution, $N(0, \sigma_1^2 I_n)$, the error vector has the $N(0, \sigma^2 I_{np})$ distribution, β being independent of the error vector.

In consideration of Lemma 3.1, after some routine but lengthy algebra, the following result can be proved.

LEMMA 5.1. *Under model (11), for any design d in* $\Omega_{t,n,p}$,
(a) the matrix C_d *is given by*

$$\begin{array}{rcl} C_d & = & \frac{1}{\sigma^2}V_d - \frac{\sigma_1^2}{n\sigma^4}N_d 1_p 1_p{}' N_d' + \frac{a\sigma_1^2}{n\sigma^2}N_d 1_p 1_p{}' H_d' \\ & & -aM_d M_d' - \frac{1}{n\sigma^2}N_d N_d' + \frac{a}{n}N_d H_d' \\ & & +\frac{a\sigma_1^2}{n\sigma^2}H_d 1_p 1_p{}' N_d' - \frac{a^2\sigma_1^2}{n}H_d 1_p 1_p{}' H_d' + \frac{a}{n}H_d N_d' - \frac{a^2\sigma^2}{n}H_d H_d', \end{array} \tag{12}$$

where a is a constant involving the design parameters, σ *and* σ_1, $H_d = [N_d 1_p, \cdots, N_d 1_p\ ]$ *is a* $t \times p$ *matrix and* V_d, M_d, N_d *are as in (6) and (7).*
(b)

$$P^{01}M_{d_1}M_{d_1}' = 0,\ P^{01}N_{d_1} = 0,\ P^{01}H_{d_1} = 0.$$

It follows from (12) that $P^{01}C_{d_1} = mP^{01}V_{d_1}$ where m is a constant. Now, using steps similar to the proof of Theorem 3.1, the following result may be proved.

THEOREM 5.1: *Under model (11),* d_1 *is universally optimal for the separate estimation of carry-over effects in the class of all designs in* $\Omega_{t,n,p}$.

Thus the results of Theorem 3.1 remain robust under the random-subject-effect model.

REMARK 5.1. Theorems 3.1 and 5.1 show that the result of Cheng & Wu(1980) mentioned in Remark 3.2, remains robust for carry-over effects under a model with random subject effects and with direct-vs-carryover interactions.

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Appendix

Proof of Lemma 3.1. From (6), (7) and Definitions 3.1 and 3.2, one can show that

$$V_{d_1} = nt^{-3}(I_t \otimes 1_t 1_t{}') + n(p-1)t^{-2} I_t \otimes I_t, \tag{A.1}$$

where for a positive integer s, I_s stands for the identity matrix of order s. Furthermore, we have

$$N_{d_1} 1_n = (npt^{-2})(1_t \otimes 1_t). \tag{A.2}$$

Recalling the definition of P^{01} from (9) and using (A.1) and (A.2), the following statements can be proved after some algebra:

$$P^{01} V_{d_1} (P^{01})' = n(p-1)t^{-2} I_{t-1}, \quad P^{01} V_{d_1} (P^{10})' = 0, \quad P^{01} V_{d_1} (P^{11})' = 0,$$

$$P^{01} N_{d_1} = 0,$$

$$P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{01})' = 0,$$

$$P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{10})' = P^{01}(N_{d_1} 1_n)(N_{d_1} 1_n')(P^{11})' = 0,$$

and

$$P^{01} M_{d_1} M_{d_1}' = 0.$$

By (10), we have $A_{d_1} = P^{01} C_{d_1} (P^{01})' = P^{01} V_{d_1} (P^{01})' = n(p-1)t^{-2} I_{t-1}$. Thus A_{d_1} is completely symmetric and the Lemma is proved.

Proof of Lemma 3.2. From (10) it is clear that $P^{01} C_d (P^{01})' - A_d$ is nonnegative definite for all d in $\Omega_{t,n,p}$. Again, as $V_d - C_d$ is nonnegative definite for all d in $\Omega_{t,n,p}$, $P^{01} V_d (P^{01})' - P^{01} C_d (P^{01})'$ is nonnegative definite for all such d. Hence,

$$Trace(A_d) \leq Trace(P^{01} V_d (P^{01})') = Trace(P^{01} C_{d_1} (P^{01})') = Trace(A_{d_1})$$

for all d in $\Omega_{t,n,p}$. This completes the proof.