Calibration model transfer, update and maintenance for on-line application. Comparison of the three existing approaches

Chimiométrie 2009

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Outline

I. **Context = Quality by Design**

II. Methods for real-time-release model transfer, update and maintenance

III. Presentation of the case study

IV. Results for the comparison of the 3 approaches

V. Conclusions

Quality by Design

Based on **Moheb Nasr's slides** (FDA) – 27 April 2009 at AAPS modelling workshop

Outline

- Quality by Design (QbD)
- Models in a QbD approach
  - Models for design space
  - Models for control strategy and continual improvement
- Concluding comments

Model Maintenance and Update

In a QbD approach, process learning does not stop at product launch

- Design space can be reassessed and updated
- Models that are part of the control strategy may need to be periodically reassessed and updated

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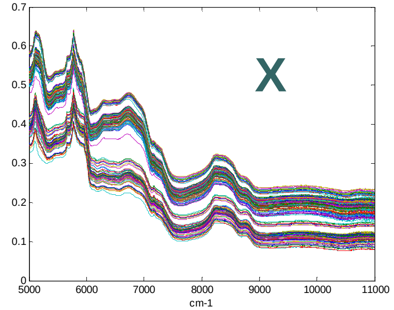
Need for robustness improvement

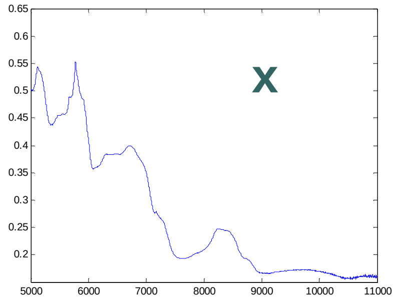
CALIBRATION



\+ **y** → Model **b**

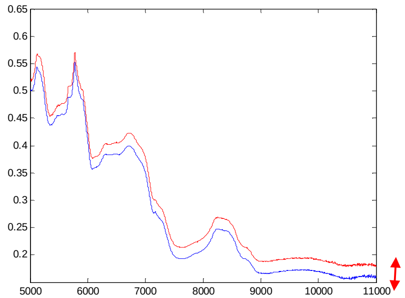
$$y = \mathbf{x}^{\mathrm{T}}\,\mathbf{b} + e$$

PREDICTION



\+ Model **b** → $\hat{y}$

NEW SOURCE OF VARIABILITY (G)
+
PREDICTION



$\delta\mathbf{x}$

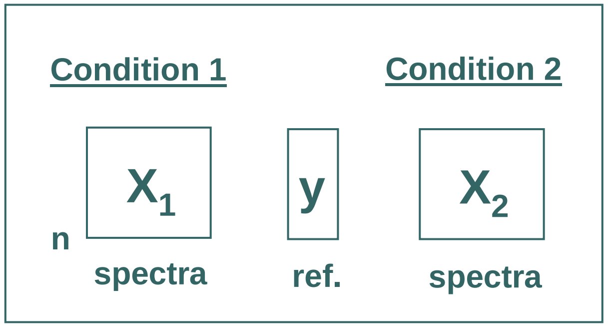
Minimize → Robustness improvement

\+ Model **b** → $\hat{y} + \delta\hat{y}$

$$|\delta\hat{y}| = \|\delta\mathbf{x}\| \,.\, \|\mathbf{b}\| \,.\, |\cos(\delta\mathbf{x},\mathbf{b})|$$

1st scenario = standardisation set available

- Standardisation set available:
  - Measurement of a set of standard samples under the different conditions
  - Source of variability G value is measurable (e.g. NIR instrument change)



→ **Existing approaches:**

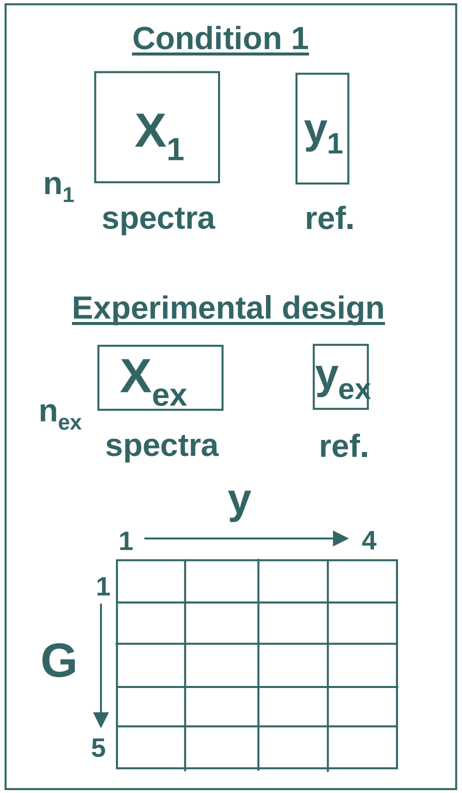
Piecewise Direct Standardisation (PDS)

Piecewise Reverse Standardisation (PRS)

Bias / slope

2^{nd} scenario = small experimental design available

- Small experimental design available:
  - Measurement of a set of samples under the new different conditions
  - Source of variability G value is not necessarily measurable



→ **Existing approaches:**

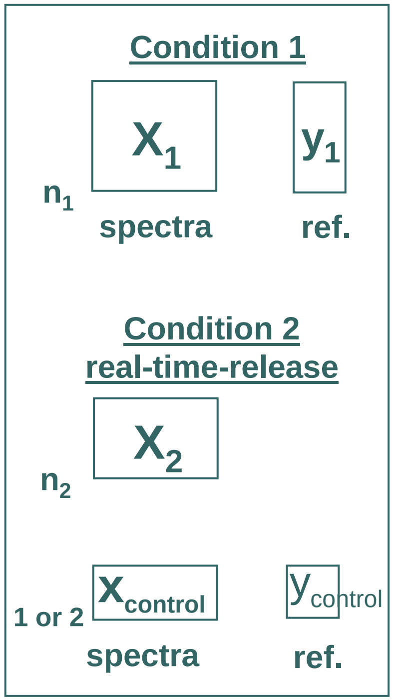
External Parameter Orthogonalisation (EPO)

Orthogonal Signal Correction (OSC) on experimental design

Generalised Least Squares (GLS)

3rd scenario = only a few reference control points available

- Few (1 or 2) reference control points available:
  - Neither standard sample nor small experimental design
  - Source of variability G value is not measured



→ **Existing approaches:**

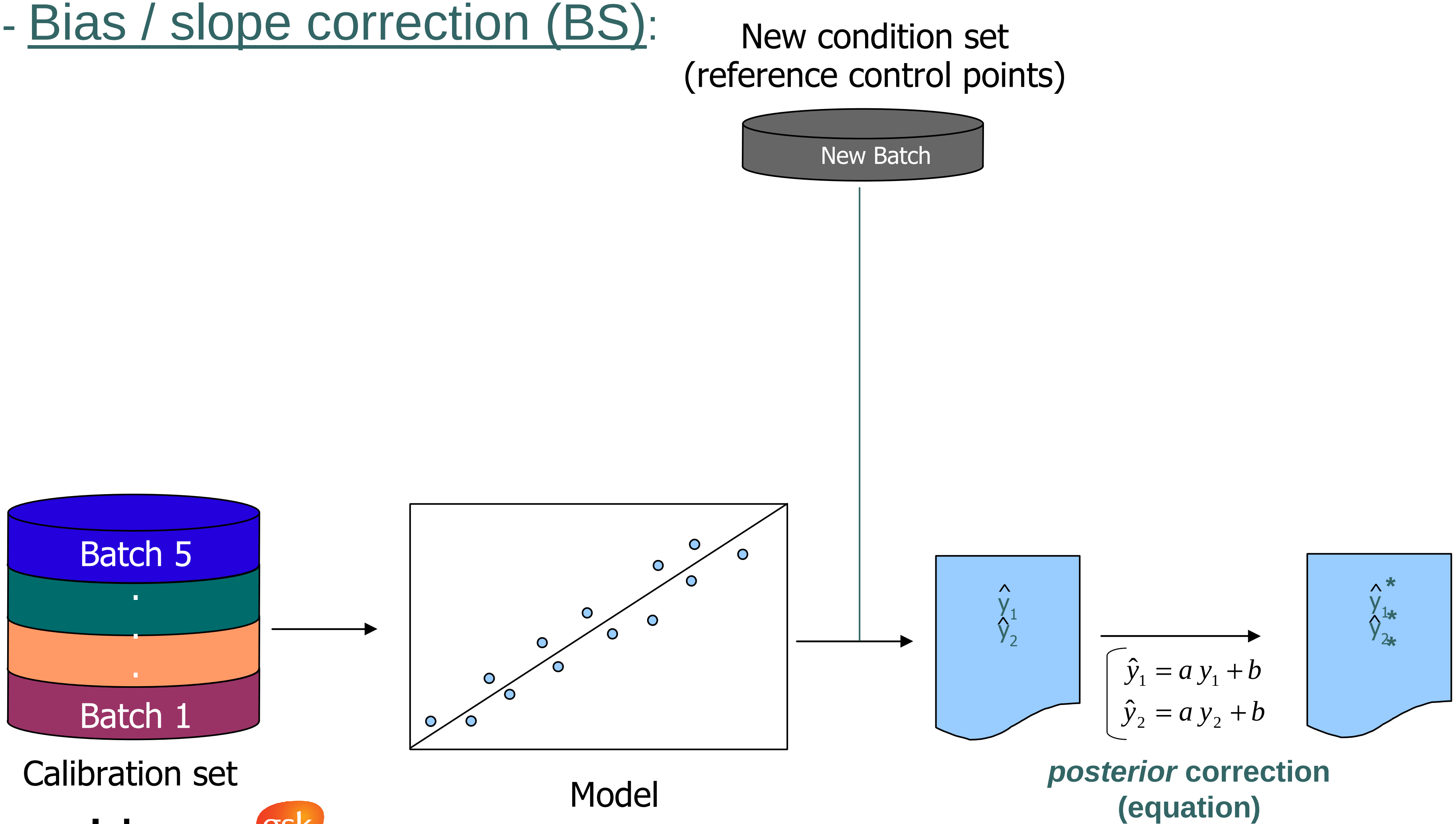
Bias / slope

Model re-development (global / exhaustive updating)

Dynamic Orthogonal Projection (DOP)

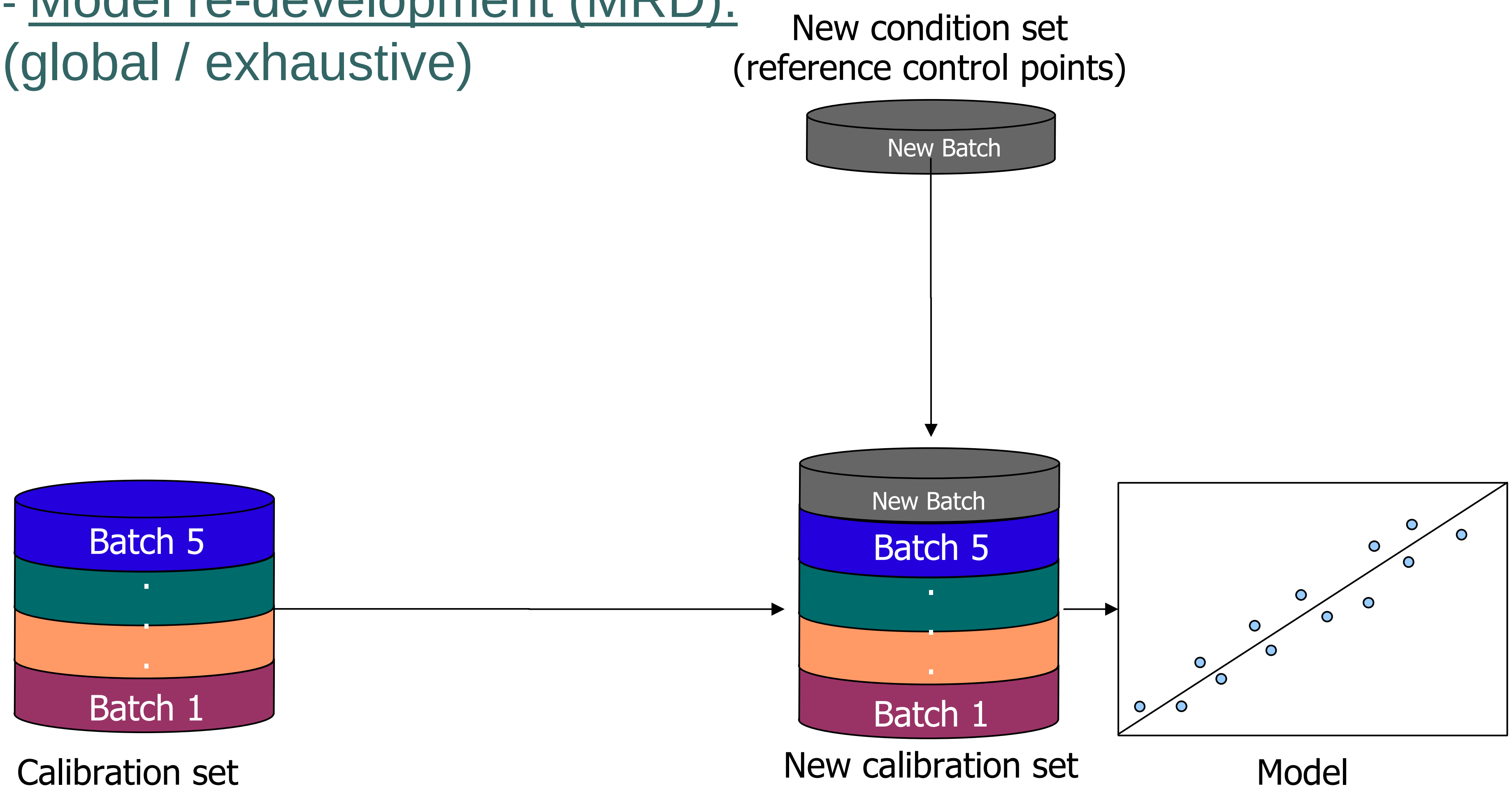
3rd scenario = only a few reference control points available → 1st approach

- Bias / slope correction (BS):



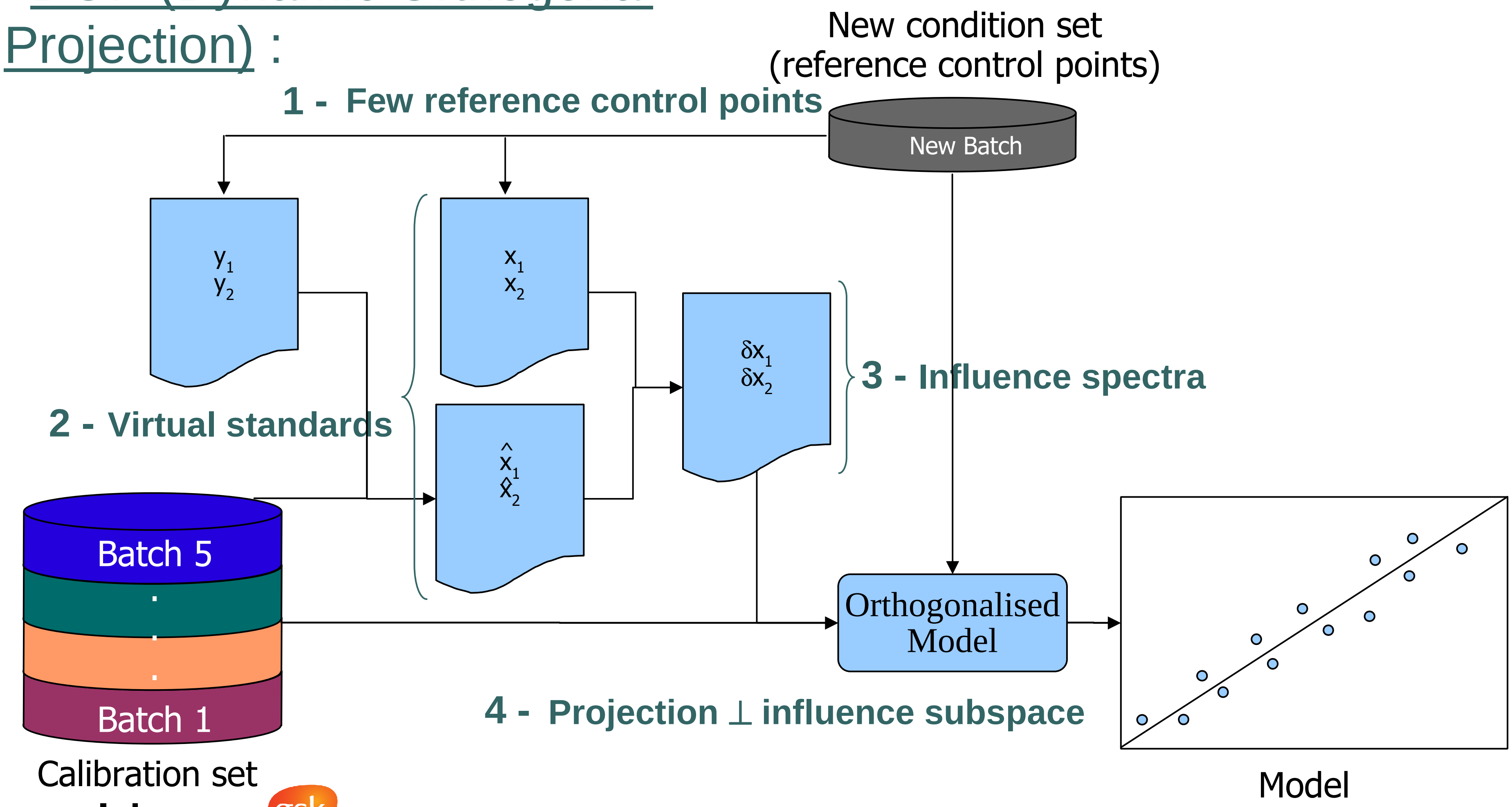
3rd scenario = only a few reference control points available → 2nd approach

- Model re-development (MRD):
(global / exhaustive)



3^{rd} scenario = only a few reference control points available → 3^{rd} approach

- DOP (Dynamic Orthogonal Projection) :



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Application

- Solid drug product

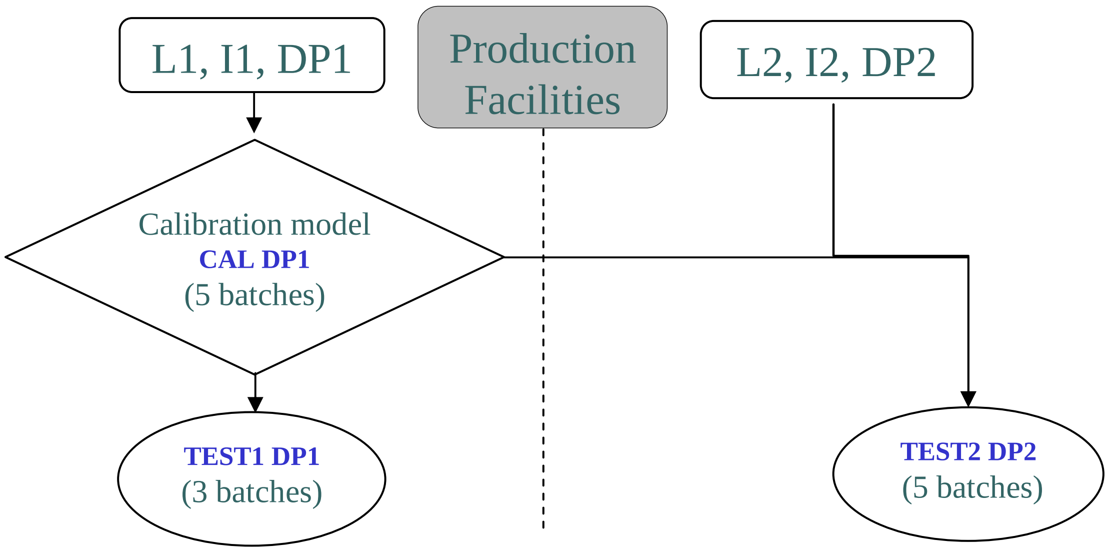
- Drying process (fluid-bed dryer)

- On-line NIR monitoring of a quality critical attribute = solvent residuals

- Reference method by GC

Data flowchart

L1 & L2: Production lines
I1 & I2: Instruments
DP1 & DP2: Drug Products (PSDs)

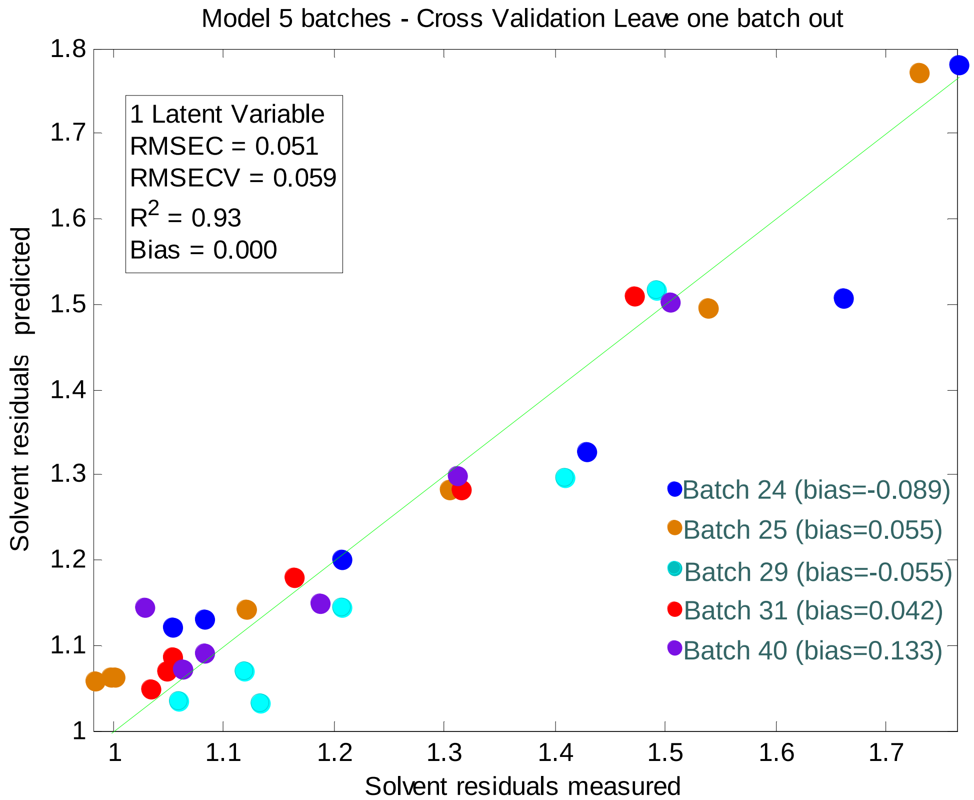


❶ **Small drift effect = batch effect**

❷ **Large block effects = line, instrument and product effects**

Calibration model

Calibration by leave-one-batch-out Cross-Validation after outlier removal



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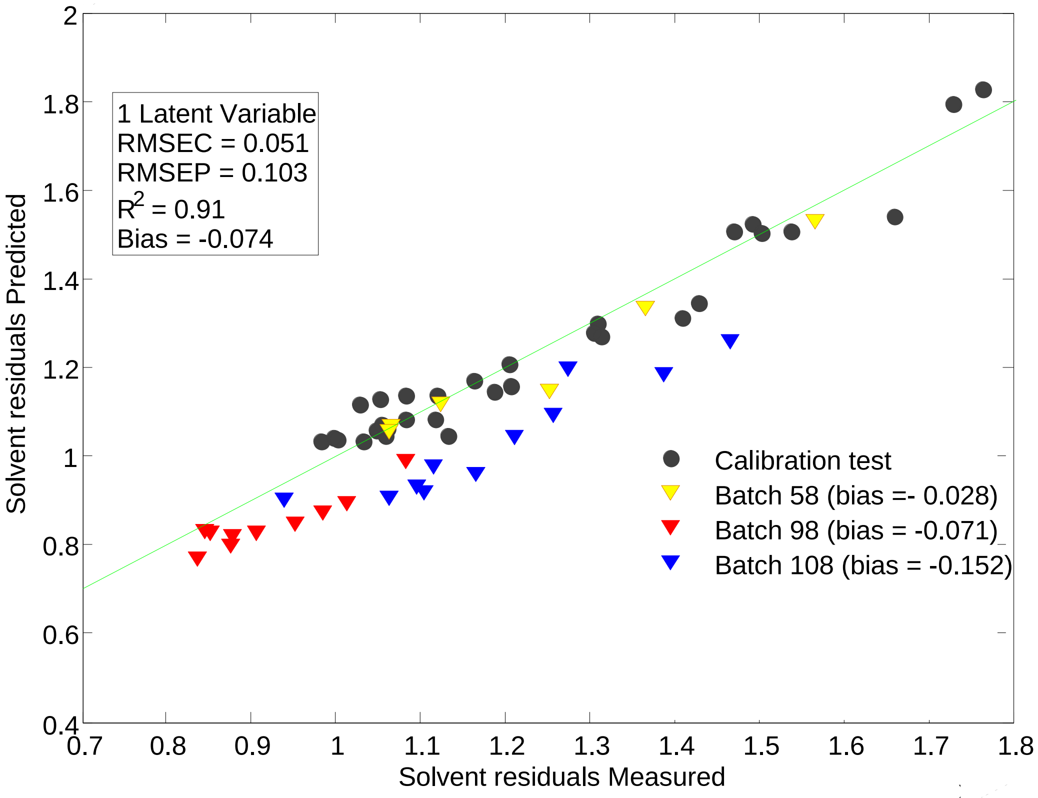
1 – Small drift effect = batch effect

Test on TEST1 DP1 (same line, instrument and product)



1 – Small drift effect = batch effect

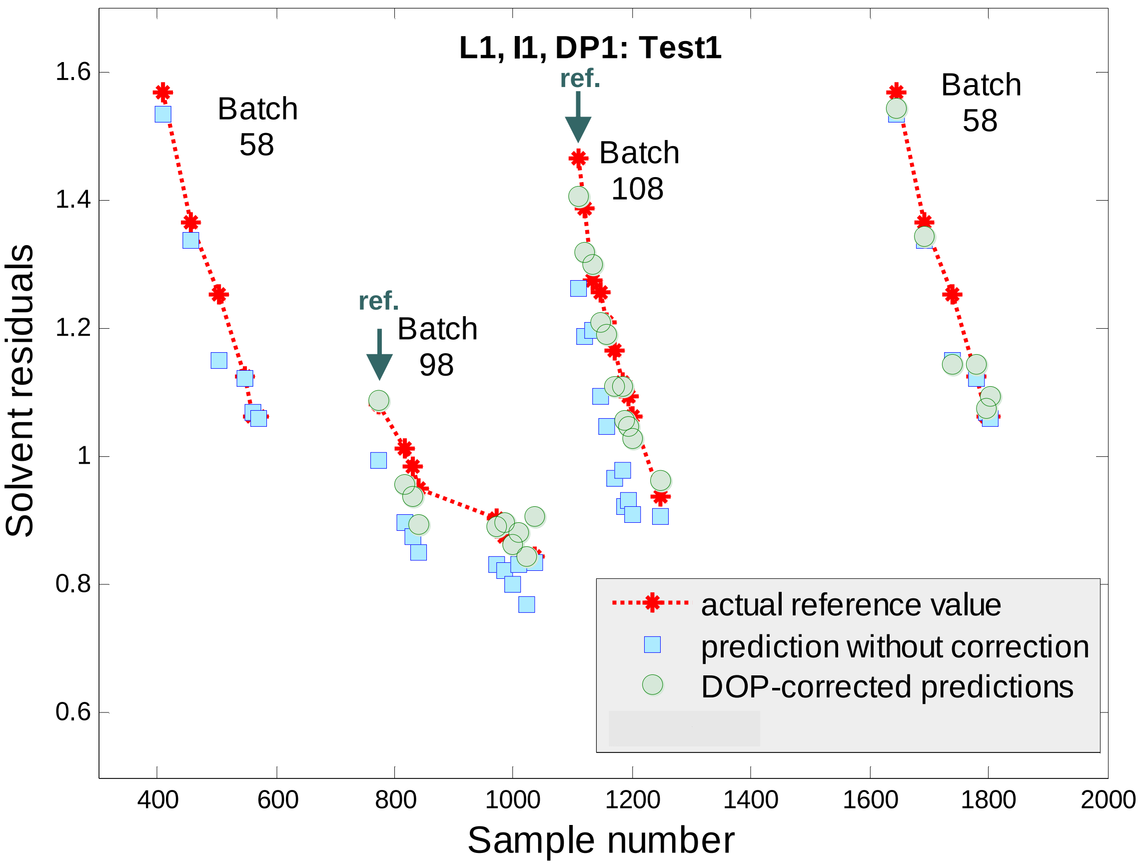
Corrections using the 3 approaches on TEST1 DP1 (same line, instrument and product)

			Figures of Merit	Without correction (1LV)	Bias and slope correction	Model update: Model re-development (2LV)	Model update: DOP correction (1LV)	*Reference control points*
Batch effect	L1, I1, DP1	Batch 58	SEP BIAS R^2	0.046 -0.028 0.965				*0*
Batch effect		Batch 98	SEP BIAS R^2	0.079 -0.071 0.835		0.036 -0.004 0.807	0.038 -0.006 0.797	*1 (1st)*
Batch effect		Batch 108	SEP BIAS R^2	0.160 -0.152 0.887	0.079 -0.045 0.815	0.037 -0.025 0.969	0.032 -0.014 0.963	*1 (1st)*
No more batch effect	L1, I1, DP1	Batch 58	SEP BIAS R^2		0.172 0.155 0.856	0.048 0.009 0.945	0.044 -0.012 0.956	*0*

MRD and DOP outperform BS when the influence factor disappears

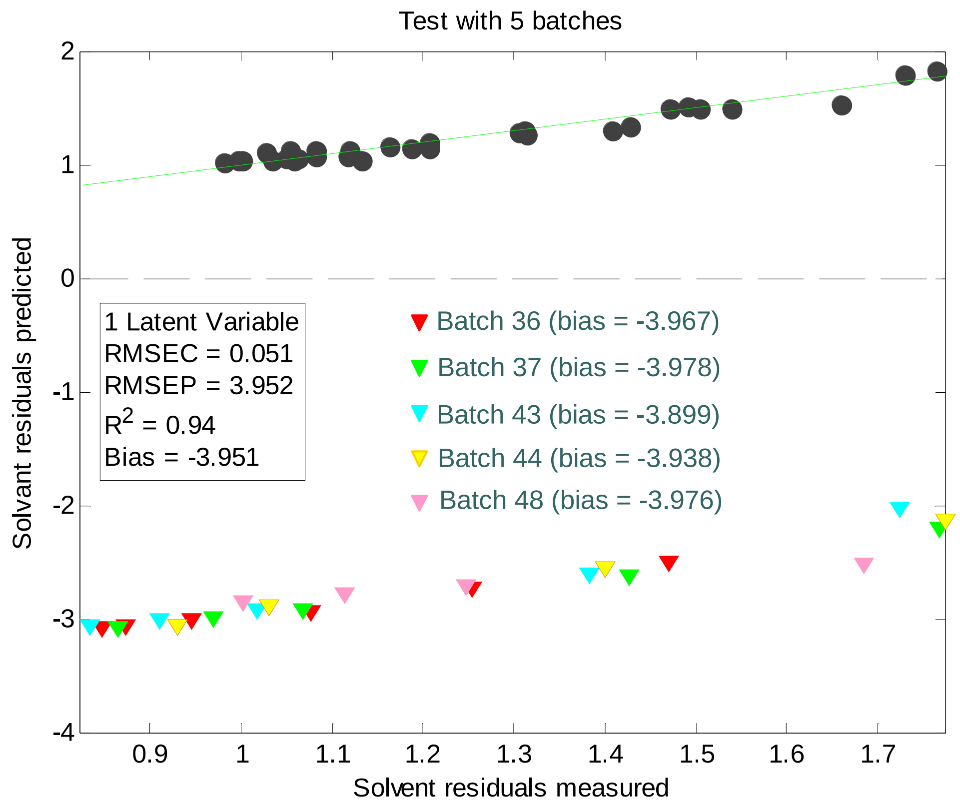
1 – Small drift effect = batch effect

DOP correction on TEST1 DP1 (same line, instrument and product)



2 – Large block effects = line, instrument and product effects

Test on TEST2 DP2 (different line, instrument and product)



2 – Large block effects = line, instrument and product effects

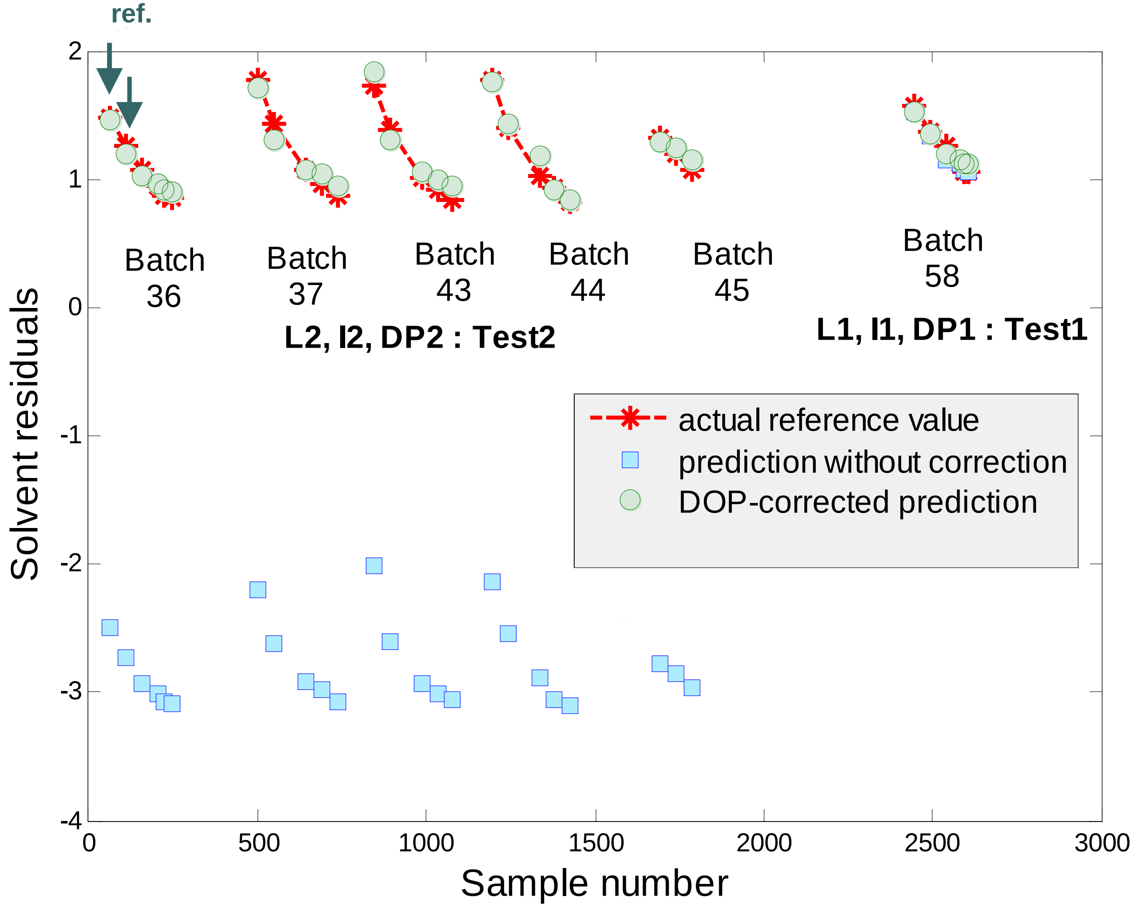
Corrections using the 3 approaches on TEST2 DP2 (different line, instr. and prod.)

			Figures of Merit	Without correction (1LV)	Bias and slope correction (1LV)	Model update: Model re-development (2LV)	Model update: DOP correction (1LV)	*Reference control points*
All effects	L2, I2, DP2	Batch 36	SEP BIAS R^2	3.967 -3.967 0.989	0.054 0.038 0.974	0.096 0.069 0.925	0.043 0.001 0.969	*2 (1st and 2nd)*
		Batch 37	SEP BIAS R^2	3.979 -3.978 0.989	0.059 0.014 0.977	0.110 0.051 0.931	0.076 0.001 0.959	*0*
		Batch 43	SEP BIAS R^2	3.901 -3.900 0.949	0.110 0.089 0.970	0.141 0.116 0.954	0.088 0.056 0.967	*0*
		Batch 44	SEP BIAS R^2	3.938 -3.938 0.996	0.062 0.053 0.993	0.129 0.104 0.961	0.069 0.032 0.975	*0*
		Batch 45	SEP BIAS R^2	4.061 -4.061 0.944	0.069 -0.059 0.916	0.119 0.107 0.815	0.056 0.032 0.860	*0*
No more effect	L1, I1, DP1	Batch 58	SEP BIAS R^2	0.046 -0.028 0.965	3.582 3.581 0.952	0.044 0.003 0.951	0.045 0.008 0.952	*0*

DOP outperforms MRD for strong effects when very few references

2 – Large block effects = line, instrument and product effects

DOP correction on TEST2 DP2 (different line, instrument and product)



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Conclusions

✓ Different algorithms for model maintenance or transfer when neither standardisation set nor small experimental design is available: bias/slope correction (BS), model re-development (MRD) and DOP correction

✓ DOP and MRD outperform BS when the influence factor disappears

✓ DOP outperforms MRD when using a minimal number of reference control points, especially for strong effects (product effect)

➔ DOP is the most suited to specific applications (quick model update, costly reference control points, start of a new condition of manufacturing, …)

✓ MRD can only be used when a large number of reference control points are available