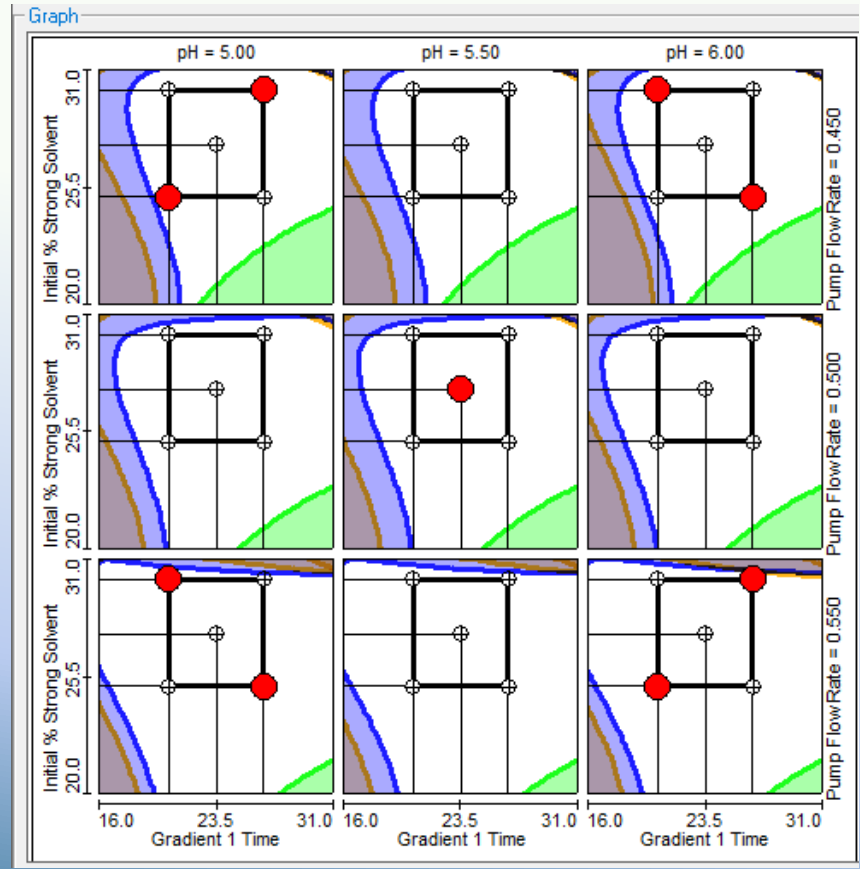
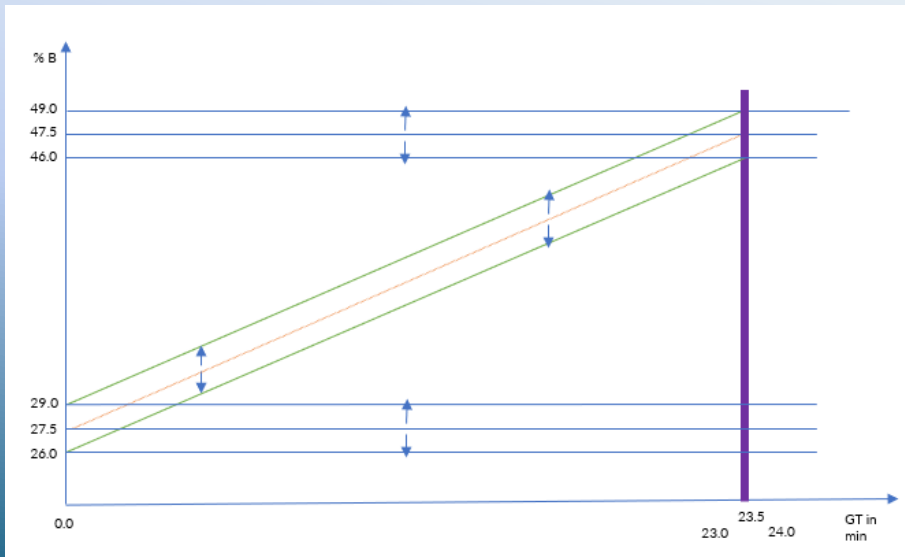


ASSESSING GRADIENT ROBUSTNESS IN FUSION QBD 9.9.2

Traditional (Shifting a Gradient)

vs.

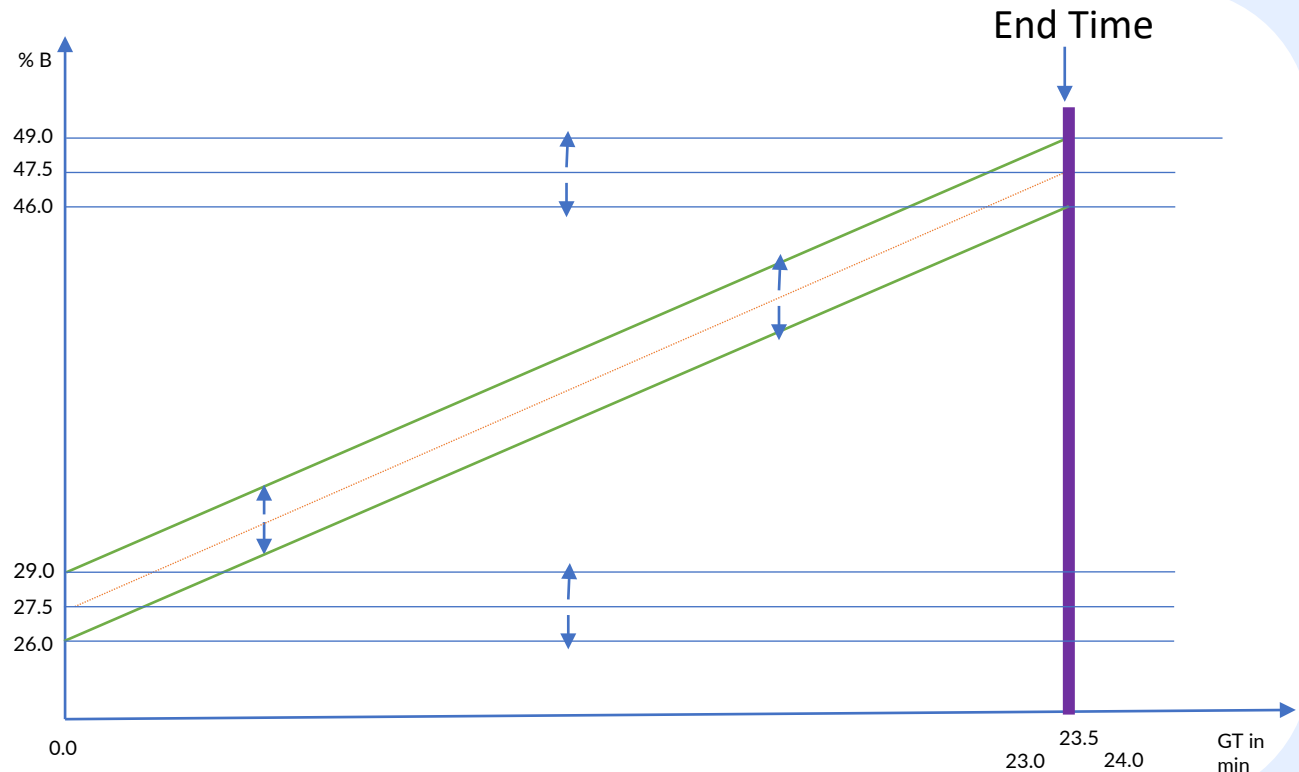
Modern (Multivariate Experiment)



How to Characterize Robustness for a Gradient?

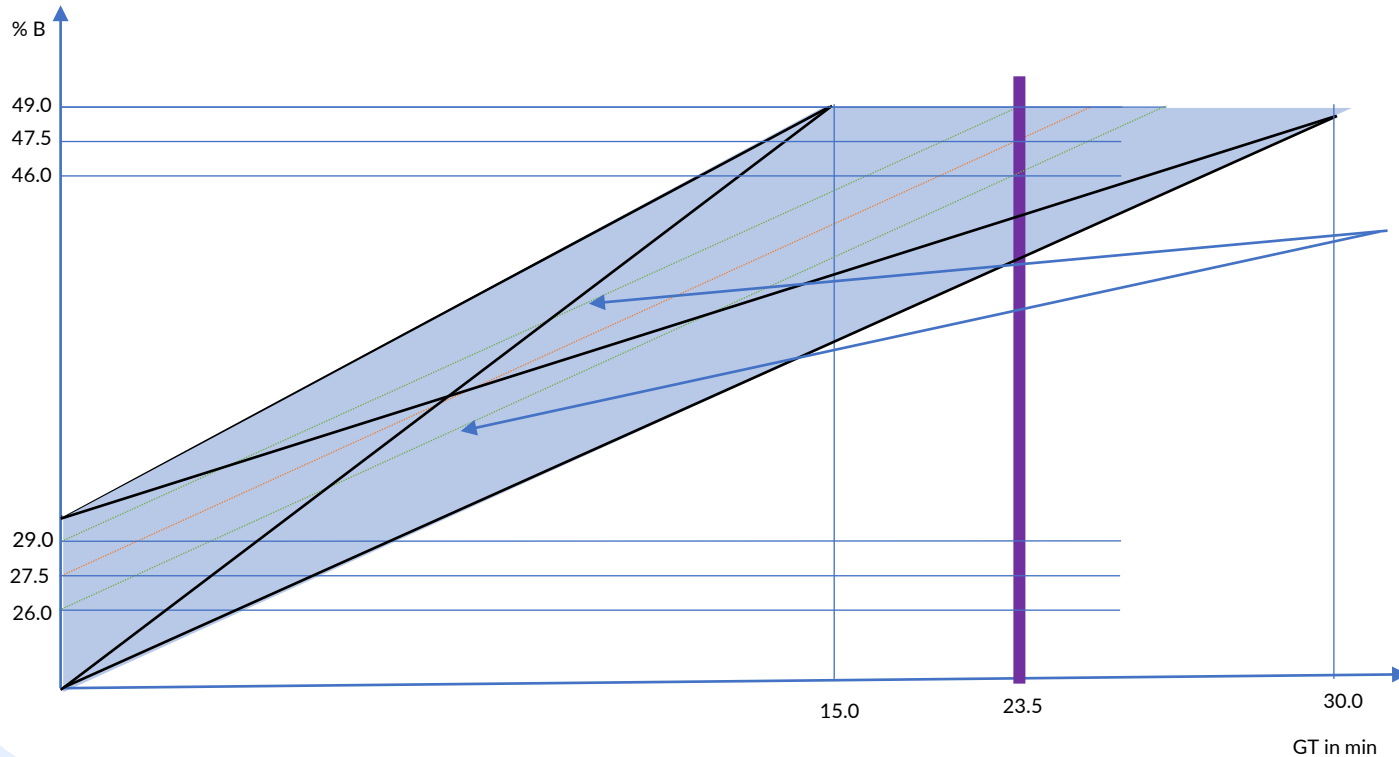
With a traditional approach analysts usually study the robustness of a gradient by simply shifting the initial and final percentage of the around the setpoint of the organic mobile phase while keeping Gradient Time and Slope as a constant, e.g.:

- %Bi = 26 – 29%;
- GT = 23.5 min
- %Be = 46 – 29%



However, in Fusion QbD such an approach is not required and for that reason a design like this is not provided by the software.

Optimization Design for Gradient Variation in Fusion QbD 9.9.2

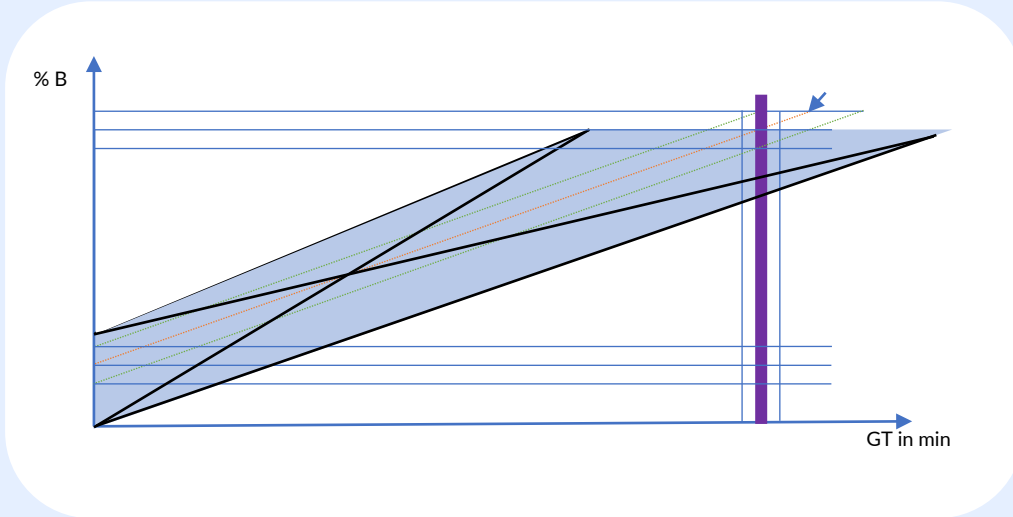


The shifted gradient ramps from the traditional approach (green lines) are both included in the studied gradient variation.

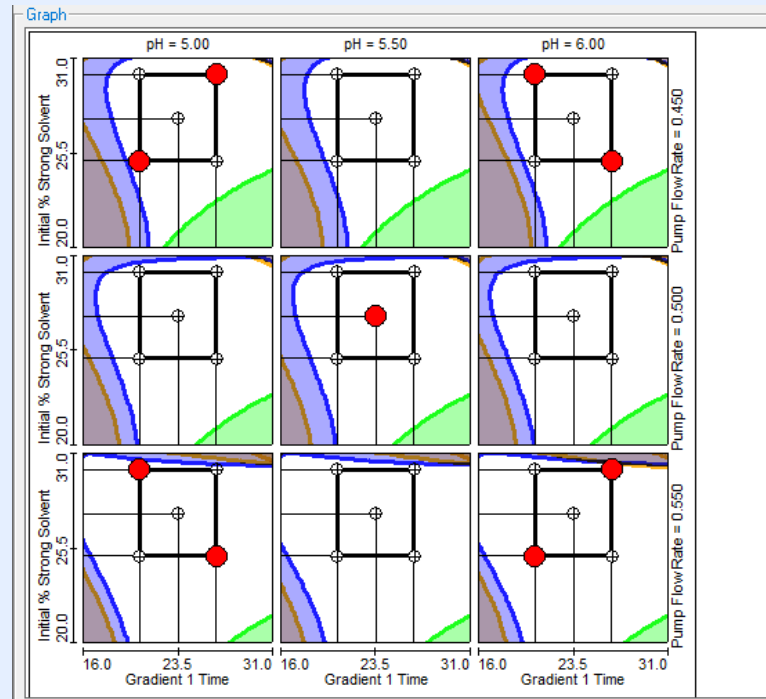
In a multivariate experiment %Bi and GT can be studied simultaneously by covering a much broader range (shaded region below) compared to a traditional approach, e.g.

- %Bi = 20 – 30%
- GT = 15 - 30 min

Fusion QbD: Full Characterization of the Method Operable Design Region (MODR) also in Terms of Robustness



- From a single optimization experiment the entire range can be characterized in terms of mean performance and robustness.
- In a multivariate study, not only the combination of single parameters such as %BI and GT is characterized, but the entire multivariate design region. The example shows us different pH and flow settings as well.
- The shaded regions stand for method settings, where our method goals are not met, the combined unshaded region shows us, where all method goals are met simultaneously.
- Cpk - Robustness Responses are included as method goals (orange shadows).

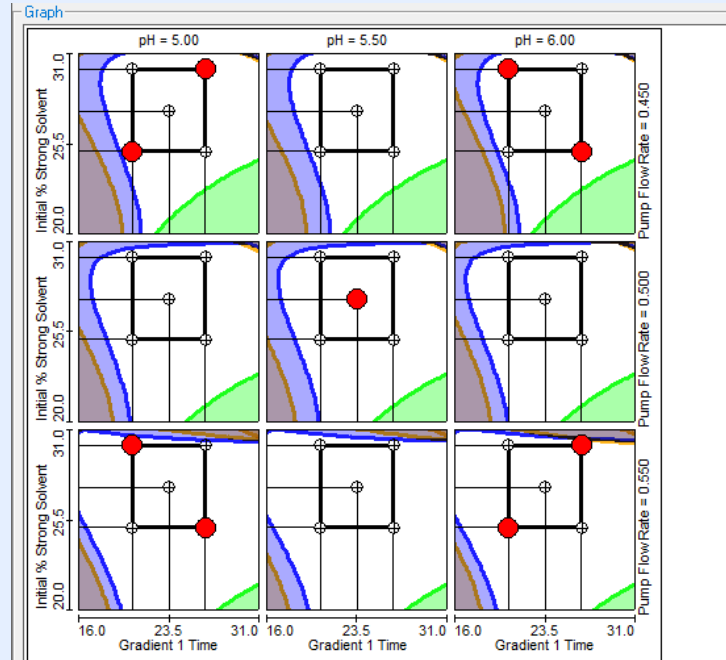
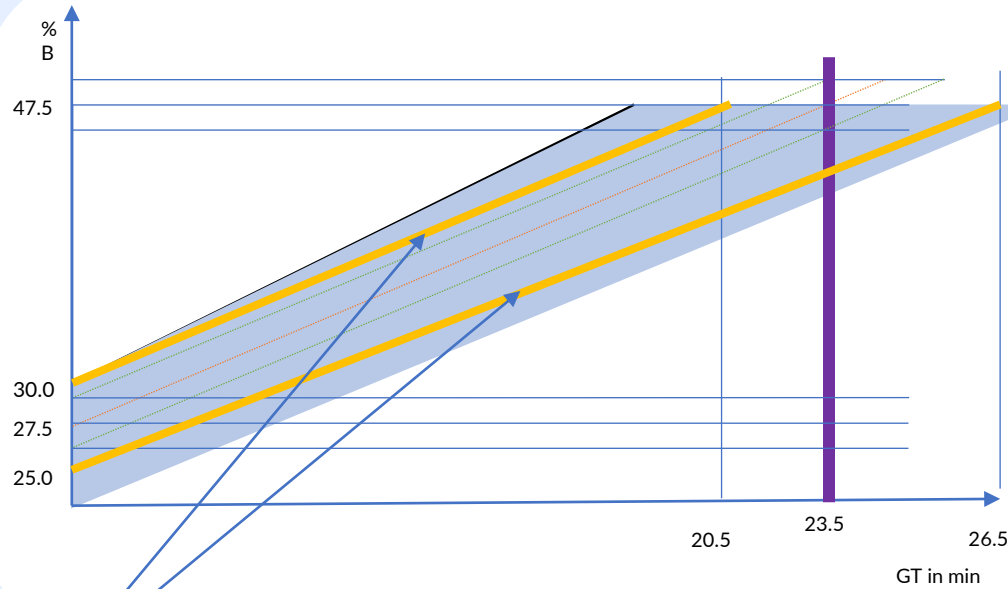


Overlay Rs-Map

Response Settings

Name	Units	Goal	Lower Bound	Upper Bound	Color
<input checked="" type="checkbox"/> Rs-Map Response	*	Maximize	2,000		Blue
<input type="checkbox"/> Imp E - Retention Time		---	---	---	---
<input type="checkbox"/> Imp E - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/> Imp D - Retention Time		Minimize		13.50	Green
<input type="checkbox"/> Imp D - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/> Imp C - ResolutionW50 - Cpk	*	Maximize	1,330		Orange
<input checked="" type="checkbox"/> Imp B - ResolutionW50 - Cpk	*	Maximize	1,330		Orange

Identifying Settings for a Robust Method



- A rectangle can be inserted into the overlay graphs in a way, that it is located inside the unshaded region in all 9 plots.
- Yellow lines in the gradient plot above reflect the rectangle settings in the Fusion overlay graphs.
- Robust method settings are identified for the following conditions:
 - Bi [%] = 25 – 30
 - GT [min] = 20.5 – 26.5
 - pH = 5.00 – 6.00
 - Flow [ml/min] = 0.450 – 0.550
 - Temperature [°C] = 40*

Overlay | Rs-Map

Response Settings

	Name	Units	Goal	Lower Bound	Upper Bound	Color
<input checked="" type="checkbox"/>	Rs-Map Response	*	Maximize	2.000		Blue
<input type="checkbox"/>	Imp E - Retention Time		---	---	---	---
<input type="checkbox"/>	Imp E - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/>	Imp D - Retention Time		Minimize		13.50	Green
<input type="checkbox"/>	Imp D - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/>	Imp C - ResolutionW50 - Cpk	*	Maximize	1.330		Orange
<input checked="" type="checkbox"/>	Imp B - ResolutionW50 - Cpk	*	Maximize	1.330		Orange

*Only 4 variable factors can be displayed in the trellis graph at a time.

Verification Runs

Reports

APR Report 2 | APR 2 | Update Graph

View as Report

Axis Variable: X Gradient 1 Time (B) min 16.0 31.0
Y Initial % Strong Solvent (C) % 20.0 31.0

Horizontal Trellis Variable: pH (E) Low 5.00 Middle 5.50 High 6.00
Vertical Trellis Variable: Pump Flow Rate (A) mL/min Low 0.450 Middle 0.500 High 0.550

Oven Temperature: 40.0

Verification Run Settings

Include Independently Adjustable Ranges Rectangle

Variable	Lower Bound	Upper Bound	Center Point	Pointer Coordinate
Gradient 1 Time	20.5	26.5	23.5	
Initial % Strong Solvent	25.0	30.0	27.5	

Verification Runs Include Verification Runs in Report

Res IV: 8 Runs + CP Show Verification Run Labels

Run ID	Pump Flow Rate	Gradient 1 Time	Initial % Strong Solvent	Oven Temperature	pH
APR_2_A1_2	0.450	26.5	30.0	40.0	5.00
APR_2_A1_3	0.450	20.5	25.0	40.0	5.00
APR_2_A3_1	0.550	20.5	30.0	40.0	5.00
APR_2_A3_4	0.550	26.5	25.0	40.0	5.00
APR_2_B2_5	0.500	23.5	27.5	40.0	5.50
APR_2_C1_1	0.450	20.5	30.0	40.0	6.00
APR_2_C1_4	0.450	26.5	25.0	40.0	6.00
APR_2_C3_2	0.550	26.5	30.0	40.0	6.00
APR_2_C3_3	0.550	20.5	25.0	40.0	6.00

Graph

Overlay | Rs-Map

Response Settings

Name	Units	Goal	Lower Bound	Upper Bound	Color
<input checked="" type="checkbox"/> Rs-Map Response	*	Maximize	2,000		Blue
<input type="checkbox"/> Imp E - Retention Time		---	---	---	---
<input type="checkbox"/> Imp E - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/> Imp D - Retention Time		Minimize		13.50	Green
<input type="checkbox"/> Imp D - USP Asymmetry		---	---	---	---
<input checked="" type="checkbox"/> Imp C - ResolutionW50 - Cpk	*	Maximize	1.330		Orange
<input checked="" type="checkbox"/> Imp B - ResolutionW50 - Cpk	*	Maximize	1.330		Orange

In Fusion 9.9.2

- Verification runs can easily be exported for a subset of representative methods (red spots on the rectangles)
- After data acquisition and processing the processed results and chromatograms can be imported back to Fusion for reporting purposes.

Contact us for more Information



Fusion QbD® is a mature LC method development software especially designed for AQbD approaches in the pharmaceutical industry.

If you want to better understand, how robustness of an analytical method can be simulated and characterized for the entire design region, please contact us for a **free software demo**.

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

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