DOE-Exercise WILLGE (Optimization)

Chemical synthesis using the Willgerodt-Kindler reaction

In This Tutorial You Will Learn How to

- Create a fractional factorial design
- Analyze experimental data using the Analysis wizard
- Complement a fractional factorial design with new experiments

Background

The Willgerodt-Kindler reaction, a rearrangement that takes place when aryl-alkyl-ketones are heated in the presence of sulfur and an amine, is difficult to explain. One way to investigate the reaction mechanism is to find the factors that have the greatest influence on the reaction. The data presented here are drawn from the thesis of Torbjörn Lundstedt, Umeå University, 1986.

Objectives

- Set up a screening design
- To determine which factors are the most important in the reaction, by means of a fractional factorial design.
- Understand the effects of a lurking nonlinear effect that's not covered by the screening design.
- Learn how to upgrade a fractional factorial design to a design that supports a model with square terms using complement design.

The objective of the investigation is to screen which factors that have a strong influence on process the yield.

Responses

	Name	Abbreviation	Units	Condition	Objective	Min	Target	Max
1	**Yield**	Yield	%	Required	Maximize	90	100	

The process Proportion Sulfur/Ketone (mol/mol), proportion Amine/Ketone (mol/mol), temperature (°C), grain size of Sulfur (mm), stirring speed (rpm).

Factors

	Name	Abbreviation	Units	Type	Settings
1	**SulfKet**	SulfK	mol/mol	Quantitative	5 to 11
2	**MorfKet**	MorfK	mol/mol	Quantitative	6 to 10
3	**Temp**	Temp	°C	Quantitative	100 to 140
4	**PartSize**	PSize	mm	Quantitative	0.1 to 0.2
5	**Stirring**	Stirr	RPM	Quantitative	300 to 700
+	*Add...*				

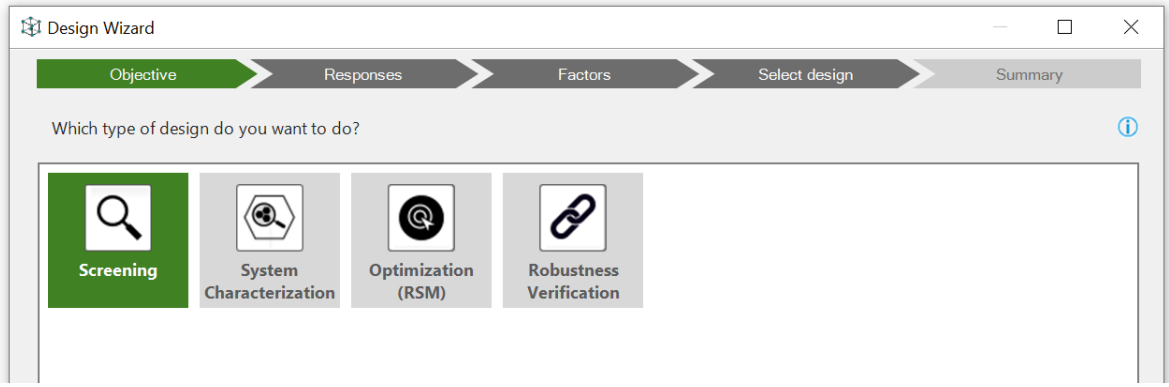
Specification

	1	2	3	4	5	6	7	8	9	10
	Exp No	Exp Name	Run Order	Incl/Excl	SulfKet	MorfKet	Temp	PartSize	Stirring	Yield
1	1	N1	10	Incl	5	6	100	0.1	700	11.5
2	2	N2	14	Incl	11	6	100	0.1	300	55.8
3	3	N3	12	Incl	5	10	100	0.1	300	55.7
4	4	N4	15	Incl	11	10	100	0.1	700	75.1
5	5	N5	11	Incl	5	6	140	0.1	300	78.1
6	6	N6	18	Incl	11	6	140	0.1	700	88.9
7	7	N7	8	Incl	5	10	140	0.1	700	77.6
8	8	N8	6	Incl	11	10	140	0.1	300	84.5
9	9	N9	17	Incl	5	6	100	0.2	300	16.5
10	10	N10	3	Incl	11	6	100	0.2	700	43.7
11	11	N11	1	Incl	5	10	100	0.2	700	38
12	12	N12	16	Incl	11	10	100	0.2	300	72.6
13	13	N13	19	Incl	5	6	140	0.2	700	79.5
14	14	N14	4	Incl	11	6	140	0.2	300	91.4
15	15	N15	2	Incl	5	10	140	0.2	300	86.2
16	16	N16	5	Incl	11	10	140	0.2	700	78.6
17	17	N17	7	Incl	8	8	120	0.15	500	82.6
18	18	N18	13	Incl	8	8	120	0.15	500	85.6
19	19	N19	9	Incl	8	8	120	0.15	500	83.9

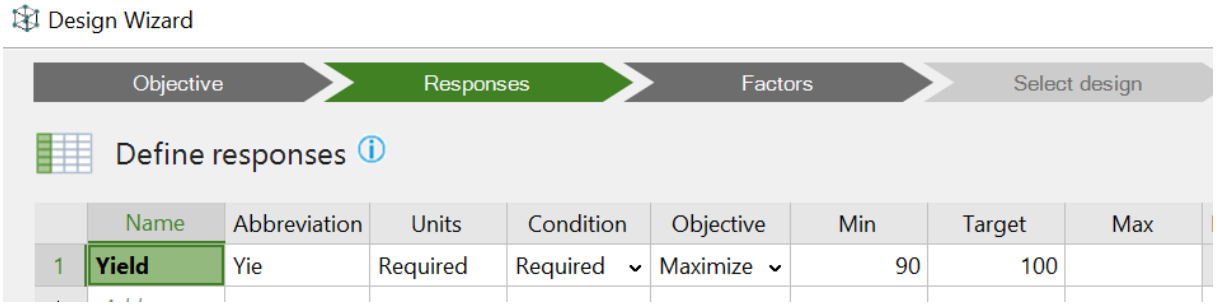
Design Wizard

Step 1: Generate a 2^{5-1} fractional factorial design in MODDE®. Enter the response values.

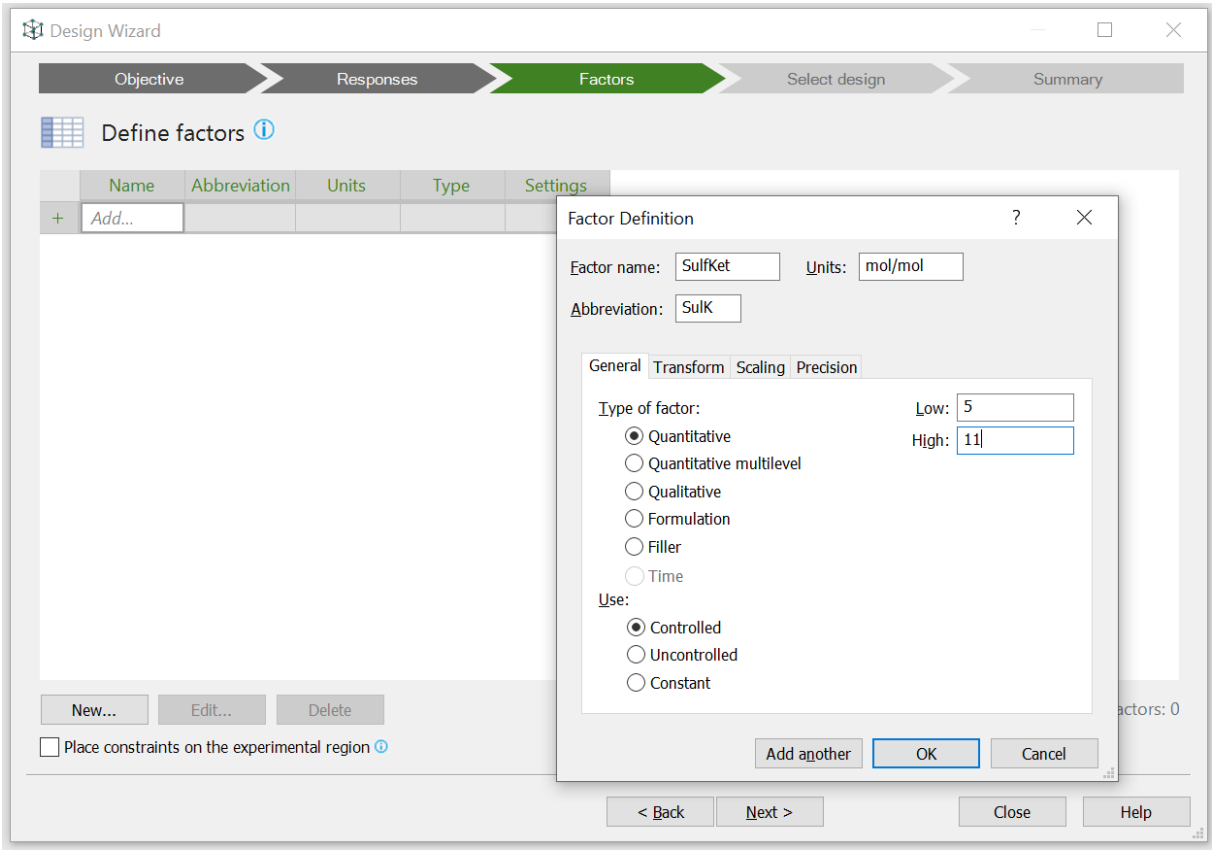
Select File/New/Experimental Design/Screening and step through the Design Wizard as shown below. Click Next.

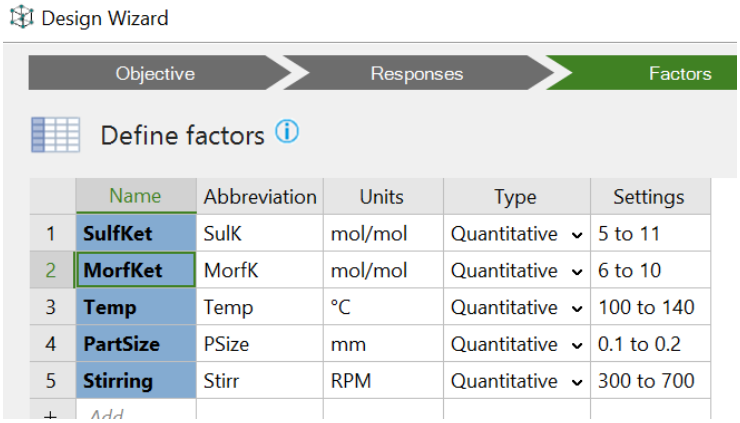


Enter response settings and click next.



Add factors by using factor definition dialog or by entering directly in the table.

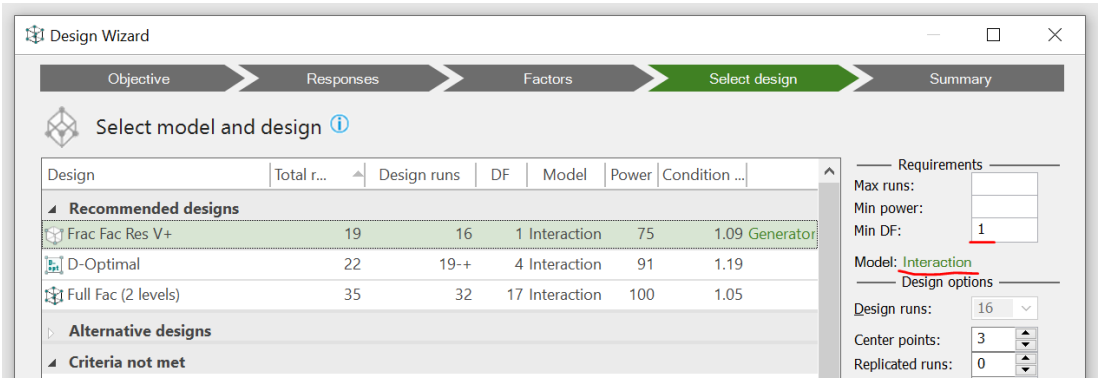




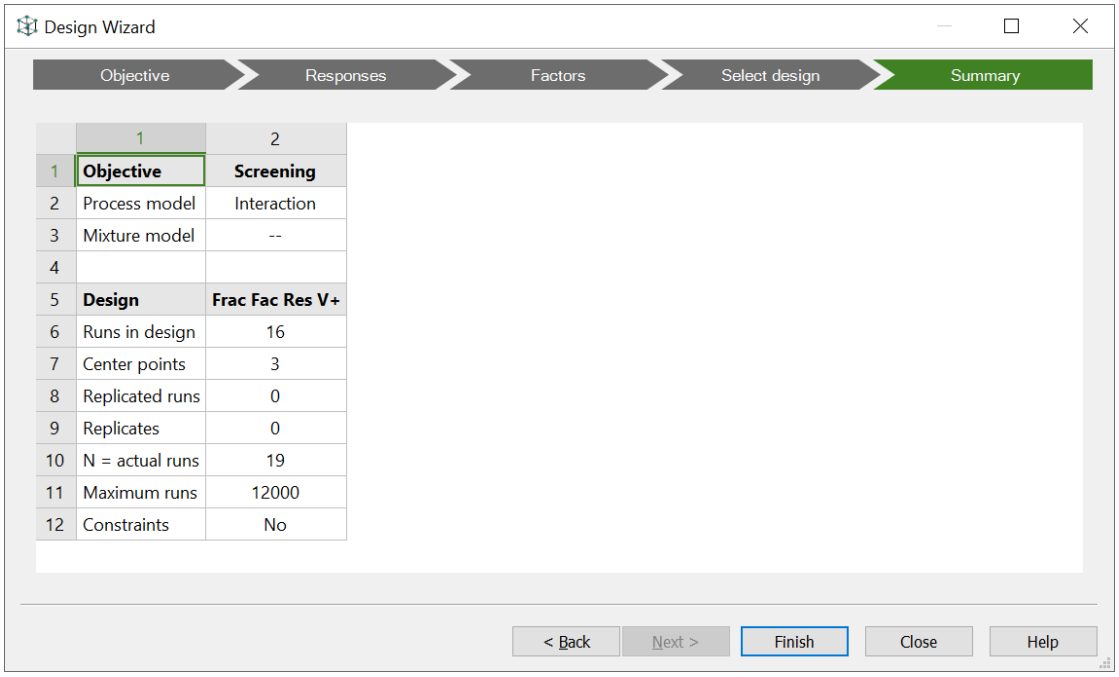
	Name	Abbreviation	Units	Type	Settings
1	**SulfKet**	SulK	mol/mol	Quantitative	5 to 11
2	**MorfKet**	MorfK	mol/mol	Quantitative	6 to 10
3	**Temp**	Temp	°C	Quantitative	100 to 140
4	**PartSize**	PSize	mm	Quantitative	0.1 to 0.2
5	**Stirring**	Stirr	RPM	Quantitative	300 to 700

Click next.

Set requirement for minimum degrees of freedom (DF) to 1 and select interaction model.



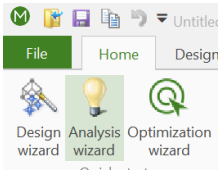
Select Frac Fac Res V+ and click next.



Inspect the summary and click Finish.

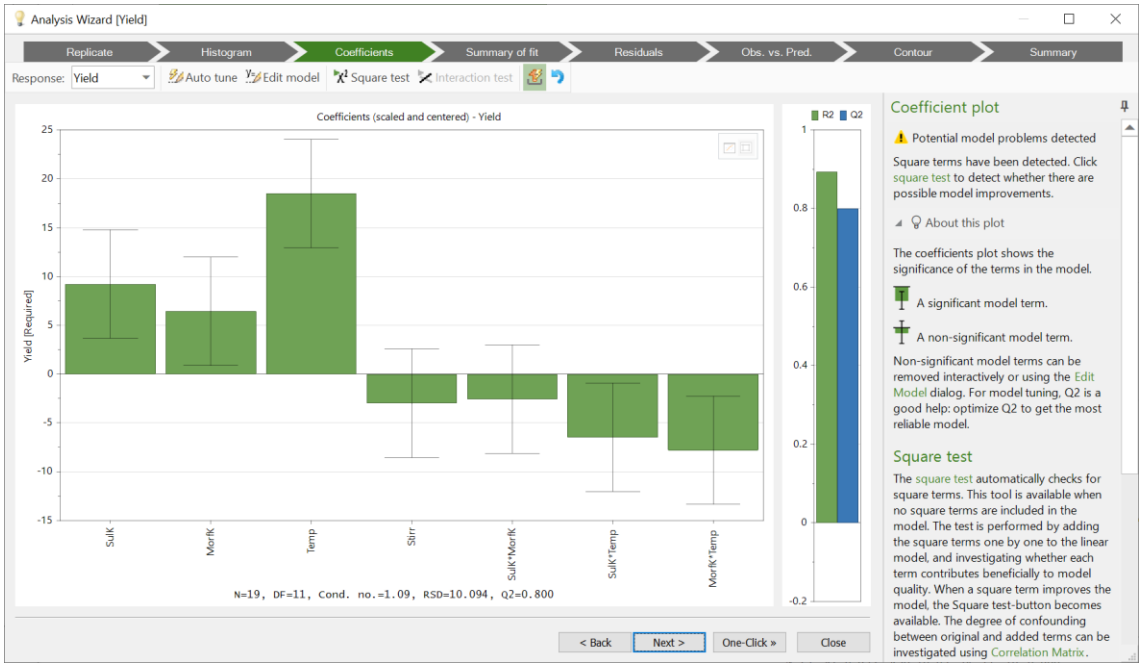
Analysis Wizard

Step 2: Analyze the data and identify potential square terms.



Start the Analysis wizard and work through the steps in the wizard:

Refine the model by removing the smallest insignificant coefficients. Use auto tune for automatic model refinement.



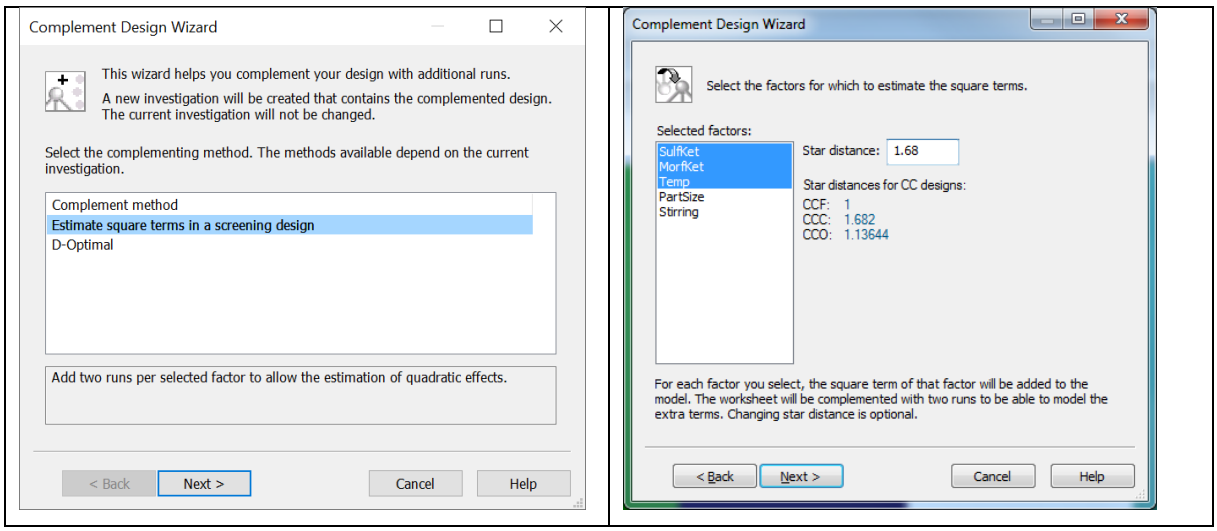
You will be alerted of this need by MODDE, run Square test to identify potential square terms.

Complement Design With New Runs

Step 3: Complement design to identify significant square terms

The initial screening design was upgraded to an optimization design. Design augmentation is easily accomplished in MODDE® using the Complement Design Wizard, which offers different options depending on what the user wants to do. In our example, the original investigator decided to upgrade the screening design to an RSM design.

Click File | New | Complement Design to open the wizard shown below. Then select Estimate square terms in a screening design.



The screening design was extended by including additional trials for the three most important factors. The star distance was set to 1.68, which implies that the original design, together with its complement, corresponds to a CCC design in the three selected factors.

Thus, two experiments for each selected factor will be added to the worksheet allowing estimation of square terms. Additionally, three center-points will be added to allow confirmation that the second set of experiments is on the same level as the first set of experiments.

The final worksheet, consisting of the 19 original runs and the 9 new runs, is presented below. Note that MODDE® calculates the star distance to five decimal places. To make it reasonable adjust factor values to the precision that can be managed. In addition, 0.15 mm

sulfur particles were not available, so all experiments in the second phase were conducted using 0.1 mm sulfur.

The updated design supports a quadratic model in the three first factors. Furthermore, we can see that a new factor, denoted $Block, has been appended by the software. The addition of a block factor makes it possible to determine whether there are systematic differences between the two blocks (different times) of experiments and to quantify these.

Worksheet

	1	2	3	4	5	6	7	8	9	10	11
	Exp No	Exp Name	Run Order	Incl/Excl	SulfKet	MorfKet	Temp	PartSize	Stirring	$Block	Yield
1	1	N1	18	Incl	5	6	100	0.1	700	-1	11.5
2	2	N2	4	Incl	11	6	100	0.1	300	-1	55.8
3	3	N3	8	Incl	5	10	100	0.1	300	-1	55.7
4	4	N4	2	Incl	11	10	100	0.1	700	-1	75.1
5	5	N5	9	Incl	5	6	140	0.1	300	-1	78.1
6	6	N6	1	Incl	11	6	140	0.1	700	-1	88.9
7	7	N7	3	Incl	5	10	140	0.1	700	-1	77.6
8	8	N8	12	Incl	11	10	140	0.1	300	-1	84.5
9	9	N9	6	Incl	5	6	100	0.2	300	-1	16.5
10	10	N10	14	Incl	11	6	100	0.2	700	-1	43.7
11	11	N11	19	Incl	5	10	100	0.2	700	-1	38
12	12	N12	17	Incl	11	10	100	0.2	300	-1	72.6
13	13	N13	7	Incl	5	6	140	0.2	700	-1	79.5
14	14	N14	15	Incl	11	6	140	0.2	300	-1	91.4
15	15	N15	11	Incl	5	10	140	0.2	300	-1	86.2
16	16	N16	5	Incl	11	10	140	0.2	700	-1	78.6
17	17	N17	16	Incl	8	8	120	0.15	500	-1	82.6
18	18	N18	10	Incl	8	8	120	0.15	500	-1	85.6
19	19	N19	13	Incl	8	8	120	0.15	500	-1	83.9
20	20	C20	23	Incl	2.96	8	120	0.1	500	1	48.5
21	21	C21	22	Incl	13.04	8	120	0.1	500	1	91.5
22	22	C22	21	Incl	8	4.64	120	0.1	500	1	58.5
23	23	C23	25	Incl	8	11.36	120	0.1	500	1	94.7
24	24	C24	20	Incl	8	8	86.4	0.1	500	1	14.4
25	25	C25	24	Incl	8	8	153.6	0.1	500	1	94.1
26	26	N26	26	Incl	8	8	120	0.1	500	-1	83.9
27	27	N27	27	Incl	8	8	120	0.1	500	-1	84.2
28	28	N28	28	Incl	8	8	120	0.1	500	-1	83.2

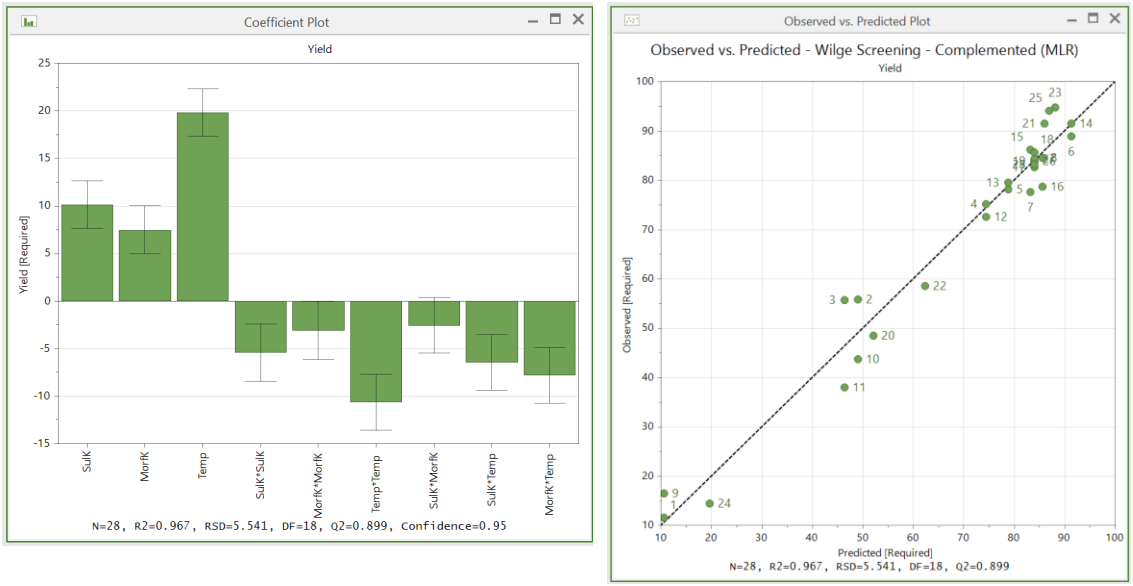
Step 4: Analysis the new model

When complementing a design in MODDE the default model will be the same as the current model from the screening plus square terms for the selected factors and a term for the added block factor.

Stepp through the analysis wizard and interpret the plots by the guidance in the panel to the right.

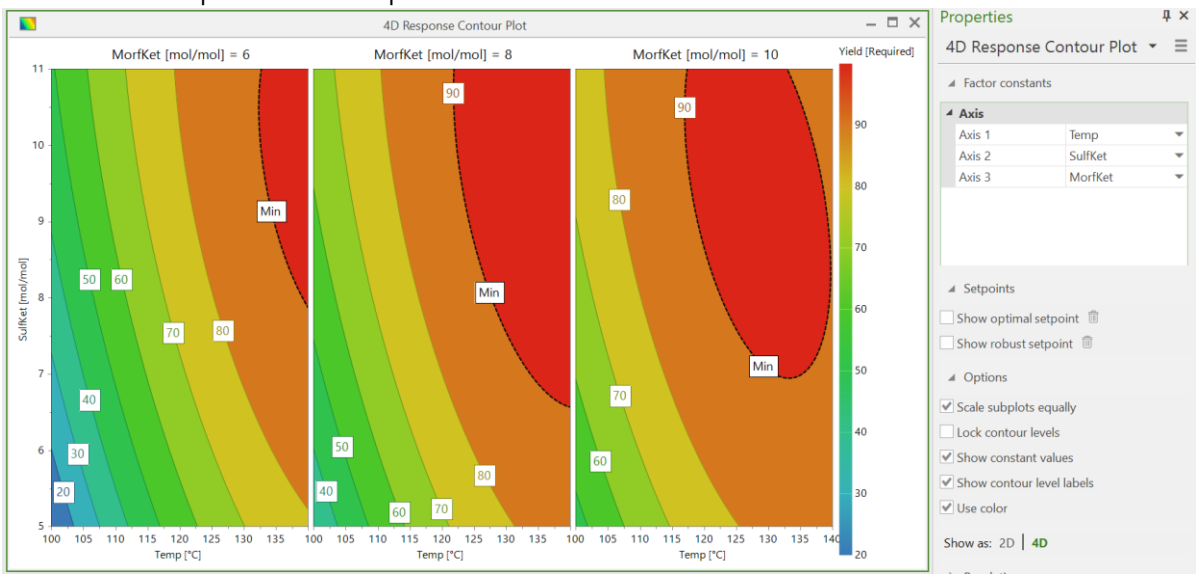
From the replicate plot an interesting observation can be made. The variation among the six replicates is exceptionally small and the replicate variation in the complement part is even smaller. The consequence of this is that no matter how we revise the model, the Model Validity in the Summary of Fit plot will almost certainly be low. The expectations on the model will be very high due to extreme precision in the replicates in comparison with the model residuals. Since the model is very good with no outliers, there is no need to worry about the low model validity.

Exclude the factors PSize and Stirr (small influence) and the interaction term Temp*PSize from the model. The block factor is not significant which indicates that there is no systematic shift in results depending on when the experiments were performed. Remove the block factor from the model.



The final model corresponds to the full quadratic model for the three factors SulfK, MorfK and Temp. A higher temperature gives a higher Yield, up to a specific level pointed out by the negative square contribution. Given the location of the replicated center points in the replicate plot, the presence of quadratic effects is as expected.

Use the 4D-response surface plot to visualize the model.



The original investigation found optimal conditions to be SulfK = 9.37, MorfK = 8.1 and Temp = 135.4, where the Yield is predicted to be ≈ 94.3%.

You can identify the optimal setpoint by using the Optimization wizard in MODDE, this is however beyond the scope of this tutorial.

Conclusions

This example illustrates the value of the working principle of first conducting a careful, but shallow, screening investigation and thereafter a detailed optimization study. The screening phase identified three factors as being more influential than the others and an unresolved non-linear effect. When examining these three factors at the optimization stage, an area of very high yield was identified. A variability analysis predicted a region for yield expectations at optimal operating conditions.

The appropriateness of this region of operability was later checked experimentally by Torbjörn Lundstedt, who obtained yields of 94.3% and 96.7% in the verification experiments. The yields obtained were much higher than those previously reported in the literature (< 70%). Interestingly, these experiments also led to a better understanding of the mechanism of the Willgerodt-Kindler reaction pathway.