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Optimal Repeated Measurements for Two Treatment Designs with Dependent Observations: The Case of Compound Symmetry

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Abstract: In this paper, we construct optimal repeated measurement designs of two treatments for estimating direct effects, and we examine the case of compound symmetry dependency. We present the model and the design that minimizes the variance of the estimated difference of the two treatments. The optimal designs with dependent observations in a compound symmetry model are the same as in the case of independent observations.

Keywords: repeated measurement designs; compound symmetry

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1. Introduction

In repeated measurement designs, a sequence of treatments is applied to each experimental unit (e.u.). In particular, one treatment is applied in each period. For example, for two treatments, A and B, and three periods, a possible sequence is ABA, which means that the treatments A, B, and A are respectively applied at the beginning of each of the three periods. The direct effect of a treatment is the effect of the treatment which is applied in the period that is examined. The residual effect is the effect of the treatment which is applied in the period preceding the period that is examined. In the case of two treatments, A and B, the direct τ_{A} and τ_{B} can be estimated. In every period, a treatment is applied, so either τ_{A} or τ_{B} is estimable. In this paper, the parameter of interest is the difference of direct effects $\tau = \tau_{\mathrm{A}} - \tau_{\mathrm{B}}$.

Most researchers who have investigated repeated measurement designs, such as [1–6], have been occupied with universally optimal designs where the observations are independent. However, researchers have also shown interest in designs with dependent observations, as in the cases of [7–11].

The model we use in this paper, and which is presented below, was first introduced by Hedayat and Afsarinejad [12,13]. In previous research [14,15] using this model, the author of this article studied two treatment designs under the assumption that consecutive observations were independent. Building on that previous work, in the present article the author examines the case of compound symmetry dependency. The aim is to find a design that corresponds to a minimum variance estimator.

2. The Model

A compound symmetry model has the following characteristics:

(i) For each sequence, the variance matrix is of the form $\mathbf{\Sigma}_{\mathrm{m}} = a\mathbf{I}_m + b\mathbf{J}_m$, where $\mathbf{I}_m$ is the unit $m \times m$ matrix, and $\mathbf{J}_m$ is the $m \times m$ matrix where all elements are equal to 1 (m is the number of periods).

(ii) The observations corresponding to different treatment sequences (different e.u.) are independent, and the number of sequences is 2^m.

The goal is to find the design that corresponds to the minimum variance estimator. I show that, in this case, the optimal design regarding the direct effect is the same as in the model of independent observations, and only the variance of the estimator is different.

The model is [12]:

$$y_{ijk} = \mu + \tau + \pi_j + \delta_{i,j-1} + \gamma_i + \zeta_k + e_{ijk} \tag{1}$$

j corresponds to the j-th period, $j = 1, 2, \ldots, m$;
i corresponds to the i-th sequence, $i = 0, 1, \ldots 2^m - 1$;
k corresponds to the unit $k = 1, 2, \ldots, n$;
τ_A, τ_B: are direct effects of treatments A and B;
π_j: is the effect of the j-th period;
δ_A, δ_B: are the residual effects of A and B;
γ_i: is the effect of the i-th sequence; and
ζ_k: is the effect of the k-th e.u. (subject effect), which is a random variable, independent of the error e_{ijk}.

The errors e_{ijk} are assumed to be independent. However, the quantities $\zeta_k + e_{ijk}$ are independent only between sequences and not within sequences.

The overparameterized model vector form of the above model is written as:

$$\mathbf{Y} = \tau_A \boldsymbol{\tau}_A + \tau_B \boldsymbol{\tau}_B + \delta_A \boldsymbol{\delta}_A + \delta_B \boldsymbol{\delta}_B + \pi_1 \boldsymbol{\pi}_1 + \cdots + \pi_m \boldsymbol{\pi}_m + + \gamma_0 \boldsymbol{\gamma}_0 + \cdots + \gamma_q \boldsymbol{\gamma}_q + \mathbf{e} \tag{2}$$

where $q = 2^m - 1$ and $\mathbf{Y}, \boldsymbol{\tau}_A, \boldsymbol{\tau}_B, \boldsymbol{\delta}_A, \boldsymbol{\delta}_B, \boldsymbol{\pi}_1, \cdots \boldsymbol{\pi}_m, \boldsymbol{\gamma}_0, \cdots \boldsymbol{\gamma}_q, \mathbf{e}$ are $1 \times mn$ vectors; the direct effect vector is 1 if the treatment is A, and zero if it is B. For example, for the sequence ABB $\ldots$, $\boldsymbol{\tau}_{\mathbf{A}} = \begin{bmatrix} 1 \\ 0 \\ 0 \\ \vdots \end{bmatrix}$ and, in the same way, $\boldsymbol{\tau}_{\mathbf{B}}$, $\boldsymbol{\delta}_{\mathbf{A}}$, $\boldsymbol{\delta}_{\mathbf{B}} \boldsymbol{\pi}_{\iota}$ and $\boldsymbol{\gamma}_{\iota}$ are defined so that $\boldsymbol{\tau}_{\mathbf{A}} + \boldsymbol{\tau}_{\mathbf{B}} = 1_{\mathbf{mn}}$, $\boldsymbol{\delta}_{\mathbf{A}} + \boldsymbol{\delta}_{\mathbf{B}} + \boldsymbol{\pi}_1 = 1_{\mathbf{mn}}$, and $\boldsymbol{\pi}_1 + \boldsymbol{\pi}_2 + \ldots + \boldsymbol{\pi}_{\mathbf{m}} = 1_{\mathbf{mn}}$. Also, 1 when the ith unit is employed, and 0 elsewhere, so $\boldsymbol{\gamma}_0 + \boldsymbol{\gamma}_1 + \boldsymbol{\gamma}_2 + \ldots + \boldsymbol{\gamma}_{2^{\mathbf{m}}-1} = 1_{\mathbf{mn}}$. So, in equation (2) there are linearly dependent vectors.

Keeping only the linear independent vector [16], the model (2) is transformed to

$$E(\mathbf{Y}) = \tau(\boldsymbol{\tau}_A - \boldsymbol{\tau}_B) + \delta(\boldsymbol{\delta}_A - \boldsymbol{\delta}_B) + \pi_1 \boldsymbol{\pi}_1 + \cdots + \pi_{m-1} \boldsymbol{\pi}_{m-1} + + \gamma_0 \boldsymbol{\gamma}_0 + \cdots + \gamma_{q-1} \boldsymbol{\gamma}_{q-1}$$

where $q = 2^m - 1$. In a vector form:

$$\mathbf{Y} = \mathbf{X}\mathbf{b} + \mathbf{e} \Leftrightarrow \mathbf{Y} = \begin{pmatrix} \mathbf{X}_1 & \mathbf{X}_2 \end{pmatrix} \begin{pmatrix} \mathbf{b}_1 \\ \mathbf{b}_2 \end{pmatrix} \tag{3}$$

where $\mathbf{Y}$ is (mn) $\times$ 1, the design matrix $\mathbf{X}$ is (mn) $\times$ s, $\mathbf{b}$ is s $\times$ 1, $\mathbf{e}$ is (mn) $\times$ 1, and s is the number of unknown parameters. If we are interested only in some and not in all of the parameters, then we write $\mathbf{b}' = \begin{pmatrix} \mathbf{b}_1' & \mathbf{b}_2' \end{pmatrix}$, where $\mathbf{b}_1$ is the r parameters of interest, and $\mathbf{b}_2$ is the s-r remaining parameters.

We assume only one parameter of interest for the difference of the direct effects, $\tau = \tau_A - \tau_B$, which can be considered as the direct effect of A in the case of $\tau_B = 0$. In order to guarantee the estimability of the model, we postulate the restrictions $\tau_B = 0, \pi_m = 0, \gamma_{2^m-1} = 0$.

The matrix $\mathbf{X}_1$ corresponds to the coefficients of $\boldsymbol{\tau}$, and the matrix $\mathbf{X}_2$ corresponds to the coefficients of the rest of the non-random variables. Let us assume $\mathbf{V} = \mathbf{X}_2(\mathbf{X}_2{}^{\mathbf{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}_2)^{-1}\mathbf{X}_2{}^{\mathbf{T}}$ is a $(mn) \times (mn)$ matrix, P the projection matrix of $\mathbf{X}_2$, $\mathbf{P} = \mathbf{X}_2(\mathbf{X}_2{}^{\mathbf{T}}\mathbf{X}_2)^{-1}\mathbf{X}_2{}^{\mathbf{T}}$ and $\boldsymbol{\Sigma}$ are the $(mn) \times (mn)$ variance matrix of the observations.

From the ordinal least-squares equations, we derive the following relation for the estimation of the main effect τ:

$$(\mathbf{X}_1^{\mathbf{T}}\boldsymbol{\Sigma}^{-1}\mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}}\boldsymbol{\Sigma}^{-1}\mathbf{V}\boldsymbol{\Sigma}^{-1}\mathbf{X}_1)\hat{\boldsymbol{\tau}} = \mathbf{X}_1^{\mathbf{T}}\boldsymbol{\Sigma}^{-1}(\mathbf{I} - \mathbf{P}\boldsymbol{\Sigma}^{-1})\mathbf{Y}$$

We also have

$$\mathrm{var}(\tau) = \sigma^2 \left(\mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{V} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1\right)^{-1} = \sigma^2 \mathbf{Q}^{-1} \tag{4}$$

3. The Case of Compound Symmetry

The observations are dependent within sequences with variance matrix $\boldsymbol{\Sigma}_{\mathrm{m}}$. The observations from different sequences are independent, therefore:

$$\boldsymbol{\Sigma} = \begin{bmatrix} \boldsymbol{\Sigma}_{\mathbf{m}} & 0 & \cdots & 0 \\ 0 & \boldsymbol{\Sigma}_{\mathbf{m}} & \cdots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & 0 & \cdots & \boldsymbol{\Sigma}_{\mathbf{m}} \end{bmatrix} \text{ and } \mathbf{V} = \begin{bmatrix} \mathbf{V}_{\mathbf{m}0} & 0 & \cdots & 0 \\ 0 & \mathbf{V}_{\mathbf{m}1} & \cdots & 0 \\ & & \ddots & \vdots \\ 0 & 0 & \cdots & \mathbf{V}_{\mathbf{mq}} \end{bmatrix}$$

where $q = 2^m - 1$ and $\mathbf{V}_{mj} = \mathbf{X}_{2j} \left(\mathbf{X}_{2j}{}^{\mathbf{T}} \boldsymbol{\Sigma}_m{}^{-1} \mathbf{X}_{2j}\right)^{-1} \mathbf{X}_{2j}{}^{\mathbf{T}}$.

In order to obtain a sequence enumeration, the binary enumeration system was used, with 0 corresponding to A, and 1 to B. Thus, we obtained the enumerations $0, 1, \ldots, 2^m - 1$. For example, if we have five periods and the sequence BABBA, then this is the 13th sequence, since $BABBA \leftrightarrow 1 \cdot 2^0 + 0 \cdot 2^0 + 1 \cdot 2^2 + 1 \cdot 2^3 + 0 \cdot 2^4 = 13$. For two periods, we have four sequences, that is, $\mathrm{AA} \leftrightarrow 0, \mathrm{BA} \leftrightarrow 1, \mathrm{AB} \leftrightarrow 2, \mathrm{BB} \leftrightarrow 3$. For three periods (two treatments) we have eight sequences:

A	**B**	**A**	**B**	**A**	**B**	**A**	**B**
A	**A**	**B**	**B**	**A**	**A**	**B**	**B**
A	**A**	**A**	**A**	**B**	**B**	**B**	**B**
u_0	u_1	u_2	u_3	u_4	u_5	u_6	u_7

where $\mathrm{u_i}$ i = 0, 2, 3, 4, 5, 6, 7 is the number of units that received the i-th sequence of treatments. The sequences that we obtain by substituting A for B and vice versa are called dual or reversal designs. Observe that for these sequences, we obtain the enumeration 7 − i, i = 0, 1, 2, 3.

Proposition 1. *For a repeated measurement design with m periods, n experimental units, and a variance matrix* $\boldsymbol{\Sigma}$ *that consists of n diagonal block matrices of the form* $\boldsymbol{\Sigma}_{\mathrm{m}} = a\mathbf{I}_m + b\mathbf{J}_m$,

$$\left(\mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{V} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1\right) = \frac{1}{a} \left(\mathbf{X}_1^{\mathbf{T}} \mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}} \mathbf{P} \mathbf{X}_1\right)$$

where $\mathbf{P} = \mathbf{X}_2 \left(\mathbf{X}_2{}^{\mathbf{T}} \mathbf{X}_2\right)^{-1} \mathbf{X}_2{}^{\mathbf{T}}$.

Proof. Let $\widetilde{\mathbf{X}}_1 = \boldsymbol{\Sigma}^{-1/2} \mathbf{X}_1, \widetilde{\mathbf{X}}_2 = \boldsymbol{\Sigma}^{-1/2} \mathbf{X}_2$, and $\widetilde{\mathbf{Y}} = \boldsymbol{\Sigma}^{-1/2} \mathbf{Y}$. Then

$$\left(\mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}} \boldsymbol{\Sigma}^{-1} \mathbf{V} \boldsymbol{\Sigma}^{-1} \mathbf{X}_1\right) = \mathbf{X}_1^{\mathbf{T}} \mathbf{X}_1 - \widetilde{\mathbf{X}}_1^{\mathbf{T}} \mathbf{P} \widetilde{\mathbf{X}}_1$$

where $\widetilde{\mathbf{P}} = \widetilde{\mathbf{X}}_2 \left(\widetilde{\mathbf{X}}_2{}^{\mathbf{T}} \widetilde{\mathbf{X}}_2\right)^{-1} \widetilde{\mathbf{X}}_2{}^{\mathbf{T}}$. In other words, $\widetilde{\mathbf{P}}$ is the matrix of the orthogonal projection to $\mathbf{R}(\widetilde{\mathbf{X}}_2)$. □

$\mathbf{X}_{1j}$ j $= 0, 1, 2 \ldots m$ is the $m \times 1$ matrix of $\boldsymbol{\tau}$ in the j-th sequence, and $\mathbf{X}_{2j}$ j $= 0, 1, 2 \ldots m$ is the $mx(m + 2^m)$ matrix of the parameters $\mu, \pi_1, \pi_2, \ldots \pi_{m-1}, \delta_A, \delta_{\mathrm{B}}, \gamma_1, \gamma_2, \ldots, \gamma_q$, where $q = 2^m - 1$.

For example, for three periods (m = 3), we have the matrices:

$$X_1 = \begin{bmatrix} \mathbf{X}_{10}\}u_0 \\ \mathbf{X}_{11}\}u_1 \\ \vdots \\ \mathbf{X}_{17}\}u_7 \end{bmatrix} \text{ and } X_2 = \begin{bmatrix} \mathbf{X}_{20} \\ \mathbf{X}_{21} \\ \vdots \\ \mathbf{X}_{27} \end{bmatrix}$$

For the linear space $\mathbf{R}(\widetilde{\mathbf{X}}_{\mathbf{2j}})$ and for any sequence (m observations) $\mathbf{R}(\widetilde{\mathbf{X}}_{\mathbf{2j}}) = \mathbf{R}(\mathbf{X}_{\mathbf{2j}})$, we observe the following:

(i) The matrix $(a\mathbf{I}_m + b\mathbf{J}_m)$ is positive definite, so the matrix $(a\mathbf{I}_m + b\mathbf{J}_m)^{-\frac{1}{2}}$ is also positive definite, and we conclude that:

$$(a\mathbf{I}_m + b\mathbf{J}_m)^{-\frac{1}{2}} = \frac{1}{a}(\mathbf{I}_m - \frac{b}{a+bm}\mathbf{J}_m) \Leftrightarrow (a\mathbf{I}_m + b\mathbf{J}_m)^{-\frac{1}{2}} = \frac{1}{\sqrt{a}}(\mathbf{I}_m - \delta\mathbf{J}_m)$$

where $\delta = \frac{\sqrt{\frac{a}{a+bm}}}{m}$, $1 - \delta \cdot m > 0$, and we have $\widetilde{\mathbf{X}}_{2j} = \frac{1}{\sqrt{\alpha}}(\mathbf{I_m} - \boldsymbol{\delta}\mathbf{J_m})^{-1}\mathbf{X}_{2j}$.

(ii) The coefficients of the general mean are 1, so $1_{\mathbf{m}} \in \mathbf{R}(\mathbf{X}_{\mathbf{2j}})$ and.

$$\frac{1}{\sqrt{a}}(\mathbf{I}_m - \delta\mathbf{J}_m) \cdot 1_{\mathbf{m}} = \frac{1}{\sqrt{a+bm}}1_{\mathbf{m}} \Rightarrow 1_{\mathbf{m}} \in R(\widetilde{\mathbf{X}}_{2j})$$

(iii) If $\mathbf{z}$ is another column vector, and $\mathbf{z} \in \mathbf{R}(\mathbf{X}_{\mathbf{2j}})$, then

$$\frac{1}{\sqrt{a}}(\mathbf{I}_m - \delta\mathbf{J}_m)z = \frac{1}{\sqrt{a}}(\mathbf{z} - \delta(1_{\mathbf{m}}^{\mathbf{T}}\mathbf{z})1_{\mathbf{m}}) \Rightarrow z \in R(\widetilde{\mathbf{X}}_{2j}) \Leftrightarrow R(\widetilde{\mathbf{X}}_{2j}) = R(\mathbf{X}_{2j})$$

(iv) If $\widetilde{\mathbf{P}}_{\mathbf{m}}$ is the matrix of the orthogonal projection to the linear space $\mathbf{R}(\widetilde{\mathbf{X}}_{\mathbf{2j}})$, then $\widetilde{\mathbf{P}}_{\mathbf{m}j} = \mathbf{P}_{\mathbf{m}j}$, where $\mathbf{P}_{mj} = \mathbf{X}_{2j}(\mathbf{X}_{2j}{}^{\mathbf{T}}\mathbf{X}_{2j})^{-1}\mathbf{X}_{2j}{}^{\mathbf{T}}$ is the matrix of the orthogonal projection to $\mathbf{R}(\mathbf{X}_{\mathbf{2j}})$ and $\mathbf{P}_{\mathbf{mj}} \cdot 1_{\mathbf{m}} = 1_{\mathbf{m}} \Rightarrow \mathbf{P}_{\mathbf{mj}} \cdot \mathbf{J}_{\mathbf{m}} = \mathbf{J}_{\mathbf{m}}$. From the above, we conclude that:

$$(\widetilde{\mathbf{X}}_{1j}^{\mathbf{T}}\widetilde{\mathbf{X}}_{1j} - \widetilde{\mathbf{X}}_{1j}^{\mathbf{T}}\widetilde{\mathbf{P}}_{mj}\widetilde{\mathbf{X}}_{1j}) = \widetilde{\mathbf{X}}_{1j}^{\mathbf{T}}\widetilde{\mathbf{X}}_{1j} - \widetilde{\mathbf{X}}_{1j}^{\mathbf{T}}\widetilde{\mathbf{P}}_{mj}\widetilde{\mathbf{X}}_{1j} = \frac{1}{a}(\mathbf{X}_{1j}^{\mathbf{T}}\mathbf{X}_{1j} - \mathbf{X}_{1j}^{\mathbf{T}}\mathbf{P}_{mj}\mathbf{X}_{1j})$$

$$(\mathbf{I}_m - \widetilde{\mathbf{P}}_{\mathbf{mj}})\widetilde{\mathbf{X}}_{1j} = \frac{1}{\sqrt{a}}(\mathbf{I}_m - \mathbf{P}_{\mathbf{mj}})(\mathbf{I}_m - \delta\mathbf{J}_{\mathbf{m}})\mathbf{X}_{1j} = \frac{1}{\sqrt{a}}(\mathbf{I}_m - \mathbf{P}_{\mathbf{mj}})\mathbf{X}_{1j}$$

$$(\widetilde{\mathbf{X}}_1^{\mathbf{T}}\widetilde{\mathbf{X}}_1 - \widetilde{\mathbf{X}}_1^{\mathbf{T}}\widetilde{\mathbf{P}\mathbf{X}}_1) = \sum_{j=0}^{q}(\widetilde{\mathbf{X}}_{\mathbf{1}j}^{\mathbf{T}}\widetilde{\mathbf{X}}_{\mathbf{1}j} - \widetilde{\mathbf{X}}_{\mathbf{1}j}^{\mathbf{T}}\widetilde{\mathbf{P}}_{mj}\widetilde{\mathbf{X}}_{\mathbf{1}j}) = \frac{1}{a}(\mathbf{X}_1^{\mathbf{T}}\mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}}\mathbf{P}\mathbf{X}_1)$$

Corollary 1. *The designs that result in the estimators with the minimum variance, i.e.,* $\text{minvar}(\hat{\tau})$ *are exactly the optimal designs of the model with independent observations. In this case, the variance* $\text{var}(\hat{\tau})$ *is multiplied by* α:

$$\text{var}(\tau) = \sigma^2(\mathbf{X}_1^{\mathbf{T}}\mathbf{X}_1 - \mathbf{X}_1^{\mathbf{T}}\mathbf{P}\mathbf{X}_1)^{-1} = \sigma^2 a \cdot (\mathbf{Q}^*)^{-1}$$

$\sigma^2(Q^*)^{-1}$ *is the variance of the optimal designs in the model with independent observations).*

Proof. From the previous proof, we conclude that the variance of the estimator of the direct effect, which is given by Formula (3), equals to

$$\text{var}(\tau) = \sigma^2 a \cdot (\mathbf{Q}^*)^{-1}$$

□

Comments: (1) If we consider that an observation can influence another observation, the e.u are correlated, and the correlation is given by ρ, $-1 < \rho < 1$. Dependent observations are often considered observations of the same cluster [17]. A simple example of dependency appears when children of the same mother are included in a sample. Due to their common household environment and genes, it is expected that these children have a greater chance of having the same characteristics.

(2) In the case of compound symmetry, the variance matrix of each sequence observations is $\boldsymbol{\Sigma}_{\mathrm{m}} = (1-\rho)\mathbf{I}_m + \rho\mathbf{J}_m$, so $\alpha = 1-\rho$, and $b = \rho$. In order for the matrix to be positive definite, the condition $-\frac{1}{m-1} < \rho < 1$ is necessary. If $\rho = 0$, then we obtain the model with independent observations and $\alpha = 1$.

(3) The variance of the estimator of the direct effect, $\mathrm{var}(\hat{\tau})$, decreases when the correlation coefficient ρ increases and it approaches 0, when ρ approaches 1, since $\alpha = 1-\rho$.

(4) For two periods with dependent observations, the 2×2 variance matrix of the observations in the compound symmetry model is $\boldsymbol{\Sigma}_2 = (1-\rho)\mathbf{I}_2 + \rho\mathbf{J}_2$. The optimal design for this model is the same as the optimal design for independent observations for every ρ, $-1 < \rho < 1$.

For an even n, such an optimal design is obtained when to the sequences AA and AB correspond to $n/2$ e.u, while for an odd n, the optimal design is obtained when to the sequences AA and AB correspond to $(n-1)/2$ and $(n+1)/2$ e.u., respectively [11]. The reverse sequences BB, BA also correspond to an optimal design with: $\mathrm{var}(\tau) = \sigma^2(1-\rho)(\mathbf{Q}^*)^{-1}$

(5) As illustrated, the examined model with dependent observations is also associated with variance matrices $\boldsymbol{\Sigma}$ for which the optimal designs are the same as the ones of the model with independent observations [14,18].

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