What´s new in MODDE Pro 11

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Technology for Productivity

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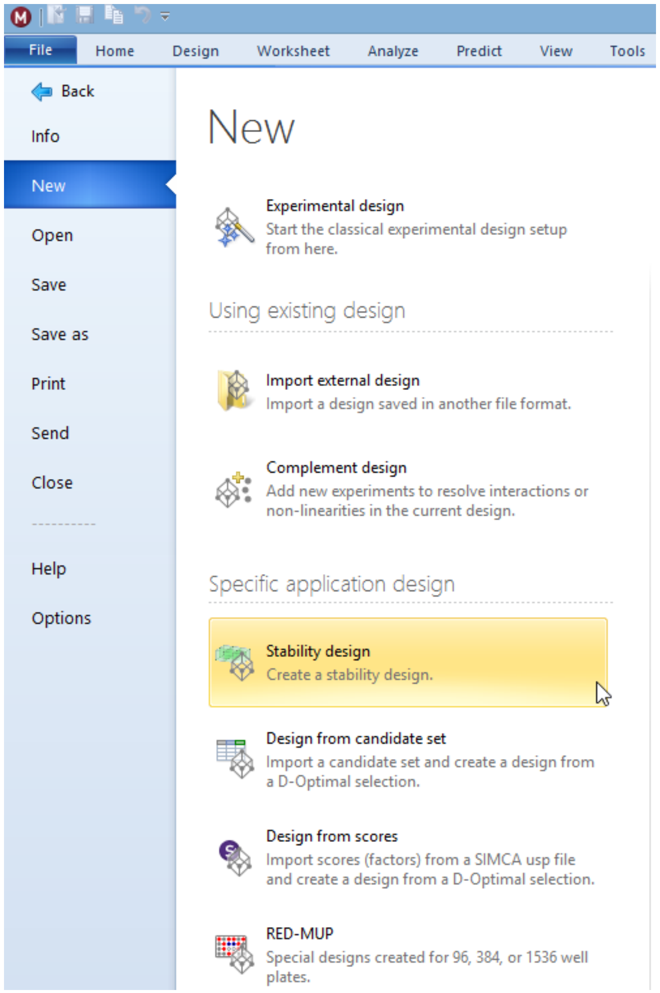
Stability testing

Introduction to stability testing

- A pharmaceutical product in storage may change its quality characteristics with time.
- A product is considered stable as long as its quality characteristics remain within specifications.
- The shelf life of a product corresponds to the number of days it remains stable at the recommended storage conditions.
- The process of collecting experimental data for estimating and verifying a product´s shelf life is called stability testing.
- With the release of MODDE Pro 11, MKS Umetrics introduces a new class of reduced combinatorial designs that are especially well suited to the needs of stability testing

File / New / Stability Designs



Stability design

Stability designs can be used for an efficient evaluation of product stability. The stability designs use a novel multilevel design strategy. The designs, distributed over a time sequence, fit the standard matrixing schedule used for pharmaceutical stability studies. Any type of study designed as a sequence of investigations can be efficiently mastered using the stability designs.

Matrixing

- Full testing of all factor combinations is done at 0 and 36 months
- Reduced testing is carried out at all other time points
  - Usually, 3, 6, 9, 12, 18 & 24 months
  - Only subsets of the factor combinations are tested
  - Common reductions are the one-half and the one-third reduction
- Ideally, the various reductions tested at 3, 6, 9, 12, 18 & 24 months should be complementary
  - All factor combinations are investigated at least once in each type of reduction
  - *Balancing* - it is advantageous if all levels of any qualitative or multilevel factor are exploited the same number of times in each reduction

Design wizard to define the investigation

- Time factor pre-configured (can be modified)

Design Wizard

Define factors

Factors: 1 (1 process, 0 mixture)

	Name	Abbr.	Units	Type	Use	Settings	Transform	Precision
1	Time	T	month	Time	Controlled	0; 3; 6; 9; 12; 18; 24; 36		
		Double-click here	to add	a new factor				

- Additional factors defined in the usual way...

Factors

	Name	Abbr.	Units	Type	Settings	Transform	Precision
1	Time	Time	month	Time	0; 3; 6; 9; 12; 18; 24; 36		
2	Strength	Str	mg	Quantitative	10 to 20	None	0,25
3	Batch	Batch		Qualitative	Batch 1; Batch 2; Batch 3		
4	Package	Pack		Qualitative	Pack A; Pack B; Pack C; Pack D		
		Double-click here	to add	a new factor			

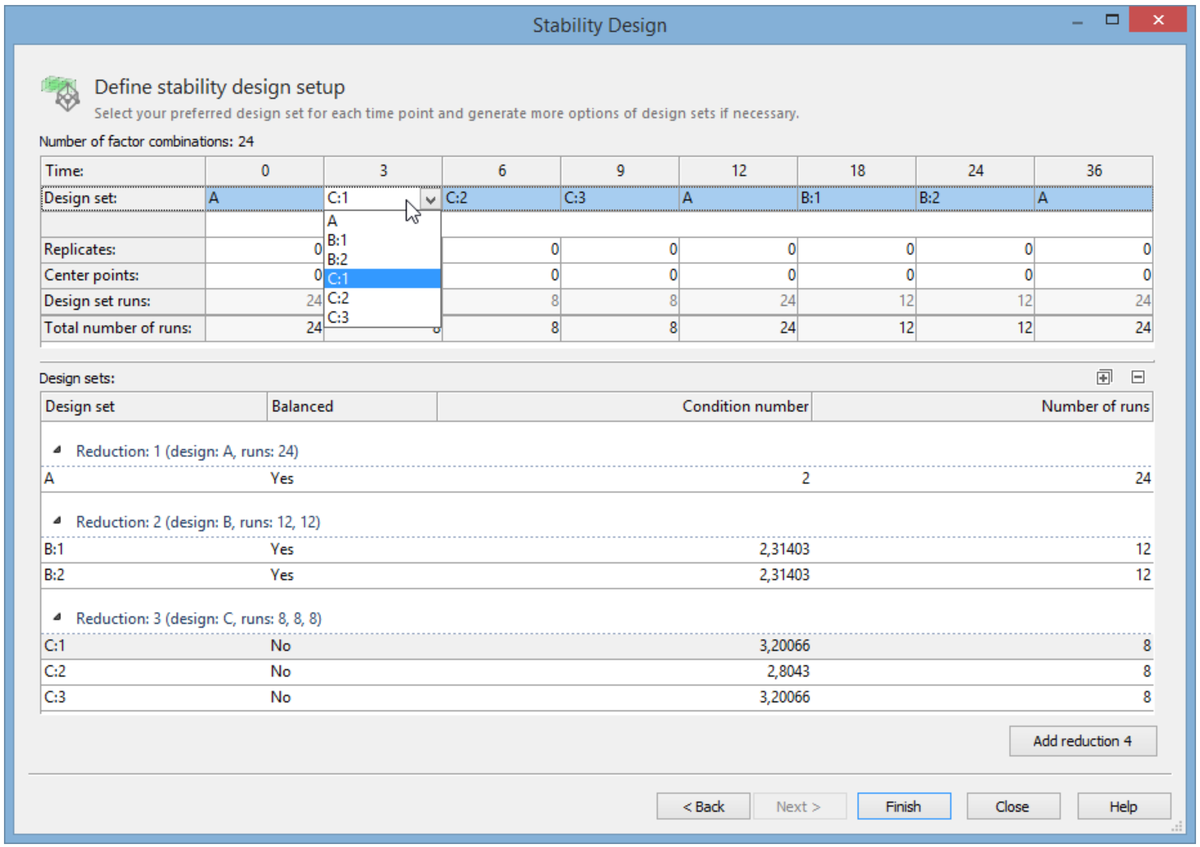
- ... as well as the response(s)

Responses

	Name	Abbr.	Units	Transform	Type	Min	Target	Max
1	Impurities	Imp		None	Regular			2
		Double-click here	to add	a new response				

Define stability design setup page

- Which Reductions to use and when is easy to regulate
- Additional reductions can be added



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Worksheet – some differences

- Combination ID: There will be as many Combination IDs as there are factor combinations (excluding Time), i.e. 24 in our example.
- Exp Name: Modified naming structure for each experimental run, which indicates Combination ID and time point.
- Two list boxes. Enable subset selections of the experiments to be done. Subset selections can be accomplished based on the factor combinations and time points.

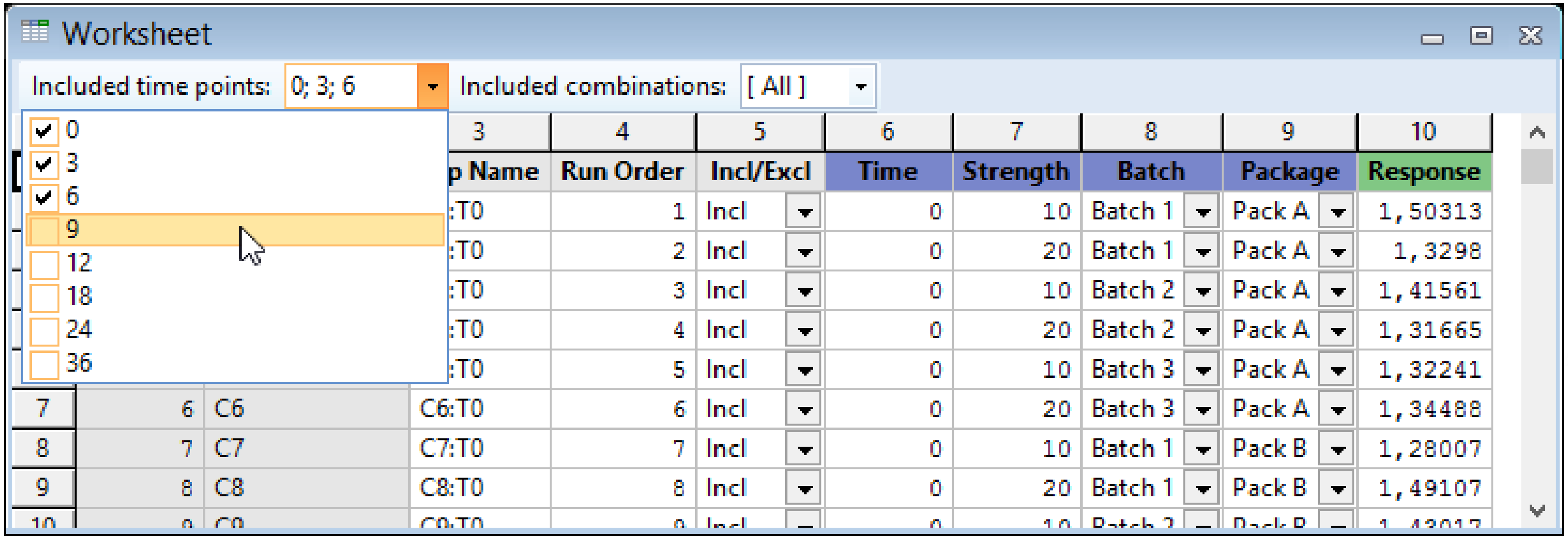
Worksheet

Included time points: [All]   Included combinations: [All]

	1	2	3	4	5	6	7	8	9	10
1	Exp No	Combination ID	Exp Name	Run Order	Incl/Excl	Time	Strength	Batch	Package	Impurities
2	1	C1	C1:T0	1	Incl	0	10	Batch 1	Pack A	
3	2	C2	C2:T0	2	Incl	0	20	Batch 1	Pack A	
4	3	C3	C3:T0	3	Incl	0	10	Batch 2	Pack A	
5	4	C4	C4:T0	4	Incl	0	20	Batch 2	Pack A	
6	5	C5	C5:T0	5	Incl	0	10	Batch 3	Pack A	
7	6	C6	C6:T0	6	Incl	0	20	Batch 3	Pack A	
8	7	C7	C7:T0	7	Incl	0	10	Batch 1	Pack B	
9	8	C8	C8:T0	8	Incl	0	20	Batch 1	Pack B	
10	9	C9	C9:T0	9	Incl	0	10	Batch 2	Pack B	

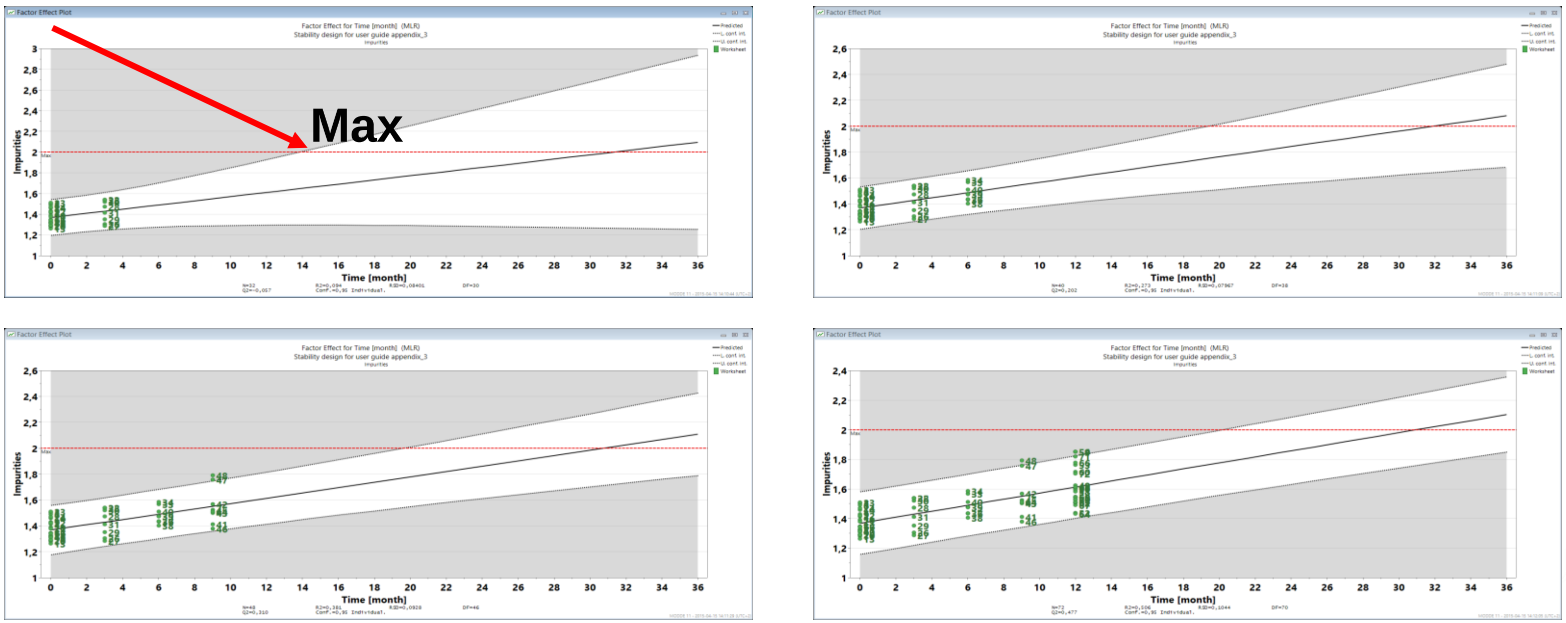
Early stage data analysis – time factor

- In the early stages, say after 6 or 9 months, the focus lies on trending, i.e., understanding what will likely be the development trajectory of the response with time
  - Simple regression model, usually Time is used as the single factor
  - Subset selection of experiments representing different time spans is easily accomplished by using the list boxes of the worksheet.



Visualization predicted trajectory

- The Factor Effect plot is used
- Impurities trajectory plotted after 3, 6, 9 and 12 months
- Better precision in predictions over time (more data points)



- Judging from this early stage trend analysis, we are at risk of violating the 36 months Max setting of the response!

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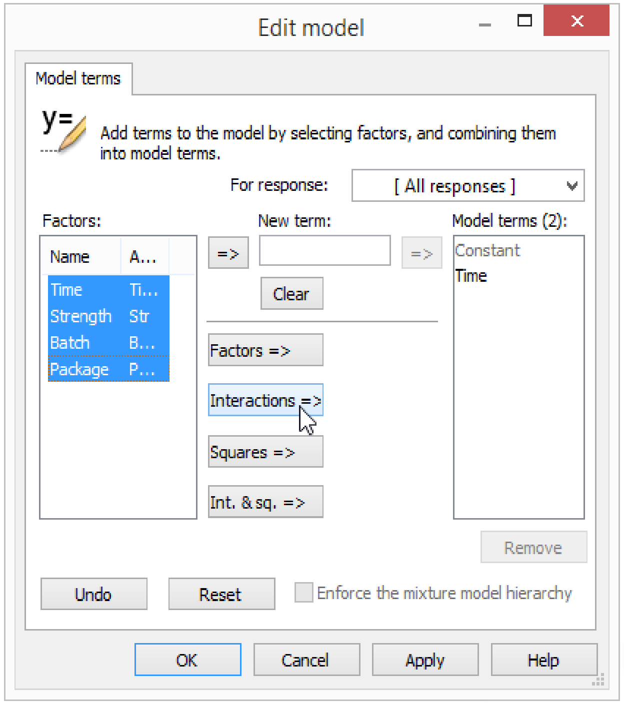
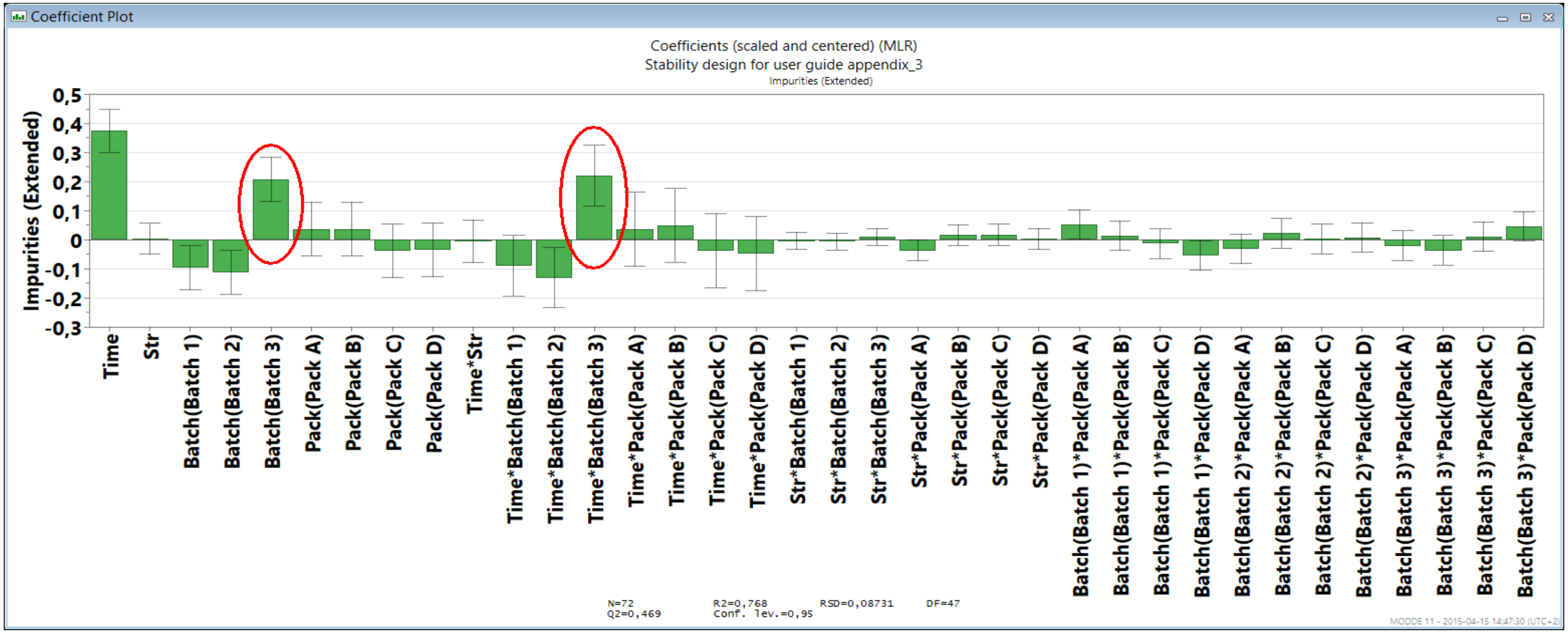
Early stage data analysis – all terms

- Worrying increase in the predicted level of Impurities towards the end of the stability test
- It is of relevance to investigate the impact of the other three factors on Impurities
- The regression model must be modified so that it includes all possible main and interaction effects;
  - On the Home tab, click Edit model.



Plot of regression coefficients

- Model for 0-12 months: Batch 3 is associated with a rapid and unacceptable increase in the level of Impurities.
  - This batch should be excluded from further consideration; it will not comply with the final 36 months acceptance criterion



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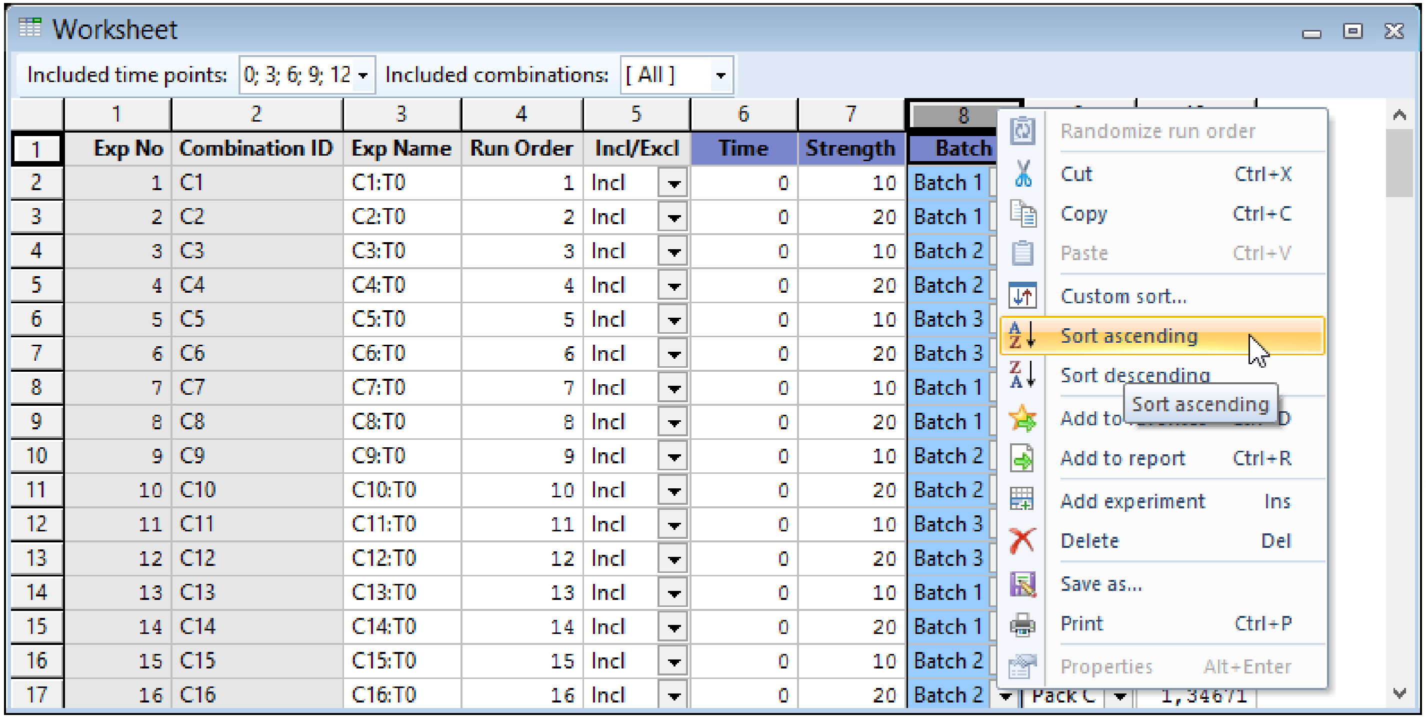
Late stage data analysis – Batch 3 exclusion

- All samples including this factor setting need to be excluded from the data analysis.
  - Sort the MODDE worksheet according to the Batch factor.
  - Then simply mark all rows containing Batch 3 and in the Incl/Excl column select the setting Excl.



	1	2	3	4	5	6	7	8
1	Exp No	Combination ID	Exp Name	Run Order	Incl/Excl	Time	Strength	Batch
2	1	C1	C1:T0	1	Incl	0	10	Batch 1
3	2	C2	C2:T0	2	Incl	0	20	Batch 1
4	3	C3	C3:T0	3	Incl	0	10	Batch 2
5	4	C4	C4:T0	4	Incl	0	20	Batch 2
6	5	C5	C5:T0	5	Incl	0	10	Batch 3
7	6	C6	C6:T0	6	Incl	0	20	Batch 3
8	7	C7	C7:T0	7	Incl	0	10	Batch 1
9	8	C8	C8:T0	8	Incl	0	20	Batch 1
10	9	C9	C9:T0	9	Incl	0	10	Batch 2
11	10	C10	C10:T0	10	Incl	0	20	Batch 2
12	11	C11	C11:T0	11	Incl	0	10	Batch 3
13	12	C12	C12:T0	12	Incl	0	20	Batch 3
14	13	C13	C13:T0	13	Incl	0	10	Batch 1
15	14	C14	C14:T0	14	Incl	0	20	Batch 1
16	15	C15	C15:T0	15	Incl	0	10	Batch 2
17	16	C16	C16:T0	16	Incl	0	20	Batch 2

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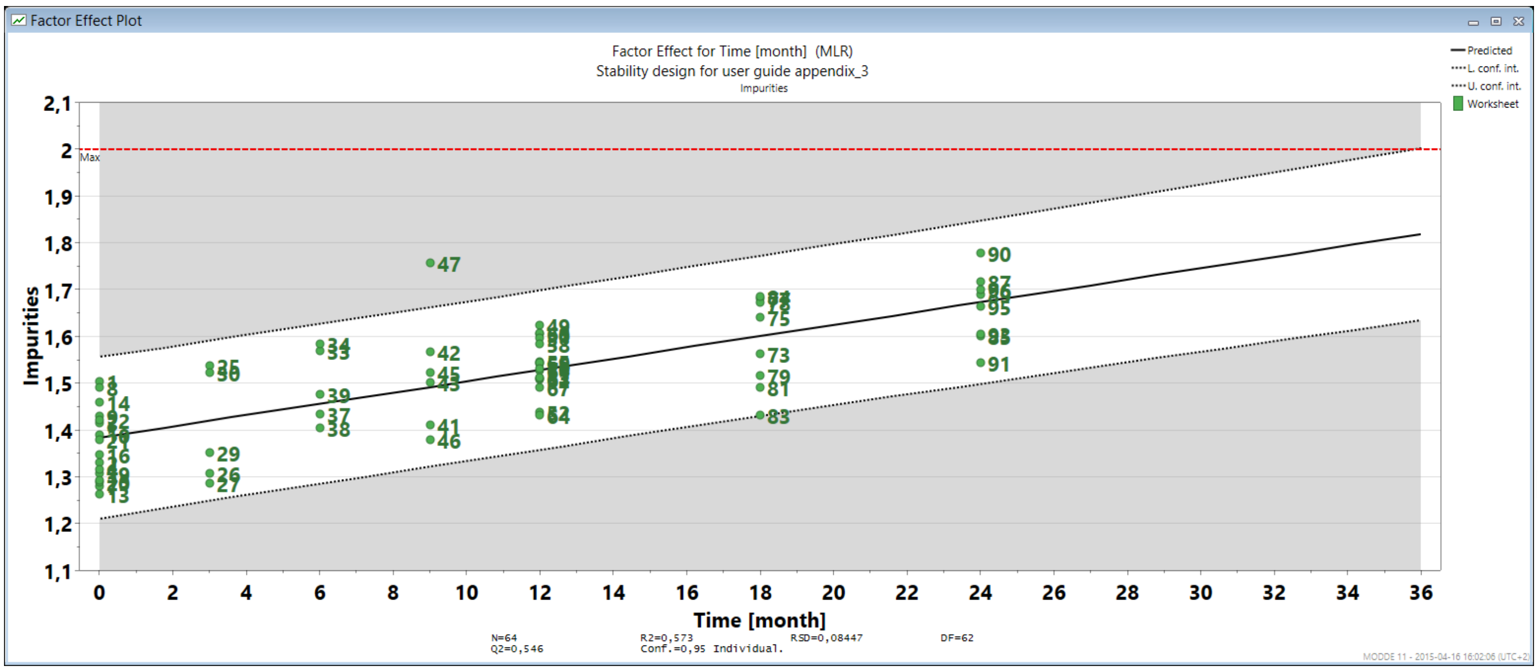
Late stage data analysis – Look at trajectory

- A model for a larger time span (0-24 months) was calculated using Time as the single factor.
- The conclusion is that the 36 months acceptance criterion will be met



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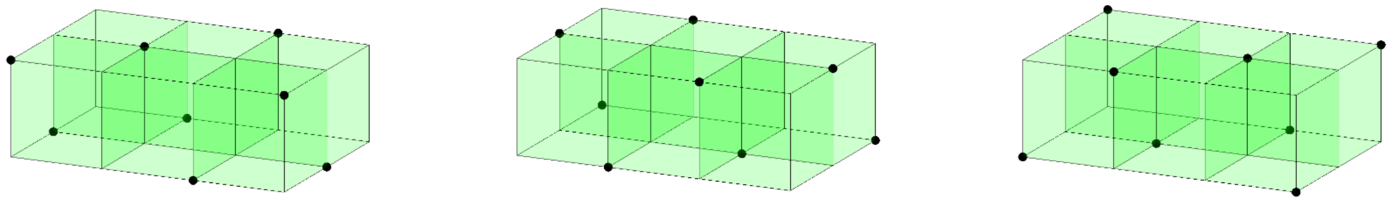
Conclusions

- The new design family for stability testing is based on reduced combinatorial design sets that are perfectly complementary when superimposed on top of one another



- The novel stability designs are very flexible and apt for matrixing
  - All factors levels are tested at an early stage
  - Allows the user to detect and remove elements in the experimental scheme that cause instability
  - Early removal of uninteresting elements and zooming-in on critical features facilitate optimal use of the available testing resources

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New features for design space estimation

New features and deafult settings

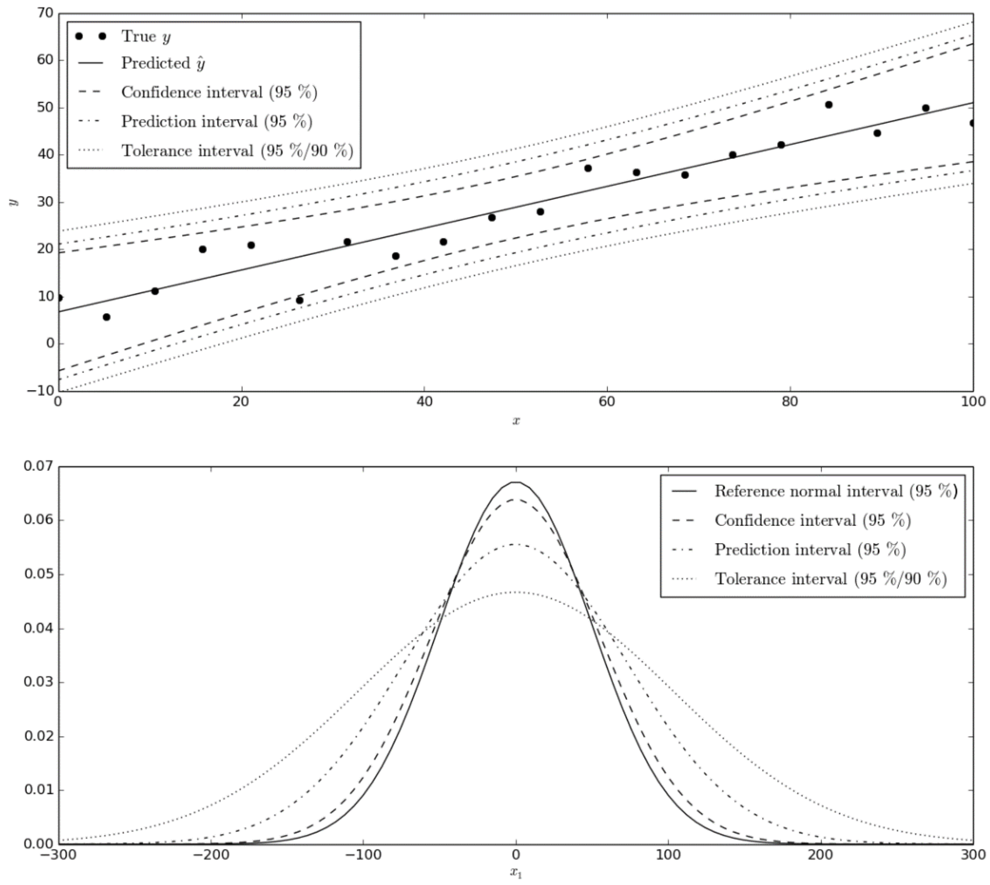
- Several supported uncertainty interval estimates
  - Will profoundly affect the size of the resulting design space
- Enhanced design space explorer tool
  - Inscribed hypercube (interactive)
  - PAR connection better worked out
- New defaults
  - Probability of failure =1%, DPMO = 10.000
  - Interval estimate = prediction

Uncertainty interval estimates

- A possibility to set three types of interval estimates for the probability function
- Interval estimates
  - Confidence interval (MODDE 10)
    - Average prediction interval
  - Prediction interval (Default for MODDE Pro 11)
    - Next observation interval
  - Tolerance interval
    - Next population interval

- See detailed information in Statistical appendix

Interval distributions



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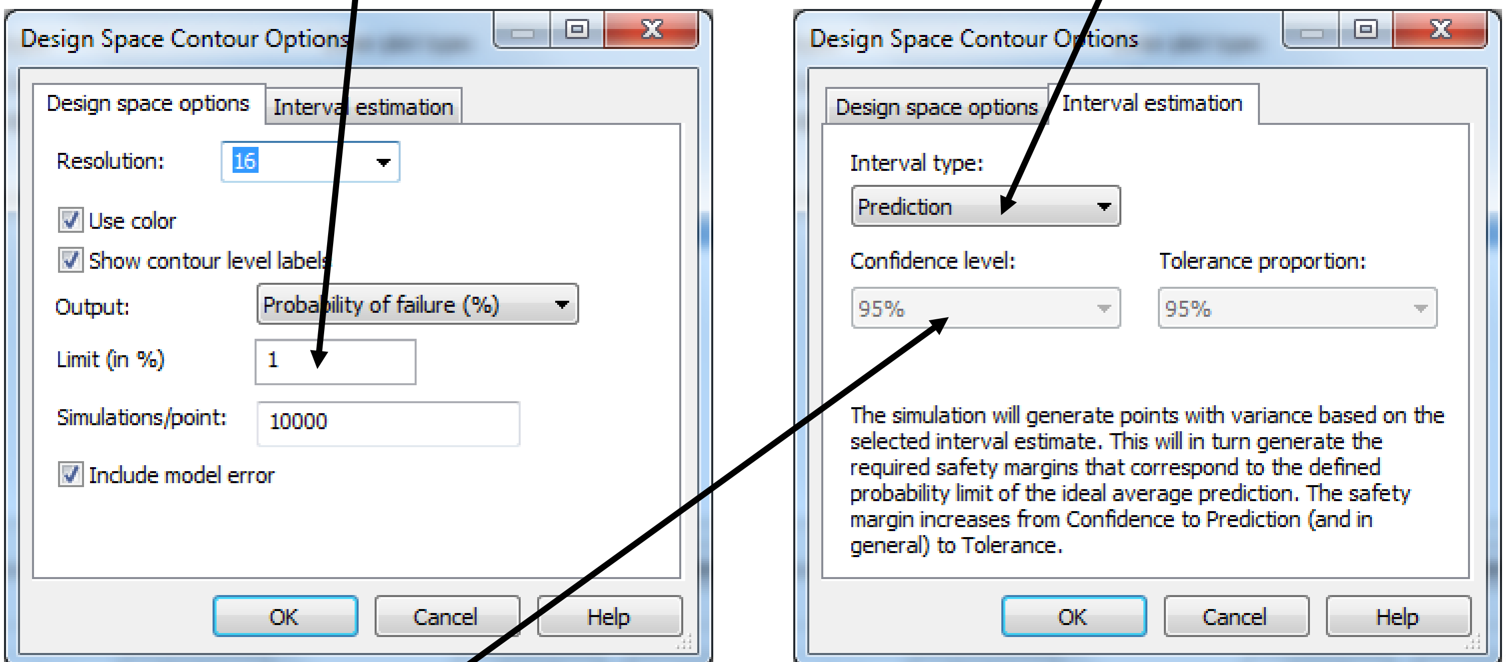
MODDE user guide

- **Confidence interval**
  - This interval encloses average of the true population, with some confidence, and is mainly used to illustrate the variance of the model coefficients.
- **Prediction interval**
  - This interval encloses a region within which we are confident that the next observation will fall.
- **Tolerance interval**
  - This interval encloses a region within which we are confident that some proportion of future samples will fall.

- The *Confidence interval* and *Prediction interval* require an acceptance level, *i.e.*, roughly speaking a probability. It is usually expressed as the *Confidence level* (90 %, 95 % or 99 %). The *Tolerance interval* requires an acceptance level, but also requires a parameter for the fraction of future samples that fall within the interval, called the *Tolerance proportion*. The default setting in MODDE for evaluation of model parameters is *Confidence interval* at 95 %. The default setting for design space is *Prediction interval* at 99 %.

Design space, interval settings

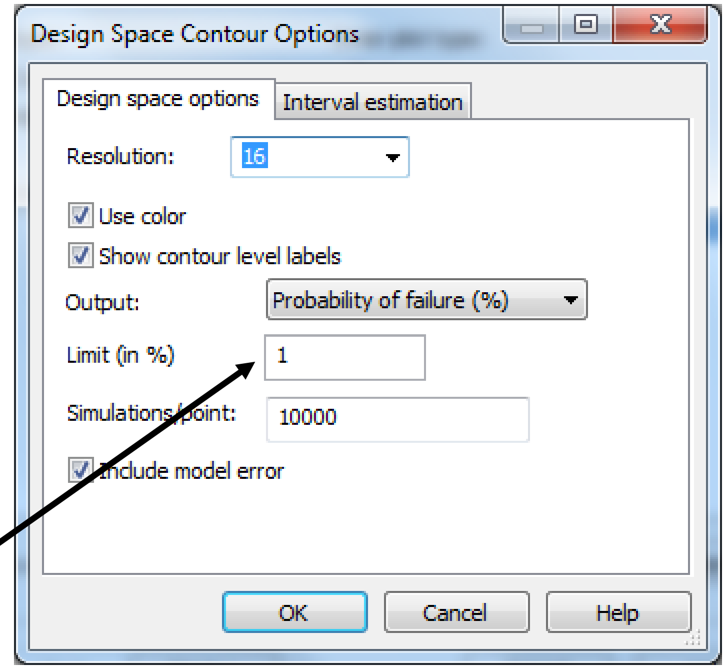
- Default: 1% probability of failure limit using prediction interval type

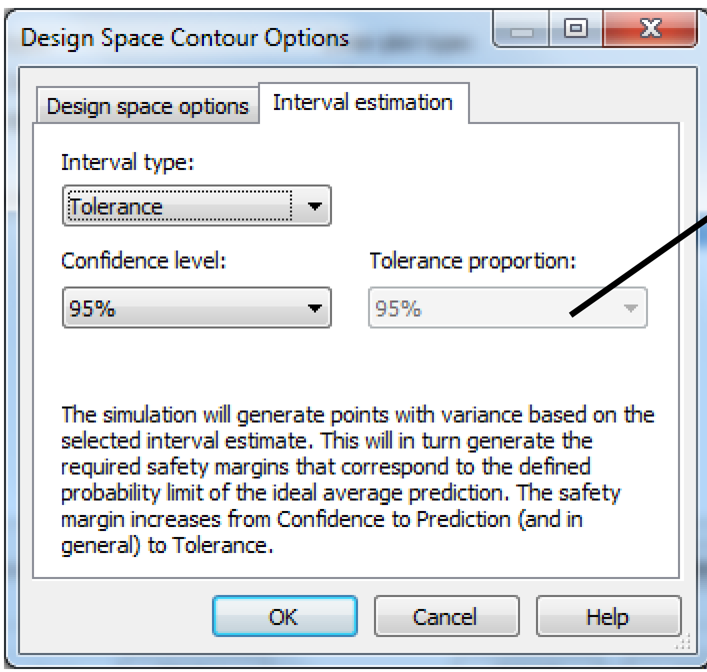


- Confidence level setting depends on setting for Limit (in %) and is therefore inactive; should be interpreted as 99% if Limit is 1%

Tolerance settings

- Tolerance is different
- Default 1% of the distribution is accepted





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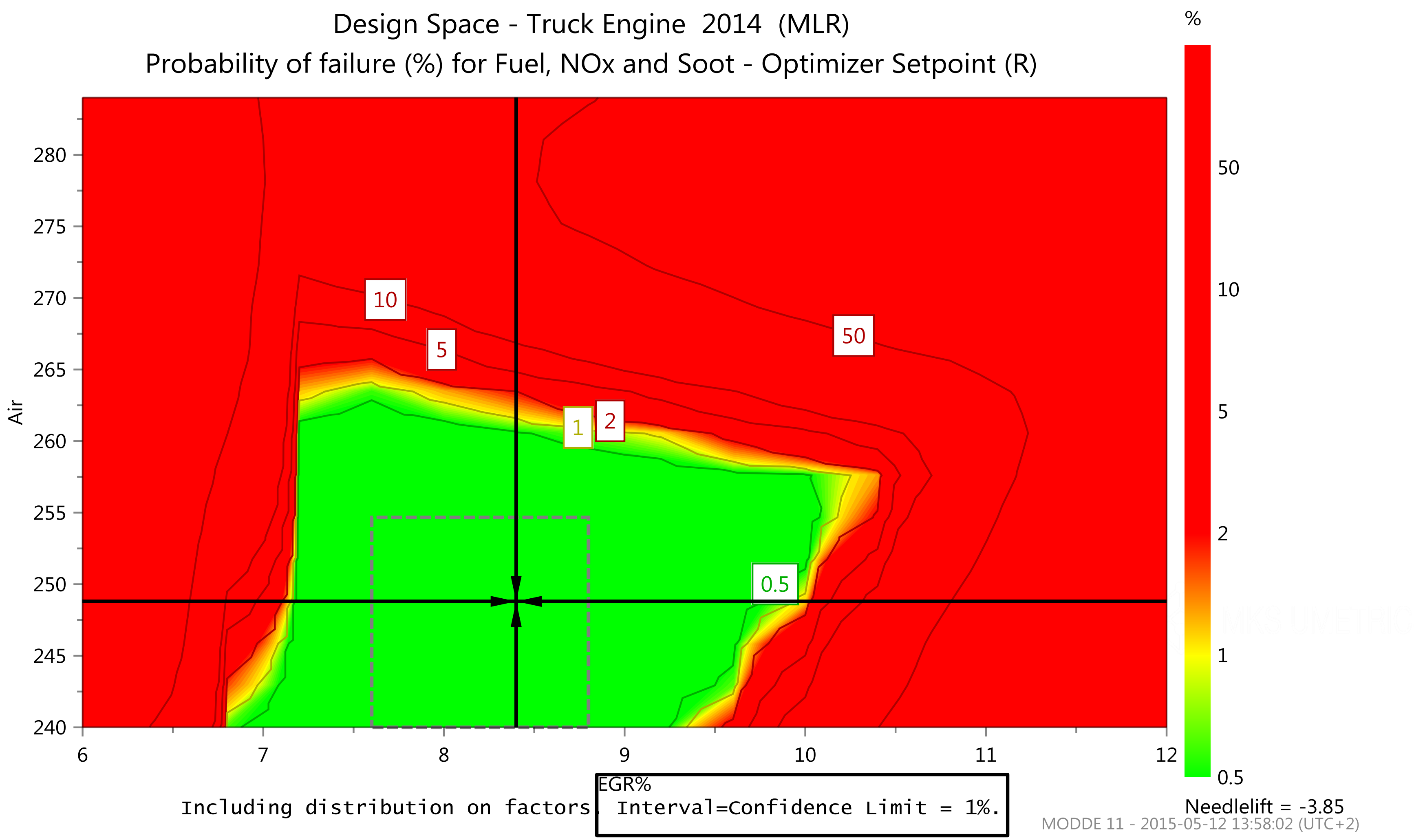
Design Space Explorer as in M10.1



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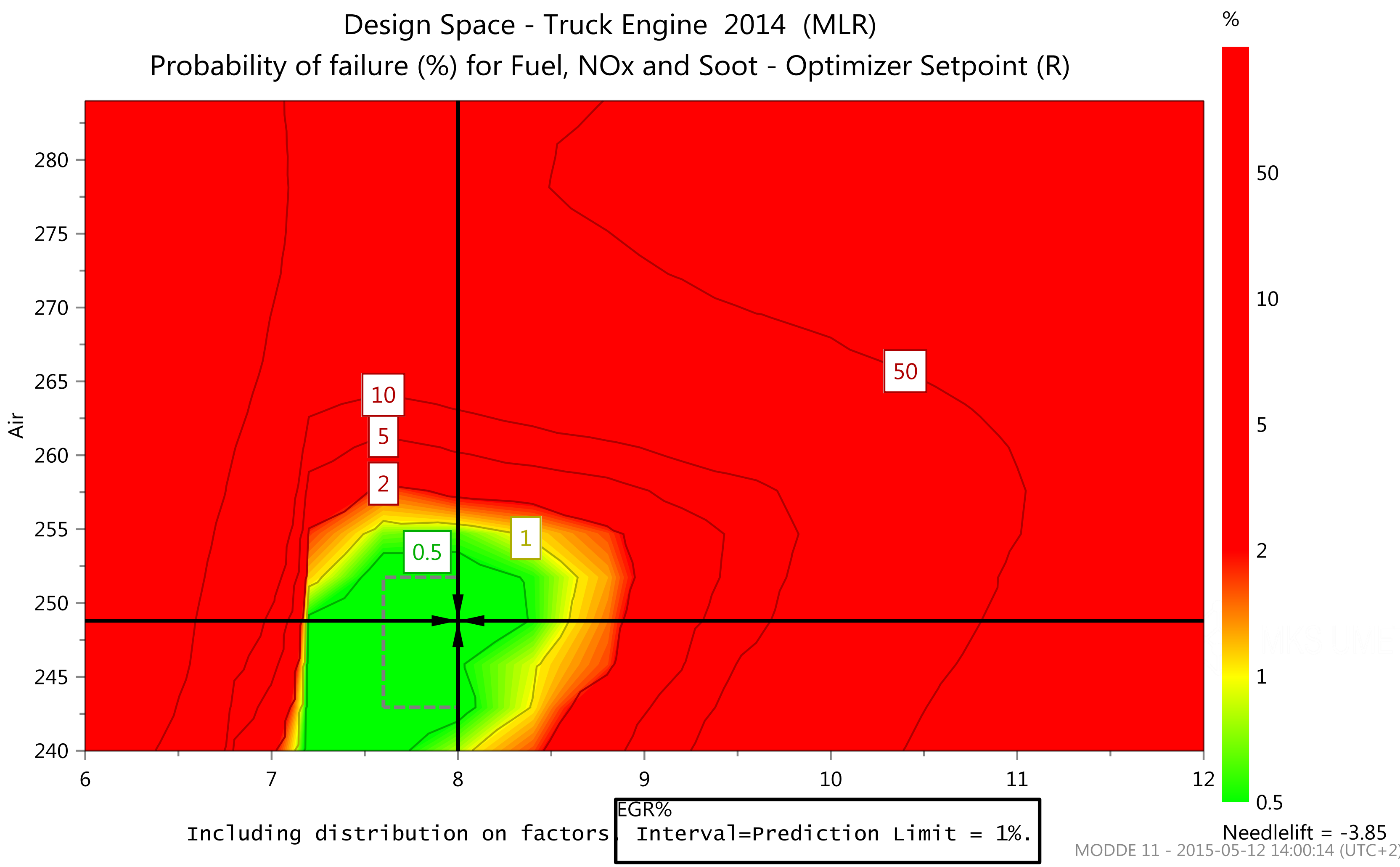
Design Space Explorer M11



Proven acceptable ranges – Approach 1

- *Approach 1. Based on the robust setpoint.*
  The hypercube range field of the design space explorer is used in this mode. The black T-lines extending out from the robust setpoint co-ordinate indicate the individual ranges for the factors, i.e., the largest allowable range of a process parameter, while keeping all other parameters constant at their setpoint value.

Design space hypercube

Factor	Setpoint	Role	Hypercube low edge	Hypercube high edge	Hypercube range
Air	242,933	Free	240	242,933	
EGR%	8,4	Free	7,2	8,4	
Needlelift	-5,00933	Free	-5,39467	-4,624	

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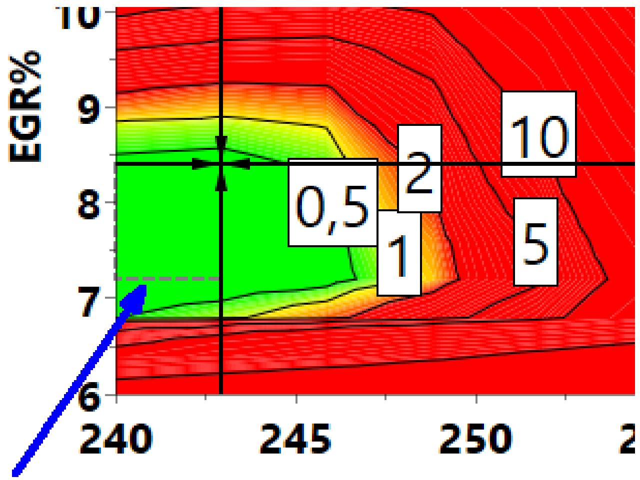
Proven accepble ranges – Approach 2

- *Approach 2. Based on the dotted hypercube frame.*
  The dotted frame in the design explorer plot (below) designates the largest possible *regular* hypercube that can be inserted into the *irregular* design space volume. How this regular hypercube extend into many dimensions is given by the green bars seen in the Hypercube range part in the previous slide. The green bars mark the *mutual ranges* within which all factors can be changed at the same time without further restrictions.



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Proven acceptable ranges – Approach 3

- Approach 3 is reminiscent of approach 1, but is based on a *distribution* around a setpoint. Such distributions are attained using the Setpoint analysis functionality in MODDE.

Setpoint Analysis - Optimizer Setpoint (R)

Factor	Low	Setpoint	High	Std. dev.	Role	Distrib...	Estimated acceptable range
Air	237.158	242.933	248.708	2.94643	Free	Normal	
EGR%	7.50375	8.4	9.29625	0.45727	Free	Normal	
Needlelift	-6.00277	-5.00933	-4.01589	0.506855	Free	Normal	

Response	Min	Target	Max	Criterion	Cpk	DPMO	Predicted response profile
Fuel		210	250	Minimize	0.84831	5040	
NOx		10	25	Minimize	1.52088	0	
Soot		0.05	1	Minimize	1.27672	5660	

Total DPMO: 10700, DPMO limit: 10000. Samples: 50000. Interval=Prediction

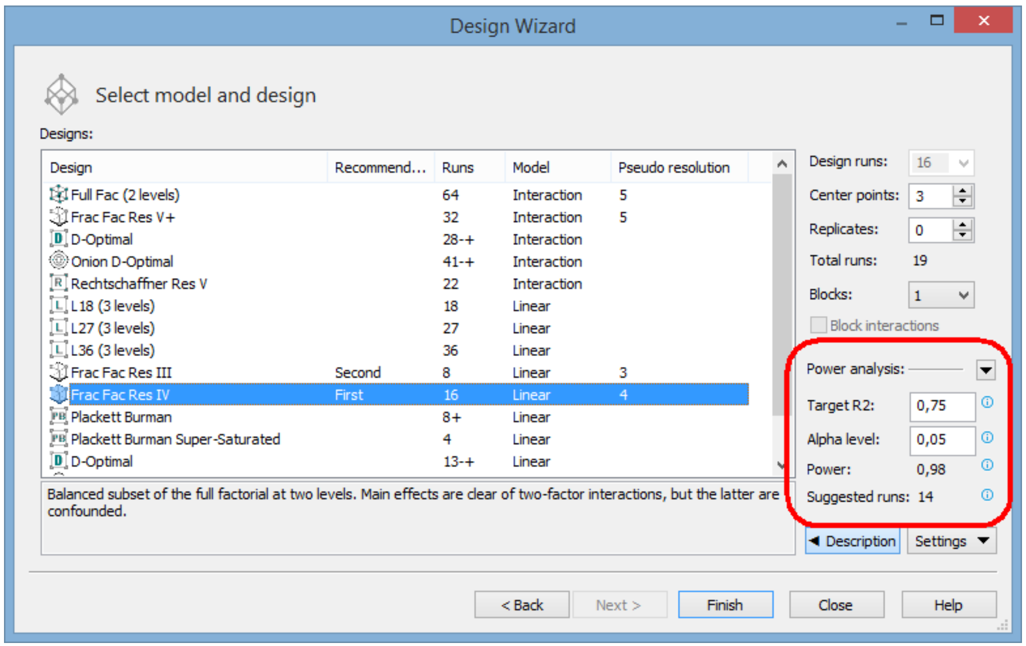
Miscellaneous new features

Miscellaneous new features

- Power estimation of new designs
- New screening design family: Reduced combinatorial designs
- Prediction plot updates
  - Uncertainty interval estimates include confidence, prediction and tolerance options
  - Original response data are displayed
  - Transformed factors back-transformed to original unit
- Unicode to support all character sets

Design power

- Power denotes our ability to detect a significant effect
  - How many runs are required in order to detect a significant effect?
  - It is assumed that least one regression coefficient is significant
  - Input is expected (target) R2 for the investigation and alpha level
  - Output is Power and suggested (= necessary) number of runs to reach a power of at least 0.8



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New screening design family

- Alternative to D-optimal
- Easy balancing w r t multilevel factors

Design Wizard

Select model and design

Designs:

Design	Recommend...	Runs	Model	Pseudo resolution
Full Fac (Mixed)		768	Interaction	
D-Optimal		51-+	Interaction	
D-Optimal	Second	13-+	Linear	
Reduced Combinatorial	First	13-+	Linear	

Design runs: 13
Center points: 0
Replicates: 0
Total runs: 13

Combinatorial designs are generated from a strict combinatorial perspective in order to create a reduced design with a balanced distribution of all factor settings. The algorithm selecting the points treats multilevel and qualitative factors equally.

Power analysis:

◀ Description | Settings ▼

< Back | Next > | Close | Help

Factors

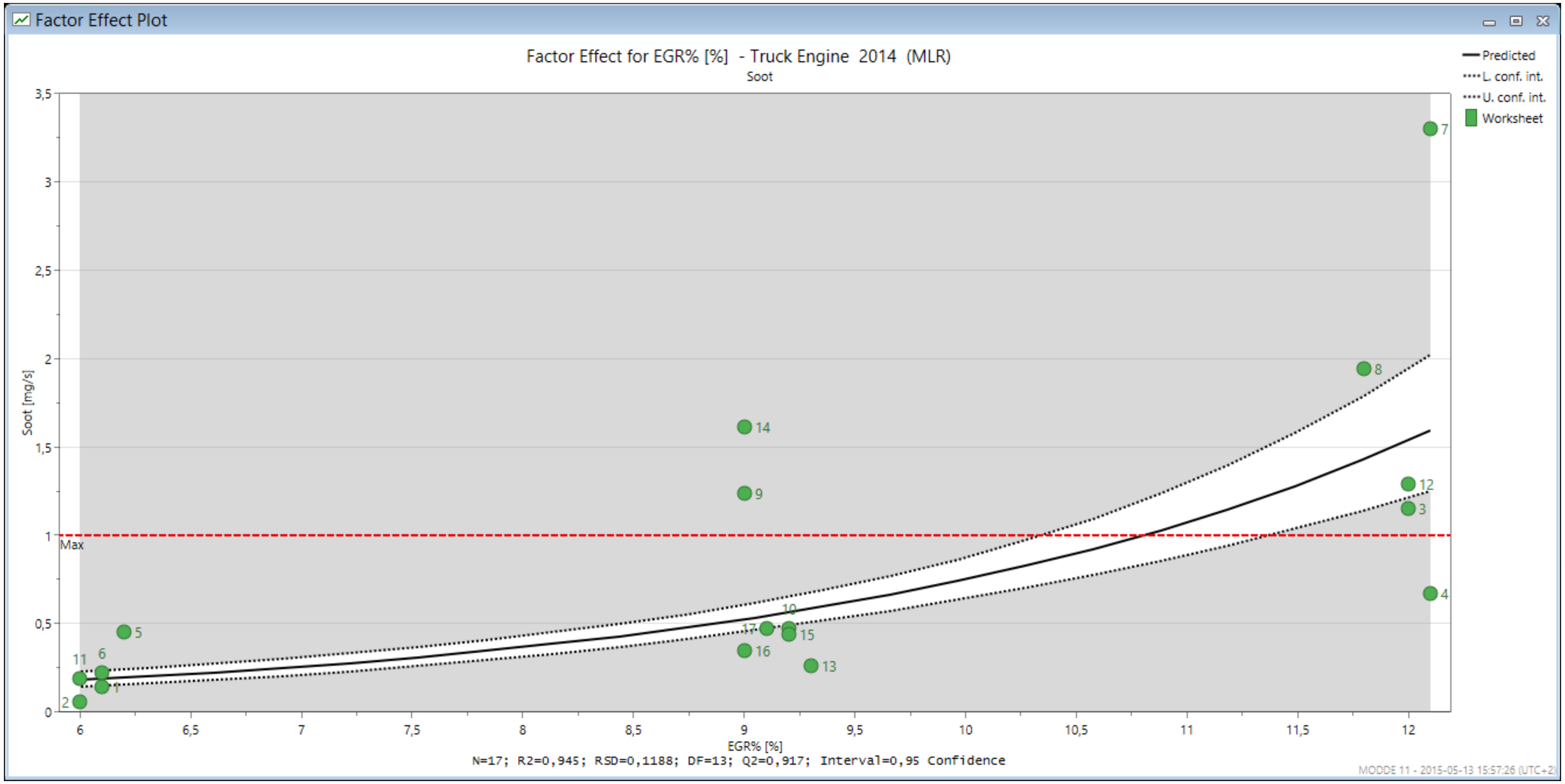
	Name	Abbr.	Units	Type	Settings	Transform	Precision
1	x1	x1		Quantitative	-1 to 1	None	0,05
2	x2	x2		Quantitative	-1 to 1	None	0,05
3	x3	x3		Quantitative	-1 to 1	None	0,05
4	x4	x4		Quantitative	-1 to 1	None	0,05
5	x5	x5		Quantitative	-1 to 1	None	0,05
6	x6	x6		Quantitative	-1 to 1	None	0,05
7	x7	x7		Multilevel	1; 2; 3; 4	None	0,075
8	x8	x8		Qualitative	A; B; C		

Worksheet

	1	2	3	4	5	6	7	8	9	10	11	12
1	Exp No	Exp Name	Run Order	Incl/Excl	x1	x2	x3	x4	x5	x6	x7	x8
2	1	N1	4	Incl	1	1	−1	1	−1	1	1	A
3	2	N2	1	Incl	−1	1	−1	−1	1	−1	1	B
4	3	N3	14	Incl	1	−1	1	−1	−1	−1	1	C
5	4	N4	2	Incl	−1	−1	−1	1	1	−1	2	A
6	5	N5	12	Incl	−1	−1	1	1	−1	1	2	B
7	6	N6	11	Incl	−1	1	−1	−1	−1	1	2	C
8	7	N7	13	Incl	1	−1	1	−1	1	1	3	A
9	8	N8	3	Incl	1	−1	−1	1	−1	−1	3	B
10	9	N9	5	Incl	−1	1	1	1	1	1	3	C
11	10	N10	9	Incl	−1	1	1	−1	−1	−1	4	A
12	11	N11	8	Incl	1	−1	−1	−1	1	1	4	B
13	12	N12	7	Incl	1	1	1	1	1	−1	4	C
14	13	N13	10	Incl	−1	1	−1	−1	−1	1	2	C
15	14	N14	15	Incl	−1	1	1	1	1	1	3	C
16	15	N15	6	Incl	−1	−1	−1	1	1	−1	2	A

Prediction plot updates

- Measured values are seen
- Possibility to change uncertainty interval type
- Transformed factors are back-transformed



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