



Simplifying Progress

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**SARTORIUS**

# Introduction to MODDE® 13

Umetrics® Suite MODDE® is focused on delivering a full design of experiment solution, from creating an investigation plan to analyze results and support decision making base on scientific principles.

MODDE® 13 is focused on improving Design Selection and making Optimization easier and more powerful.

With MODDE® 13 you get the new Optimization Wizard that complements the reworked Design Wizard and updated Analysis Wizard.



# Response and Factors



Responses								
	Name	Abbreviation	Units	Condition	Objective	Min	Target	Max
1	<b>Drug Antibody Ratio</b>	DAR		Required ▾	Target ▾	3,4	3,9	4,4

Drug Antibody Ratio is set up as Required

Required responses are quality attributes with hard specifications that must be fulfilled. They define sweet spot, design space and are used in robust setpoint calculations

Target, will influence the Design Space and Optimal Set-Point

Factors Settings that define the volume of the design Precision will influence the Design Space and Setpoint Exploration

Factors						
	Name	Abbreviation	Units	Type	Settings	Precision
1	<b>Protein Concentration</b>	Conc.	mg/mL	Quantitative ▾	5 to 15	0,1
2	<b>Temperature</b>	Temp	C	Quantitative ▾	16 to 26	0,1
3	<b>pH</b>	pH		Quantitative ▾	6,8 to 7,8	0,01
4	<b>Reduction time</b>	Time	min	Quantitative ▾	60 to 180	1



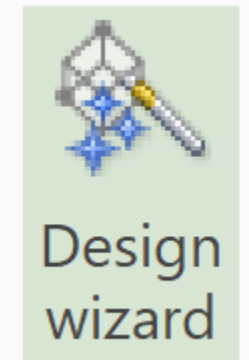
# A Full Factorial Design with Worksheet

The starting design is classical design.

Full Factorial design with 16 experiments in corners and 3 center-points

This design will give a model with 4 main terms and 6 interaction terms

1	2	3	4	5	6	7	8	9
Exp No	Exp Name	Run Order	Incl/Excl	Protein Concentration	Temperature	pH	Reduction time	Drug Antibody Ratio
1	N1	14	Incl	5	16	6,8	60	
2	N2	2	Incl	15	16	6,8	60	
3	N3	7	Incl	5	26	6,8	60	
4	N4	8	Incl	15	26	6,8	60	
5	N5	13	Incl	5	16	7,8	60	
6	N6	19	Incl	15	16	7,8	60	
7	N7	4	Incl	5	26	7,8	60	
8	N8	6	Incl	15	26	7,8	60	
9	N9	16	Incl	5	16	6,8	180	
10	N10	5	Incl	15	16	6,8	180	
11	N11	1	Incl	5	26	6,8	180	
12	N12	18	Incl	15	26	6,8	180	
13	N13	10	Incl	5	16	7,8	180	
14	N14	17	Incl	15	16	7,8	180	
15	N15	9	Incl	5	26	7,8	180	
16	N16	11	Incl	15	26	7,8	180	
17	N17	3	Incl	10	21	7,3	120	
18	N18	12	Incl	10	21	7,3	120	
19	N19	15	Incl	10	21	7,3	120	



# Performed Experiments

It is very common that the performed experiments varies to a small extent from the original Workset

Here we can see that Protein Concentration and Temperature are spot on while pH and Reduction time vary to a small extent.

MODDEs Condition number is used to measure the difference between the two designs and here it increased from 1.06 to 1.13.

As a rule of thumb, for screening designs, a Condition number below 3.0 is a good design

2	3	4	5	6	7	8	9
Exp Name	Run Order	Incl/Excl	Protein Concentration	Temperature	pH	Reduction time	Drug Antibody Ratio
N1	7	Incl	5	16	6,81	61	2,825
N2	5	Incl	15	16	6,74	181	4,075
N3	15	Incl	5	26	6,81	180	3,939
N4	10	Incl	15	26	6,74	60	3,84
N5	17	Incl	5	16	7,83	180	3,968
N6	13	Incl	15	16	7,78	60	4,121
N7	19	Incl	5	26	7,83	60	3,803
N8	9	Incl	15	26	7,78	181	4,119
N9	4	Incl	10	21	7,26	120	3,921
N10	6	Incl	10	21	7,26	120	3,925
N11	14	Incl	10	21	7,26	120	3,968
N12	8	Incl	5	16	6,78	180	3,666
N13	1	Incl	15	16	6,78	60	3,488
N14	18	Incl	5	26	6,78	60	3,127
N15	16	Incl	15	26	6,78	180	4,178
N16	3	Incl	5	16	7,87	60	3,502
N17	12	Incl	15	16	7,77	180	4,198
N18	11	Incl	5	26	7,87	180	4,012
N19	2	Incl	15	26	7,77	60	4,227



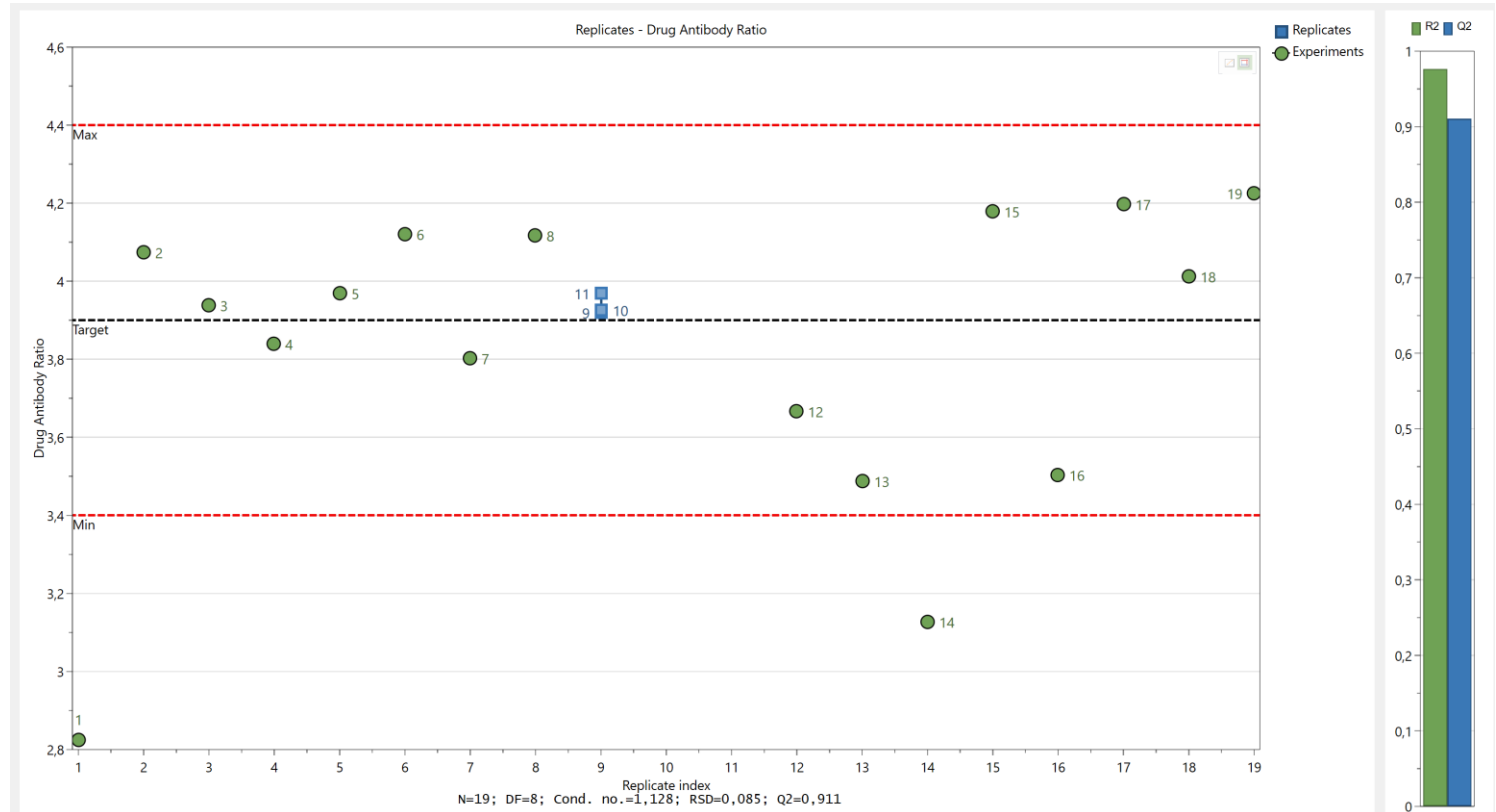
# Excellent Replicates in the Center Close to Target

The replicates **Blue Squares** are close to Target

Seventeen (17) of Nineteen (19) Experiment are inside the specifications

A strong model as **R2** and **Q2** are high

With many experiments inside specifications and a high R2 gives a high probability for a large Design Space

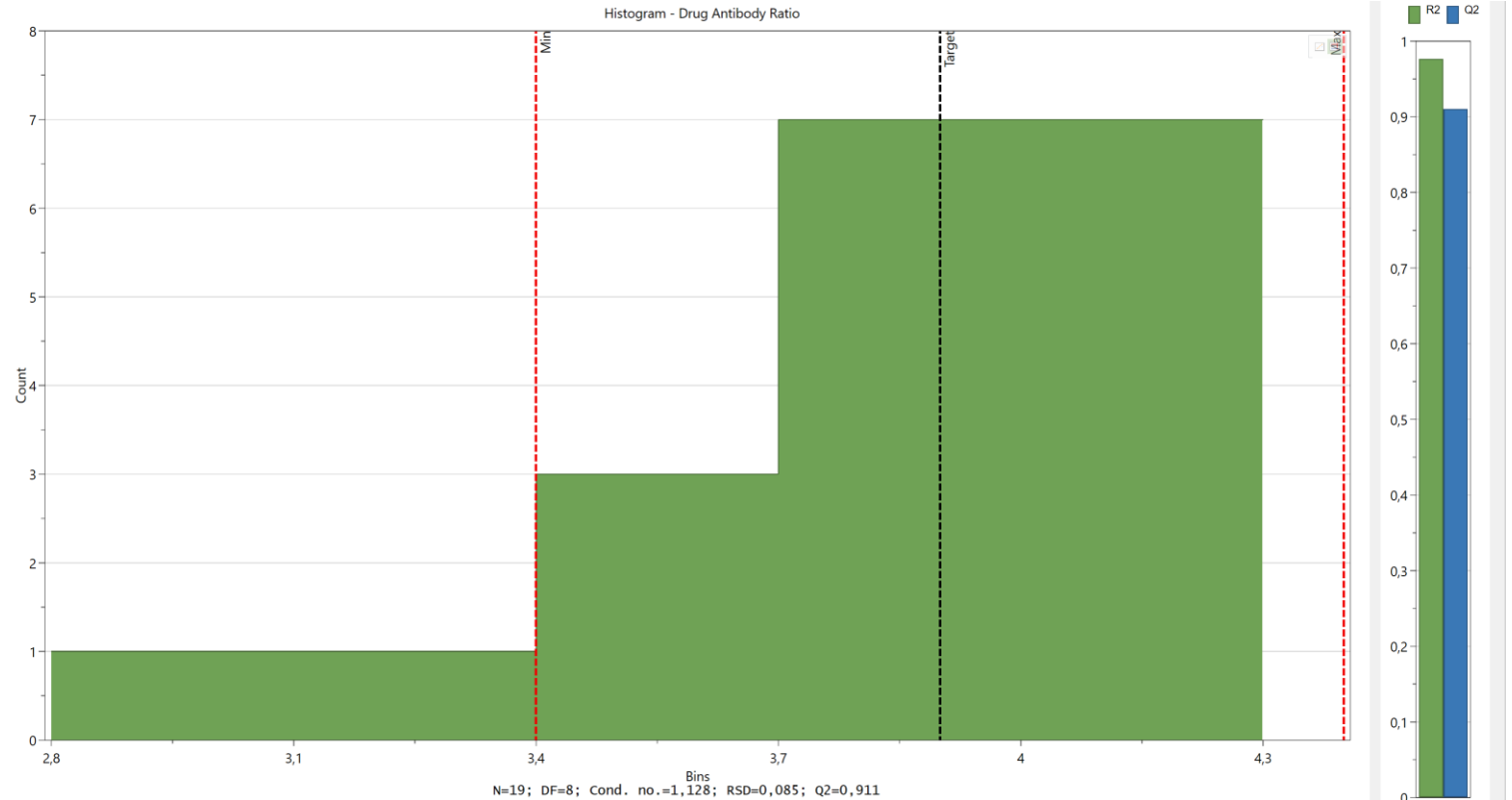




# Slight Skewed Histogram

Ideally the Histogram should look like a Gaussian curve

Here it is slightly skewed but as the model R2/Q2 are both high this has a limited impact

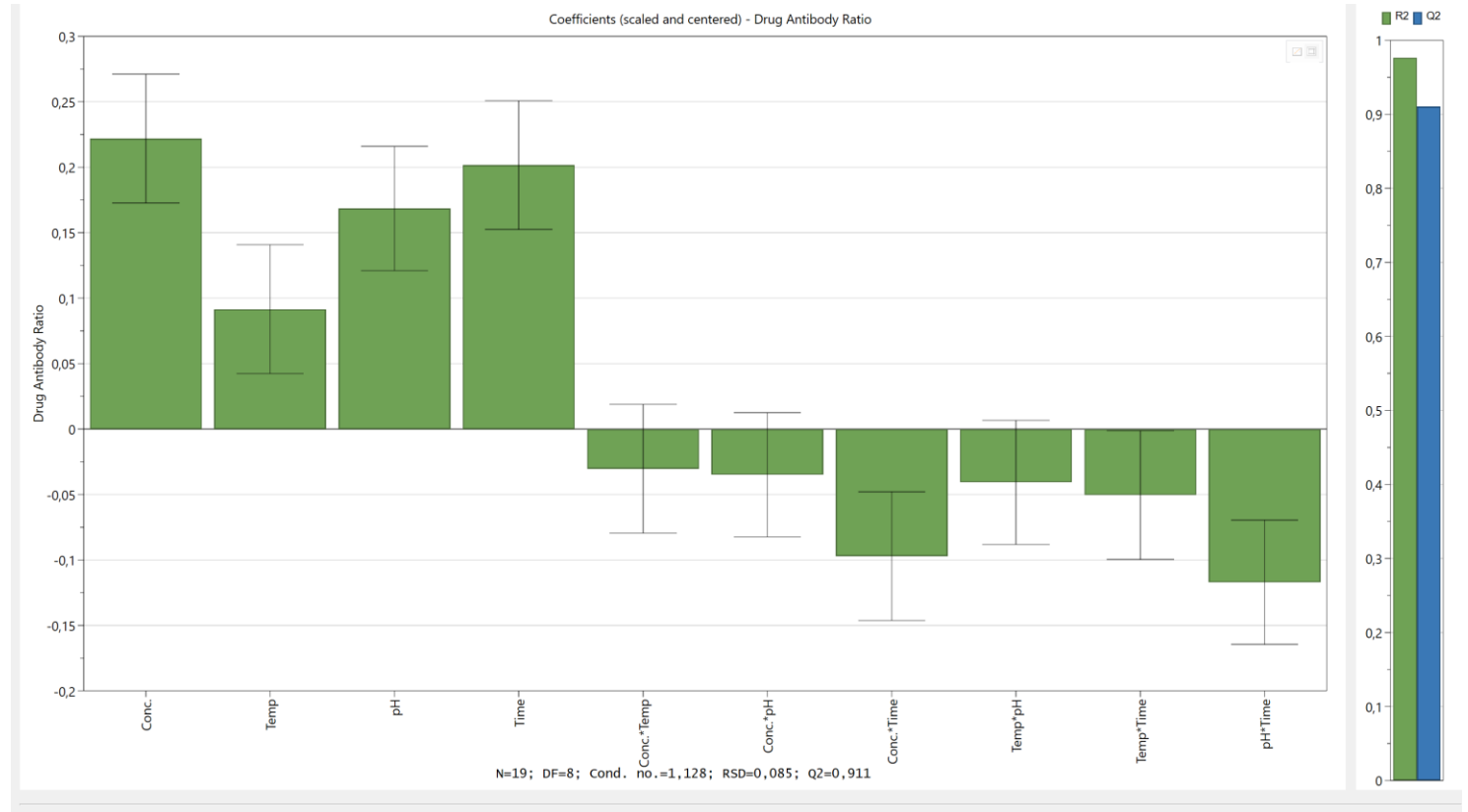




# Coefficients for First Model

The first model has the 4 main terms and the six interaction terms

The confidence bar passes zero for some of interaction terms and these will be scrutinized for removal





# Model after Auto tune

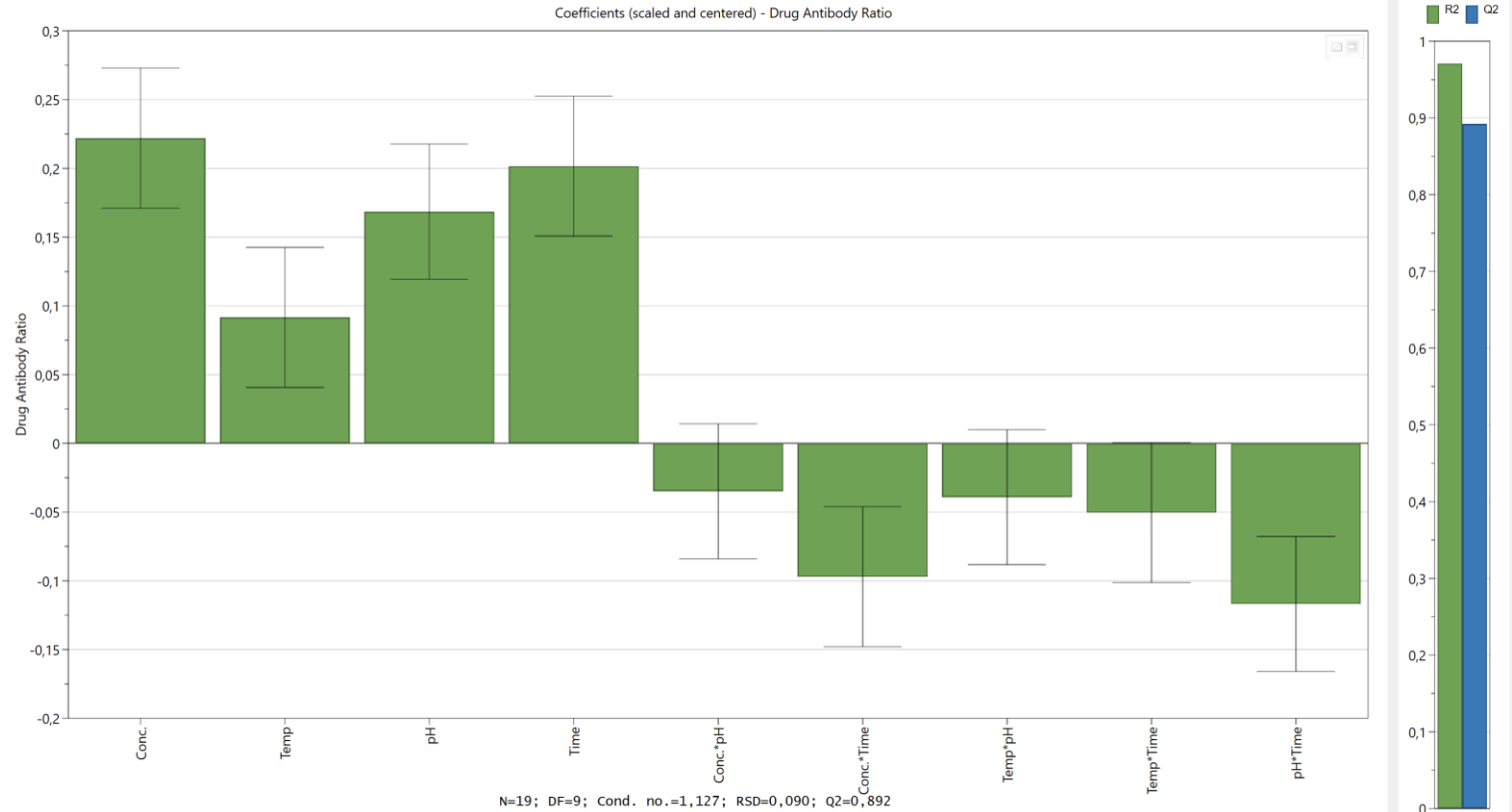
Here we have removed the smallest coefficient

There are two ways to continue

- Removing the smallest coefficient and continue so until all coefficients are significant
- The auto tune function is based on increasing the  $Q^2$ . The auto tune function has two advantages
  - Fast and easy
  - Result independent of user
- We will continue with auto tune, only  $\text{Conc} \cdot \text{Temp}$  was removed



Analysis wizard

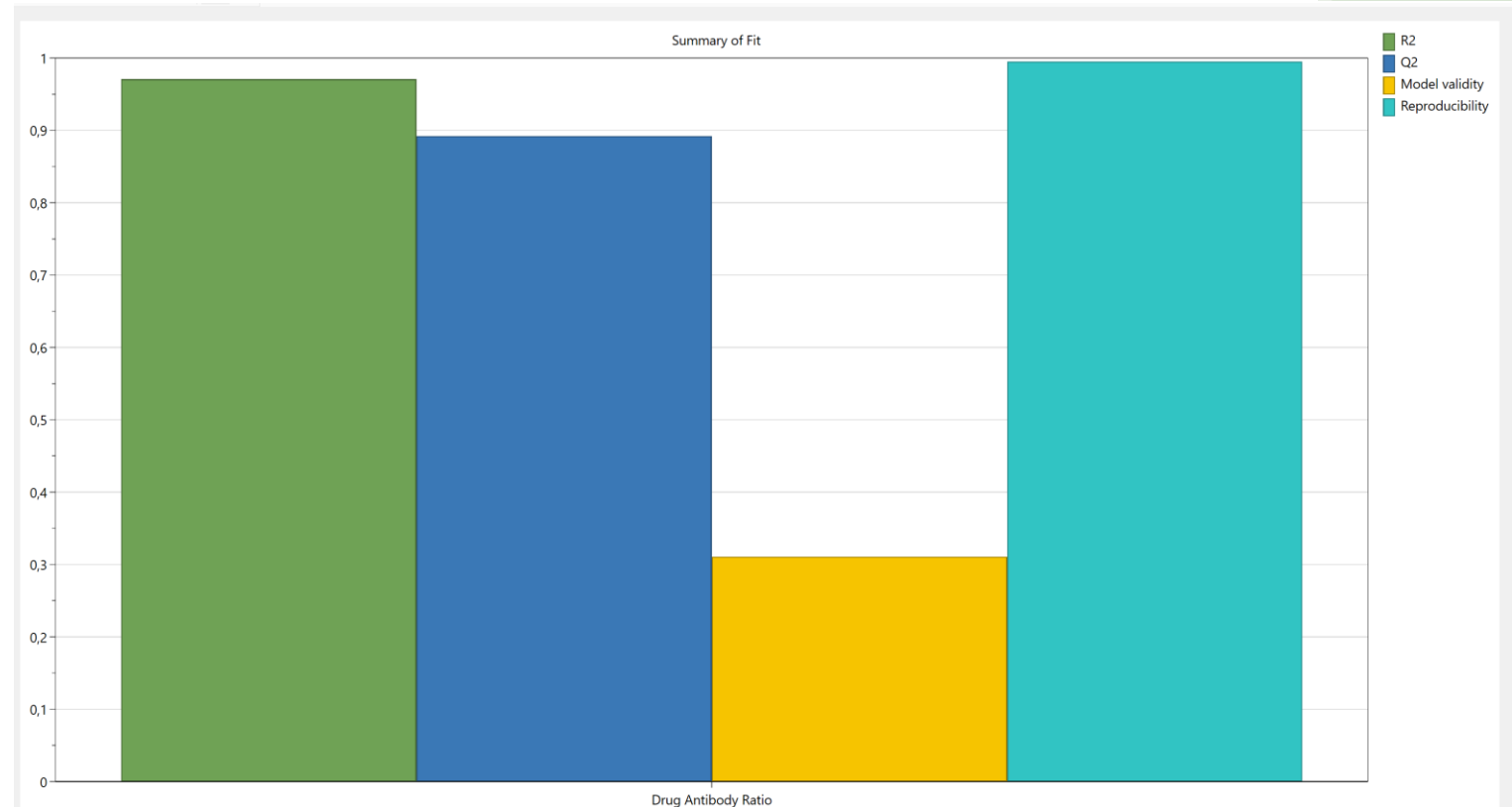




# Summary of Fit Plot Describing an Excellent Model

The quality of the model is summarized with four bars

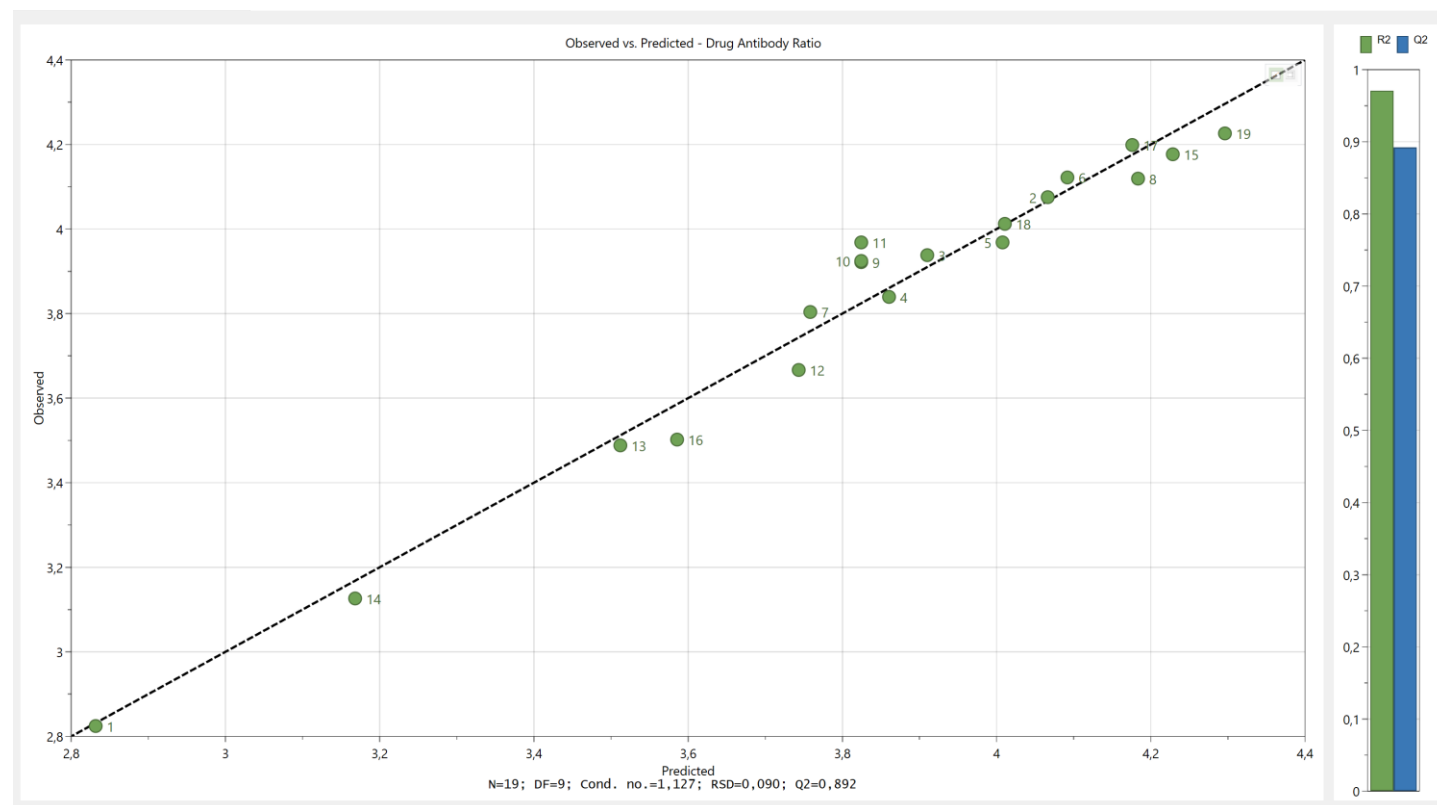
- **R<sup>2</sup>** describes how well the model fits to the data
- **Q<sup>2</sup>** describes how well the model can predict the data
- **Reproducibility** is very high as the replicates was very close together
- **Model Validity** is a bit low but that is common when **Reproducibility** is very high
  - Statistical artifact





# Observed vs Predicted Plot Describing an Excellent Model

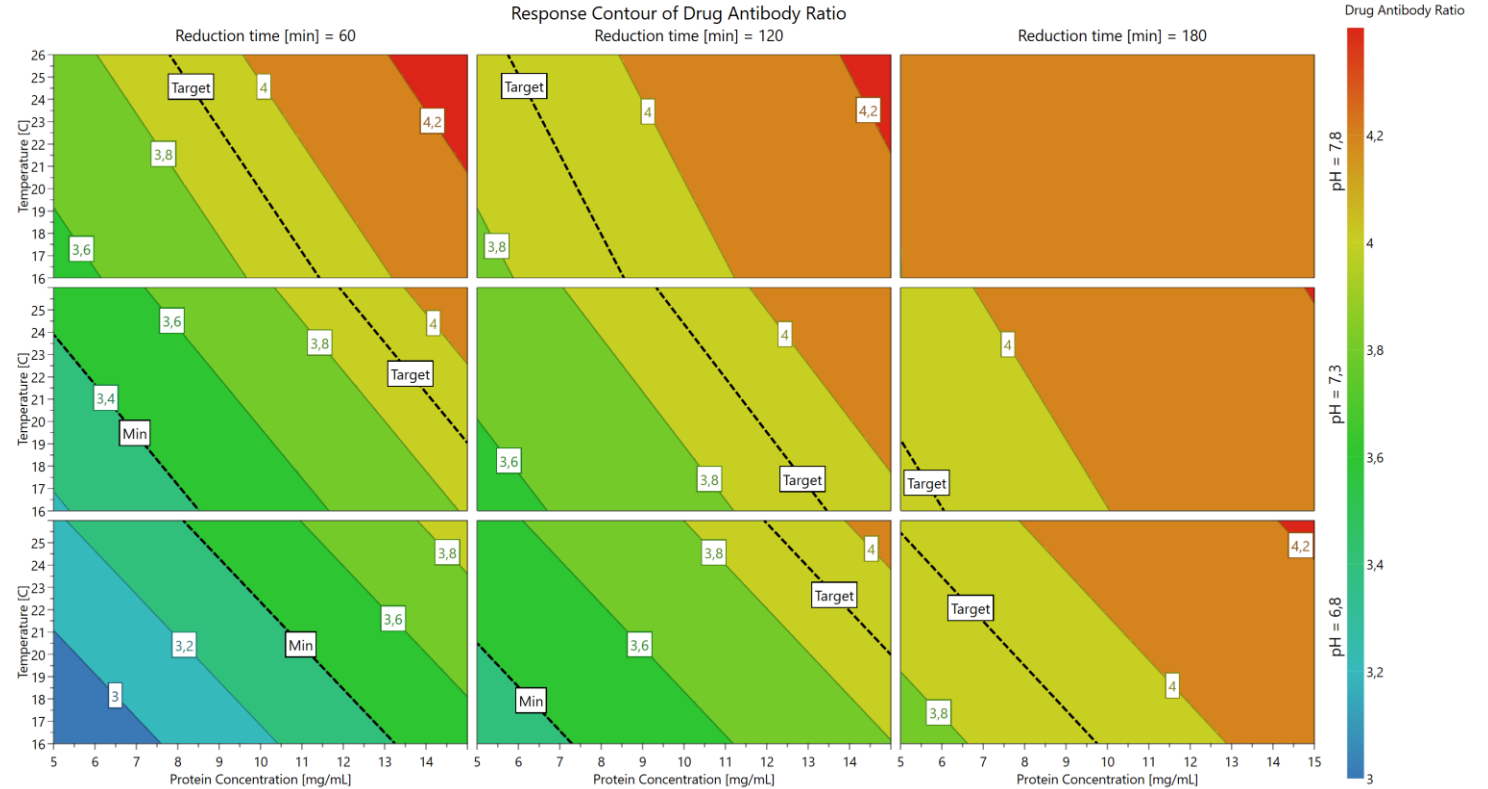
With a R2 of 0.97 the experimental points will be very close to the line



# 4-D Contour Plot

This overview plot has been added to the Analysis wizard

We can see that the lower left corner in the lower left plot are below the minimum value of 3.4. All the remaining area are within the specifications



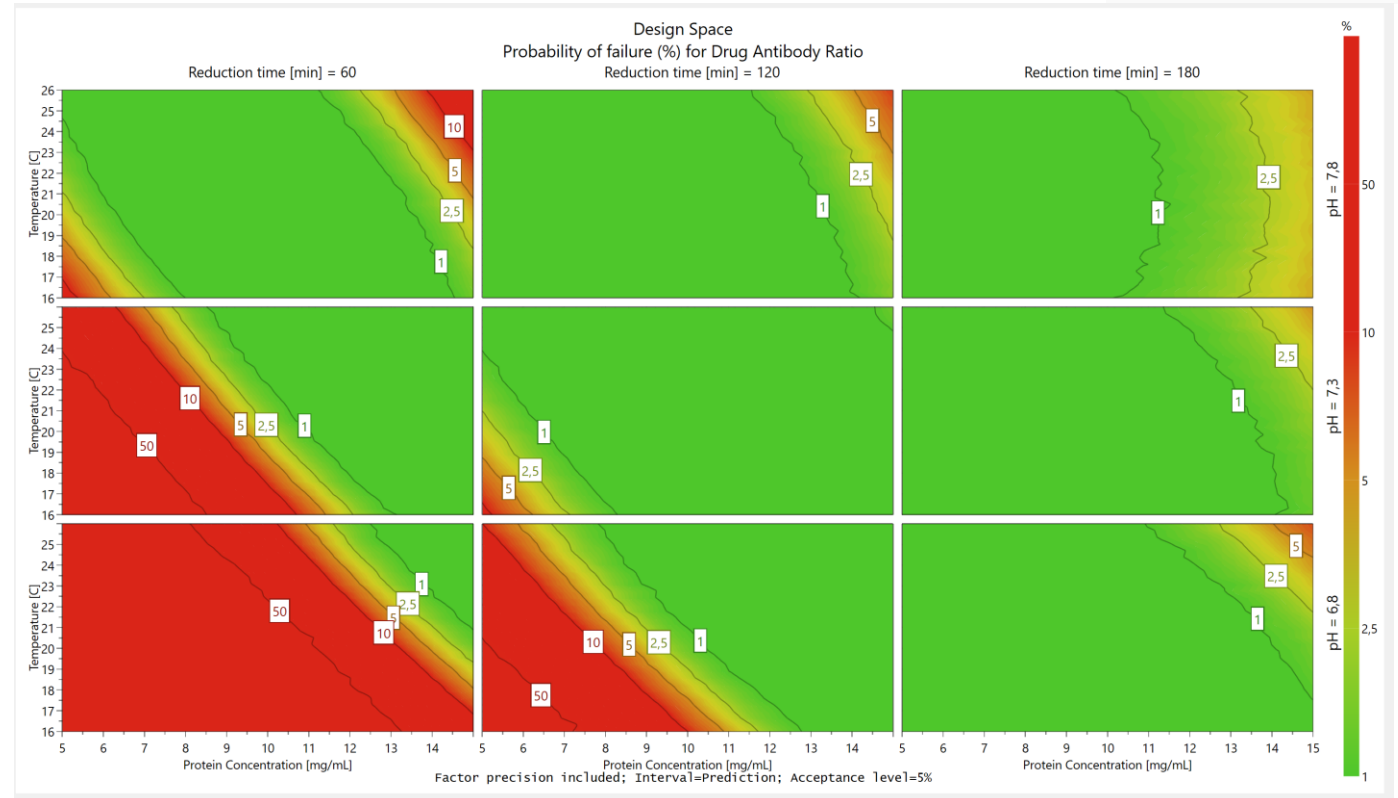


# Design Space Plot Gives You the Safe Area in Green

Design space is a part of MODDE that has become much more user user-friendly.

The next part is to find the area where the possibility of being within the specifications are high.

In this case the acceptance level is 5% using the Prediction Interval




# Robust Set-point is the Center of the Green Area

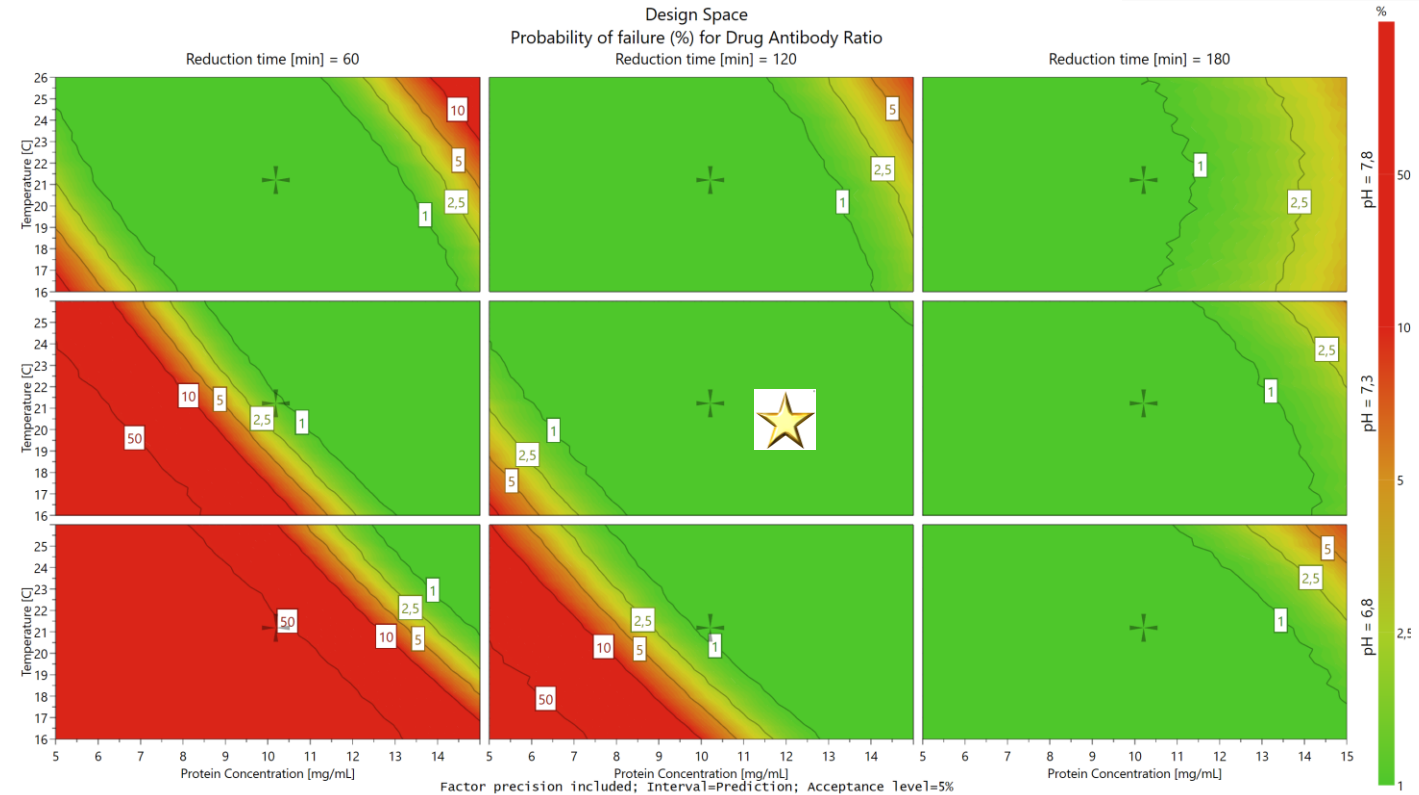


Optimization wizard

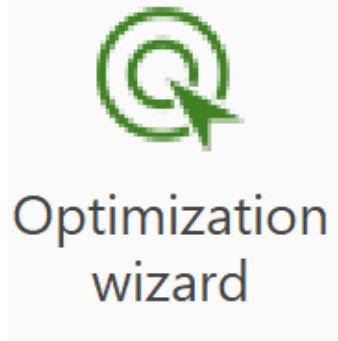
The Robust Set-point 

is the point furthest away from any red area. This is usually the start point for production runs.

Favorite Set-point is a point that the user find most practical or economical 



# Summary in numbers



## Robust set-point coordinates

- Protein Concentration 10.20 mg/ml
- Temperature 21.2 C
- pH 7.32
- Reduction time 122.4 min

## Practical set-point

- Protein Concentration 12.20 mg/ml
- Temperature 20 C
- pH 7.33
- Reduction time 115 min

## Summary

Settings used and setpoints found during the current session of the optimization wizard.

### Response settings

Name	Condition	Objective	Min	Target	Max	Predicted min	Predicted max
Drug Antibody Ratio	Required	Target	3,4	3,9	4,4	2,81743	4,30765

### Factor settings

Name	Units	Settings	Precision	NOR
Protein Concentration	mg/mL	5 to 15	0,1	1
Temperature	C	16 to 26	0,1	2
pH		6,8 to 7,8	0,01	0,2
Reduction time	min	60 to 180	1	30

### Robust setpoint

Probability of failure: 0,042% (interval: Prediction)

Response	Value	Unit	Prob.of failure	Cpk
Drug Antibody Ratio	3,865		0,042%	1,489

Factor	Value	Unit	Robust low edge	Robust high edge	Hypercube low edge	Hypercube high edge
Protein Concentration	10,200	mg/mL	5,000	15,000	8,333	14,333
Temperature	21,200	C	16,000	26,000	19,333	25,333
pH	7,320		6,800	7,800	7,133	7,733
Reduction time	122,400	min	60,000	180,000	100,000	180,000

# Summary



Optimization  
wizard

It is not common to get a large Design Space from a screening design, but this design did fulfill the important criteria

Excellent chemical knowledge that supported the selection of appropriate factor ranges

Good bookkeeping of experiments and entering the correct values into the Performed Experiments Worksheet

Excellent execution of the design with very small replication noise and no outliers



# Acknowledgements

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Thank you.

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