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# On Construction of Two-stage Response Surface Designs

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**Abstract**: Consider the common situation in many response surface applications. In the first stage, a two-level design and central point(s) have been conducted, and the analysis indicated that the curvature of the response surface is significant. In such a scenario, a second stage of experiments is called for so that a second order model can be fitted. The problem of constructing two-stage response surface designs with high efficiency is studied in this paper. The focus will be on the design of experiment for the second stage. The appropriateness of the well-known *D*-optimal criterion for designing the second stage experiments is first discussed. A new criterion, *C*-optimality, is then proposed to find design points in the second stage, *given* the points in the first stage. The proposed criterion is a weighted sum of efficiency measures from four subsets of parameters in a second order model. By selecting suitable weights, one can construct two-stage response surface designs with evenly high estimation efficiencies for all the parameters. A construction algorithm is then introduced. The superiorities of new designs are demonstrated by a thorough comparison with existing designs.

Keywords: Central composite design, D-efficiency, response surface design, second order model.

## 1. Introduction

A pharmaceutical company had been working on finding the best production condition to increase the productivity of penicillin. The target quantity (response variable) is the productivity of penicillin measured in kilogram per hour. Four variables (fermentation time, fermentation temperature, percentage of starch in the culture stuff, and Stirring speed) are considered to influence the productivity of penicillin in a complicated way. For example, high fermentation temperature and high percentage of starch in the culture stuff speed up the production of penicillium mold which secrete penicillin. However, high density of penicillium mold restrain the secreting of penicillin. Hence, the temperature and percentage of starch should be controlled to keep the density of penicillium mold at a suitable level. Long fermentation time certainly leads to increasing of the total amount of penicillin produced, but to decreasing of the amount of penicillin produced per hour since the ability of penicillium mold for secreting penicillin decreases after some time.

Since the experiment is costly and time-consuming, the engineer considered to conducting the experiment in two stages with a total of at most 20 runs. In the first stage, she had used the two-level eight-run  $2_{IV}^{4-1}$  fractional factorial, together with four replicates of the central point, i.e., the point with all the variables at intermediate level. After the first stage of the 12 runs, all the four variables had been found significant, and so did the curvature of the response surface.

The engineer had then decided to conduct eight more runs in the second stage

experiment to fit a second order model

$$E(y) = \beta_0 + \sum_i \beta_i x_i + \sum_{i < j} \beta_{ij} x_i x_j + \sum_i \beta_{ii} x_i^2, \qquad (1)$$

where E(y) is the expectation of the response variable  $y, x_i's$  are the production condition variables, and  $\beta's$  are parameters to be estimated. The problem was: how can we plan the additional eight runs? Originally, she had considered to use the eight "face points", *i.e.*, the points with one variable at low or high level and the others at intermediate level. But after a verification, she found that the parameters for the cross-product terms in the model would not be identifiable in such designs. It is desirable that the experimental runs in the second stage must be able to offer information on the cross-product terms. Furthermore, since the experiment is to be conducted in two stages, the experimental runs can only be randomized in each stage. So a blocking factor z (z = 1 when the run is in the first stage, and z = 0when the run is in the second stage) should be considered in the second order model. Thus the model becomes

$$E(y) = \beta_0 + \sum_i \beta_i x_i + \sum_{i < i} \beta_{ii} x_i x_j + \sum_i \beta_{ii} x_i^2 + \gamma z.$$
(2)

Under such a model, we offer the optimal design for the second stage, *given* the design points in the first stage (typically a two-level fractional factorial design with center points). Two principles to be considered are the model identifiability and the estimation efficiency. This paper is organized as follows. A new criterion for two-stage response surface design is proposed in Section 2. An algorithm for the construction of two-stage response surface designs based on the new criterion is described in Section 3. These newly constructed designs are then compared with other related designs in Section 4. Conclusion remarks are given in Section 5.

#### 2. Construction of Two-Stage Response Surface Designs

An important concern in the construction of experimental designs is the trade-off between estimation efficiency and run size economy. Run size is typically limited by real-life considerations, such as budget or time. For a given run size, the optimal design can be constructed via maximizing certain optimality criteria, such as estimation efficiency. In this paper, we discuss the problem of constructing two-stage designs for second order response surface analysis based on the following practical considerations:

- (i) In the first stage, a two-level fractional factorial with  $N_1$  points is employed, accompanied by  $N_0$  central point replicates (for significant tests of main effects and finding potential curvature of the response surface).
- (ii) Given the  $N_1 + N_0$  points in the first stage,  $N_2$  design points are to be selected at the second stage, for fitting a second order model. These  $N_2$  points (most likely with three-level) for the second stage should be selected to obtain the highest estimation efficiency based on certain criterion.

Assume that y is the response variable,  $x_1, ..., x_k$  are continuous variables considered to influence the response, and a cubic experimental region is standardized to  $[-1, 1]^k$ . The second order model (1) has a total of p = (k+2)(k+1)/2 parameters. But since the experimental runs cannot be conducted in a completely random order in a two-stage experiment, Model (1) should be replaced by Model (2), in which a blocking parameter is involved. The empirical model for Model (2) can be written in a typical vector-matrix form:

 $E(Y) = X\beta$ , where Y is the N-vector of observed responses,  $\beta$  is the (p+1)-vector of parameters, X is the  $N \times (p+1)$  model matrix with each row corresponding a run. The least squares estimator of the parameter vector is  $\hat{\beta} = (X'X)^{-1}X'Y$ , with variance-covariance matrix proportional to  $(X'X)^{-1}$ .

The most well-known and popularly used design criterion is probably the *D*-efficiency, defined as  $D = |X'X|^{1/(p+1)} / N$  (the larger, the better). An implicit assumption for D-criterion is that all parameters are equally important. As will be discussed below, this may not be appropriate for the two-stage design. When we use the D-criterion in the construction of two-stage response surface designs, the estimation efficiencies of the parameters are often unevenly distributed, i.e., the parameters may be estimated with very different efficiencies. Note that different sets of parameters influence the response surface in different aspects: for example, linear term parameters determine its center, cross-product term parameters determine its principal axes, and pure quadratic term parameters determine its shape, etc. Hence, any set of parameters with low estimation efficiencies will distort an aspect of the response surface greatly. Moreover, in the construction of a two-stage response surface design, estimation efficiency may be required for some special set(s) of parameters. For example, when a  $2_V^{k-m}$  fractional factorial or a  $2^k$  full factorial is used in the first stage, all the parameters related to the linear and cross-product terms can be estimated with sufficient high efficiency in the first stage. Thus, the points in the second stage should be selected so that the parameters related to the quadratic terms can be estimated as accurately as possible.

To overcome these problems, here we propose a new criterion, called *C*-efficiency. To define *C*-efficiency, we divide the parameters in Model (2) into five groups. Group *I* includes the constant term  $\beta_0$ , group *L* includes the *k* linear parameters ( $\beta_i, i = 1, ..., k$ ), group *B* includes the k(k-1)/2 bilinear parameters ( $\beta_{ij}, 1 \le i < j \le k$ ), group *Q* includes the *k* pure quadratic parameters ( $\beta_{ii}, i = 1, ..., k$ ), and group *b* includes the blocking parameter  $\lambda$ , which is a nuisance parameter. The model matrix *X* is also divided accordingly as  $X_I, X_L, X_B, X_O$  and  $X_b$ . Define

$$D_{j} = N^{-1} \left| X_{j}' X_{j} - X_{j}' X_{-j} (X_{-j}' X_{-j})^{-1} X_{-j}' X_{j} \right|^{1/k_{j}}, \quad j = I, L, B, Q,$$
(3)

where  $X_{-j}$  is the complementary sub-matrix of  $X_j$  in X,  $k_j$  is the number of columns in  $X_j$ .  $D_j$  measures the estimation efficiency of the parameters in group j for j = I, L, B, Q. The *C*-efficiency is then defined as

$$C = D_I^{w_I} D_L^{w_L} D_B^{w_B} D_O^{w_Q}, (4)$$

where  $w_I, w_L, w_B, w_Q$  are nonnegative weights and  $w_I + w_L + w_B + w_Q = 1$ . In the definition of *C*, the weights represent the importance of the parameter sets – more important parameter sets carry heavier weights. For different first-stage points, one can specify different weights to *C*. The following specifications of the weights are recommended.

- (i) Among the four sets of parameters, set I is usually less important compared with other three sets, and hence we propose to set  $w_I = 0$ . However, if the experimenter considers the intercept is as important as other parameters, positive weight  $w_I > 0$  can be used.
- (ii) Since the pure quadratic parameters can not be estimated at all in the first stage, it is the most important to raise the estimation efficiency of the parameter set Q. Hence, we propose to set  $w_0$  to carry the largest weight.

- (iii) When the first stage design is a two-level resolution *III* fractional factorial  $(2_{III^*}^{k-m})$  design, some linear parameters are confounded with bilinear parameters in the first stage, hence we propose to set  $w_I = 0$ ,  $w_L = w_B = 1/4$  and  $w_Q = 1/2$ ;
- (iv) When the first stage design is a two-level resolution *IV* fractional factorial  $(2_{IV}^{k-m})$  design, some bilinear parameters are confounded with each other in the first stage, hence we propose to set  $w_I = w_L = 0$ ,  $w_B = 1/3$  and  $w_O = 2/3$ ;
- (v) Finally, when the first stage design is a two-level resolution V fractional factorial  $(2_V^{k-m})$  design or the  $2^k$  full factorial design, all the linear and bilinear parameters can be estimated in the first stage, hence we propose to set  $w_I = w_L = w_B = 0$ , and  $w_Q = 1$ .

Given a set of  $N_1 + N_0$  first-stage points and a set of weights,  $w_I, w_L, w_B, w_Q$ , the C value is maximized in selecting  $N_2$  second-stage points.

#### **3. Construction Algorithm**

Many algorithms have been proposed in the literature for the construction of designs by improving a pre-specified criterion iteratively. Basically, these algorithms are either row-wise exchanging or column-wise exchanging. Here a row represents a point (a run), and a column represents the coordinates of a variable in the design. Let d denote a design involving k variables and N runs, produced after a step in the computational process. A row-wise exchange algorithm improves d in the next step by exchanging one or several row(s) in it, while a column-wise algorithm does the job by exchanging one or several columns. Typical row-wise exchange algorithms are introduced in Fedorov [5], Cook and Nachtsheim [3], and Johnson and Nachtsheim [7].

In the construction of two-stage RSD's, we tried the two types of algorithms: both the row-wise exchanging and column-wise exchanging algorithms. In our cases, the  $N_1$ two-level points and  $N_0$  central points from the first stage are fixed, so an improved procedure is only processed to find the  $N_2$  points for the second stage. Here we prefer the column-wise algorithms over row-wise algorithms, for the following observations. Firstly, it is sometimes desirable to have the symmetric property, namely, the proportions of the three levels,  $\{-1, 0, +1\}$ , in the N runs are the same for all the k variables so that the parameters can be estimated with equal efficiencies. Such a symmetric condition can be easily integrated into the column-wise algorithms, but is difficult for the row-wise algorithms. Secondly, for a column to be improved, instead of exchanging it by another candidate column, the pair-wise exchanging strategy exchanges two different elements of this column repeatedly until the best improvement of the design criterion is achieved. The pair-wise exchanging strategy replaces the column to be exchanged by selecting a column from a subset of the candidate columns, and hence, significantly reduces the computational time. Moreover, in the pair-wise exchanging strategy, the symmetric condition mentioned above is naturally kept, provided that the condition is satisfied in the original design. For more details of pair-wise exchanging strategy, see Li and Wu [8]. Finally, we found that column-wise algorithms cooperated with a pair-wise exchanging strategy are much faster than row-wise algorithms in finding good RSD's. Usually, a row-wise algorithm requires twice or three times of computation time to obtain an equally good design as a column- wise algorithm does.

A column-wise algorithm is performed for 300 to 500 randomly selected initial designs, for each of which the criterion is improved iteratively. Let  $d = (d_1, ..., d_k)$  be a design to be improved, where  $d_j$  is the *j*-th column; and the criterion to be optimized (maximized) be *C*. Each iteration includes following steps:

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- (i) Arrange the columns in an order  $d_{(1)}, ..., d_{(k)}$  so that when  $d_{(j)}$  is deleted, the *C* value is the *j*-th largest for the subdesign involving remaining k-1 columns. Select the first *m* columns  $d_{(1)}, ..., d_{(m)}$  as the columns to be exchanged for  $1 \le m \le k$ .
- (ii) For  $d_{(1)}$ , using the pair-wise strategy iteratively on it so that C values are improved until no more improvement can be achieved.
- (iii) Repeat Step 2 for  $d_{(j)}$ , j = 2,...,m.

After all the initial designs are optimized, there are usually more than one designs have the largest C value, among which one can be selected as the design to be used according to other considerations.

In the procedure, when m=1 only one column is exchanged in each iteration, while when m=k all the columns are exchanged in each iteration. For the case m=1, the iterative process converges rapidly, but the chance of obtaining an optimal design is small. While for the case m=k, the iterative process converges too slowly for large k, but the chance of obtaining an optimal design is large. It is found that an intermediate m is a better choice to get a trade-off between the two extreme cases. Li and Wu [8] recommend to use m=5 in the construction of supersaturated designs where k is large (*e.g.*, larger than 20). In our experience, we recommend to use m=3 because k is usually less than 10 in the construction of RSD. Instead of maximizing C directly, equivalently, we maximize

$$\log C = w_I \log D_I + w_L \log D_L + w_B \log D_B + w_O \log D_O.$$

Since 
$$D_j = N^{-1} \{ |X'X| / |X'_jX_j| \}^{1/k_j}$$
 for  $j = I, L, B, Q$ , we have

$$\log C = -\log N + \sum_{j=I, L, B, Q} \frac{w_j}{k_j} \log |X'X| - \sum_{j=I, L, B, Q} \frac{w_j}{k_j} \log |X'_j|.$$

Thus we need not to compute  $D_j$  for j = I, L, B, Q directly, but only compute |X'X|and  $|X'_jX_j|$  for j = I, L, B, Q, consequently reducing the computation times by avoiding the computation of an inverse matrix in each  $D_j$ . Furthermore, the computation of |X'X|can be further simplified. Let  $X_x$  be the submatrix in the model matrix X, constituted by columns involving a factor with the linear column x, which is to be substituted by another linear column y, and let  $X_-$  be the complimentary submatrix of  $X_x$  in the original X. Note that  $X_x$  consists of k+1 columns, which are the linear column x, the square column of x, and the k-1 bilinear columns involving x. Then

$$|X'X| = |X_{-}'X_{-}| |X_{x}'X_{x} - X_{x}'X_{-}(X_{-}'X_{-})^{-1}X_{-}X_{x}|.$$

When column x is substituted by column z, the first factor,  $|X_{-}'X_{-}|$ , in the above expression for the updated |X'X| is kept unchanged, only the second factor is updated by  $|X_{z}'X_{z} - X_{z}'X_{-}(X_{-}'X_{-})^{-1}X_{-}X_{z}|$ , where  $X_{z}$  is the submatrix in the updated X, constituted by columns involving the linear column z. Hence, when a column x is updated by a column z, we need not recompute the updated |X'X|, but only  $|X_{z}'X_{z} - X_{z}'X_{-}(X_{-}'X_{-})^{-1}X_{-}X_{z}|$ , which is the determinant of a square matrix of order (k+1). Moreover, since, for each column to be exchanged in a column exchange procedure, there may be many pairs to be exchanged, the saving of computation time is significant. The computations of  $|X_{i}'X_{i}|$  for j = I, L, B, Q can be simplified in the same way.

#### 4. Comparisons

Morris [9] compared four kinds of response surface designs: central composited design (CC designs, Box and Wilson [1]); small composite designs (SC designs, Draper and Lin, [4]); augmented pairs designs (AP designs); and Box and Behnken designs (BB designs). The criteria he used are the generalized standard deviation, GLD, and the generalized standard deviations for the three groups of parameters:  $GLD_L$  for group L;  $GLD_B$  for group B; and  $GLD_Q$  for group Q. These criteria are the inverse of square root of  $D, D_L$ ,  $D_B$ , and  $D_Q$ , respectively. The overall conclusion in Morris [9] is that CC design is the best, judged by  $GLD, GLD_L$  and  $GLD_B$ ; while judged by  $GLD_Q$ , AP and BB designs are equally best.

Note that among these four types of designs, the run sizes in the first stages are different. It is generally recognized that design with more runs is likely to have a higher efficiency. A design with higher resolution is likely to have higher estimation efficiencies for the linear and cross-product terms in Model (2). Hence it is not surprising that CC designs are always the best under the criteria of  $GLD_L$  and  $GLD_B$ , simply because they include a resolution  $V 2_V^{k-m}$  fractional factorial or even a  $2^k$  full factorial in the first stage.

In this work we compare two-stage response surface designs constructed based on D and C criteria respectively with three designs: HC designs (Hartley [6]), SC designs, and AP designs. These design are also known as "systematically constructed designs," and they have the same two-level points, a single central point in the first stage, and the same total run number for the second stage. The number of central point replicates certainly influence the estimation efficiency of a design. We include a single central point in each design to keep the design as small as possible. Since different types of systematically constructed designs have different run sizes for a given k, the comparisons are separated for these three types of systematically constructed designs.

Minimal response surface designs (designs with the run size N = p) can be used under model (1), but cannot be used under model (2), which has p+1 parameters. Thus our comparisons are generally based on model (2) if the designs are not minimal, but based on model (1) only if the designs are minimal.

In the comparisons, the weights  $w_I, w_L, w_B$ , and  $w_Q$  in *C* were selected differently for different situations as proposed at the end of Section 2. The comparisons are presented in Table 1, in which the *D*,  $D_L$ ,  $D_B$ , and  $D_Q$  values are compared. From Table 1, the following conclusions can be made.

- (i) In all the cases, *C*-optimal designs have *D*-efficiencies almost as high as *D*-optimal designs, while the three types of systematically constructed designs always have low *D*-efficiencies.
- (ii) *D*-optimal designs always have the highest  $D_L$  and  $D_B$ -efficiencies. *C*-optimal designs have  $D_L$  and  $D_B$ -efficiencies almost as high as *D*-optimal designs, while the three types of systematically constructed designs always have low  $D_L$  and  $D_B$ -efficiencies.
- (iii) *D*-optimal designs have the lowest  $D_Q$ -efficiencies. In contrast, the three types of systematically constructed designs and *C*-optimal designs usually have higher  $D_Q$ -efficiencies.
- (iv) The *C* criterion has a character of spreading estimation efficiencies as evenly as possible. This is more evidently for larger  $N_2$ .

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Table 1. Design comparison on various D -efficiencies.

| k  | Design           | $N_1$ | N      | First stage Design              | W   | D    | D.    | $D_{\rm p}$ | $D_{a}$ |
|----|------------------|-------|--------|---------------------------------|---|------|-------|-------------|---------|
|    | HC SC AP         | - • 1 |        | 1 not otage 2 oorga             |   | 268  | 182   | 121         | 193     |
| 3  | Continal         | 1     | 11     | $2^{3-1}$                       | (0 1 1 1)                                       | .200 | .102  | .121        | .195    |
|    | D optimal        | 4     | 11     |                                 | $(0, -\frac{1}{4}, -\frac{1}{4}, -\frac{1}{2})$ | .572 | .400  | .433        | .115    |
|    |                  |       |        |                                 |   | .365 | .001  | .550        | .091    |
| 4  | Continual        | 8     | 17     | $2^{4-1}_{III^*}$               | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .272 | .1/0  | .211        | .130    |
|    | C-optimal        |       |        |                                 |   | .393 | .585  | .575        | .078    |
|    |                  |       |        |                                 |   | .393 | .585  | .575        | .078    |
|    | AP<br>Continual  | 8     | 37     | $2^{4-1}_{IV}$                  | $(0, 0, \frac{1}{3}, \frac{2}{3})$              | .300 | .541  | .242        | .209    |
|    | C-optimal        |       |        |                                 |   | .435 | ./19  | .540        | .185    |
|    | D-optimal        |       |        |                                 |   | .433 | .827  | ./18        | .128    |
|    | HC<br>Constinue1 | 16    | 27     | $2_{V}^{5-1}$                   | (0, 0, 0, 1)                                    | .387 | .667  | .593        | .088    |
|    | C-optimal        |       | 27     |                                 |   | .427 | . 769 | .664        | .085    |
|    | D-optimal        |       |        |                                 |   | .439 | .735  | .674        | .082    |
| -  | SC               | 11    | ~~     |                                 | 1 1 1   | .218 | .091  | .163        | .107    |
| 5  | C-optimal        | 11    | 22     | 12-run PB                       | $(0,\frac{1}{4},\frac{1}{4},\frac{1}{2})$       | .402 | .559  | .543        | .083    |
|    | D-optimal        |       |        |                                 |   | .412 | .677  | .655        | .060    |
|    | AP               |       |        | <b>o</b> 5-2                    | 1 2   | .307 | .503  | .262        | .209    |
|    | C-optimal        | 8     | 37     | $2_{IV}^{3/2}$                  | $(0, 0, \frac{1}{3}, \frac{2}{3})$              | .444 | .736  | .549        | .169    |
|    | D-optimal        |       |        |                                 | 00  | .470 | .810  | .696        | .120    |
|    | HC,SC            |       |        | <b>2</b> 6-2                    | 1 1 1   | .240 | .069  | .229        | .082    |
|    | C-optimal        | 16    | 29     | $2^{\circ}_{III^*}$             | $(0,\frac{1}{4},\frac{1}{4},\frac{1}{2})$       | .398 | .441  | .509        | .074    |
| 6  | D-optimal        |       |        |                                 | <i>L</i>  | .400 | .451  | .527        | .059    |
| Ũ  | AP               |       |        | 2 <sup>6-3</sup> <sub>III</sub> | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .279 | .479  | .201        | .209    |
|    | C-optimal        | 8     | 37     |                                 |   | .422 | .649  | .481        | .154    |
|    | D-optimal        |       |        |                                 |   | .456 | .716  | .657        | .081    |
|    | SC               |       | 37     | - 6 2                           | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .183 | .054  | .155        | .064    |
| 7  | C-optimal        | 22    |        | $2^{6-2}_{III^*}$               |   | .354 | .410  | .431        | .049    |
|    | D-optimal        |       |        |                                 | 442   | .370 | .409  | .476        | .038    |
| ,  | AP               |       |        | 4.3                             |   | .254 | .494  | .201        | .209    |
|    | C-optimal        | 8     | 37     | $2^{6-3}_{III}$                 | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .324 | .385  | .322        | .095    |
|    | D-optimal        |       |        |                                 | 442   | .385 | .392  | .467        | .058    |
|    | SC               |       |        |                                 | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .192 | .053  | .185        | .050    |
|    | C-optimal        | 30    | 47     | 36-run PB                       |   | .338 | .295  | .395        | .046    |
| 8  | D-optimal        |       |        |                                 | 4 4 2   | .357 | .363  | .441        | .035    |
| 0  | AP               |       |        |                                 |   | .239 | .526  | .190        | .224    |
|    | C-optimal        | 16    | 137    | $2^{8-4}_{IV}$                  | $(0, 0, \frac{1}{2}, \frac{2}{2})$              | .438 | .668  | .490        | .191    |
|    | D-optimal        |       |        |                                 | 3 3   | .531 | .849  | .761        | .100    |
| 9  | SC               |       |        |                                 |   | .188 | .035  | .189        | .041    |
|    | C-optimal        | 38    | 57     | 40-run PB                       | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .342 | .273  | .403        | .037    |
|    | D-optimal        |       |        |                                 |   | .347 | .223  | .426        | .022    |
|    | AP               |       | 137    | 2 <sup>8-5</sup> <sub>III</sub> | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .239 | .526  | .190        | .224    |
|    | C-optimal        | 16    |        |                                 |   | .440 | .696  | .485        | .189    |
|    | D-optimal        |       |        |                                 |   | .546 | .861  | .793        | .078    |
| 10 | SC               |       |        |                                 | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | .165 | .030  | .161        | .035    |
|    | C-optimal        | 46    | 67     | 48-run PB                       |   | .327 | .232  | .387        | .024    |
|    | D-optimal        |       |        |                                 |   | .346 | .209  | .414        | .023    |
|    | AP               | AP    |        |                                 |   | .240 | .511  | .202        | .223    |
|    | C-optimal        | 16    | 16 137 | $2^{10-6}$                      | $(0, \frac{1}{4}, \frac{1}{4}, \frac{1}{2})$    | 442  | 698   | 484         | 179     |
|    | D optimal        | 10 10 | 107    | <b>-</b> <i>I</i> II            |   | 552  | .070  | 770         | 072     |
|    | $\nu$ -optimal   |       |        |                                 | ·   | .555 | .032  | .//ð        | .0/3    |

From the comparison results, we can conclude that using of *C*-efficiency criterion in the construction of two-stage RSD's offers a good balance between the global estimation efficiency and the even distribution of estimation efficiencies among groups of parameters. The proposed method for the construction of two-stage RSD's offers a convenience for experiment planners on how to design  $N_2$  points for the second stage, given the design points in the first stage. Two criteria – D and C, can be used in selecting these design points in the second stage. As pointed out by one referee, the design efficiencies for quadratic coefficients  $(D_Q's)$  are rather low. This is due to the fact that the quadratic terms are typically confounded with the intercept for most second-order response surface designs.

Consider the penicillin example introduced at the beginning. In this case k = 4,  $N_1 = 8$  and  $N_0 = 4$ . The second order model (2) has p+1=16 parameters – one constant term, four linear terms, six cross-product terms, four pure quadratic terms, and one blocking term. Since the four central point replicates offers only one degree of freedom, for Model (2), we will need the minimal of  $N_2 = 16 - 8 - 1 = 7$  points. Using the *D* and *C* criterion, we constructed designs with  $N_2 = 8$ , 16 and 24, respectively. For the *C* criterion, we use weights  $w_I = w_L = 0$ ,  $w_b = 1/3$  and  $w_q = 2/3$ , since the first stage includes a  $2_{IV}^{4-1}$  fractional factorial in which the group of linear parameters can be estimated with enough high accuracy. The efficiency qualities of these designs are compared in Table 2, and the *C*-optimal designs with  $N_2 = 8$ , which were recommended to the pharmaceutical engineer, are presented in Tables 3. From Table 2, we can see that the  $D_Q$  efficiency increases with  $N_2$  for both types of designs, but *C*-optimal designs have higher  $D_Q$  values than *D*-optimal designs by about 10% to 25%.

| $N_2$ | Design    | D    | $D_{_L}$ | $D_{R}$ | $D_Q$ | $r_{Q}^{**}$ |  |
|-------|-----------|------|----------|---------|-------|--------------|--|
| 8     | C-optimal | .351 | .538     | .420    | .087  | 1 10         |  |
|       | D-optimal | .372 | .544     | .499    | .079  | 1.10         |  |
| 16    | C-optimal | .432 | .689     | .565    | .154  | 1.26         |  |
|       | D-optimal | .446 | .789     | .667    | .122  | 1.20         |  |
| 24    | C-optimal | .445 | .739     | .595    | .170  | 1.24         |  |
|       | D-optimal | .452 | .802     | .672    | .136  |              |  |

Table 2. Comparison C- and D-optimal RSD's.

\*: The first stage is  $2_{IV}^{4-1}$ , k = 4, w = (0, 0, 1/3, 2/3).

\*\*: The ratio of  $D_Q$ :  $D_Q$  for C- optimal and  $D_Q$  for D-optimal.

Table 3. The second stage of *C*- and *D*-optimal RSD'S for the penicillin experiment whose first stage design is a  $2_{IV}^{4-1}$  fractional factorial with four center points.

| D-optimal |    |     |     | C-optimal |     |     |     |
|-----------|----|-----|-----|-----------|-----|-----|-----|
| 1         | 1  | 1   | 1   | 1         | 1   | 1   | 1   |
| 1         | 1  | - 1 | 1   | - 1       | 0   | - 1 | - 1 |
| - 1       | -1 | - 1 | 1   | 1         | -1  | 0   | 1   |
| -1        | 1  | - 1 | - 1 | - 1       | 0   | 1   | 0   |
| 0         | -1 | 1   | - 1 | 0         | 0   | 1   | - 1 |
| - 1       | 0  | 1   | - 1 | 0         | 1   | - 1 | 0   |
| 1         | 1  | 0   | 1   | 0         | -1  | 0   | 1   |
| - 1       | -1 | 1   | 0   | - 1       | - 1 | 0   | 0   |

### 5. Concluding Remarks

Two-stage response surface design is very common and very useful. In this paper, we consider the case where the experimental region is a k-dimensional cubic standardized to  $[-1, 1]^k$ , the first stage experiment consisted of two-level points and central point replicates, and the second stage experiment consisted of three-level points. The second order models (1) and (2) are used. The problem we studied is how to select the second-stage points given the first-stage design points.

A new criterion C for such a two-stage setting is proposed. Its log function is a weighted sum of log functions of  $D_s$ -efficiencies for subsets of parameters. The weights can be selected to emphasize the importance of subsets of parameters. The criterion C has an advantage over the well known criterion D in this case that the estimation accuracy can be evenly spread among the parameters.

A column-wise exchanging algorithm with pair-wise exchanging strategy is also proposed and described in details. This algorithm is generally faster than row-wise exchanging algorithms, and has the advantage that the symmetric condition can be naturally kept in the computation process.

Comparisons of *C*-optimal RSD's with those able to be conducted in two stages under a fair base (in term of identical number of runs, *etc*) are presented. The comparisons show that *C*-optimal RSD's are better than other RSD's for the criterions D,  $D_L$ ,  $D_B$  and  $D_Q$ .

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