Parallel-curve assessment in JMP

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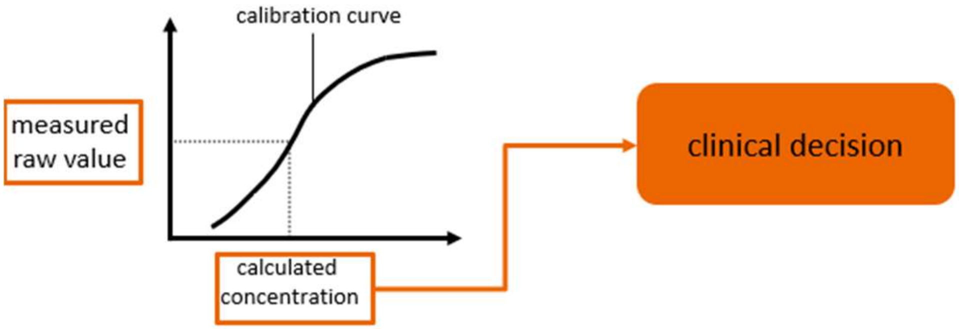
A typical hemostasis product
INNOVANCE vWF Activity

Generation of clinical results

Important for diagnosis and treatment monitoring

Working principle of many assays:

- Within a controlled chemical reaction, a raw value is generated for a given sample.
- Comparison of raw value of **unknown** patient sample with a sequence of raw values of a reference material („calibrator“) with **known concentration**



Calibration Chain

Certificate of Traceability

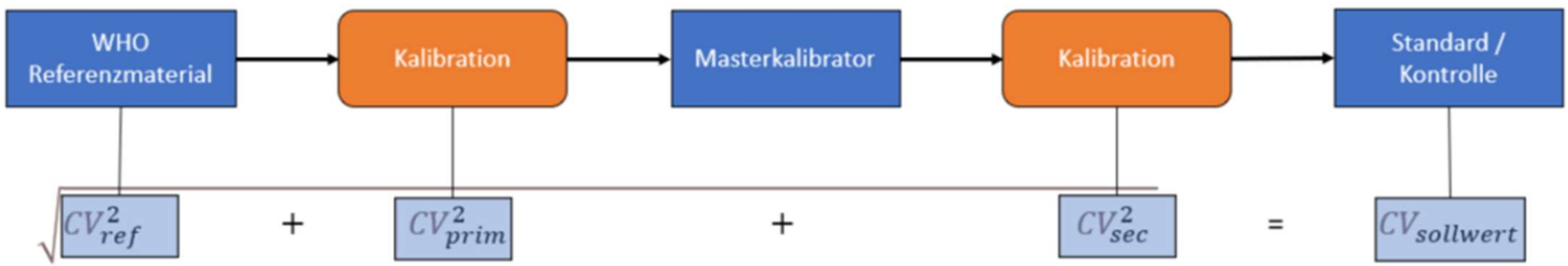


Abbildung 2: Berechnung der Unsicherheit des Sollwertes aus der Kalibrationskette. Sowohl das WHO Referenzmaterial als auch jede Kalibration der Kalibrationskette führen zu einer Vergrößerung der Unsicherheit des finalen Sollwertes.

Accurate calibrations are important!

Calibration by interpolation (forward calibration)

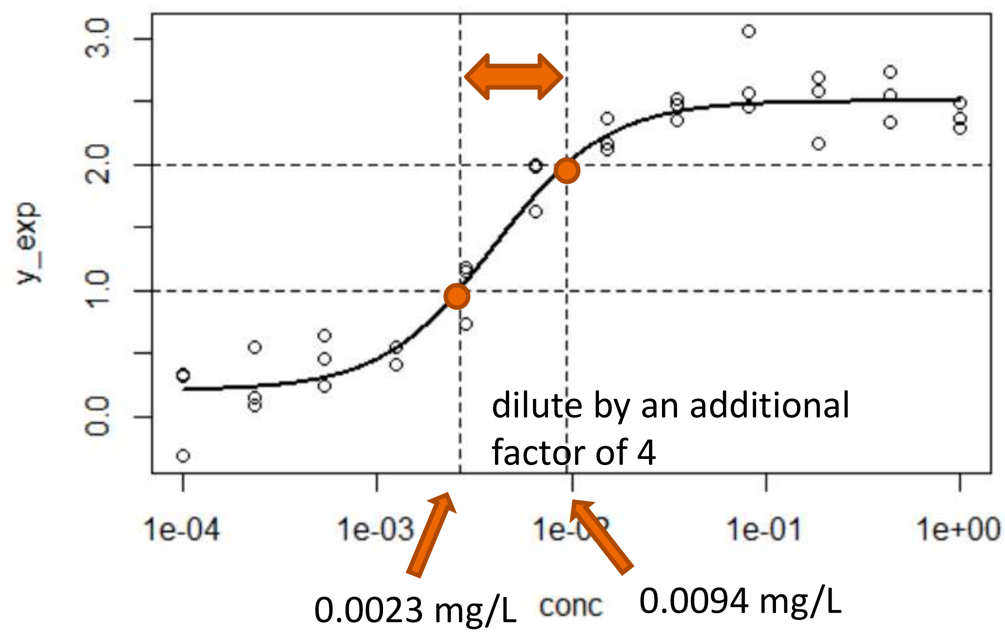
Basic approach

- Create reference curve with parent standard
- Treat new standard **as a sample**
- Predilute standard into reference curve
- Determine concentration by interpolation

- Optionally predilute differently (to ensure relative dilutional linearity)
- **back-calculated results** should all agree, and average will be final value

Example: (0.0023 mg/L **x 4** + 0.0094 mg/L)/2
= (0.0092 + 0.0094)/2 mg/L =0.0093 mg/L

- CV can be used as an indirect check of “compatibility” (lack of matrix effects)



Calibration by alignment
Extending the idea of multiple interpolations

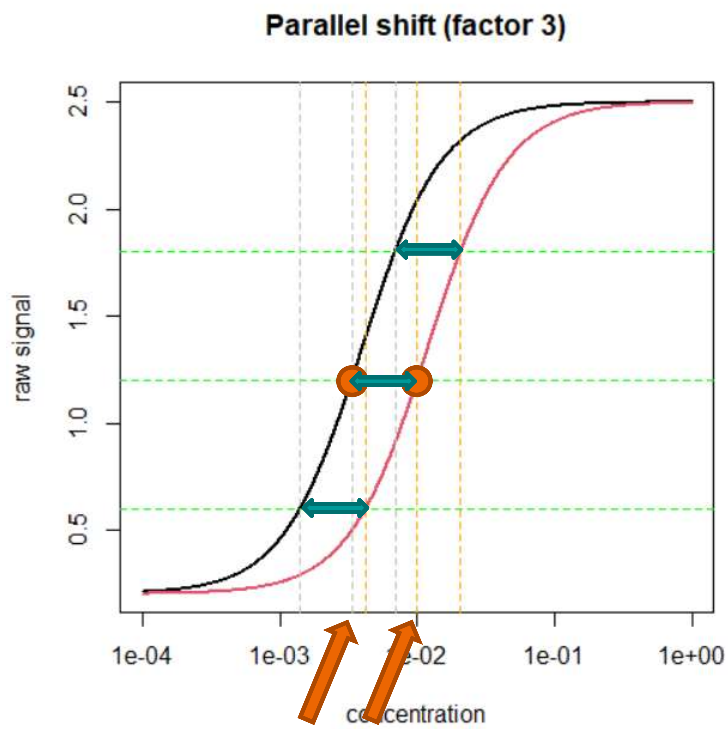
- Treat new candidate standard similar to parent standard (i.e. full dilution series)
- Fit curves to both data sets
- Investigate horizontal (multiplicative) shift at a larger number of raw values
- Concentration ratio can be observed as horizontal shift (on a log-concentration axis)

Advantage compared to forward calibration

- More information
- Calibration across relevant signal range
- Possibility to evaluate the dilutional linearity

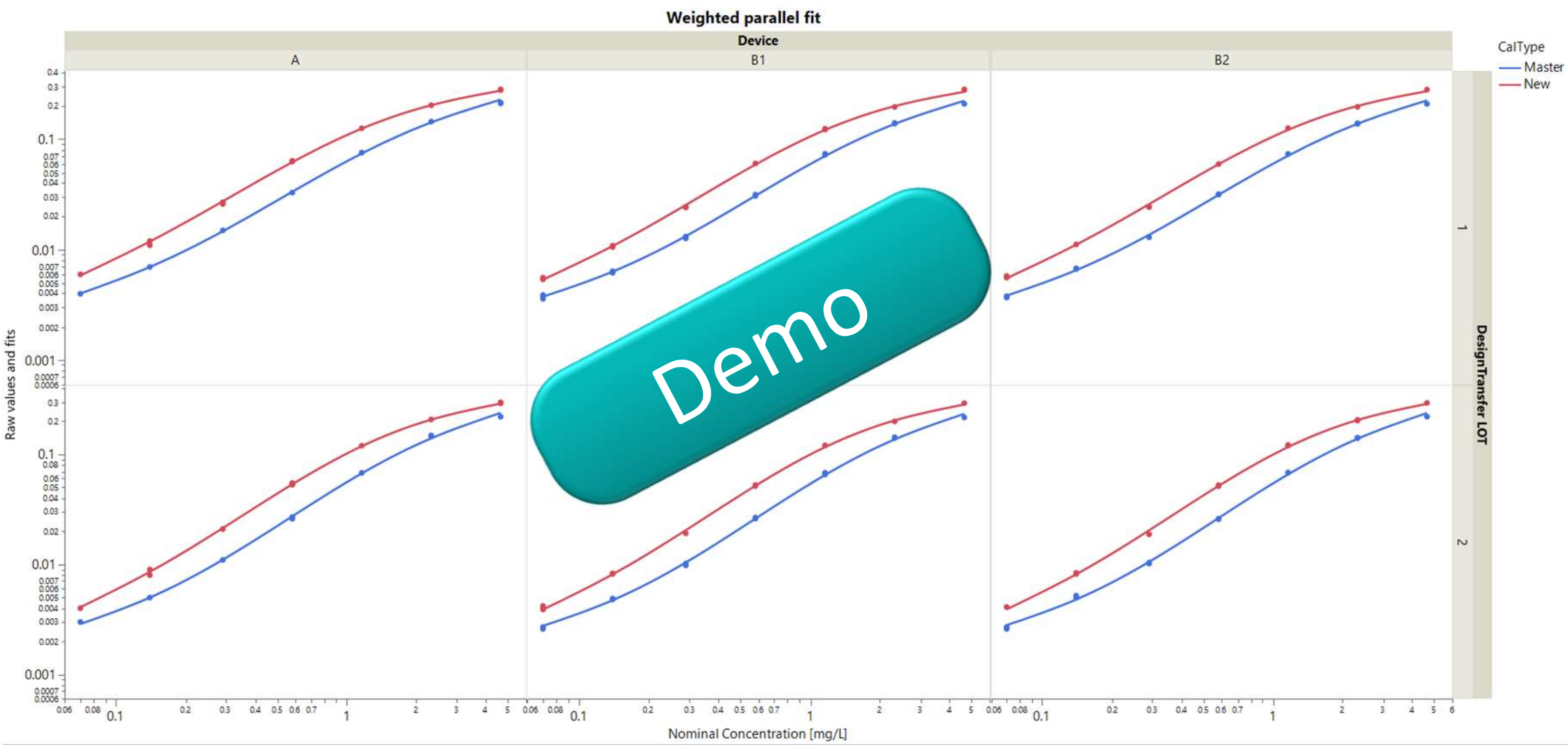
Disadvantage or lost opportunity

- “Pedestrian approach” does allow for **statistical tests** to assess equal asymptotes and equal slope, i.e. full **parallelism of curves**



True alignment – (non-)parallel-curve model

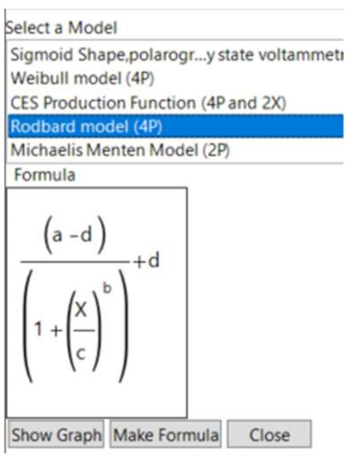
Implementation in JMP Nonlinear Platform



Screenshots to illustrate main steps (1)

Implementation in JMP Nonlinear Platform

Rodbard model in non-linear platform



Solution

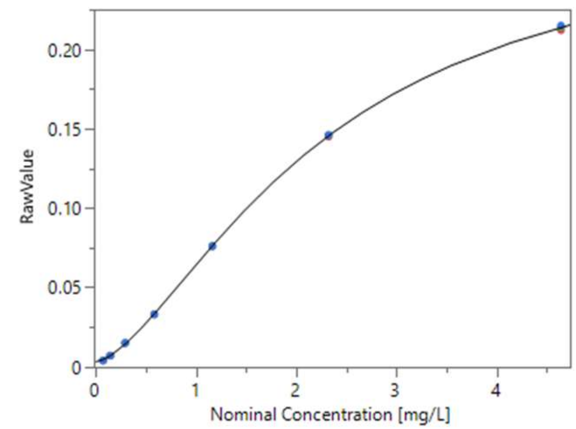
SSE	DFE	MSE	RMSE
0.0000081567	17	4.7981e-7	0.0006927

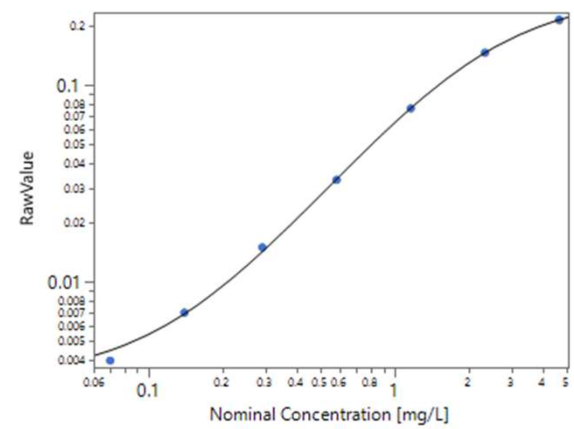
Parameter	Estimate	ApproxStdErr	Lower CL	Upper CL
a	0.0032387421	0.00033554	0.0025204	0.00394411
b	1.5513977569	0.01836675	1.5124578	1.59063368
c	2.2730816486	0.03180968	2.20889213	2.34406035
d	0.2832964397	0.00265329	0.27788854	0.28916654

Solved By: Analytic Gauss-Newton

Correlation of Estimates

	a	b	c	d
a	1.0000	0.6968	-0.4197	-0.5363
b	0.6968	1.0000	-0.8716	-0.9140
c	-0.4197	-0.8716	1.0000	0.9768
d	-0.5363	-0.9140	0.9768	1.0000





Screenshots to illustrate main steps (2)

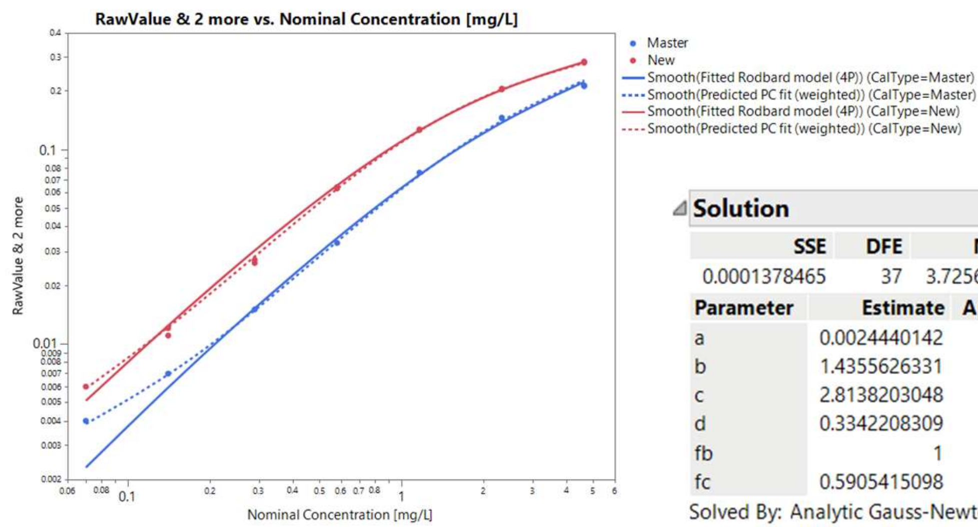
Implementation in JMP Nonlinear Platform

Generalization to parallel-curve model (with or without weight)

Parameters

New Parameter...
a = 0
b = 2.174
c = 1
d = 0.2174
fc = 1

$$\frac{(a - d)}{\left(1 + \left(\frac{\textit{Nominal Concentration [mg/L]}}{\left(c \cdot \text{If}\left(\begin{array}{ll} \textit{CalType} == \text{"Master"} & \Rightarrow 1 \\ \text{else} & \Rightarrow fc \end{array}\right)\right)}\right)^{b}\right)} + d$$



Solution

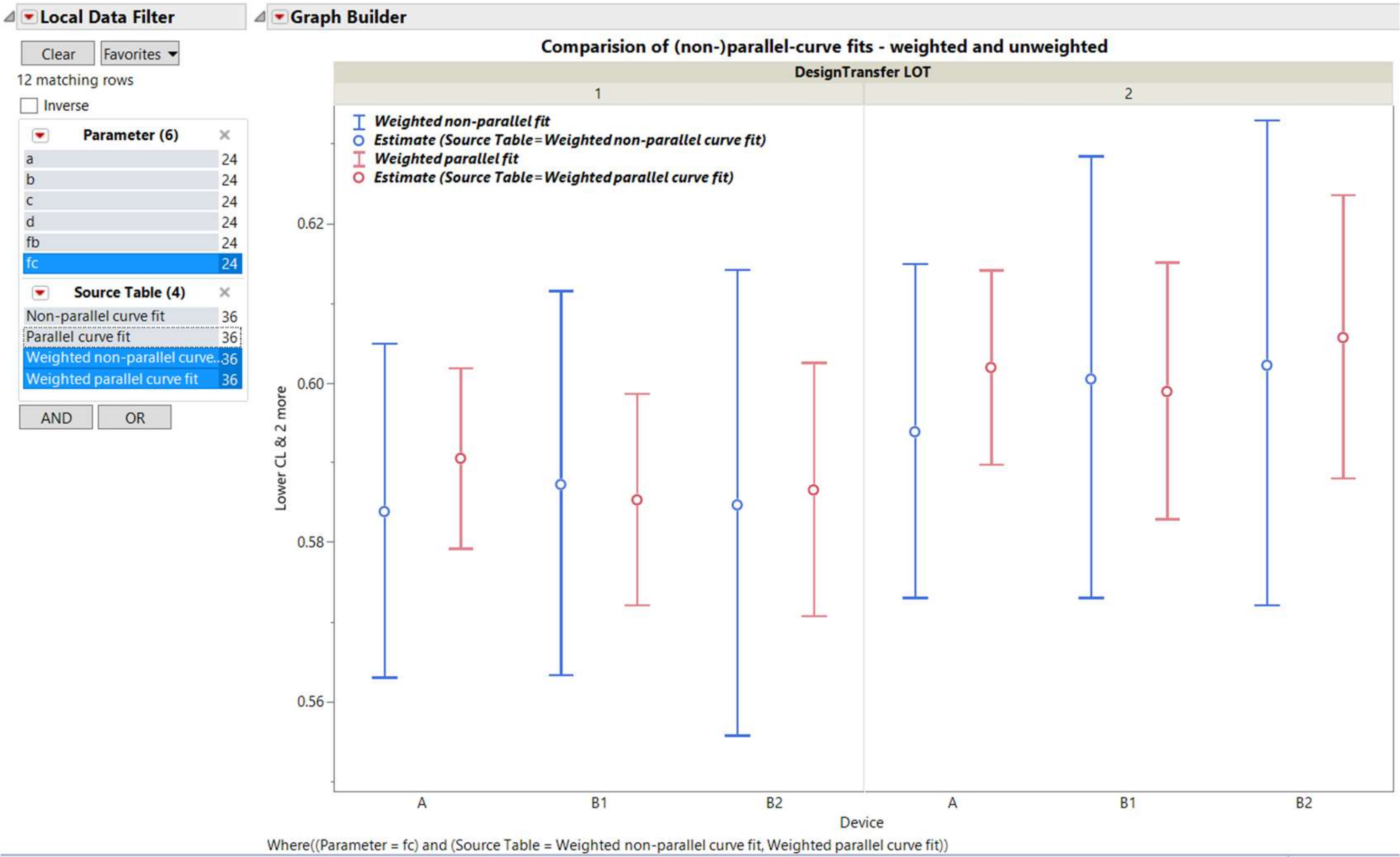
SSE	DFE	MSE	RMSE
0.0001378465	37	3.7256e-6	0.0019302

Parameter	Estimate	ApproxStdErr	Lower CL	Upper CL
a	0.0024440142	0.00011331	0.002208	0.00267246
b	1.4355626331	0.01635347	1.40203852	1.46962982
c	2.8138203048	0.09350854	2.63128998	3.02010341
d	0.3342208309	0.00797883	0.318518	0.35150764
fb	1	.	.	.
fc	0.5905415098	0.0055776	0.57928133	0.60190619

Solved By: Analytic Gauss-Newton

Screenshots to illustrate main steps (3)

Implementation in JMP Nonlinear Platform



Summary

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- Extension of **Rodbard model** from JMP Model Library
- Elegant statistical method compared to other forms of calibration
- Analysis of master and new calibrator material in **one statistical model**
- Parameter estimates obtained with **confidence intervals**
- Equivalence tests for equal slope (or equal asymptotes) can easily be incorporated

Idea can be extended

- Non-linear platform can be used for any complex prediction that can be parametrized

Thank you!

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BACKUP SLIDES

Parametrisierung für 4PL „Logit-log“-Modell

Äquivalenz zu Rodbard-Parametrisierung

$\mathrm{logit}(p) = ln(p/(1-p))$ hat Wertebereich von -∞ bis ∞ für $p \in]0,1[$

Beispiel einer **verallgemeinerten linearen Regression** (Generalized Linear Model = GLM):

- Verlange $\mathrm{logit}(p) = a + bx$ (ebenfalls Wertebereich von -∞ bis ∞)
- Da Konzentration bei 0 beginnt, setze x = ln(conc), also

$$ln[p\ /(1-p)] = a + b\ \times ln(conc)$$

Standard 2PL-Parametrisierung	**Verallgemeinerung auf 4PL**	alternative **Rodbard-Parametrisierung**
$p = \frac{1}{1+\exp(-(a+b\ \times \ln(conc)))}$	$y = y_{min} + \frac{y_{max} - y_{min}}{1+\exp(-(a+b\ \times \ln(conc)))}$	$y = y_{min} + \frac{y_{max} - y_{min}}{1+\left(\frac{conc}{c_{50}}\right)^{-b}}$