Chemometric Methods for the Kinetic Hard-modelling of Spectroscopic Data

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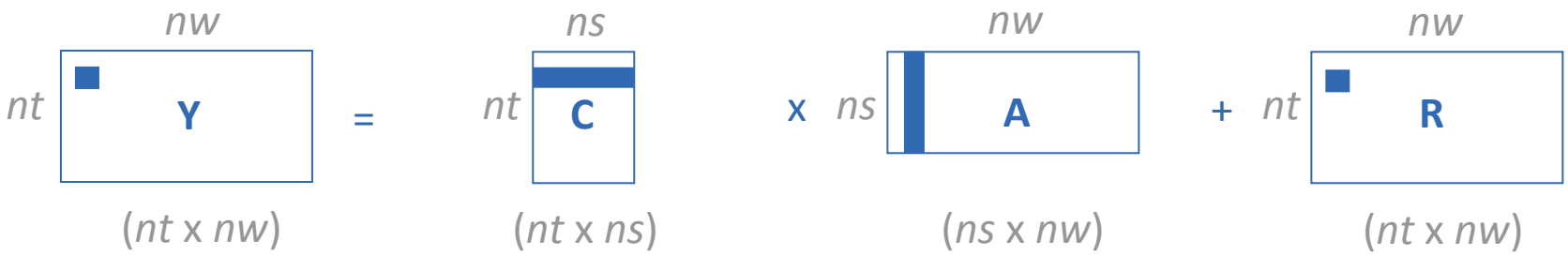
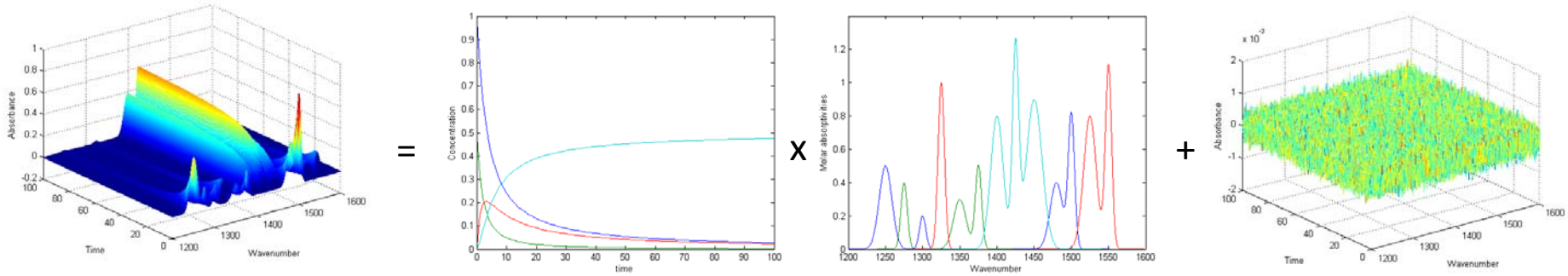
What is Chemometrics?

- Chemometrics is the chemical discipline that uses mathematical and statistical methods to:
  - (a) design or select optimal measurement procedures and experiments, and
  - (b) provide maximum chemical information by analyzing chemical data

Matthias Otto (2007)
From: Chemometrics – Statistics and Computer Application in Analytical Chemistry

Beer's law





$$A + B \xrightarrow{k_1} C$$

$$A + C \xrightarrow{k_2} D$$

Direct fitting

Beer's law

$$\mathbf{Y} = \mathbf{C}\,\mathbf{A}$$

Modelled part

$\mathbf{C}_{\text{modelled}} = \text{function}(\mathbf{k})$

$\mathbf{A}_{\text{modelled}} = \text{function}(\boldsymbol{\theta})$

Linear counter part

- Implicit calibration
- Explicit calibration

$\mathbf{A} = \mathbf{C}^{+}_{\text{modelled}}\mathbf{Y}$ [1]

$\mathbf{A} = (\mathbf{C}^{+}\mathbf{Y})_{\text{calibration}}$

$\mathbf{C} = \mathbf{Y}\mathbf{A}^{+}_{\text{modelled}}$ [2]

$\mathbf{C} = (\mathbf{Y}\mathbf{A}^{+})_{\text{calibration}}$

Least squares fitting

$$\min_{\mathbf{k}} \left\| \mathbf{Y} - \mathbf{C}_{\text{modelled}}\mathbf{A} \right\|^2$$

$$\min_{\boldsymbol{\theta}} \left\| \mathbf{Y} - \mathbf{C}\mathbf{A}_{\text{modelled}} \right\|^2$$

$$\min_{\mathbf{k}} \left\| \mathbf{C} - \mathbf{C}_{\text{modelled}} \right\|^2$$

[1] $\mathbf{C}^{+} = \left(\mathbf{C}^{\mathsf{T}}\mathbf{C}\right)^{-1}\mathbf{C}^{\mathsf{T}}$ [2] $\mathbf{A}^{+} = \mathbf{A}^{\mathsf{T}}\left(\mathbf{A}\mathbf{A}^{\mathsf{T}}\right)^{-1}$

Indirect (inverse) fitting

Inverse model

$$\mathbf{C} = \mathbf{Y}\mathbf{B}_C \qquad \mathbf{A} = \mathbf{B}_A\mathbf{Y}$$

Modelled part

$$\mathbf{C}_{modelled} = \text{function}(\mathbf{k}) \qquad \mathbf{A}_{modelled} = \text{function}(\boldsymbol{\theta})$$

Linear counter part

- Implicit calibration
- Explicit calibration

$$\mathbf{B}_C = \mathbf{Y}^{+}\mathbf{C}_{modelled} \qquad \mathbf{B}_A = \mathbf{A}_{modelled}\mathbf{Y}^{+}$$

$$\mathbf{B}_C = (\mathbf{Y}^{+}\mathbf{C})_{calibration} \qquad \mathbf{B}_A = (\mathbf{A}\mathbf{Y}^{+})_{calibration}$$

Least squares fitting

$$\min_{\mathbf{k}} \left\| \mathbf{C}_{modelled} - \mathbf{Y}\mathbf{B}_C \right\|^2$$

$$\min_{\boldsymbol{\theta}} \left\| \mathbf{A}_{modelled} - \mathbf{B}_A\mathbf{Y} \right\|^2$$

$$\min_{\mathbf{k}} \left\| \mathbf{C} - \mathbf{C}_{modelled} \right\|^2$$

Modelling concentrations (C) or spectra (A) ?

Modelling **C**

Based on a first-principles model (the kinetic rate law)

Depends on a limited number of kinetic parameters, e.g. rate constants **k** (1 x *nr*)

Modelling **A**

Based on the modelling of **A** using Gaussian functions

Depends on a large number of parameters θ, which are difficult to determine

Requires a subsequent modelling of **C** to determine kinetic parameters, e.g. rate constants **k** (1 x *nr*)

Fitting method used in Parts 2 and 3

- Direct fitting by modelling concentrations (**C**)

$$\min_{\mathbf{k}} \left\| \mathbf{Y} - \mathbf{C}_{\text{modelled}}(\mathbf{k})\mathbf{A} \right\|^2$$

- using implicit and explicit calibration of the pure component spectra (**A**)
  - Implicit calibration: (i.e. calibration-free)

$$\mathbf{A} = \mathbf{C}^{+}_{\text{modelled}}(\mathbf{k})\mathbf{Y}$$

  - Explicit calibration: (also called Strategy 2)

$$\mathbf{A} = \left(\mathbf{C}^{+}\mathbf{Y}\right)_{\text{calibration}}$$

Modelling concentration profiles using the rate law

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

$$\mathbf{k} = \begin{bmatrix} k_1 & k_2 \end{bmatrix}$$

Modelling concentration profiles using the rate law

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

$$\mathbf{k} = [k_1 \; k_2]$$

A	B	C	D
0	0	1	0
0	0	0	1

P (*nr* x *ns*)

-

A	B	C	D
1	1	0	0
1	0	1	0

E (*nr* x *ns*)

=

A	B	C	D
-1	-1	1	0
-1	0	-1	1

N (*nr* x *ns*)

Modelling concentration profiles using the rate law

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

$$\mathbf{k} = [k_1 \; k_2]$$

A	B	C	D
0	0	1	0
0	0	0	1

P (*nr* x *ns*)

-

A	B	C	D
1	1	0	0
1	0	1	0

E (*nr* x *ns*)

=

A	B	C	D
-1	-1	1	0
-1	0	-1	1

N (*nr* x *ns*)

***nr* = 2 kinetic rate laws**

$$\begin{cases} \dfrac{dx_{t,1}}{dt} = k_1 c_{t,A}^{e_{1,1}} c_{t,B}^{e_{1,2}} c_{t,C}^{e_{1,3}} c_{t,D}^{e_{1,4}} = k_1 c_{t,A}^{1} c_{t,B}^{1} \\ \dfrac{dx_{t,2}}{dt} = k_2 c_{t,A}^{e_{2,1}} c_{t,B}^{e_{2,2}} c_{t,C}^{e_{2,3}} c_{t,D}^{e_{2,4}} = k_2 c_{t,A}^{1} c_{t,C}^{1} \end{cases}$$

Modelling concentration profiles using the rate law

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

$$\mathbf{k} = [k_1 \; k_2]$$

	A	B	C	D
	0	0	1	0
	0	0	0	1

P (*nr* x *ns*)

-

	A	B	C	D
	1	1	0	0
	1	0	1	0

E (*nr* x *ns*)

=

	A	B	C	D
	-1	-1	1	0
	-1	0	-1	1

N (*nr* x *ns*)

***ns* = 4 concentration profiles (System of ODE)**

$$\begin{cases} \frac{dc_{t,A}}{dt} = n_{1,1}\frac{dx_{t,1}}{dt} + n_{2,1}\frac{dx_{t,2}}{dt} = -1\cdot\frac{dx_{t,1}}{dt} - 1\cdot\frac{dx_{t,2}}{dt} \\ \frac{dc_{t,B}}{dt} = n_{1,2}\frac{dx_{t,1}}{dt} + n_{2,2}\frac{dx_{t,2}}{dt} = -1\cdot\frac{dx_{t,1}}{dt} + 0\cdot\frac{dx_{t,2}}{dt} \\ \frac{dc_{t,C}}{dt} = n_{1,3}\frac{dx_{t,1}}{dt} + n_{2,3}\frac{dx_{t,2}}{dt} = 1\cdot\frac{dx_{t,1}}{dt} - 1\cdot\frac{dx_{t,2}}{dt} \\ \frac{dc_{t,D}}{dt} = n_{1,4}\frac{dx_{t,1}}{dt} + n_{2,4}\frac{dx_{t,2}}{dt} = 0\cdot\frac{dx_{t,1}}{dt} + 1\cdot\frac{dx_{t,2}}{dt} \end{cases}$$

***nr* = 2 kinetic rate laws**

$$\begin{cases} \frac{dx_{t,1}}{dt} = k_1 c_{t,A}^{e_{1,1}} c_{t,B}^{e_{1,2}} c_{t,C}^{e_{1,3}} c_{t,D}^{e_{1,4}} = k_1 c_{t,A}^{1} c_{t,B}^{1} \\ \frac{dx_{t,2}}{dt} = k_2 c_{t,A}^{e_{2,1}} c_{t,B}^{e_{2,2}} c_{t,C}^{e_{2,3}} c_{t,D}^{e_{2,4}} = k_2 c_{t,A}^{1} c_{t,C}^{1} \end{cases}$$

Modelling concentration profiles using the rate law

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

$$\mathbf{k} = [k_1 \; k_2]$$

	A	B	C	D
	0	0	1	0
	0	0	0	1

P (*nr* x *ns*)

-

	A	B	C	D
	1	1	0	0
	1	0	1	0

E (*nr* x *ns*)

=

	A	B	C	D
	-1	-1	1	0
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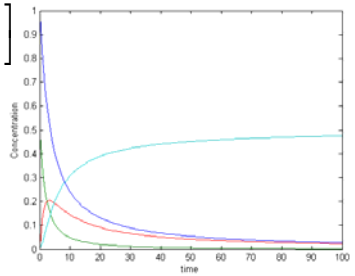
***nr* = 2 kinetic rate laws**

$$\begin{cases} \frac{dx_{t,1}}{dt} = k_1 c_{t,A}^{e_{1,1}} c_{t,B}^{e_{1,2}} c_{t,C}^{e_{1,3}} c_{t,D}^{e_{1,4}} = k_1 c_{t,A}^{1} c_{t,B}^{1} \\ \frac{dx_{t,2}}{dt} = k_2 c_{t,A}^{e_{2,1}} c_{t,B}^{e_{2,2}} c_{t,C}^{e_{2,3}} c_{t,D}^{e_{2,4}} = k_2 c_{t,A}^{1} c_{t,C}^{1} \end{cases}$$

Numerical integration

$$\mathbf{C} = [\mathbf{c}_{t,A} \; \mathbf{c}_{t,B} \; \mathbf{c}_{t,C} \; \mathbf{c}_{t,D}]$$



The System of ODE is integrated with initial concentrations $\mathbf{c_0} = [c_{0,A} \; c_{0,B} \; c_{0,C} \; c_{0,D}]$

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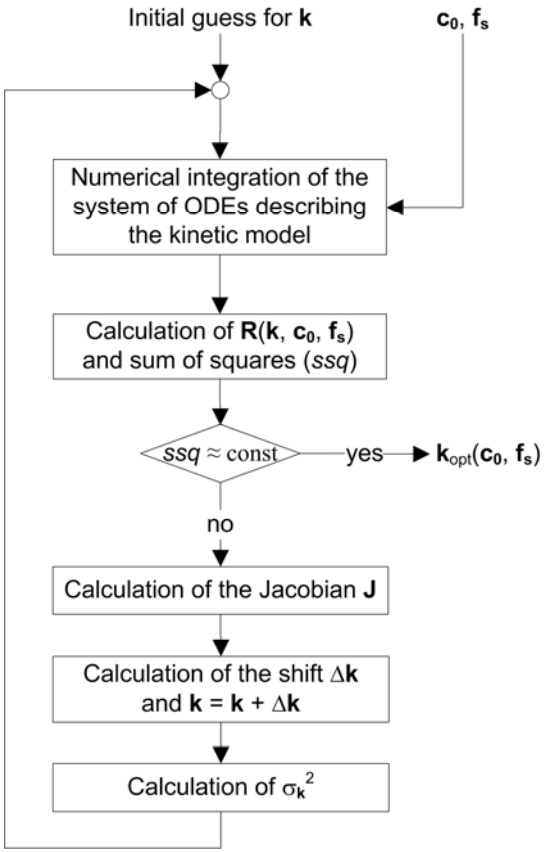
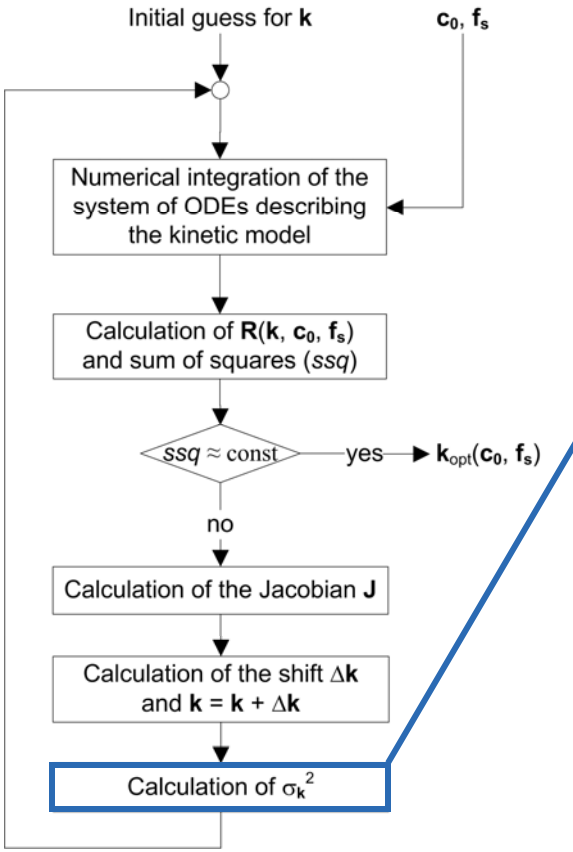
Newton-Gauss algorithm $\min_{\mathbf{k}} \left\| \mathbf{Y} - \mathbf{C}_{\text{modelled}} \mathbf{A} \right\|^2$



Newton-Gauss algorithm

$$\min_{\mathbf{k}} \left\| \mathbf{Y} - \mathbf{C}_{\text{modelled}} \mathbf{A} \right\|^2$$



Newton-Gauss algorithm delivers an estimate of the uncertainties in the optimised parameters (k)

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \operatorname{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2$$

$\boldsymbol{\sigma}_{\mathbf{k}}^2$ — Variance of the optimised parameters **k** (1 x *nr*)

$\operatorname{diag}(\cdot)$ — Operator extracting a vector of diagonal elements from a matrix

$\mathbf{H} = \left(\frac{\partial \mathbf{R}}{\partial \mathbf{k}}\right)^{\mathsf{T}} \left(\frac{\partial \mathbf{R}}{\partial \mathbf{k}}\right)$ — Sensitivity of the residuals **R** with respect to the optimised parameters **k**

$\sigma_{\mathbf{r}}^2$ — Variance of the residuals

Error propagation in Newton-Gauss algorithm

Classical estimation of uncertainties: $\boldsymbol{\sigma}_{\mathbf{k}}^2 = \mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2$

Problem: this estimation ($\boldsymbol{\sigma}_{\mathbf{k}}^2$) is lower than the variance calculated by repetition of the experiments.

Error propagation in Newton-Gauss algorithm

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Problem: this estimation ($\boldsymbol{\sigma}_{\mathbf{k}}^2$) is lower than the variance calculated by repetition of the experiments.

Uncertainties and error propagation (easily extendable):

$\boldsymbol{\sigma}_{\mathbf{k}}^2 =$

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Error propagation in Newton-Gauss algorithm

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Problem: this estimation ($\boldsymbol{\sigma}_{\mathbf{k}}^2$) is lower than the variance calculated by repetition of the experiments.

Uncertainties and error propagation (easily extendable):

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \boxed{\mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2}$$

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \qquad \boldsymbol{\sigma}_{\mathbf{k,r}}^2$$

Error propagation in Newton-Gauss algorithm

Classical estimation of uncertainties: $\boldsymbol{\sigma}_{\mathbf{k}}^2 = \mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2$

Problem: this estimation ($\boldsymbol{\sigma}_{\mathbf{k}}^2$) is lower than the variance calculated by repetition of the experiments.

Uncertainties and error propagation (easily extendable):

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2 + \mathrm{diag}\left[\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)^{\mathrm{T}} \mathrm{DIAG}\left(\boldsymbol{\sigma}_{\mathbf{c_0}}^2\right)\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)\right]$$

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \boldsymbol{\sigma}_{\mathbf{k,r}}^2 + \boldsymbol{\sigma}_{\mathbf{k},\mathbf{c_0}}^2$$

DIAG = operator generating a diagonal matrix from the corresponding vector argument

Error propagation in Newton-Gauss algorithm

Classical estimation of uncertainties:

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2$$

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Uncertainties and error propagation (easily extendable):

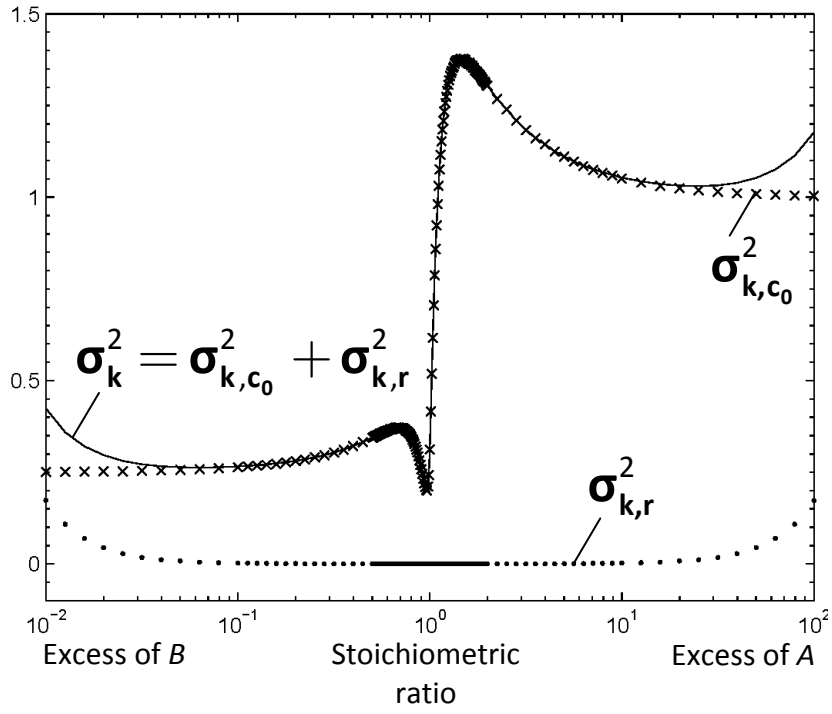
$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \mathrm{diag}\left(\mathbf{H}^{-1}\right)\sigma_{\mathbf{r}}^2 + \mathrm{diag}\left[\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)^{\mathrm{T}} \mathrm{DIAG}\left(\boldsymbol{\sigma}_{\mathbf{c_0}}^2\right)\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)\right] + \mathrm{diag}\left[\left(\frac{\partial \mathbf{k}}{\partial \mathbf{f_s}}\right)^{\mathrm{T}} \mathrm{DIAG}\left(\boldsymbol{\sigma}_{\mathbf{f_s}}^2\right)\left(\frac{\partial \mathbf{k}}{\partial \mathbf{f_s}}\right)\right]$$

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \boldsymbol{\sigma}_{\mathbf{k,r}}^2 + \boldsymbol{\sigma}_{\mathbf{k},\mathbf{c_0}}^2 + \boldsymbol{\sigma}_{\mathbf{k,f}}^2$$

DIAG = operator generating a diagonal matrix from the corresponding vector argument

Simulation: $A + B \xrightarrow{k_1} C$

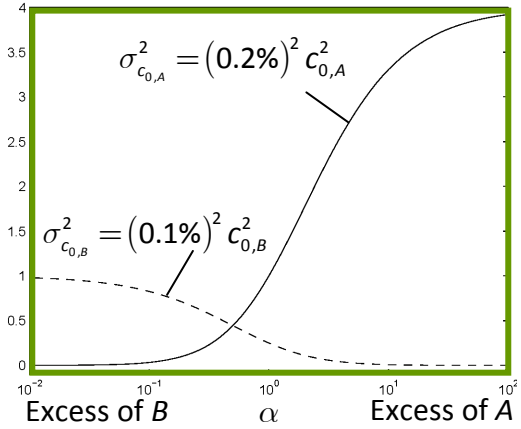
$$\sigma_k^2 = \sigma_{k,r}^2 + \sigma_{k,c_0}^2 \quad \text{with} \quad \sigma_{k,c_0}^2 = \text{diag}\left[\left(\frac{\partial k}{\partial c_0}\right)^T \text{DIAG}\left(\sigma_{c_0}^2\right)\left(\frac{\partial k}{\partial c_0}\right)\right]$$



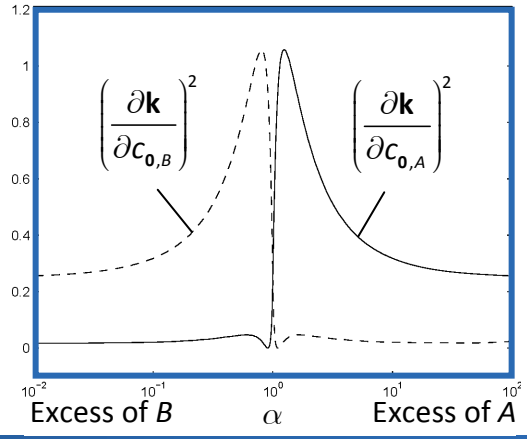
$$\alpha = c_{0,A} / c_{0,B} \quad \text{with } c_{0,A} + c_{0,B} = 1 \text{ mol} \cdot \text{L}^{-1}$$

Different uncertainties in the initial concentrations due to sampling

Asymmetry in σ_{k,c_0}^2



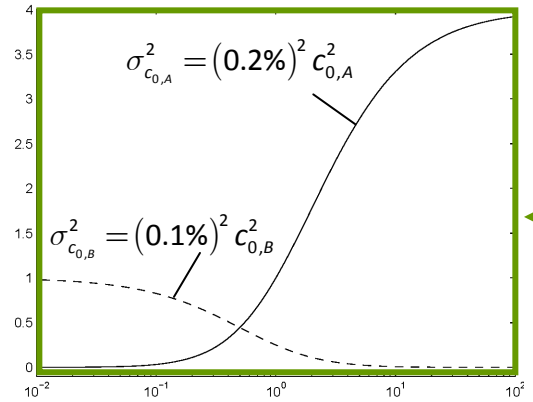
Maxima / Minima in σ_{k,c_0}^2



Simulation: optimal experimental conditions

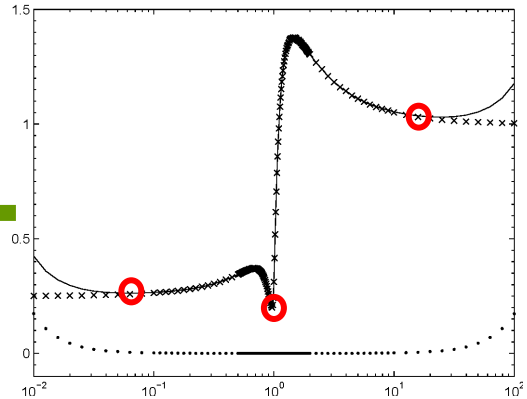
$$A + B \xrightarrow{k_1} C$$

$$\boldsymbol{\sigma}_{\mathbf{k}}^2 = \boldsymbol{\sigma}_{\mathbf{k,r}}^2 + \boldsymbol{\sigma}_{\mathbf{k},\mathbf{c_0}}^2 \approx \boldsymbol{\sigma}_{\mathbf{k},\mathbf{c_0}}^2 = \mathrm{diag}\left[\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)^{\mathrm{T}} \mathrm{DIAG}\left(\boldsymbol{\sigma}_{\mathbf{c_0}}^2\right)\left(\frac{\partial \mathbf{k}}{\partial \mathbf{c_0}}\right)\right]$$



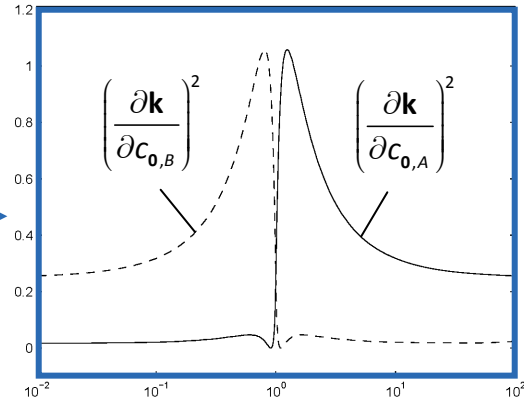
Excess of *B* $\alpha = c_{0,A} / c_{0,B}$ Excess of *A*

Excess in the species with the lowest uncertainty in its initial concentration (here *B*)



Excess of *B* $\alpha = c_{0,A} / c_{0,B}$ Excess of *A*

This curve was validated by Monte-Carlo sampling (10 000 points)

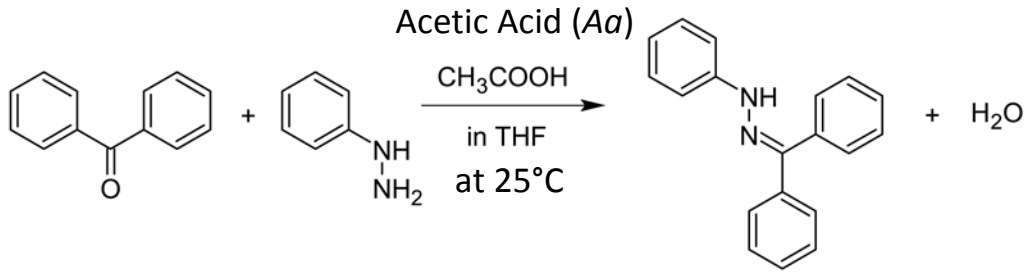


Excess of *B* $\alpha = c_{0,A} / c_{0,B}$ Excess of *A*

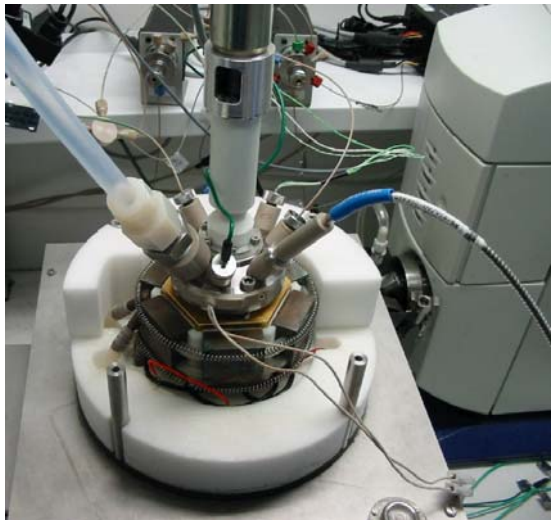
Under exact stoichiometric conditions ($\alpha = 1$)
Under pseudo-first order conditions ($\alpha \in]\infty, 10] \cup [0.1, 0[$)

Experimental reaction

Overall reaction:



Benzophenone (*B*) + Phenylhydrazine (*P*) → Benzophenone-Phenylhydrazone (*BP*) + Water



Reactor: CRC.v4 with FT-IR and UV-vis

Kinetic mechanism:

$$B + P + Aa \xrightarrow{k} BP + Aa$$

Experimental conditions:

25°C, dosing *Aa*, followed in mid-IR (1200–1650 cm^{-1}) and UV-vis (240–400 nm).
$c_{0,B}$ = 0.40033 (±0.292%) mol·L^{-1}, $c_{0,P}$ = 1.19737 (±0.292%) mol·L^{-1}, $c_{0,Aa}$ = 0 mol·L^{-1}
$c_{dos,Aa}$ = 17.48376 (±0%) mol·L^{-1}, dosing rate = 8.17 (±0.14%) mL·min^{-1} in 0.6 min.

17 repetitions

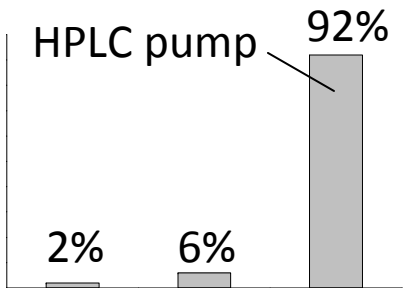
Experimental results

	UV-vis		mid-IR	
	k [a]	σ_k [a]	**k** [a]	σ_k [a]
Experimental (mean and standard deviation over 17 repetitions)	1.76(8)	**0.02(8)**	1.73(9)	**0.05(4)**
Predicted by error propagation	-	**0.02(3)**	-	**0.02(2)**
Literature	1.40 [b]	-	1.51 [b]	-
	1.65 [c]	-	1.65 [c]	-

[a] in $L^2 \cdot mol^{-2} \cdot s^{-1} \times 10^{-4}$

[b] Carvalho et al., Talanta, 68 (2006), 1190-1200

[c] Billeter et al., Chemom. Intell. Lab. Syst., (2009), submitted



$$\sigma_k^2 = \sigma_{k,r}^2 + \sigma_{k,c_0}^2 + \sigma_{k,f}^2$$

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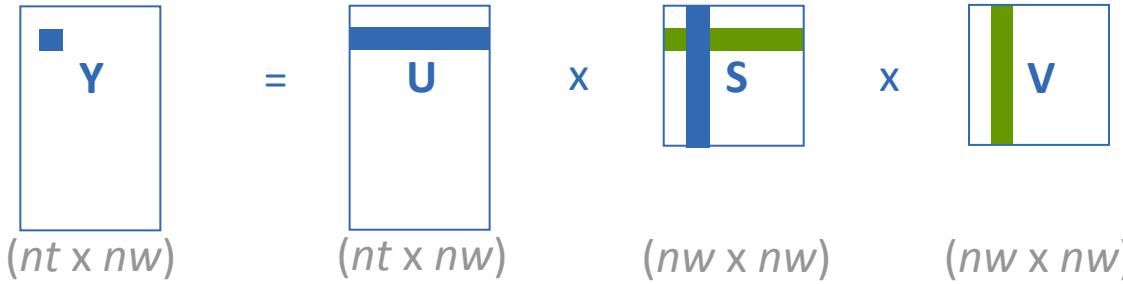
Singular Value Decomposition (SVD)

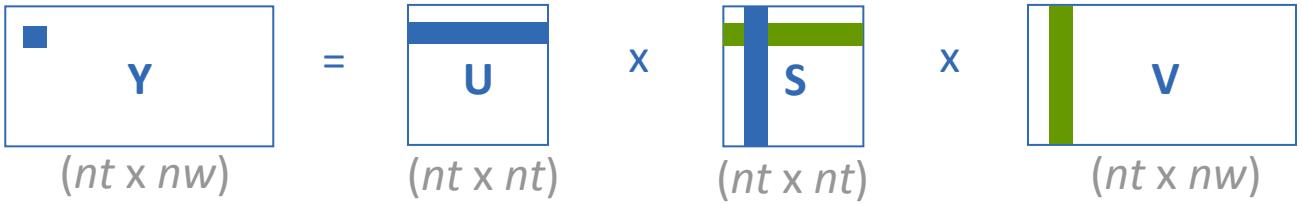
$$\mathbf{Y} = \mathbf{U}\,\mathbf{S}\,\mathbf{V}$$

U : Matrix of orthonormal column eigenvectors
S : Matrix of singular values
V : Matrix of orthonormal row eigenvectors

nw < nt



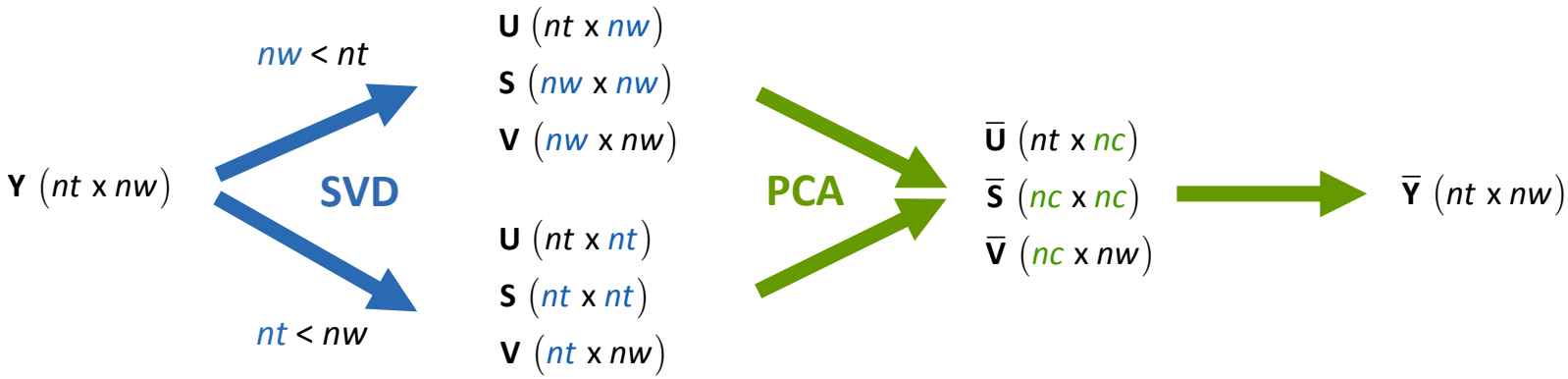
nt < nw



Principal Component Analysis (PCA)

$$\mathbf{Y} = \mathbf{U}\,\mathbf{S}\,\mathbf{V} \qquad \mathbf{R} = \mathbf{Y} - \bar{\mathbf{Y}} = \text{noise}$$

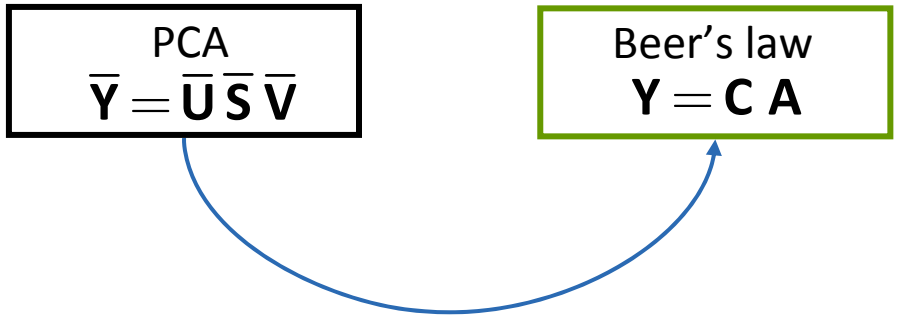
Reduction of the dimensionality to *nc*,
i.e. the number of significant singular values (or eigenvectors)



nt or *nw* factors

nc factors

Target Factor Analysis (TFA)



nc = number of significant factors

ns = number of reactive species

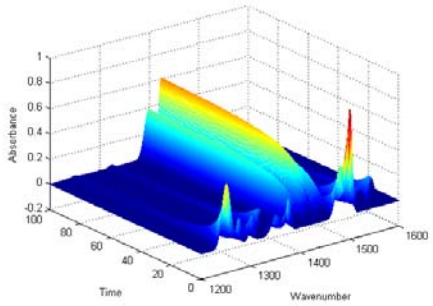
TFA: Relationship between PCA and Beer's law

$$\bar{\mathbf{C}}\,(nt \times nc) = \bar{\mathbf{U}}\,(nt \times nc)\,\mathbf{T} \neq \mathbf{C}\,(nt \times ns)$$
$$\bar{\mathbf{A}}\,(nc \times nw) = \mathbf{T}^{-1}\,\bar{\mathbf{S}}\,\bar{\mathbf{V}}\,(nc \times nw) \neq \mathbf{A}\,(ns \times nw)$$

Where **T** is a transformation matrix of dimensions (*nc* x *nc*)

Rank deficiency in spectroscopy

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

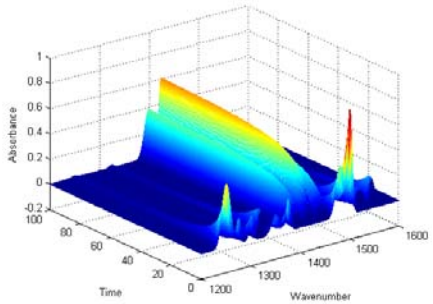


Y

Rank deficiency in spectroscopy

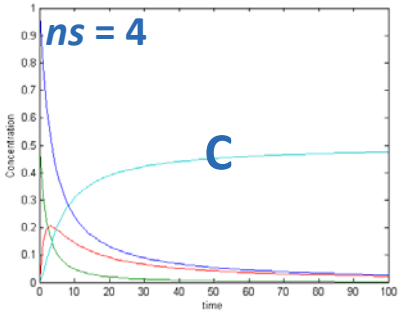
Beer's law (*ns* = 4 species) Y = CA

$$\begin{cases} A + B \xrightarrow{k_1} C \\ A + C \xrightarrow{k_2} D \end{cases}$$

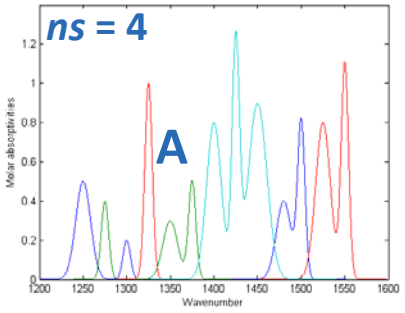


Y

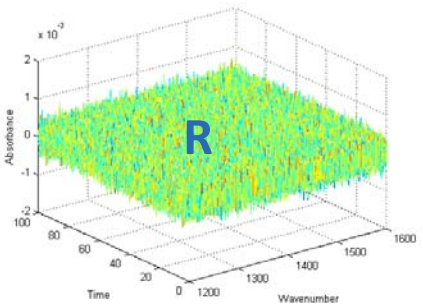
=



x



+



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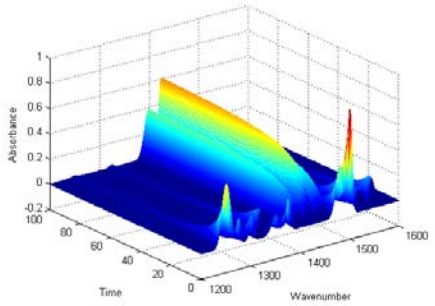
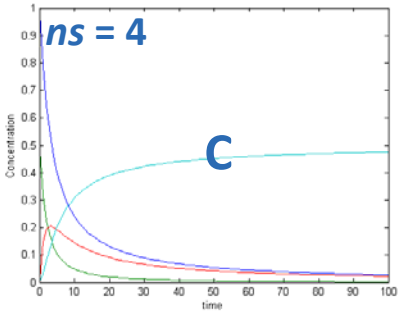
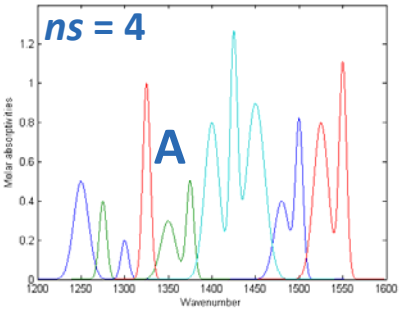
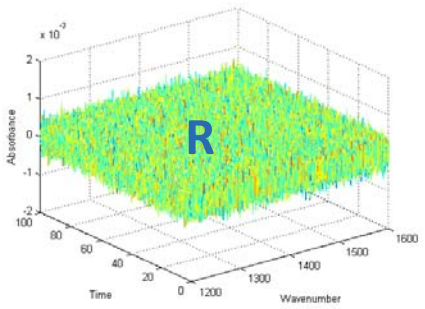
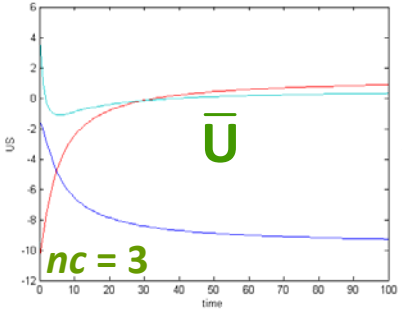


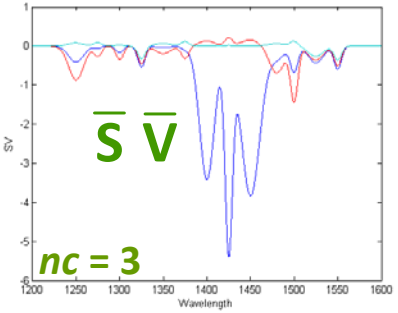
Y = 

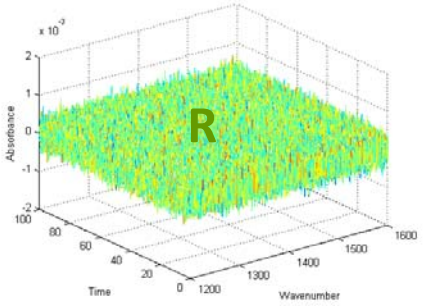
x 

+ 

PCA (*nc* = 3 factors) $\bar{Y} = \bar{U}\,\bar{S}\,\bar{V}$

= 

x 

+ 

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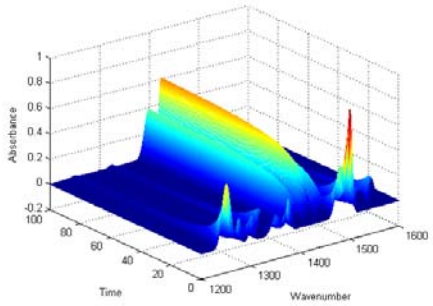
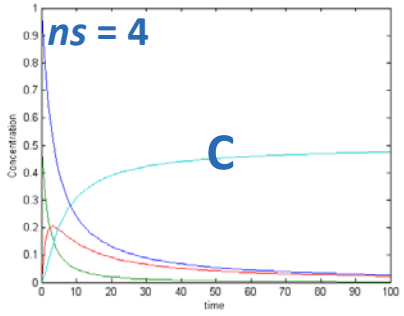
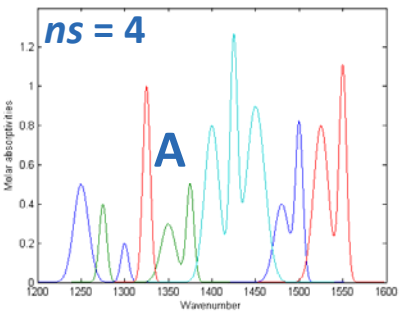


Y

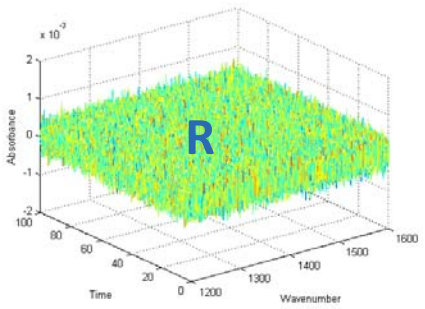
=



x

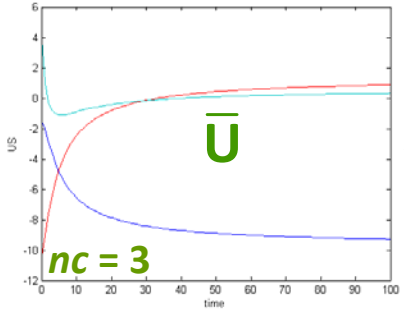


+

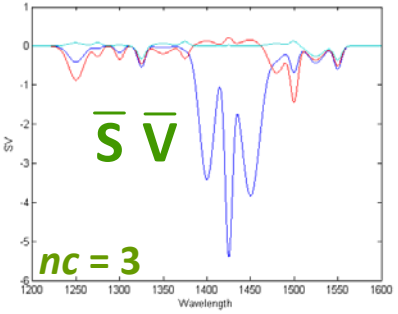


PCA (*nc* = 3 factors) $\bar{Y} = \bar{U}\,\bar{S}\,\bar{V}$

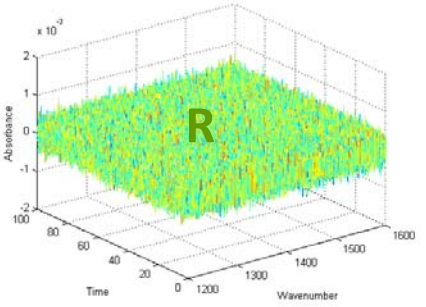
=



x



+



Spectroscopic data **Y** are rank deficient when:

significant factors (*nc*) in PCA < number of reactive species (*ns*) ⇔ rank(**Y**) < *ns*

Sources and problems of rank deficiency

$$\mathbf{Y} = \mathbf{C}\,\mathbf{A}$$

Rank deficiencies in **Y** is due to:

Linear dependencies in **C** and/or Linear dependencies in **A**

Mathematical dilemma in case of implicit calibration

A cannot be computed by $\mathbf{C}^{+}\mathbf{Y}$ as **A** is not unique

Not discussed here

All spectra in **A** are assumed to be linearly independent

Example: two species that are consumed or generated at the same rate

rank(**Y**) = min [rank(**C**), rank(**A**)] = rank(**C**)

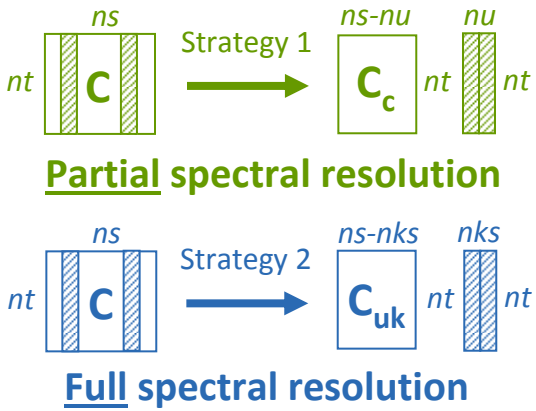
Strategies to treat rank deficiency in kinetic hard-modelling by implicit calibration

Strategies to treat rank deficiency in kinetic hard-modelling by implicit calibration

- **Model (Beer's law) reduction**

  Strategy 1: define *nu* uncoloured species

  Strategy 2: include *nks* known spectra in the analysis (explicit calibration)



Strategies to treat rank deficiency in kinetic hard-modelling by implicit calibration

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  Strategy 1: define *nu* uncoloured species

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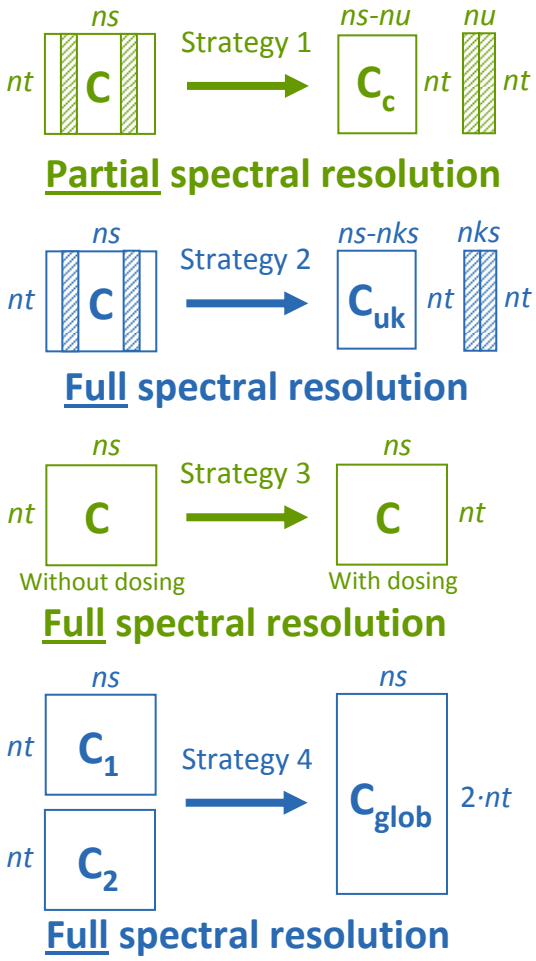
- **Rank augmentation**

  Strategy 3: dose one or more species in *nf* dosing steps

  Strategy 4: perform *ne* additional experiments by varying the initial concentrations (second order global analysis in global mode)



Strategies to treat rank deficiency in kinetic hard-modelling by implicit calibration

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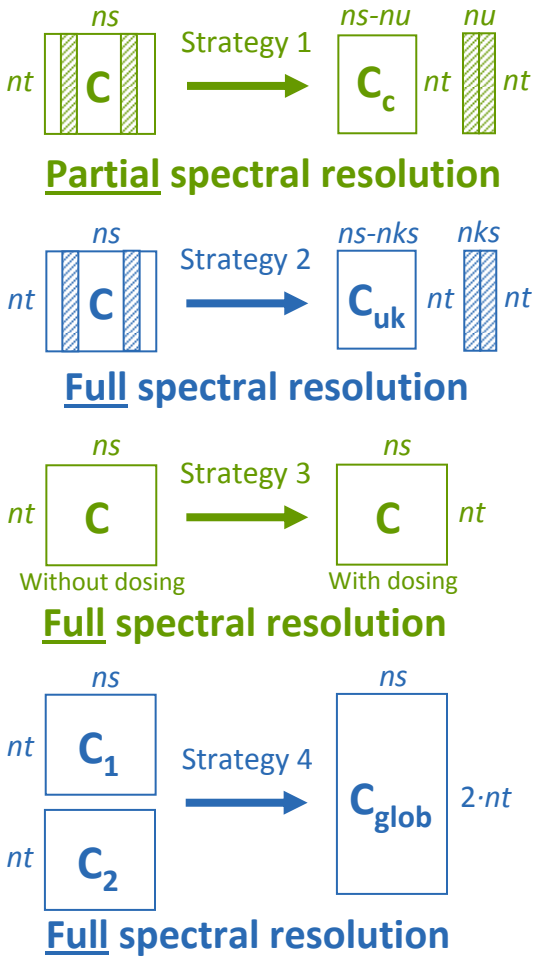
How to define the species to include in these four Strategies ?



Rank and kernel of the concentration matrix (C)

- ***nc* = rank (Y) = rank (C)**

  number of linearly independent columns or rows of **Y** or **C**

  The rank of **Y** or **C** defines the maximum number of columns (species) to keep in Strategy 1 (*ns* – *nu*) and Strategy 2 (*ns* – *nks*)

- **ker C**

  vector space spanned by the vectors forming the null space **0** when multiplied by **C**

  e.g. ker $\mathbf{C} = \begin{bmatrix} 0.8 & 0.1 \\ -0.3 & -0.7 \\ 0 & 0 \\ 0.5 & -0.6 \end{bmatrix} \begin{matrix} A \\ B \\ C \\ D \end{matrix}$

  (1) ker **C** defines a mass balance equation: **C** (ker **C**) = **0**

  (2) ker **C** defines which columns of **C** are:

  (a) linearly dependent (rows comprised by non-zeros entries in ker **C**) or

  (b) linearly independent (rows comprised by zeros in ker **C**)

Interpretation of the kernel of C

	Species without zero rows in ker C	Species with zero rows in ker C
kernel of C	**linearly dependent from the other species**	**linearly independent from the other species**
Strategy 1:	define this species as uncoloured	define this species as coloured
Strategy 2:	providing its pure spectrum avoids rank deficiency	providing its pure spectrum does not avoid rank deficiency
Strategy 3:	dosing this species breaks rank deficiency	dosing this species does not break rank deficiency
Strategy 4:	varying its initial concentration breaks rank deficiency	varying its initial concentration does not break rank deficiency

A time invariant matrix Ω equivalent to C

$$\boldsymbol{\Omega} = \begin{bmatrix} \left(\mu\mathbf{1}\right)^{\bullet\mathbf{E}^T}\,\mathrm{DIAG}\left(\mathbf{k}\right)\mathbf{N} \\ \hline \mathbf{c_0} \\ \hline \mathbf{C_{in}} \\ \hline \mathbf{C_0^{ne}} \end{bmatrix} \quad \left(ns + 1 + nf + ne \times ns - nu - nks\right)$$

μ	an arbitrary positive scalar different from 0 and 1
1 (*ns* x *nr*)	matrix comprised of ones
E (*nr* x *ns*)	matrix of reactant coefficients
$\bullet\mathbf{E}^T$	element-wise raise to the power of $\mathbf{E}^T$
DIAG	operator generating a diagonal matrix from a vector argument

k (1 x *nr*)	vector of rate constants
N (*nr* x *ns*)	matrix of stoichiometric coefficients
$\mathbf{c_0}$ (1 x *ns*)	vector of initial concentrations
$\mathbf{C_{in}}$ (*nf* x *ns*)	matrix of the dosing concentrations corresponding to the *nf* dosing steps
$\mathbf{C_0^{ne}}$ (*ne* x *ns*)	matrix of the varied initial concentrations corresponding to the *ne* additional experiments

Validation of this time invariant matrix:

☑ Equivalence can be mathematically proven

☑ Extensively tested on various mechanisms

Advantages of the time invariant approach:

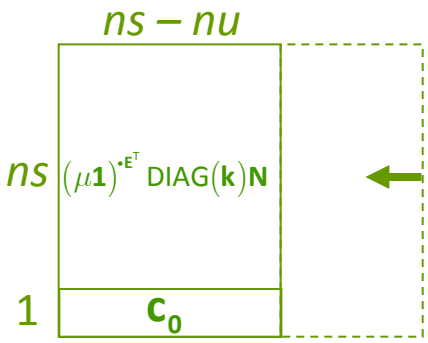
- No numerical integration required
- Analytical (symbolic) relationship between the experimental conditions ($\mathbf{c_0}$, $\mathbf{C_{in}}$,…)

Strategies to treat rank deficiency applied to Ω

Model reduction

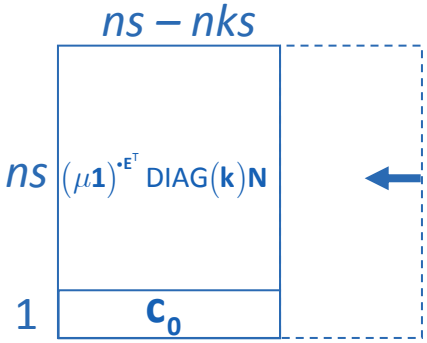
Strategy 1

nu uncoloured species



Strategy 2

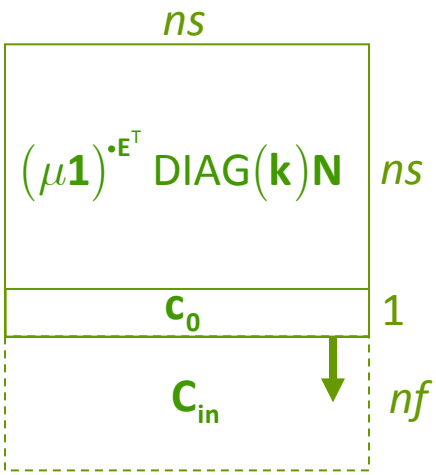
nks known pure spectra



Rank augmentation

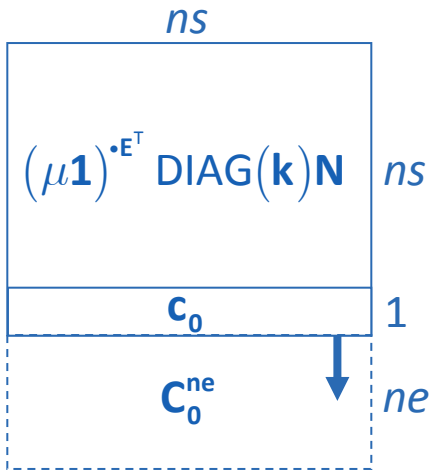
Strategy 3

nf dosing steps

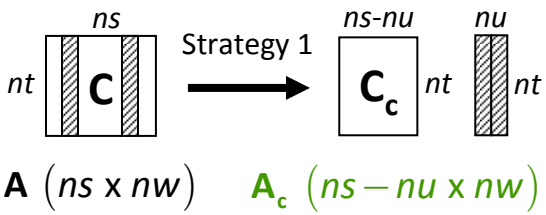


Strategy 4

ne varied initial concentrations



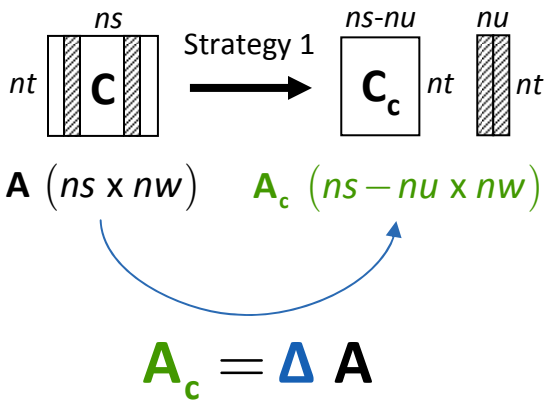
Spectral consequence of Strategy 1 (defining uncoloured species)



Spectral contribution of the *nu* uncoloured species is linearly transferred into the fitted pure component spectra of the coloured species.

The **fitted component spectra A_c** of the (*ns*–*nu*) coloured species are comprised of **linear combinations** of the *ns* **true pure component spectra A**.

Spectral consequence of Strategy 1 (defining uncoloured species)



$$\mathbf{A_c} = \mathbf{\Delta}\ \mathbf{A}$$

(Spectral balance)

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The **fitted component spectra $\mathbf{A_c}$** of the (*ns*–*nu*) coloured species are comprised of **linear combinations** of the *ns* **true pure component spectra A**.

$$\mathbf{\Delta}\ (ns - nu \times ns) = \mathbf{C_c^+ C} = \left(\mathbf{\Omega}\big|_{\substack{\text{comprised of}\\ \text{coloured species}}}\right)^+ \mathbf{\Omega}\big|_{\substack{\text{comprised of}\\ \text{all species}}}$$

Example: calculation of the kernel

$$A + B \xrightarrow{k_1} C$$
$$A + C \xrightarrow{k_2} D$$

$$\boldsymbol{\Omega} = \left[\frac{(\mu\mathbf{1})^{\bullet \mathbf{E}^T}\ \mathrm{DIAG}(\mathbf{k})\mathbf{N}}{\mathbf{c_0}}\right] = \begin{array}{c} \begin{matrix} A & B & C & D \end{matrix} \\ \left[\begin{array}{cccc} -\mu k_1 - \mu k_2 & -\mu k_1 & \mu k_1 - \mu k_2 & \mu k_2 \\ -\mu k_1 - k_2 & -\mu k_1 & \mu k_1 - k_2 & k_2 \\ -k_1 - \mu k_2 & -k_1 & k_1 - \mu k_2 & \mu k_2 \\ -k_1 - k_2 & -k_1 & k_1 - k_2 & k_2 \\ \hline c_{0,A} & \alpha c_{0,A} & 0 & 0 \end{array}\right] \end{array}$$

$$\ker\ \boldsymbol{\Omega} = \begin{bmatrix} -\alpha \\ 1 \\ 1-\alpha \\ 1-2\alpha \end{bmatrix} \begin{matrix} A \\ B \\ C \\ D \end{matrix}$$

Matlab code (8 lines)

```
>> syms c0A alpha mu k1 k2
>> N       = [-1 -1 1 0; -1 0 -1 1];
>> E       = [1 1 0 0; 1 0 1 0];
>> k       = [k1, k2];
>> c0      = [c0A, alpha*c0A, 0, 0];
>> one     = ones(size(E'));
>> omega   = [(mu*one).^(E')*diag(k)*N; c0];
>> null(omega)
ans =
      -alpha
           1
       1-alpha
     1-2*alpha
```

$$\alpha = \frac{c_{0,B}}{c_{0,A}}$$

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If $\alpha = 1$, species C is linearly independent from the others

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```
>> syms c0A alpha mu k1 k2
>> N          = [-1 -1 1 0; -1 0 -1 1];
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ans =
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$$\ker \boldsymbol{\Omega} = \begin{bmatrix} -\alpha \\ 1 \\ 1-\alpha \\ 1-2\alpha \end{bmatrix} \begin{matrix} A \\ B \\ C \\ D \end{matrix}$$

If $\alpha = 1$, species *C* is linearly independent from the others

If $\alpha = 0.5$, species *D* is linearly independent from the others

Matlab code (8 lines)

```
>> syms c0A alpha mu k1 k2
>> N       = [-1 -1 1 0; -1 0 -1 1];
>> E       = [1 1 0 0; 1 0 1 0];
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>> null(omega)
ans =
      -alpha
           1
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If $\alpha = 1$, species *C* is linearly independent from the others

If $\alpha = 0.5$, species *D* is linearly independent from the others

If $\alpha \neq 1$ or 0.5, all species are linearly dependent from the others

Matlab code (8 lines)

```
>> syms c0A alpha mu k1 k2
>> N       = [-1 -1 1 0; -1 0 -1 1];
>> E       = [1 1 0 0; 1 0 1 0];
>> k       = [k1, k2];
>> c0      = [c0A, alpha*c0A, 0, 0];
>> one     = ones(size(E'));
>> omega   = [(mu*one).^(E')*diag(k)*N; c0];
>> null(omega)
ans =
      -alpha
           1
       1-alpha
     1-2*alpha
```

$$\alpha = \frac{c_{0,B}}{c_{0,A}}$$

Example: design of experiments

$$A + B \xrightarrow{k_1} C$$
$$A + C \xrightarrow{k_2} D$$

$$\ker \mathbf{\Omega}\ (4 \times 1) = \begin{bmatrix} -\alpha \\ 1 \\ 1-\alpha \\ 1-2\alpha \end{bmatrix} \begin{matrix} A \\ B \\ C \\ D \end{matrix}$$

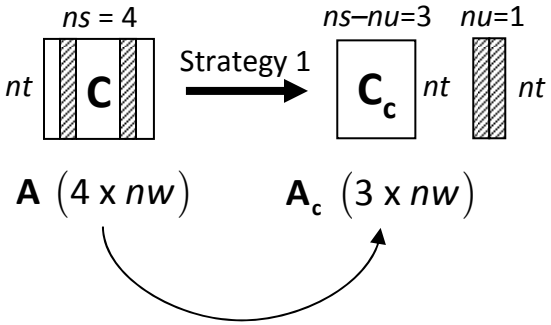
ns = 4 species

Dimension of the kernel is one, i.e. only one species has to be considered in Strategies 1 – 4

Strategy	$\alpha = 1$				$\alpha = 0.5$				$\alpha \neq 1$ or 0.5			
	A	***B***	***C***	***D***	***A***	***B***	***C***	***D***	***A***	***B***	***C***	***D***
(1): define one uncoloured species	0/1	0/1	0	0/1	0/1	0/1	0/1	0	0/1	0/1	0/1	0/1
(2): provide one known pure spectrum	0/1	0/1	0	0/1	0/1	0/1	0/1	0	0/1	0/1	0/1	0/1
(3): dose one species	0/1	0/1	0	0/1	0/1	0/1	0/1	0	0/1	0/1	0/1	0/1
(4): vary one initial concentration	0/1	0/1	0	0/1	0/1	0/1	0/1	0	0/1	0/1	0/1	0/1

1: uncoloured, pure spectrum provided, dosed or initial concentration varied
0: coloured, pure spectrum not provided, not dosed or initial concentration not varied

Example: spectral consequence of Strategy 1 (defining uncoloured species)



$$\mathbf{A_c} = \mathbf{\Delta}\,\mathbf{A}$$

(Spectral balance)

Let's define species *A* uncoloured

All species

$$\mathbf{\Omega}\big|_{\text{comprised of all species}} = \begin{array}{c} \begin{matrix} A & B & C & D \end{matrix} \\ \left[\begin{array}{cccc} -\mu k_1 - \mu k_2 & -\mu k_1 & \mu k_1 - \mu k_2 & \mu k_2 \\ -\mu k_1 - k_2 & -\mu k_1 & \mu k_1 - k_2 & k_2 \\ -k_1 - \mu k_2 & -k_1 & k_1 - \mu k_2 & \mu k_2 \\ -k_1 - k_2 & -k_1 & k_1 - k_2 & k_2 \\ \hline c_{0,A} & \alpha c_{0,A} & 0 & 0 \end{array}\right] \end{array}$$

Coloured species

$$\mathbf{\Omega}\big|_{\text{comprised of coloured species}} = \begin{array}{c} \begin{matrix} 'B' & 'C' & 'D' \end{matrix} \\ \left[\begin{array}{ccc} -\mu k_1 & \mu k_1 - \mu k_2 & \mu k_2 \\ -\mu k_1 & \mu k_1 - k_2 & k_2 \\ -k_1 & k_1 - \mu k_2 & \mu k_2 \\ -k_1 & k_1 - k_2 & k_2 \\ \hline \alpha c_{0,A} & 0 & 0 \end{array}\right] \end{array}$$

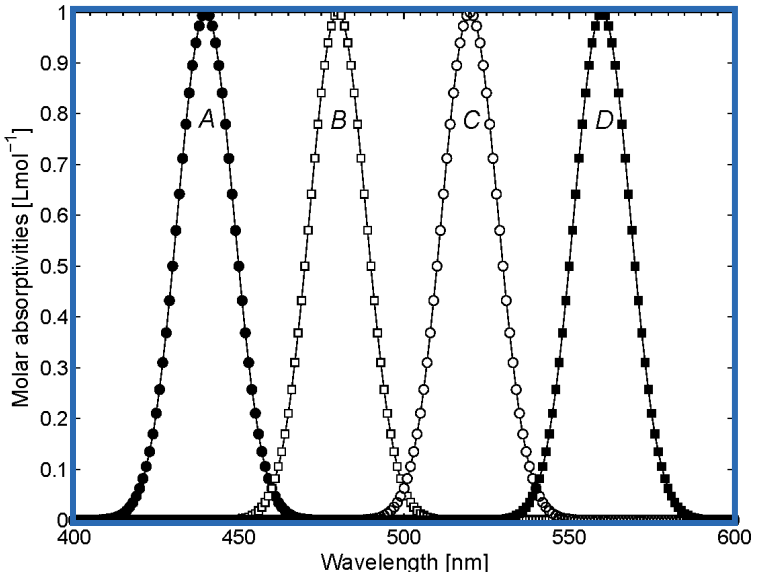
All species

$$\mathbf{\Delta}\ (3 \text{ x } 4) = \left(\mathbf{\Omega}\big|_{\text{comprised of coloured species}}\right)^{+} \mathbf{\Omega}\big|_{\text{comprised of all species}} = \begin{array}{c} \begin{matrix} A & B & C & D \end{matrix} \\ \left[\begin{array}{cccc} \alpha^{-1} & 1 & 0 & 0 \\ \alpha^{-1} - 1 & 0 & 1 & 0 \\ \alpha^{-1} - 2 & 0 & 0 & 1 \end{array}\right] \end{array} \begin{matrix} 'B' \\ 'C' \\ 'D' \end{matrix}$$

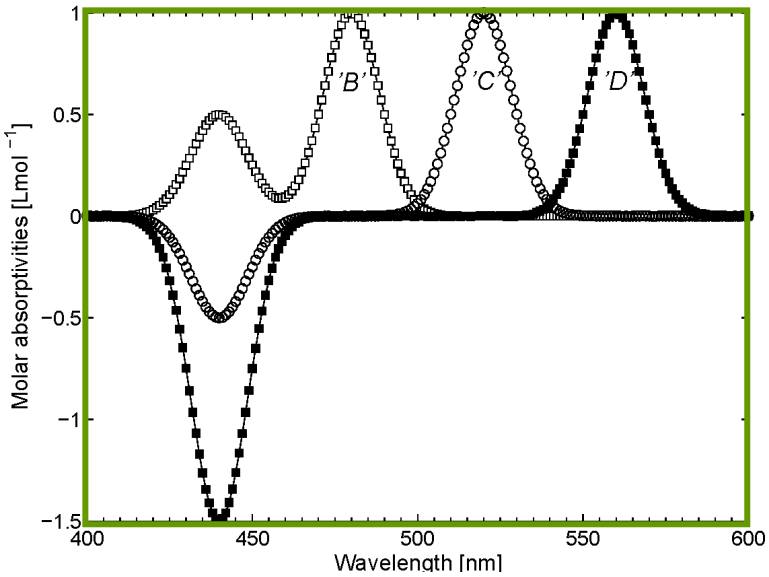
Coloured species

Example: spectral consequence of Strategy 1 (defining uncoloured species)

True: **A** (4 x *nw*)



Fitted: $\mathbf{A}_c$ (3 x *nw*)



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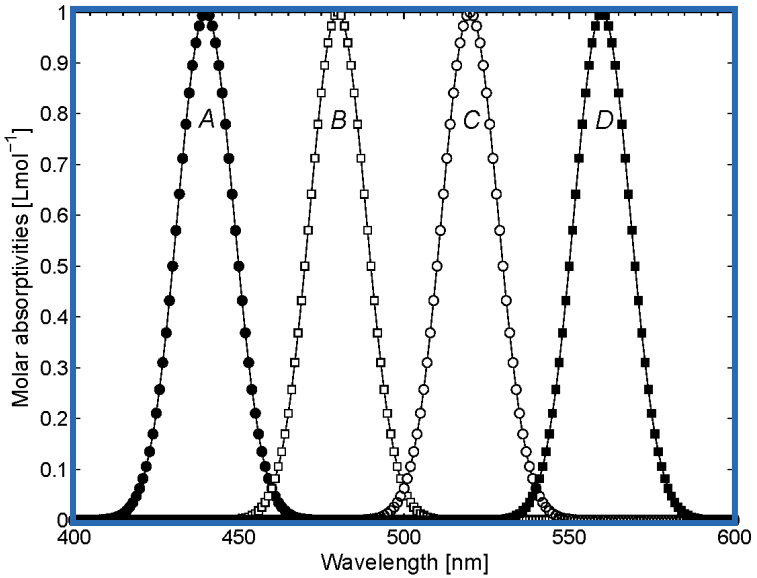
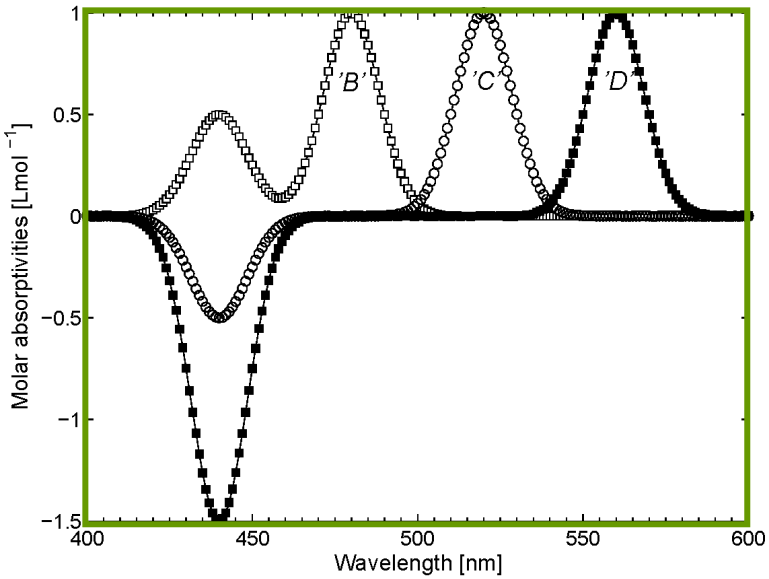


Fitted: $\mathbf{A}_c$ (3 x *nw*)



$$\begin{bmatrix} \mathbf{a}_{c\ 'B',:} \\ \mathbf{a}_{c\ 'C',:} \\ \mathbf{a}_{c\ 'D',:} \end{bmatrix} = \mathbf{\Delta}\ \mathbf{A} = \begin{bmatrix} \alpha^{-1} & 1 & 0 & 0 \\ \alpha^{-1}-1 & 0 & 1 & 0 \\ \alpha^{-1}-2 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \mathbf{a}_{A,:} \\ \mathbf{a}_{B,:} \\ \mathbf{a}_{C,:} \\ \mathbf{a}_{D,:} \end{bmatrix} = \begin{bmatrix} 0.5 \\ -0.5 \\ -1.5 \end{bmatrix} \mathbf{a}_{A,:} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \mathbf{a}_{B,:} + \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \mathbf{a}_{C,:} + \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \mathbf{a}_{D,:} \quad \text{when } \alpha = 2$$

Kinetic and spectral validation

- In kinetic hard-modelling, the validation of a kinetic mechanism is based on:

$$\mathbf{Y} = \mathbf{C}\,\mathbf{A}$$

  - **(C) The kinetic consistency** and the reproducibility of fitted kinetic parameters under different experimental conditions.
  - **(A) The spectral consistency** of fitted pure component spectra compared to independently measured ones.

Kinetic and spectral validation

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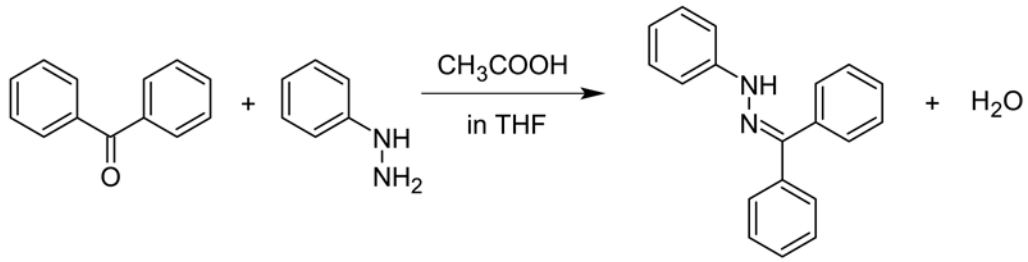
  - **(A) The spectral consistency** of fitted pure component spectra compared to independently measured ones.

The spectral validation is facilitated, when Strategy 1 is used, as linear combinations of true pure component spectra can now be explained (**Δ**) !

$$\mathbf{\Delta}\ (ns - nu \times ns) = \mathbf{C}_c^{+}\mathbf{C} = \left(\mathbf{\Omega}\big|_{\substack{\text{comprised of}\\ \text{coloured species}}}\right)^{+} \mathbf{\Omega}\big|_{\substack{\text{comprised of}\\ \text{all species}}}$$

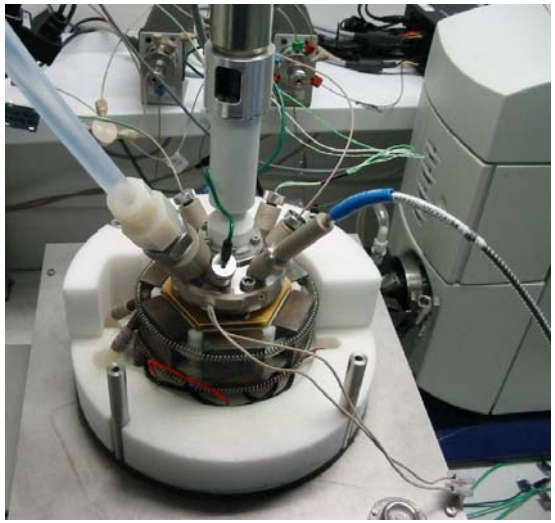
Experimental reaction

Overall reaction:



Kinetic mechanism:

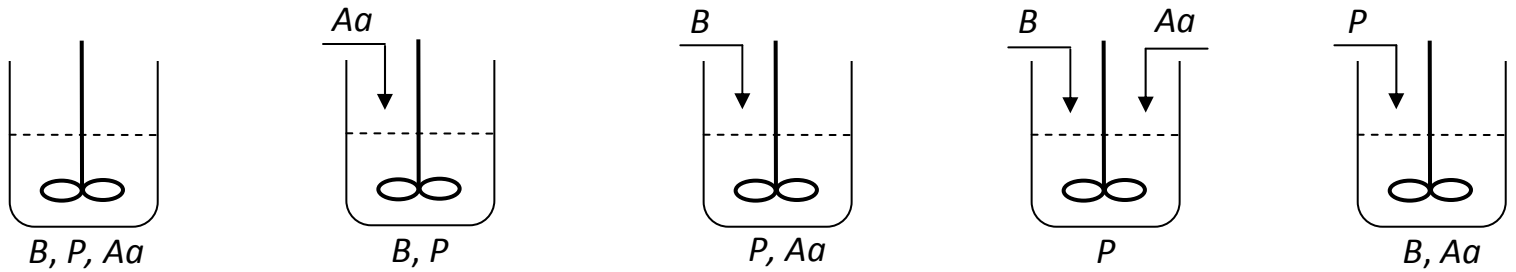
$$B + P + Aa \xrightarrow{k} BP + Aa$$



Reactor: CRC.v4 with FT-IR and UV-vis

Experimental conditions:

25°C, followed in mid-IR (1200–1650 cm^{-1}) and UV-vis (240–400 nm).



Kinetic validation of the model

Experimental conditions	Strategy [a]	Mid-IR		UV-vis	
		k [b]	Published k [b]	k [b]	Published k [b]
Batch conditions	only (1)	**1.58** (± 0.02)	**1.74** (± 0.05) [c]	**1.63** (± 0.02)	**1.77** (± 0.03) [c]
	(1) + (2)	**1.58** (± 0.02)	**1.40** [d]	**1.63** (± 0.02)	**1.51** [d]
	(1) + (4)	**1.57** (± 0.02)		**1.62** (± 0.02)	
Dosing *Aa*	(1) + (3)	**1.60** (± 0.04)		**1.65** (± 0.04)	
Dosing *B*	(1) + (3)	**1.60** (± 0.03)		**1.64** (± 0.03)	
	(1) + (3)	**1.55** (± 0.02)		**1.57** (± 0.02)	
Dosing *B* + *Aa*	only (3)	**1.59** (± 0.06)		**1.64** (± 0.06)	
Dosing *P*	(1) + (3)	**1.62** (± 0.06)		**1.67** (± 0.06)	

a) (1): defining uncoloured species, (2): providing known pure spectra, (3): dosing, (4): second order global analysis
b) in $L^2 \cdot mol^{-2} \cdot s^{-1} \times 10^{-4}$
c) Billeter et al., Chemom. Intell. Lab. Syst., 93 (2008), 120-131
c) Carvalho et al., Talanta, 68 (2006), 1190-1200

$$B + P + Aa \xrightarrow{k_1} BP + Aa$$

Kinetic validation of the model

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		k [b]	Published k [b]	k [b]	Published k [b]
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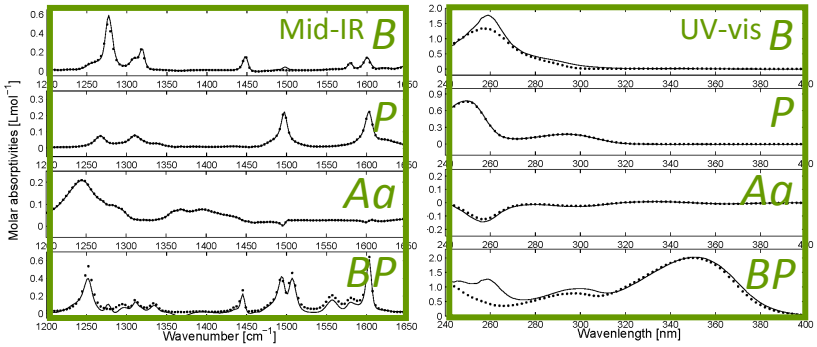
$$B + P + Aa \xrightarrow{k_1} BP + Aa$$

The model is kinetically validated

Spectral validation of the model

$$B + P + Aa \xrightarrow{k_1} BP + Aa$$

Strategy (3): dosing



Species *B* and *Aa* dosed

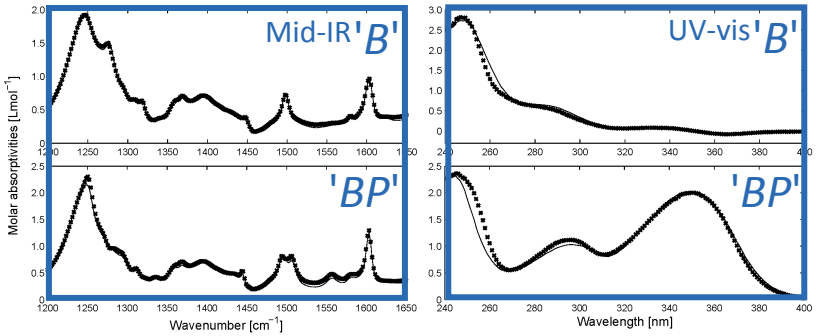
Full spectral resolution

—— Fitted spectra ●●● Measured spectra **XXX** Predicted spectra

Spectral validation of the model

$$B + P + Aa \xrightarrow{k_1} BP + Aa$$

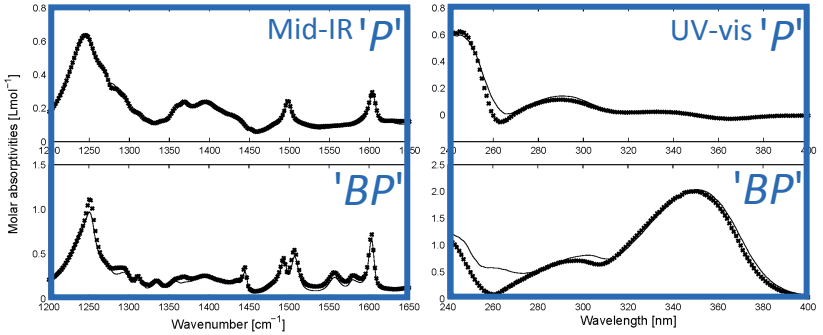
Strategy (1): uncoloured species



Species *P* and *Aa* set uncoloured

Partial spectral resolution

Strategy (1)+(2): provided known spectrum



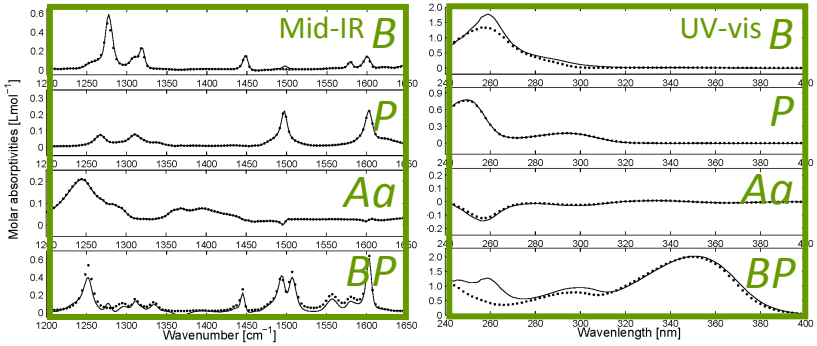
Pure spectrum of *B* provided

Aa set uncoloured

Partial spectral resolution

The model can be spectroscopically validated **with** and **without** rank deficiency!

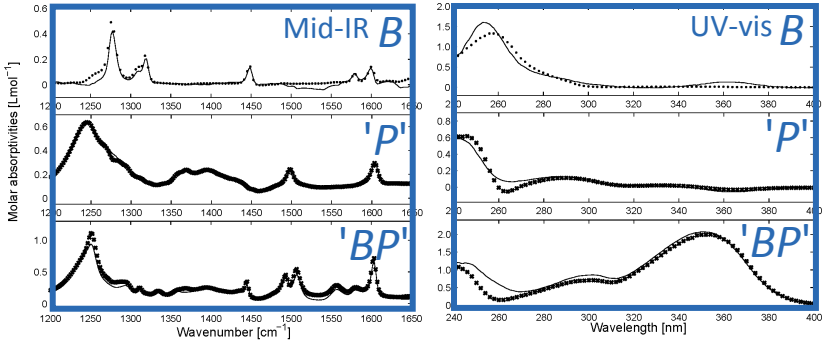
Strategy (3): dosing



Species *B* and *Aa* dosed

Full spectral resolution

Strategy (1)+(4): second order global analysis



Initial concentration of *B* varied, *Aa* set uncoloured

Partial spectral resolution

—— Fitted spectra ●●● Measured spectra **xxx** Predicted spectra

Conclusion: general methods

- **Chemometrics**
  - **Extraction** of information from complex multivariate signals
  - **Identification** of significant contributions (SVD, PCA)
  - **Support** for the elaboration of models
- **Kinetic hard-modelling of spectroscopic data**
  - **Determination** of kinetic parameters (e.g. rate constants)
  - **Assessment** of kinetic models by comparing fitted and independently measured pure component spectra (direct fitting)
  - **Calibration-free** method (implicit calibration)

Conclusion: specific methods in hard-modelling

- **Method of error propagation**
  - **Determination** of reliable uncertainties in the fitted kinetic parameters
  - **Prediction** of the experimental conditions minimising the uncertainties
- **Method for prediction of rank deficiencies and spectral validation**
  - **Design of rank deficient experiments** when Strategies 1 – 4 have to be used
  - **Interpretation** of the fitted pure component spectra when Strategy 1 (defining uncoloured species) is used
  - **Spectral validation** of rank deficient kinetic models

Acknowledgements

Group of Safety and Environmental Technology

Prof. Dr. K. Hungerbühler — **Head of the group**

Subgroup of Reaction Analysis

Dr. Y.-M. Neuhold	**Senior scientist, subgroup leader**
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Subgroup of Reaction Process Design and Optimisation

Dr. S. Papadokonstantakis — Senior scientist, subgroup leader

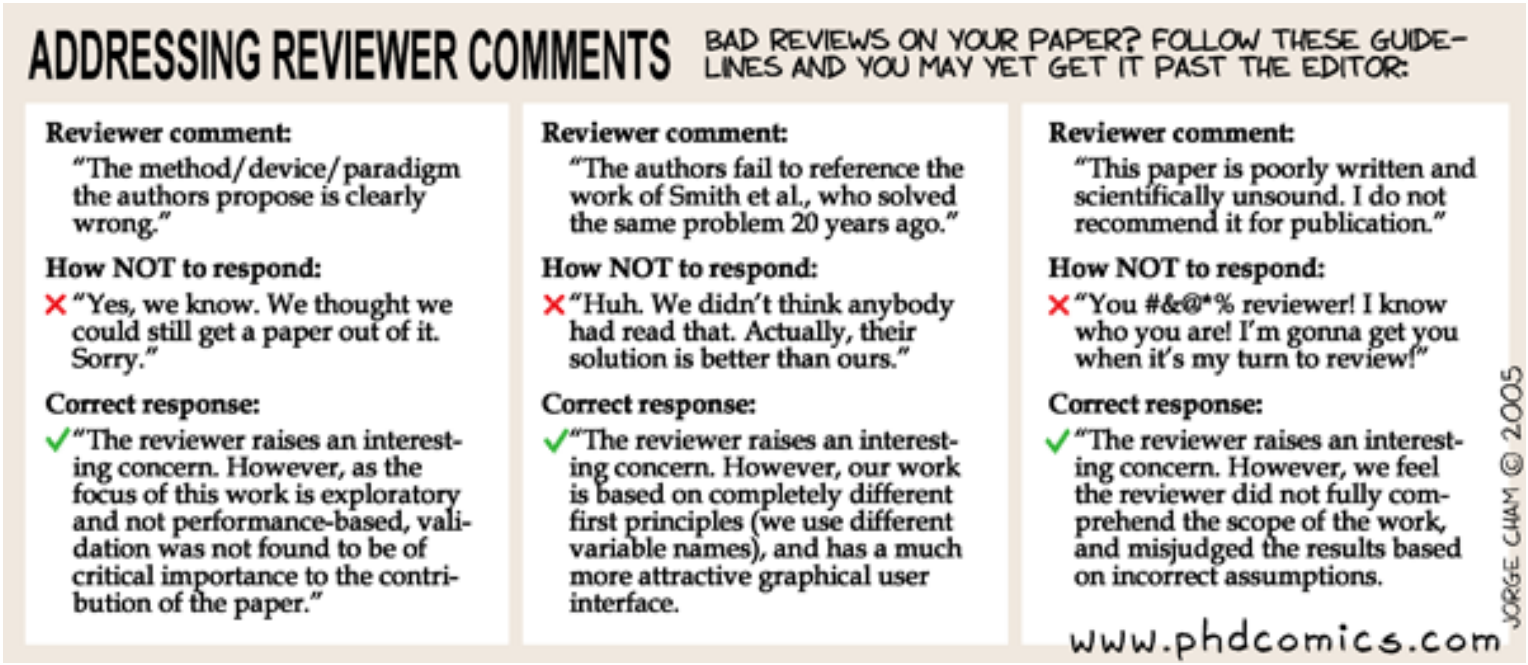
Subgroup of Separation Technologies

Dr. L. Simon — Senior scientist, subgroup leader

and all members of the group of Safety and Environmental Technology

Thank you for your attention

Any question or comment?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BAD REVIEWS ON YOUR PAPER? FOLLOW THESE GUIDELINES AND YOU MAY YET GET IT PAST THE EDITOR:
Reviewer comment:
"The method/device/paradigm the authors propose is clearly wrong."
How NOT to respond:
✗ "Yes, we know. We thought we could still get a paper out of it. Sorry."
Correct response:
✓ "The reviewer raises an interesting concern. However, as the focus of this work is exploratory and not performance-based, validation was not found to be of critical importance to the contribution of the paper."
Reviewer comment:
"The authors fail to reference the work of Smith et al., who solved the same problem 20 years ago."
How NOT to respond:
✗ "Huh. We didn't think anybody had read that. Actually, their solution is better than ours."
Correct response:
✓ "The reviewer raises an interesting concern. However, our work is based on completely different first principles (we use different variable names), and has a much more attractive graphical user interface.
Reviewer comment:
"This paper is poorly written and scientifically unsound. I do not recommend it for publication."
How NOT to respond:
✗ "You #&@*% reviewer! I know who you are! I'm gonna get you when it's my turn to review!"
Correct response:
✓ "The reviewer raises an interesting concern. However, we feel the reviewer did not fully comprehend the scope of the work, and misjudged the results based on incorrect assumptions.
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