Kinetic Modeling of Batch Slurry Reactions

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

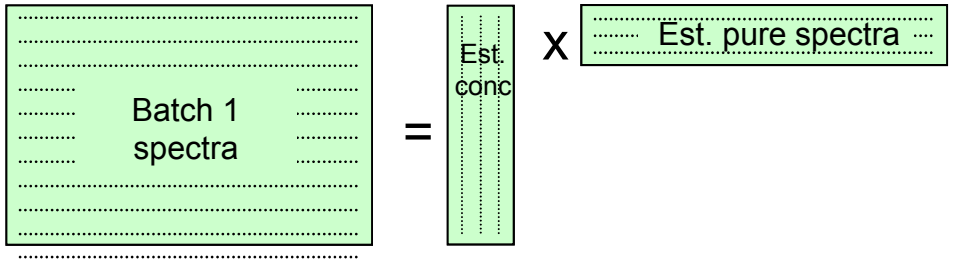
- Extend kinetic modeling approach to a prototypical slurry reaction at DuPont: sulfonylurea coupling reaction for monitoring purposes
- Make optical measurements in light-scattering medium
- Modify kinetic models to include:
  - Dissolution of starting material A & flow-in of reagent B
  - Nucleation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

Isothermal model with flow-in reagents

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

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

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



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

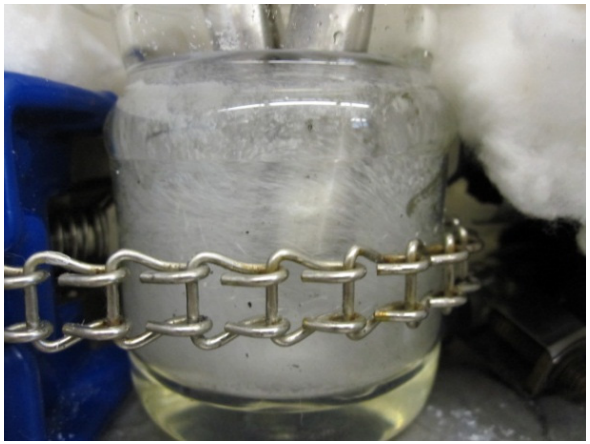
Challenges – Optical Methods in Slurries

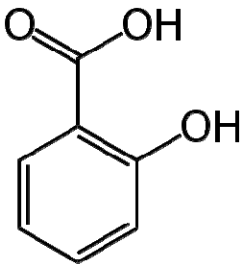
- Linear response is needed for kinetic modeling and self-modeling curve resolution
- Reflectance measurements include both light scattering and light absorption signals
  - Mathematical resolution of the two is needed to estimate solid fraction and dissolved fraction
  - Effective path length is dependent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

Project 1: modeling of dissolution of salicylic acid

$$r = k(c_{sat} - c)^n$$

- Develop a kinetic model for the dissolution of salicylic acid in a solvent mixture (52% ethanol, 48% water), based on a power law equation
  - simpler system, easily controlled
  - help gain understanding about kinetic of dissolution and crystallization in general
  - Precisely controlled conditions will facilitate model validation
- Optimize the rate constant (*k*) and the exponent (*n*) of the power law equation

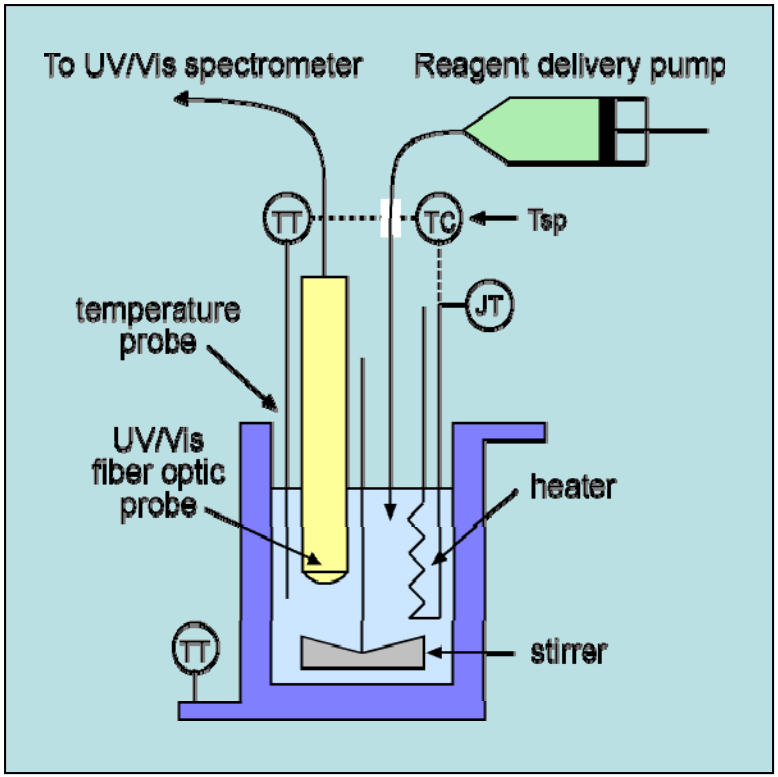




Salicylic acid
M.W. 138.12 g mol^{-1}
pKa 2.97
Monoclinic

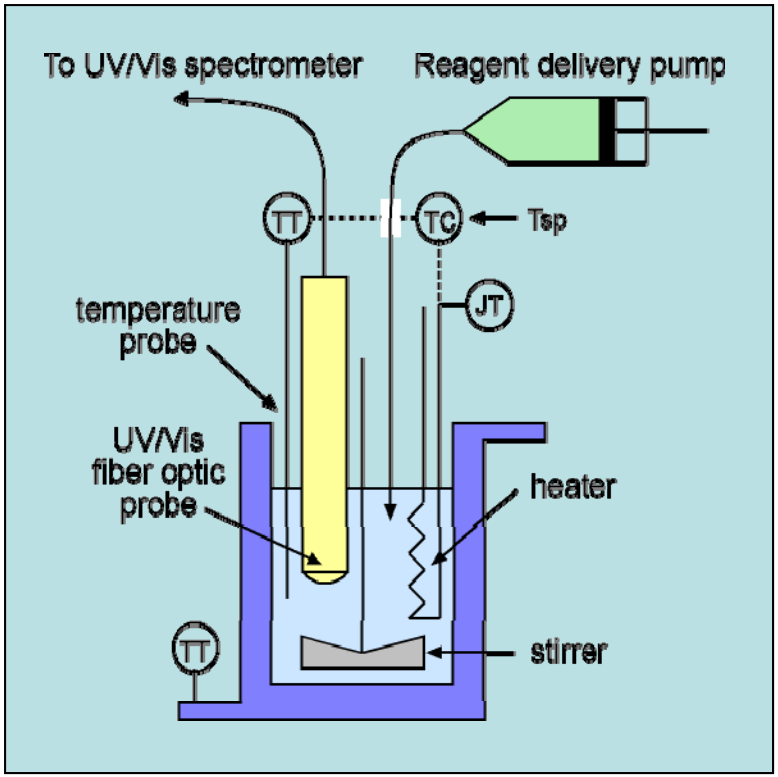
Laboratory scale batch reactors

Batch Titration Reactor

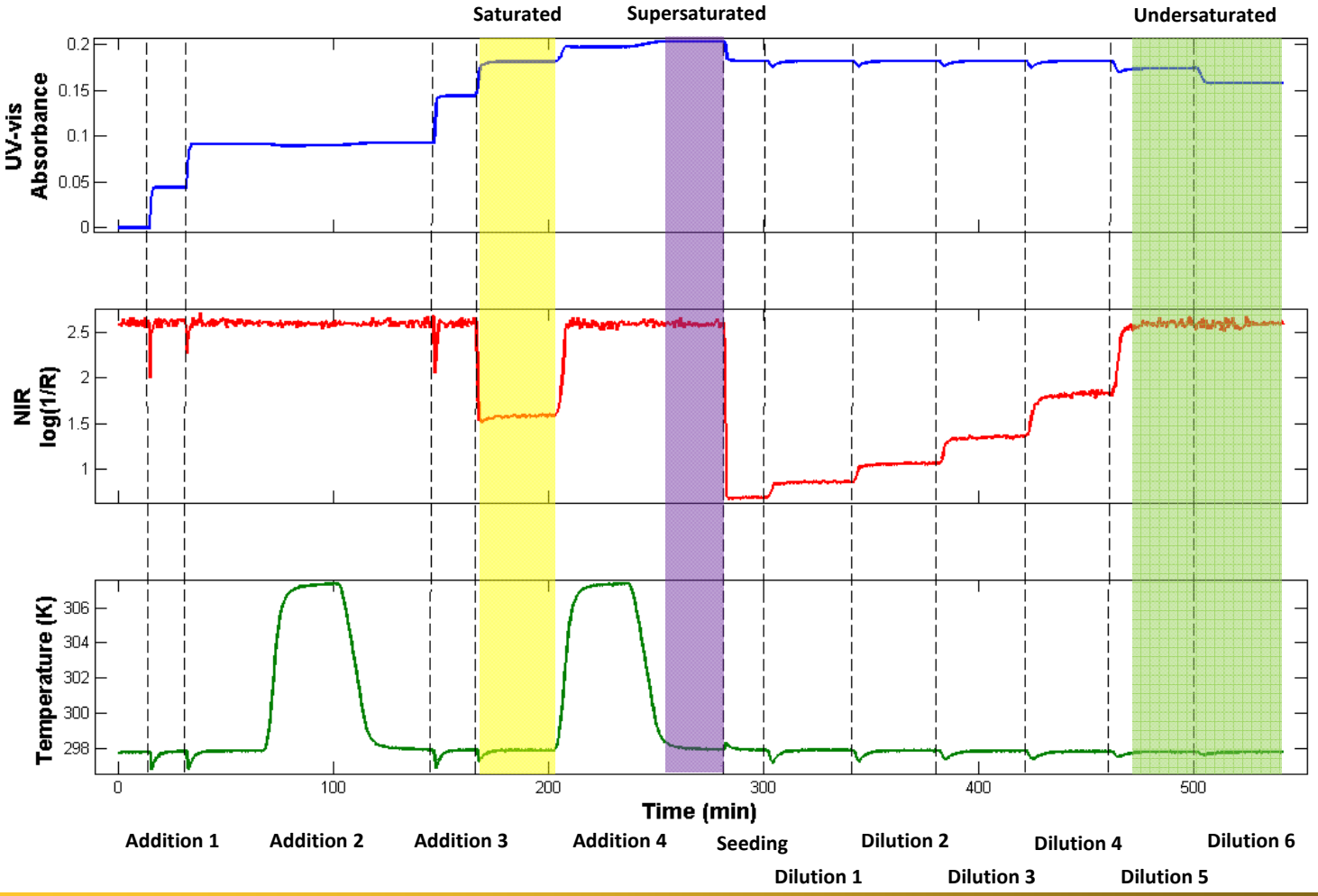


Laboratory scale batch reactors

Batch Titration Reactor



Dissolution of salicylic acid



Simplifying Assumptions

- Crystallization Rate

high theory model

$$r_c = \frac{\Phi_s MW_s k_c}{3 d_s \Phi_v} \eta_r (c - c_{sat})^g$$

low theory model

$$r_c = k_c (c - c_{sat})^g$$

- Dissolution Rate

$$r_d = \frac{2 MW_s k_d}{d_s} (c_{sat} - c)$$

$$r_d = m \cdot k_d (c_{sat} - c)^n$$

Assumptions:

Well-mixed slurries, the length of crystals, solid density, effectiveness factor, molecular weight of the solid, surface factor and volumetric shape factor do not change significantly in these experiments.

Blandin, A. et. al., *Chemical Engineering Journal*, **2001**, 81, 91-100

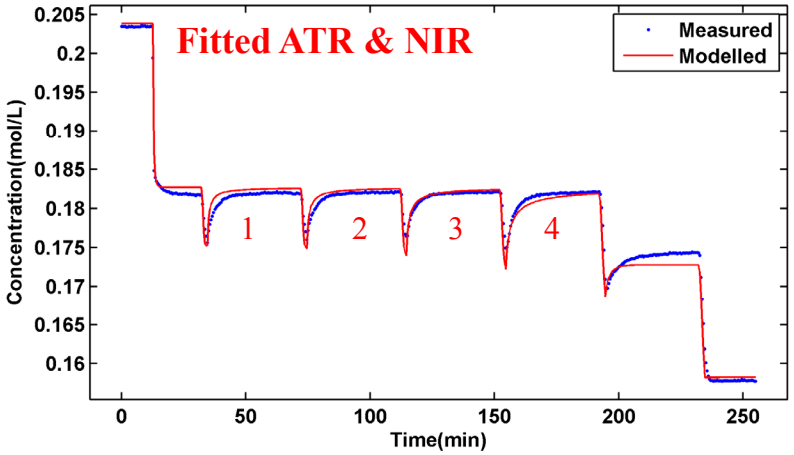
Bhattacharya A. Chemical Engineering and Processing, **2007**, 46, 573-583

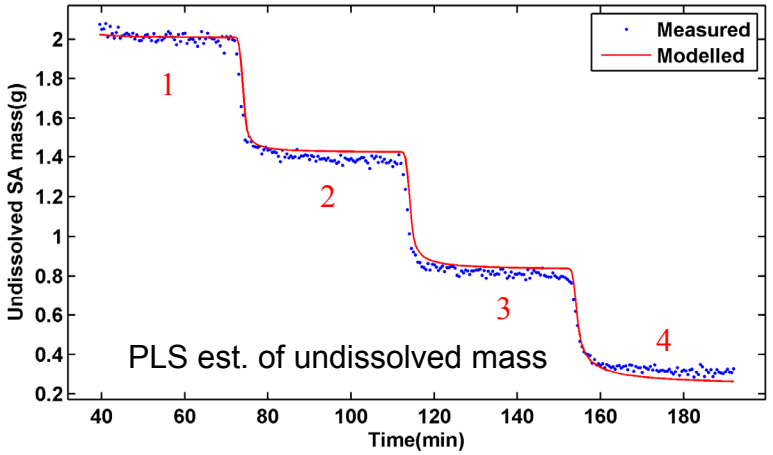
Model batch (08-29-10)

Hessian

1.0000	-0.9383	-1.0000	0.6118	0.1929	0.1540
-0.9383	1.0000	0.9384	-0.5082	-0.2022	-0.1508
-1.0000	0.9384	1.0000	-0.6116	-0.1928	-0.1540
0.6118	-0.5082	-0.6116	1.0000	0.7244	0.0860
0.1929	-0.2022	-0.1928	0.7244	1.0000	-0.0514
0.1540	-0.1508	-0.1540	0.0860	-0.0514	1.0000

UV-vis range used:: **270 – 360 nm**, NIR range used: **1100 nm**





Initial Conditions:

Dissolution rate constant (kd) = 30.00 $L^{n-1}/(mol^{n-1}min)$
Crystallization rate constant (kc) = 15.00 $L^{n-1}/(mol^{n-1}min)$
Order parameter (n) = 1.800
Order parameter (g) = 1.700
Total SA mass added (mt) = 3.1882 g
Concentration (c0) = 1.0176 (mol/L)
Saturation limit (csat) = 0.9075
Initial volume (v0) = 22.7 mL
Correction factor (cf) = 15

Optimized Parameters:

Dissolution rate constant (kd) = 22.16 $L^{n-1}/(mol^{n-1}min)$
Crystallization rate constant (kc) = 9.115 $L^{n-1}/(mol^{n-1}min)$
Order parameter (n) = 2.034
Order parameter (g) = 1.194
Saturation limit (csat) = 1.010 (mol/L)
Correction factor (cf) = 14.27

Sum of Square (SSQ) = 0.5221

Experiment 2

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

Reaction Mechanisms

Catalyzed Reaction

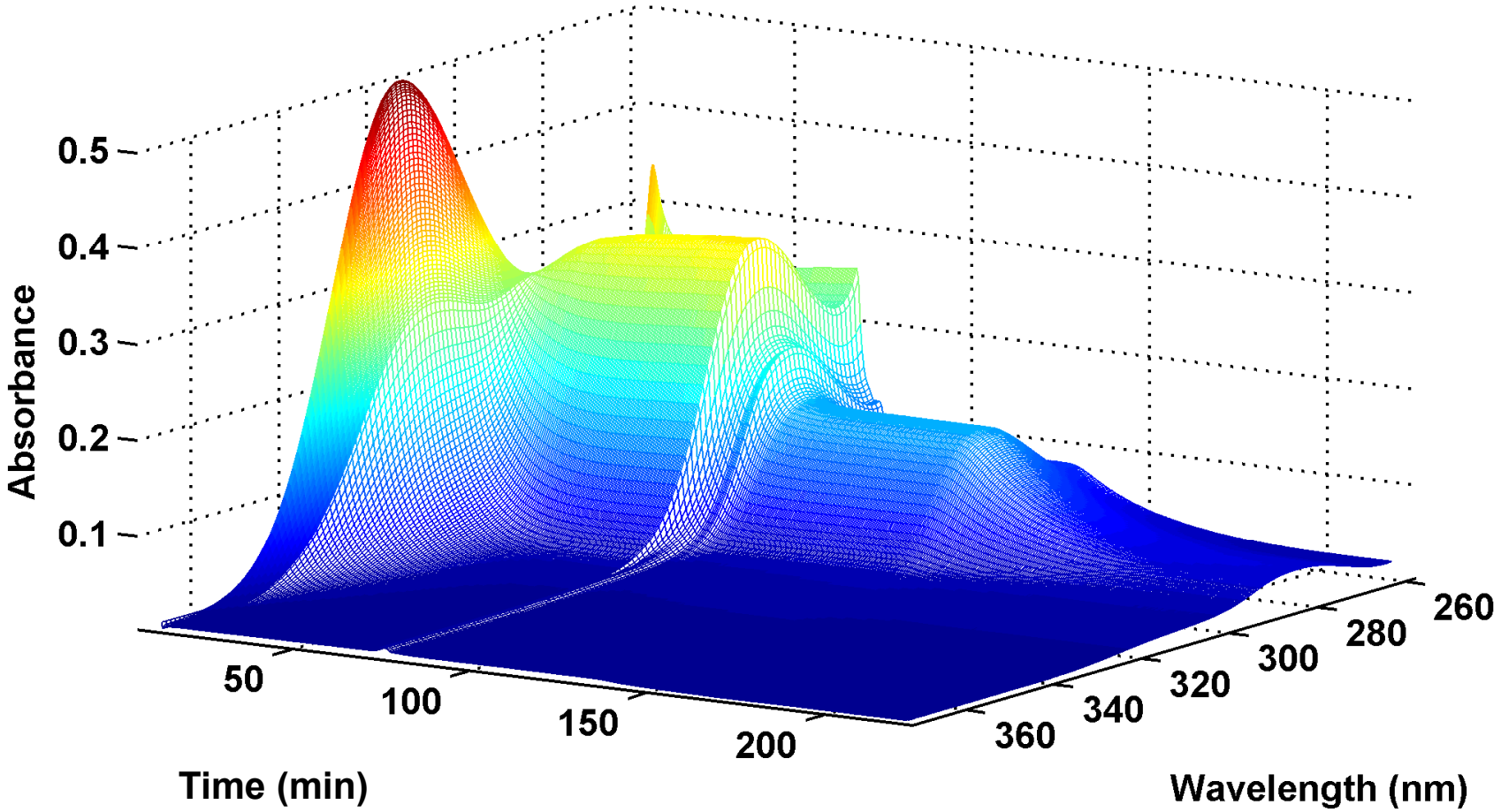
$$SA + AA \xrightarrow{k_1} ASA + HA$$

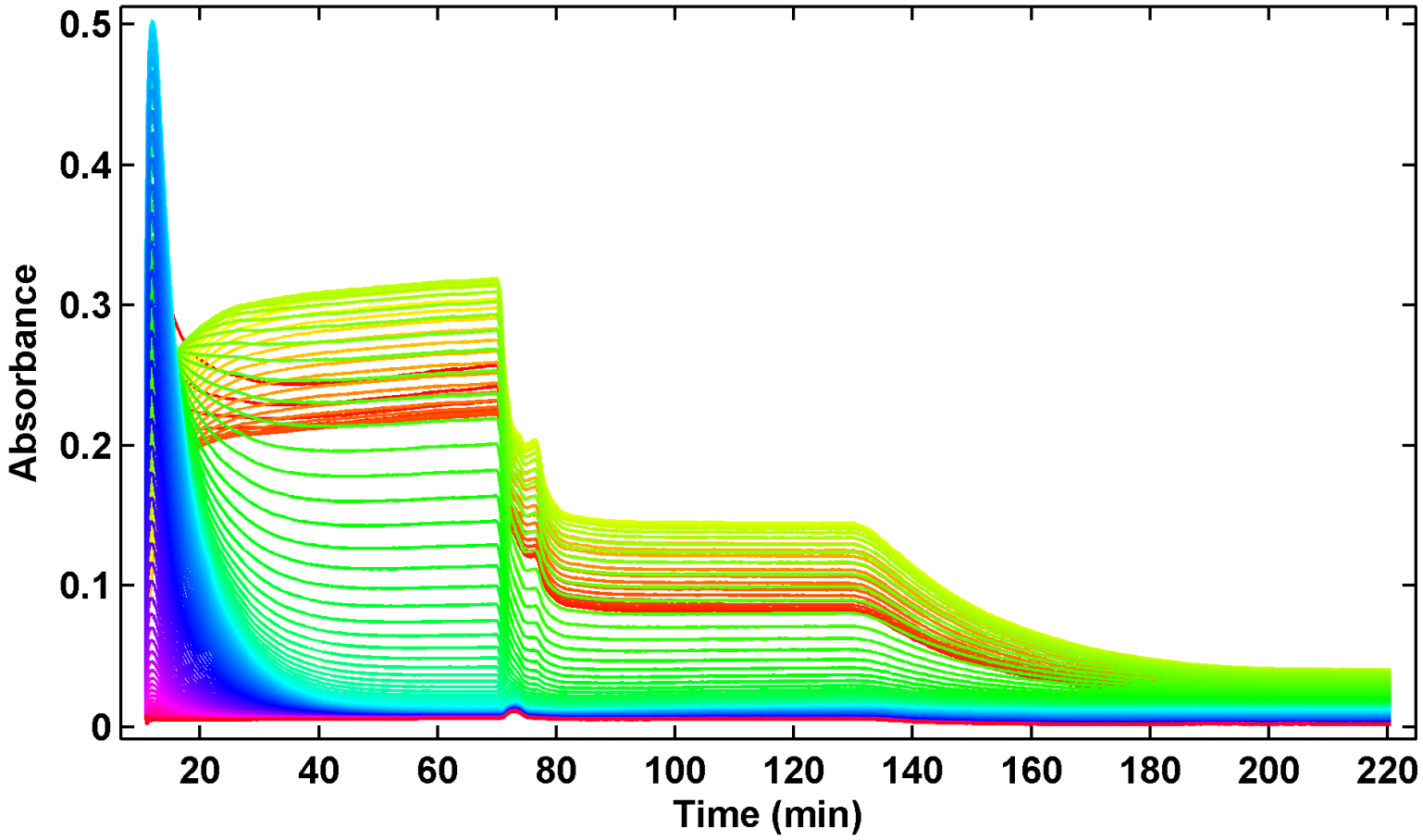
$$ASA + AA \xrightarrow{k_2} ASAA + HA$$

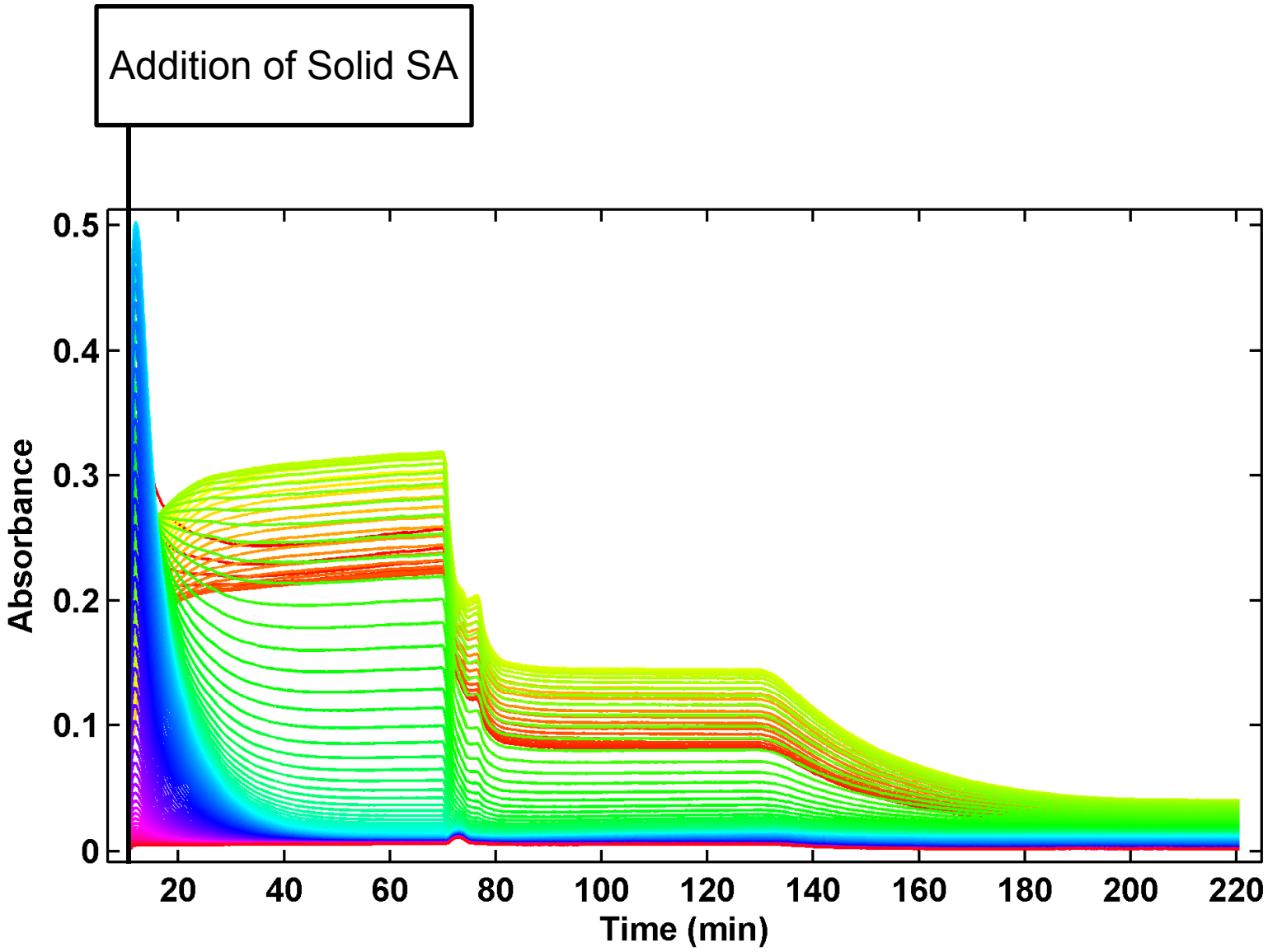
Water Addition

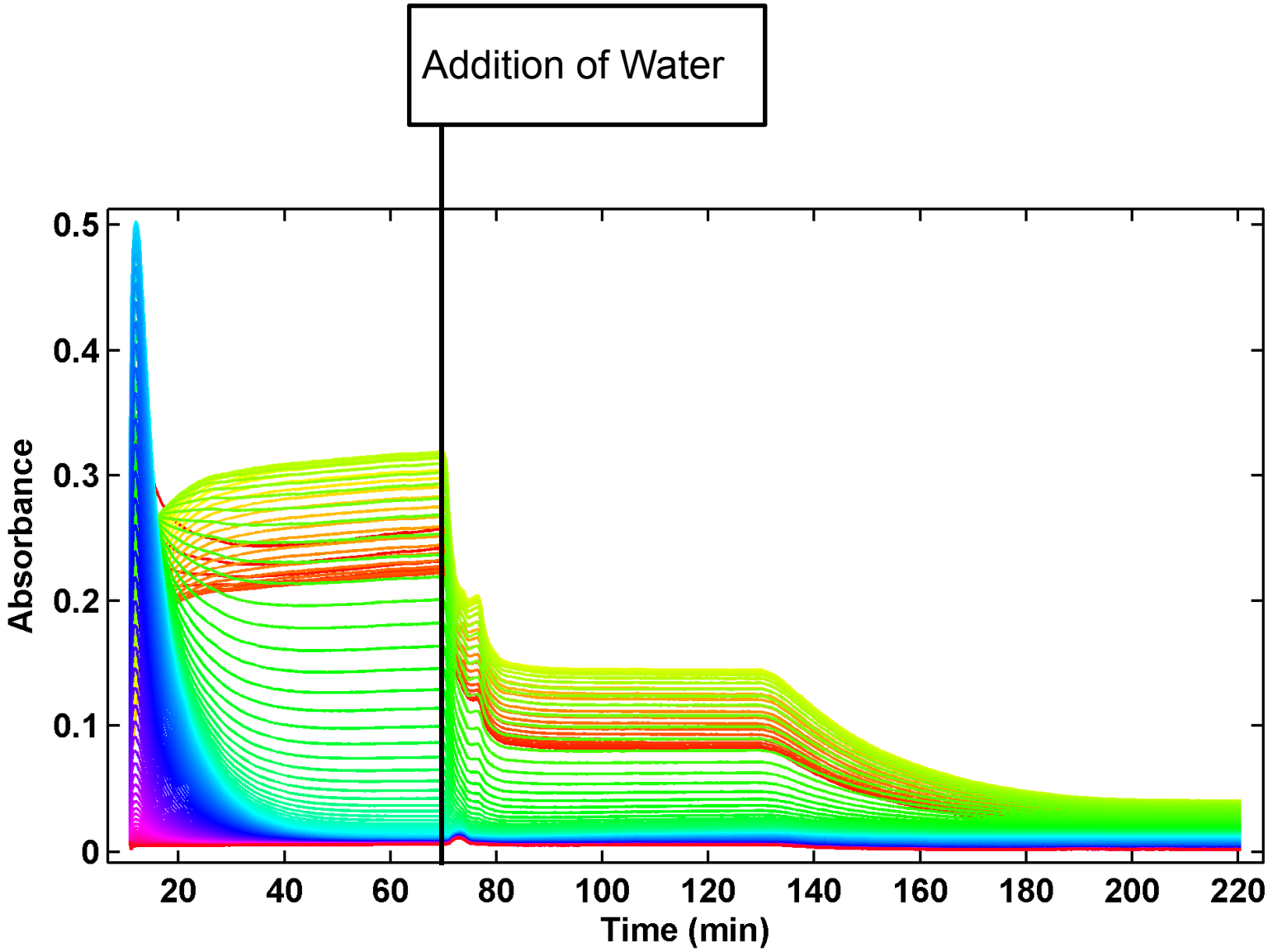
$$ASAA + H_2O \xrightarrow{k_3} ASA + HA$$

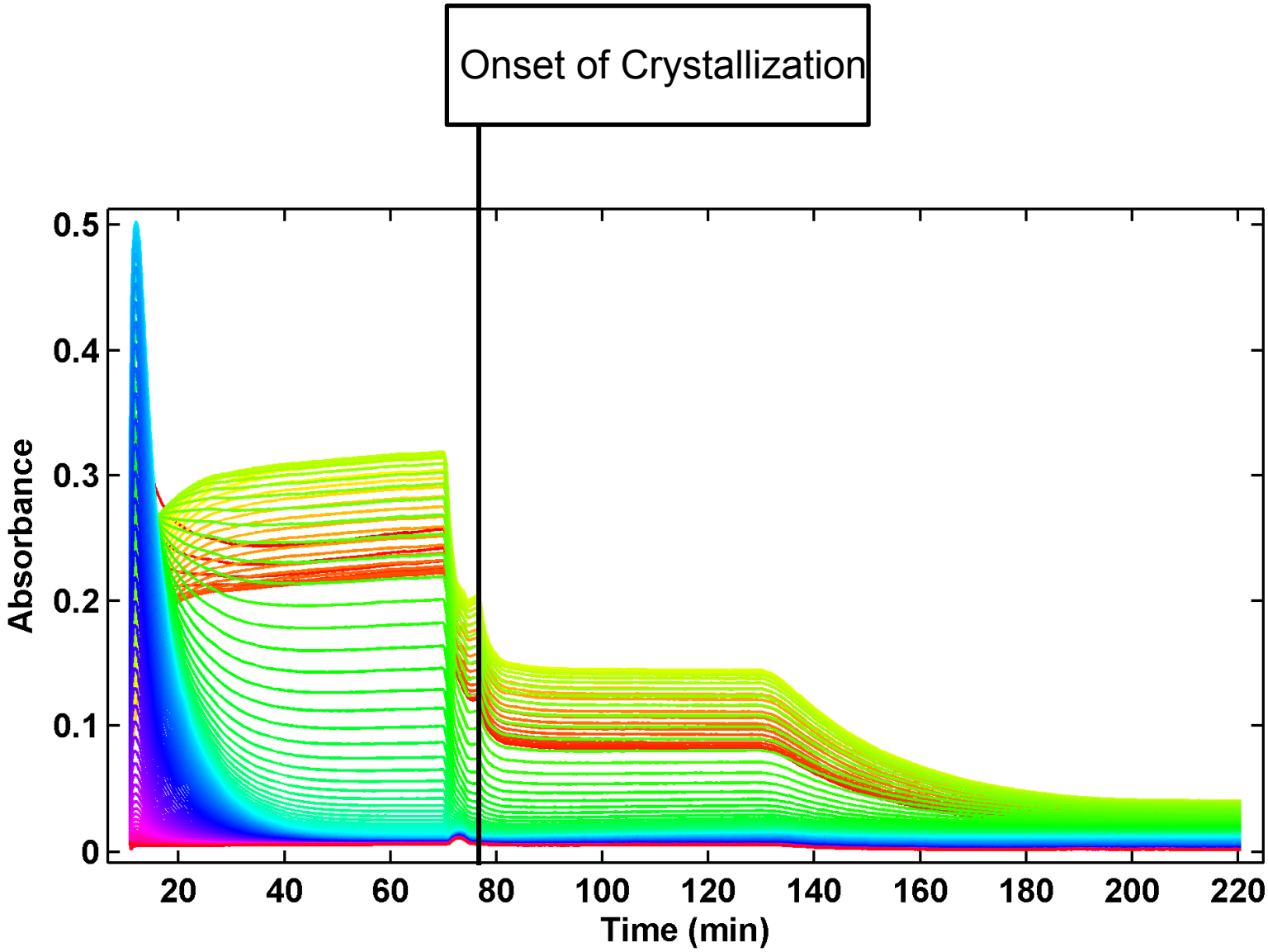
$$AA + H_2O \xrightarrow{k_4} 2HA$$

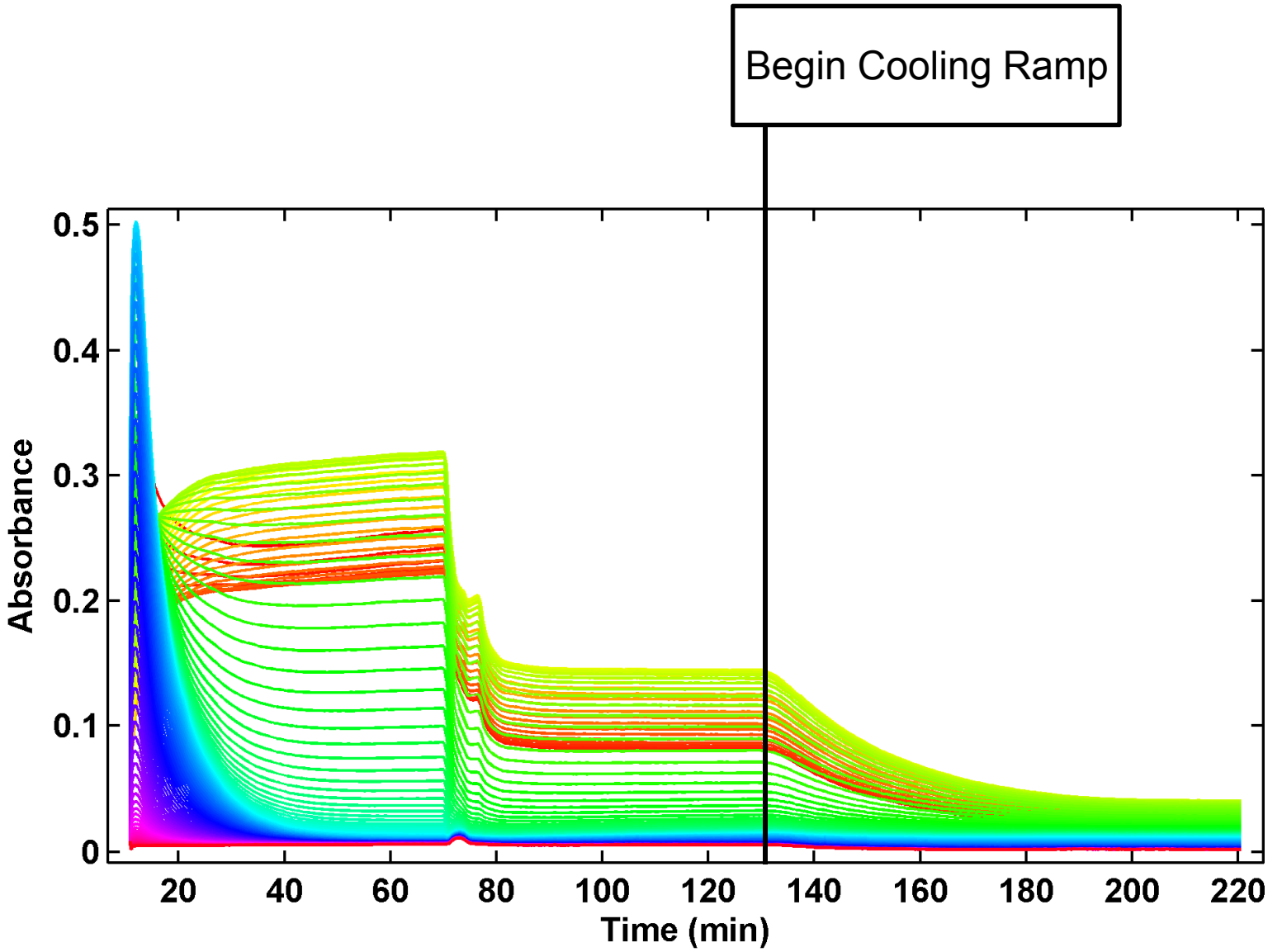

Absorbance
0.5
0.4
0.3
0.2
0.1
50
100
150
200
Time (min)
260
280
300
320
340
360
Wavelength (nm)

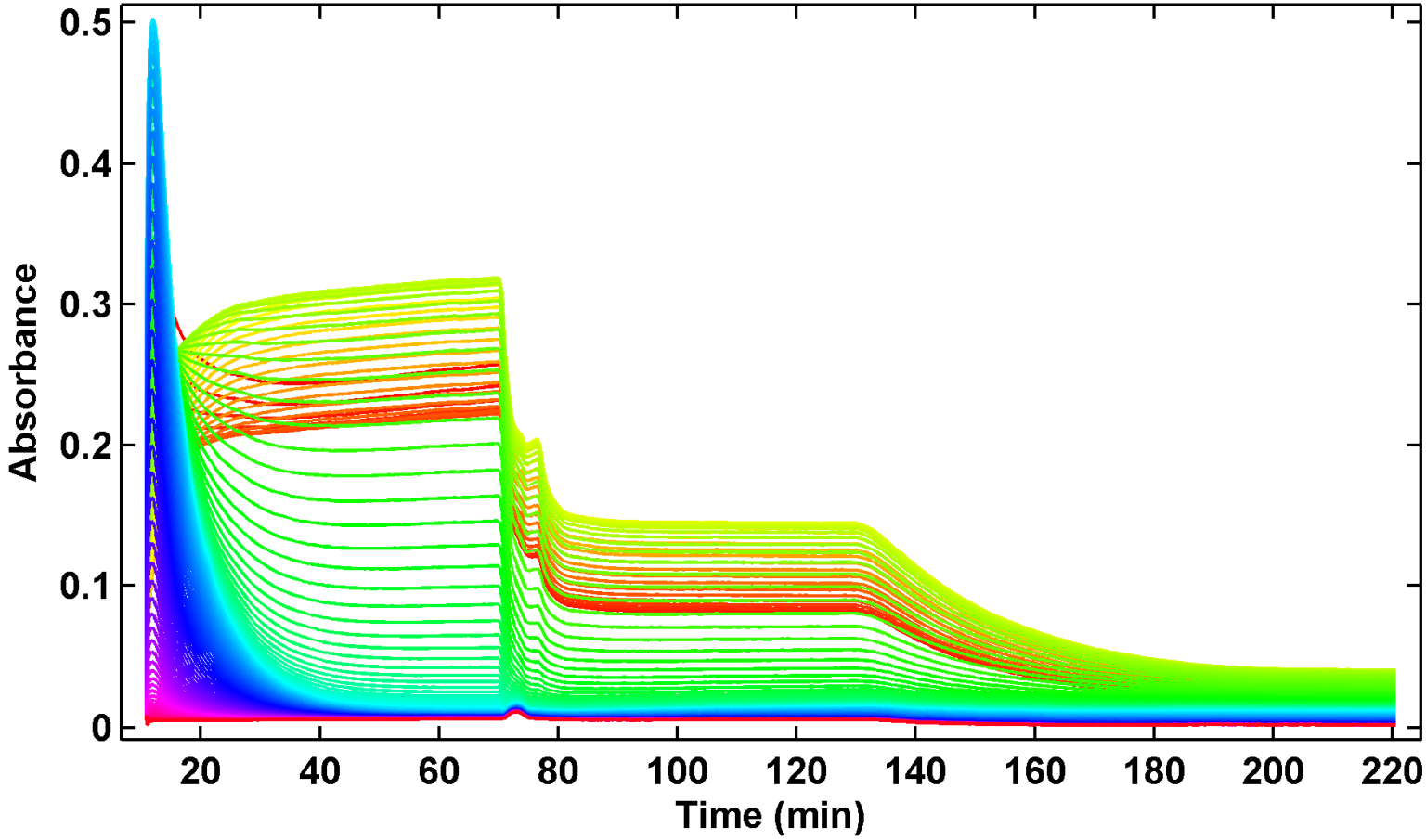

Absorbance
0.5
0.4
0.3
0.2
0.1
0
20
40
60
80
100
120
140
160
180
200
220
Time (min)


Addition of Solid SA
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)


Addition of Water
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)

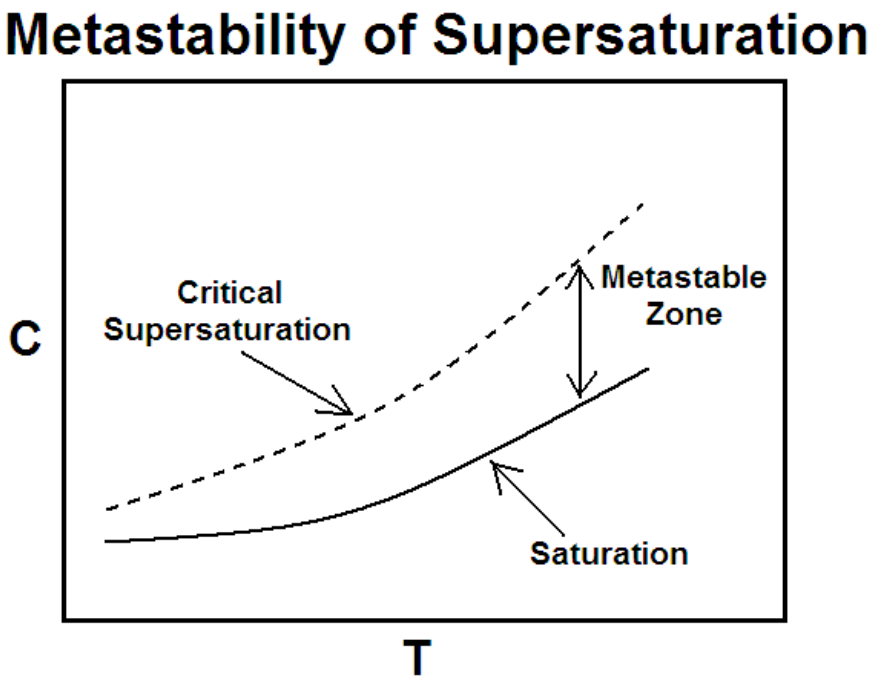

Onset of Crystallization
Absorbance
0.5
0.4
0.3
0.2
0.1
0
20
40
60
80
100
120
140
160
180
200
220
Time (min)


Begin 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)


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



Differential Equations

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

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

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

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

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

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

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

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

Differential Equations

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

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

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

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

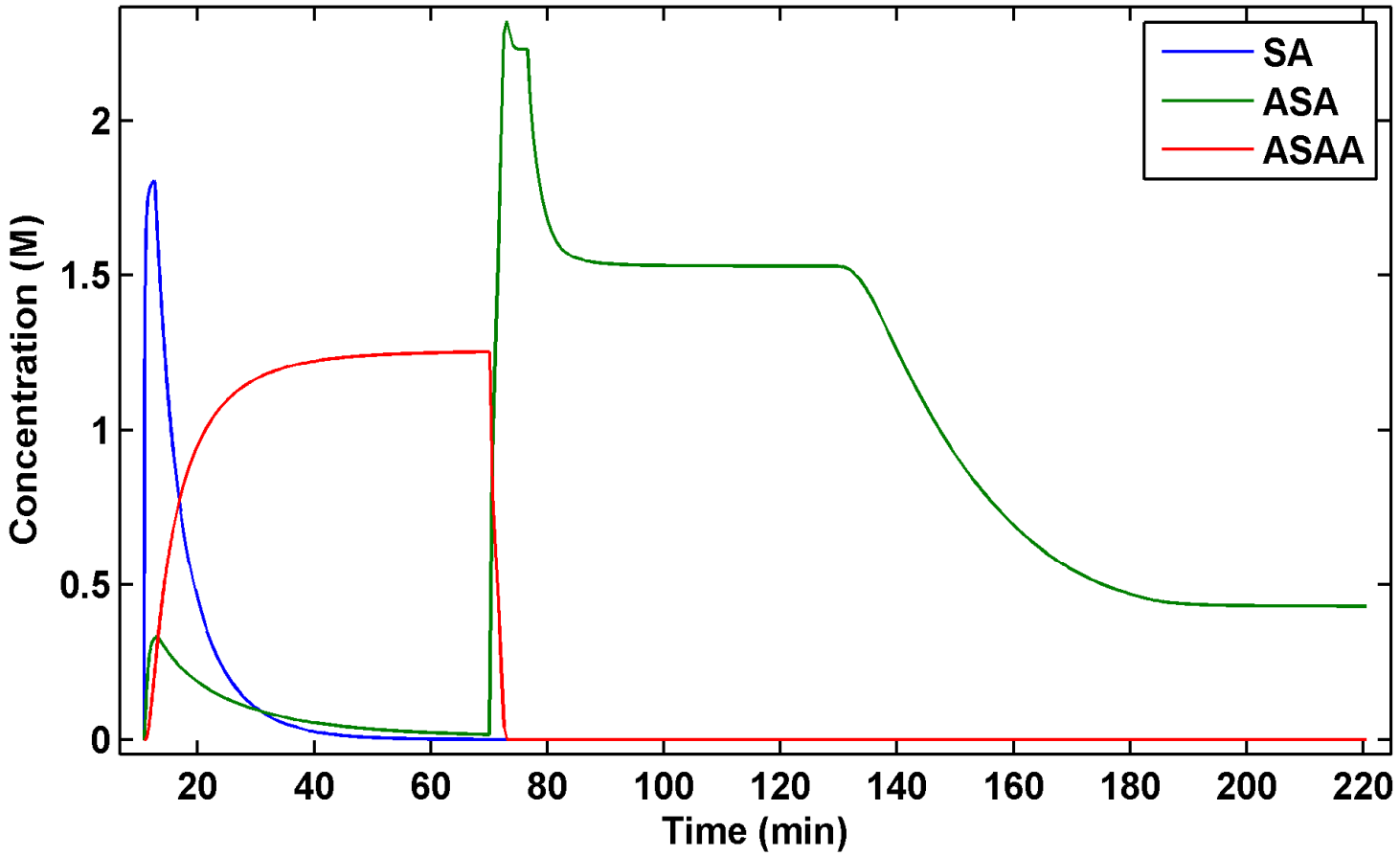
$$\frac{d[\mathrm{AA}]}{dt} = -r_1 - r_2 - r_4 - \frac{dV}{dt}\frac{[\mathrm{AA}]}{V}$$

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

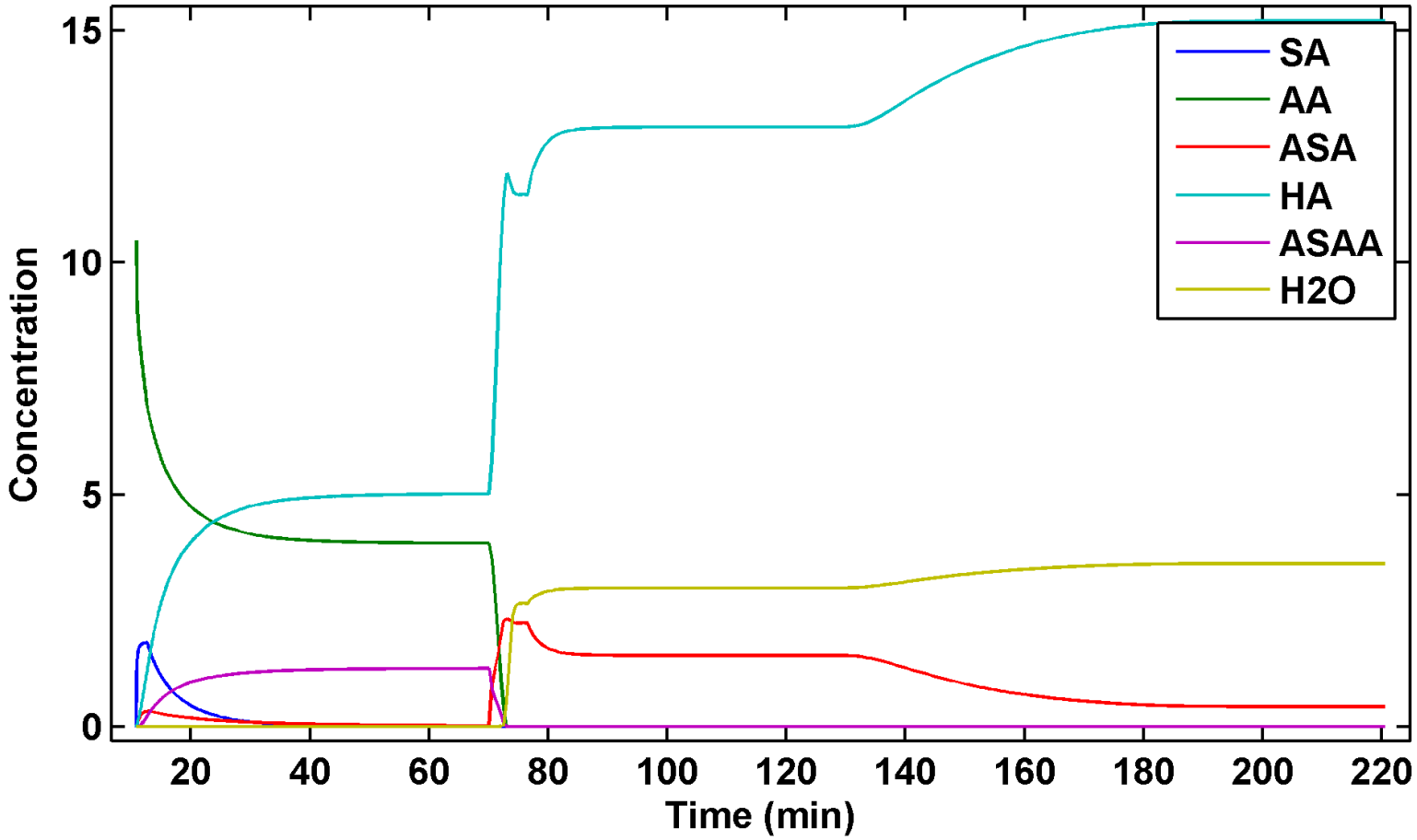
$$\frac{d[\mathrm{HA}]}{dt} = r_1 + r_2 + r_3 + r_4 - \frac{dV}{dt}\frac{[\mathrm{HA}]}{V}$$

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

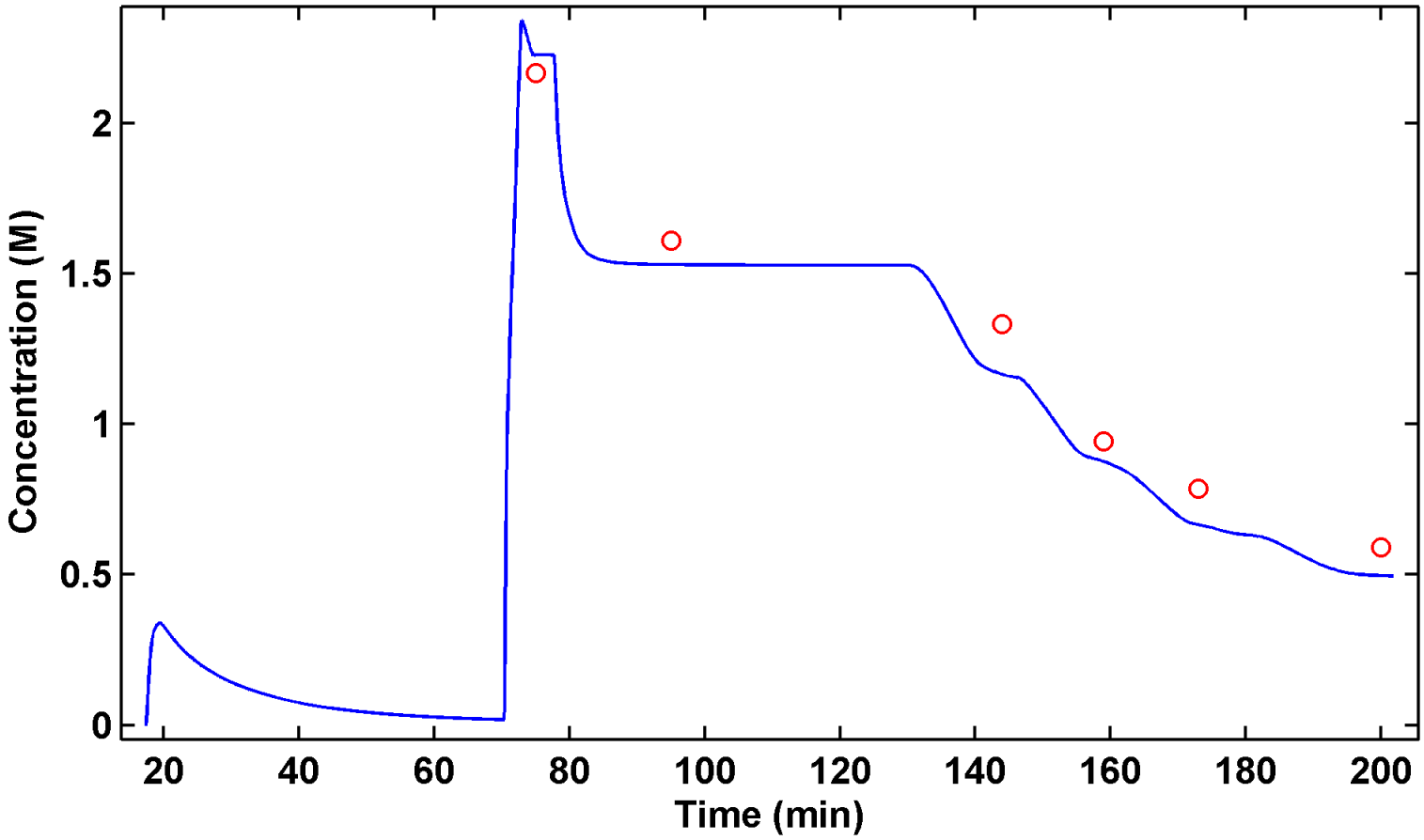
Concentration Profile of Active Species



Concentration Profiles of All Species



Validation of ASA Concentration Profiles by HPLC – Preliminary results

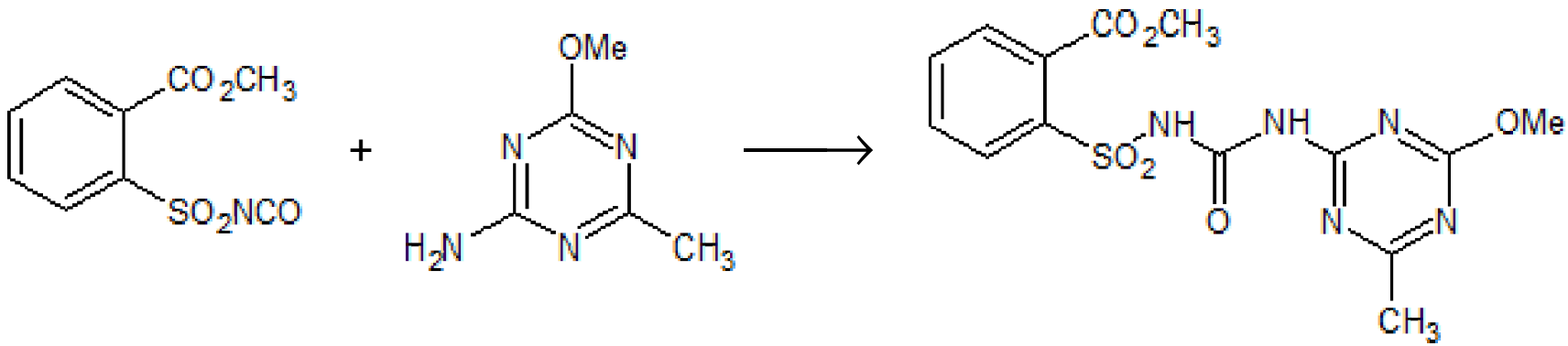


Project 3: modeling of sulfonylurea coupling reaction

- Develop a combined kinetic model for the reaction, dissolution and crystallization for the slurry-based sulfonylurea coupling reaction.
- Use NIR diffuse reflectance spectroscopy[3] and kinetic model for monitoring purpose, and to perform endpoint and fault detections.
- Use High Performance Liquid Chromatography (HPLC) samples taken from the reaction mixture to validate kinetic models

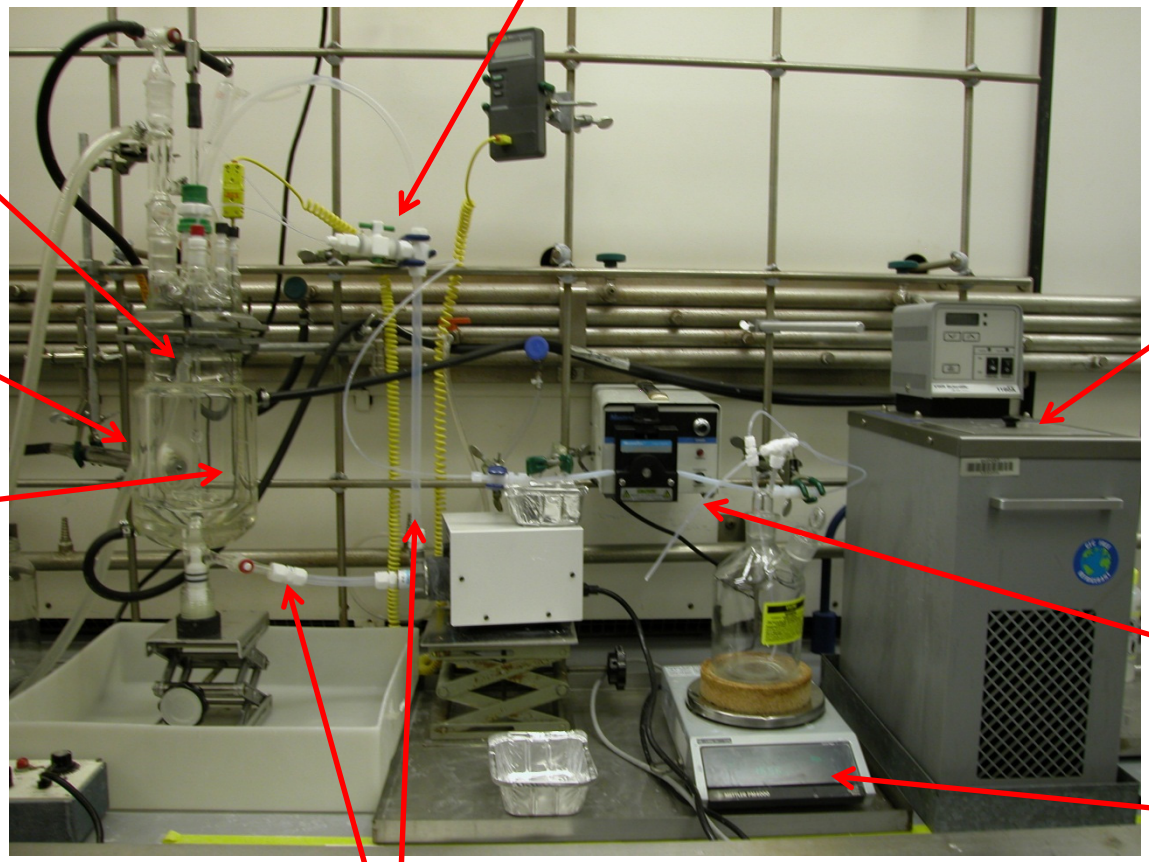
Barrett P., Smith B. et al. (2005). Organic Process Research & Development 9: 348-355.

Sulfonyl Urea Coupling Reaction

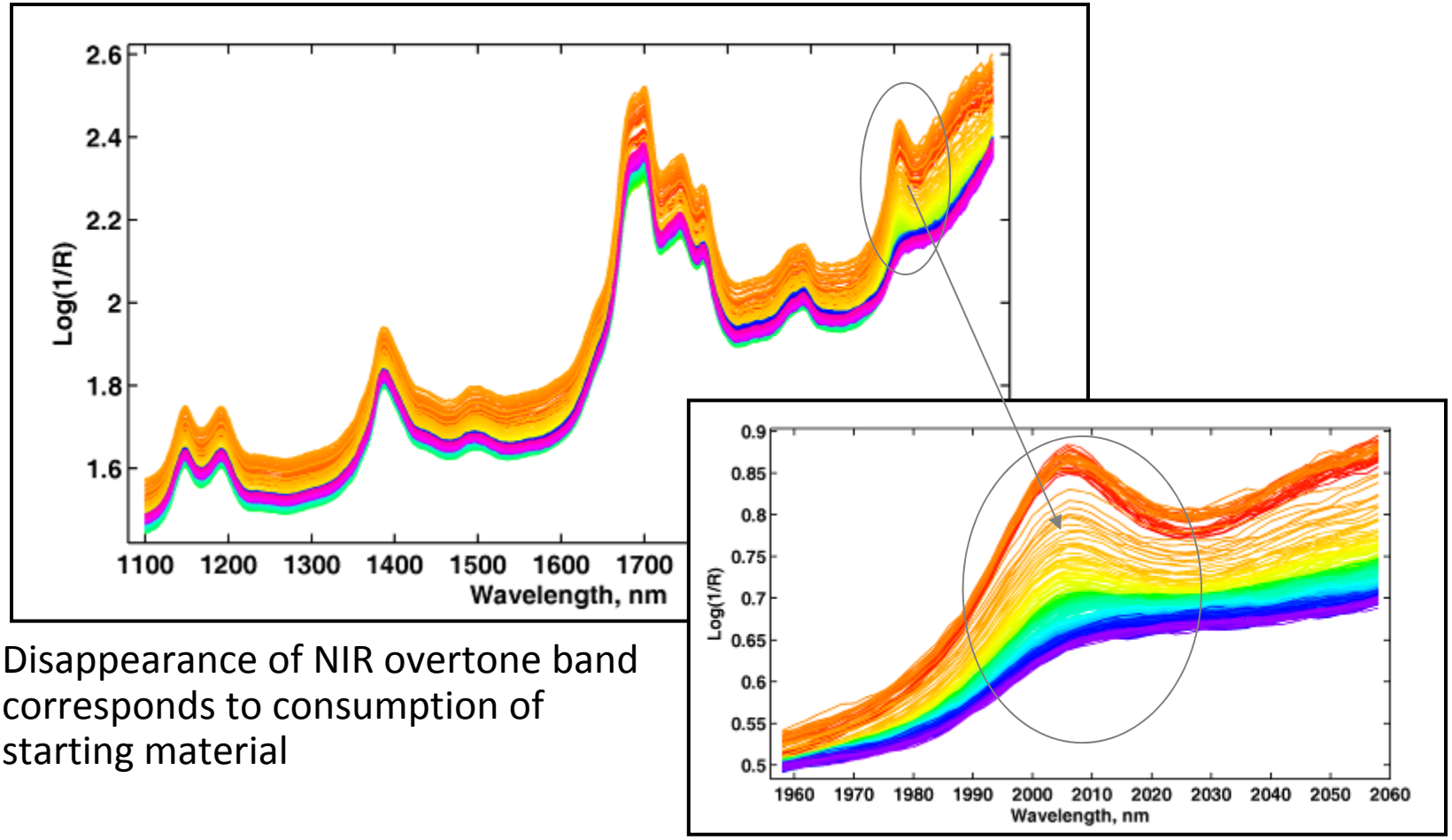


CMBSI	A4098	T6376
benzoic acid 2-[(Isocyanato)sulfonyl]-methyl ester	2-amino-4-methoxy-6-methyl-1,3,5-triazine	metsulfuron methyl

Apparatus setup at DuPont

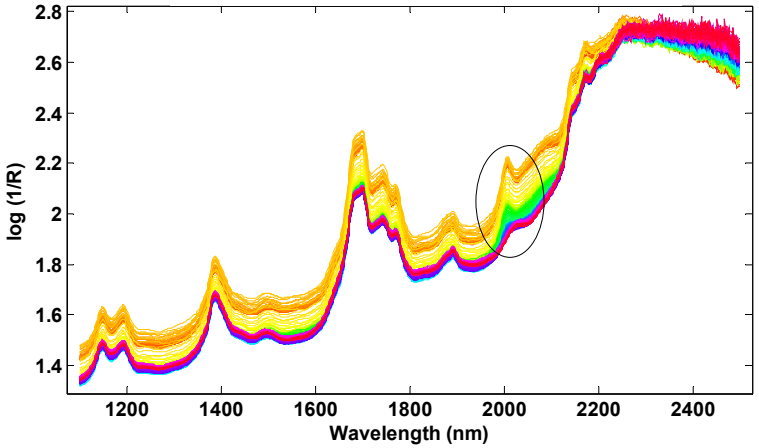


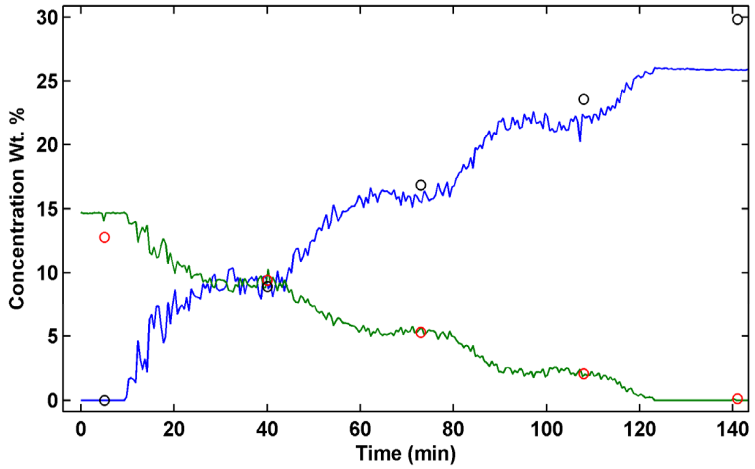
Sample batch slurry system



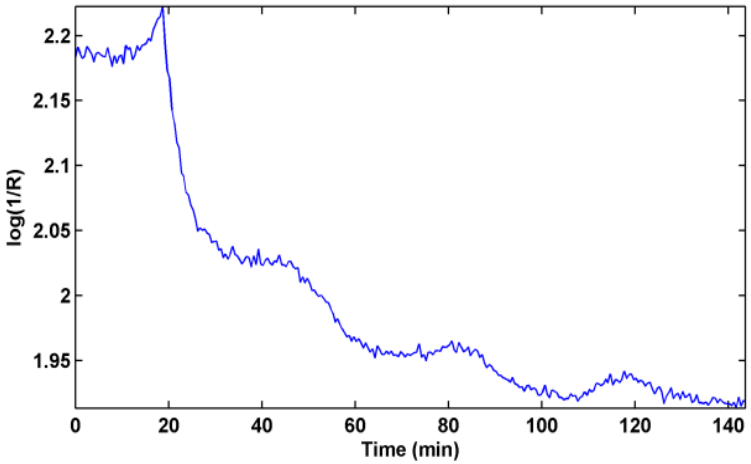
- Disappearance of NIR overtone band corresponds to consumption of starting material

Sulfonylurea coupling reaction (NIR)

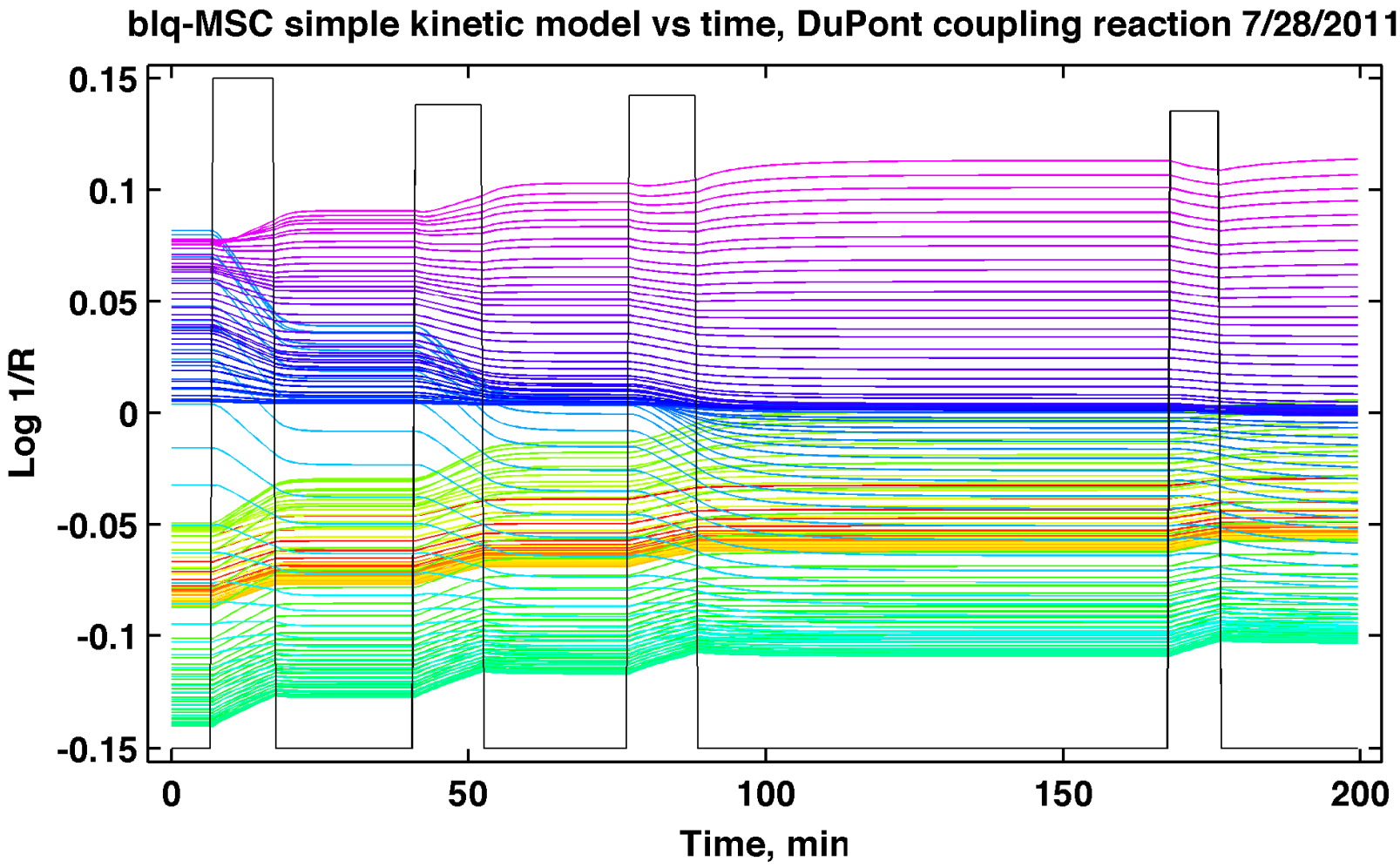




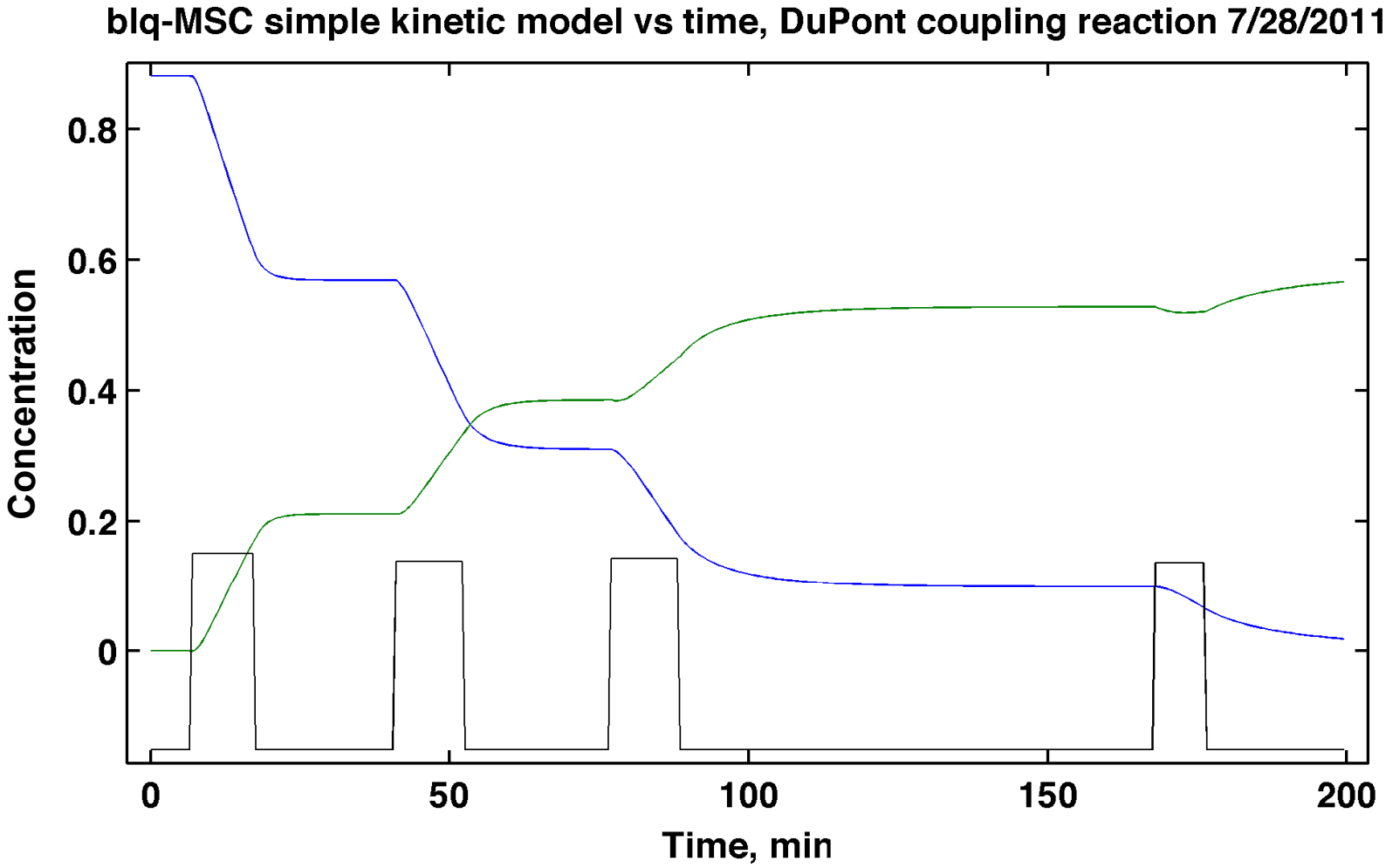
At 2010 nm



Modeling the Coupling Reaction



Coupling Reaction - Kinetic Fitting Results



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GOALI

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- Dr. Paul Gemperline (ECU)
  - Dr. Julien Billeter
  - Chun Hsieh
  - Chad Adkins
  - Ethan Chiappisi
  - Kristian Scott
- Dr. Liguo Song (UT)
  - Dr. David S. Cho
- Dr. Frank Chambers (OSU)

Consultant
- Dr. Kelsey Cook (NSF)