Sparse Sampling D-Optimal Designs in Quadratic Regression With Random Effects[1]

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Abstract

In mixed effect models the variability of the regression parameters has substantial influence on the choice of the optimal design. If less observations per individual are possible than parameters are to be estimated, the optimality results of single-group designs no longer hold.

1 Introduction

In population pharmacokinetic studies the blood samples of individuals are evaluated together in one model, assuming that the same regression function can be used for all subjects, with slightly different parameters for the different individuals. These differences from the population mean are modeled by random variables. The purpose of this article is to study the design for quadratic regression in mixed effect models, in the case of two allowed observations per individual. Taking many blood samples of one individual is costly, unethical and in some cases even not possible. If less observations are being made than parameters are to be estimated, the occuring D-optimal individual design, will lead to a singular information matrix. The use of population designs with different observation groups helps to construct estimates for the population parameter vector.
Cheng[2] and Atkins and Cheng[1] provide D-optimal designs for quadratic regression with random intercept, considering two observations per subject. In this article we generalize these results to polynomial regression with random slope and random curvature.
In section 2 we introduce the mixed effects model. Section 3 will introduce D-optimal designs for quadratic regression with random parameters, considering less observations per individual than parameters are to be estimated. We will show results on the efficiency of D-optimal designs compared to a trivial three-group design.

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2 The model

In the considered mixed model, the j-th observation of individual i, taken at the experimental setting x_{ij} in a design region X, is modeled by

$$\begin{aligned} Y_{ij} &= f(x_{ij})^T \tilde{\beta}_i + \epsilon_{ij}, \text{ where} \\ \epsilon_{ij} &\sim N(0, \sigma^2) \\ \tilde{\beta}_i &= \beta + b_i \text{ and } b_i \sim N_p(0, \sigma^2 D). \end{aligned}$$

The vector β is the p-dimensional vector of population parameters, and b_i is the vector of individual effects. For quadratic regression $\beta = (\beta_1, \beta_2, \beta_3)^T \in \mathbb{R}^3$. It is assumed that the covariance matrix of the individual effects is a diagonal matrix:

$$D = diag(d_1, d_2, d_3) = \begin{pmatrix} d_1 & 0 & 0 \\ 0 & d_2 & 0 \\ 0 & 0 & d_3 \end{pmatrix}.$$

To interpret the matrix an example may help: If we assume $d_2 = d_3 = 0$ the regression functions of the individuals would differ in the intercept $\tilde{\beta}_1$ only.

The observation errors ϵ_i and the individual effects b_i are assumed to be independent. The vector of the m_i observations taken from individual i is then described by

$$Y_i = F_i \tilde{\beta}_i + \epsilon_i,$$

where $F_i = (f(x_{i1}), ..., f(x_{im_i}))^T$ is the design matrix for the observations of individual i. Then the individual discrete design can be represented by

$$\xi_i = (x_{i1}, ..., x_{ik_i}, m_{i1}, ..., m_{ik_i}) \text{ with } \sum_{j=1}^{k_i} m_{ij} = m_i.$$

The integer m_{ij} represents the number of replicated measurements in the experimental setting x_{ij}. For discrete designs m_{ij} are integers. For arbitrary $m_{ij} \in \mathbb{R}^+$ with $\sum_{j=1}^{k_i} m_{ij} = m_i$ we call ξ_i an approximate individual design.
With the normality of the random error term and the individual effects, the observation vector Y_i has the marginal distribution

$$Y_i \sim N_{m_i}(F_i \beta, \sigma^2 (F_i D F_i^T + I_{m_i})).$$

Let the matrices F, G, V_i and V be defined as

$$\begin{aligned} F &:= (F_1^T, ..., F_n^T)^T, \\ G &:= diag((F_1, ..., F_n)), \\ V_i &:= (F_i D F_i^T + I_{m_i}) \text{ and} \\ V &:= diag(V_1, ..., V_n). \end{aligned}$$

Then the model for all observations is described by

$Y = F\beta + Gb + \epsilon \sim N_{\sum m_i}(F\beta, \sigma^2 V)$, where $b = (b_1^T, ..., b_n^T)$, $\epsilon = (\epsilon_1^T, ..., \epsilon_n^T)^T$.

If we consider the case that the matrix F has full column rank and that the parameter variance matrix D is known, the population parameter vector β can be estimated using the weighted least squares estimator:

$$\hat{\beta} = (F^T V^{-1} F)^{-1} F^T V^{-1} Y.$$

Target of the design optimization is to minimize in some sense the covariance of the estimator $\hat{\beta}$:

$$cov(\hat{\beta}) = \sigma^2 (F^T V^{-1} F)^{-1}.$$

This optimization task is equivalent to maximizing the information matrix, which is of the form:

$$\mathfrak{M}_{pop} := \sum_{i=1}^{n} F_i^T V_i^{-1} F_i.$$

D-optimal designs minimize the volume of the confidence ellipsoid, what is equivalent to maximizing the determinant of the information matrix.
To turn the discrete optimization problem in a continuous one, we allow approximate more-group designs:

$$\zeta := (\xi_1, ..., \xi_k, \omega_1, ..., \omega_k) \text{ with } \sum_{i=1}^{k} \omega_i = 1.$$

This means that $100 \times \omega_i\%$ of the population will be observered unter the discrete individual design ξ_i. For the construction of D-optimal designs and to prove the optimality, we can use the multivariate form of the Equivalence Theorem[3] with the sensitivity function g_ζ:

$$g_\zeta(\xi) := Tr F_\xi \mathfrak{M}_{pop}(\zeta)^{-1} F_\xi^T V_\xi^{-1},$$

for a population design ζ and an individual design ξ with F_ξ being the design matrix of the design ξ.

For approximate individual designs Schmelter[4] proved that D-optimal approximate single-group designs retain their optimality even if more-group designs are allowed. Optimal approximate individual designs can be realized only in few cases. For the special case of two observations per individual in quadratic regression, single-group designs would lead to singular information matrices. It is obivous that they lose their optimality. In the next section we will construct D-optimal designs for quadratic regression under the assumption of random effects with variance matrices $D_1 = diag(d_1, 0, 0)$, $D_2 = diag(0, d_2, 0)$ and $D_3 = diag(0, 0, d_3)$ and that the individual designs consist of two observations only, whereas the population designs are assumed to be approximate more-group designs.

3 D-Optimal designs for quadratic regression with random parameters

It is obvious that approximate single-group designs lose their optimality, if less observation per individual can be taken than parameters are to be estimated.

For the case of one sample per individual, it is rather easy to calculate D-optimal designs:

Theorem 1. *Assume $X = [-1, 1]$, $D = D_k$, $k = 1, 2, 3$ and $F_i = (1, x_i, x_i^2)$, with $x_i \in X$. The D-optimal design $\zeta^*_{d_k}$ for estimating the population parameter vector β is of the form*

$$\zeta^*_{d_k} = \begin{pmatrix} -\alpha_{d_k} & 0 & \alpha_{d_k} \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}$$

with $\alpha_{d_k} = 1$ for $k = 1, 2$ and with α_{d_k} being dependent of the variance in the parameter β_3 for $k = 3$.

Proof: Invariance considerations yield the symmetric structure of D-optimal designs in quadratic regression. The sensitivity function for the case $k = 1$ and the design $\zeta^*_{d_1}$ has the form

$$g_{\zeta^*_{d_1}}(x) = 3 - 4.5x^2 + 4.5x^4.$$

For $x \in X$ we get $g_{\zeta^*_{d_1}} \leq 3$. For the sensitivity function in the case $k = 2$ and the design $\zeta^*_{d_2}$, for $x \in X$ follows:

$$g_{\zeta^*_{d_2}}(x) = \frac{3(2 - 3x^2 + d_2x^2 + 3x^4 + d_2x^4)}{2(1 + d_2x^2)} \leq \frac{3(2 + 2d_2x^2)}{2(1 + d_2x^2)} = 3.$$

In the case d_3 with

$$\alpha_{d_3} = \begin{cases} 1 & \text{for } d_3 \leq 3 \\ \sqrt[4]{\frac{3}{d_3}} & \text{for } d_3 > 3 \end{cases}$$

follows for $d_3 > 3$

$$g_{\zeta^*_{d_3}}(x) = \frac{3(2\alpha_{d_3}^4 - 3x^2\alpha_{d_3}^2 + d_3x^2\alpha_{d_3}^6 + 3x^4 + d_3x^4\alpha_{d_3}^4)}{2(1 + d_3x^4)\alpha_{d_3}^4} = 3.$$

For $d_3 \leq 3$ we have to show

$$\begin{aligned} & g_{\zeta^*_{d_3}}(x) = \frac{3(2 - 3x^2 + d_3x^2 + 3x^4 + d_3x^4)}{2(1 + d_3x^4)} \leq 3 \\ \Leftrightarrow \quad & 2 - 3x^2 + d_3x^2 + 3x^4 + d_3x^4 \leq 2(1 + d_3x^4) \\ \Leftrightarrow \quad & -x^2(x-1)(x+1)(d_3 - 3) \leq 0. \end{aligned}$$

Since $x \in [-1, 1]$, we obtain $g_{\zeta^*_{d_3}}(x) \leq 3$ for $d_3 \leq 3$. □

Graßhoff et al.[5] show for linear regression with one observation per individual and a random effect covariance matrix of the form $D = diag(d_1, d_2)$ that the design

$$\zeta^*_D = \begin{pmatrix} -1 & 1 \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$$

retains its optimality for $d_1 \geq d_2$. In the case of quadratic regression, the D-optimal design for D_1 and D_2 will retain its optimality for $D = diag(d_1, d_2, 0)$ even if $d_2 > d_1$. For general $D = diag(d_1, d_2, d_3)$ the D-optimal Design retains its optimality as long as the unequality

$$(3 + 3d_1 + d_2) \geq d_3$$

is fullfilled.

For the case of two oberservations per individual, the calculation of D-optimal designs complicates. According to Cheng[2] and Atkins and Cheng[1], the D-optimal design for the random intercept case with two observations per individual, will be an approximate three-group design of the form

$$\zeta^*_{d_1} = \begin{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} & \begin{pmatrix} 1 \\ \alpha_{d_1} \end{pmatrix} & \begin{pmatrix} -1 \\ -\alpha_{d_1} \end{pmatrix} \\ \omega_{d_1} & \frac{1}{2}(1 - \omega_{d_1}) & \frac{1}{2}(1 - \omega_{d_1}) \end{pmatrix},$$

where $\alpha_{d_1} \in (-1, 1)$ and $\omega_{d_1} \in (0, 1)$ depend on the variance of the intercept. Due to invariance considerations, the D-optimal information matrix in the case with random effects and two observations per individual will be of the form

$$\mathfrak{M}_{pop}(\zeta) = \begin{pmatrix} a & 0 & b \\ 0 & c & 0 \\ b & 0 & d \end{pmatrix} \qquad (1)$$

with

$$\begin{aligned} a &= \sum_{i=1}^{k} \frac{\omega_i}{detV_i}(2 + d_2(x_i - y_i)^2 + d_3(x_i^2 - y_i^2)^2) \\ b &= \sum_{i=1}^{k} \frac{\omega_i}{detV_i}(x_i^2 + y_i^2 - d_2 x_i y_i (x_i - y_i)^2) \\ c &= \sum_{i=1}^{k} \frac{\omega_i}{detV_i}(x_i^2 + y_i^2 + d_1(x_i - y_i)^2 + d_3 x_i^2 y_i^2 (x_i - y_i)^2) \\ d &= \sum_{i=1}^{k} \frac{\omega_i}{detV_i}(x_i^4 + y_i^4 + d_1(x_i^2 - y_i^2)^2 + d_2 x_i^2 y_i^2 (x_i - y_i)^2) \end{aligned}$$

and an arbitrary more-group design

$$\zeta := \begin{pmatrix} \begin{pmatrix} x_1 \\ y_1 \end{pmatrix} & \dots & \begin{pmatrix} x_k \\ y_k \end{pmatrix} \\ \omega_1 & \dots & \omega_k \end{pmatrix}.$$

Let the sensitivity function g_ζ be defined as

$$g_\zeta(x,y) := Tr F(x,y) \mathfrak{M}_{pop}(\zeta)^{-1} F(x,y)^T V(x,y)^{-1},$$

for a design ζ and

$$F(x,y) := \begin{pmatrix} 1 & x & x^2 \\ 1 & y & y^2 \end{pmatrix}, \quad V(x,y) := (F(x,y) D F(x,y)^T + I_2).$$

Theorem 2. *Assume $X = [-1,1]$, $D = D_2$ and $F_i = F(x_i, y_i)$ with $x_i, y_i \in X$. The D-optimal design $\zeta^*_{d_2}$ for estimating the population parameter vector β is of the form*

$$\zeta^*_{d_2} = \begin{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} & \begin{pmatrix} \alpha_{d_2} \\ -\alpha_{d_2} \end{pmatrix} \\ 1-\omega_{d_2} & \omega_{d_2} \end{pmatrix}$$

with α_{d_2} and ω_{d_2} being dependent of the variance in the parameter β_2.

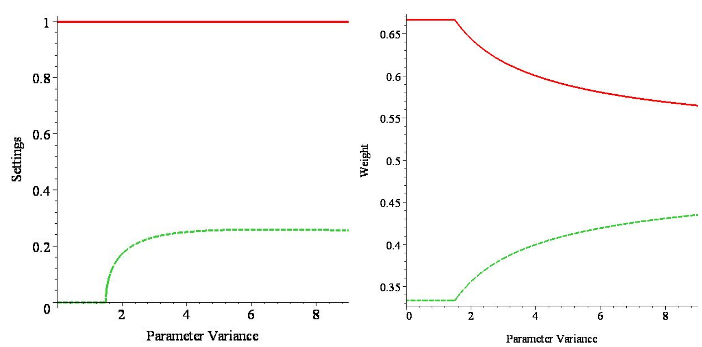

Figure 1: The figure shows the optimal experimental settings in dependence of the variance for the case D_2 and the according optimal weights.

Proof: Let

$$\begin{aligned} \tilde{g}_\zeta(x,y) &:= det(V(x,y))(ad-b^2)c(g_\zeta(x,y)-3) \\ \tilde{g}_{\zeta;x}(x) &:= \tilde{g}_\zeta(x,-x) \\ \tilde{g}_{\zeta;1}(x) &:= \tilde{g}_\zeta(x,1), \end{aligned}$$

with a, b, c and d as defined in (1).
For D-optimal designs the modified sensitivity function $\tilde{g}_\zeta$ will be nonpositive and

will be 0 for support points of the D-optimal design. Support points will be located on the border of the design region or will be local maxima of the function $\tilde{g}_\zeta$. For the case of random slope, the modified sensitivity function $\tilde{g}_\zeta$ is of the form

$$\begin{aligned}\tilde{g}_\zeta(x,y) &= -2bc(x^2+y^2-d_2xy(x-y)^2)+ac(x^4+y^4+d_2x^2y^2(x-y)^2)\\ &\quad -b^2(x^2+y^2)+ad(x^2+y^2)+dc(2+d_2(x-y)^2)\\ &\quad -3c(1+d_2(x^2+y^2))(ad-b^2)\end{aligned}$$

and it can be easily seen that $\tilde{g}_\zeta(x,y)=\tilde{g}_\zeta(y,x)=\tilde{g}_\zeta(-x,-y)=\tilde{g}_\zeta(-y,-x)$.
With symmetry considerations follows that local maxima of $\tilde{g}_\zeta$ can be located in points $(-x,x)$ only. The function $\tilde{g}_{\zeta;x}$ is a polynomial of order 6 with even exponents only. In support points of the D-optimal design, the function $\tilde{g}_{\zeta;x}$ will have roots and local maxima. We assume that the point $(-1,1)$ supports the optimal design. It follows that the function $\tilde{g}_{\zeta;x}$ has maximal 4 roots on the interval $[-1,1]$.
From now on, we assume that the D-optimal design is of the form

$$\zeta_2=\begin{pmatrix}\begin{pmatrix}1\\-1\end{pmatrix} & \begin{pmatrix}\alpha\\-\alpha\end{pmatrix}\\ 1-\omega & \omega\end{pmatrix}$$

By analyzing and solving the problems

$$\tilde{g}_{\zeta_2;x}(-1)=\tilde{g}_{\zeta_2;x}(1)=\tilde{g}_{\zeta_2;x}(-\alpha)=\tilde{g}_{\zeta_2;x}(\alpha)=0,$$

$$\frac{\partial\tilde{g}_{\zeta;x}}{\partial x}(\alpha)=\frac{\partial\tilde{g}_{\zeta;x}}{\partial x}(-\alpha)=0 \text{ and}$$

$$\frac{\partial^2\tilde{g}_{\zeta;x}}{\partial^2 x}(\alpha),\frac{\partial^2\tilde{g}_{\zeta;x}}{\partial^2 x}(-\alpha)<0$$

we get the following result for the optimal support point α^*:

$$\alpha^*=\begin{cases}0 & \text{for } d_2\le 1.5\\ \sqrt{\frac{(4d_2+2+\sqrt{1+2d_2})(4d_2-3\sqrt{1+2d_2})}{4d_2(8d_2+4+8\sqrt{1+2d_2}d_2+5\sqrt{1+2d_2})}} & \text{for } d_2>1.5\end{cases}$$

with weights ω^* on α^*:

$$\omega^*=\begin{cases}1/3 & \text{for } d_2\le 1.5\\ \frac{4d_2+1-\sqrt{1+2d_2}}{8d_2+3} & \text{for } d_2>1.5.\end{cases}$$

For $d_2\le 1.5$ the analysis of the modified sensitivity function would lead to complex support points, which exceed the design region. To prove the D-optimality for $d_2\le 1.5$, it is sufficient to show that $\tilde{g}_{\zeta_2;x}(x)\le 0$ and $\tilde{g}_{\zeta_2;1}(x)\le 0$, what is obvious since for $x\in(-1,1)$ and $d_2\le 1.5$:

$$\tilde{g}_{\zeta_2;x}(x)=\frac{16x^2(x^2-1)(2d_2(3x^2-1)+3)}{9(1+2d_2)}\le 0$$

$$\tilde{g}_{\zeta_2;1}(x)=\frac{8x^2(x+1)((3x-5)d_2+3(x-1))}{9(1+2d_2)}\le 0.$$

For the case $d_2 > 1.5$, only nonpositivity on the border of the design region is left to be shown. Since $\tilde{g}_{\zeta_2;1}(-1) = 0$,

$$\tilde{g}_{\zeta_2;1}(x) = (x+1)\hat{g}_{\zeta_2;1}(x)$$

with $\hat{g}_{\zeta_2;1}(x)$ being a polynomial of third degree in x. It can be shown that

$$\hat{g}_{\zeta_2;1}(-1) < 0 \text{ and } \hat{g}_{\zeta_2;1}(1) < 0.$$

It follows that the function $\hat{g}_{\zeta_2;1}(x)$ has not more than 2 roots on $(-1, 1)$. If the function has only one root on the intervall, then this will be a local maximum. Let $x^*(d_2)$ denote the maximizing x for $\hat{g}_{\zeta_2;1}$ in dependence of d_2. Then it can be shown that the function $\hat{g}_{\zeta_2;1}(x^*(d_2))$ is monotonly decreasing in d_2. Since

$$\hat{g}_{\zeta_2;1}(x^*(1.5)) = \hat{g}_{\zeta_2;1}(0) = 0,$$

the D-optimality follows for all $d_2 \geq 1.5$. □

The sensitivity function of designs, and by this the optimal designs, strongly depend on the variance in the random parameters. For D_1 and D_2 and two observations per individual the structures of the D-optimal designs differ and the D-optimal designs always depend on the variance. One would expect, that for D_3 similar results can be obtained. It is in some way surprising that the D-optimal design for random curvature will not depend on the variance in the curvature:

Theorem 3. *Assume $X = [-1, 1]$, $D = D_3$ and $F_i = F(x_i, y_i)$ with $x_i, y_i \in X$. The D-optimal design $\zeta^*_{d_3}$ for estimating the population parameter vector β is of the form*

$$\zeta^*_{d_3} = \begin{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} & \begin{pmatrix} 0 \\ 0 \end{pmatrix} \\ 2/3 & 1/3 \end{pmatrix},$$

independent of the variance in the parameter β_3.

Proof: Note that for the design $\zeta^*_{d_3}$ as defined in the theorem, the sensitivity function has the form:

$$\begin{aligned} & g_{\zeta^*_{d_3}}(x,y) := Tr F(x,y)\mathfrak{M}_{pop}(\zeta^*_{d_3})^{-1}F(x,y)^T V(x,y)^{-1} \\ = & \frac{3(d_3(x^2y^2((x-y)^2+4)+4(x^2-y^2)^2)-3(x^2+y^2-x^4-y^4)+4)}{4(1+d_3(x^4+y^4))}. \end{aligned}$$

Assume $g_{\zeta^*_{d_3}}(\hat{x}, \hat{y}) > 3$ for $\hat{x}, \hat{y} \in [-1, 1]$. Then

$$\begin{aligned} & d_3(\hat{x}^2\hat{y}^2((\hat{x}-\hat{y})^2+4)+4(\hat{x}^2-\hat{y}^2)^2)-3(\hat{x}^2+\hat{y}^2-\hat{x}^4-\hat{y}^4) > 4d_3(\hat{x}^4+\hat{y}^4) \\ \Leftrightarrow \quad & \hat{x}^2\hat{y}^2(\hat{x}-\hat{y}+2)(\hat{x}-\hat{y}-2)d_3 > 3(\hat{x}^2+\hat{y}^2-\hat{x}^4-\hat{y}^4). \end{aligned}$$

Since $\hat{x}, \hat{y} \in [-1, 1]$,

$$\hat{x}^2\hat{y}^2(\hat{x}-\hat{y}+2)(\hat{x}-\hat{y}-2)d_3 \leq 0, \text{ whereas } 3(\hat{x}^2+\hat{y}^2-\hat{x}^4-\hat{y}^4) \geq 0.$$

With this contradiction follows that no pair $(\hat{x}, \hat{y})$ exists, with $g_{\zeta^*_{d_3}}(\hat{x}, \hat{y}) > 3$. The multivariate form of the Equivalence Theorem yields D-optimality. □

It is obvious that the two-observation more-group designs are less D-efficient than the D-optimal single-group designs with approximate individual designs. Already more interesting is the efficiency of a trivial design

$$\zeta_B = \begin{pmatrix} \begin{pmatrix} 1 \\ -1 \end{pmatrix} & \begin{pmatrix} 1 \\ 0 \end{pmatrix} & \begin{pmatrix} -1 \\ 0 \end{pmatrix} \\ 1/3 & 1/3 & 1/3 \end{pmatrix},$$

compared to the optimal designs in the cases $D = D_2$ and $D = D_3$. Cheng[2] shows similar results for random intercepts, which were included in the table. For random intercepts the decrease in efficiency is much slower than for random slope or random curvature. This can be explained by the optimal design structure, which is for $D = D_1$ similar to the trivial design.

Table 1: D-efficiency of the trivial design ζ_B compared to the D-optimal two-observation designs

$\rho = \frac{d_k}{d_k+1}$	efficiency for $k = 1$	efficiency for $k = 2$	efficiency for $k = 3$
0	1	1	1
0.1	0.99950	0.99918	0.99918
0.2	0.99820	0.99666	0.99666
0.3	0.99631	0.99243	0.99243
0.4	0.99397	0.98647	0.98647
0.5	0.99126	0.97872	0.97872
0.6	0.98826	0.96905	0.96905
0.7	0.98500	0.95229	0.95738
0.8	0.98153	0.92311	0.94354
0.9	0.97788	0.87795	0.92735

4 Discussion

In the present simple model of quadratic regression, the optimal design in cases when only two observations are allowed, strongly depends on the variance in the parameters. For isolated variances in the slope or the curvature of the regression function, the optimal design could be explicitly calculated. If more than one parameter has random effects, the model complicates. In examples for this case could be seen that one of the design structures derivated for the cases $D = D_1$, $D = D_2$ or $D = D_3$ leads to the D-optimal design. This leads to the assumption that one parameter dominates the design and that the domination is dependent of the variance ratios. In relation to this, it will be very interesting, to analyze the design for cases, if two or more parameters at the same time influence the design.

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