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Multicriteria steepest ascent

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Abstract

A simple multiresponse steepest ascent procedure has been developed by combining the standard steepest ascent method with multicriteria decision making. The steepest ascent method is one of the older methods in response surface methodology. It can be applied in optimization where the operability region is so large that a very complex function would be needed to fit an empirical function. With steepest ascent, local designs and local models in a part of the operability region are used to find a direction where the response is improved most. Experiments performed along a line in that direction will reveal the region of interest. There the response may be fitted with a second degree equation. The problem of multiresponse steepest ascent is that directions of improvement have to be combined into one direction. In general, the directions of improvement indicated by the individual responses are different and they may even be opposite. In this paper, steepest ascent has been adapted to the use of more responses by combination of the directions of steepest ascent to a simultaneous direction of interest. The combination is made by consideration of the obtainable improvements of the responses in the response space. These improvements can be calculated from the centre point (of the local design) response values and the response values at a fixed distance of the centre point. As an example, the method has been applied to a tablet optimization. This optimization problem had two responses and two independent variables.

1. Introduction

When there are several responses which have to be optimized, there are several problems that a researcher may encounter. These problems are

selection of the region of interest and determination of a suitable combination of responses. In this paper, some of the problems related to the multiresponse situation are discussed, and an attempt is made to solve these problems with the aid of steepest ascent. The general strategy for the multiresponse problem is then applied to a problem in pharmaceutical technology. The mod-

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ifications to use several responses involves a pareto optimality [1] related decision strategy for finding the direction of interest.

1.1. Multiresponse problems

The problem of multiresponse optimization has often been examined and can be found in many publications (see, e.g., refs. [1–7]). In short, the problem is that the various responses may attain their optimum values at different settings of the independent variables. Therefore, it is necessary that some sort of weighing is made to obtain an overall criterion of quality. This weighing can be based on the optimization goal or on the obtainable responses. With the first method, first the goals and the relative importance of the responses are determined. This ranking is incorporated in a function which combines the responses into an overall criterion. With the second method, first the obtainable response values are examined. Based on these response values, it is decided which deviation from the optimization goal is acceptable. Various techniques for this step are given in ref. [1].

The design aspects of the multiresponse problem concern the selection of a region of interest for all responses and the construction of a design suitable to model all responses. This latter part is a minor problem when the responses (and thus models) are sufficiently smooth. In general, factorial and central composite designs are feasible for several responses. Thus, there is no fundamental problem in using the same design points when there are several responses.

The problem of the selection of the region of interest requires a different approach. The scope of the problem can be seen in Fig. 1. There are two responses dependent on one independent variable. The first response reaches its optimum value at $x = 4$, the second at $x = 11$. There is no region where both are optimal. So, if a design should be constructed for these responses it should either contain many x settings so that both response surfaces can be estimated over the complete design space, or a part of the region should be used. Estimation of models for the whole design space requires a larger design, since

Fig. 1. Two responses with different regions of interest.

the responses must be modelled with more complex models. For most practical problems, this larger design is too large to be of interest. When only a part of the design space is used, then the problem is which part should be selected.

When there is only one response, there are other ways (steepest ascent methods) to search for the region of interest. For instance, when in Fig. 1 y_1 must be optimized, and observations are made at $x = 1$ and $x = 2$, then it is clear that additional observation at $x = 3$ can yield a better response. This way, for a certain penalty (less knowledge of the response surface), it is possible to optimize a system with a smaller number of design points.

2. Steepest ascent

The steepest ascent method [8–11] is especially suitable for problems where the region of interest is not known a priori. The standard method for the steepest ascent as used with one response is shown in Box et al. [8]. It can be extended to any number of independent variables and one response. The procedure is as follows.

A small (fractional) factorial design is used to evaluate the effect of the independent variables. It is assumed that the variables do not have any quadratic effects. This can be checked with an additional (replicated) centre point (Fig. 2). The analysis of the data consists of two parts. The first part is the estimation of the effects, the second part is a check whether quadratic and interaction

Fig. 2. Variable design for steepest ascent.

effects are present. Usually at the start of an optimization, the response surface can be approximated with linear effects. With two independent variables this means that the response can be depicted as a plane above the design space (Fig. 3). With more independent variables a similar construction exists but it cannot be visualized. The response can be increased most efficiently by a change in the independent variables in the

Fig. 3. Planar response surface.

Fig. 4. First local design (left) line of steepest ascent and second local design (right). The second local design is larger for detection of curvature.

direction of the steepest ascent. In order to check the increase of the response, additional design points are situated in the direction of the steepest ascent (Fig. 4) and measurements are made. Additional design points are situated further from the design. This is continued until these points do not result in an actual improvement of the response. At this stage, a new design is constructed around the best point found. This design is usually chosen somewhat larger than the first design. This is because the first order effects are expected to be smaller and thus must be detected with higher precision and to detect the second order effects which are expected. The second design yields the same kind of information as the first design. If there are no second order effects then a new path of steepest ascent is followed. If there are quadratic effects, the response probably reaches its optimum value near or in the covered design space. This latter means that new design points must be added to allow for estimation of the quadratic effects. Based on the newest design (which combines the last standard design with, e.g., axial points) local models can be constructed, and an optimum can be found.

3. Multiresponse modifications of steepest ascent

3.1. Introduction

In many optimizations there are several responses. For instance, in tablet optimization these could be tablet crushing strength, friability and

disintegration time. Each of these responses has its own direction of steepest ascent. These can be the same direction, as may be expected for crushing strength and friability, but they may also be in opposing directions (e.g., disintegration time and crushing strength). Clearly, these directions have to be combined in a smart way for the selection of the direction of greatest interest.

The method by which the directions are combined is called multicriteria steepest ascent (MC-SA) and is based on the multicriteria decision making/pareto optimal (MCDM/PO) method [1–3]. Other implementations of the multicriteria direction search method, based on methods of response weighing are also possible but will not be pursued in this paper.

A secondary problem which occurs when several responses are improved by steepest ascent is the problem of quadratic effects and second order interactions. With the 'one response' steepest ascent these are clear indicators that a (local or global) optimum value exists in a certain region. With multiresponse steepest ascent the presence of such effects for a response indicates that for that response a (local or global) optimum is in the experimental region. However, this is not sufficient proof that an acceptable combination of the response values can be obtained in the current region. It is even conceivable that the 'optimal' combination of response values can only be obtained in a region where all responses show linear effects of the responses.

In the following sections first the PO method is explained. Then the modifications for using MCSA with only linear dependent responses are given. To illustrate this method a small example is given. Then adaptations of the MCSA method for the presence of curvature are given.

3.2. Multicriteria decision making

The pareto optimal technique is a practical tool for finding a best combination of response values; it can be used whenever models exist which predict the response values in the design space. Then, with a grid over the independent variables, the design space can be scanned and response values can be predicted. This results in

Fig. 5. Responses as (y_1, y_2) doublets. The circles are inferior points, the dots are PO points.

a set of possible combinations of response values. All these combinations of responses are then compared with each other. All points which are worse in all response values than other points are obviously discarded. Points which are better in some response values but worse in other are pareto optimal with respect to each other. This means that they cannot be proven to be inferior. In Fig. 5 an example of a set of response values is shown with two responses. This means that each setting of the independent variables results in a doublet (y_1, y_2) . The points indicated with an open circle are non-PO points. These points are all inferior with respect to both responses to at least one of the PO points (indicated with a dot). The PO points are retained because they are the best points. Excluding the situation where one setting yields the best values for all responses, there are several PO points. With suitable graphical methods [1] from the set of PO points a preferred point can be chosen.

3.3. Multicriteria steepest ascent with linear dependent responses

A simple adaptation of the PO method to translate settings of the independent variables within the region of interest into outward directions is not difficult. When the predicted responses along a circle or hyper-sphere around the centre of the design are used to generate PO points instead of points throughout the experi-

mental region then each of the points can directly be coupled to a direction. The direction of interest can be calculated from the (PO) point with the preferred settings, by calculating the vector from the middle of the design to the coordinates of the PO point.

The common plots for the use of PO can easily be adapted to the use of MCSA. The MCDM plot, which shows feasible responses as (y_1, y_2) pairs can be enhanced with a point representing the centre, thereby indicating both obtainable values and change in the responses. It is also possible to show the change when moving further away by showing both the PO points near to the centre (e.g., at one unit distance) and further from the centre (e.g., at two or three units distance). The points with the same direction are then joined.

3.4. Example with two linear responses

An example will show the direction search method more clearly. Suppose a local design in two independent variables is made around the origin. A duplicated centre point and four measurements according to a factorial design (levels -1 and 1), resulted in two response surfaces described by the following formulas:

$$y_1 = 12 - 3x_1 + 5x_2$$

$$y_2 = 4 + x_1 - 8x_2 \quad (1)$$

Both responses have to be maximized. Around the point $x_1 = 0, x_2 = 0$ increase or decrease of the responses is dependent on the change of the independent variables, x_1 and x_2 . This change can be represented by examining the responses on a circle with radius $\sqrt{2}$ around $x_1 = 0, x_2 = 0$ (Fig. 6). This radius is chosen because the design points $((-1, -1), (-1, 1), (1, -1), (1, 1))$ are on this circle. The $(y_1$ and $y_2)$ response values estimated at these settings are given in Fig. 7. Since the responses values are all estimated at the same distance (in the independent variable space) from the centre, they give information about the changes of response values associated with a change in the settings of the independent values. Otherwise stated, the difference between the cen-

Fig. 6. Settings (x_1, x_2) doublets used to predict response values.

tre point response values and the predicted response values is proportional to the slopes (y_1, y_2) values which are predicted when the x settings are changed in the respective direction. This figure is therefore essential to determine what change in response values is preferred.

Only a part of the response values (y_1, y_2) are of interest since both responses have to be maximized. The interesting points are the PO points. These are given by the dots. The other points are not of interest because for each of these points there is at least one point with higher predicted values for both responses. In Fig. 7 the response value at the centre of the circle is given as a star. This point can be used to examine how the response values change. The changes of response values are caused by changes in settings, as given

Fig. 7. PO points in the first example. (○) Non-PO points; (●) PO points; (*) response at the centre point.

Fig. 8. PO points at $\sqrt{2}$ (+) and 4 (4) units distance from the centre.

in Fig. 6. When in this figure a line is drawn from the centre point and past the point linked to the preferred settings, then this line depicts the direction of the greatest interest.

In Fig. 8 an enhancement of Fig. 7 is given. Here not only PO points at $\sqrt{2}$ units distance are given (the plus marks) but also PO points at four units distance (the 4s). The points with the same direction are joined by lines. The lines begin at the point representing the centre of the design space. Of course the PO points at four units distance are the result of severe extrapolation. This means that these points must be interpreted as an indication rather than as prediction.

The problem is the choice of the PO point/direction. The figures clearly depict the consequences which are expected to be found from the feasible choices. It is possible to increase either response quickly, but the consequence is that the other response is decreased. It is also possible to increase both responses, but then the improvement of the responses is relatively slow. A lot depends on the acceptable response values. If one of the responses is well within its acceptable region then the preferred direction could be the direction which combines a constant value of this response with an increase of the other variable.

The next step in the MCSA method is measurement of additional observations in the selected direction. The first of these could be twice as far from the origin as the original design points (say two or three units in the scale used). De-

pending on the obtained results, additional observations can be taken. At a certain point the new observations will offer no improvement. This of course is dependent on the judgement of the researcher since several responses are used. Here, a new design can be used to provide information about the local response surfaces. In this stage several possibilities exist. Responses may not be approximated well by a planar surface, or the objectives of the study may be attained.

3.5. Direction search with curved response surfaces

When, in steepest ascent, the model shows curvature then it is assumed that the optimum value can be found within the region of interest. Therefore, the design is extended to allow estimation of the curvature (interactions and quadratic effects). With the extended design new models are constructed and the optimum settings and response values are calculated.

With several responses a number of situations can exist. As a guideline, the three distinct situations which are possible when there are two responses will be discussed. These situations are: (i) both response surfaces have curvature, (ii) one response surface has curvature and one has not and (iii) both response surfaces are planar. This latter case is already discussed in the previous section. In the other two situations the first step is to extend the design with extra observations for the estimation of the curvature.

When both responses show curvature then it is expected that the (local) optima of both responses can be found in or near the experimental region. Therefore, the combined optimum should also be in or near the experimental region. The standard MCDM/PO method can be used for finding an optimum combination of response values. The difficult situation therefore is a combination of linear and curved responses.

When there are both planar and curved response surfaces then either a direction of interest must be found or a combination of responses within the current experimental region may be accepted. The presence of an acceptable combination of responses can be examined with pareto optimality. When there is no acceptable combina-

Fig. 9. Obtainable responses at one and two units distance.

tion then a direction of interest must be found on a curved response surface. This leads to a more complicated direction search. Consideration of steepest ascent with one curved response clearly shows that the direction of steepest ascent depends on the distance and on the starting point. More formally stated, the direction which results in the largest increase when one unit is travelled is different from the direction which results in the largest increase when several units are travelled. Furthermore, when another centre is used, then the direction of interest will change. With planar response surfaces this is not the case. A logical step therefore is the examination of the change of

Fig. 10. PO points at 1–4 units distance. Points are joined when in the same direction.

Fig. 11. Independent variable settings resulting in the PO points.

response at different distances from the centre point. In the MCSA method, *mutatis mutandis*, the best trade-off between the response values gradually changes at different distances from the centre. It is also possible, for instance if there are ridges in the response surface, that the direction of the greatest interest changes noteworthy if predictions further from the centre are examined. An example (shown below) will show this easily (see Figs. 9–11).

The consequence of usage of different distances from the origin is that there is an increasing amount of extrapolation. Consequently, care should be taken not to trust too much on the furthest points.

A good method to depict the changes in the responses with respect to different directions and distances was already shown in Fig. 8. However, the situation is now more complicated since not all lines start at the centre point and not all lines end at the largest distance. This means that travel in a certain direction can be PO if a certain distance is traversed, but not with another distance. A consequence is in the calculation of the PO directions. In the planar case the directions could be calculated once, after which the PO directions are valid at any distance. With the presence of curved response surfaces the PO directions must be calculated at several distances. The following example shows this more clearly.

3.6. Example with a curved response surface and two responses

Suppose two responses are optimized (maximized in this case) and they can be described by the formulas:

$$\begin{aligned} y_1 &= 12 - 3x_1 + 5x_2 \\ y_2 &= 3 + x_1 - 2.5x_2 - 0.1x_1x_2 + 0.7x_2^2 \end{aligned} \quad (2)$$

At a distance of one and two units, respectively, the responses are predicted (Fig. 9). When the response at the centre point (the '0' at $y_1 = 12$, $y_2 = 3$) is compared with the other responses, then it is clear that at two units distance the responses are more extreme than at one unit. It is also clear that the PO points can be divided into several sets. The first set is at the northwest of the graph. Here, y_2 increases and y_1 decreases. In the northeast direction there are points which show a small increase for both responses. Another set of PO points can be found in the southeast corner of the graph. Here, y_1 increases, but consequently y_2 decreases.

The PO points and their settings at distance 1, 2, 3 and 4 are set in the corresponding Figs. 10 and 11. In these figures the observations which have the same direction are joined with a line. The distance of the points from the origin (in terms of coded x variables) is given by the symbol used. In Fig. 10 the dot is the origin, with responses: ($y_1 = 12$, $y_2 = 3$). By following the lines indicating the new response values at increasing distances, a suitable choice of direction can be made. In this case the direction of the greatest interest could be the direction where y_1 and y_2 are both increased at the same time, but then only small improvements of both responses are possible. An alternative are the directions in the southeast corner (Fig. 10). Here after a small distance y_2 is decreased while y_1 is increased but at a larger distance this changes in an increase in both y_1 and y_2 .

In Fig. 11, it can be seen that not all directions are acceptable at all distances. Especially in the directions where x_1 is changed most (consequently x_2 is hardly changed) only limited gain is

expected. In the northeast direction, e.g., the directions are only PO at three or less than three units distance. This means that when one of these directions is selected then after three units an inferior combination of responses is expected.

3.7. Direction selection with three or more responses

When there are three or more responses then an MCDM plot (y_1 vs. y_2) cannot be used. It is most easy to use a stacked MCDM plot [1,12] to examine this situation, but it is also possible to use biplots [1]. A stacked MCDM plot (Fig. 12) essentially is a stack of plots of the PO points. The PO points are all given an index number, that belongs to settings of the independent variables. For each response a plot can be made of the index number (horizontal axis) against the response value (vertical axis). In a stack of these plots every PO point has a unique horizontal position, given by the index number. The response values are given by the positions on the vertical axis.

The stacked MCDM plot can be adapted for the use of PO directions. The enhancements consist of two parts. The first part is the presentation of the responses at the centre point. Horizontal lines at the respective centre point response levels are sufficient. The second part is the presentation of the effect of curved response surfaces. The most simple method is (again) the use of different symbols for the PO directions at the different distances.

It is clear that these plots contain a lot of information and can be very confusing. The plot in the following example (Fig. 13) is not the most clear of the feasible plots. With the aid of color (on a computer screen) the structure of the responses can be shown more easily. By choosing the order of the index variable as sorted by one of the responses it is possible to obtain a clear picture. Several stacked plots with PO directions sorted by different responses can be used to improve insight in the data structure.

The feasibility of biplots to depict the PO directions is currently under investigation.

Fig. 12. Stacked PO-responses plot.

Fig. 13. Stacked MSA plot, three variables. 1–4: responses at distance 1–4. Horizontal lines are levels at centre point.

3.8. Example plot with three responses

In this example three responses have to be maximized. Two of these follow linear models and one has a quadratic model. The models are used for the construction of a stacked MCSA plot. The three models are:

$$\begin{aligned} y_1 &= 12 - 3x_1 + 5x_2 \\ y_2 &= 4 + x_1 - 8x_2 \\ y_3 &= 3 + x_1 - 2.5x_2 - 0.1x_1^2 + 0.7x_2^2 \end{aligned} \quad (3)$$

To select a direction of greatest interest, the PO points on circles with diameter 1 to 4 are calculated from sets of 40 points. These points

can better be described as points with polar coordinates (angle, distance) divided into four groups (distance 1, 2, 3 and 4) with in each group 40 points with evenly spread angles. In Fig. 13 these points are given. The horizontal axis is the angle indicating the place on the circle; this represents the direction in which one proceeds. The horizontal lines in the plots indicate the response levels at the centre.

Since the end of the horizontal axis is the same as the beginning of the horizontal axis (the circle restarts after 360°), it is clear that there is one arc which has acceptable responses. One of the more interesting directions is the direction with $\theta \approx 240^\circ$. With this direction all responses are in-

Fig. 14. Flow sheet for multi-response steepest ascent.

creased. Somewhat less interesting directions are those on the end of the arc. The direction with $\theta \approx 60^\circ$ is only acceptable if three or more units are travelled. Similar, at direction $\theta \approx 160^\circ$ after one unit of travel sub-optimal responses are expected.

3.9. Description of the total method

The total method consists of the parts which are now described. A flow sheet (Fig. 14) is used to summarize the following steps.

- The first stage is selection of the region of interest.

- A fractional factorial design with additional centre point is constructed for the total number of variables.

- Observations are made according to the design.

- The observed values are modelled. In the first phase it is expected that planar models are sufficient.

- To examine the effects of the variables, settings are generated on circles or spheres around the centre of the design space. These circles determine points at one to four units (in the independent variable space) from the centre.

- Predictions on the generated settings according to the selected models are made.

- The MCDM/PO method is used to select the settings with pareto optimal predictions.

- A graphical display is used to select the best of the PO points. This point is connected to a direction (from origin to settings) in the independent variable space.

- One point on the line near to the centre is selected and a measurement is made. If this observation is satisfactory a setting further away is selected and observations are made.

- New observations further along the line are added until it is felt that the last observations indicate that further continuation along the line is not necessary. This may be because a suitable combination of observations is found or because observed values are too far out of the preferred range.

- Around one of the settings used a new design will be made.

- As with the first region of interest, a design is constructed and the data are modelled.

- If a planar response surface is sufficient and the combinations of responses are not acceptable, then a new line of greatest interest is constructed and followed. The action points after this point are not used but the above mentioned points are repeated.

- If there are non-linear effects of the independent variables then extra settings are generated. Measurements are made on the new settings and models are constructed.

- A grid is constructed in the independent variables design space and predictions are made at the settings of the grid with the selected models.

- If the combinations of responses are not acceptable then the feasibility of a new line of greatest interest is examined. The action points after this point are not used but the above mentioned points are repeated.

- MCDM is used to select the preferred combination of responses.

- The preferred setting is checked with a new observation.

- If the observed values deviate too much from the calculated value then the final parts of the procedure are checked and whether necessary new observations are made.

4. Example

4.1. Introduction

In order to demonstrate the strategy a problem is chosen from pharmaceutical technology. In this example, tablets are prepared with varying amounts of filler binders. There are three filler binders, microcrystalline cellulose, α -lactose monohydrate and anhydrous β -lactose. The composition of mixtures of three components can be described as fractions. In this example, however, it is more practical to convert these fractions to two mathematically independent variables, w_1 and w_2 . This is described in a separate section. The tablets have two properties which are of interest, these are crushing strength and disintegration

time. The crushing strength has to be maximized, the disintegration time has to be minimized.

4.2. Materials

The filler binders used were α -lactose monohydrate 100 mesh and anhydrous β -lactose (Pharmatose^R DCL 21), both supplied by DMV, NL-Veghel and microcrystalline cellulose (Avicel^RPH 102) from FMC Europe S.A., B-Brussels. The tablets were lubricated with magnesium stearate Pharm. Eur. grade from OPG, NL-Utrecht.

4.3. Tablet preparation

The filler binders were mixed for 15 min in a Turbula^R mixer (model 2P, W.A. Bachofen, CH-Basle) at a rotation speed of 90 rpm. After addition of 0.5% magnesium stearate the mixing was continued for 5 min. Tablets with a weight of 250 mg and a diameter of 9 mm were prepared on a hydraulic press (ESH Testing, Ltd., UK-Brierley Hill) at a compaction force of 10 kN and a compaction speed of 2 kN/s.

4.4. Tablet properties

The crushing strength was determined between 15 and 120 min after compaction with a Schleuninger 4M tester (Dr. Schleuninger Production AG, CH-Solothurn). The presented data are the means of ten determinations.

Disintegration time was determined between 15 and 120 min. after compaction using the Pharm. Eur. apparatus with water ($37^\circ \pm 1^\circ\text{C}$) as a test fluid. The tests were performed without

disks. The presented data are the means of six tablets.

4.5. Coordinates

Since the original variables are mixture variables, it is most convenient to convert them to mathematically independent variables (w_1 and w_2). A suitable conversion method can be found in Cornell [13]. This conversion is excellent since there are no distortions. Points with equal distance in the mixture space have also equal distance in the independent variable space. The conversion method yields (0,0) at the mixture composition (1/3,1/3,1/3). The mixture compositions (1,0,0), (0,1,0) and (0,0,1) result in (w_1, w_2) coordinates of respectively (1.6330, 0), (−0.8165, 1.4142), (−0.8165, −1.4142).

4.6. First design

It was decided that the first design would be a factorial design with duplicated centre point around (0,0) with levels ± 0.15 . The response values and compositions according to this design can be found in Table 1. A first examination of the data shows that the crushing strength values are very well, but the disintegration time is much too high. Therefore the major optimization goal at this stage became decrease of the disintegration time.

Based on the experimental results it was found that for disintegration time a simple linear model is sufficient.

$$D = 207.1 + 65.6 - 505.6$$

Table 1
First local design with observed values

Run	w_1	w_2	Anhydrous β -lactose	α -Lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)	Disintegration time (s)
1	0.15	0.15	0.3946	0.3557	0.2497	76.1	142
2	0	0	0.3333	0.3333	0.3333	86.1	213
3	−0.15	0.15	0.2721	0.4170	0.3109	87.9	113
4	−0.15	−0.15	0.2721	0.3109	0.4170	100.8	274
5	0	0	0.3333	0.3333	0.3333	84.3	214
6	0.15	−0.15	0.3946	0.2497	0.3557	110.5	285

This model has a residual mean square error of 75 and $R^2_{adj} = 0.9842$.

For crushing strength, however, no suitable model could be found. From the data it is clear that there is some kind of interaction (mathematically $w_1^*w_2$), but also that there is a quadratic effect (w_1^2 or w_2^2). The former does not present any problems, since it can be estimated with the data. Of the quadratic effect however it is impossible to determine whether it is w_1^2 or w_2^2 . Therefore it was decided that the design would be extended with a star design. However, since one of the directions (decrease in w_2) was not appropriate, it was decided not to extend the design in that direction. This fourth direction was not appropriate because it seemed that it combined increase in crushing strength with increase in disintegration time. As already stated, with the response values found, decrease of the disintegration time had the highest priority. Additionally to the star points, the centre point was duplicated in order to distinguish block effects. The responses and compositions according to this design can be found in Table 2. The data now indicated a simple model for disintegration time.

$$D = 211.5 + 122.2 - 473.6$$

Fig. 15. First local model, PO responses at 0.2–0.5 units distance.

This model has a residual mean square error of 213 and $R^2_{adj} = 0.9406$.

The crushing strength needed a more complex model:

$$C = 85.4 - 5.0 * w_1 - 78.6 * w_2 - 234.4 * w_1 + 156.8 * w_1^2 + 219.7 * w_2^2 - 7.1 * Block$$

This model has a residual mean square error of 0.95 and $R^2_{adj} = 0.9929$. The Block effect is the

Table 2
Additional design points for the first local design

Run	w_1	w_2	Anhydrous β -lactose	α -Lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)	Disintegration time (s)
7	0	0.2	0.3333	0.4040	0.2626	71.1	131
8	-0.2	0	0.2517	0.3742	0.3742	85.9	173
9	0.2	0	0.4150	0.2925	0.2925	82.9	247
10	0	0	0.3333	0.3333	0.3333	78.6	227

Table 3
Design points along the first direction of interest, together with predicted and observed values

Run	w_1	w_2	Anhydrous β -lactose	α -lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)		Disintegration time (s)	
						Pred.	Obs.	Pred.	Obs.
11	-0.10	0.17	0.2517	0.4973	0.2517	84.5		117	
	-0.15	0.26				93.2		70	
	-0.20	0.35				108.0	57.4	23	114
	-0.25	0.43				129.0		-24	
12	-0.30	0.52	0.2108	0.5783	0.2109		48.7		79
13	-0.40	0.69	0.1700	0.6599	0.1700		39.6		68

difference between the first group of design points and the second group of design points.

In order to find a preferred direction of interest, the pareto optimal directions were calculated. The distances used were 0.2 to 0.5 units. The PO points are depicted in Fig. 15. The direction indicated in this figure was selected. This direction was preferred since with this direction a combination of increase in the crushing strength and decrease of the disintegration time was predicted.

The predicted and observed values along the line are given in Table 3. As can be seen, after only three runs this line is discontinued. To understand this decision it should be noted that a crushing strength of less than 50 N is hardly an acceptable value. With this in mind it was decided to discontinue the line after run 13. The next stage is a local design around design point 12.

When the observed values on the line are examined then it seems that the observed values are totally different from the predicted values. Especially with crushing strength an increase is predicted, while a decrease is found. With disintegration time there is somewhat more success. Here a decrease is predicted and also found, but the decrease is not as much as was predicted. These large deviations are not surprising since there is quite some extrapolation (0.4 units from the centre) even for the predictions at run 11. Overall the tablet properties hardly seem to improve.

The second local design was chosen around design point number 12. When this design was initially drawn, it appeared that design points 11 and 13 were very near to the proposed design

Fig. 16. First line of steepest ascent (line with large dots), second local design (square), rejected design points (circles) and actually used design points for second local design (small dots).

points. This can be seen in Fig. 16. Here the line of steepest ascent is given by the large dots. The design constructed by using a 2^2 design with centre point is given by the square with the small closed and the larger open dots. These latter points are near to the points which were observed for the line of steepest ascent. There are several methods to use the information of these points. They can either be supplemented to form a factorial design or they can be supplemented to form a design which is feasible for both planar and curved response surfaces. This latter approach was chosen. It was decided that the points with the larger open dots were to be shifted slightly to new locations, as indicated with the other small dots. The second local design consisted therefore of the design points depicted with the small dots and the centre point. It was assumed that either

Table 4
Second local design with observed values

Run	w_1	w_2	Anhydrous β -lactose	α -lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)	Disintegration time (s)
14	-0.3	0.52	0.2108	0.5783	0.2109	51.1	72
15	-0.15	0.67	0.2721	0.6007	0.1272	48.3	78
16	-0.45	0.37	0.1496	0.5559	0.2945	60.5	76
17	-0.1	0.42	0.2925	0.5021	0.2054	60.7	99
18	-0.5	0.62	0.1292	0.6545	0.2163	41.0	81

there would be no quadratic interactions, thus allowing planar models, or, when there was interaction, that the observations from the line of steepest ascent would be sufficient to determine which quadratic effects were present.

The observed values at this stage are given in Table 4. With these data the model for disintegration time was more difficult to construct than for crushing strength. The preferred model for crushing strength was:

$$C = 68.9 - 23.9 \cdot w_1 - 28.0 \cdot w_2 + 77.4 \cdot w_1^* w_2^* + 2.8 \cdot \text{Block}$$

with a residual mean square error of 4.4 and an $R^2_{\text{adj}} = 0.9337$.

The preferred model for disintegration time was:

$$D = 265.3 + 228.6 \cdot w_1 - 499.2 \cdot w_2 - 353.3 \cdot w_1^* w_2^* + 314.4 \cdot w_2 d_2$$

with a residual mean square error of 92.3 and $R^2_{\text{adj}} = 0.6164$.

The Block effect is now the difference between the runs on the line of steepest ascent and the new design points. Although the model fit for disintegration time was not very good, it was decided that it was sufficient to allow use of the MCSA method.

With the aid of the models again predictions are made at 0.2–0.5 units distance and the sets of PO directions were selected. These are shown in Fig. 17. Based on this figure it was decided to select the indicated direction (250° in the w_1, w_2 space). With this direction a slight increase of the crushing strength and a large decrease of the disintegration time were predicted. This direction was preferred over the left neighboring line because it offered a much larger increase of the crushing strength while the decrease in the dis-

Fig. 17. Second local model, PO responses at 0.2–0.5 units distance.

tegration time was only slightly less. The other neighboring line offered an even larger increase in the crushing strength, however here the disintegration time decreased less.

When the selected line was examined in the mixture variables space then it appeared that the amount of anhydrous β -lactose decreased fast along this line and after slightly more than 0.5 units distance the edge of the mixture triangle was reached. Therefore it was decided that first two experiments were to be made; these were on this line at 0.3 and 0.5 units distance. The results of these experiments can be found in Table 5.

As can be seen this was a successful choice. The crushing strength increased faster than expected while at the same time the disintegration time decreased faster than expected. The deviations between the predicted and the observed values are not large. If it were possible this line would be continued. However, since the line crossed the edge of the design space this was not possible.

Table 5

Design points along the second direction of interest, together with predicted and observed values

Run	w_1	w_2	Anhydrous β -lactose	α -Lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)		Disintegration time (s)	
						Pred.	Obs.	Pred.	Obs.
19	-0.58	0.42	0.0958	0.5995	0.3047	52.3	57.3	64	55
20	-0.77	0.35	0.0190	0.6137	0.3673	56.7	71.2	48	26

When a line of interest crosses the edge of the design space with a small angle, the edge and the line of interest have almost the same direction. It is then possible to use the edge beyond the point where the edge and the line of interest have crossed. In this case however, the line of greatest interest crossed the edge of the design space almost orthogonally and it was decided to continue with a local design.

For this third local design it was decided to place the design along the edge of the design space. This was implemented by using a 2^2 design with 0.1 fraction between the design points. Two points had compositions without anhydrous β -lactose and two points had 0.1 fraction anhydrous β -lactose, an additional centre point had 0.05 fraction anhydrous β -lactose. This design was slightly larger than the previous local designs. The settings and observed values are given in Table 6.

Based on these data, local models were constructed. Since the amount of data was so small it was not easy to determine the correct models. Especially for crushing strength, where an interaction ($w_1^*w_2$) was present, no significant model could be determined. The presence of the interaction term follows from the model ANOVA. It can also be seen in the raw data. Then it should be noted that at one edge ($w_2 = 0.21$) there is hardly any change in crushing strength (71.6 vs. 72.8 N) when w_1 is changed (fraction anhydrous β -lactose is changed), while at the opposite edge there is a difference of 6 units (48.2 vs. 56.3 N). With disintegration time a planar model was sufficient.

The preferred model for crushing strength was:

$$C = 99.5 + 16.2^*w_1 - 139.6^*w_2 - 99.6^*w_1^*w_2$$

Fig. 18. PO points at the third local design.

with a residual mean squared error of 22.2 and $R_{adj}^2 = 0.8038$.

The preferred model for disintegration time was:

$$D = 172.2 + 166.4^*w_1 - 41.0^*w_2$$

with a residual mean squared error of 9.8 and $R_{adj}^2 = 0.9784$.

Since the obtained values indicate that a composition with a good trade-off between the responses is within the region covered with this design, it was decided to use these models to determine pareto optimal points within this region. The resulting combinations of responses can be found in Fig. 18. The PO points are (in composition terms) all along the edge of the design space (no anhydrous β -lactose present). On this edge a trade-off can be made. When there is more microcrystalline cellulose, the tablets are harder and they disintegrate slower; when there is more α -lactose monohydrate, then the tablets are softer and disintegrate faster.

Table 6
Third local design with observed values

Run	w_1	w_2	Anhydrous β -lactose	α -Lactose monohydrate	Microcrystalline cellulose	Crushing strength (N)	Disintegration time (s)
21	-0.82	0.49	0	0.675	0.325	56.3	17
22	-0.57	0.21	0.1	0.525	0.375	71.6	69
23	-0.69	0.35	0.05	0.6	0.35	67.5	38
24	-0.81	0.21	0	0.575	0.425	72.8	29
25	-0.57	0.49	0.1	0.625	0.275	48.2	58

4.7. Discussion

In Fig. 19 all design points are depicted. This shows where the path of the greatest interest is in the design space. It is clear that in the first stage a non-optimal direction was selected. A better direction (w_1, w_2 space) than 330° would be 270° or 280° degrees. Then the region of the final local design would be found immediately. The question is now whether this direction could be found after the first local design. After the first local design this direction is only PO after 0.2 or 0.3 units distance. Directions which are PO at all distances were preferred.

The major problem of the MCSA method is to find the distance from the centre where the most informative predictions can be made. On the one hand it can be argued that with extrapolation the prediction error increases rapidly and that the models are possibly incorrect outside the region covered by the design. On the other hand it is not practical to measure near to the centre and as a consequence predictions should be made further from the centre. With this in mind and using the experimental results it might be best to consider the predictions at 1.5 units from the centre (0.3 in

the example) as predictions and the predictions further from the centre as indications. However, these indications may not be neglected in case of a curved response surface. It is a matter of further research to find which distances result in the most informative PO directions. However, since slightly wrong directions can be corrected with a next local design, this is not a problem which prohibits use of the method.

5. Conclusion

Steepest ascent is a general technique which is extended to deal with two and three responses by introduction of pareto optimal directions. The pareto optimal direction technique provides suitable choices for the direction of the preferred improvement. This is implemented as the multi-criteria steepest ascent.

Complicated statistics are not required. The necessary calculations and graphical tools are available or can easily be programmed.

However, several parts of the optimization must be further examined. Among these is the distance between the predictions and the centre of the design space. When the models are extrapolated too far then the predicted responses will deviate from the observed responses. Another problem of the optimization is the use of five or more response values. The stacked PO plot which is shown is acceptable with three or four responses, but with five or more responses it is not practical to use this method. The decision procedure and feasible plots to depict the trade-off for such situations are being examined.

Fig. 19. Design points in mixture triangle. (●) Design points of local designs; (■) design points of first line of interest; (▶) design points of second line of interest.

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