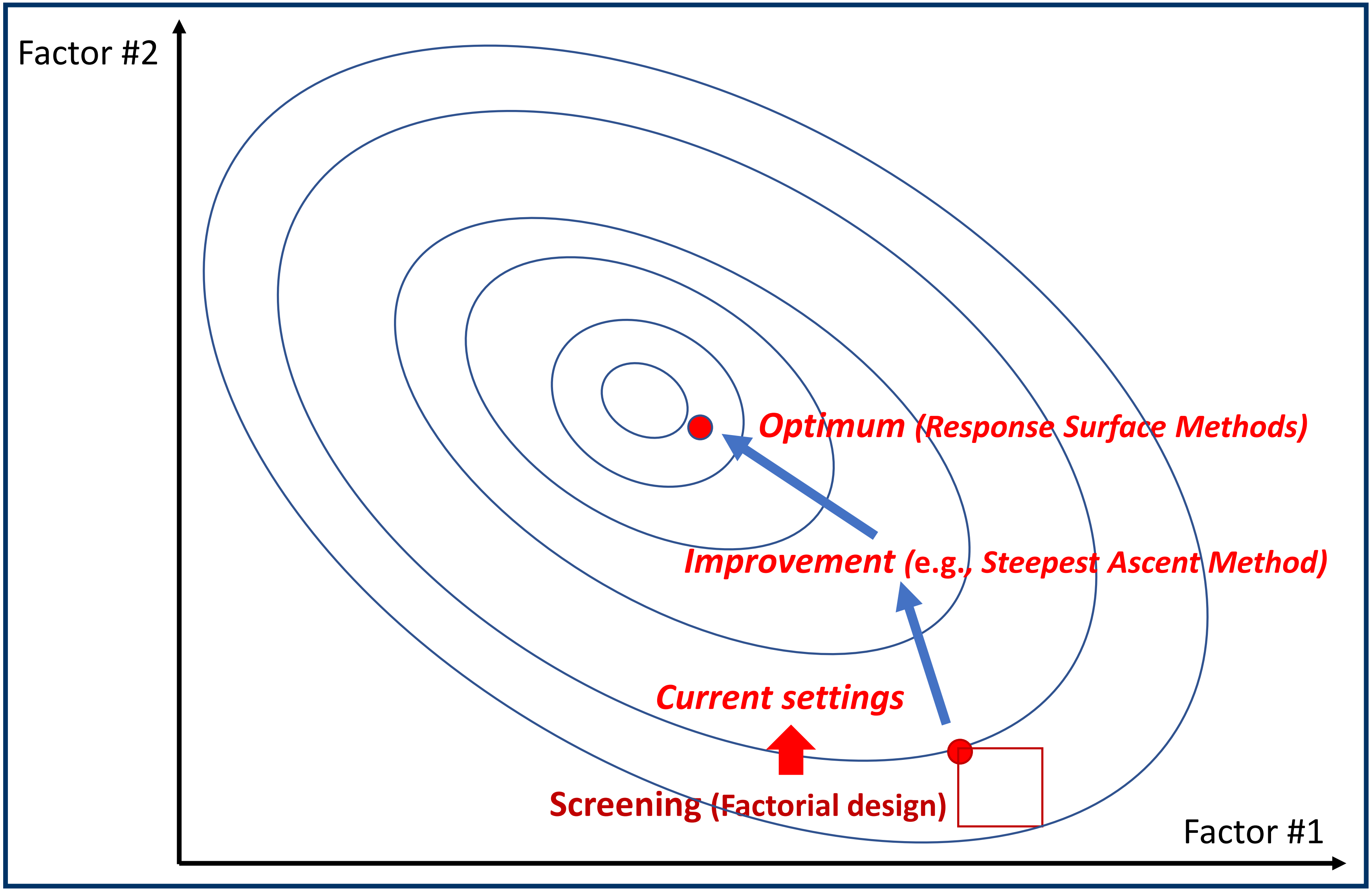
Process Optimization with Designed Experiments



As emphasized by the figure, once the screening of factors is completed, using, for example, factorial design, process optimization can be achieved through the following steps:

- ***improvement*** - approaching optimum by repeated change of factor settings;

  - tools: Box-type EVolutionary OPeration (EVOP), Simplex optimization, steepest ascent method

- ***determination of optimum*** **-** finding optimal factor settings;

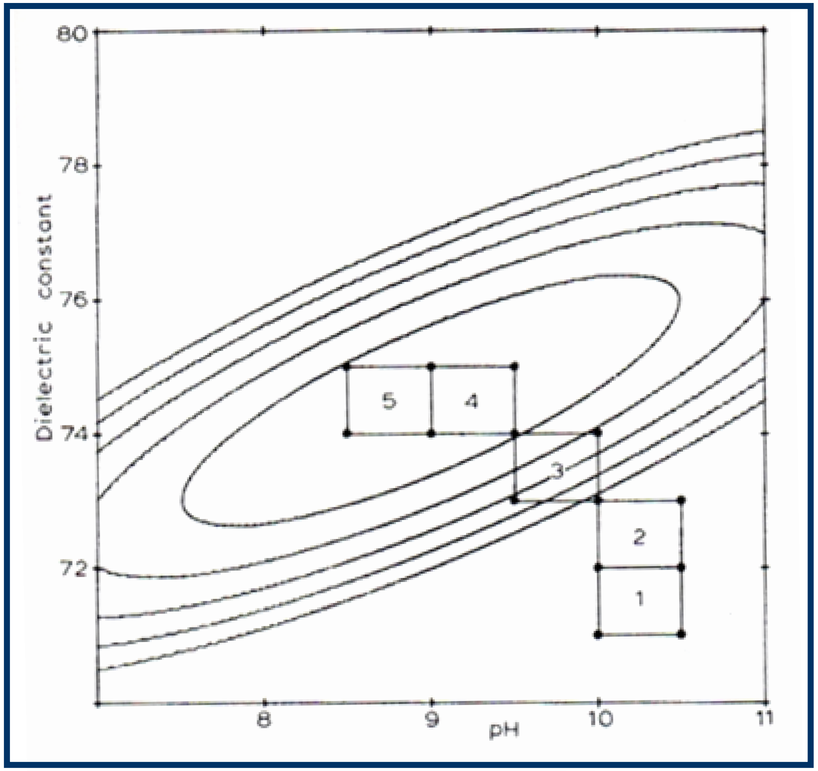
  - tool: response surface methods like Central Composite Design or Box-Behnken Design + ***analysis of response surface***

Box-type Evolutionary Operation (Box-EVOP)

Evolutionary Operation was proposed in 1957 by Box as a method of routine plant operation, carried out by manufacturing personnel with minimum assistance from the research and development staff, aiming at dealing with modifications of optimal conditions in a full-scale process, due, for example, to variations in raw materials, environmental changes or operating personnel.

EVOP consists of systematically introducing small changes in the levels of the operating factors under consideration, usually employing a 2^k design.

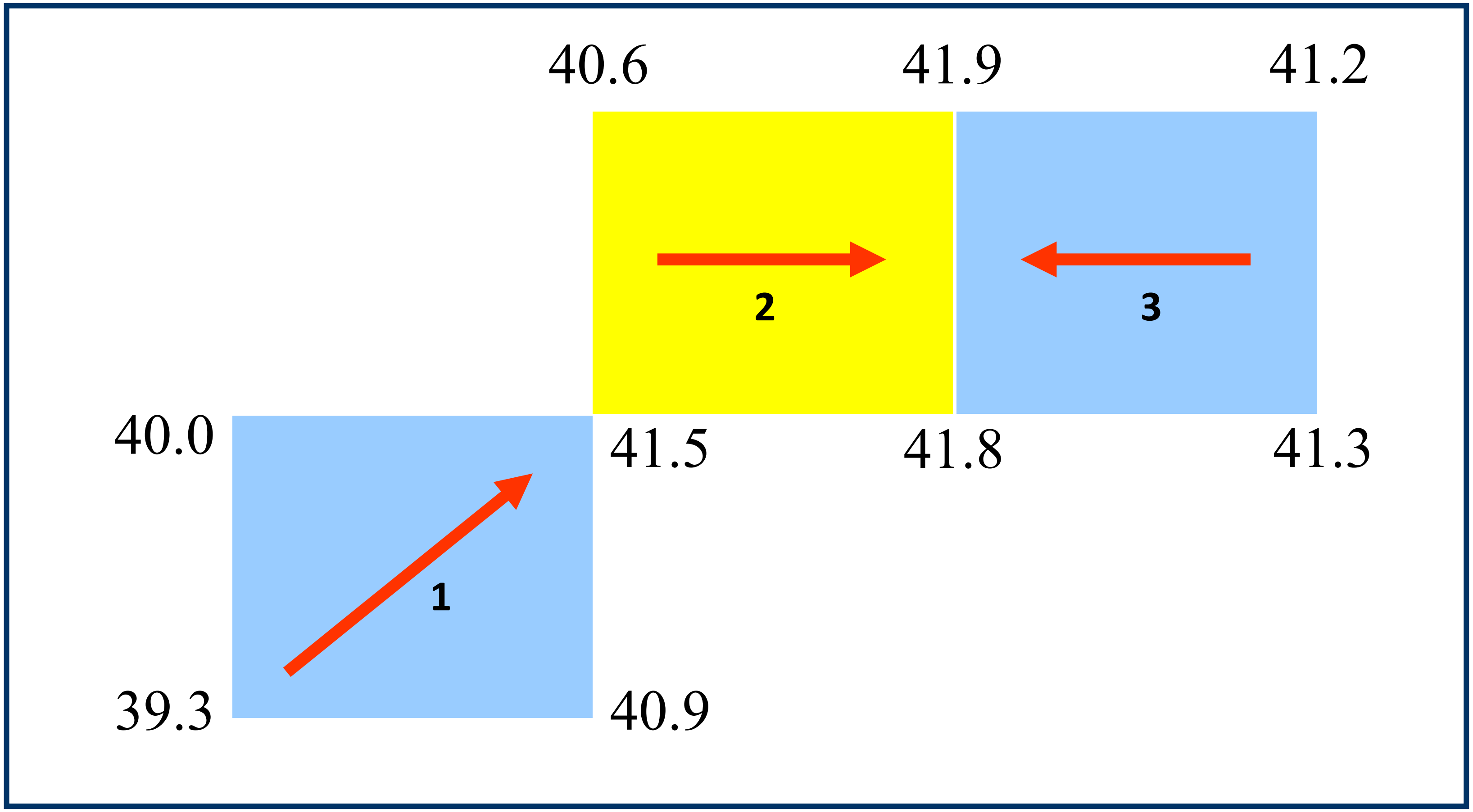
The simplest example of Box-EVOP is based on a 2^2 design, i.e., the one referred to a response depending on two factors, as shown in the figure on the right:



Each square in the figure indicates the four measurements performed for each cycle of the 2^2 design.

In the example the highest response was reached with cycle #5:

The Box-EVOP principle is explained in the following figure:



Numbers reported in the figure represent responses obtained for each cycle of the 2^2 design. The direction of largest increase is easily inferred from cycle #1, thus the upper-right vertex (response = 41.5) becomes the lower-left vertex of cycle #2. Once measurements of cycle #2 are completed the new direction of largest increase is inferred, thus two vertexes of cycle #2 are common with cycle #3. Responses obtained with cycle #3 indicate that the maximum response is observed at the border between cycles #2 and #3.

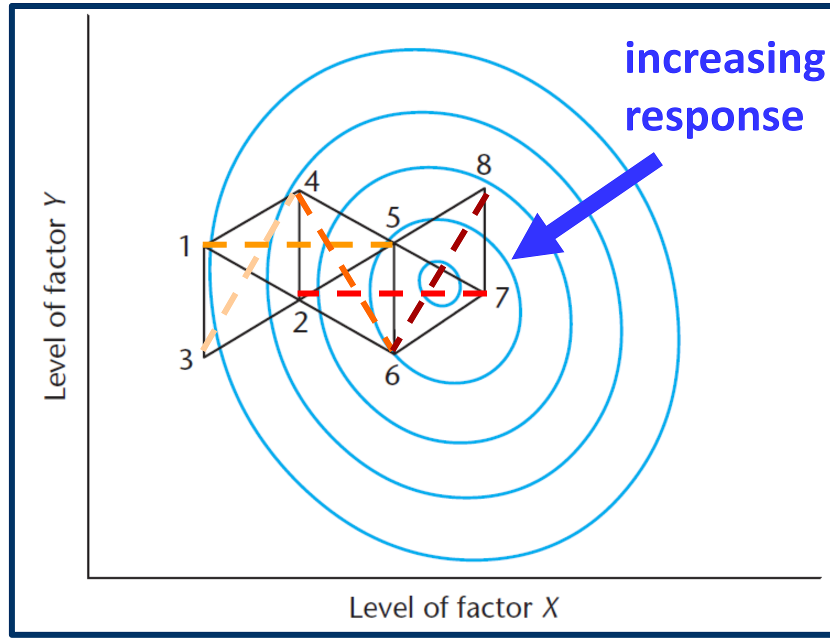
Simplex optimization

Simplex optimization may be applied when all the factors are continuous variables.

A simplex is a geometrical figure which has k + 1 vertices, with k being the number of factors.

In the optimization of two factors the simplex will therefore be a triangle.

Simplex optimization with constant step sizes is illustrated by the figure on the right:

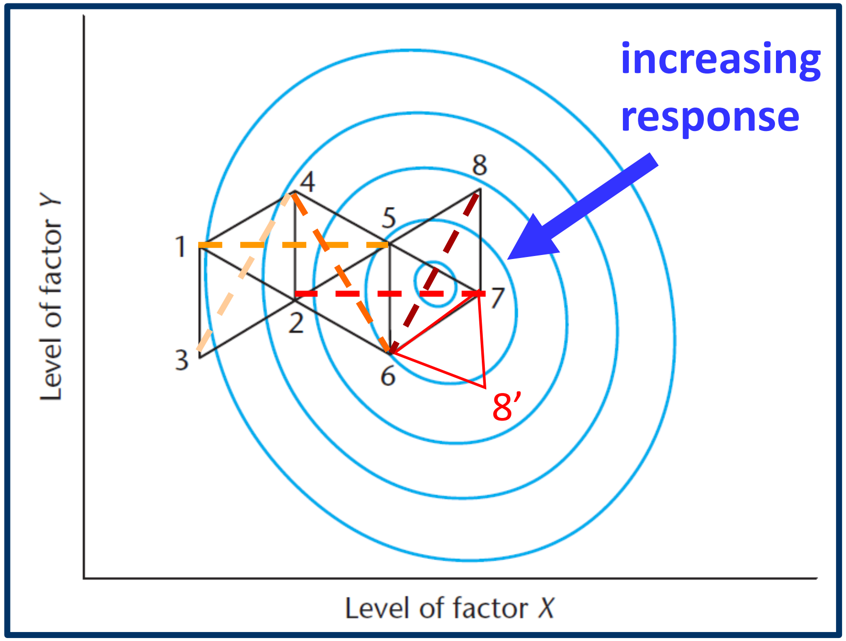


The initial simplex is defined by points labelled 1, 2 and 3. In the first experiments the response is measured at each of the three combinations of factor levels given by the vertices of this triangle.
The worst response in this case is found at point 3 and it is logical to suggest that a better response might be found at a point which is the reflection of 3 with respect to the line joining 1 and 2, i.e., at point 4. A new simplex is thus defined by points 1, 2 and 4.

Following the same procedure, new combinations of factors to be tested are represented by points 5, 6, 7 and 8.

The procedure stops at point 8, since the response obtained at this point, like the one obtained at point 6, is lower than those obtained at points 5 and 7.

This feature is typical of a simplex location close to the maximum of the response surface, yet, depending on the shape of the latter, oscillations of this kind may occur even when the simplex is not close to the optimum.



In this circumstance improvements can be made sometimes by reflecting the next-worst point rather than the worst one, to move the simplex in a new direction. In the present case it would be point 5, thus vertex 8’ would be obtained after simplex reflection, with a response comparable to the one observed for points 5 and 6.

In practice, a point closer to the optimum could be found by considering the point located halfway on the segment shared by the last two simplexes (the segment between points 5 and 7).

When more than two factors are involved, no graphical representation can be made for the approach to optimum, thus the procedure is entirely based on calculation.

An example referred to 5 factors is reported in the following table:

	Factors					Response
	A	B	C	D	E	
Vertex 1	1.0	3.0	2.0	6.0	5.0	7
Vertex 2	6.0	4.3	9.5	6.9	6.0	8
Vertex 3	2.5	11.5	9.5	6.9	6.0	10
Vertex 4 (rejected)	2.5	4.3	3.5	6.9	6.0	6
Vertex 5	2.5	4.3	9.5	9.7	6.0	11
Vertex 6	2.5	4.3	9.5	6.9	9.6	9
(i) Sum (excluding vertex 4)	14.50	27.40	40.00	36.40	32.60	
(ii) Sum/k (excluding vertex 4)	2.90	5.48	8.00	7.28	6.52	
(iii) Rejected vertex (i.e. 4)	2.50	4.30	3.50	6.90	6.00	
(iv) Displacement = (ii) – (iii)	0.40	1.18	4.50	0.38	0.52	
(v) Vertex 7 = (ii) + (iv)	3.30	6.66	12.50	7.66	7.04	

The simplex has six vertices in this case (note that it is not essential for each factor to have a different level for each of the vertices).

Vertex 4 is rejected, since it leads to the worst response. The new vertex, 7, is obtained through steps (i) to (v) shown below in the table.

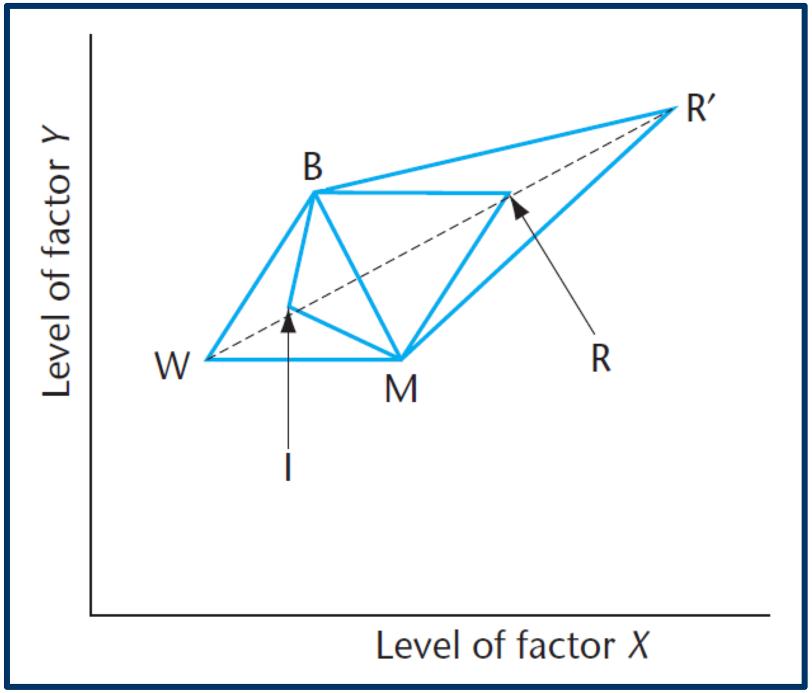
One of the key aspects of the simplex method is the choice of the initial simplex.
Indeed, if it is too small, too many experiments may be needed to approach the optimum; if it is too big, the precision of optimum determination might be poor.

One vertex of the initial simplex is usually located in the currently accepted levels of the factors, then the simplex size can be evaluated in relation to the ranges that factors can assume realistically.

Actually, a simplex with variable step size can also be adopted.

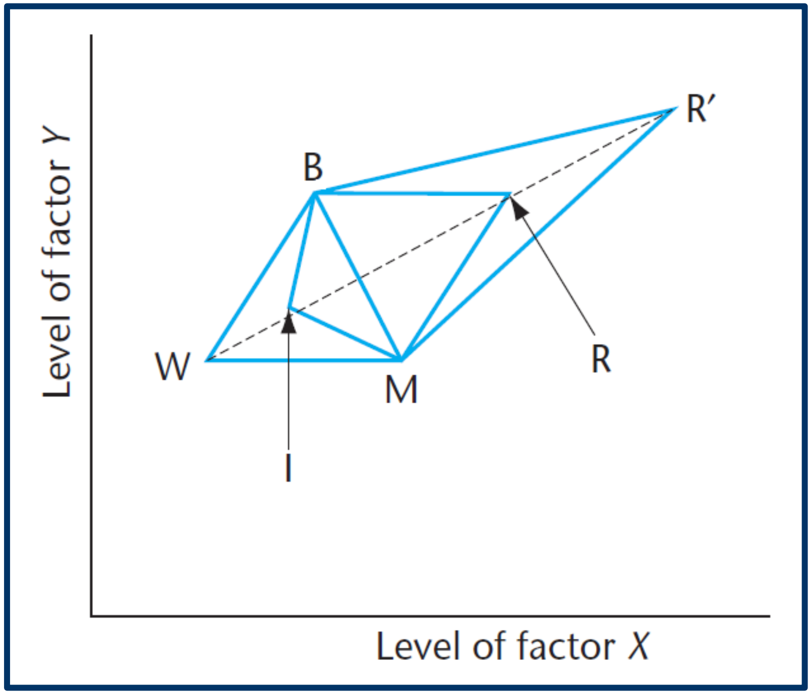
In the figure points W, M and B represent worst, medium and best responses obtained with the first simplex, respectively.
The new point obtained with a fixed-size simplex is R.

If R gives a better response than B (and, then, also of M), the simplex may be moving in the right direction, thus the simplex size is doubled and point R’ is obtained.
If the response at R’ is lower than that at B, R could be close to the optimum.



If the response at point R is worse than those obtained at points B and M a smaller simplex (usually having a size that is half of that used before) can be used when making a reflection around segment BM, leading to point I.

Further evaluations will depend on the response obtained at point I.



The use of variable-size simplex implies that, in the case of two factors, triangles are usually equilateral in the first steps, then they become isosceles.

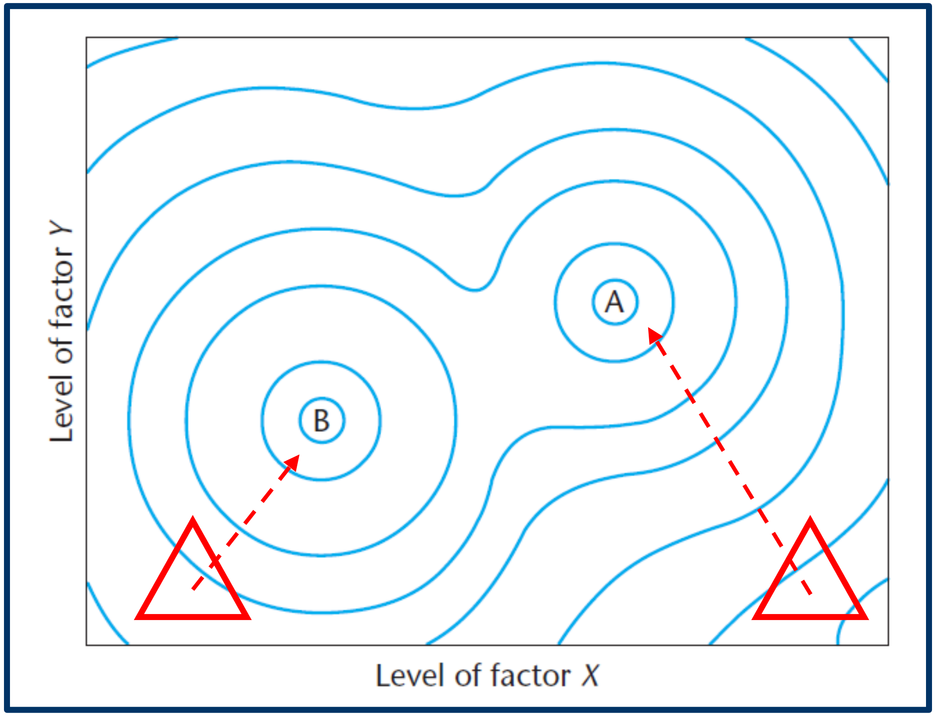
The benefit of this approach is using a large simplex in the first steps, to explore the response surface better, then its size is contracted, to allow a more accurate finding of the optimum.

Notably, the number of experiments required in the simplex method does not increase rapidly with the number of factors. For this reason, all factors which might reasonably be thought to have an effect on the response should be included in the optimization.

Simplex optimization has some disadvantages. As always, difficulties may arise if the random measurement errors are larger than the slope of the response surface near the optimum.

Moreover, the small number of experiments performed, while usually advantageous in practice, means that little information is gained on the overall shape of the response surface.

Occasionally response surfaces with more than one maximum occur, as the one shown as contour plot in the figure on the right.



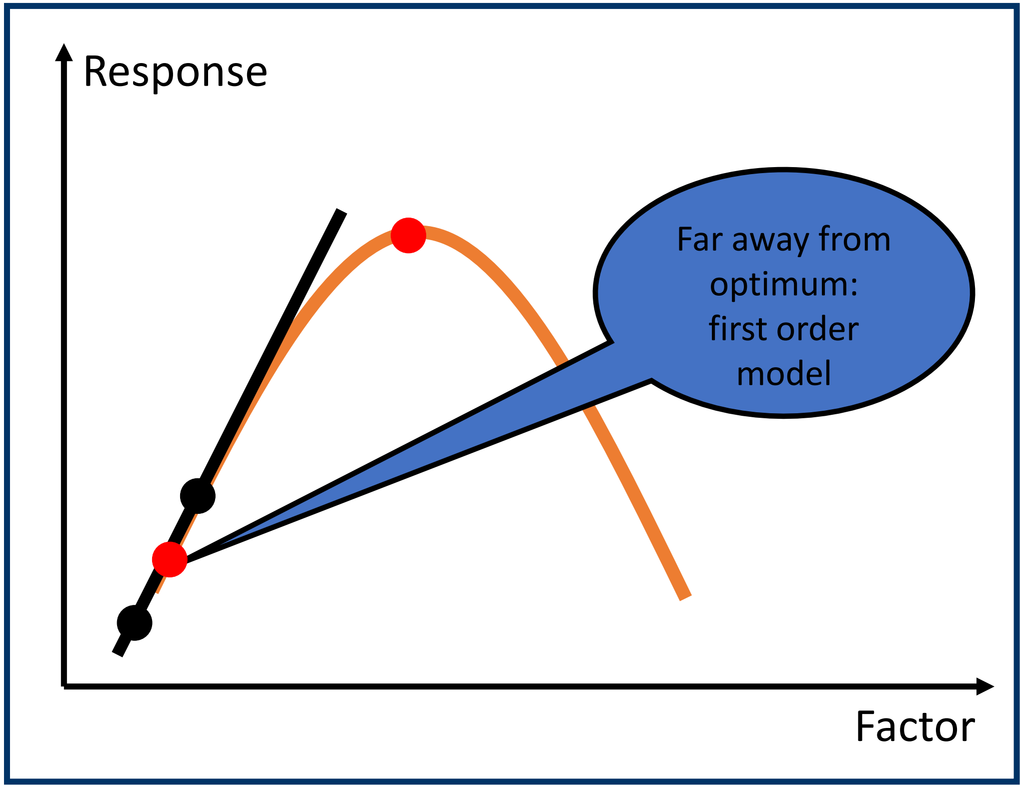
In this case simplex optimization methods might locate a local optimum such as A, rather than the true optimum B.

Starting the optimization process in a second region of the factor space and verifying if the same optimum conditions are obtained or not is the preferred method for checking this issue.

Method of Steepest Ascent

The method of steepest ascent is a procedure adopted to move sequentially along the path leading to the maximum increase in the response. Of course, if minimization is desired, then the procedure corresponds to the method of steepest descent.

At great distances from the optimum, a first-order model is usually considered an adequate approximation of the true surface in a small region of the factors. This consideration can be easily appreciated on a single dimension:

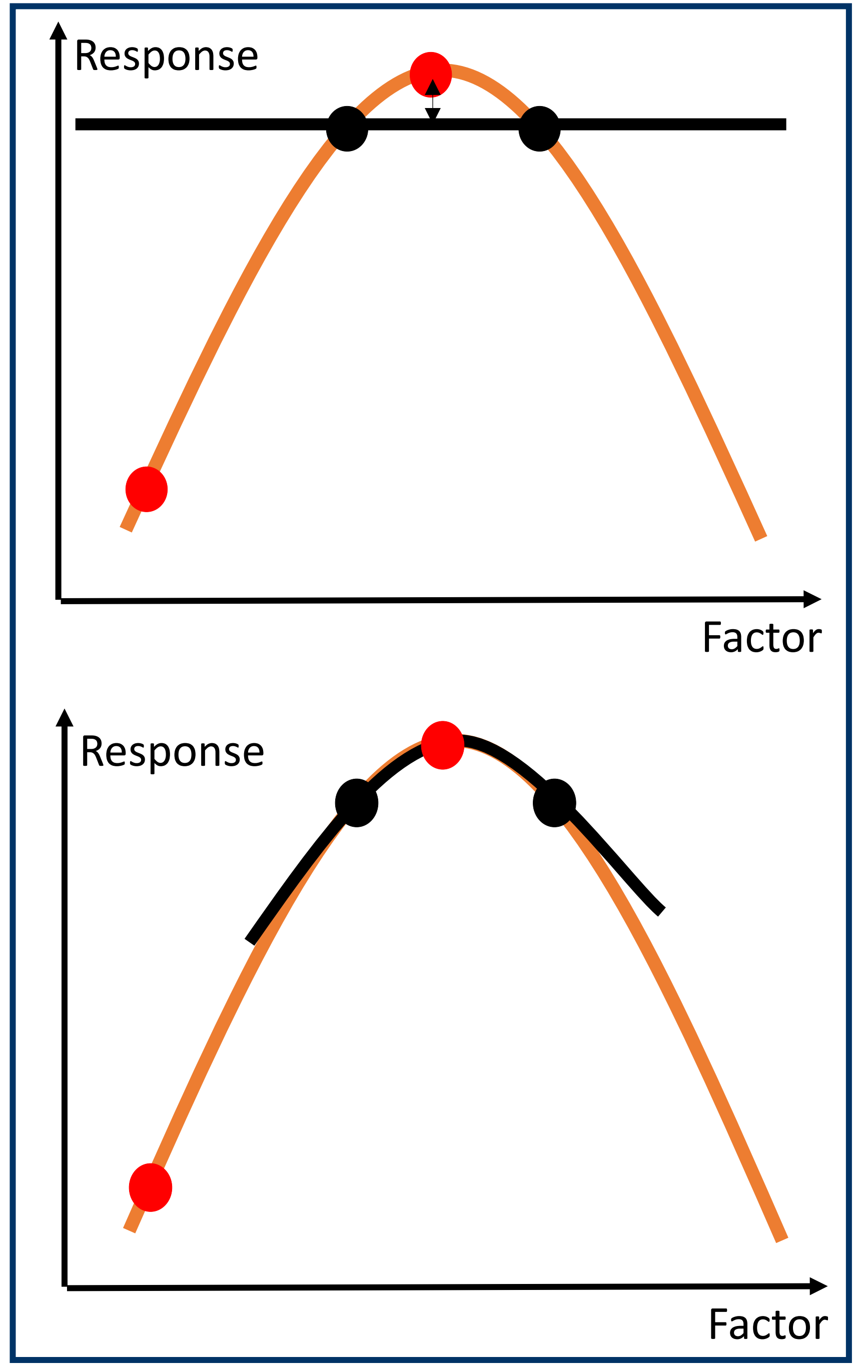


A first-order model is thus used for fitting:

$$\hat{y} = \hat{\beta}_0 + \sum_{i=1}^{k} \hat{\beta}_i x_i$$

When the optimal response is approached a first-order model can suffer from a significant lack-of-fit:

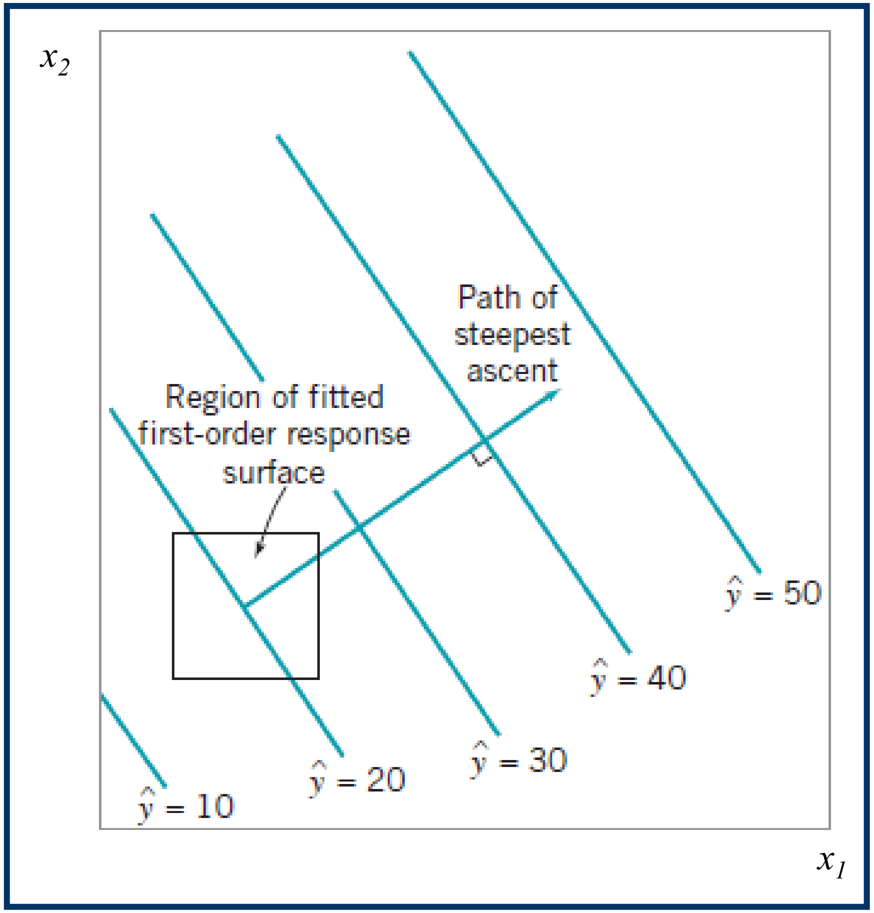
A second-order model may approximate the real response much better:



When two factors are considered, the direction of steepest ascent is normal to the fitted response surface contours.

The line passing through the center of the region of interest and normal to the fitted surface contours is considered as the path of steepest ascent .
The steps along the path are proportional to the magnitudes of the regression coefficients.

The experimenter determines the actual amount of movement along this path based on process knowledge or other practical considerations.

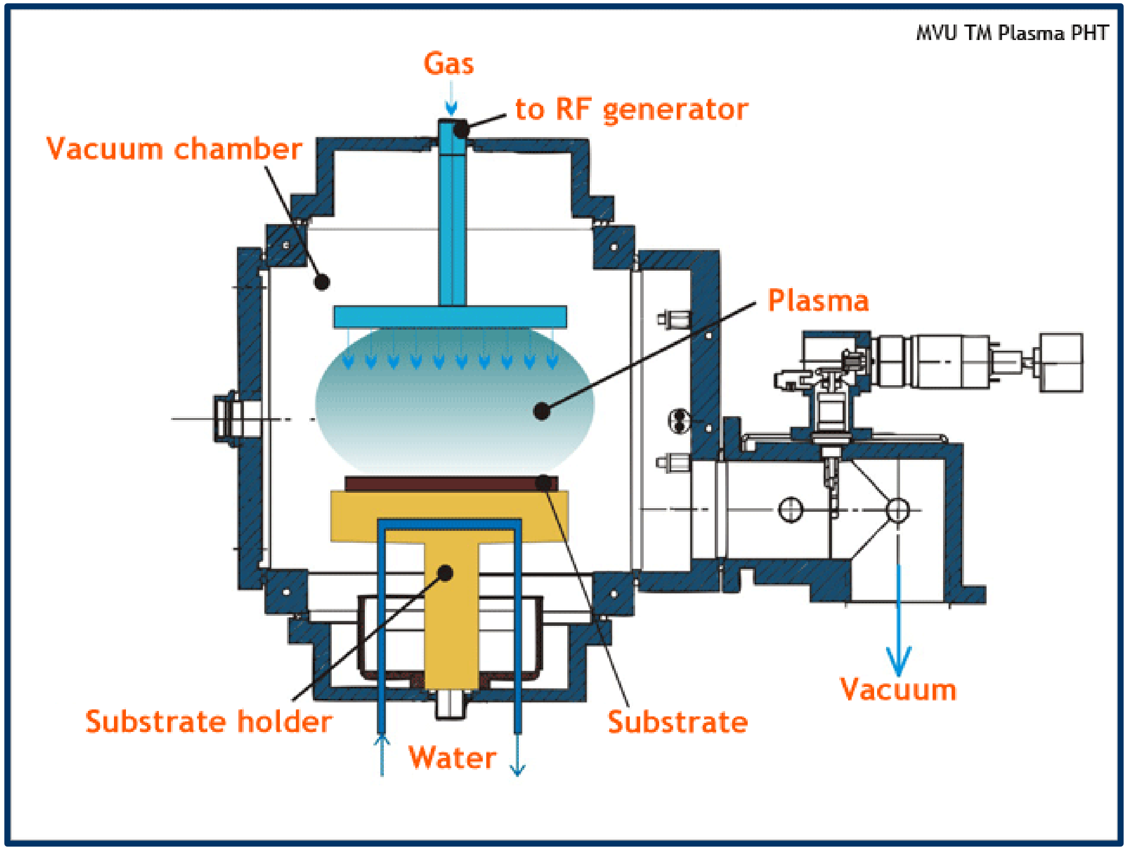


Experiments are conducted along the path of steepest ascent until no further increase in response is observed or until the desired response region is reached.

In the first case, a new first-order model may be fitted, a new direction of steepest ascent determined, and, if necessary, further experiments conducted in that direction until the experimenter ***feels*** that the process is near to the optimum (or to a desired value).

An example of Process Optimization based on Design of Experiment approaches

The example deals with the development of a silicon nitride (Si_3N_4) etching process based on a single-wafer plasma etcher. The process uses C_2F_6 as the reactant gas.
It is possible to change the gas flow, the power applied to the cathode, the pressure in the reactor chamber, and the spacing between the anode and the cathode (gap).
Several response variables would usually be of interest in this process, but in this example the etch rate for silicon nitride is considered.



Four factors

1. gas flow
2. power
3. pressure
4. electrode spacing

One response

1. etch rate

G.Z. Yin and D.W. Jillie, *Solid State Technology*, May 1987, pp. 127-132

As a first step a 2^4 factorial design was adopted for screening purposes:

Design Factor Level	Gap A (cm)	Pressure B (m Torr)	C_2F_6 Flow C (SCCM)*	Power D (W)
Low (–)	0.80	450	125	275
High (+)	1.20	550	200	325

*SCCM = Standard Cubic Centimeters Per Minute

Run	A (Gap)	B (Pressure)	C (C_2F_6 flow)	D (Power)	Etch Rate (Å/min)
1	–1	–1	–1	–1	550
2	1	–1	–1	–1	669
3	–1	1	–1	–1	604
4	1	1	–1	–1	650
5	–1	–1	1	–1	633
6	1	–1	1	–1	642
7	–1	1	1	–1	601
8	1	1	1	–1	635
9	–1	–1	–1	1	1037
10	1	–1	–1	1	749
11	–1	1	–1	1	1052
12	1	1	–1	1	868
13	–1	–1	1	1	1075
14	1	–1	1	1	860
15	–1	1	1	1	1063
16	1	1	1	1	729

The model table was thus the following, based on the consideration also of interactions between two, three and four factors:

Run		A	B	AB	C	AC	BC	ABC	D	AD	BD	ABD	CD	ACD	BCD	ABCD
1	(1)	−	−	+	−	+	+	−	−	+	+	−	+	−	−	+
2	*a*	+	−	−	−	−	+	+	−	−	+	+	+	+	−	−
3	*b*	−	+	−	−	+	−	+	−	+	−	+	+	−	+	−
4	*ab*	+	+	+	−	−	−	−	−	−	−	−	+	+	+	+
5	*c*	−	−	+	+	−	−	+	−	+	+	−	−	+	+	−
6	*ac*	+	−	−	+	+	−	−	−	−	+	+	−	−	+	+
7	*bc*	−	+	−	+	−	+	−	−	+	−	+	−	+	−	+
8	*abc*	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−
9	*d*	−	−	+	−	+	+	−	+	−	−	+	−	+	+	−
10	*ad*	+	−	−	−	−	+	+	+	+	−	−	−	−	+	+
11	*bd*	−	+	−	−	+	−	+	+	−	+	−	−	+	−	+
12	*abd*	+	+	+	−	−	−	−	+	+	+	+	−	−	−	−
13	*cd*	−	−	+	+	−	−	+	+	−	−	+	+	−	−	+
14	*acd*	+	−	−	+	+	−	−	+	+	−	−	+	+	−	−
15	*bcd*	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
16	*abcd*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

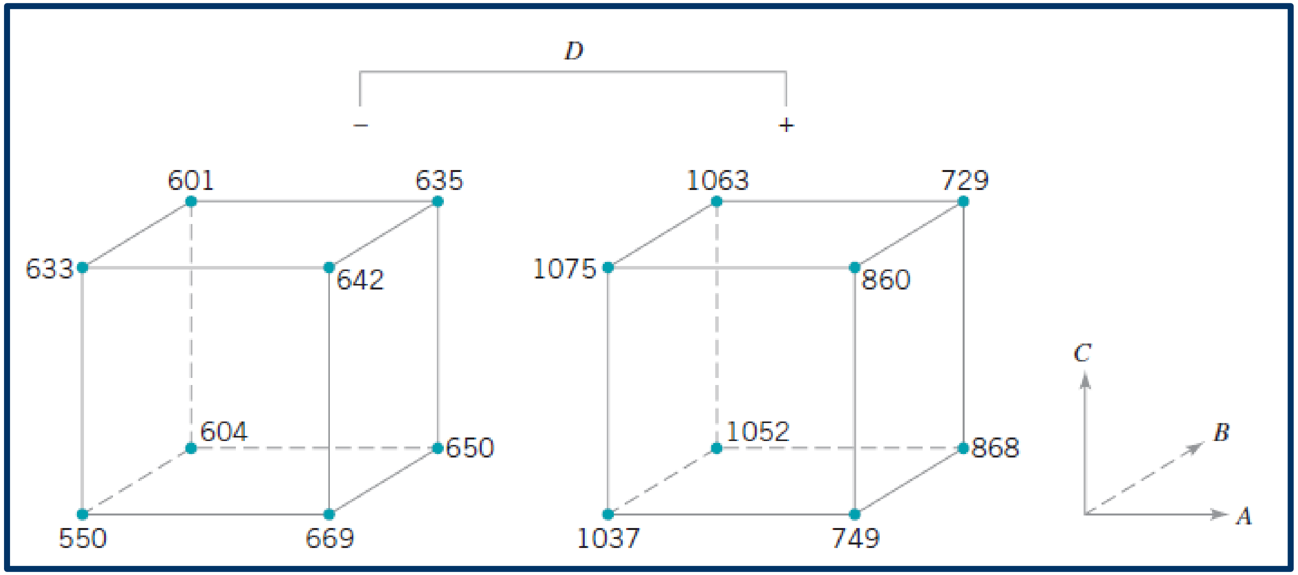
Since no replicates were performed it was not possible to estimate, on a statistical basis, the significance of each factor.

However, in the analysis of variance the three- and four-factor interactions could be pooled to form the error mean square (this is an acceptable assumption provided that those interactions are not significant).

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F_0
A	41,310.563	1	41,310.563	20.28
B	10.563	1	10.563	< 1
C	217.563	1	217.563	< 1
D	374,850.063	1	374,850.063	183.99
AB	248.063	1	248.063	< 1
AC	2,475.063	1	2,475.063	1.21
AD	94,402.563	1	99,402.563	46.34
BC	7,700.063	1	7,700.063	3.78
BD	1.563	1	1.563	< 1
CD	18.063	1	18.063	< 1
Error	10,186.815	5	2,037.363	
Total	531,420.938	15		

As inferred from F_0 values, factors A and D and their interaction (AD) seem to have a significant effect on the response.

Responses obtained for different combinations of the four factors can be visualized as in the following figure:



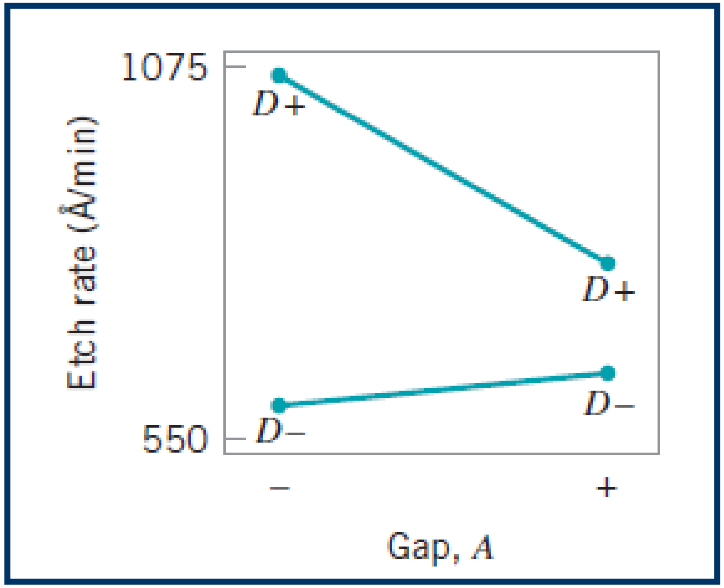
The effects of factors and of the interactions were calculated as usual:

As suggested by ANOVA, the most relevant factors were A, the electrode gap, and D, the power.

$$
\begin{aligned}
A &= -101.625 & AD &= -153.625 \\
B &= -1.625 & BD &= -0.625 \\
AB &= -7.875 & ABD &= 4.125 \\
C &= 7.375 & CD &= -2.125 \\
AC &= -24.875 & ACD &= 5.625 \\
BC &= -43.875 & BCD &= -25.375 \\
ABC &= -15.625 & ABCD &= -40.125 \\
D &= 306.125 & &
\end{aligned}
$$

As inferred from the previous figure, and as shown directly in the figure on the right, the effect of increasing the electrode gap on the etch rate is opposite, according to the value of power:

The interaction between the two factors is thus relevant.



Consequently, high etch rates are obtained at high power settings and narrow gap widths.

Since two of the four factors, i.e., the electrode gap (x_1) and the power (x_4), significantly affect etch rate, a model based only on these main effects can be adopted:

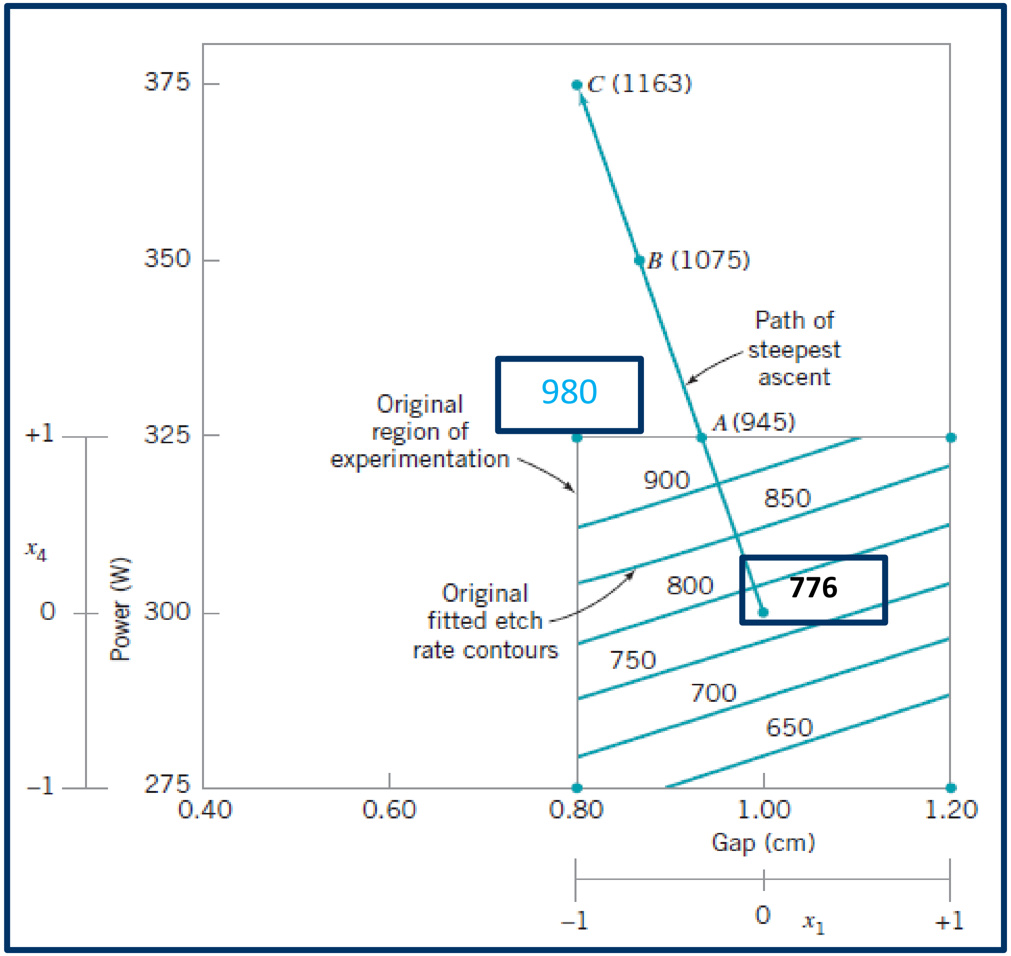
$$\hat{y} = 776.0625 - 50.8125x_1 + 153.0625x_4$$

$$\hat{y} = b_0 + b_1 x_1 + b_4 x_4$$

The contour plot resulting from this model is shown in the figure on the right:

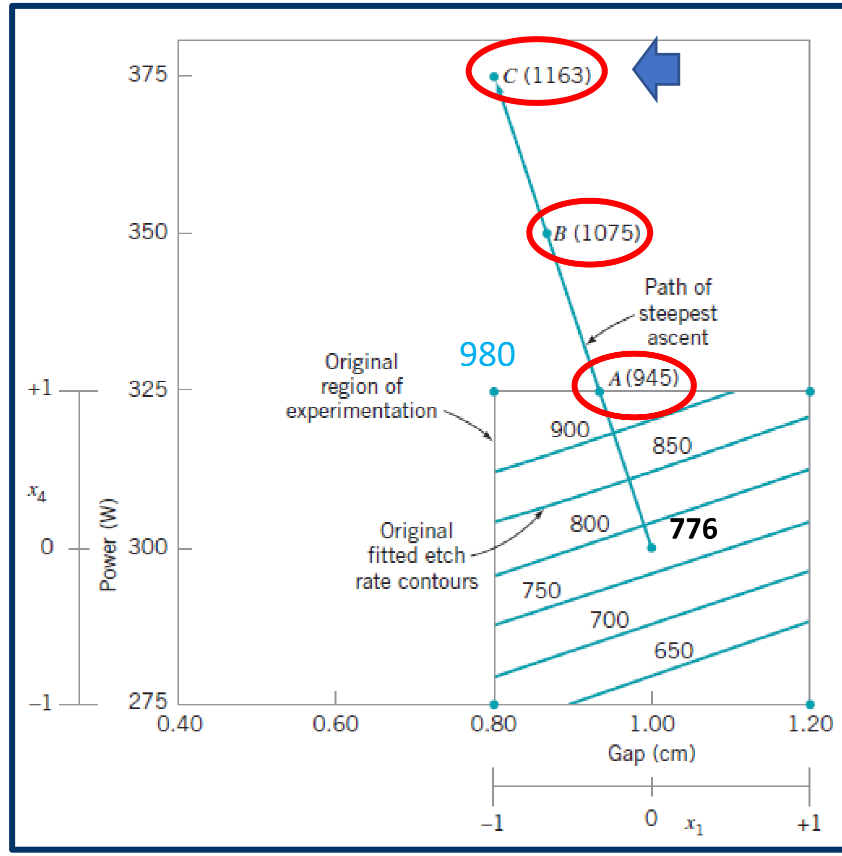
The original region of experimentation, delimited by gaps between 0.8 and 1.2 cm and powers between 275 and 325 W, is evidenced in the figure.

Notably, the maximum etch rate obtained within the original region of experimentation, was approximately 980 Å/min.



Since the engineers needed to run the process at an etch rate of 1100–1150 Å/min, the method of steepest ascent was adopted to move away from the original region of experimentation to increase the etch rate.

An examination of the plot shows that, to move away from the design center, i.e., the point (x_1 = 0, x_4 = 0), a path having a slope of 153.0625/(-50.8125) $\cong$ -3 has to be adopted:



Since the engineers decided to use 25 W of power as the basic step size, and this value is equivalent to a step of 1 in the coded variable x_4, a change of $\Delta x_4/(-3)$ = -0.33 for the x_1 variable, equivalent to -0.067 cm in the electrode gap, was applied.

The maximum etch rate observed along the path of steepest ascent was 1163 Å/min, compatible with the process requirements, and was achieved for a power of 375 W and an electrode gap of 0.8 cm.

Response Surface Method (RSM)

Response surface methodology (RSM) is a collection of mathematical and statistical techniques that are useful for modeling and analysis in applications where a response of interest is influenced by several variables and the objective is to optimize this response.

To illustrate the general idea of RSM, suppose that a chemical engineer wishes to find the levels of reaction temperature (x_1) and reaction time (x_2) that maximize the yield (y) of a process. The process yield is a function of the levels of temperature and time:

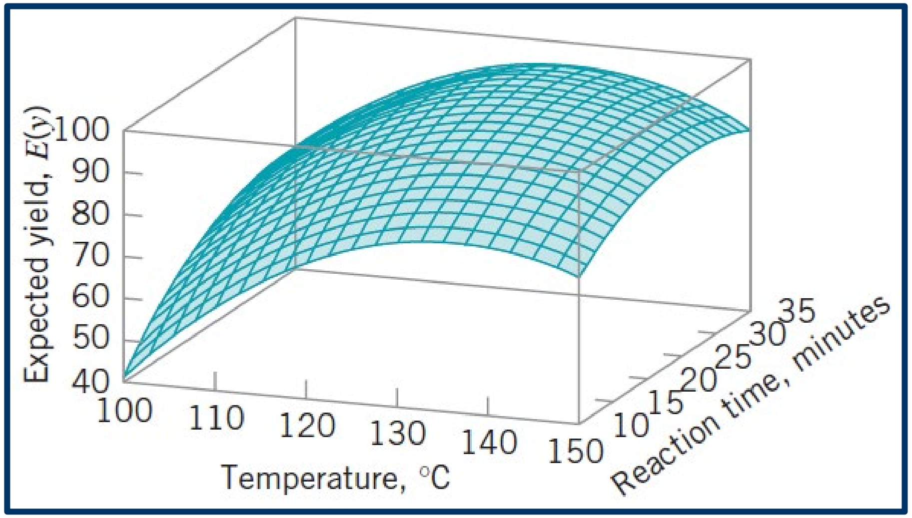
$$y = f(x_1, x_2) + \varepsilon$$

The surface represented by:

$$E(y) = f(x_1, x_2)$$

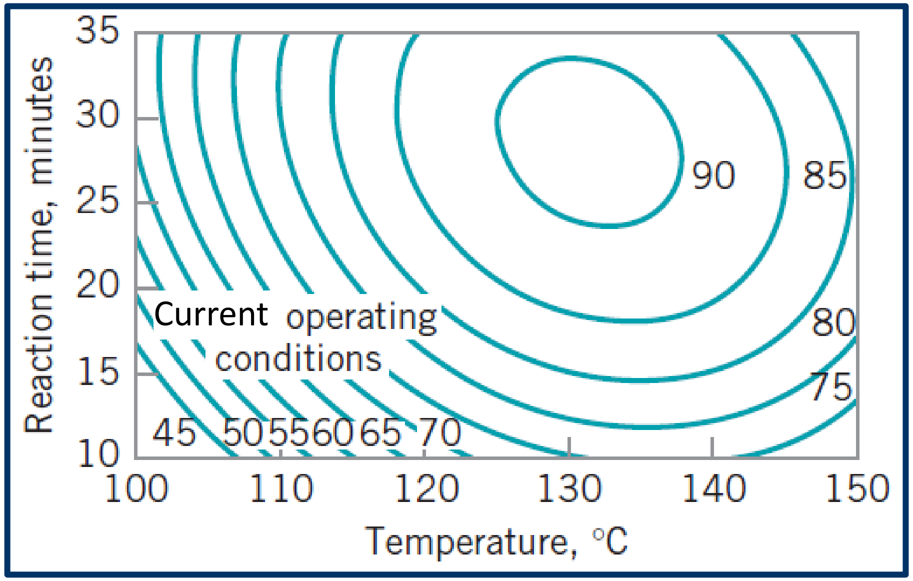
where E(y) denotes the expected value of the response, is called a response surface.

The response surface may be represented graphically as in the figure on the right, i.e., as a plot in a three-dimensional space:

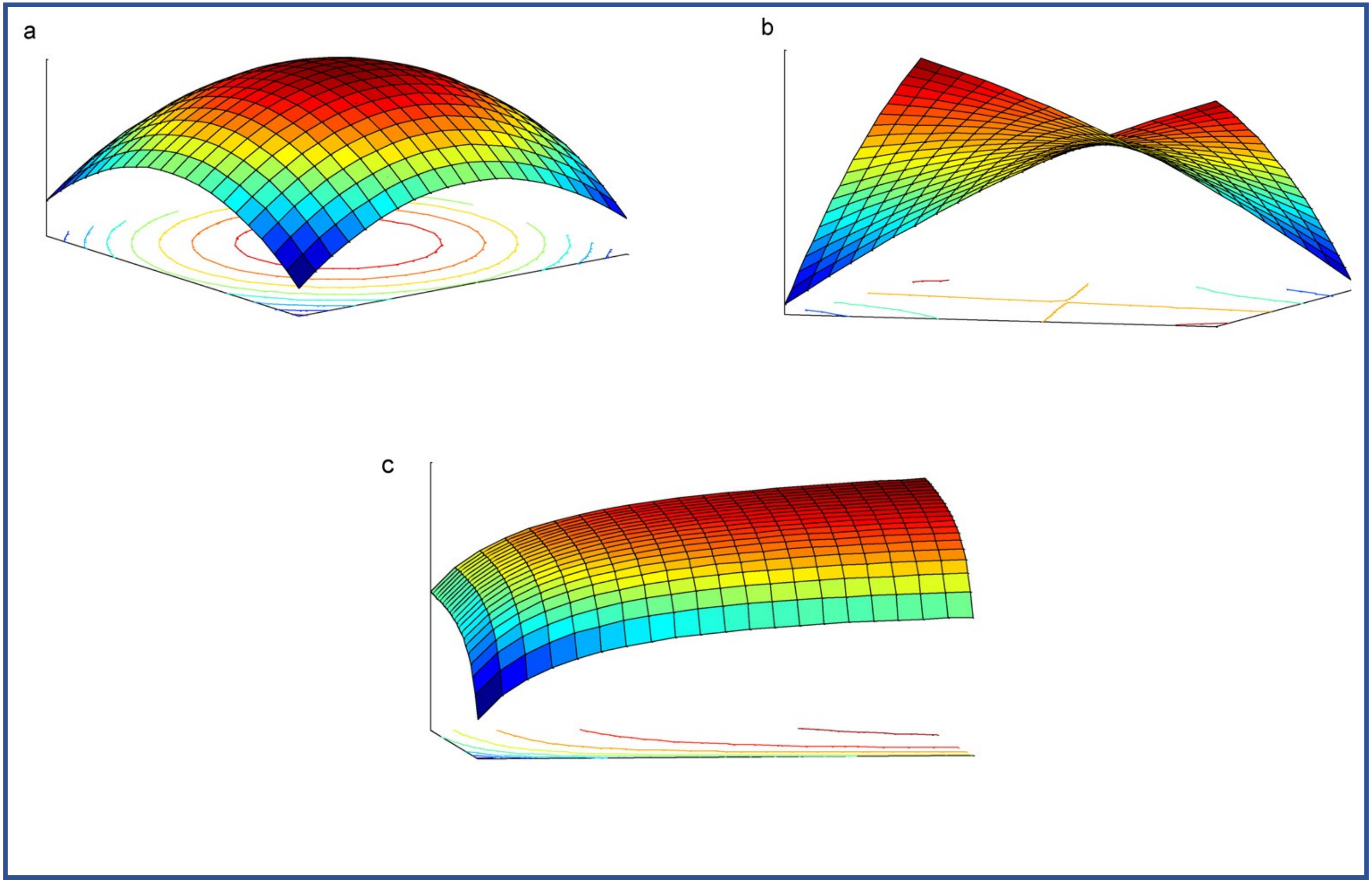


Alternatively, a contour of the response surface may be represented in the (x_1, x_2) plane:

Each contour corresponds to a particular height of the response surface.



Examples of response surfaces displaying a maximum (a), no maximum (b) or a plateau (c), respectively, are shown in the following figure: :



Since the relationship between the response and the independent variables is unknown in most RSM problems, the first step of the approach is finding a suitable approximation of the relationship between the response and the factors.

A low-order polynomial is usually employed at this aim.

Specifically, a first-order model:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_k x_k + \varepsilon$$

or a second-order model, if there is curvature in the system:

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<j=2} \sum^{k} \beta_{ij} x_i x_j + \varepsilon$$

are adopted.

The method of least squares is used to estimate the parameters in the approximating polynomials.
If the fitted surface is an adequate approximation of the true response function, the analysis of the fitted surface will be approximately equivalent to the analysis of the actual system.

When the starting point on the response surface is remote from the optimum, like in one of the figures shown before, there is little curvature in the system and the first-order model can be appropriate, since the goal is leading the experimenter rapidly and efficiently to the vicinity of the optimum.

Once the region of the optimum has been found, a more elaborate model, such as the second-order model, may be employed, and an analysis may be performed to locate the optimum.

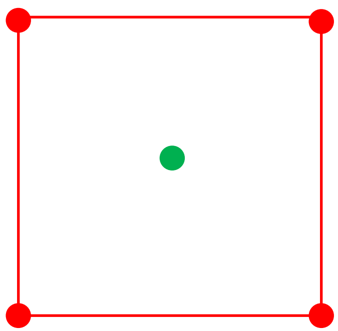
It is worth noting that RSM can guarantee only convergence to a local optimum.

Two main types of designs are typically related to RSM:

1) Central Composite Designs (CCD)
2) Box-Behnken designs

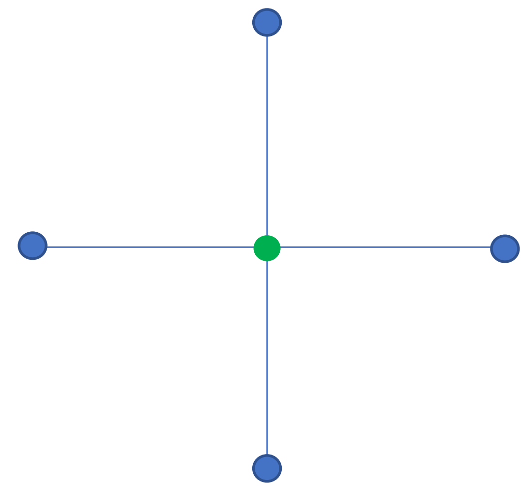
Central Composite Designs (CCD)

Central composite designs (also called Box-Wilson designs) are obtained from the combination of two designs.
When 2 factors are involved the following designs are combined:

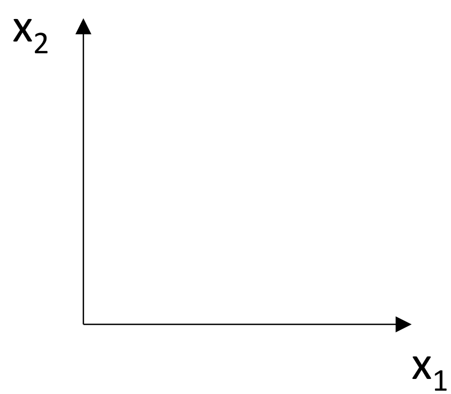


Complete factorial design
2 factors, 2 levels

+



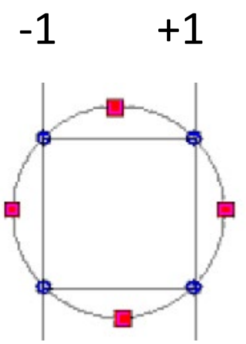
4 tip - star



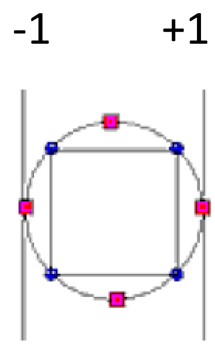
In particular, along with the complete 2^2 factorial design, a star design, based on the combination of an experiment at the center of the experimental domain and a certain number (4, 6, 8) of experiments located symmetrically around it, is performed.

More than one experiment is usually performed in the center of the design, in order to estimate the response variance and the model validity.

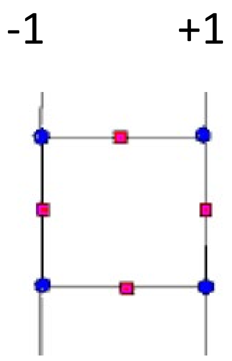
The type of CCD depends on the choice of levels related to the star design:



Circumscribed
CCC



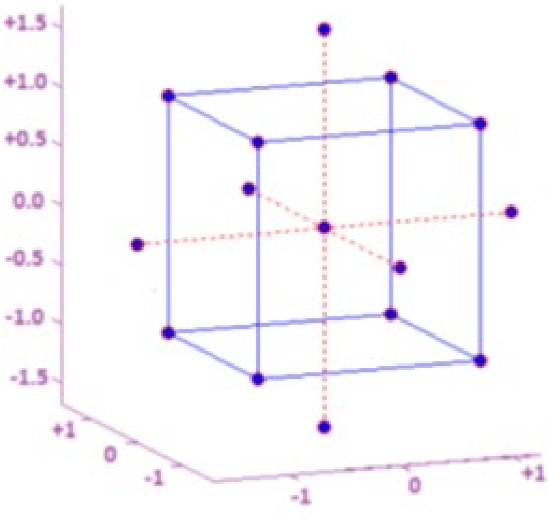
Internal or inscribed
CCI



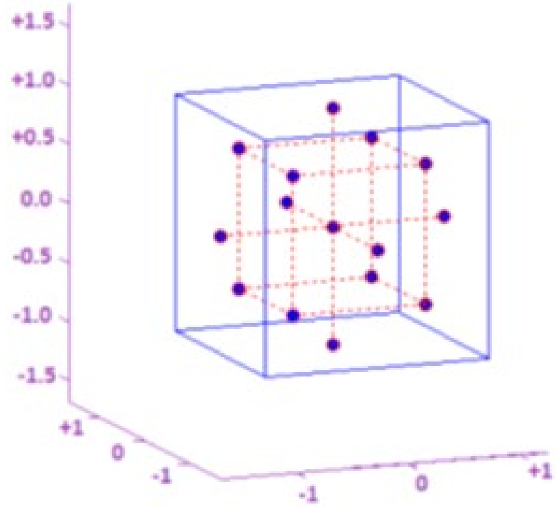
Face-centered
CCF

Notably, only the CCC has points located outside the (-1, 1) interval. CCC and CCI require 5 levels of each factor, whereas CCF only 3.

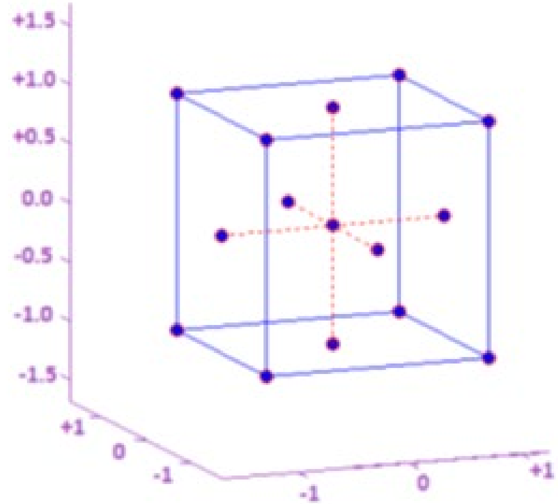
When 3 factors are considered, the following design types can be obtained:



Circumscribed
CCC



Internal or inscribed
CCI



Face-centered
CCF

In this case a six tip-star design is combined with the factorial design.

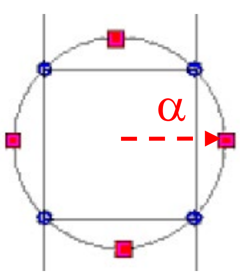
The combinations of levels to be explored for CCC designs based on two or three factors (variables) are reported in the following table:

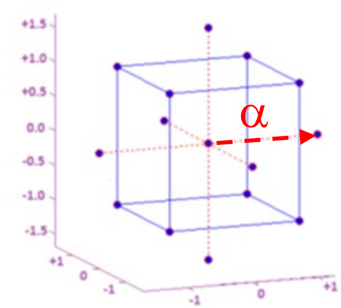
Two variables

x_1	x_2	
-1	-1	Factorial design
1	-1	
-1	1	
1	1	
0	0	Centre points
$-\alpha$	0	Axial points
α	0	
0	$-\alpha$	
0	α	

Three variables

x_1	x_2	x_3	
-1	-1	-1	Factorial design
1	-1	-1	
-1	1	-1	
1	1	-1	
-1	-1	1	
1	-1	1	
-1	1	1	
1	1	1	
0	0	0	Centre point
$-\alpha$	0	0	Axial points
α	0	0	
0	$-\alpha$	0	
0	α	0	
0	0	$-\alpha$	
0	0	α	





The number of experiments is given by $2^k + 2k + n_0$, where k is the number of factors and n_0 represents the number of replicates obtained for the central point:

Number of variables	2	3	4	5
Number of experiments in the factorial design	4	8	16	32
Number of axial points	4	6	8	10
Value of α	1.414	1.682	2.000	2.378

The value of α can be inferred from specific formulas. In the case of CCC designs :

$$\alpha = N^{1/4}$$

where N is the number of experiments included in the factorial design.

If $k = 2$, $N = 4$ and $N^{1/4} = 4^{1/4} = (4^{1/2})^{1/2} = 2^{1/2} = 1.414$;

if $k = 3$, $N = 8$ and $N^{1/4} = 8^{1/4} = (8^{1/2})^{1/2} = 2.828^{1/2} = 1.682$, etc.

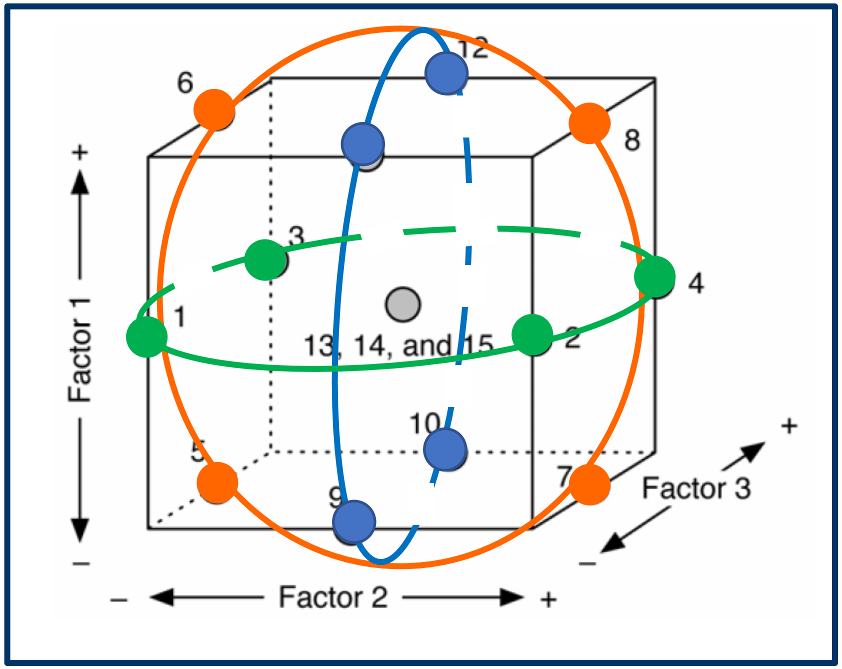
Box-Behnken Designs

In 1960 Box and Behnken proposed designs allowing a direct implementation of second-degree models.

All the factors have three levels: –1, 0, and 1. These designs are easy to carry out and have the property of sequentiality, i.e., it is possible to study k factors and still have the option to add new ones without losing the results from the trials already carried out.

The experimental points are placed not at the corners but in the middle of the edges and in the center of a cube (or hypercube).

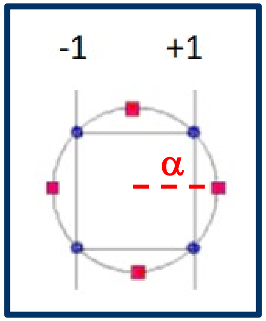
This arrangement means that all experimental points are equidistant from the center of the study domain, that is, on a sphere (or hypersphere), depending on the number of dimensions. Center points are added to the hypersphere center.



In the figure the representation of a Box-Behnken design referred to 3 factors, corresponding to a cube, is shown. A sphere protruding through each face of the cube and including all points (but the central one) on its surface is also shown.

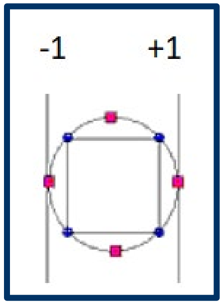
Comparison between Surface Response Designs

CCC designs (5 levels per factor)



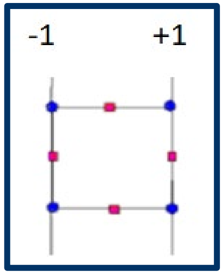
Provide high quality predictions over the entire design space but require factor settings outside the range of the factors in the factorial part.
Factor spacings can be reduced to ensure that $\pm\alpha$ values for each coded factor correspond to feasible (reasonable) levels.

CCI designs (5 levels per factor)



Use only points within the factor ranges originally specified but do not provide predictions over the entire design space with quality comparable to that of CCC designs.

CCF designs (3 levels per factor)



Provide relatively high quality predictions over the entire design space and do not require points outside the original factor range; however, they give poor precision for estimating pure quadratic coefficients.

Box-Behnken designs (3 levels per factor)

The lack of points in the corners of the design space may be useful when combinations of extreme values shoud be avoided.

A comparison between CCC/CCI, CCF and Box-Behnken designs for three factors is described in the following table:

CCC (CCI)				CCF				Box-Behnken			
Rep	X_1	X_2	X_3	Rep	X_1	X_2	X_3	Rep	X_1	X_2	X_3
1	-1	-1	-1	1	-1	-1	-1	1	-1	-1	0
1	+1	-1	-1	1	+1	-1	-1	1	+1	-1	0
1	-1	+1	-1	1	-1	+1	-1	1	-1	+1	0
1	+1	+1	-1	1	+1	+1	-1	1	+1	+1	0
1	-1	-1	+1	1	-1	-1	+1	1	-1	0	-1
1	+1	-1	+1	1	+1	-1	+1	1	+1	0	-1
1	-1	+1	+1	1	-1	+1	+1	1	-1	0	+1
1	+1	+1	+1	1	+1	+1	+1	1	+1	0	+1
1	-1.682	0	0	1	-1	0	0	1	0	-1	-1
1	1.682	0	0	1	+1	0	0	1	0	+1	-1
1	0	-1.682	0	1	0	-1	0	1	0	-1	+1
1	0	1.682	0	1	0	+1	0	1	0	+1	+1
1	0	0	-1.682	1	0	0	-1	3	0	0	0
1	0	0	1.682	1	0	0	+1				
6	0	0	0	6	0	0	0				
Total Runs = 20				Total Runs = 20				Total Runs = 15			

For three factors the Box-Behnken design offers some advantage, since it requires a fewer number of runs. For 4 or more factors this advantage disappears.

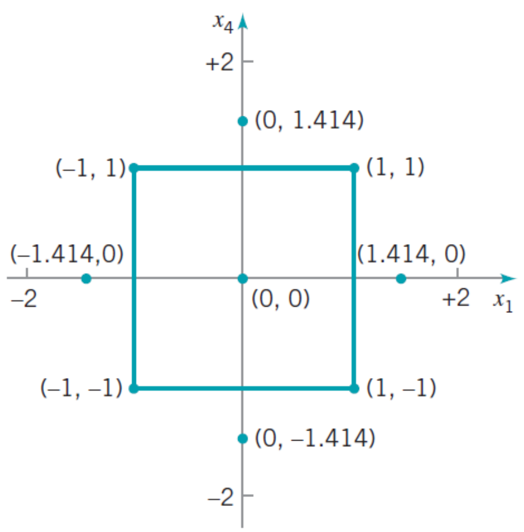
An example of use of Central Composite Design in a response surface method

The use of CCD in a response surface method can be described by reconsidering the optimization of the silicon nitride etch process on a single-wafer plasma etcher.

As shown before, using the steepest ascent approach, a gap between electrodes of 0.8 cm and a power of 375 W were found to provide etching rates (1163 Å/min) near the desired operating region for the process (1100-1150 Å/min).

The experimenters decided to explore the maximum rate region more closely by running an experiment that would support a second-order response surface model, based on a central composite design, with four replicates in the central point. Etch uniformity was also evaluated:

Observation	Gap (cm)	Power (W)	Coded Variables x_1	x_4	Etch Rate y_1(Å/m)	Uniformity y_2(Å/m)
1	0.600	350.0	−1.000	−1.000	1054.0	79.6
2	1.000	350.0	1.000	−1.000	936.0	81.3
3	0.600	400.0	−1.000	1.000	1179.0	78.5
4	1.000	400.0	1.000	1.000	1417.0	97.7
5	0.517	375.0	−1.414	0.000	1049.0	76.4
6	1.083	375.0	1.414	0.000	1287.0	88.1
7	0.800	339.6	0.000	−1.414	927.0	78.5
8	0.800	410.4	0.000	1.414	1345.0	92.3
9	0.800	375.0	0.000	0.000	1151.0	90.1
10	0.800	375.0	0.000	0.000	1150.0	88.3
11	0.800	375.0	0.000	0.000	1177.0	88.6
12	0.800	375.0	0.000	0.000	1196.0	90.1



The complete second order model for the etch rate was:

$$\hat{y}_1 = 1168.50 + 57.07x_1 + 149.64x_4 - 1.62x_1^2 - 17.63x_4^2 + 89.00x_1x_4$$

The ANOVA table for this model (obtained with the Minitab software) was:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	5	238898	238898	47780	38.59	0.000
Linear	2	205202	205202	102601	82.87	0.000
Square	2	2012	2012	1006	0.81	0.487
Interaction	1	31684	31684	31684	25.59	0.002
Residual Error	6	7429	7429	1238		
Lack-of-Fit	3	5952	5952	1984	4.03	0.141
Pure Error	3	1477	1477	492		
Total	11	246327				

The contribution due to square terms was thus found to be not statistically significant.

This result was confirmed by the t-test performed on model coefficients:

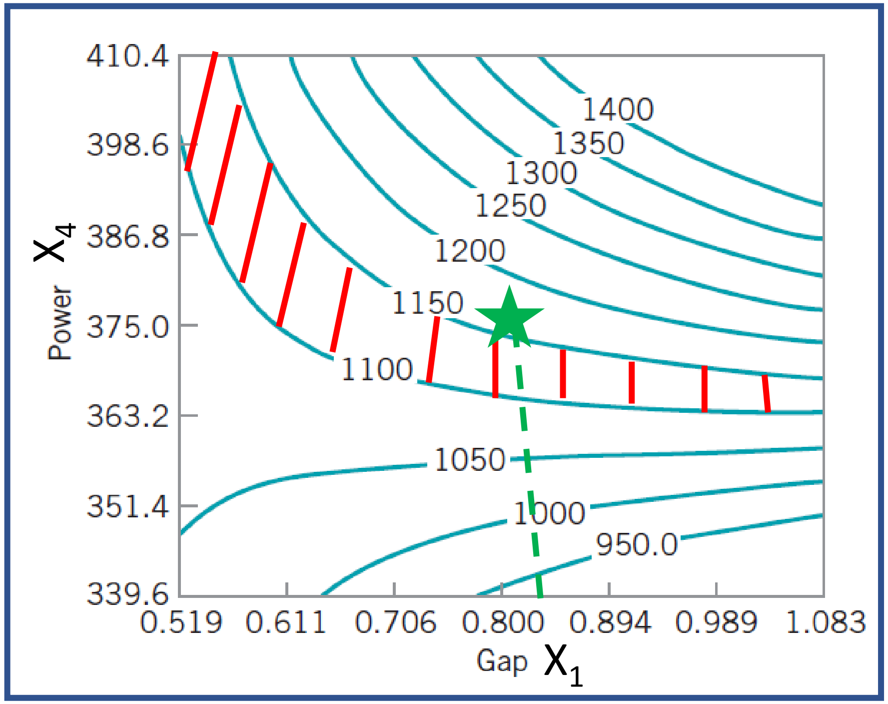
Term	Coef	SE Coef	T	P
Constant	1168.50	17.59	66.417	0.000
A	57.07	12.44	4.588	0.004
B	149.64	12.44	12.029	0.000
A*A	-1.62	13.91	-0.117	0.911
B*B	-17.63	13.91	-1.267	0.252
A*B	89.00	17.59	5.059	0.002

A first - order model with interaction was thus considered:

$$\hat{y}_1 = 1155.7 + 57.1x_1 + 149.7x_4 + 89x_1x_4$$

Based on the resulting contour plot, all combinations of variables x_1 and x_4 included in the region emphasized in the figure were found to provide an etch rate included in the 1100 – 1150 Å/min range.

The best combination of variables determined previously and the path leading towards it are also indicated in the figure.



Turning to the etch uniformity, meant as the standard deviation of the thickness of the material layer applied to the wafer surface, the equation for the second-order model was:

$$\hat{y}_2 = 89.275 + 4.681x_1 + 4.352x_4 - 3.400x_1^2 - 1.825x_4^2 + 4.375x_1x_4$$

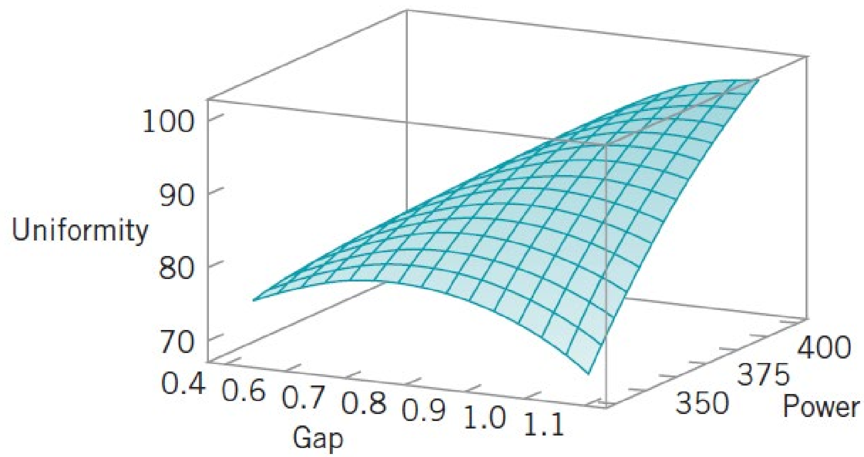
The ANOVA and the t-statistics for the model terms tables were the following:

Source	DF	Seq SS	Adj SS	Adj MS	F	P
Regression	5	486.085	486.085	97.217	75.13	0.000
Linear	2	326.799	326.799	163.399	126.28	0.000
Square	2	82.724	82.724	41.362	31.97	0.001
Interaction	1	76.563	76.563	76.563	59.17	0.000
Residual Error	6	7.764	7.764	1.294		
Lack-of-Fit	3	4.996	4.996	1.665	1.81	0.320
Pure Error	3	2.768	2.768	0.923		
Total	11	493.849				

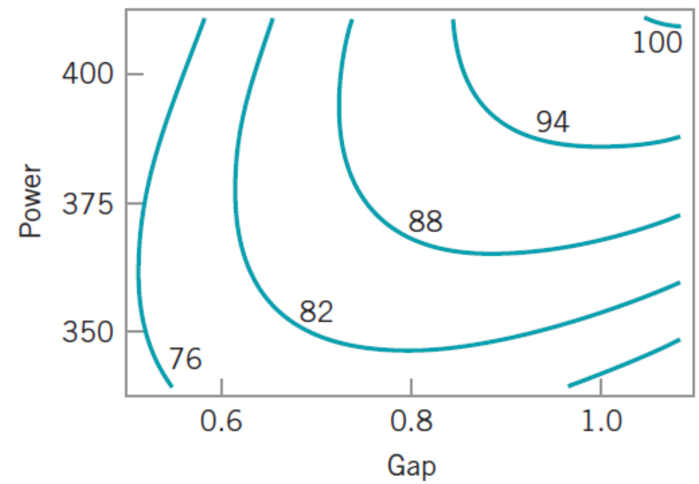
Term	Coef	SE Coef	T	P
Constant	89.275	0.5688	156.963	0.000
A	4.681	0.4022	11.639	0.000
B	4.352	0.4022	10.821	0.000
A*A	-3.400	0.4496	-7.561	0.000
B*B	-1.825	0.4496	-4.059	0.007
A*B	4.375	0.5688	7.692	0.000

Since all terms were significant, the experimenters confirmed the quadratic model.

The following response surface and contour plot were thus obtained:



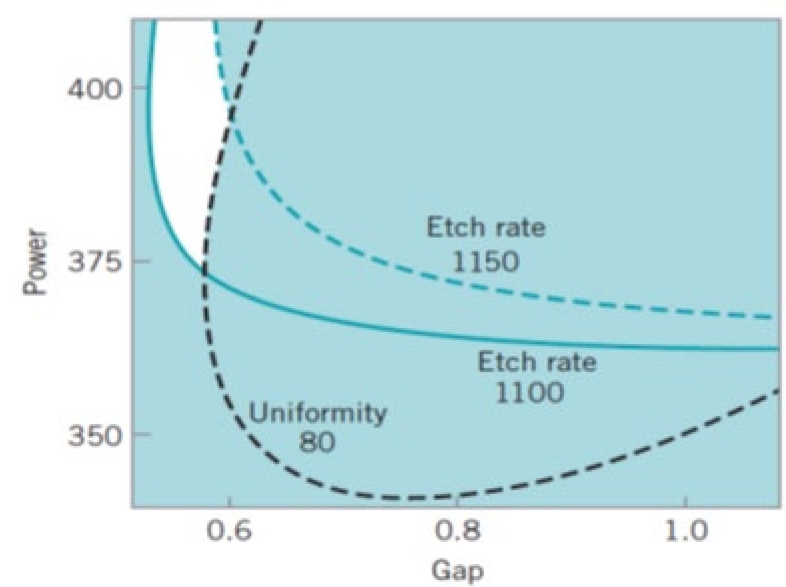
response surface



contour plot

Since only uniformity values not exceeding 80 could be considered acceptable, an overlay with the contour plot referred to etch rate was adopted to find the best compromise for the two responses:

The unshaded region in the overlay plot was thus found as the one providing an acceptable process performance.



A further example of use of Central Composite Design for RSM

The synthesis of an amine from a ketone was complicated by the generation of a by-product. Three two-level factors were considered to deal with this problem:

1. Ketone concentration (x_1)
2. Concentration of the scavenger used to remove water (x_2)
3. Temperature (x_3)

Two responses were considered:

1. Amine percent yield (minimum acceptable value: 85%)
2. By-product percentage (maximum acceptable value: 10%)

A Central Composite Design for three factors was adopted.

A second-order model including quadratic terms and also interactions between couple of factors was considered:

$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i<j} \sum \beta_{ij} x_i x_j + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \epsilon$$

The model matrix was the following:

2³ factorial design

axial points

central point

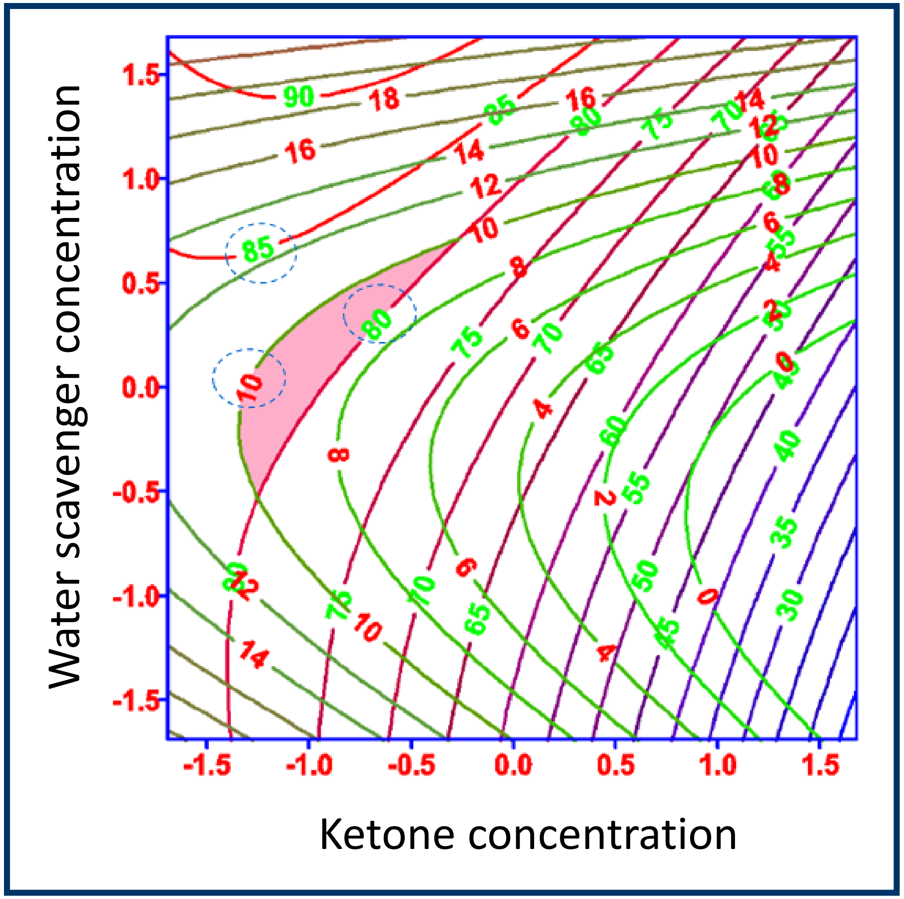
m	X_1	X_2	X_3	X_1^2	X_2^2	X_3^2	$X_1 X_2$	$X_1 X_3$	$X_2 X_3$
1	-1.0000	-1.0000	-1.0000	1	1	1	1	1	1
1	-1.0000	-1.0000	1.0000	1	1	1	1	-1	-1
1	-1.0000	1.0000	-1.0000	1	1	1	-1	1	-1
1	-1.0000	1.0000	1.0000	1	1	1	-1	-1	1
1	1.0000	-1.0000	-1.0000	1	1	1	-1	-1	1
1	1.0000	-1.0000	1.0000	1	1	1	-1	1	-1
1	1.0000	1.0000	-1.0000	1	1	1	1	-1	-1
1	1.0000	1.0000	1.0000	1	1	1	1	1	1
1	-1.6818	0	0	2.82843	0	0	0	0	0
1	1.6818	0	0	2.82843	0	0	0	0	0
1	0	-1.6818	0	0	2.82843	0	0	0	0
1	0	1.6818	0	0	2.82843	0	0	0	0
1	0	0	-1.6818	0	0	2.82843	0	0	0
1	0	0	1.6818	0	0	2.82843	0	0	0
1	0	0	0	0	0	0	0	0	0

Experimental data and model coefficients were the following:

Amine yield	By-product yield
81.3	10.5
85.2	5.3
91.4	7.9
91.2	4.7
50.4	2.7
72.4	6.7
77.2	5.7
93.2	11.7
85.3	1.7
60.9	1.
79.2	10.3
97.1	14.3
70.3	4.7
85.8	5.1
85.1	2.

	Amine yield	By-product yield
b_0	84.938	1.911
b_1	-7.098	-0.203
b_2	6.869	0.844
b_3	4.962	0.166
b_{11}	-4.018	-0.107
b_{22}	1.303	3.764
b_{33}	-2.268	1.148
b_{12}	3.938	1.4
b_{13}	4.288	2.3
b_{23}	-1.263	0.5

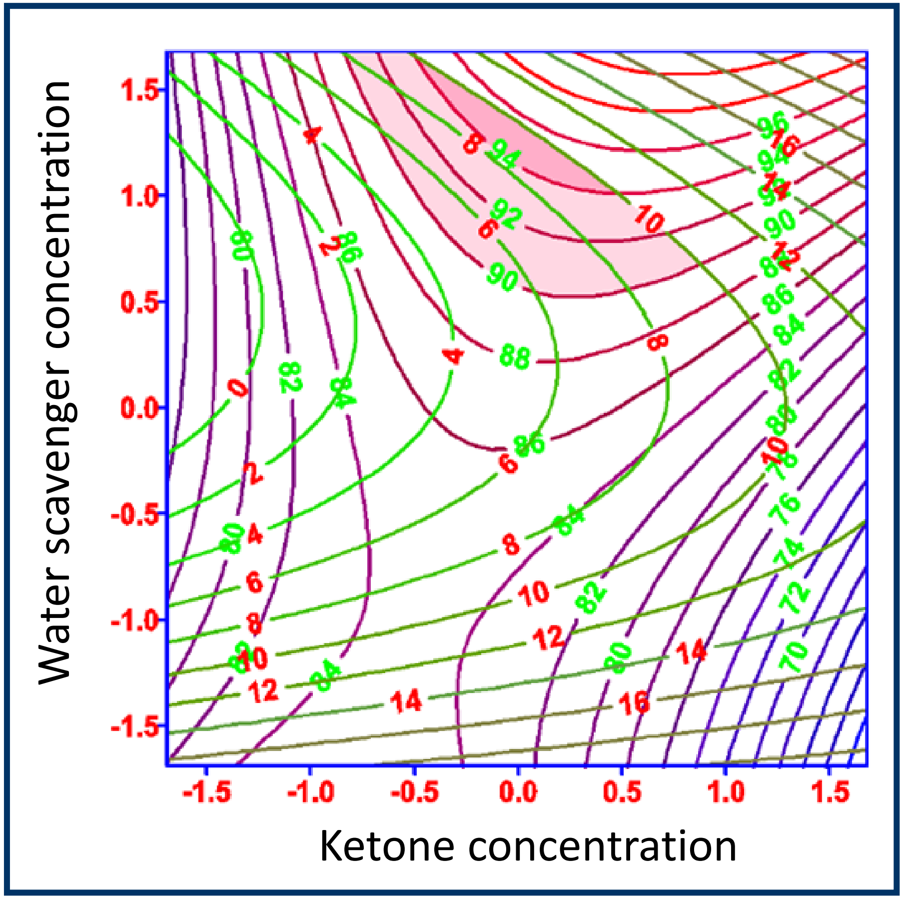
The overlay of contour plots was performed first by considering the lower level of temperature:



In the figure red lines refer to amine yield, green lines to the by-product percentage.

The pink-colored zone includes almost satisfying combinations of factors, with amine yield comprised between 80 and 85% and by-product yields between 8 and 10%.

The overlay of contour plots at the higher level of temperature was the following:



In this case a region corresponding to amine yields higher than 90% and by-product percentages lower than 10% could be found.

These conditions were generally better than those obtained at lower temperature.

An example of use of Box-Behnken design in a response surface method

The effect of pH, temperature and substrate (p-phenylenediamine, PPD) concentration on the kinetics of reaction rate under catalysis by the enzyme ceruloplasmin (CP) (a copper-including enzyme able to oxidize Fe^{2+} into Fe^{3+} *in vivo*) was preliminarily evaluated using a 2^3 factorial design, for screening purposes.

pH and PPD concentration were found to have an influence on the reaction kinetics, whereas the variation of temperature did not have a significant effect, thus a Box-Behnken design was performed at a fixed temperature of 37°C.

pH and the concentrations of PPD and CP were selected as 3-level factors:

Factors	*Low*	*High*	*Units*	*Continuous*
[PPD]	0,5	27,3	mM	Yes
pH	4,8	6,4		Yes
[CP]	0,7	26,0	mg/L	Yes

15 runs were performed, considering 3 replicates in the central point of the design.

The following results, expressed as reaction rates (min^{-1}), were obtained:

Run	*[PPD] (mM)*	*pH*	*[CP] (mg/L)*	*Reaction rate (min^{-1})*
1	0.5	4.8	13.35	6.58
2	27.3	5.6	0.7	5.27
3	27.3	5.6	26.0	37.2
4	13.9	6.4	26.0	33.63
5	0.5	5.6	26.0	14.95
6*	13.9	5.6	13.35	23.8
7	13.9	4.8	26.0	26.02
8	13.9	4.8	0.7	1.0
9	27.3	6.4	13.35	20.67
10	0.5	5.6	0.7	1.87
11	13.9	6.4	0.7	4.4
12*	13.9	5.6	13.35	24.43
13*	13.9	5.6	13.35	23.29
14	0.5	6.4	13.35	8.21
15	27.3	4.8	13.35	12.67

* Replicates in the central point

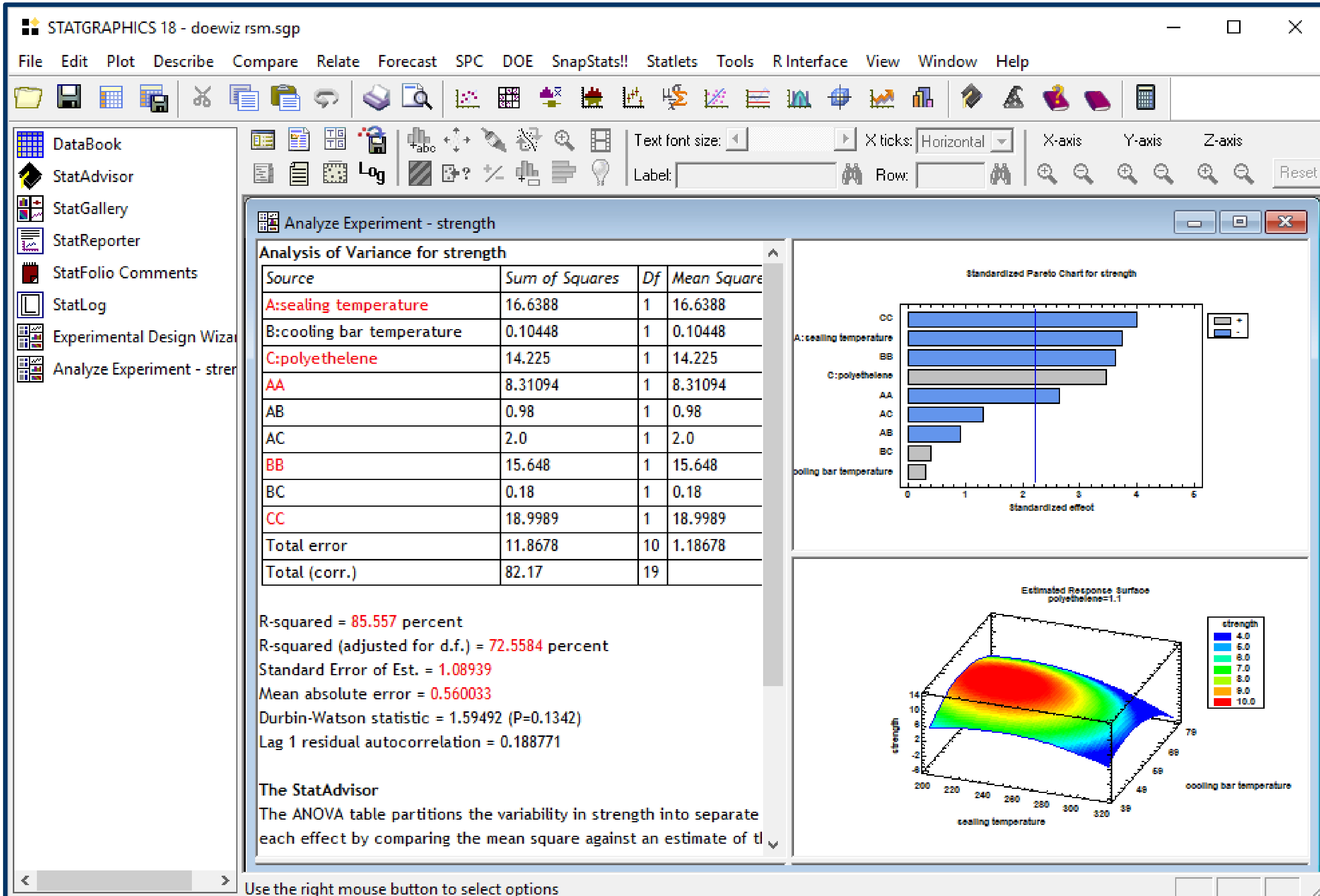
Calculations of estimated effects with the corresponding standard error were performed using the Statgraphics software:

Effect	*Estimate*	*Stnd. Error*	*V.I.F.*
average	23,86	1,08637	
A:[PPD]	11,05	1,33052	1,0
B:pH	5,145	1,33052	1,0
C:[CP]	24,8	1,33052	1,0
AA	-13,2825	1,95848	1,01111
AB	3,185	1,88164	1,0
AC	9,425	1,88164	1,0
BB	-10,3725	1,95848	1,01111
BC	2,135	1,88164	1,0
CC	-4,7925	1,95848	1,01111

Note that the already defined Variance Inflation Factor, V.I.F. , is equal to $1/(1-R^2_j)$ where R^2_j represents the square of correlation coefficient obtained from an ordinary least square regression in which variable X_j is modeled as a function of all the other explanatory variables.

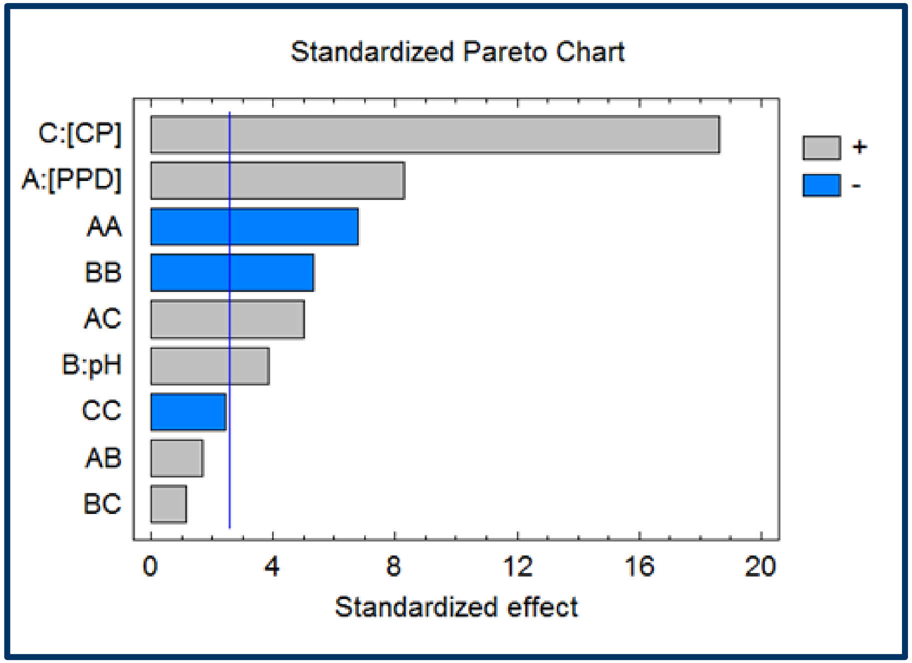
A V.I.F. close to unity implies that R^2_j is close to 0, i.e., that variable X_j is almost not correlated at all with other variables.

This is a snapshot of the Statgraphics 18 software related to the Design of Experiments:



The ANOVA table and standardized Pareto Chart were also obtained with the same software:

Source	*Sum of Squares*	*Df*	*Mean Square*	*F-Ratio*	*P-Value*
A:[PPD]	244,205	1	244,205	68,97	0,0004
B:pH	52,9421	1	52,9421	14,95	0,0118
C:[CP]	1230,08	1	1230,08	347,42	0,0000
AA	162,854	1	162,854	46,00	0,0011
AB	10,1442	1	10,1442	2,87	0,1513
AC	88,8306	1	88,8306	25,09	0,0041
BB	99,3127	1	99,3127	28,05	0,0032
BC	4,55823	1	4,55823	1,29	0,3080
CC	21,2013	1	21,2013	5,99	0,0581
Total error	17,7029	5	3,54058		
Total (corr.)	1901,49	14			



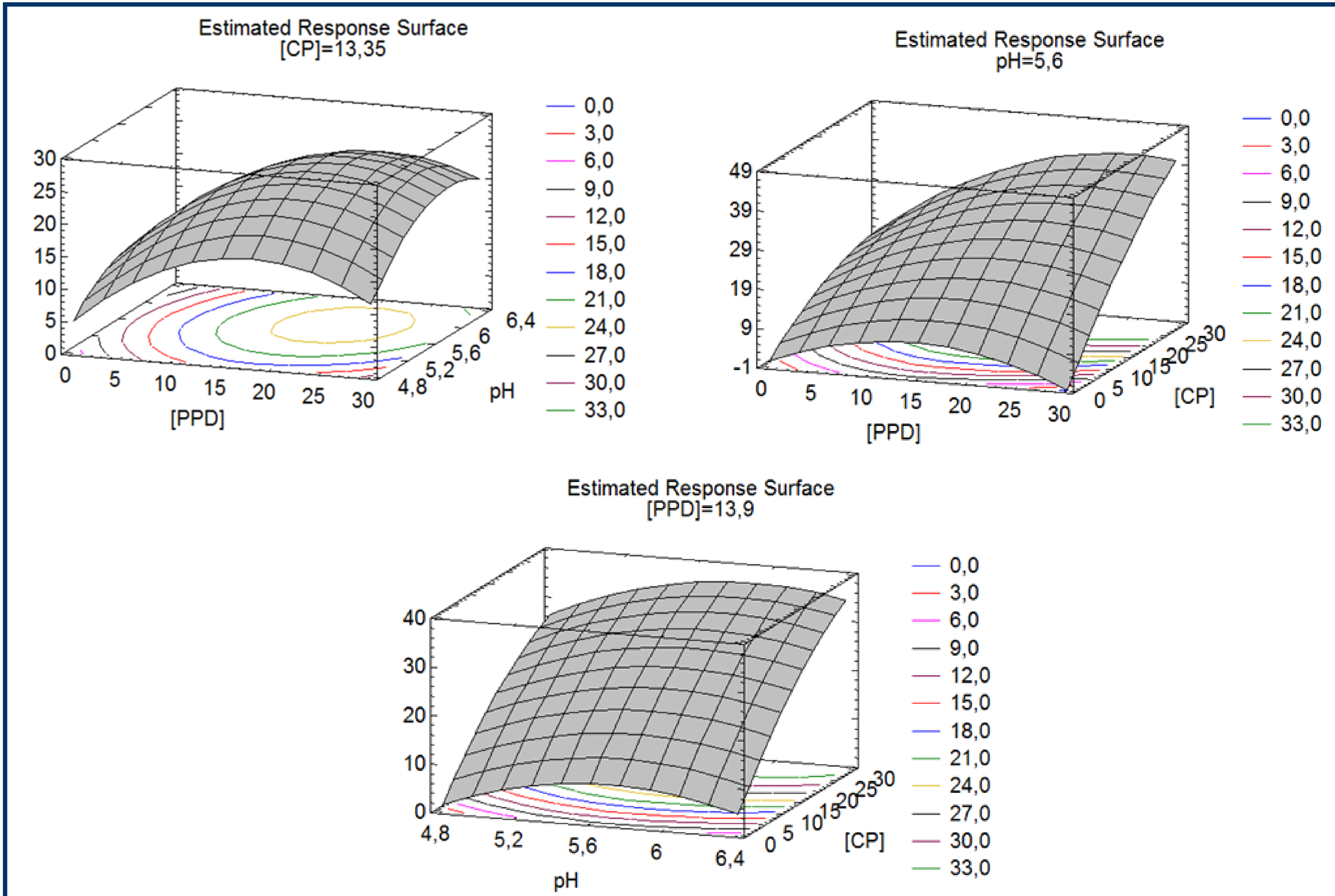
The following regression coefficients were obtained:

Coefficient	*Estimate*
constant	-252,298
A:[PPD]	0,237488
B:pH	90,5019
C:[CP]	0,402914
AA	-0,0369862
AB	0,148554
AC	0,0278007
BB	-8,10352
BC	0,105484
CC	-0,0149745

The equation of the fitted model for the reaction rate was, then:

-252,298 + 0,237488*[PPD] + 90,5019*pH + 0,402914*[CP] - 0,0369862*[PPD]^2 + 0,148554*[PPD]*pH + 0,0278007*[PPD]*[CP] - 8,10352*pH^2 + 0,105484*pH*[CP] - 0,0149745*[CP]^2

Since three variables were selected, response surfaces could be represented as 3D-plots only after fixing one of them:



The optimum value and the path of steepest ascent could be finally determined:

Optimum value = 38,9715

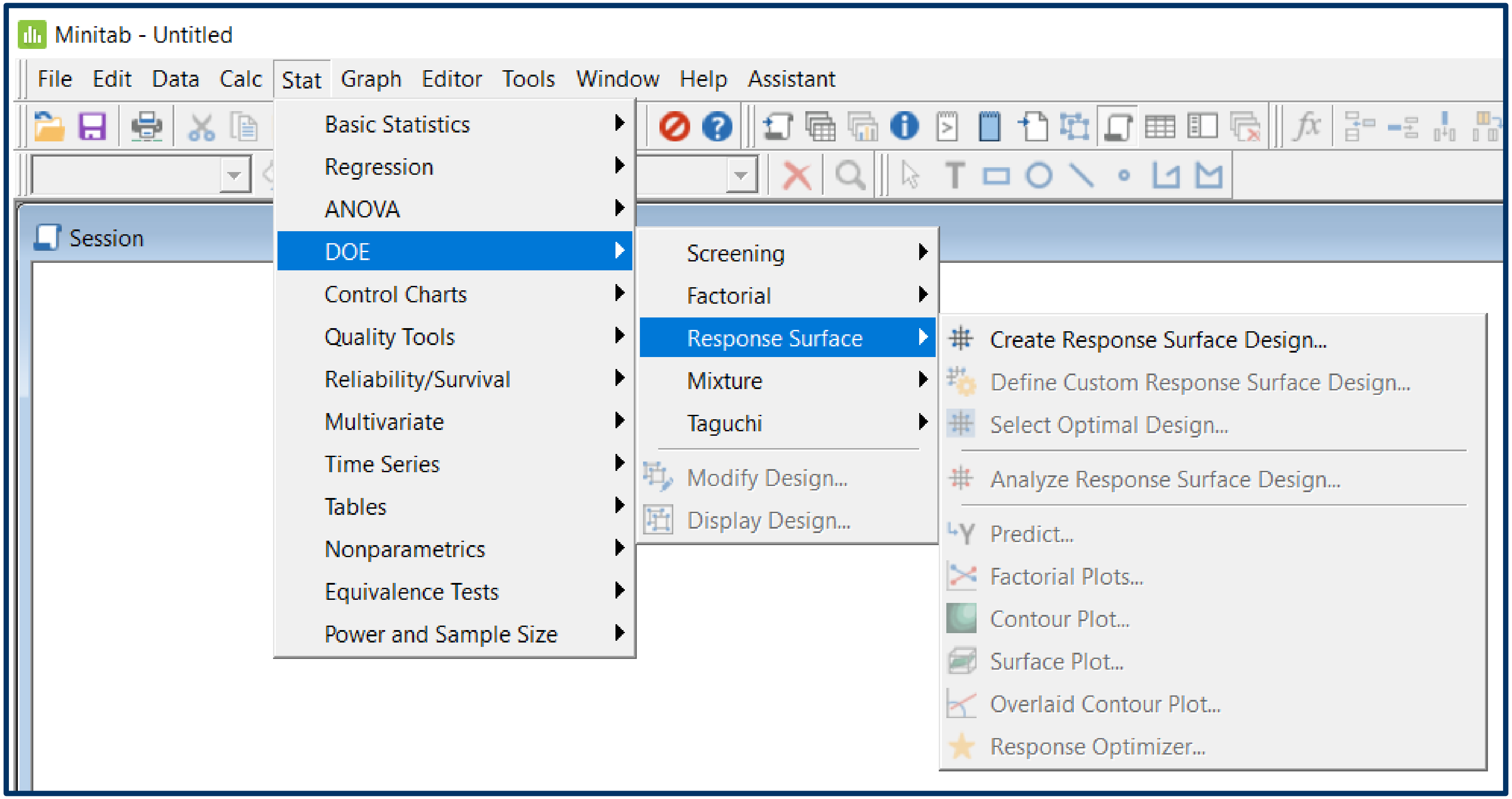
Factor	*Low*	*High*	*Optimum*
[PPD]	0,5	27,3	25,0236
pH	4,8	6,4	5,98213
[CP]	0,7	26,0	26,0

Path of Steepest Ascent

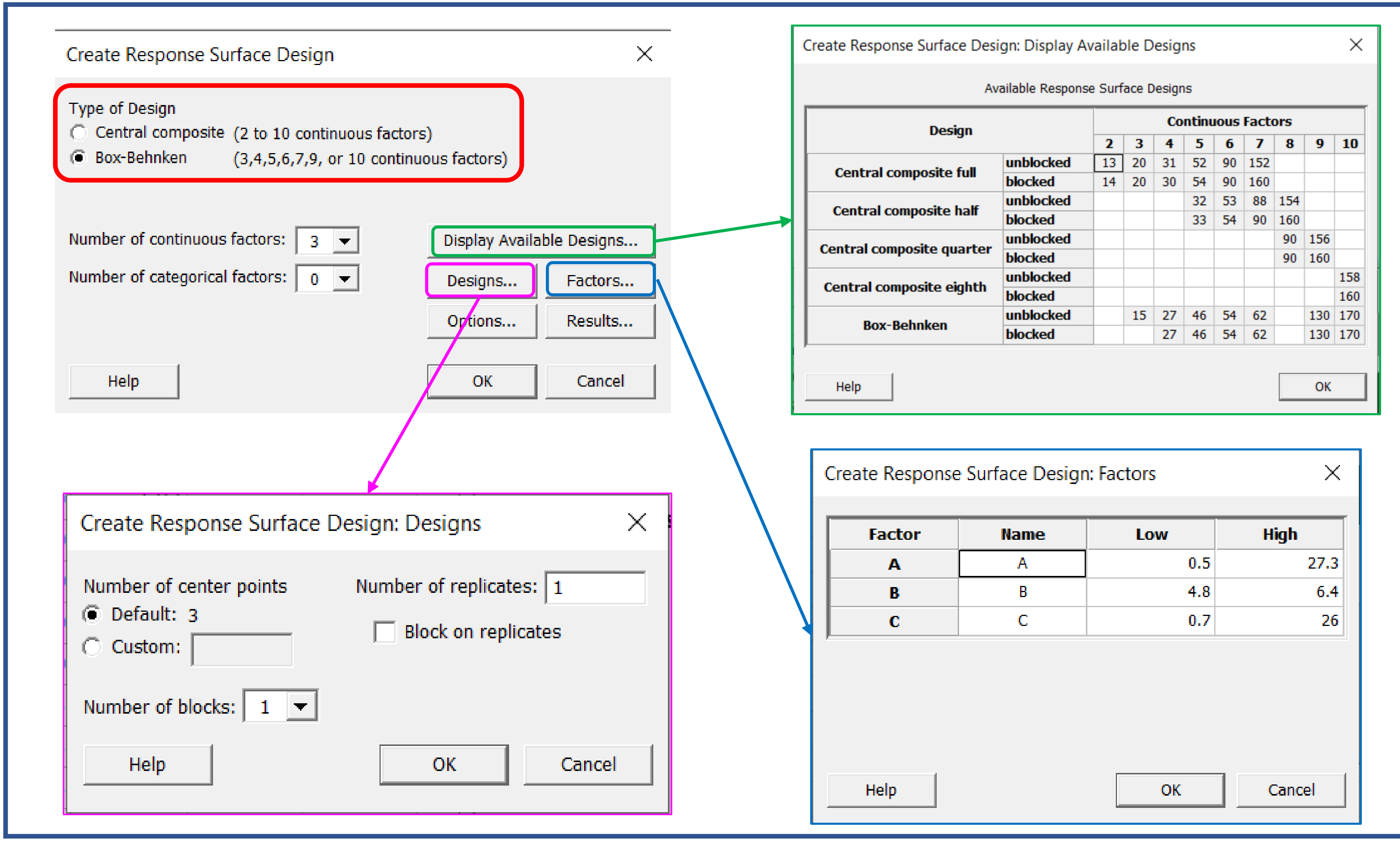
[PPD] (mM)	*pH*	*[CP] (mg/L)*	*Predicted reaction rate (min-1)*
13,9	5,6	13,35	23,84
14,9	5,62787	15,4641	26,3747
15,9	5,65576	17,5644	28,8149
16,9	5,68369	19,6529	31,1638
17,9	5,71165	21,7314	33,4238
18,9	5,73966	23,8014	35,5972
19,9	5,76773	25,8641	37,6858
20,9	5,79584	27,9207	39,6911
21,9	5,82401	29,9721	41,6143
22,9	5,85223	32,0191	43,4566
23,9	5,88051	34,0624	45,2187

Use of Minitab 18 to perform calculations on designs of experiments for RSM

Calculations on RSM designs of experiments can be performed by Minitab 18 after accessing the Stat > DOE > Response Surface path, and choosing the Create Response Surface Design… command:



The type of design can be selected in the corresponding window:



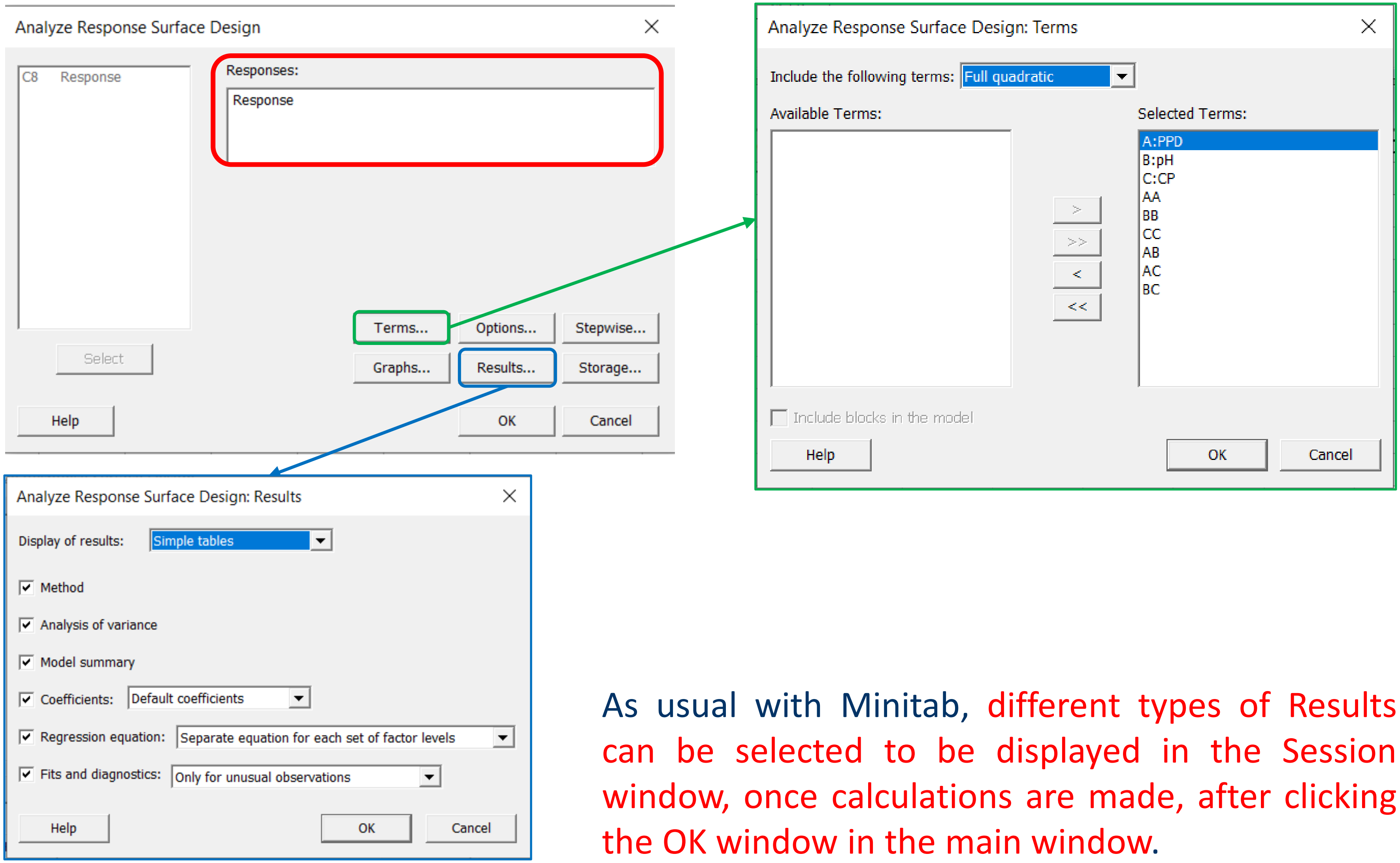
As an example, if the Box-Behnken design is selected with 3 continuous factors, whose low and high limits correspond to those of the ceruloplasmin kinetics experiment, the following table of factors is created in the Minitab worksheet and responses can then be inserted:

Worksheet 2 ***

↓	C1	C2	C3	C4	C5	C6	C7	C8
	StdOrder	RunOrder	PtType	Blocks	PPD	pH	CP	Response
1	13	1	0	1	13.9	5.6	13.35	23.80
2	14	2	0	1	13.9	5.6	13.35	24.43
3	15	3	0	1	13.9	5.6	13.35	23.29
4	11	4	2	1	13.9	4.8	26.00	26.02
5	5	5	2	1	0.5	5.6	0.70	1.87
6	12	6	2	1	13.9	6.4	26.00	33.63
7	7	7	2	1	0.5	5.6	26.00	14.95
8	6	8	2	1	27.3	5.6	0.70	5.27
9	9	9	2	1	13.9	4.8	0.70	1.00
10	2	10	2	1	27.3	4.8	13.35	12.67
11	4	11	2	1	27.3	6.4	13.35	20.67
12	3	12	2	1	0.5	6.4	13.35	8.21
13	8	13	2	1	27.3	5.6	26.00	37.20
14	1	14	2	1	0.5	4.8	13.35	6.58
15	10	15	2	1	13.9	6.4	0.70	4.40

Note that generic names of factors, A, B and C can be replaced by the actual names in the corresponding column headings of the worksheet.

The Response Surface Design can be analysed using the Analyze Response Surface Design… command in the Stat > DOE > Response Surface path. The corresponding window enables the selection of the response column and setting different conditions for analysis:



As usual with Minitab, different types of Results can be selected to be displayed in the Session window, once calculations are made, after clicking the OK window in the main window.

Here are the main results that can be found in the Session window after calculations:

Box-Behnken Design

Design Summary

Factors:	3	Replicates:	1
Base runs:	15	Total runs:	15
Base blocks:	1	Total blocks:	1

Center points: 3

Design Table (randomized)

Run	Blk	A	B	C
1	1	0	0	0
2	1	0	0	0
3	1	0	0	0
4	1	0	-1	1
5	1	-1	0	-1
6	1	0	1	1
7	1	-1	0	1
8	1	1	0	-1
9	1	0	-1	-1
10	1	1	-1	0
11	1	1	1	0
12	1	-1	1	0
13	1	1	0	1
14	1	-1	-1	0
15	1	0	1	-1

Response Surface Regression: Response versus PPD; pH; CP

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	9	1884.55	209.39	58.61	0.000
Linear	3	1529.02	509.67	142.66	0.000
PPD	1	244.21	244.21	68.35	0.000
pH	1	53.25	53.25	14.90	0.012
CP	1	1231.57	1231.57	344.71	0.000
Square	3	252.12	84.04	23.52	0.002
PPD*PPD	1	162.00	162.00	45.34	0.001
pH*pH	1	99.22	99.22	27.77	0.003
CP*CP	1	21.16	21.16	5.92	0.059
2-Way Interaction	3	103.41	34.47	9.65	0.016
PPD*pH	1	10.14	10.14	2.84	0.153
PPD*CP	1	88.83	88.83	24.86	0.004
pH*CP	1	4.43	4.43	1.24	0.316
Error	5	17.86	3.57		
Lack-of-Fit	3	17.21	5.74	17.59	0.054
Pure Error	2	0.65	0.33		
Total	14	1902.42			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
1.89017	99.06%	97.37%	85.45%

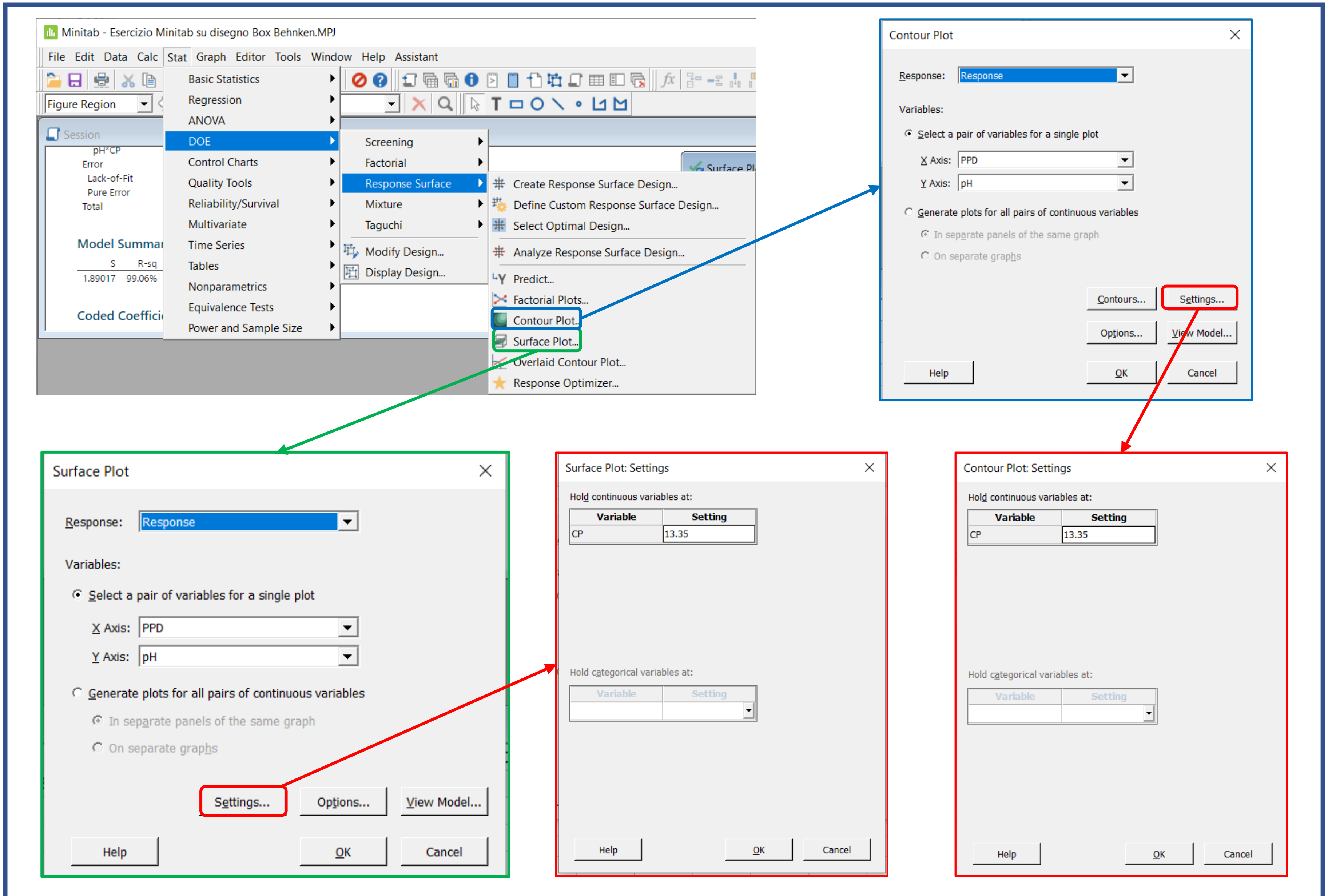
Regression Equation in Uncoded Units

Response = -252.3 + 0.235 PPD + 90.5 pH + 0.411 CP - 0.03689 PPD*PPD - 8.10 pH*pH - 0.01496 CP*CP + 0.1486 PPD*pH + 0.02780 PPD*CP + 0.1040 pH*CP

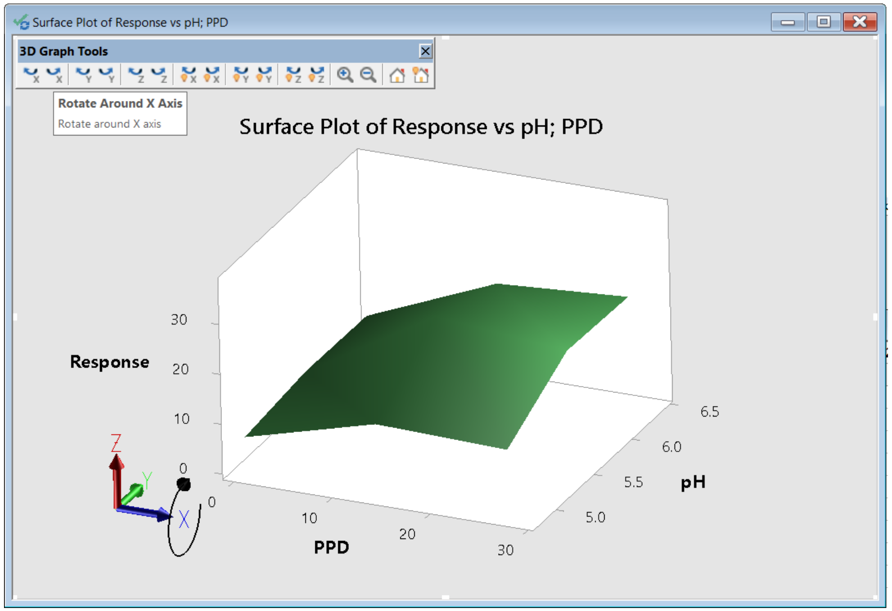
Coded Coefficients

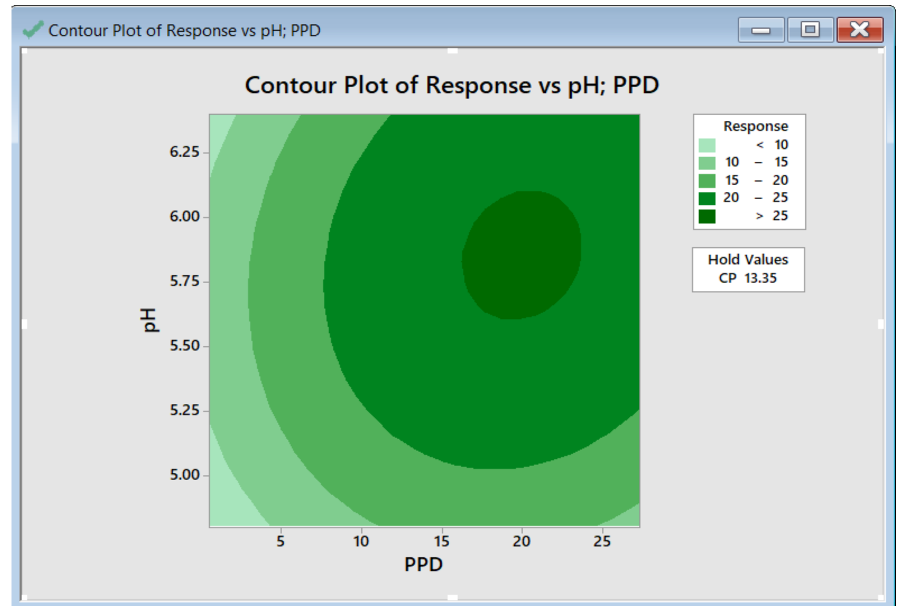
Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	23.84	1.09	21.85	0.000	
PPD	5.525	0.668	8.27	0.000	1.00
pH	2.580	0.668	3.86	0.012	1.00
CP	12.407	0.668	18.57	0.000	1.00
PPD*PPD	-6.624	0.984	-6.73	0.001	1.01
pH*pH	-5.184	0.984	-5.27	0.003	1.01
CP*CP	-2.394	0.984	-2.43	0.059	1.01
PPD*pH	1.593	0.945	1.69	0.153	1.00
PPD*CP	4.713	0.945	4.99	0.004	1.00
pH*CP	1.053	0.945	1.11	0.316	1.00

As for screening designs, graphical representations of results, either as contour or as surface plots, can be made using the Stat > DOE > Response Surface menu:

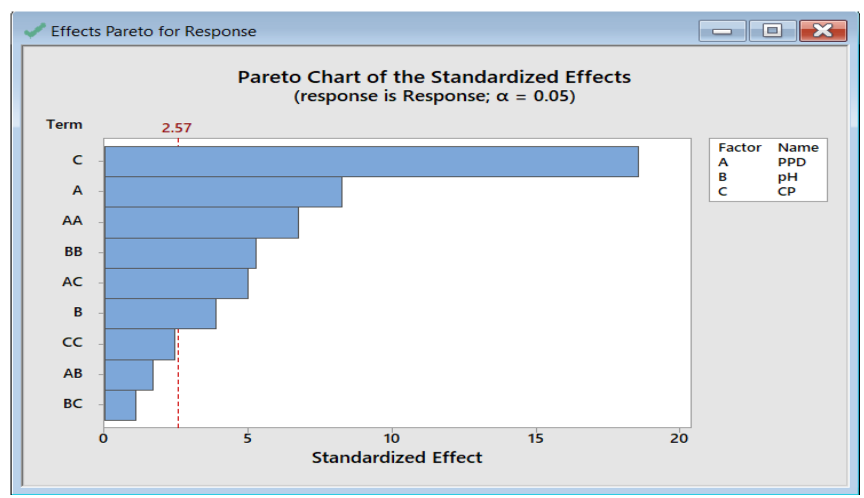


Here are examples of surface and contour plots obtained for data referred to the ceruloplasmin kinetics, fixing one of the three factors (in the specific case, [CP] = 13.35 mg/L, i.e., the average between the maximum and the minimum value adopted for this factor):





The Pareto Chart for standardized effects is obtained as a further graph, obtained upon appropriate selection inside the Graphs sub-window in the Analyze Response Surface Design window.



Example of an entire optimization procedure

After performing a 2^2 factorial design for screening purposes, a time of 35 min and a temperature of 155 °F were found as the best combination of the two factors, leading to a reaction yield of 40%.
Since this result was considered far from the optimum, the steepest ascent approach was adopted to search for an improvement.

The region of exploration to fit the first-order model was 30-40 min of reaction time and 150-160 °F for temperature.

Variables were coded using the following equations:

Reaction time

$$x_1 = \frac{\xi_1 - 35}{5}$$

Reaction temperature

$$x_2 = \frac{\xi_2 - 155}{5}$$

The following experimental design was adopted, based on a 2^2 factorial design augmented by five center points, obtained on the operating conditions found after the screening step:

Natural Variables		Coded Variables		Response
ξ_1	ξ_2	x_1	x_2	y
30	150	−1	−1	39.3
30	160	−1	1	40.0
40	150	1	−1	40.9
40	160	1	1	41.5
35	155	0	0	40.3
35	155	0	0	40.5
35	155	0	0	40.7
35	155	0	0	40.2
35	155	0	0	40.6

The resulting first-order model (with no interaction) was:

$$\hat{y} = 40.44 + 0.775x_1 + 0.325x_2$$

The adequacy of the model was investigated through different steps:

1. Estimate of error from replicated measurements: $\hat{\sigma}^2 = 0.0430$

2. Contribution of interaction between factors x_1 and x_2:

$$\hat{\beta}_{12} = \tfrac{1}{4}[(1 \times 39.3) + (1 \times 41.5) + (-1 \times 40.0) + (-1 \times 40.9)] = \tfrac{1}{4}(-0.1) = -0.025$$

3. Significance of interaction between factors x_1 and x_2:

$$SS_{\text{Interaction}} = \frac{(-0.1)^2}{4} = 0.0025 \qquad F = \frac{SS_{\text{Interaction}}}{\hat{\sigma}^2} = \frac{0.0025}{0.0430} = 0.058$$

Since the F value is much lower than the critical value $F_{1,4}$ at $\alpha = 0.05$, the interaction can be considered not significant.

4. Check for quadratic effects (curvature):

This check consists in comparing the average of the four responses obtained in the factorial design:

$$\bar{y}_F = (39.3+40.0+40.9+41.5)/4 = 40.425$$

with the average response obtained in the centre of the design:

$$\bar{y}_C = (40.3 + 40.5 + 40.7 + 40.2 + 40.6)/5 = 40.46$$

The difference between these values represents a measure of the model curvature:

$$\bar{y}_F - \bar{y}_C = 40.425 - 40.46 = -0.035$$

The following sum of squares is related to the pure quadratic contribution:

$$SS_{\text{Pure Quadratic}} = \frac{n_F n_C (\bar{y}_F - \bar{y}_C)^2}{n_F + n_C} = \frac{(4)(5)(-0.035)^2}{4 + 5} = 0.0027$$

where n_F and n_C represent the number of data in the factorial part and in the center of the design, respectively.

Since the realization of the F statistic:

$$F = \frac{SS_{\text{Pure Quadratic}}}{\hat{\sigma}^2} = \frac{0.0027}{0.0430} = 0.063$$

is much lower than the $F_{1,4}$ critical value at $\alpha = 0.05$, quadratic effects can be considered not significant.

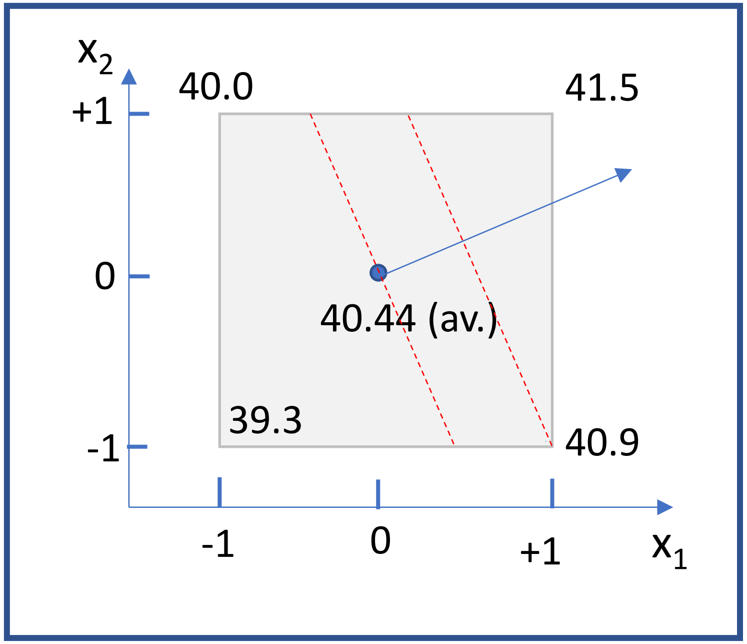
The following ANOVA table provides a summary of all contributions:

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F_0	P-Value
Model (β_1, β_2)	2.8250	2	1.4125	47.83	0.0002
Residual	0.1772	6			
(Interaction)	(0.0025)	1	0.0025	0.058	0.8215
(Pure quadratic)	(0.0027)	1	0.0027	0.063	0.8142
(Pure error)	(0.1720)	4	0.0430		
Total	3.0022	8			

Interaction and quadratic effects are thus not significant (note that the corresponding P-Values are much higher than α) and a first order dependence is ascertained.

The check indicates that we are still far from the optimum, where such a dependence is not reasonable, thus an improvement step, e.g., based on the steepest ascent approach, is required.

Steepest ascent approach



Based on the results obtained from the first measurements, i.e., on the model found for the response:

$$\hat{y} = 40.44 + 0.775x_1 + 0.325x_2$$

a potential path for the increase of response is the one indicated with the blue arrow in the figure, i.e., the normal to red lines, representing combinations of variables with the same response in the contour plot.

It can be easily seen that a +1 variation in the x_1 coded variable, i.e., a 5 min increase in the reaction time, corresponds to an increase of 0.42 (0.325/0.775) for the x_2 variable, when moving along the blue arrow.

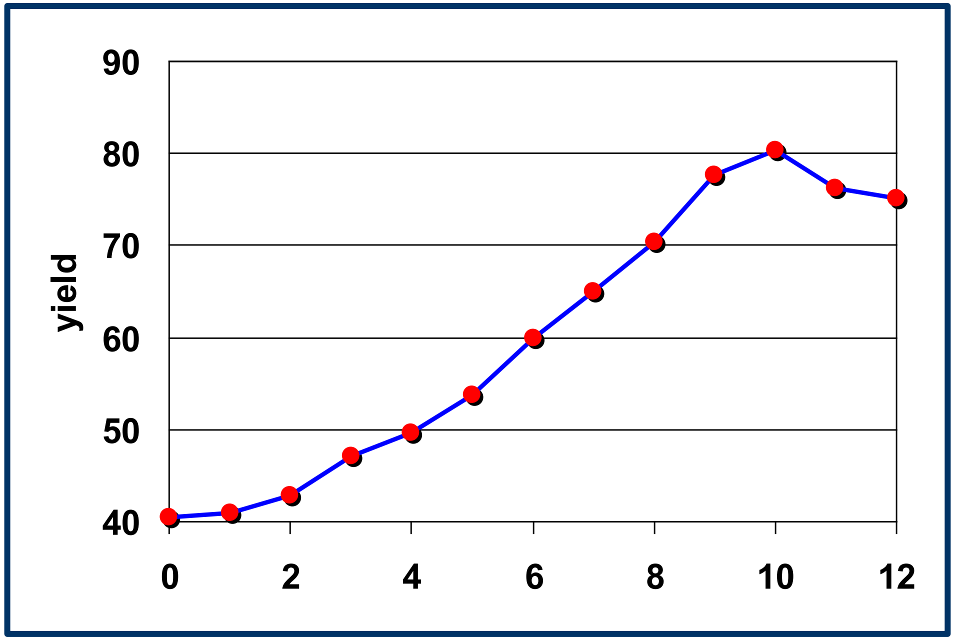
In terms of the actual variable, the reaction temperature, a 0.42 increase corresponds to about 2 °F:

$$x_2 = \frac{\xi_2 - 155}{5} \quad \Rightarrow \quad \Delta\xi_2 = 5 \times \Delta x_2 = 5 \times 0.42 = 2.1^\circ F$$

The steepest ascent experiment can thus be described by the following table:

Steps	Coded Variables x_1	Coded Variables x_2	Natural Variables ξ_1	Natural Variables ξ_2	Response y
Origin	0	0	35	155	
Δ	1.00	0.42	5	2	
Origin + Δ	1.00	0.42	40	157	41.0
Origin + 2Δ	2.00	0.84	45	159	42.9
...					
Origin + 9Δ	9.00	3.78	80	173	77.6
Origin + 10Δ	10.00	4.20	85	175	80.3
Origin + 11Δ	11.00	4.62	90	179	76.2
Origin + 12Δ	12.00	5.04	95	181	75.1

This graph emphasizes the evolution of response, with a maximum (80.3) reached after 10 increases of variables:



It is now clear that a new model has to be adopted to fit data in a range around 85 min of reaction time and 175 °F of temperature.

If another first-order model was adopted, just as a trial, the following equations would then be required for variable coding:

$$x_1 = \frac{\xi_1 - 85}{5} \qquad x_2 = \frac{\xi_2 - 175}{5}$$

Data obtained by considering a design like the one adopted before would be:

Natural Variables		Coded Variables		Response
ξ_1	ξ_2	x_1	x_2	y
80	170	−1	−1	76.5
80	180	−1	1	77.0
90	170	1	−1	78.0
90	180	1	1	79.5
85	175	0	0	79.9
85	175	0	0	80.3
85	175	0	0	80.0
85	175	0	0	79.7
85	175	0	0	79.8

The new first-order model would then be:

$$\hat{y} = 78.97 + 1.00x_1 + 0.50x_2$$

The analysis of variance for this model, including checks for interaction and for purely quadratic contribution, would be performed as before:

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F_0	P-Value
Regression	5.00	2			
Residual	11.1200	6			
(Interaction)	(0.2500)	1	0.2500	4.72	0.0955
(Pure quadratic)	(10.6580)	1	10.6580	201.09	0.0001
(Pure error)	(0.2120)	4	0.0530		
Total	16.1200	8			

As apparent, the purely quadratic contribution is significant, as expected, since there has been an approach to the actual maximum of the response surface.

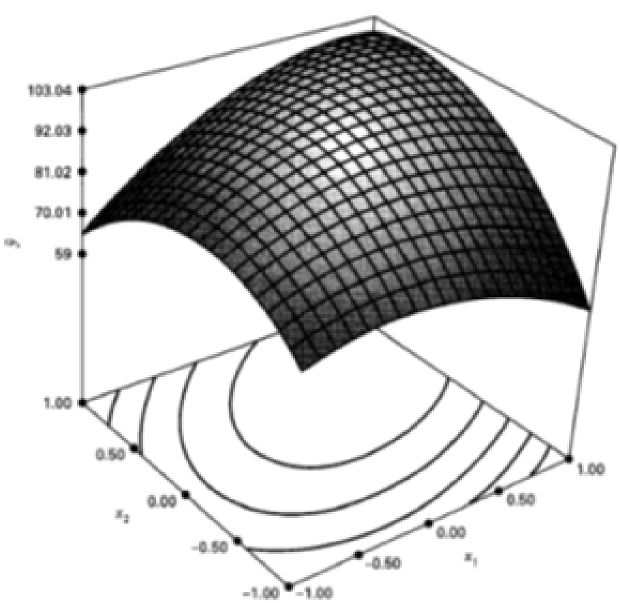
A second-order response surface has then to be considered to complete the optimization.

A second-order model like the following one:

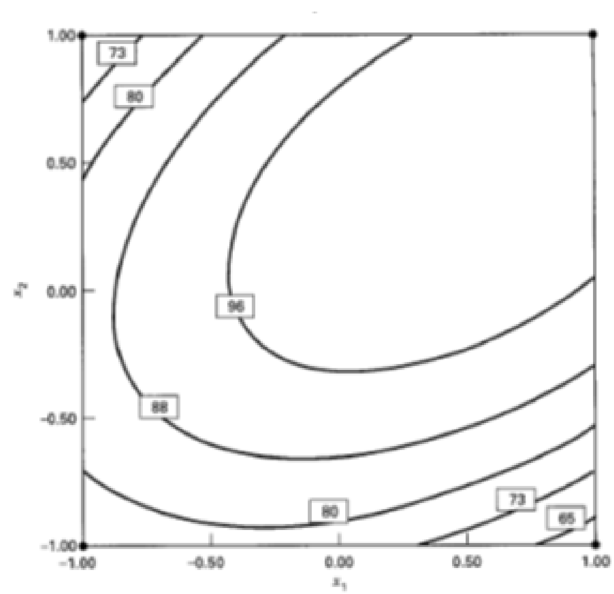
$$y = \beta_0 + \sum_{i=1}^{k} \beta_i x_i + \sum_{i=1}^{k} \beta_{ii} x_i^2 + \sum_{i<j}\sum \beta_{ij} x_i x_j + \epsilon$$

is usually suitable to find the optimum set of operating conditions when curvature has to be also considered.

Generally speaking, the set of x_1, x_2,…x_k factors that optimize the predicted response is the one leading all partial derivatives of response with respect to variables to become equal to 0. The resulting point in the k-dimensional space is called the stationary point.

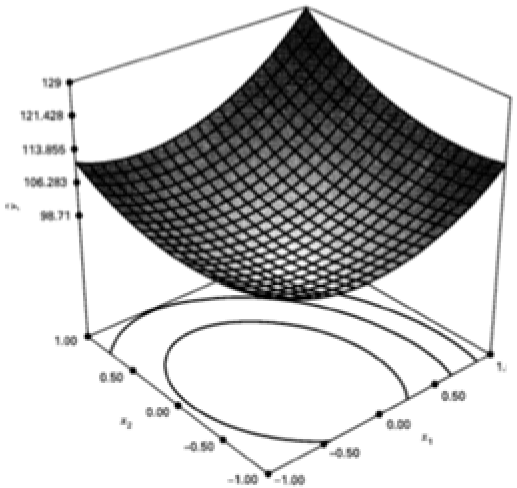


response surface

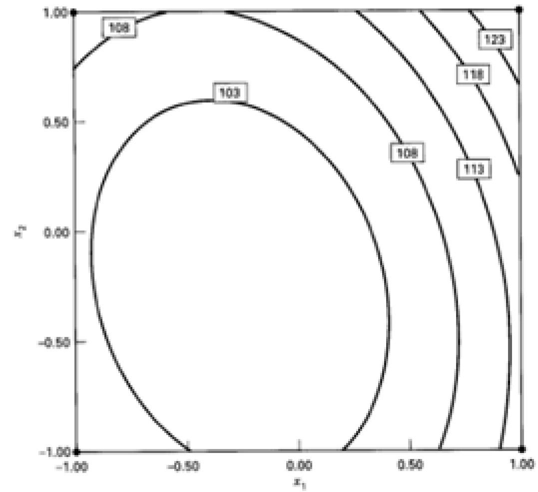


contour plot

In principle, a stationary point might also correspond to a point of minimum response:

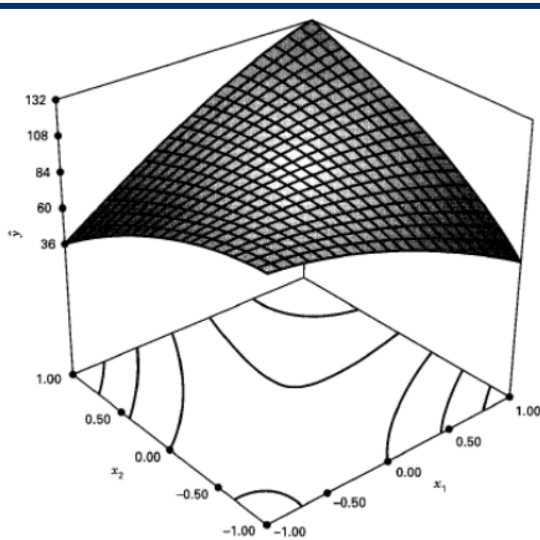


response surface

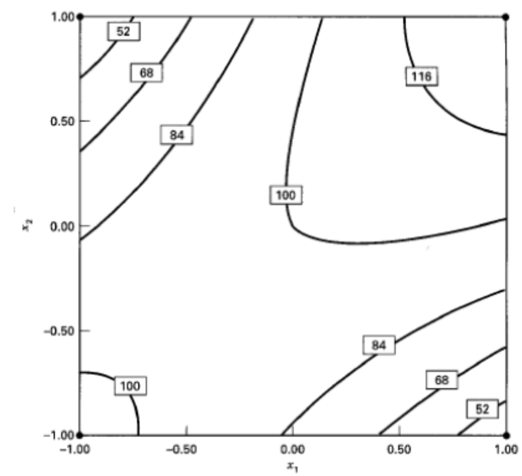


contour plot

or to a saddle point:



response surface



contour plot

Contour plots, easily generated by computer software for response surface analysis, play a very important role in the study of the response surface, enabling a characterization of the shape of the surface and the location of the optimum with a reasonable precision.

A mathematical solution for the location of the stationary point can be obtained by writing the second-order model in matrix notation:

$$\hat{y} = \hat{\beta}_0 + \mathbf{x}'\mathbf{b} + \mathbf{x}'\mathbf{B}\mathbf{x}$$

with:

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_k \end{bmatrix} \qquad \mathbf{b} = \begin{bmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \vdots \\ \hat{\beta}_k \end{bmatrix} \qquad \mathbf{B} = \begin{bmatrix} \hat{\beta}_{11}, & \hat{\beta}_{12}/2, & \ldots, & \hat{\beta}_{1k}/2 \\ & \hat{\beta}_{22}, & \ldots, & \hat{\beta}_{2k}/2 \\ & & \ddots & \\ \text{sym.} & & & \hat{\beta}_{kk} \end{bmatrix}$$

and **x’** being the transpose of **x**

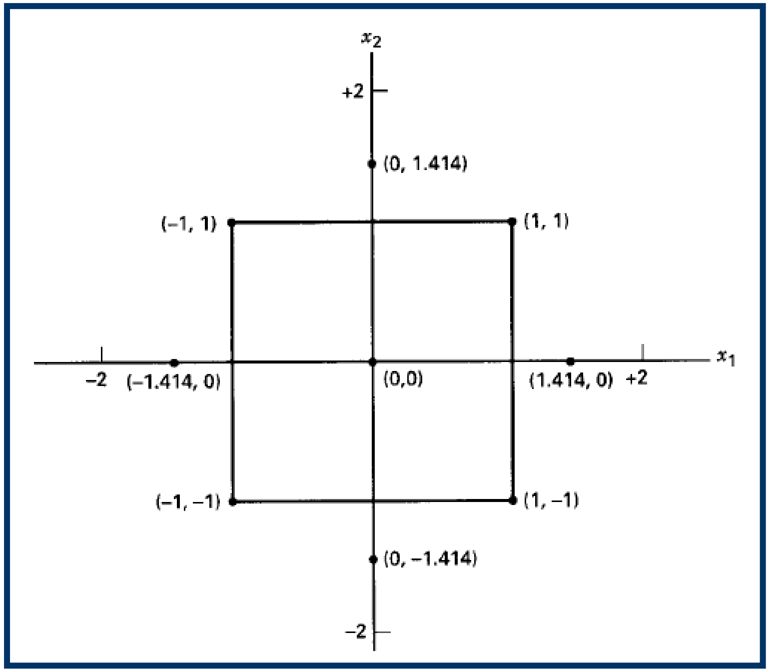
As apparent, **b** is a (k × 1) vector including first-order regression coefficients, **B** is a (k × k) symmetric matrix, whose main diagonal elements correspond to pure quadratic coefficients, whereas off-diagonal elements correspond to one-half of the mixed quadratic coefficients.

The stationary point can be found by equating to 0 the derivative of the expected response with respect to the elements of vector x’:

$$\frac{\partial \hat{y}}{\partial \mathbf{x}'} = \mathbf{b} + 2\mathbf{B}\mathbf{x} = \mathbf{0} \Rightarrow \mathbf{x}_s = -\tfrac{1}{2}\mathbf{B}^{-1}\mathbf{b} \Rightarrow \hat{y} = \hat{\beta}_0 + \mathbf{x}_s'\mathbf{b} - \tfrac{1}{2}\mathbf{x}_s'\mathbf{B}\mathbf{B}^{-1}\mathbf{b} = \hat{\beta}_0 + \tfrac{1}{2}\mathbf{x}_s'\mathbf{b}$$

Response surface approach starting from a central composite design

In the specific example, a central composite design (CCD) was adopted to proceed with the response surface approach:



Natural Variables		Coded Variables		Response
ξ_1	ξ_2	x_1	x_2	y_1 (yield)
80	170	−1	−1	76.5
80	180	−1	1	77.0
90	170	1	−1	78.0
90	180	1	1	79.5
85	175	0	0	79.9
85	175	0	0	80.3
85	175	0	0	80.0
85	175	0	0	79.7
85	175	0	0	79.8
92.07	175	1.414	0	78.4
77.93	175	−1.414	0	75.6
85	182.07	0	1.414	78.5
85	167.93	0	−1.414	77.0

The blue, red and green rectangles in the table represent, respectively, the 2^2 factorial design, the 5 replicates obtained in the design center and the four-tip star design, with $\alpha = N^{1/4}$, where N is the number of experiments in the factorial part, thus $\alpha = (4)^{1/4} = 1.414$.

The ANOVA table is the following:

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	28.25	5	5.65	79.85	<0.0001
A	*7.92*	*1*	*7.92*	*111.93*	*<0.0001*
B	*2.12*	*1*	*2.12*	*30.01*	*0.0009*
A^2	*13.18*	*1*	*13.18*	*186.22*	*<0.0001*
B^2	*6.97*	*1*	*6.97*	*98.56*	*<0.0001*
AB	*0.25*	*1*	*0.25*	*3.53*	*0.1022*
Residual	0.50	7	0.071		
Lack of Fit	*0.28*	*3*	*0.094*	*1.78*	*0.2897*
Pure Error	*0.21*	*4*	*0.053*		
Cor Total	28.74	12			

The following table summarizes the model coefficients and related information:

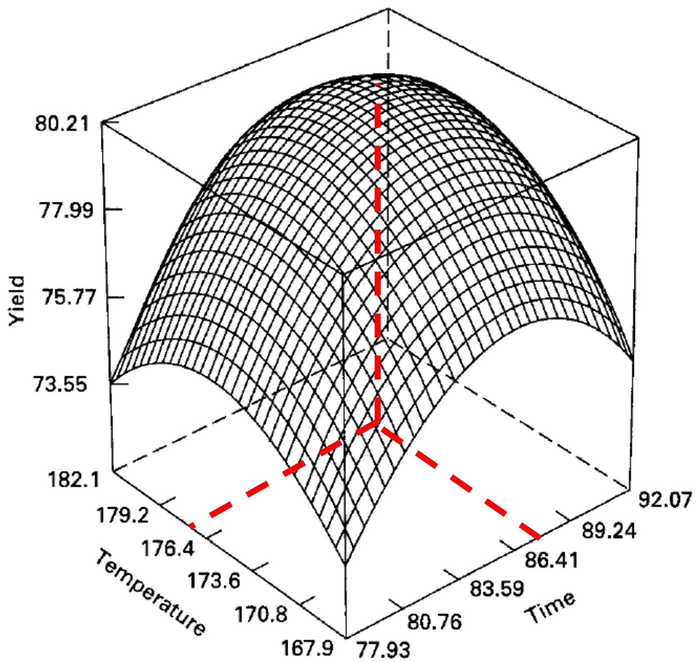
Factor	Coefficient Estimate	DF	Standard Error	95% CI Low	95% CI High	VIF
Intercept	79.94	1	0.12	79.66	80.22	
A-time	0.99	1	0.094	0.77	1.22	1.00
B-temp	0.52	1	0.094	0.29	0.74	1.00
A^2	−1.38	1	0.10	−1.61	−1.14	1.02
B^2	−1.00	1	0.10	−1.24	−0.76	1.02
AB	0.25	1	0.13	−0.064	0.56	1.00

The final equations of the model, in terms of coded and actual factors, respectively, are:

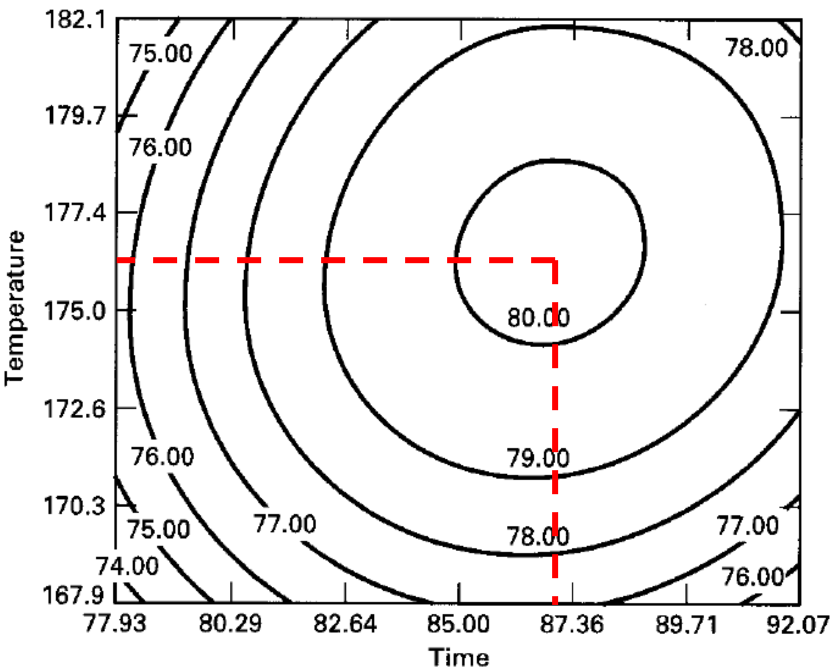
$$\text{Yield (y)} = 79.94 + 0.995\ A + 0.515\ B - 1.376\ A^2 - 1.001\ B^2 + 0.250\ AB$$

$$\text{Yield (y)} = -1430.5 + 7.8\ \text{time} + 13.3\ \text{temp} - 0.055\ \text{time}^2 - 0.04\ \text{temp}^2 + 0.01\ \text{time temp}$$

They correspond to the following response surface and contour plot:



response surface



contour plot

Coded co-ordinates corresponding to the maximum response (stationary point) can be obtained through calculations on matrices, as shown before:

$$\mathbf{b} = \begin{bmatrix} 0.995 \\ 0.515 \end{bmatrix} \qquad \mathbf{B} = \begin{bmatrix} -1.376 & 0.1250 \\ 0.1250 & -1.001 \end{bmatrix}$$

$$\mathbf{x}_s = -\tfrac{1}{2}\mathbf{B}^{-1}\mathbf{b} = -\tfrac{1}{2}\begin{bmatrix} -0.7345 & -0.0917 \\ -0.0917 & -1.0096 \end{bmatrix}\begin{bmatrix} 0.995 \\ 0.515 \end{bmatrix} = \begin{bmatrix} 0.389 \\ 0.306 \end{bmatrix}$$

In order to find the actual values of variables corresponding to the maximum response these coordinates have to be uncoded:

$$0.389 = \frac{\xi_1 - 85}{5} \qquad 0.306 = \frac{\xi_2 - 175}{5}$$

$$\xi_1 = 86.95 \simeq 87 \text{ min} \qquad \xi_2 = 176.53 \simeq 176.5 \text{ °F}$$

These co-ordinates can be inferred approximately from a visual examination of the contour plot and, with a slightly greater effort, of the response surface.

Main applications of Design of Experiments

Chemical synthesis

1. Synthetic steps
2. Work up and separation
3. Reagents, solvents, catalysts
4. Structure-related reactivity and properties

Biotechnological industry

1. Pharmaceutics: formulations for drug delivery
2. Media development and optimization
3. Biochemistry
4. Separation (HPLC), assay development and optimization
5. Pharmacology: drug design
6. Process (*e.g.*, fermentation) optimization and control;

Cosmetic industry

1. Processes, production, separation, cleaning
2. Formulations: shampoos, nail polish, creams, perfumes, soaps, powders
3. Molecular structure: high potency, low toxicity, allergenicity

Drug industry

1. Pharmaceutics: formulations for drug release, hardness of pills
2. Organic chemistry: synthesis, drug design
3. Analytical chemistry: separation (HPLC) resolution and speed
4. Pharmacology
5. Process optimization and control: synthesis, fermentation, separations

Process control

1. Process optimization and control (yield, purity, throughput time, pollution, energy consumption)
2. Product quality and performance (material strength, warp, color, taste, odour)
3. Product stability versus process variation

Software available for Design of Experiments

Software	Company and reference	Comments
Design-Expert	Stat-Ease Inc., http://www.statease.com/	DoE software
Fusion Pro	S-Matrix Corporation, http://www.smatrix.com/	DoE software
Modde	Umetrics, http://www.umetrics.com/modde	DoE software
Nemrod-W	LPRAI, Marseille, France http://www.nemrodw.com/html-US/design-of-experiments.html	Windows OS only. Optimal designs
Unscrambler	CAMO AS, http://www.camo.com/	Chemometric and DoE software
Virtual Column	ACROSS and the University of Tasmania, http://www.virtualcolumn.com	Chromatographic modelling software
JMP	SAS Institute Inc., http://www.sas.com/	General statistical software.
Matlab	The Mathworks Inc., http://www.mathworks.com.au	General mathematical and computing software. Statistics Toolbox contains DoE routines.
MINITAB	Minitab Inc., http://www.minitab.com	General statistical software
Origin	Microcal Software, http://www.originlab.com/	General data analysis and graphing software
R	Revolution Analytics http://www.revolutionanalytics.com/	Open source general software
SPSS	IBM, http://www-01.ibm.com/software/analytics/spss/	General statistical software
Statgraphics	Statpoint Technologies, http://www.statgraphics.com/	General statistical software
STATISTICA	StatSoft, http://www.statsoft.com	General statistical software

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Useful bibliographic material on DoE

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