Kinetic Modeling of Batch Slurry Reactions

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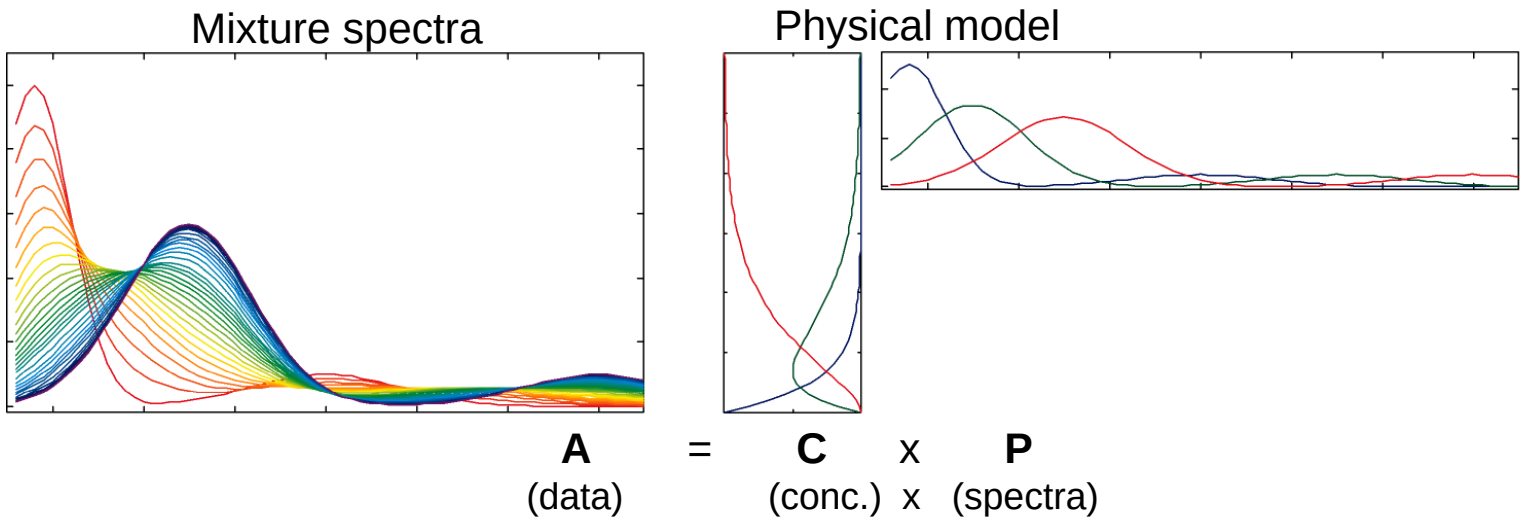
Introduction to self-modeling curve resolution (SMCR)

- SMCR analysis of mixture spectra begins with a PCA model
- Iterative least-squares fitting process used to estimate non-negative, unimodal composition profiles and non-negative spectra of the pure components
- No referee measurements or other prior information is needed.

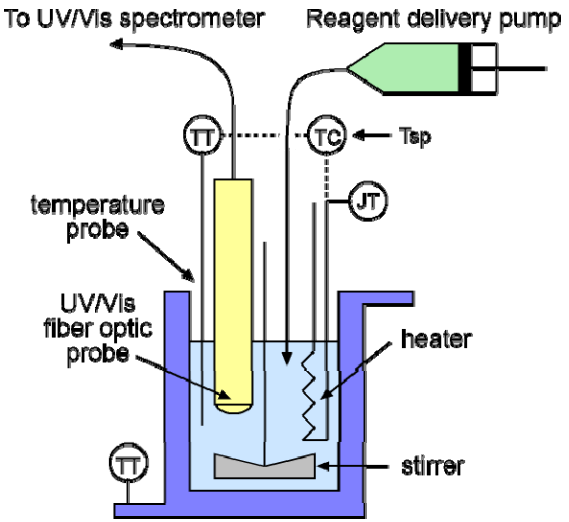


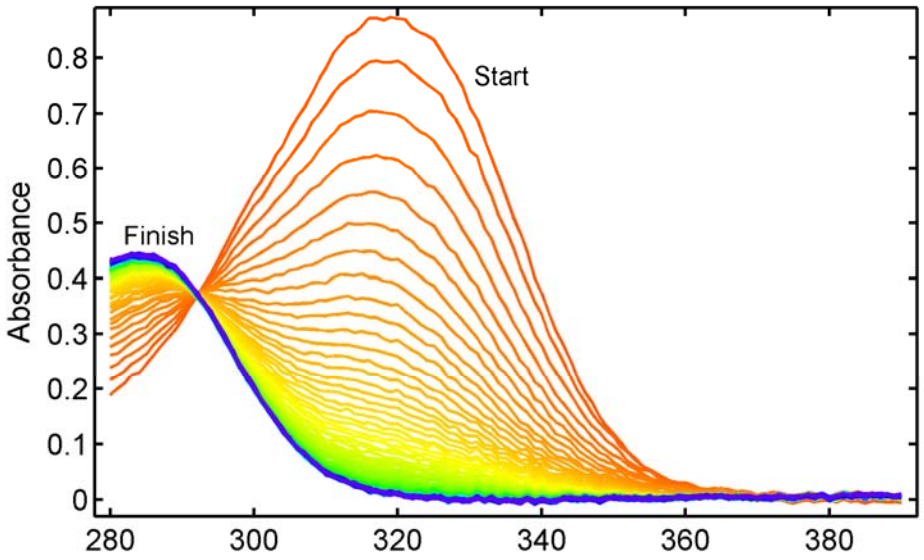
Basic SMCR algorithm

- Initial solution or "guess" is selected
  - Initial estimate of conc. profiles, $\mathbf{C}_o$: Needle search, Evolving factor analysis
  - Initial estimate of pure spectra, $\mathbf{P}_o$
  - Initial starting points ($\mathbf{C}_o$ or $\mathbf{P}_o$), seldom obey constraints
- Alternating least-squares steps used to fit the initial unconstrained solution producing better "constrained" estimates.
  - Given some estimate of **C**, find **P** such that **P** minimizes $||\mathbf{A} - \mathbf{C}\mathbf{P}^T||$ subject to constraints on **P** such as $\mathbf{P} > 0$, etc.
  - Given some estimate of **P**, find **C** such that **C** minimizes $||\mathbf{A} - \mathbf{C}\mathbf{P}^T||$ subject to constraints on **C** such as $\mathbf{C} > 0$, etc.

UV/Vis fiber-optic batch monitoring

- Reaction of salicylic acid (SA) with acetic anhydride (AA) to form acetylsalicylic acid (ASA) is exothermic
- At high conc., small changes in temperature can cause significant fluctuation in spectroscopic response
- PCA of the SA – AA reaction mixture spectra shows 3 factors instead of the expected 2 factors.



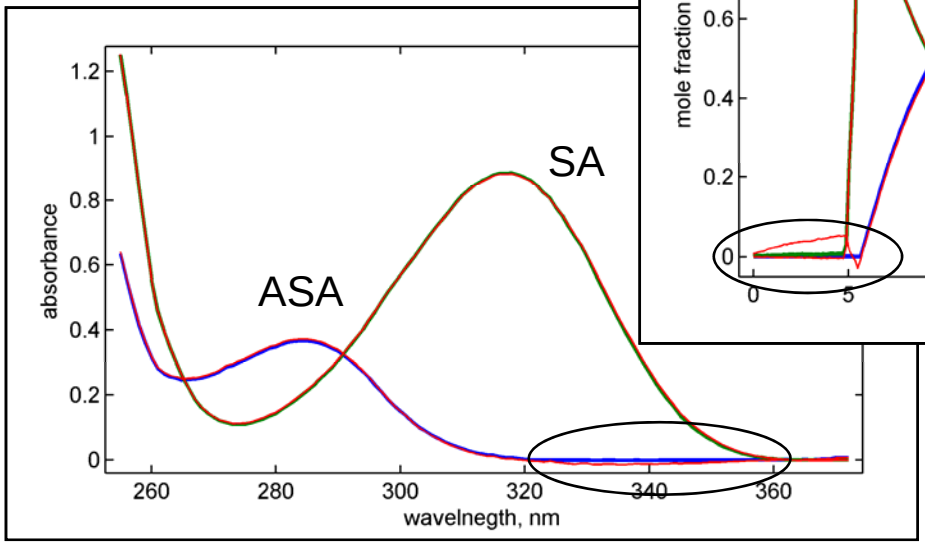


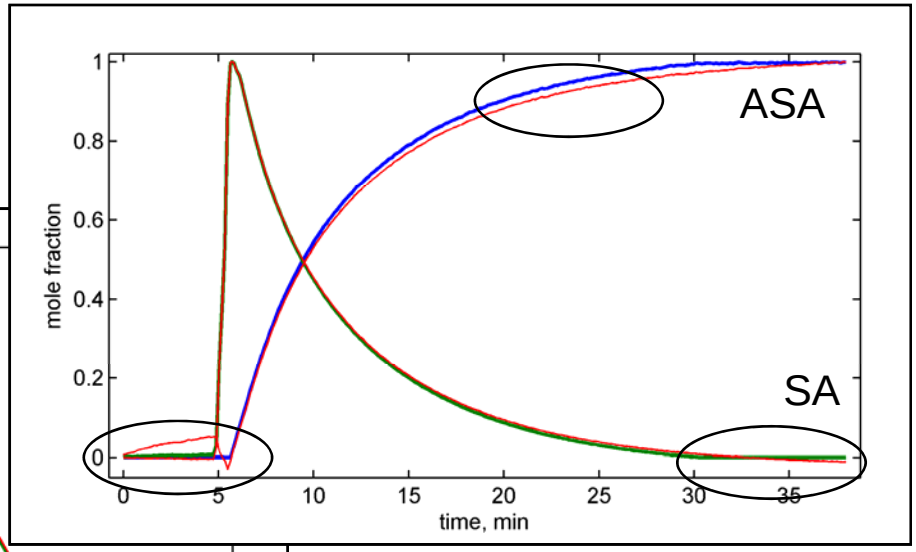
Example of constrained vs. unconstrained solution

Unconstrained fit: SSQ = 99.98% (red curves)

Constrained fit: SSQ = 99.91%

A small difference in SSQ can mean a large difference in shape





An *Implied* SMCR Research hypothesis

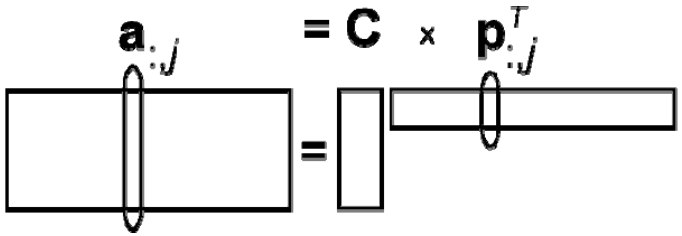
- "There exists an unconstrained bilinear model with unimodal, non-negative pure component concentration profiles and pure component non-negative spectra that fits the data matrix of measurements obtained from the evolving system".
  - Hypothesis is tested by iteratively fitting a *constrained model* until convergence.

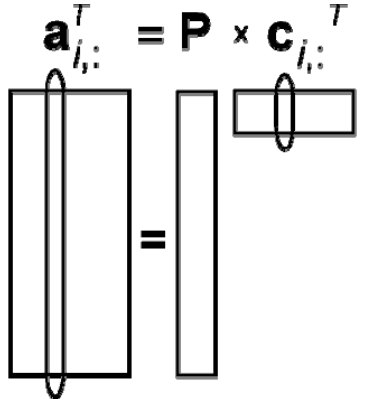
SMCR with least-squares penalty constraints

- ALS steps performed using row-wise estimation of the parameter matrix **C** or **P**
  - Given **A** and **C**, estimate constrained solutions $\mathbf{p}_j$ for each column in **A**
  - Given **A** and **P**, estimate constrained solutions $\mathbf{c}_i$ for each row in **A**
- Row-wise procedure transforms the problem to the form:

$$\mathbf{y} = \mathbf{Xb} \text{ subject to } b_{ij} = g_i$$

- **y** is augmented with **g** (the constraint goal or target value)
- **X** is augmented with **H** (1's and 0's showing location of constraints[4]
- Penalty weighting factor, λ, adjusted to give soft or hard constraints

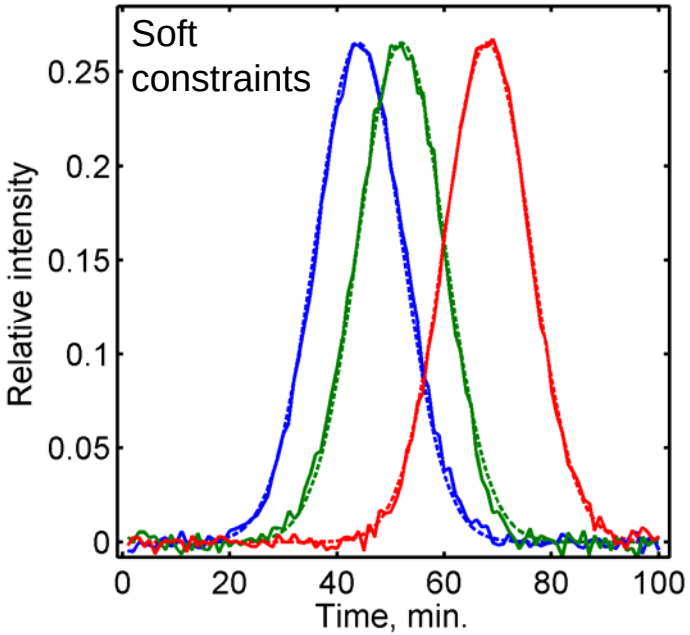


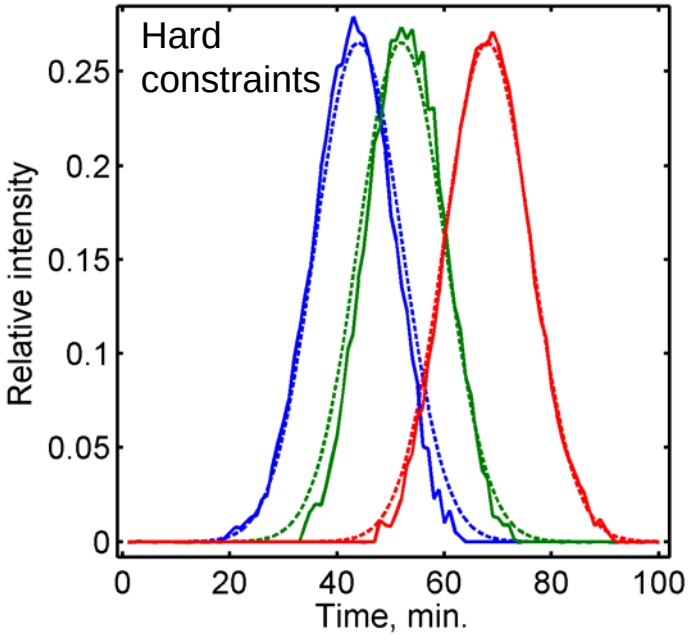


$$\begin{bmatrix} \mathbf{y} \\ \lambda\mathbf{g} \end{bmatrix} \cong \begin{bmatrix} \mathbf{X} \\ \lambda\mathbf{H} \end{bmatrix} \mathbf{b}$$

Soft vs. hard constraints

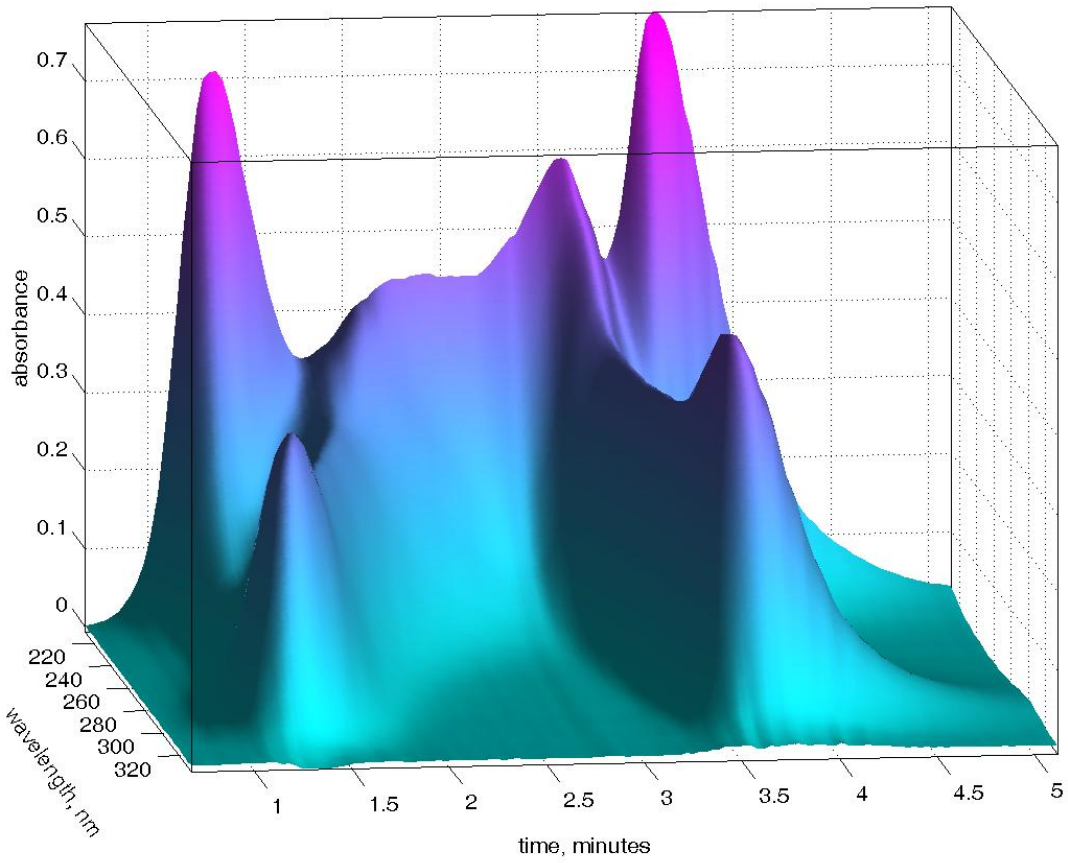
- P-ALS resolution of simulated chromatography data shows the advantage of using “soft” non-negativity constraints vs. “hard” constraints.
- Average error in peak areas: Soft: 1.9% Hard: 12.6%





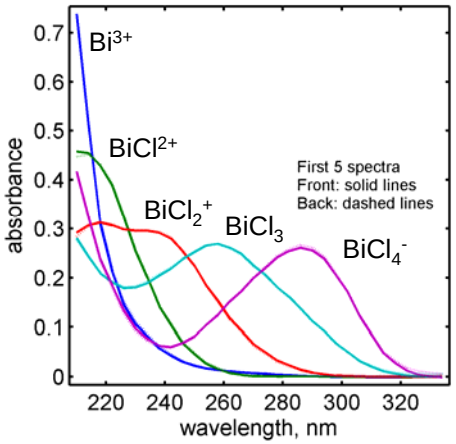
Flow injection example – resolution of equilibrium species

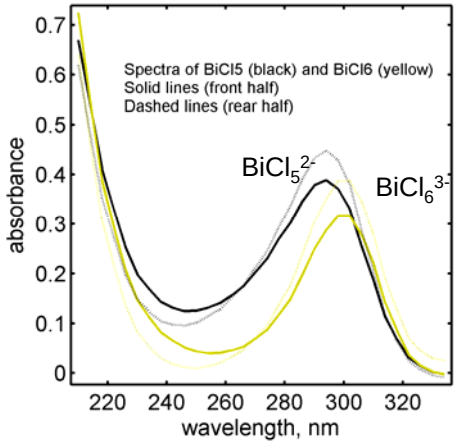
- Bolus of $Bi(ClO_4)_3$ injected into a flowing stream of HCl,
- Mixing occurs in the from and tail of the bolus
- Species observed: Bi^{3+}, $BiCl^{2+}$, $BiCl_2^{+}$, $BiCl_3$, $BiCl_4^{-}$, $BiCl_5^{2-}$, and $BiCl_6^{3-}$
- Spectral profiles measured with HPLC diode array detector

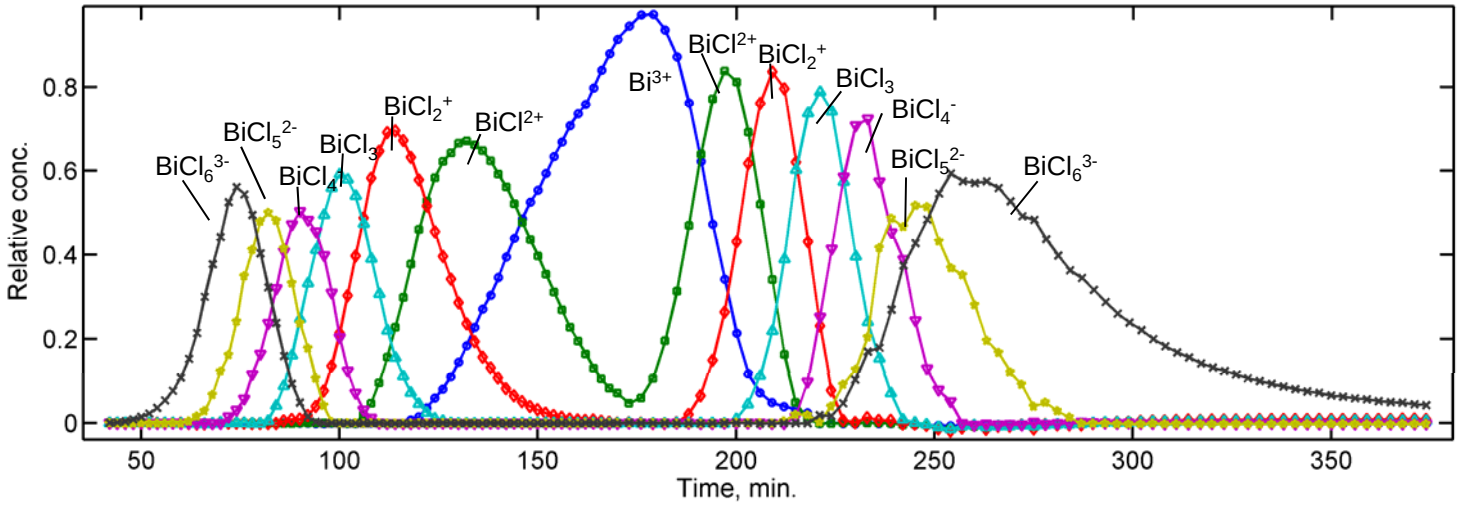


Use of reference spectra in soft equality constraints

- Pure component spectra estimated from front half of bolus were used in equality constraints to improve estimates in the second half







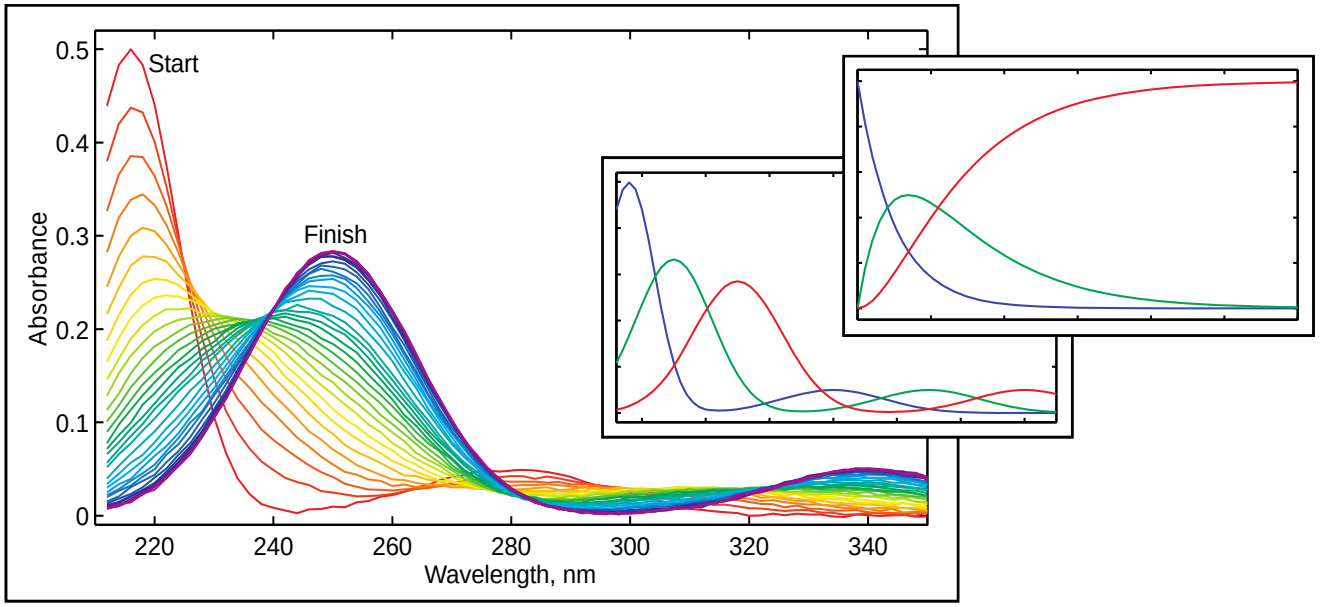
The range of feasible solutions in SMCR applications

- Most curve resolution problems have a range of feasible solutions that obey constraints
- Analytical solutions for the boundary problems were published in the mid 1980's for 2 component and 3 component mixtures[2,3].
- Published solutions were difficult to derive, complicated and hard to understand.
- Conceptually simple method for finding min/max boundaries was developed using the Matlab Optimization Toolbox.

2. Borgen, O.S.,Kowalski, B.R., *An Extenssion of the Multivariate Component-Resolution Method to Three Components, Anal. Chim. Acta.,* 174, 1-26, (1985).
3. Borgen, O.S., Davidsen, N., Mingyang, Z., Oyen, O., *The Multivariate N-Component Resolution problem with Minimum Assumptions, Mikrochim. Acta,* 2, 63-73, (1986)

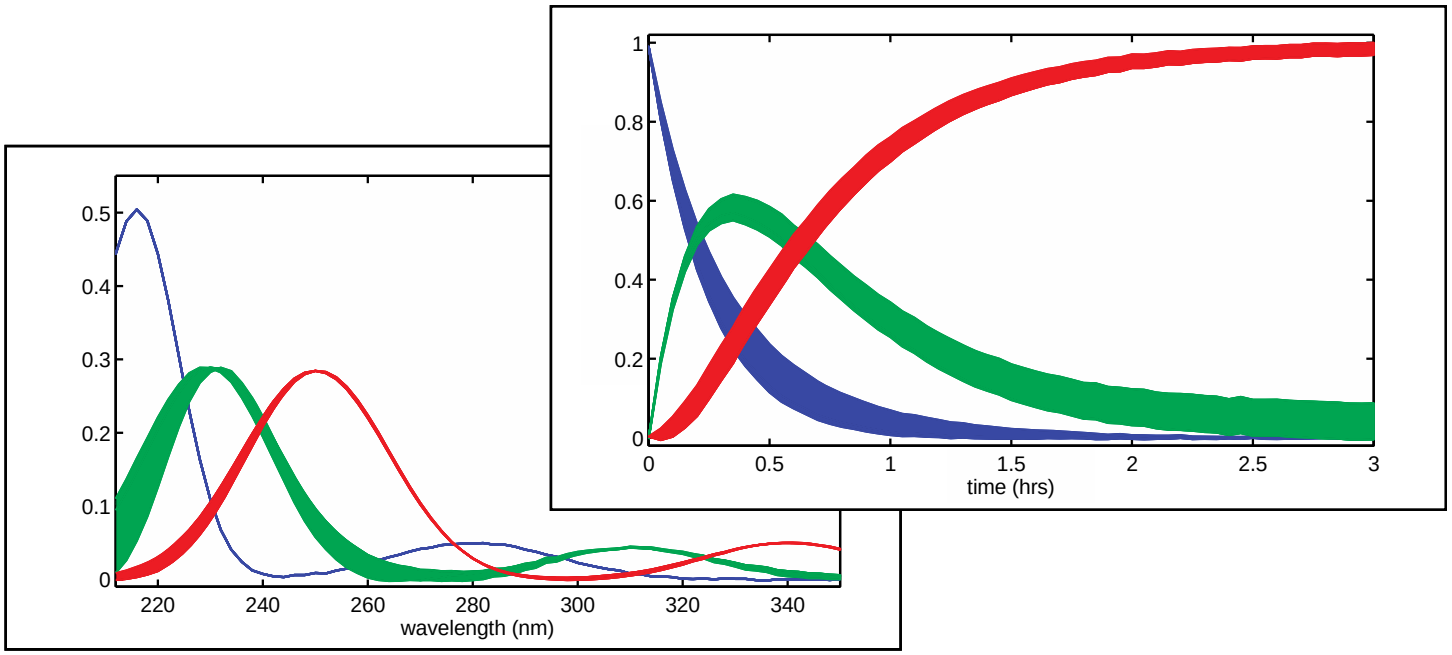
Criteria for uniqueness in SMCR frequently not met in batch process profiles

- Rank one sub-windows frequently may not be present
- Zero concentration sub-windows frequently may not be present



- The first spectrum may be pure starting material; however, at intermediate times and at the reaction end-point a mixture of starting material, intermediate(s) and product(s) may be present (see simulated profiles and mixture spectra, above)

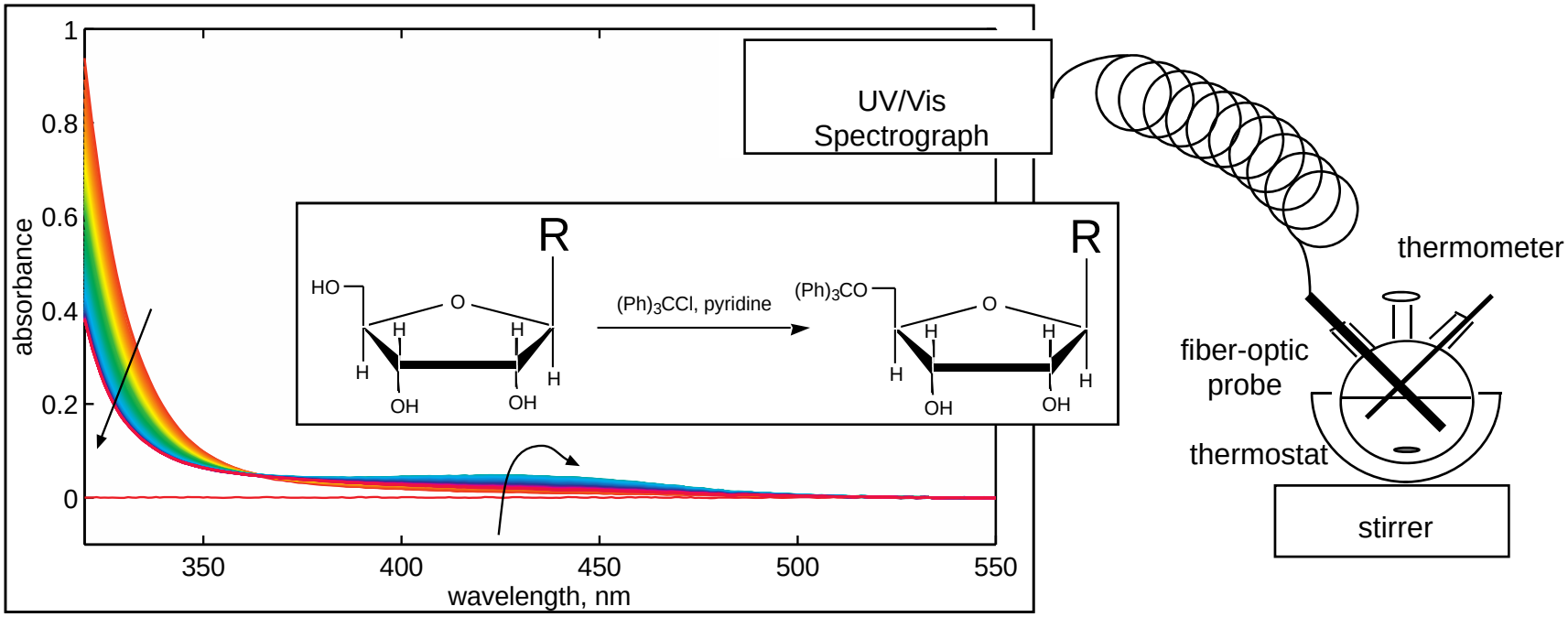
Min/max boundaries for SMCR results with non-negative constraints



Feasible bands are shown for SMCR analysis of simulated data. The starting material spectrum (blue) is held constant. Lack of zero-component regions leads to wide feasible bands in the curves for the intermediate (green) and product (red).

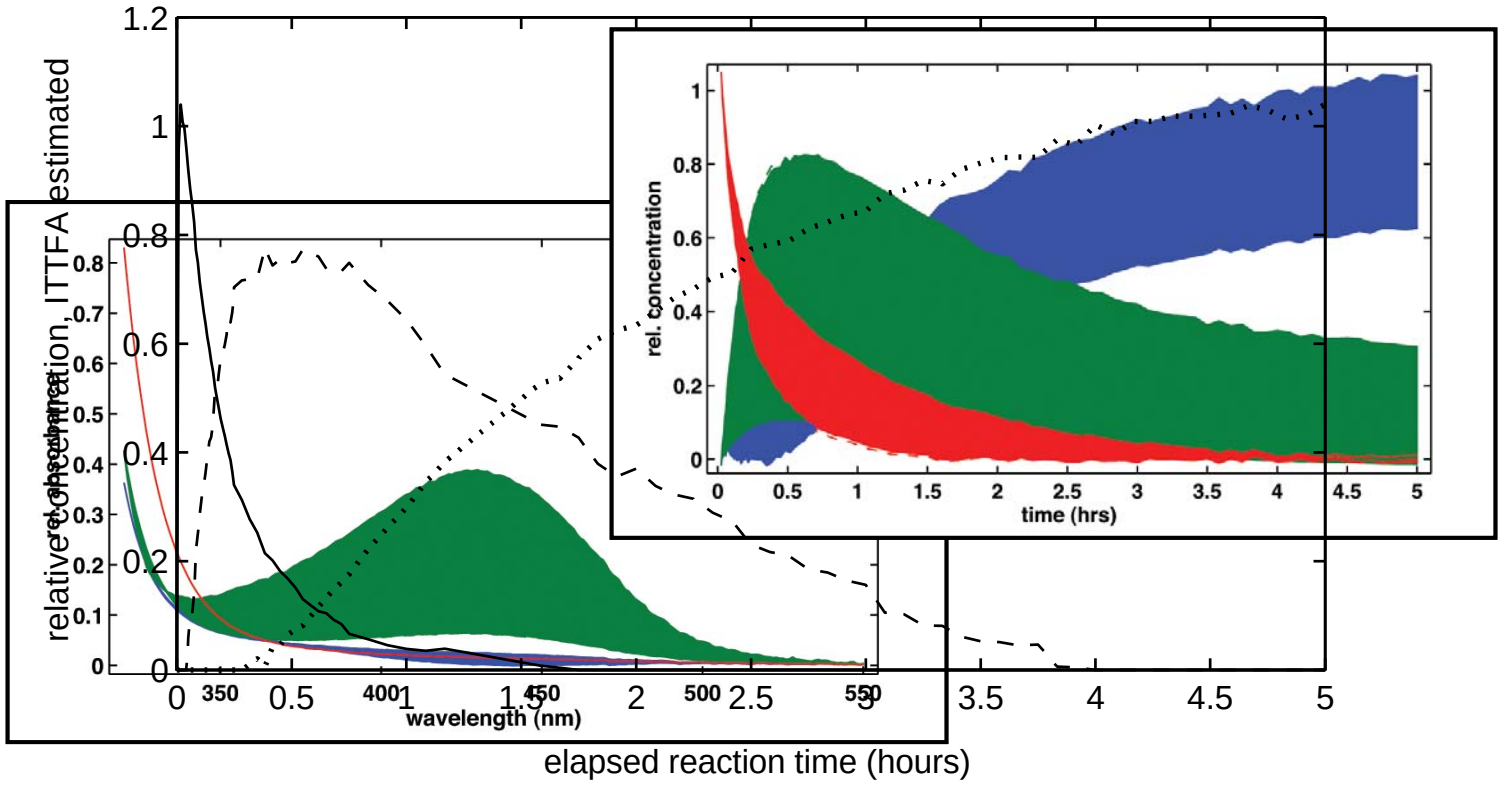
UV/vis measurement of a tritylation reaction

- Trityl chloride
  - This reaction forms a solvated reactive intermediate. Progress of the reaction can be tracked with UV/vis measurements.



The SMCR results look great, but…

are they accurate estimates of REAL profiles?



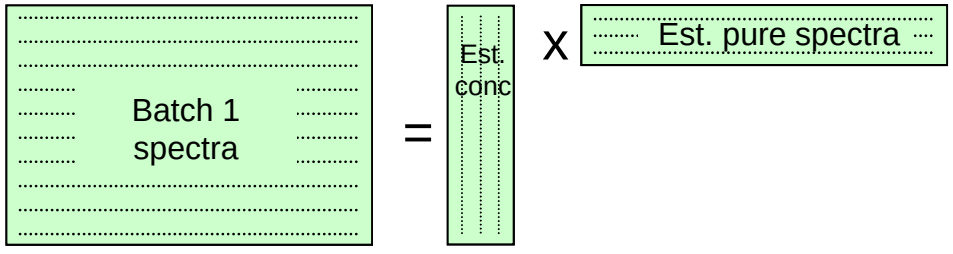
Lack of full selectivity in the measurements means that ranges of feasible solutions exist that meet non-negativity constraints. Results outside the boundaries violate non-negativity constraints, e.g., estimated composition profiles and/or spectral profiles will have one or more negative regions.

Isothermal model with flow-in reagents

$$r_1 = k_1 C_{SA} C_{AA}$$
$$r_2 = k_2 C_I$$
$$r_3 = k_3 C_W C_{AA}$$
$$r_4 = k_4 C_{ASA} C_{AA}$$

$$\frac{dC_{AA}}{dt} = -r_1 - r_3 - r_4 + \frac{C_{AAin} - C_{AA}}{V} F_{AA}$$
$$\frac{dC_I}{dt} = r_1 - r_2 - \frac{C_I}{V} F_{AA}$$
$$\frac{dC_{SA}}{dt} = -r_1 - \frac{C_{SA}}{V} F_{AA}$$

$$\frac{dC_W}{dt} = -r_3 - \frac{C_W}{V} F_{AA}$$
$$\frac{dC_{ASAA}}{dt} = r_4 - \frac{C_{ASAA}}{V} F_{AA}$$
$$\frac{dC_{HA}}{dt} = r_2 + 2r_3 + r_4 - \frac{C_{HA}}{V} F_{AA}$$
$$\frac{dV}{dt} = F_{AA}$$



Overall project goal – develop monitoring technique for batch processes involving slurries

- Extend kinetic modeling approach to a prototypical slurry reaction
- Make optical measurements in light-scattering medium
- Modify kinetic models to include:
  - Dissolution of starting material A & flow-in of reagent B
  - Nucleation and crystallization of product, P
- Develop empirical models for dissolution, nucleation and crystallization
- Kinetic models with reagent flow-in impose strict mass balance

Slurries

- A dynamic system of crystalline material suspended in a liquid medium
- Common Examples
  - Production of pharmaceuticals
  - Production of fine chemicals
  - Biological absorption of pharmaceuticals
- Dynamic processes
  - Dissolution of starting materials
  - Nucleation and crystal growth of products

- Crystal products
  - Often desire specific properties
    - Size distribution, lattice form, etc.
  - Relative rates determine properties
  - Factors governing process rates
    - Temperature
    - Rate of stirring
    - Crystal surface area
    - Attrition
    - Agglomeration

Challenges – Optical Methods in Slurries

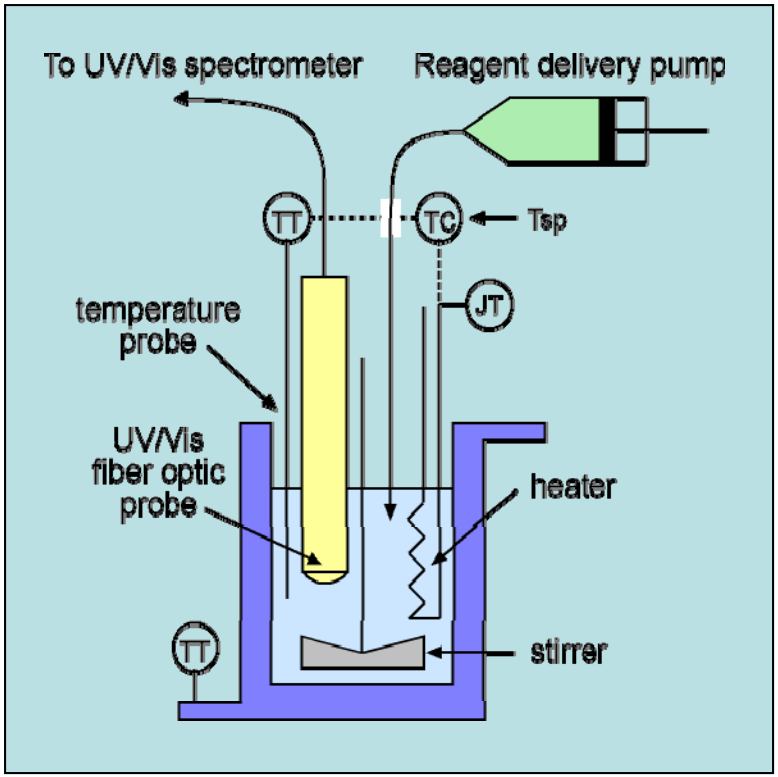
- Linear response is needed for kinetic modeling and self-modeling curve resolution
- Reflectance measurements include both light scattering and light absorption signals
  - Mathematical resolution of the two is needed to estimate solid fraction and dissolved fraction
  - Effective path length is dependent on
    - Number density of light scattering particles
    - Particle size distribution
    - Wavelength
- ATR measurements for light absorption (dissolved fraction)

Experimental demonstration

- Reaction of Salicylic Acid to form Acetylsalicylic Acid (Aspirin)
  - Simple, well understood reaction to test modeling ability
- Process includes:
  - Dissolution
  - 4 Primary Reactions
  - Crystallization

Laboratory scale batch reactors

Batch Titration Reactor



Reaction Mechanisms

Catalyzed Reaction

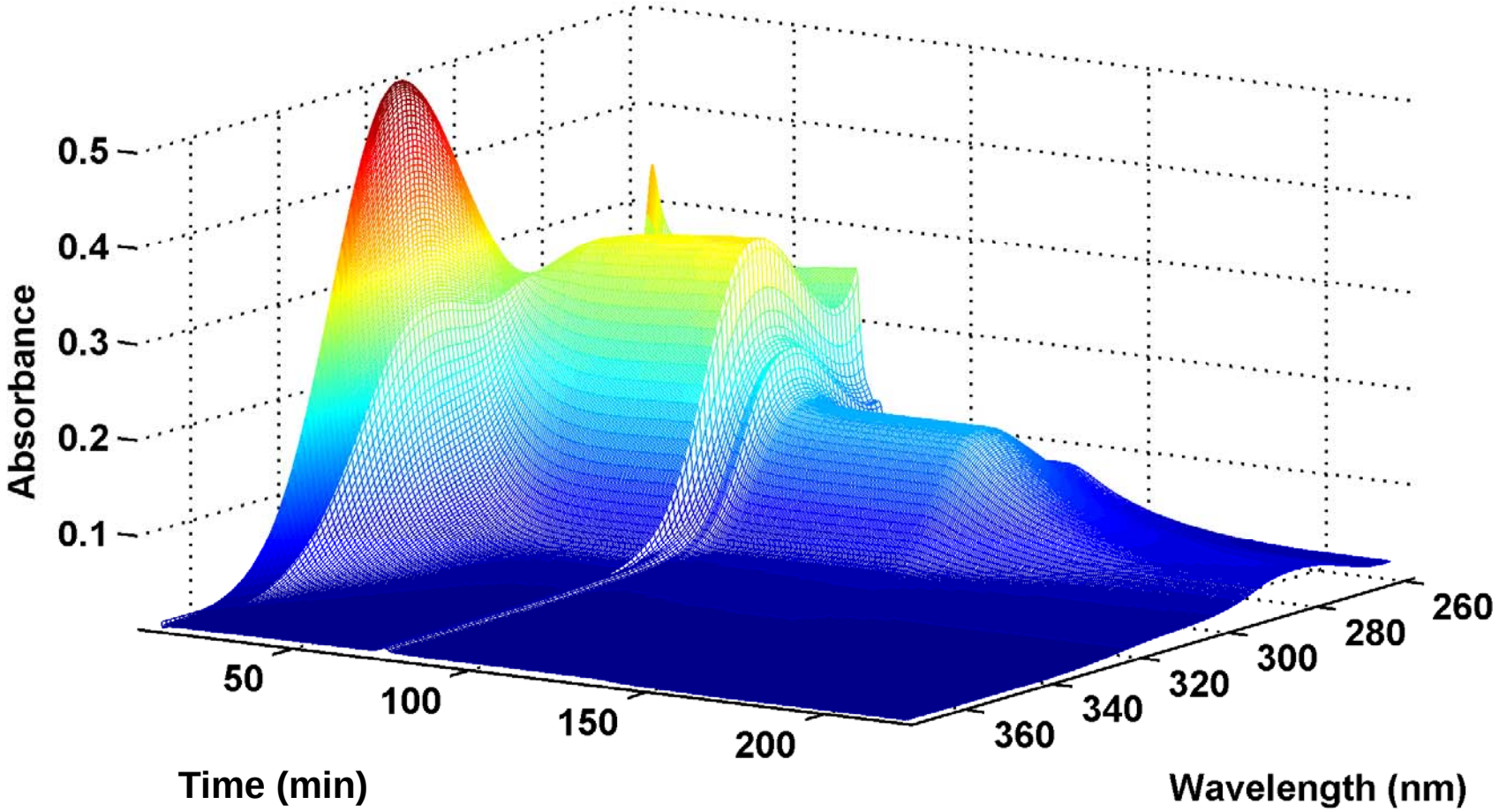
$$SA + AA \xrightarrow{k_1} ASA + HA$$

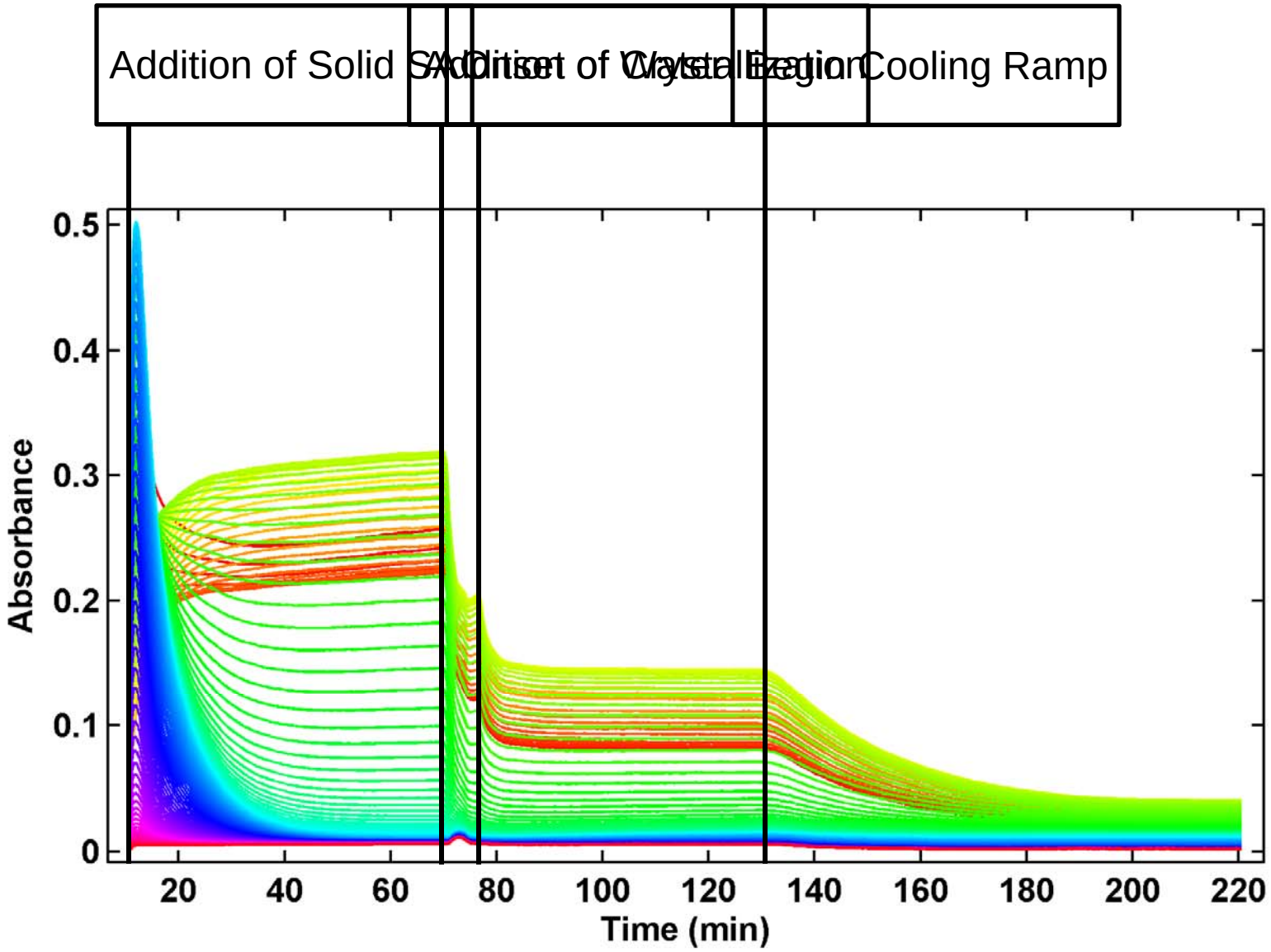
$$ASA + AA \xrightarrow{k_2} ASAA + HA$$

Water Addition

$$ASAA + H_2O \xrightarrow{k_3} ASA + HA$$

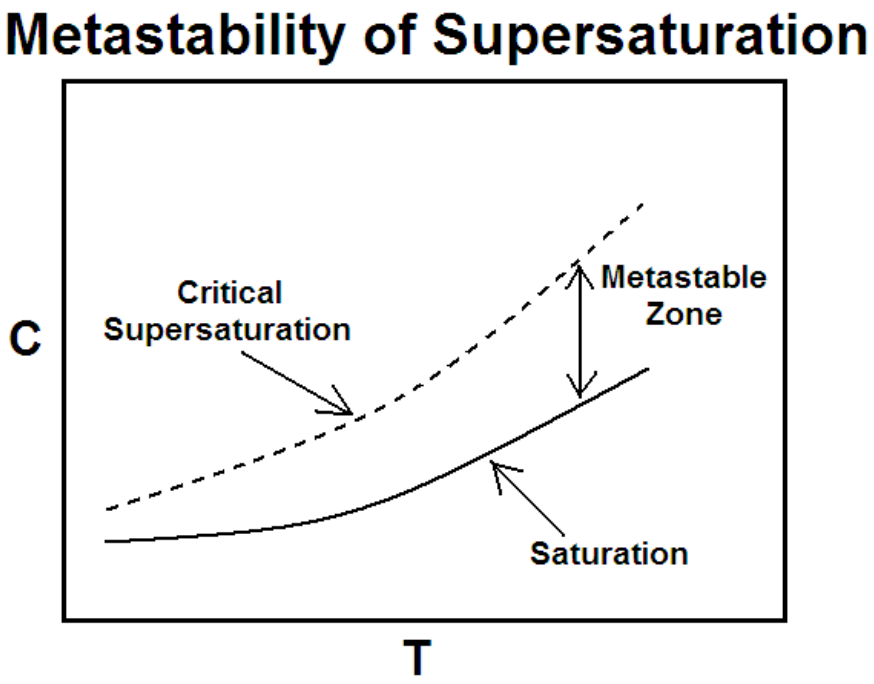
$$AA + H_2O \xrightarrow{k_4} 2HA$$


Absorbance
0.5
0.4
0.3
0.2
0.1
50
100
150
200
Time (min)
260
280
300
320
340
360
Wavelength (nm)


Addition of Solid
Addition of Water
Crystallization
Cooling Ramp
Absorbance
0.5
0.4
0.3
0.2
0.1
0
20
40
60
80
100
120
140
160
180
200
220
Time (min)

Saturation and Supersaturation

- Considered relative to equilibrium solubility
- Super-saturation
  - "Driving force" of nucleation and crystal growth
  - Metastable
  - Generated by
    - Cooling
    - Anti-solvent addition
    - Solvent evaporation



Modeling Dissolution/Growth of Solid

- High Level of Theory

$$G = \frac{dL}{dt} = \frac{\Phi_s M_s k_c}{3 d_s \Phi_v} \eta_r (C - C^*)^j$$

- With simplifying assumptions

$$G = k_g (c - c_{sat})^g \qquad D = k_d (c_{sat} - c)^d$$

Blandin, A.; Mangin, D.; Nallet, V.; Klein, J.; Bossoutrot, J. *Chemical Engineering Journal*, **2001**, 81, 91-100

Rate Laws

$$r_1 = k_1[\mathrm{SA}][\mathrm{AA}]$$

$$r_2 = k_2[\mathrm{ASA}][\mathrm{AA}]$$

$$r_3 = k_3[\mathrm{ASAA}][\mathrm{H_2O}]$$

$$r_4 = k_4[\mathrm{AA}][\mathrm{H_2O}]$$

$$r_d = k_d([\mathrm{SA}]_{sat} - [\mathrm{SA}])^{n_1}$$

$$r_c = k_c([\mathrm{ASA}] - [\mathrm{ASA}]_{sat})^{n_2}$$

Differential Equations

$$\frac{d[\mathrm{SA}]_{\mathrm{solid}}}{dt} = -r_d$$

$$\frac{d[\mathrm{SA}]}{dt} = r_d - r_1 - \frac{dV}{dt}\frac{[\mathrm{SA}]}{V}$$

$$\frac{d[\mathrm{AA}]}{dt} = -r_1 - r_2 - r_4 - \frac{dV}{dt}\frac{[\mathrm{AA}]}{V}$$

$$\frac{d[\mathrm{HA}]}{dt} = r_1 + r_2 + r_3 + r_4 - \frac{dV}{dt}\frac{[\mathrm{HA}]}{V}$$

$$\frac{d[\mathrm{ASAA}]}{dt} = r_2 - \frac{dV}{dt}\frac{[\mathrm{ASAA}]}{V}$$

$$\frac{d[\mathrm{ASA}]}{dt} = r_1 - r_2 + r_3 - r_c - \frac{dV}{dt}\frac{[\mathrm{ASA}]}{V}$$

$$\frac{d[\mathrm{H_2O}]}{dt} = -r_3 - r_4 + f\frac{[\mathrm{H_2O}]_{in}}{V} - \frac{dV}{dt}\frac{[\mathrm{H_2O}]}{V}$$

$$\frac{d[\mathrm{ASA}]_{\mathrm{solid}}}{dt} = r_c$$

Change in Volume

- Partial molar volume:

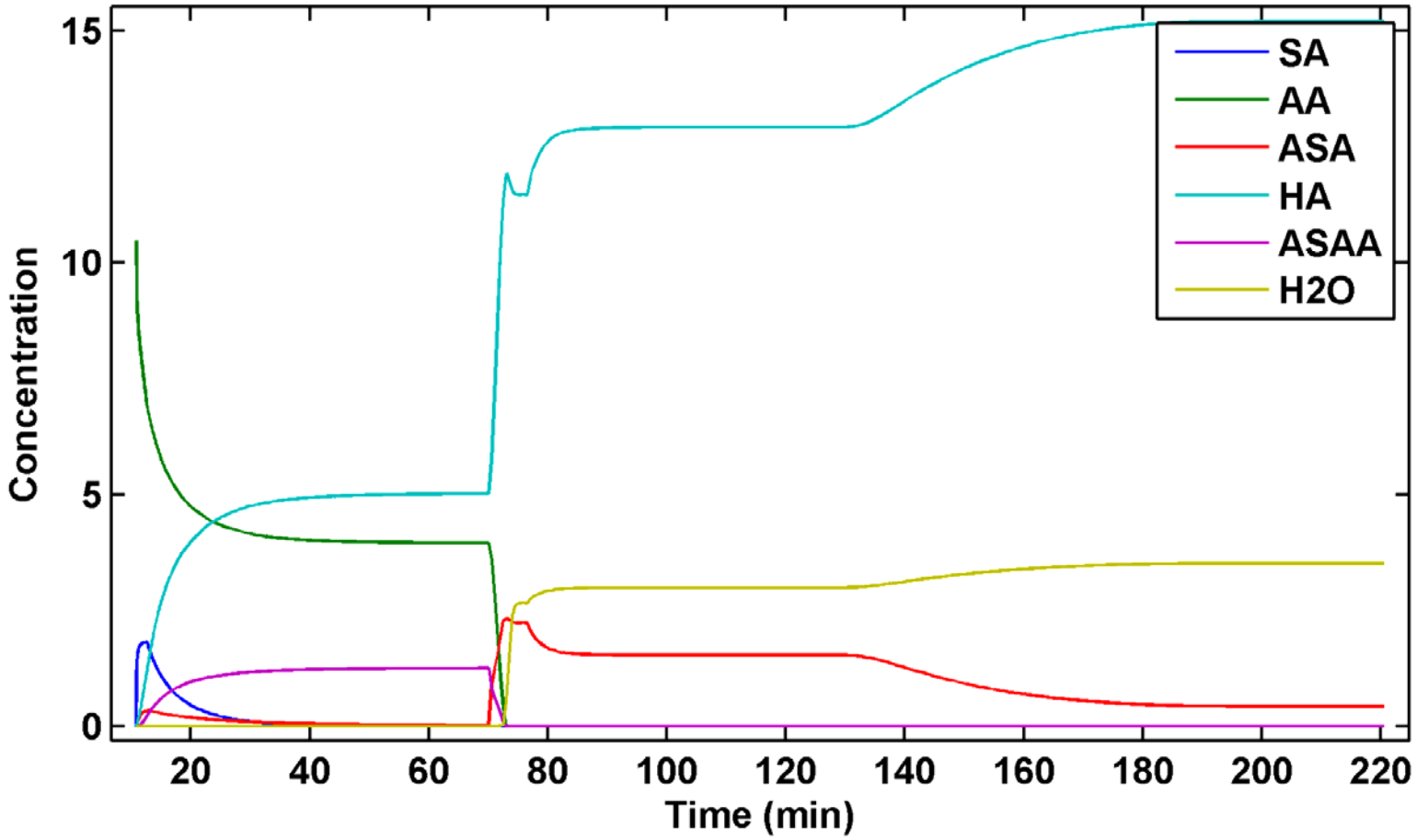
$$V_{tot} = n_1 v_1 + n_2 v_2 + \cdots + n_n v_n$$

- Change in volume as a function of time:

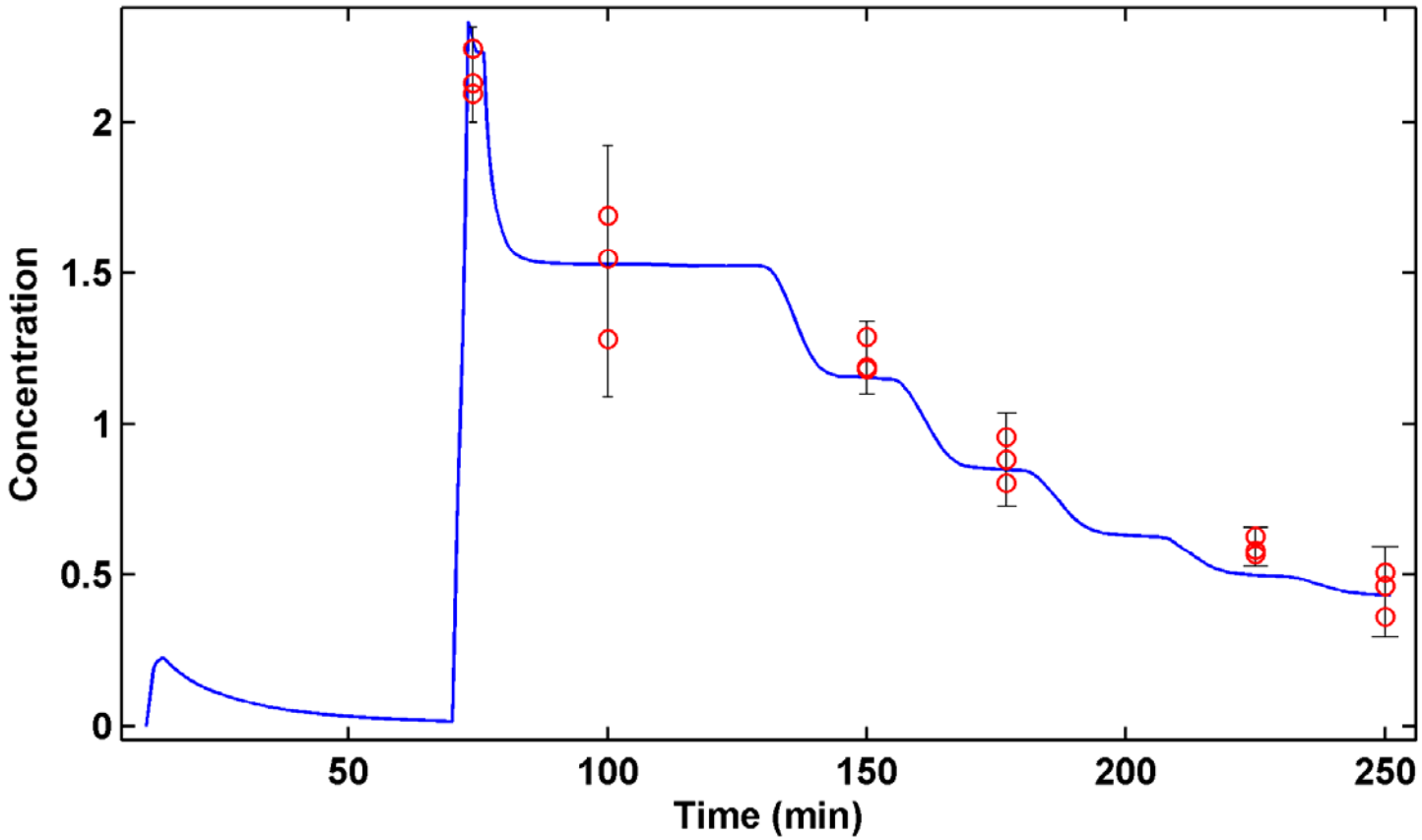
$$\frac{dV_{SA}}{dt} = v_{\mathrm{SA}}[V(r_d - r_1)]$$

$$\frac{dV}{dt} = \frac{dV_{\mathrm{SA}}}{dt} + \frac{dV_{\mathrm{AA}}}{dt} + \frac{dV_{\mathrm{ASA}}}{dt} + \frac{dV_{\mathrm{HA}}}{dt} + \frac{dV_{\mathrm{ASAA}}}{dt} + \frac{dV_{\mathrm{H_2O}}}{dt}$$

Concentration Profiles of All Species



Validation of Concentration Profiles



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GOALI

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