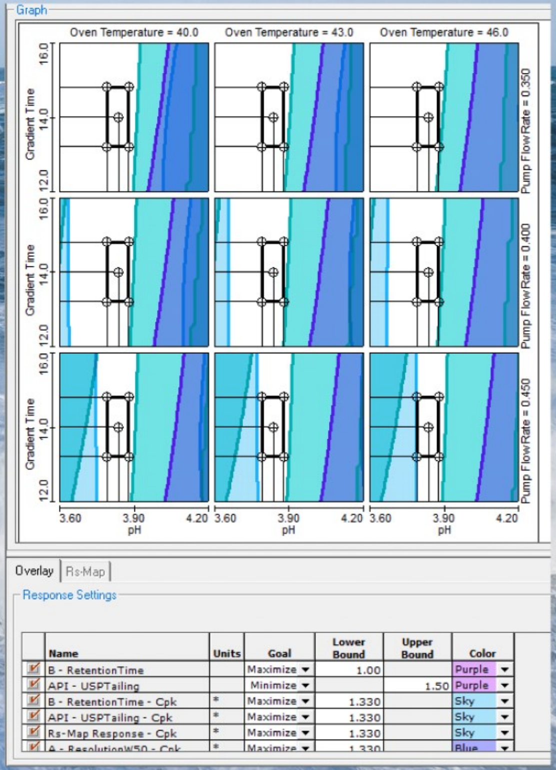
Fusion QbD®

For getting Analytical Methods as Solid as a Rock



Robustness Simulation in Fusion QbD

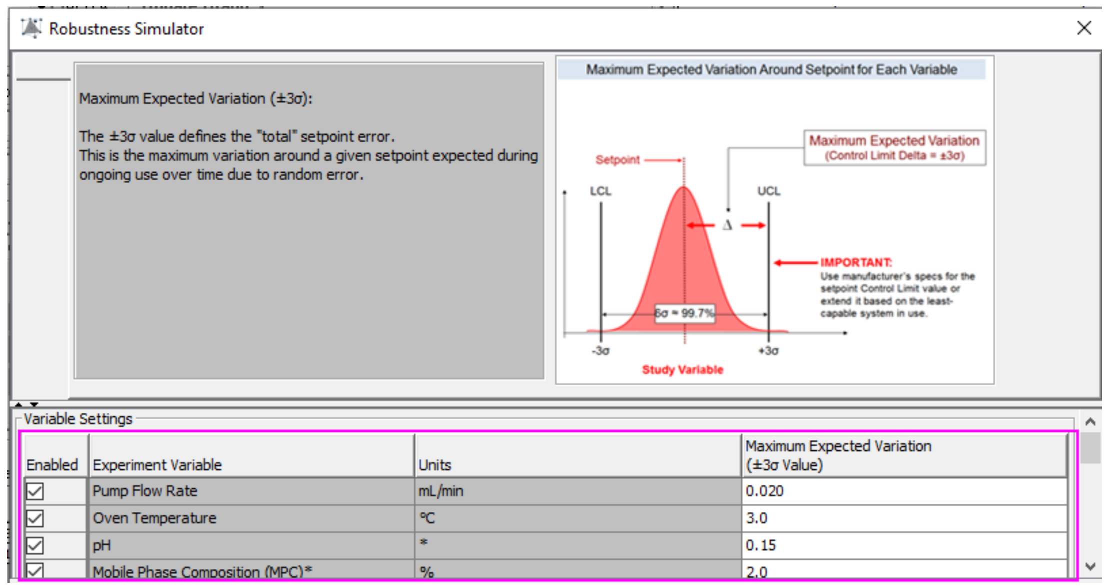
The Why and How.

Content

- What are the Benefits in Simulating Robustness?
- Robustness Simulation - How it works in short.
- How can one rely on the robustness simulations?
- Are verification runs still needed?
- New in Fusion 9.9.2a SR1

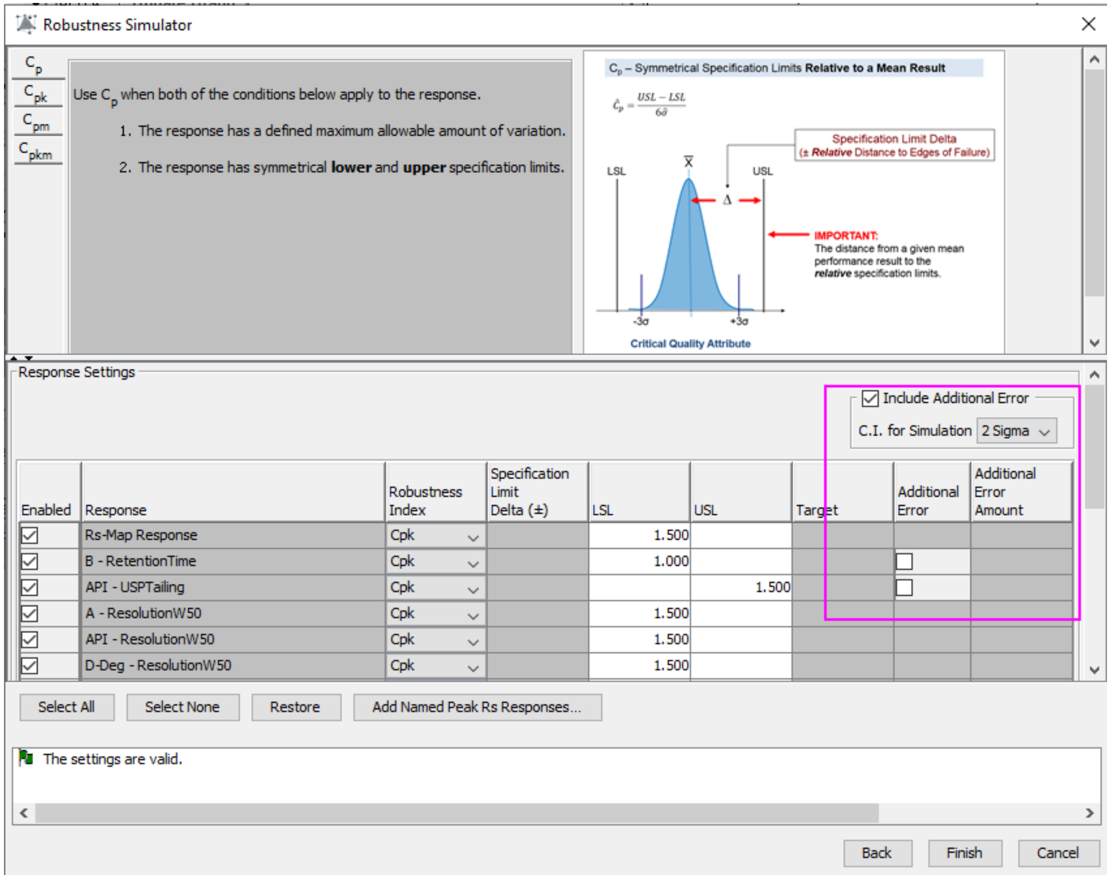
What are the Benefits in Simulating Robustness? (1)

- Characterizing robustness of your analytical method without further experiments, solely from the data models obtained for an optimization DOE study
- Accounting for maximum expected variation for each studied method parameter:
  - ➢ Set the uncertainty specified for the selected instruments (e.g. HPLC, pH-meter)
- Accounting for analytical systems, where experiments haven't been conducted, but are intended for future transfer:
  - ➢ Set the maximum expected variations for the LC system with the highest degree of uncertainty.



What are the Benefits in Simulating Robustness? (2)

- Add additional errors in order to compensate for study factors, that haven't been included in your study or simply can't be controlled

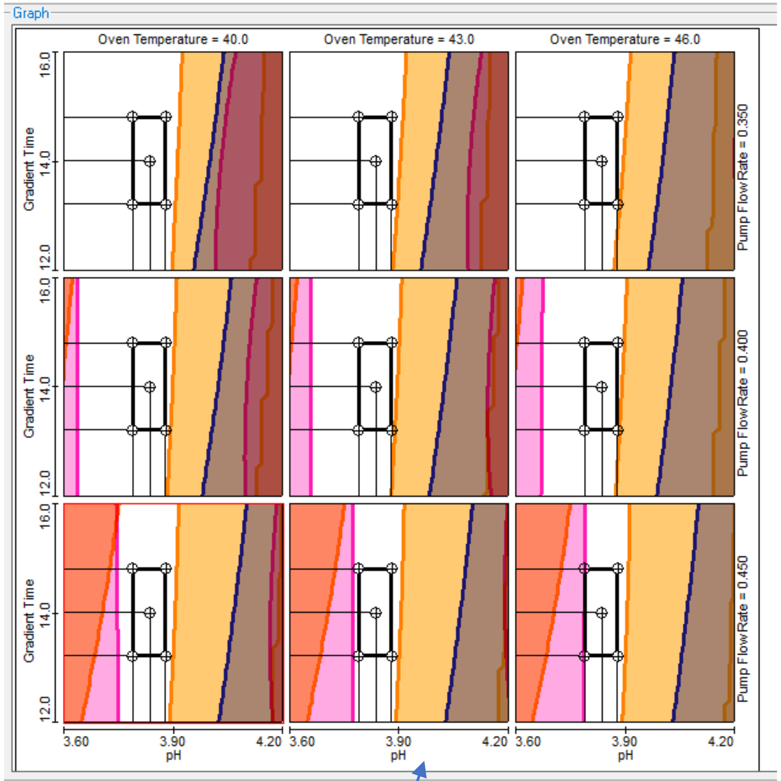


What are the Benefits in Simulating (3) Robustness?

- Substantiate specification of the entire multivariate operable region of your analytical method (MODR), where each single method parameter can be changed while keeping all other parameters constant.
- No digging in the dark: With other approaches, robustness is tested/or simulated, after the decision has been taken for a method setpoint/MODR. **BUT, what if robustness tests fail?**
    - ➢ With Fusion QbD the knowledge for the <u>**entire** multivariate experimental space</u> is already present also in terms of

Robustness Responses

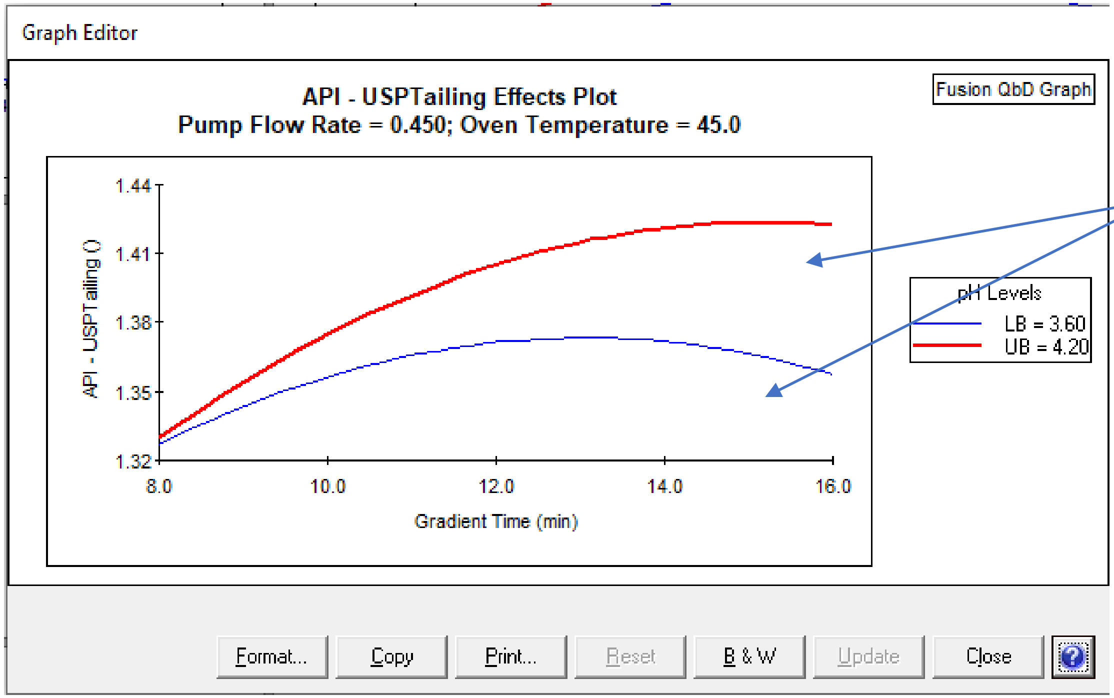
	Name	Units	Goal	Lower Bound	Upper Bound	Color
☐	A - ResolutionW50	*	---	---	---	---
☐	API - ResolutionW50	*	---	---	---	---
☐	D-Deg - ResolutionW50	*	---	---	---	---
☐	E - ResolutionW50	*		---		---
☑	[illegible]			1.00		Gray
☑	API - USPTailing		Minimize		1.50	Red
☑	B - RetentionTime - Cpk	*	Maximize	1.330		Fuschia
☑	API - USPTailing - Cpk	*	Maximize	1.330		Fuschia
☑	Rs-Map Response - Cpk	*	Maximize	1.330		Orange
☑	A - ResolutionW50 - Cpk	*	Maximize	1.330		Orange
☑	API - ResolutionW50 - Cpk	*	Maximize	1.330		Orange
☑	D-Deg - ResolutionW50 - Cpk	*	Maximize	1.330		Orange
☑	E - ResolutionW50 - Cpk	*	Maximize	1.330		Orange



Individual method parameters can be adjusted independently inside the specified rectangle.

What are the Benefits in Simulating Robustness? (4)

- Precise characterization of interaction effects considered during robustness simulation



At different pH values the peak shape develops in a different manner depending on the selected gradient time. These effects are more the rule, than an exception in chromatography.

- And last, but not least: **<u>Saving Time and Costs</u>** as with the simulation no further experiments are required for an experimental robustness study.

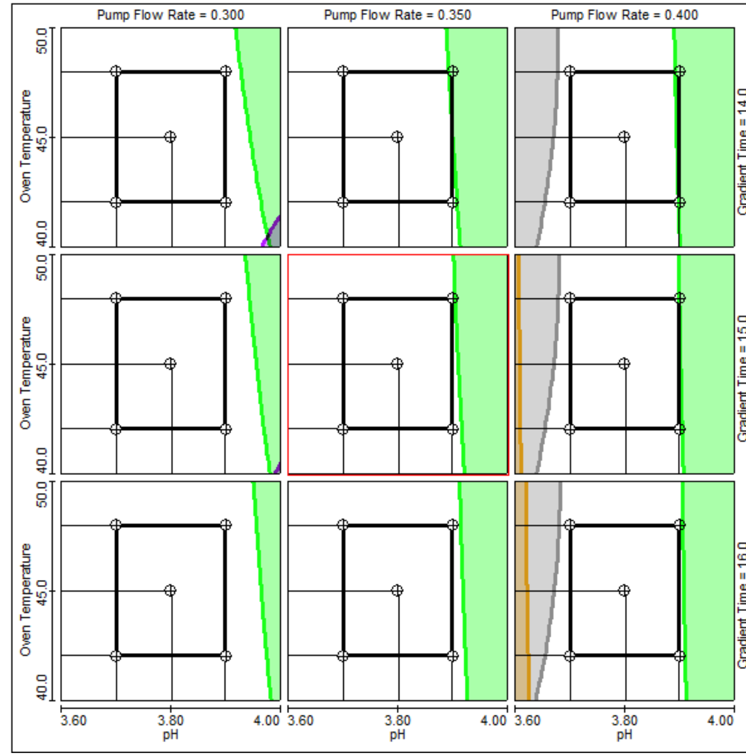
What are the Benefits in Simulating Robustness? (5)

- Support of Stage 3 in Method Lifecycle Management (Analytical Control Strategy)

    - Responses where the shaded region is close to edges of the MODR should be included in the SST of your Analytical Method

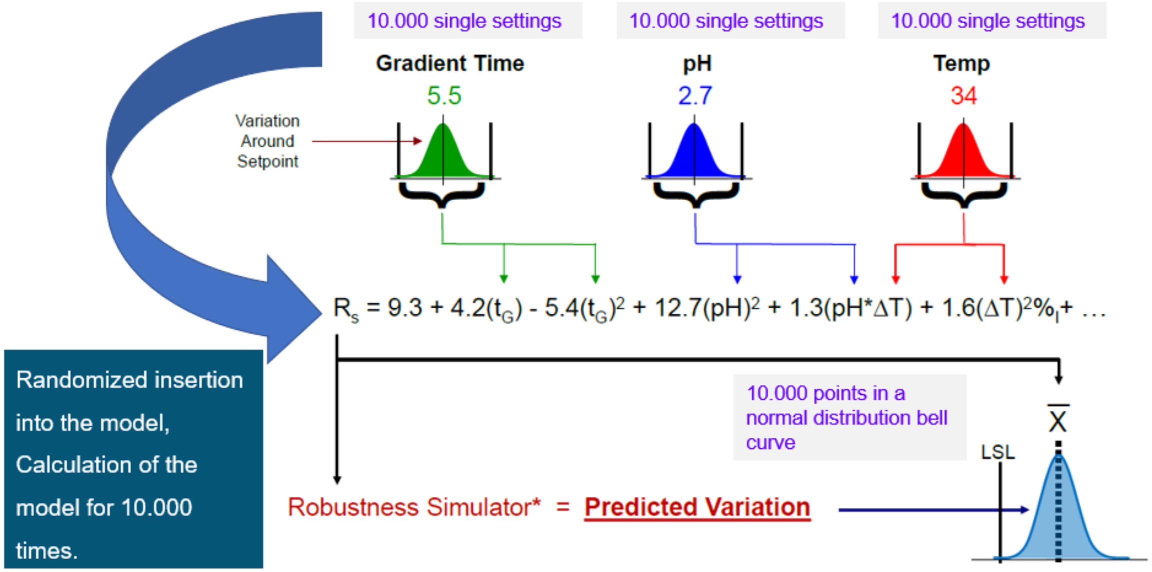
	Name	Units	Goal	Lower Bound	Upper Bound	Color
✓	A - ResolutionW50	*	Maximize	2.000		Red
✓	API - ResolutionW50	*	Maximize	2.000		Blue
✓	D-Deg - ResolutionW50	*	Maximize	2.000		Green
✓	E - ResolutionW50	*	Maximize	2.000		Orange
✓	B - RetentionTime		Maximize	1.00		Gray
✓	API - USPTailing		Minimize		1.50	Purple
✓	B - RetentionTime - Cpk	*	Maximize	1.330		Gray
✓	API - USPTailing - Cpk	*	Maximize	1.330		Purple
✓	A - ResolutionW50 - Cpk	*	Maximize	1.330		Red
✓	API - ResolutionW50 - Cpk	*	Maximize	1.330		Blue
✓	D-Deg - ResolutionW50 - Cpk	*	Maximize	1.330		Green
✓	E - ResolutionW50 - Cpk	*	Maximize	1.330		Orange

Routine Monitoring – Control Charts



Robustness Simulation - How it works in short (1)

- Robustness characteristic is obtained for each desired response (i.e. Critical Method Attribute/CMA such as Resolution, Tailing, Run Time, etc.) from already determined data models.
- Data models are recalculated a 10.000 times by feeding the models with randomized values for the expected variation of each method parameter (Critical Method Parameter, CMP), included in the study.

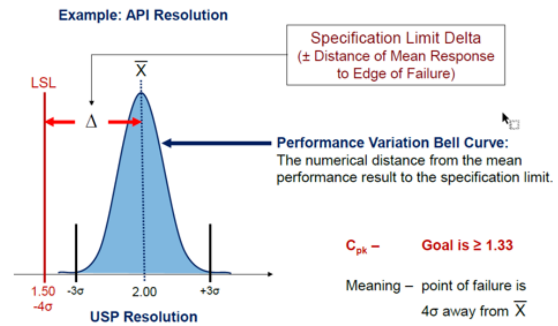


- Thus, the expected variation for each CMA in the entire experimental multivariate space can be characterized.

Robustness Simulation - How it works in short (2)

- Acceptable variation can be specified by Process Capability Metrices, e.g. C_{pk}

C_{pk} – one-sided specification limit



Calculation C_{pk} (with LSL):

$$\frac{\overline{X} - LSL}{3\sigma}$$

- Robustness responses can be added to the list of specified CMAs as additional performance goals.

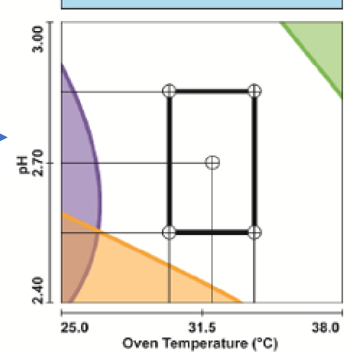
Method Performance Goals

NAME	GOAL	LOWER BOUND	UPPER BOUND	COLOR
API - Resolution	Maximize	2.00		Purple
Impurity A - Resolution	Maximize	2.00		Blue
Impurity B - Resolution	Maximize	2.00		Green
API - Tailing	Target	0.90	1.10	Orange
API - Resolution - Cpk	Maximize	1.33		Teal
Impurity A - Resolution - Cpk	Maximize	1.33		Red
Impurity B - Resolution - Cpk	Maximize	1.33		Lime
API - Tailing - Cpm	Maximize	1.33		Sky

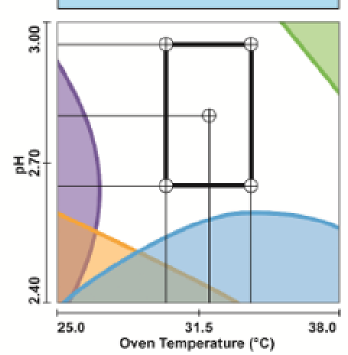
- Combination from accepted mean performance and accepted variation is shown in the overlay graph as a final unshaded region.

- This means for the entire unshaded region robustness has been demonstrated, even for the edges of the region.

Design Space & PARS – Mean Performance



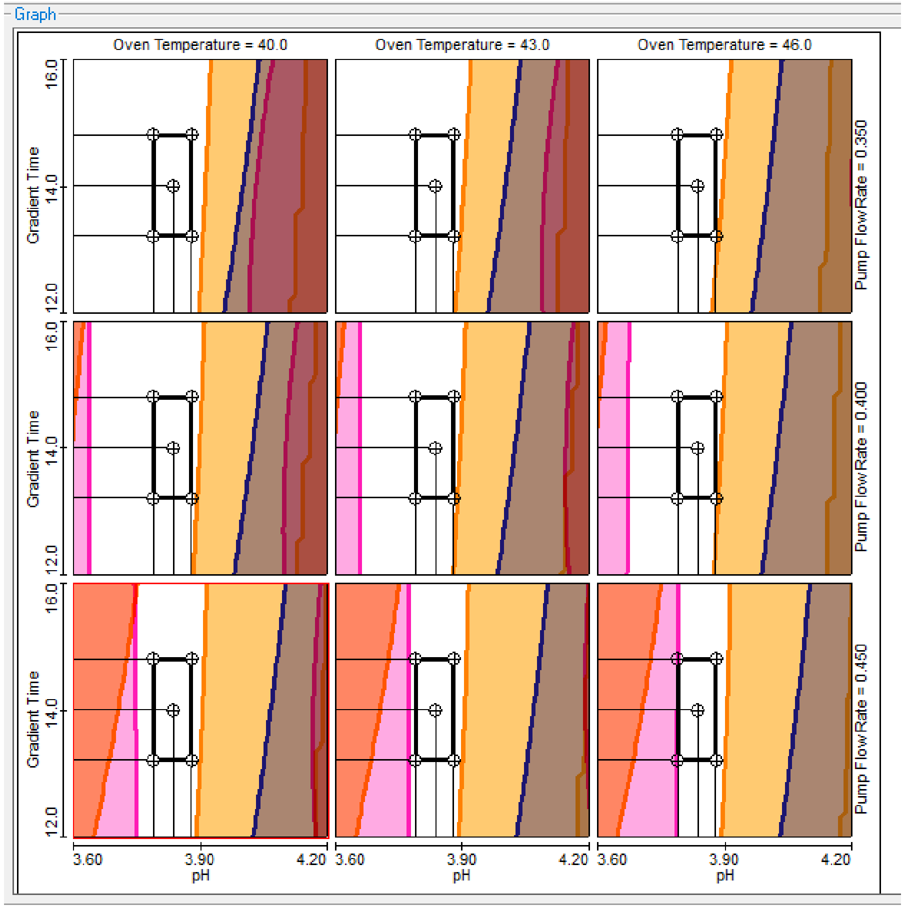
Design Space & PARS – Robust Performance



Robustness Simulation - How it works in short (3)

- A rectangular figure can then be seated into the unshaded region describing the edges for the reported part of the MODR.

!IMPORTANT: The rectangle describes different method set points and not the expected variation around a single setpoint! The expected variation is already described by the robustness responses in the graph and because of that robustness is characterized for the entire experimental space!

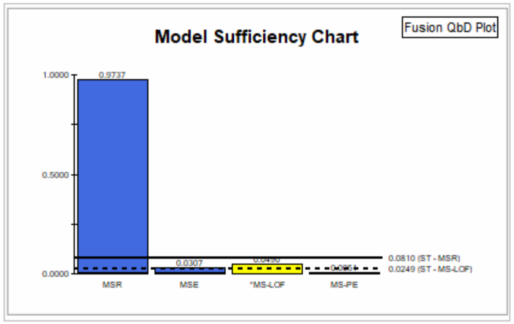


How can one rely on the robustness simulations? (1)

Make sure

- First, that only models are used, that haven been proven to be correct with a known and accepted model prediction error.

Analysis Model Summary Report: API - USPTailing

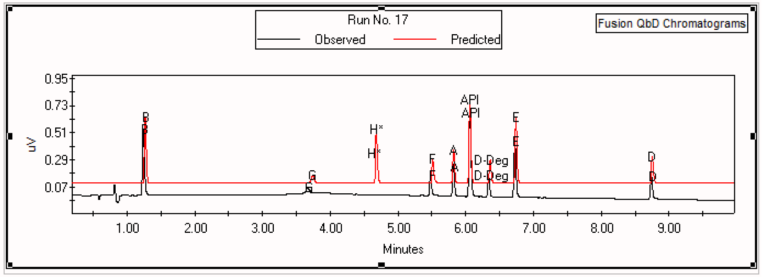


* - The model LOF is statistically significant (P-value < 0.0500)

Regression Statistic	Computed Value	Scaled Value
R Square	0.9737	---
Adj. R Square	0.9430	---
Model Error (+/- 1 Std. Dev.)	0.0103	---
Error %	0.9473	---
Expt. Error (+/- 1 Std. Dev.)	0.0042	---
MSR	0.0034	0.9737
MSE	0.0001	0.0307
MSR/MSE F-ratio	31.7156	---
MSR Significance Threshold	0.0003	0.0810
*MS-LOF	0.0002	0.0490
MS-PE	0.0000	0.0051
MS-LOF Significance Threshold	0.0001	0.0249

Predicted Results

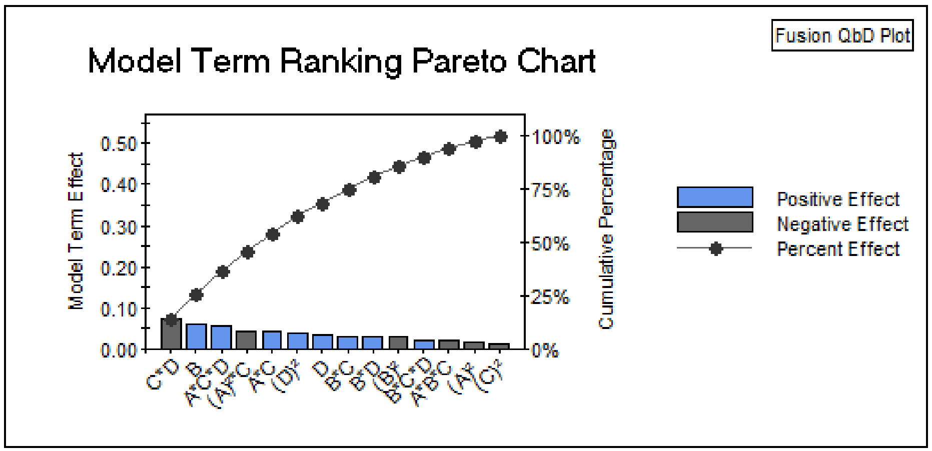
Response Name	Predicted Result	Observed Result	-2 Sigma Conf. Limit	+2 Sigma Conf. Limit
B - RetentionTime	1.27	1.26	1.25	1.29
API - USPTailing	1.35	1.36	1.32	1.38



How can one rely on the robustness simulations? (2)

Make sure

- Secondly, that all study factors having a non-negligible effect are included in the models and during robustness simulation.



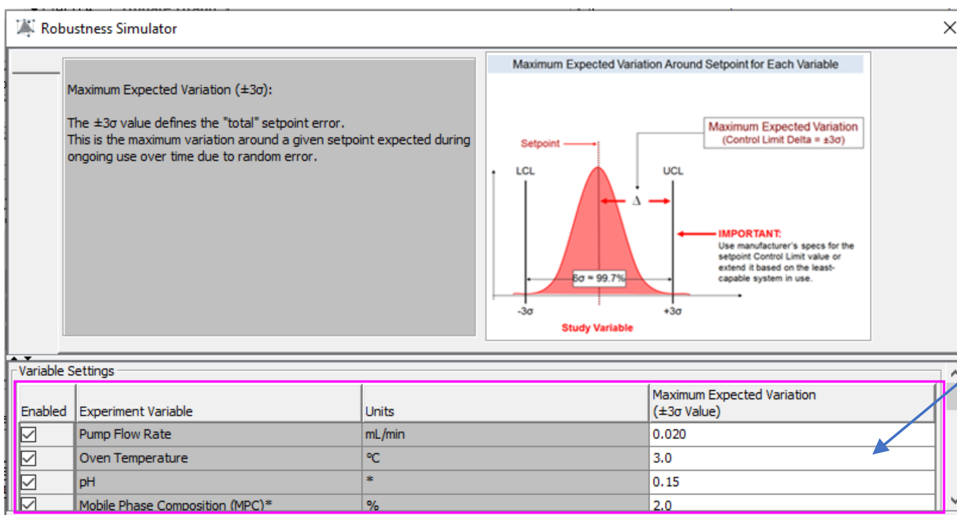
Study Variable Code Name Key

Study Variable	Units	Code Name
Pump Flow Rate	mL/min	A
Gradient Time	min	B
Oven Temperature	°C	C
pH	*	D

How can one rely on the robustness simulations? (4)

Make sure

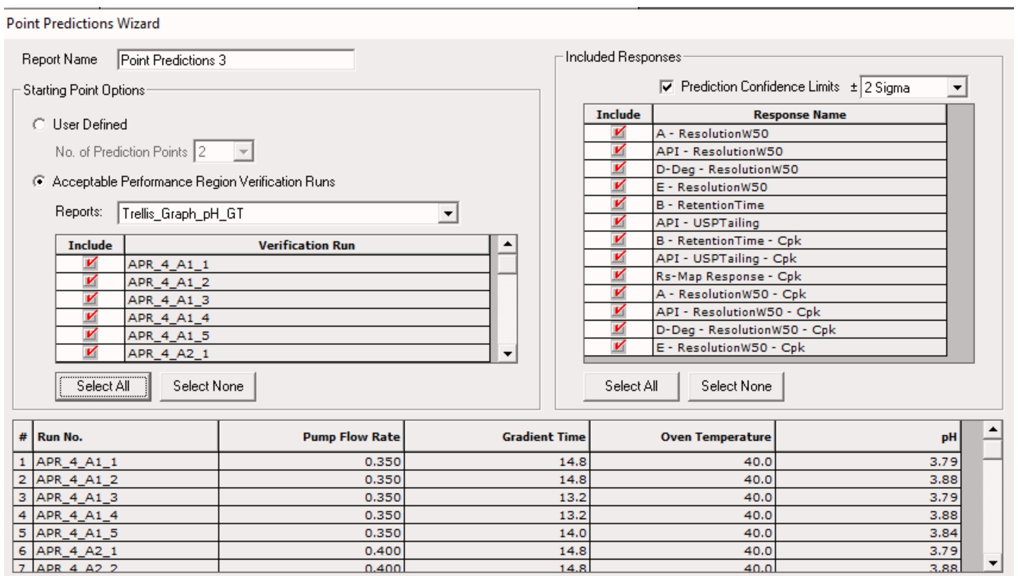
- And last, that your assumptions made for the robustness simulation are realistic, as still the expected variation around setpoint for each method parameter is <u>user-defined</u>.
  - ➢ If this variation is set too small, i.e. precision is overestimated, robustness simulation would predict methods, that are not robust.
  - ➢ If this variation is set to high, i.e. precision is underestimated, robustness simulation would predict robust methods, but one would ignore a space of suitable method settings and in a worst-case scenario even conclude, that robustness is not given inside the selected/desired experimental region.



Map your entries against the specification of your instruments or the last instrument qualification.

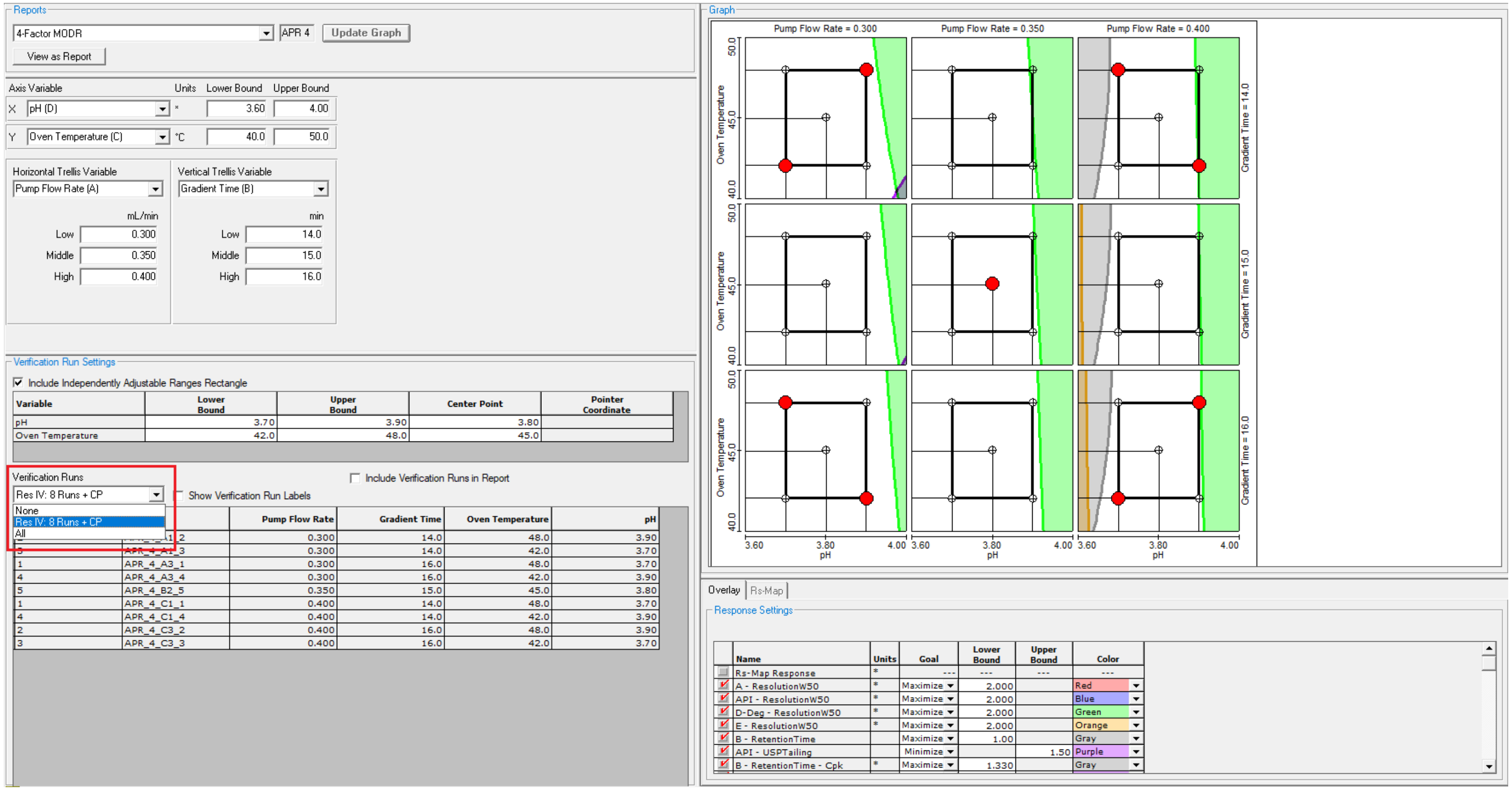
Are verification runs still needed? (5)

- If the models are valid, all CMAs having a critical impact are included in the simulation, metrics acceptance criteria are set to 1.33 and all user-defined assumptions are realistic, one can rely, actually much more, on the robustness models than on any experimental verification.
- Still, experimental verification might give additional confidence. Therefore, a subset of some challenge runs for selected method setpoints inside and at the edges of the robust region would support the model-based robustness evaluation.



New in Fusion 9.9.2a SR1:

- Selection of a representative subset of verification runs (Res IV: 8 Runs + CP)
- Automated export to the CDS as ready-to-run sequence and methods.
- Automated Importing and Reporting of Verification Run Results and Chromatograms



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Reach out to us directly for further information **info@cromingo.com**