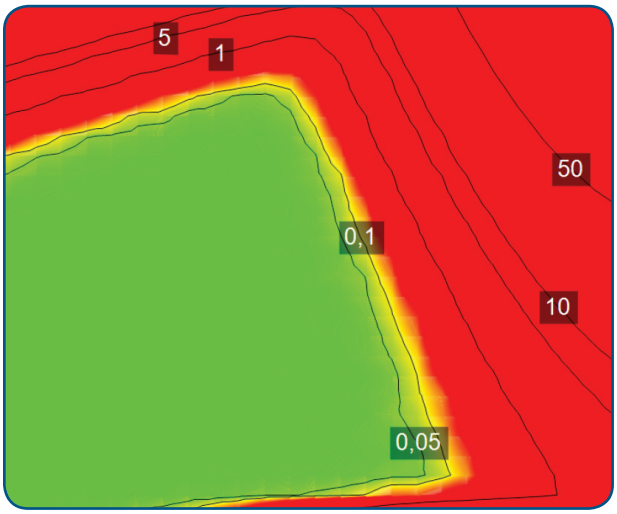
MODDE
BY UMETRICS



MODDE 9.1
Probability Contour Plot

MODDE 9.1

SOFTWARE FOR DESIGN OF EXPERIMENTS AND OPTIMIZATION

MODDE 9.1 is the latest release of MODDE software for Design of Experiments (DOE). This new release incorporates the ability to assess and visualize risk associated with experiments used to support and confirm development in applications with complex processes such as pharmaceutical development and production. It is especially useful as products/methods are transferred from development through scale up and the establishment of production processes.

The principles of Quality by Design (QbD) and Design Space are gaining increasing attention in the DOE community. Design Space tools in MODDE 9.1 present the operational region that meets the specifications according to a risk analysis, which will guide engineers in determining how likely it is that their experiments truly identify the safest operating region. These principles underline that the engineer must incorporate a risk estimate in the interpretation of the results from designed experiments.

Despite the need, this is rarely done, in part because it has been difficult to accomplish a risk estimate with conventional DOE tools and software. MODDE 9.1 addresses this weakness by enabling an easy visualization and estimation of risk. Through advanced optimization tools in combination with Monte Carlo Simulations, MODDE 9.1 produces graphs that can be interpreted as spaces or regions of factor settings where all result specifications are fulfilled and with low risk of failure.

Features

- Extended tools for Design Space estimation — Probability Contour Plot
- The effect of uncertainties in factor settings can be studied
- Risk analysis based on the user specification is shown as a contour plot in 2D or 4D

Plot Examples

To illustrate the need for improved risk assessment visualization, we'll use an example where the acceptance criterion is a result that must be less than a value of 260.

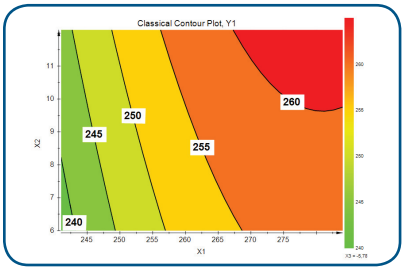


Figure 1 — Classical Contour Plot
In this plot the prediction is made with a regression model based on data from a CCF design. The specification is that Y1 shall be less that 260 but not necessarily as small as possible.

With traditional DOE, a classical tool for interpretation is a Contour Plot that shows the result of different factor settings. As shown in Figure 1, if the only acceptance criterion is that the result shall be <260 there are many possible settings for factor 1 and 2 that will fulfill the criterion. However, the classical Contour Plot gives no indication of the risk of getting a prediction >260, and no indication about safety margins as well.

In looking at the plot in Figure 1, it is rather obvious that the risk of getting a prediction >260 will increase with settings that move the user up and closer to the predicted 260 line. An alternative and more useful presentation can be the risk of failure presentation, or Contour Probability Plot shown in Figure 2. A comparison of the Risk Plot with the traditional Contour Plot shows that the risk of getting something other than 260 reaches 50% close to the 260 line in the Contour Plot. This result is unacceptable in precision production.

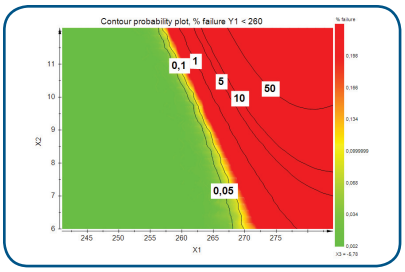


Figure 2 — Probability Plot of Figure 1
This graph shows the risk of failure when the specification is to have Y1 <260. The color setting is created from an acceptance level of 0.1% failure. The possible region for operations is significantly smaller than the one shown in the classical contour plot.

In conventional DOE, setting several result predictions with specifications on top of each other creates an overlay Contour Plot, often called a Sweet Spot Plot (Figure 3). The purpose of this plot is to illustrate the region where several specifications are fulfilled at the same time. The problem is that there is no risk estimation in the classical Sweet Spot Plot.

To address this, MODDE 9.1 incorporates the use of Monte Carlo simulations, a mathematical technique that can be used to assess risk in complex situations. Monte Carlo simulations provide a range of possible outcomes and the probabilities they will occur. MODDE 9.1 performs Monte Carlo simulations on the factor settings in the model within a given interval with a given distribution (several options are available for use depending on the nature of the problem). The result is a distribution in the prediction giving the risk of being in or out of specification, which is, in effect, the Design Space.

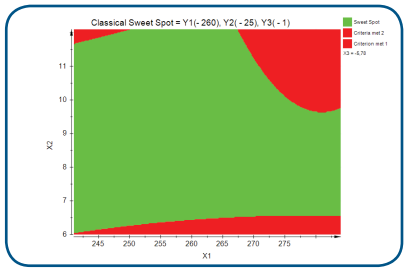


Figure 3 — Classical Sweet Spot
An overlay Contour Plot with 3 responses on top of each other. Y1+Y2+Y3 with specifications and the green area with predictions according to all specifications.

Using Monte Carlo simulation techniques and a unique visualization plot, MODDE can illustrate a region with a defined risk of failure in the same manner as a Sweet Spot Plot. We call this new plot type a Probability Contour Plot (Figure 4).

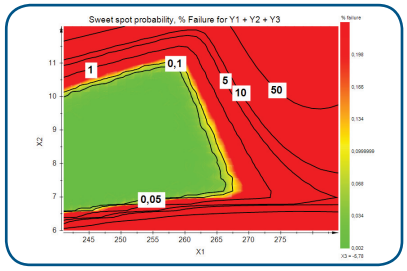


Figure 4 — MODDE 9.1 Probability Contour Plot
The low risk region is significantly smaller than the corresponding classical sweet spot region.

To identify the conditions of lowest risk you must consider what impacts the uncertainty in Y. These are the uncertainty in the process factors as well as the uncertainty in the model. When all known sources of uncertainty have been attached to the prediction model, the result is a more realistic estimate of the region where the risk for failure is low and probability that specifications will be met is high. This region is the Design Space.

With the MODDE 9.1 Probability Contour Plot you have an easy to use, robust tool to identify the Design Space required from your DOE work. MODDE 9.1 gives you a new level of interpretation and support providing a proper risk analysis in your DOE decision process.

UMETRICS
AN MKS COMPANY

Umetrics Inc.
70 W. Rio Robles Drive
San Jose, CA 95134 USA
Tel: +1 408.750.2859
Email: info.us@umetrics.com

European Sales Offices:
Umetrics AB
Stortorget 21
SE-211 34 Malmö, Sweden
Tel: +46 (0)40 6642580
Email: info.se@umetrics.com

Umetrics AB
Box 7960
SE-90719 Umeå, Sweden
Tel: +46 (0)90 184800
Email: info.se@umetrics.com

Umetrics UK Ltd.
Unit 3-4 Cowley Way
Weston Road, Crewe Cheshire
CW1 6AG, United Kingdom
Tel: +44 (0) 845 250 8106
Email: info.uk@umetrics.com

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