Kinetic modeling of dissolution and crystallization of batch reactions with *in situ* spectroscopic measurements

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Outline

- ❑ Overall Project Goal
- ❑ Background
- ❑ Motivations
- ❑ Research Projects
  - Modeling of Dissolution of Salicylic Acid
  - Modeling of Sulfonylurea Coupling Reaction
- ❑ Instrumentations
- ❑ Experimental Designs
- ❑ Models & Results Discussion
- ❑ Summary & Future Work

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 low-theory models for dissolution, nucleation and crystallization
- Kinetic models with reagent flow-in impose strict mass balance

Background

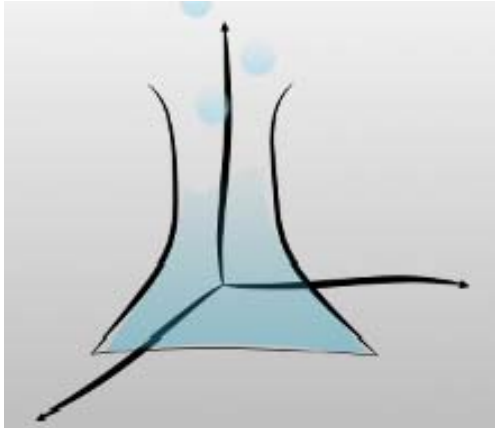
What is a slurry?

- a suspension formed when a quantity of powder is mixed into a liquid in which the solid is only slightly soluble (or insoluble)
- contain large amounts of solid and are more viscous and dense than the liquid from which they are formed
- Many batch industrial processes use slurries

Background (cont.)

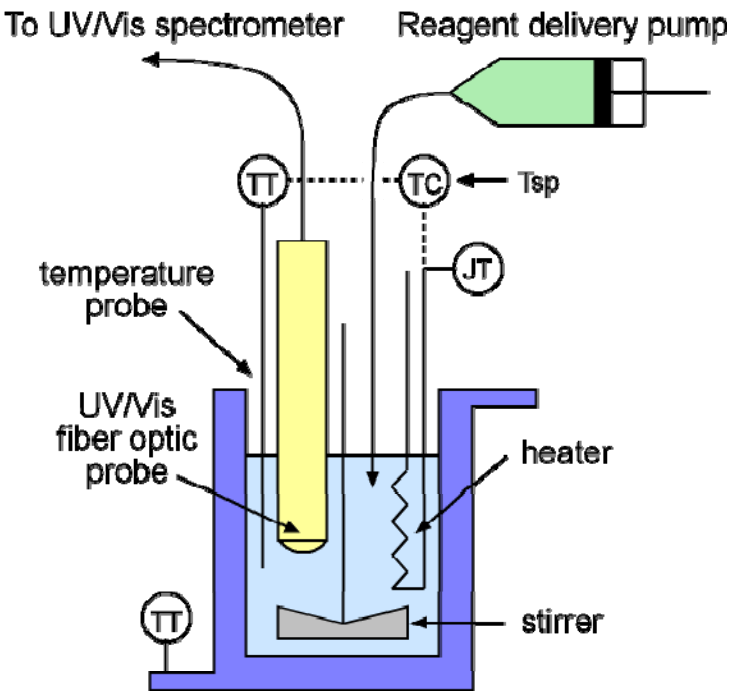
What has been done before?

- The Gemperline group has developed models for homogenous reactions
  - chemical reactions in which the reactants are in the solution phase
- Kinetic model fitting used for process control
  - detect processes upset
  - deduce reasons for processes upset
  - detect endpoint
  - forecast changes



Prior work – apparatus setup

Batch Titration Reactor



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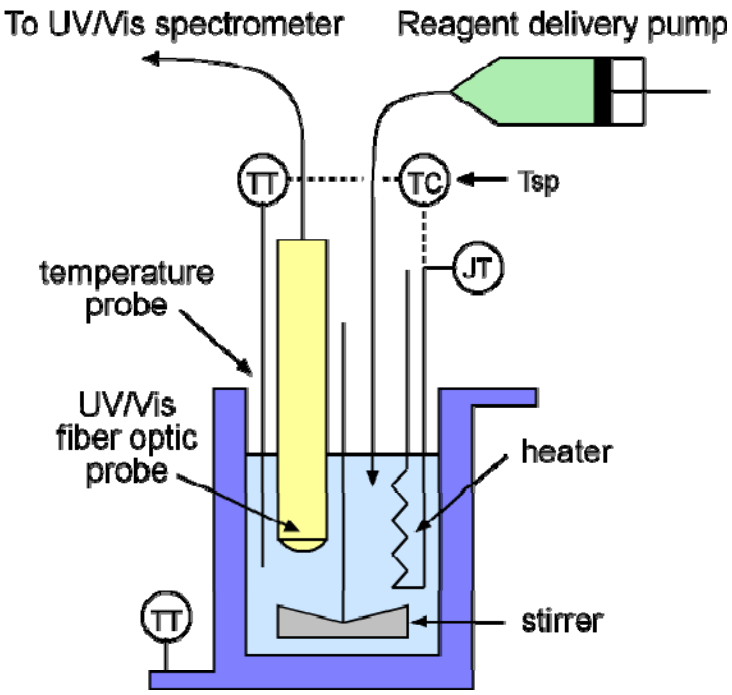
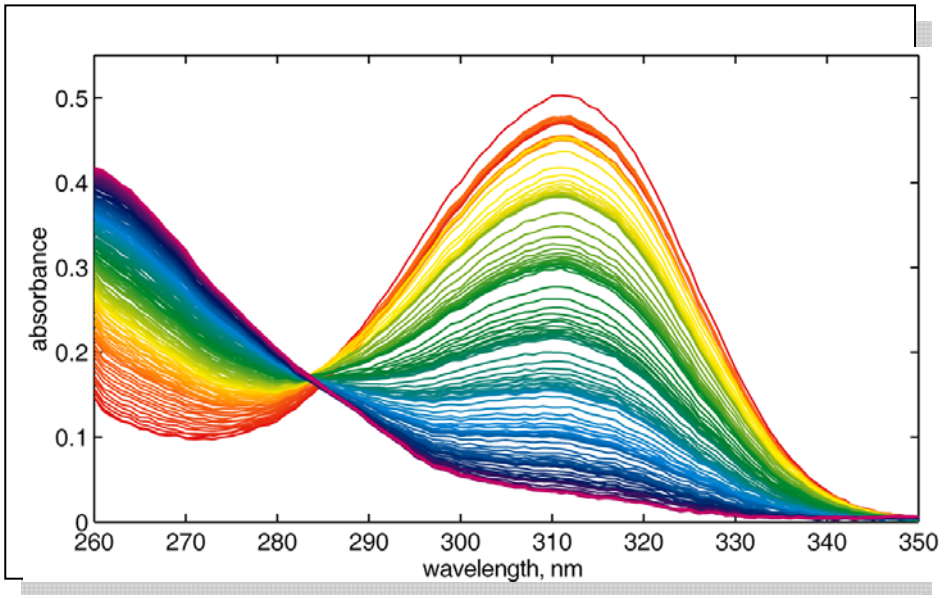


Typical batch reaction spectra: acetylation of salicylic acid

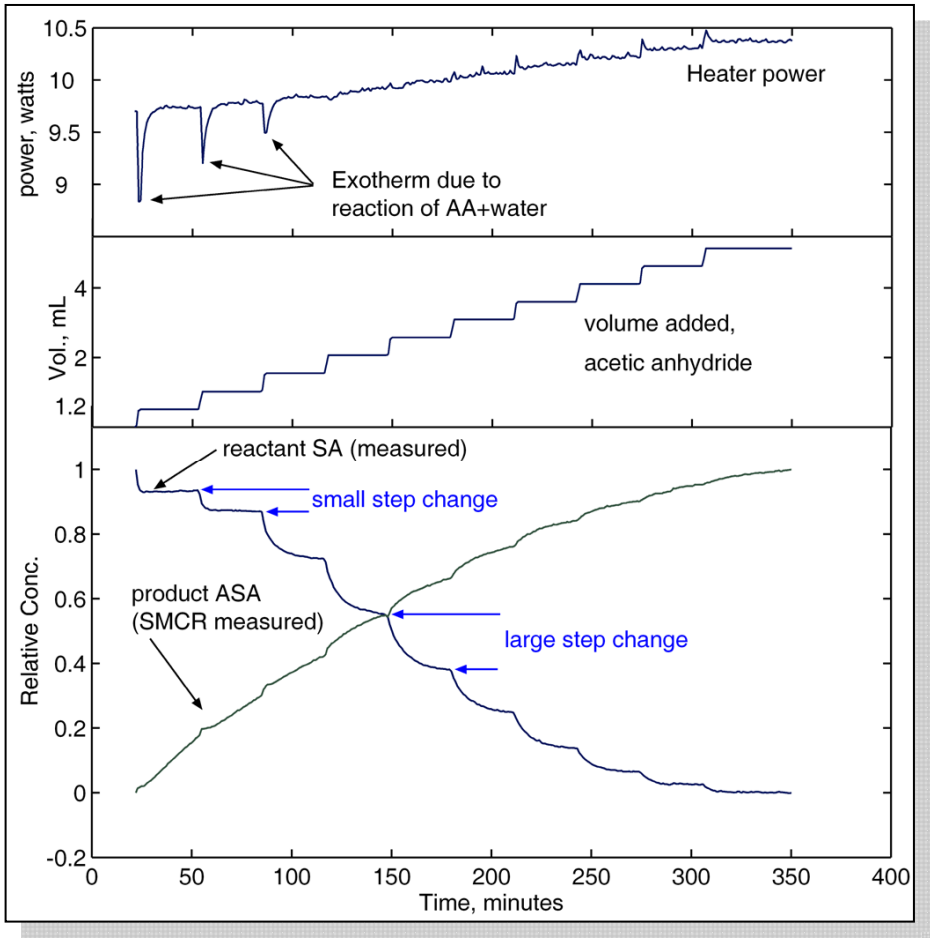
- Experimental details
  - Circulator system: Julabo F25-HD
  - Reactor type: 50 mL glass reactor
  - Initial charge:
    - 3.0 g salicylic acid
    - 15 mL acetonitrile
    - 0.2 mL H_2SO_4
  - Reagent addition
    - 0.75 mL acetic anhydride @ 0.75 mL/min.
    - 5 additions @ 25 min intervals
  - Calorimeter settings:
    - Const temp power comp mode
    - Jacket temp: 55°C
    - Reactor temp: 60°C



- UV/Vis spectra
  - Equitech CCD
  - 3 bounce ATR probe
  - Spectra recorded @ 30 s intervals

Calorimetry profiles from batch reaction

- Composition profiles estimated from SMCR
  - Fast rate of reaction observed in early steps
  - Small amt product formed in early steps
  - Large reaction exotherm in early steps



Kinetic Fitting Algorithm

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1. Postulate model

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6. Adjust model parameters to minimize **R** using nonlinear least-squares (Levenberg/Marquardt)
7. Repeat steps 3, 4, 5, and 6 until no further improvement is observed in **R** or maximum number of steps exceeded.

The reactions and model parameters

$$AA + SA \xrightarrow{k_1} I \xrightarrow{k_2} ASA + HA$$

$$AA + W \xrightarrow{k_3} 2\,HA$$

$$AA + ASA \xrightarrow{k_4} ASAA + HA$$

SA: salicylic acid
AA: acetic anhydride
I: reactive intermediate
ASA: acetyl salicylic acid
ASAA: acetylsalicylic anhydride
W: water
HA: acetic acid

Reactor is filled with SA and AA is injected in the reactor

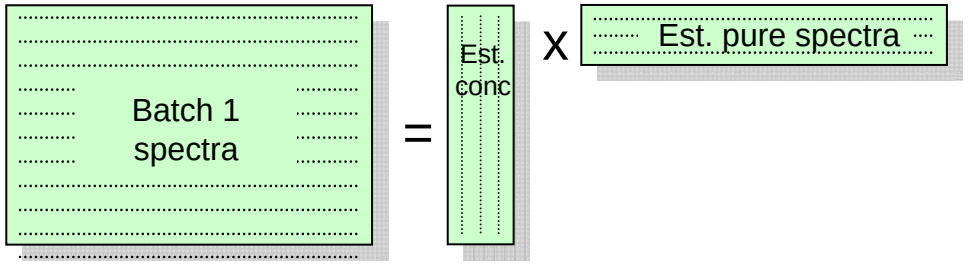
Estimated model parameters:
C_W k_1, k_2 , k_3 , k_4

Isothermal model with flow-in reagents

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

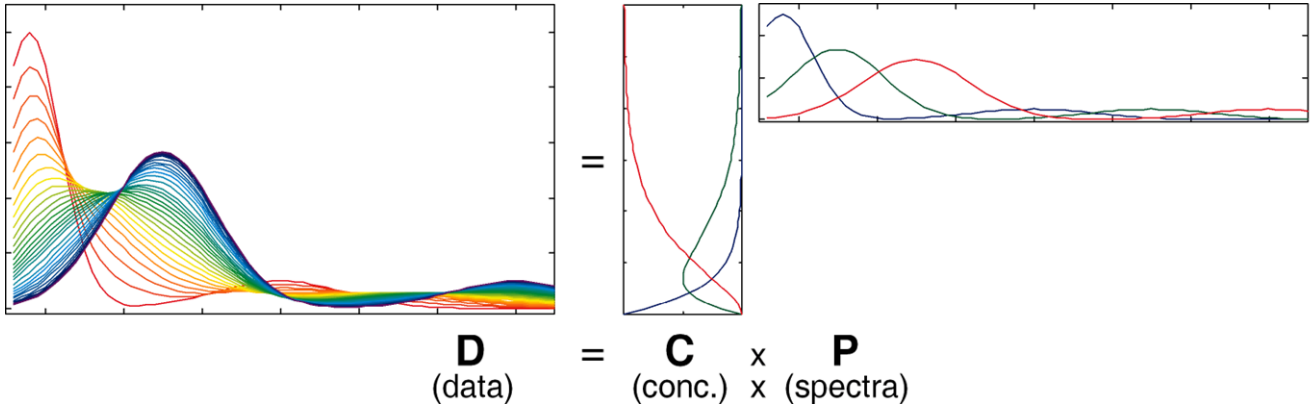
$$\frac{dC_{AA}}{dt} = -r_1 - r_3 - r_4 + \frac{C_{AAin} - C_{AA}}{V} F_{AA}$$
$$\frac{dC_I}{dt} = r_1 - r_2 - \frac{C_I}{V} F_{AA}$$
$$\frac{dC_{SA}}{dt} = -r_1 - \frac{C_{SA}}{V} F_{AA}$$

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



Kinetic fitting – details for step 5

5. Fit kinetic profiles to measured spectra using linear least-squares



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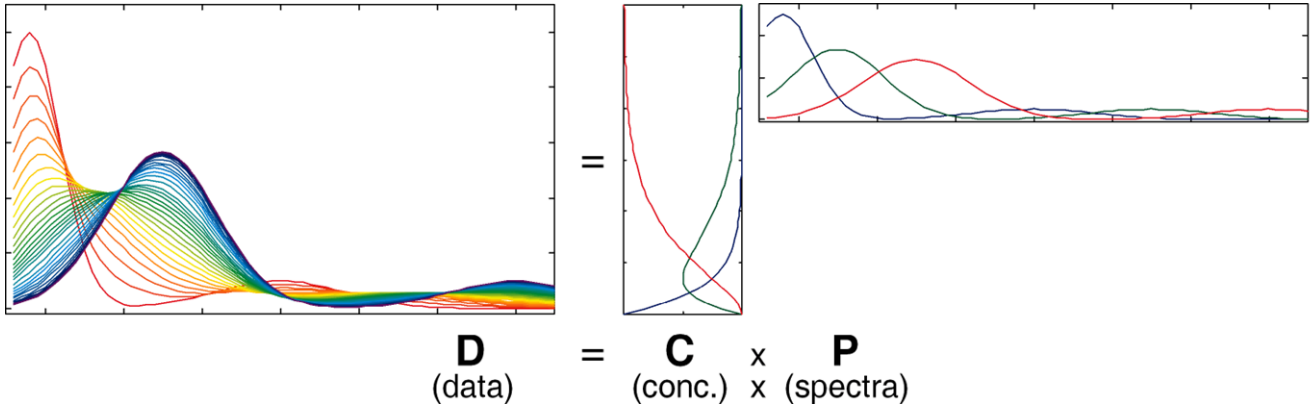


$$\hat{\mathbf{D}} = \hat{\mathbf{C}}\hat{\mathbf{P}}^{T}$$

$$\mathbf{R} = \mathbf{D} - \hat{\mathbf{D}}$$

Motivation - application to a DuPont batch slurry process

- Develop a kinetic model for a DuPont's sulfonylurea coupling reaction (heterogeneous reaction) for monitoring purposes
- Modify kinetic models to include:
  - Dissolution of starting material A & flow-in of reagent B
  - Nucleation and crystallization of product, P
  - Make optical measurements in light-scattering medium
- Kinetic models with flow-in impose strict mass balance
- Develop low-theory models for dissolution, nucleation and crystallization
  - avoid high-theory and medium-theory models (e.g. population balance equation)

High-theory model: population balance equations

Nucleation (B)

$$J_{NI} = A_I \exp[\frac{-B_I}{(\ln \beta)^2}]$$

$$J_{NII} = A_{II} S \exp[\frac{-B_{II}}{\ln \beta}]$$

Crystal Growth (G)

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

Population Balance Equation

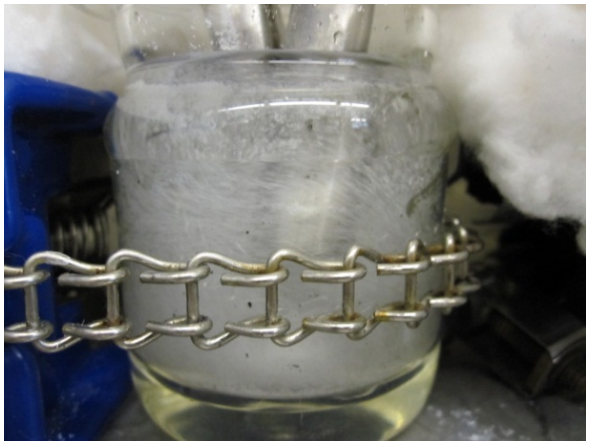
$$\frac{1}{V}\frac{\partial \psi V}{\partial t} + \frac{\partial \psi G}{\partial L} = (J_{NI} + J_{NII})\delta(L - L^*)$$

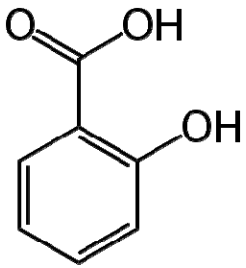
Blandin, A.; Mangin, D.; Nallet, V.; Klein, J.; Bossoutrot, J. *Chemical Engineering Journal*, **2001**, 81, 91-100

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

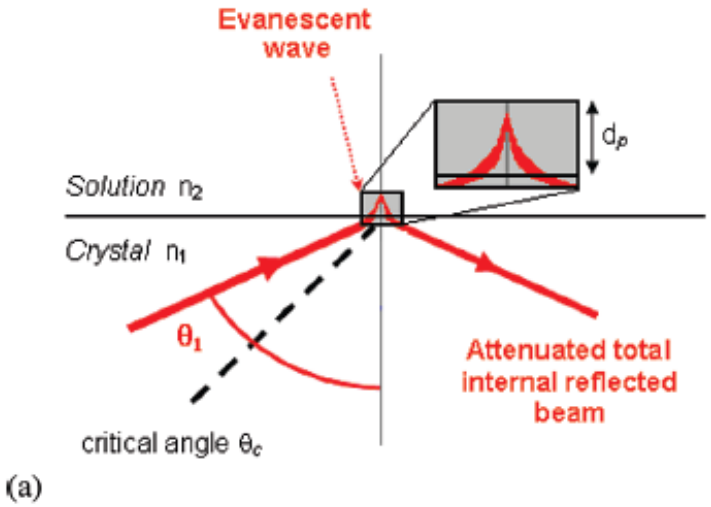




Salicylic acid
M.W. 138.12 g mol^{-1}
pKa 2.97
Monoclinic

Instrumentation – making optical measurements in light scattering systems

ATR UV-vis Spectroscopy



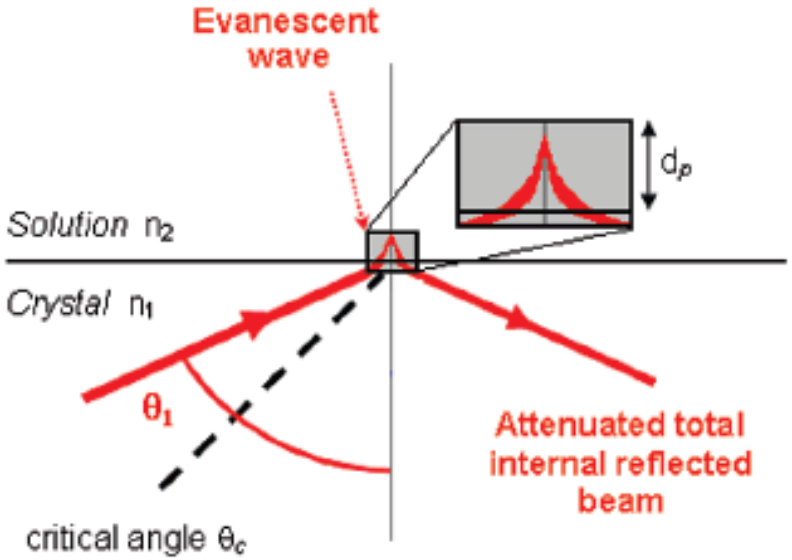
Total Internal Reflection

NIR Diffuse Reflectance Spectroscopy

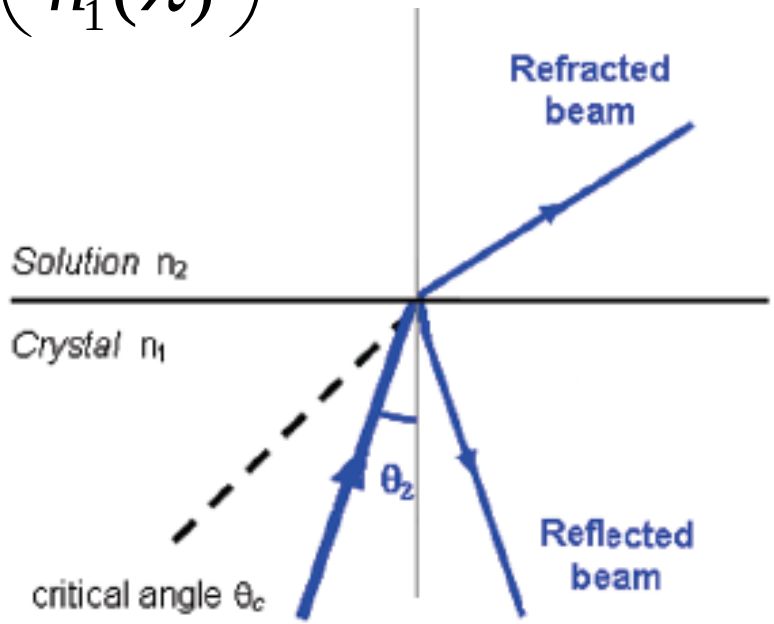
Diffuse Reflectance

Principle of attenuated total reflectance (ATR)

$$\theta_c(\lambda) = \arcsin\left(\frac{n_2(\lambda)}{n_1(\lambda)}\right)$$



Total Internal Reflection



External Reflection

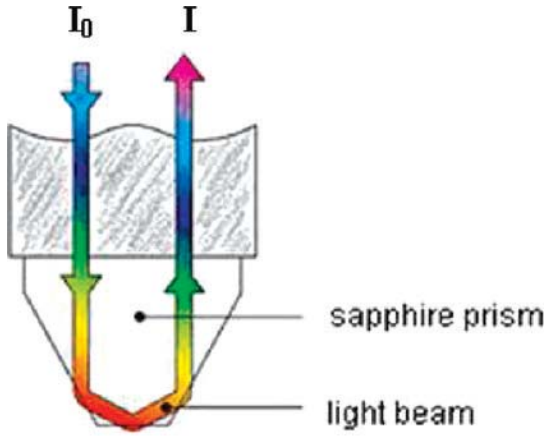
Principle of attenuated total reflectance (cont.)

Critical Refractive Index $n_{crit} = n_1 \sin\theta$

Absorbance (attenuated) $A = \log(\frac{I_0}{I})$

Beer Lambert's Law $A(\lambda) = \varepsilon(\lambda)Cl$

$l = zd_p$

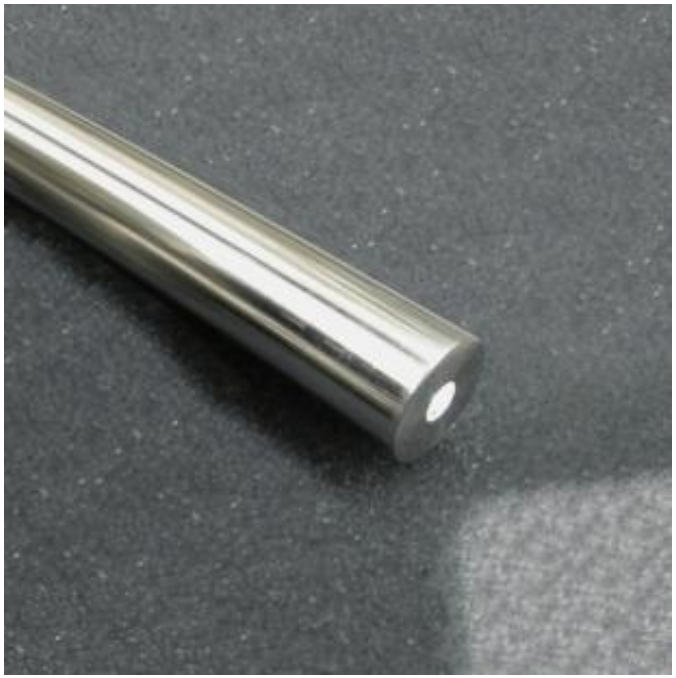


Depth of penetration $d_p = \frac{\lambda}{2\pi\sqrt{(n_1)^2 \sin^2\theta - (n_2)^2}}$

Spectroscopic probes

NIR Spectroscopy

Diffuse Reflectance Probe



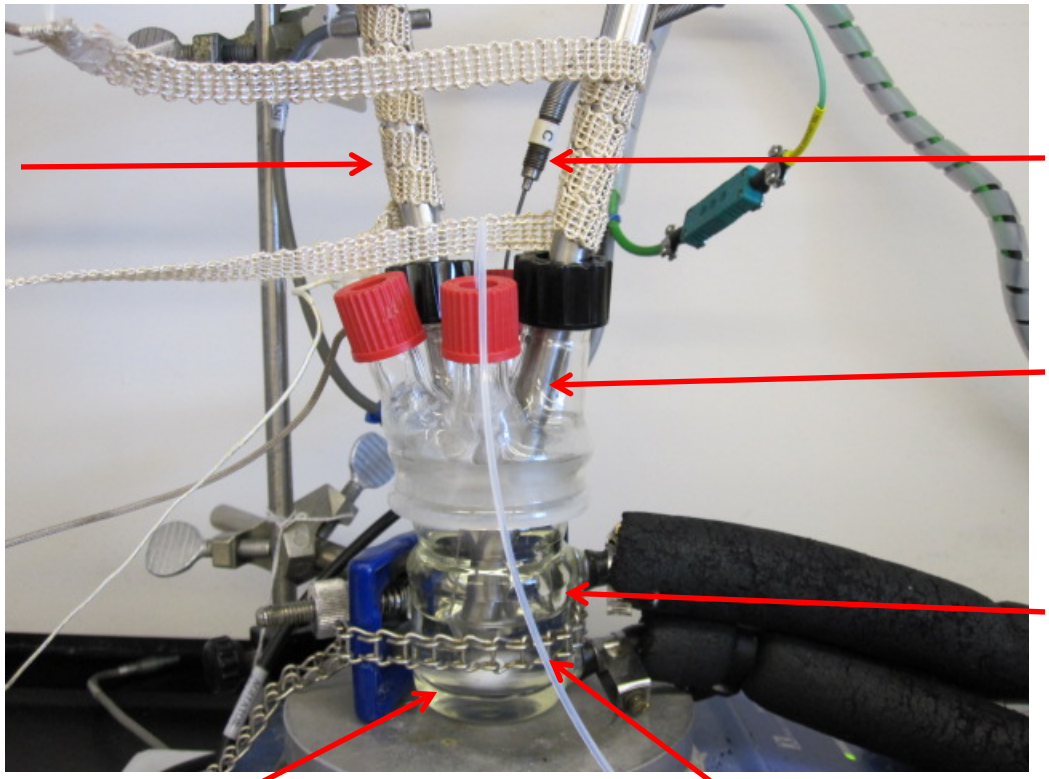
1100 nm - 2500 nm

ATR UV-vis Spectroscopy

ATR Probe (sapphire crystal)

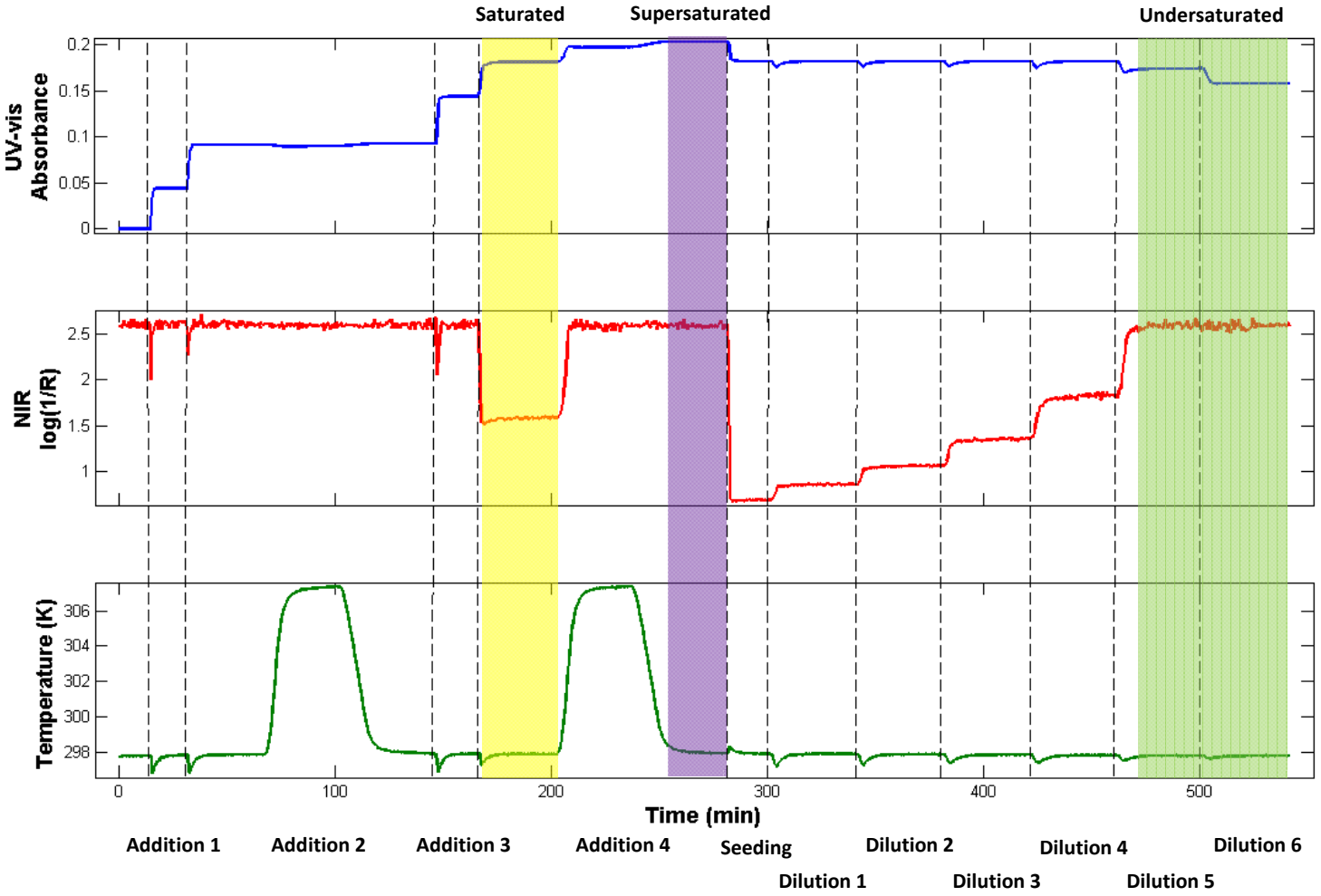
200 nm - 1020 nm

In-house miniature semi-batch reactor



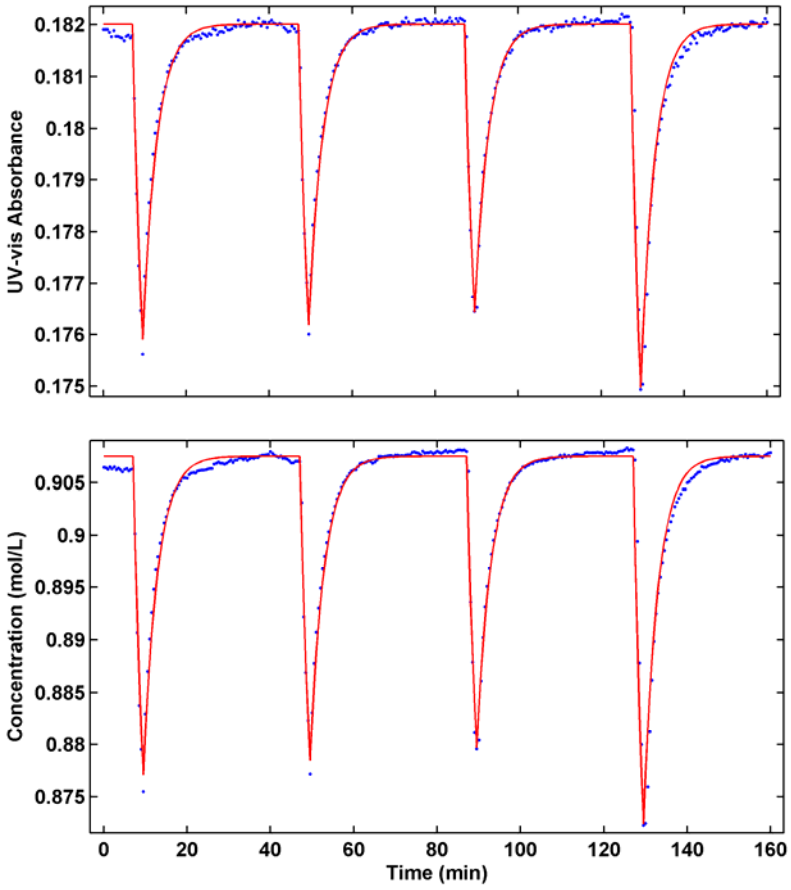
Full description of the reactor in Gemperline et al, Analytical Chemistry 76 (2004) 2575-2582

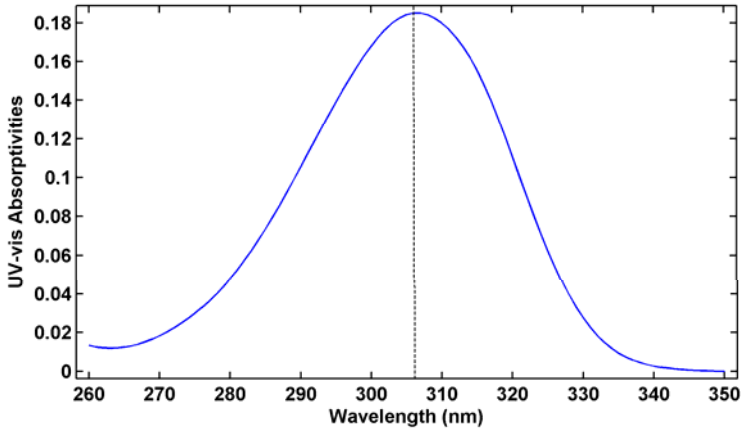
Dissolution of salicylic acid



Kinetic modeling of dissolution (UV-vis)

At 307 nm





Original model

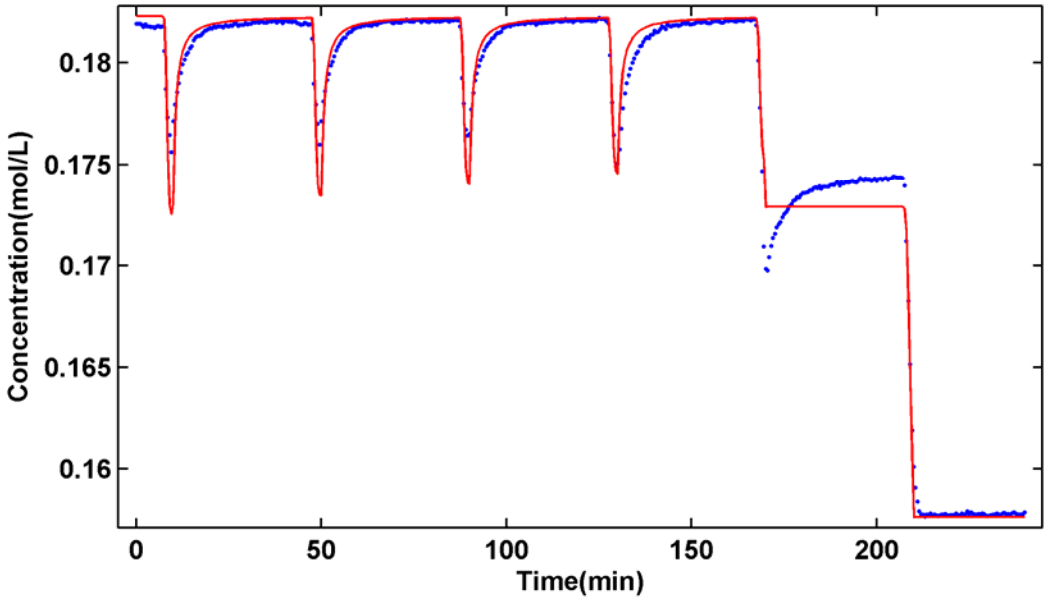
$$r = k(c_{sat} - c)^n$$

Initial conditions:

1. Initial volume (V_0)
2. Initial concentration (C_0)
3. Initial mass (m_0)
4. Saturation limit (C_{sat})
5. Flow rate (F)
6. Dosing time (t_{dos})

Adjusted parameters:

1. Rate constant (k)
2. Power coefficient (n)



Problems:

1. Significant offset for the dilution steps when the real flow rate data is applied
2. Inconsistencies of SA mass profile between modeled and measured profiles
3. Worse result when 5th and 6th dilution steps are included

Approaches

Combined soft-hard modeling

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

- Singular Vector Decomposition (SVD)

- **Problems:**
  1. The result was too good, received a perfect fit every single time!
  2. Soft modeling portion of the model dominated over hard modeling portion of the model

Modified Beer's Law

$$\mathrm{Y} = \mathrm{C} \cdot \mathrm{A} + \int m_s^{\,n}$$

- Investigated the shielding effects **(e.g. surface enhancement effects)** on ATR sapphire crystal surface by introducing term into Beer's Law

- **Problems:**
  1. Huge offset still remained for all six dilution steps

Modified kinetic model

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

Initial conditions:

1. Initial volume (V_0)
2. Initial concentration (C_0)
3. Initial mass (m_0)
4. Saturation limit (C_{sat})
5. Flow rate (F)
6. Dosing time (t_{dos})

Adjusted parameters:

1. Rate constant (k)
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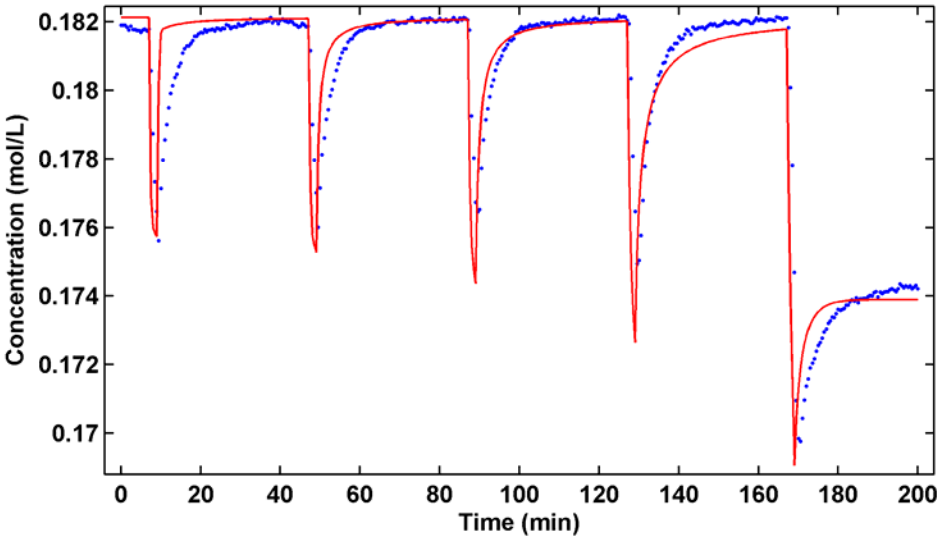


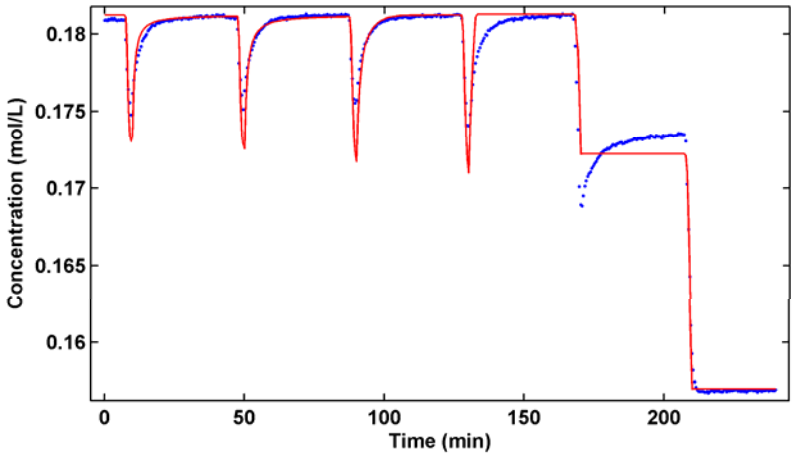
k >= 1000 L^{n-1}/(mol^{n-1}min), n = 6.85

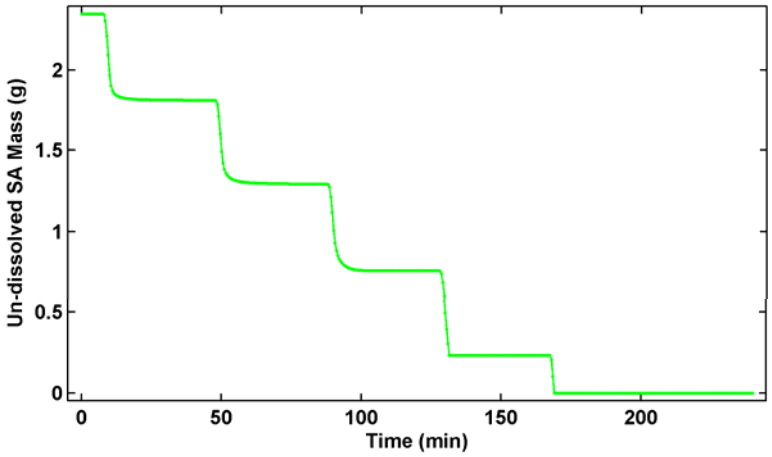
Problems:

1. Poor fitting for dilution steps 1, 4 and 5. It got worse when 6th (pure dilution) step is included
2. Optimized rate constant (k) and power coefficient (n) weren't realistic

Combined mass transfer and dissolution model

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





k_d = 1.1168 $L^{n-1}/(mol^{n-1}min)$, n = 1.80
k_m = 0.0146 $L^{n-1}/(mol^{n-1}min)$, m = 1.00

- Poor fitting for 4th and 5th dilution and dissolution steps
- Sharp decrease around 130 min

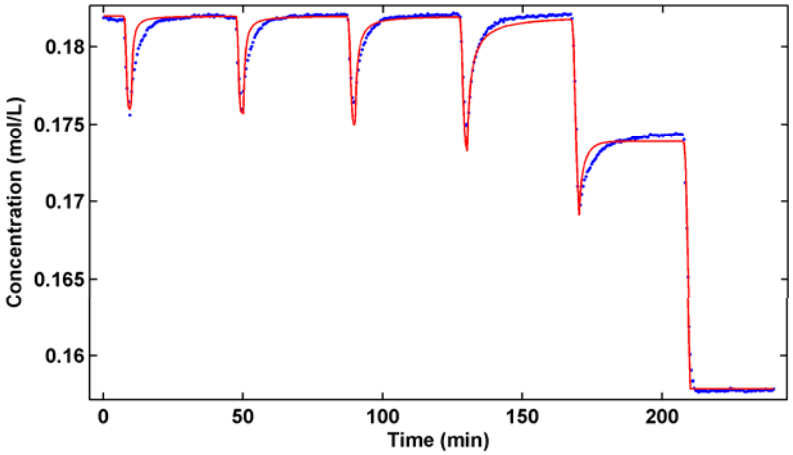
New results

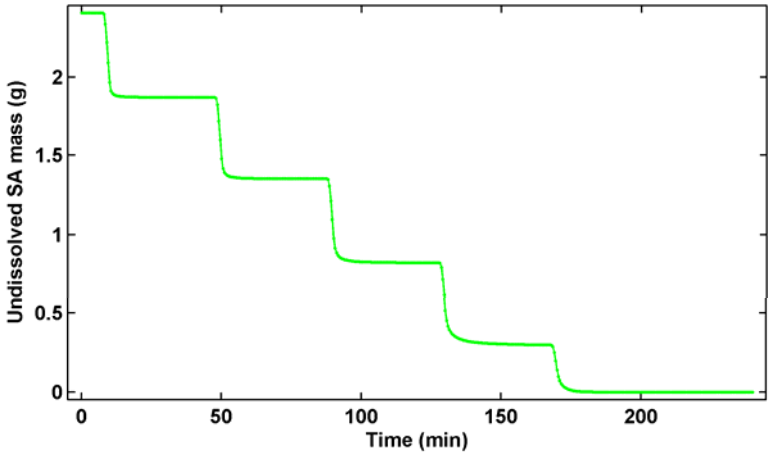
Hessian matrix

1.0000	-0.9802	0.0360	0.0120
-0.9802	1.0000	0.0385	0.0369
0.0360	0.0385	1.0000	0.8358
0.0120	0.0369	0.8358	1.0000

Modified kinetic model

$$rd = kd \cdot m \cdot (c_{sat} - c)^n$$





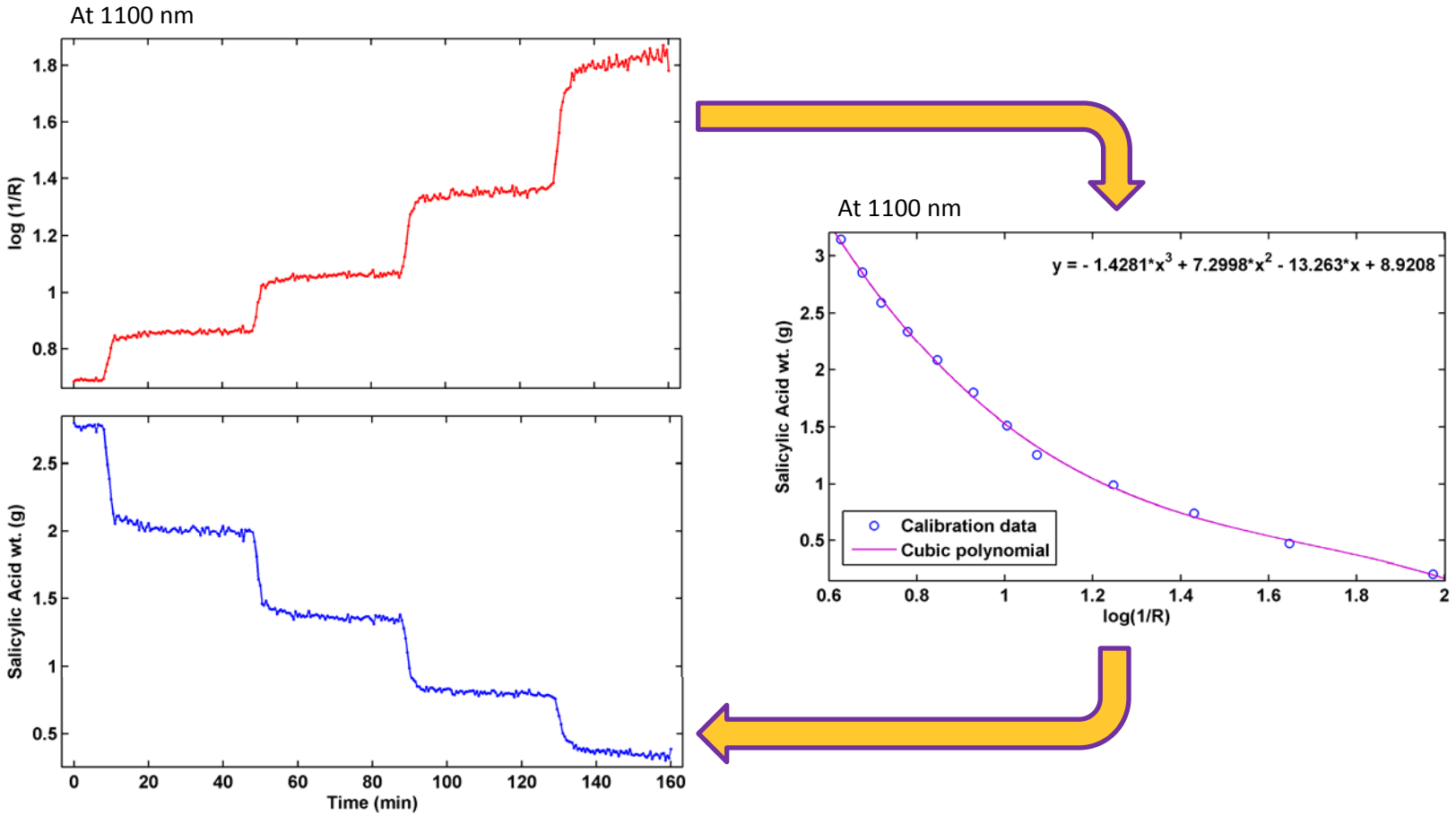
Initial conditions:

Dissolution rate constant (k_d) = 16.2106 $L^{n-1}/(mol^{n-1}min$
Order parameter (n) = 1.7357
Undissolved SA mass (m_0) = 2.3452 g
Initial volume (V_0) = 22.7 mL

Optimized Parameters:

Dissolution rate constant (k_d) = 16.2759 $L^{n-1}/(mol^{n-1}min)$
Order parameter (n) = 1.7367
Undissolved SA mass (m) = 2.40293 g
Initial volume (V_0) = 20.8 mL

Dissolution seen from solid phase (NIR)

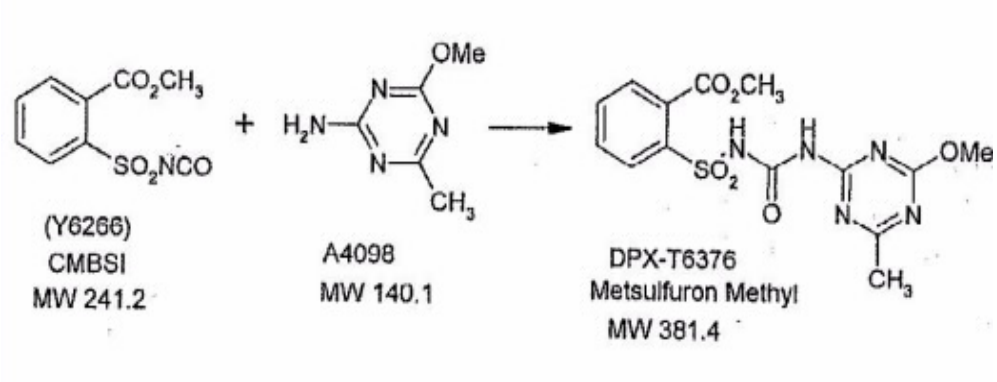


Project 2: modeling of sulfonylurea coupling reaction

- 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.

Sulfonylurea coupling reaction



Model System T6376

- Slurry-based synthesis of sulfonylureas
- A4098 and T6376 both have limited solubility in xylene
- Temperature: 80 ~ 85 Celsius
- Total Reaction Time: approx. 140 min

Reagents & Product

- A4098 (reactant) - 2-amino-4-methoxy-6-methyl-1,3,5-triazine
- Y6266 (CMBSI) - benzoic acid 2-[(Isocyanato)sulfonyl]-methyl ester
- D8055 (derivative form of CMBSI)
- T6376 (product) - Metsulfuron Methyl

Kinetic model of DuPont slurry coupling reaction (proposed)

$A_s \rightarrow A$	$r_d = k_d (C_A - C_{Asat})^d$	dissolution of A
$A + B \rightarrow P$	$r_1 = k_1 C_A C_B$	coupling reaction
$P \rightarrow P_s$	$r_n = k_n (C_P - C_{Psat})^n$	nucleation
$P \rightarrow P_s$	$r_g = k_g C_{Ps} (C_P - C_{Psat})^g$	crystal growth

$$\frac{dV}{dt} = F$$

Flow rate of B_{in}

$$\frac{dC_{As}}{dt} = -r_d - \frac{C_A}{V}F$$

Dissolution of A

$$\frac{dC_A}{dt} = r_d - r_1 - \frac{C_A}{V}F$$

Reaction of A

$$\frac{dC_B}{dt} = -r_1 + \frac{C_{Bin} - C_B}{V}F$$

Reaction of B

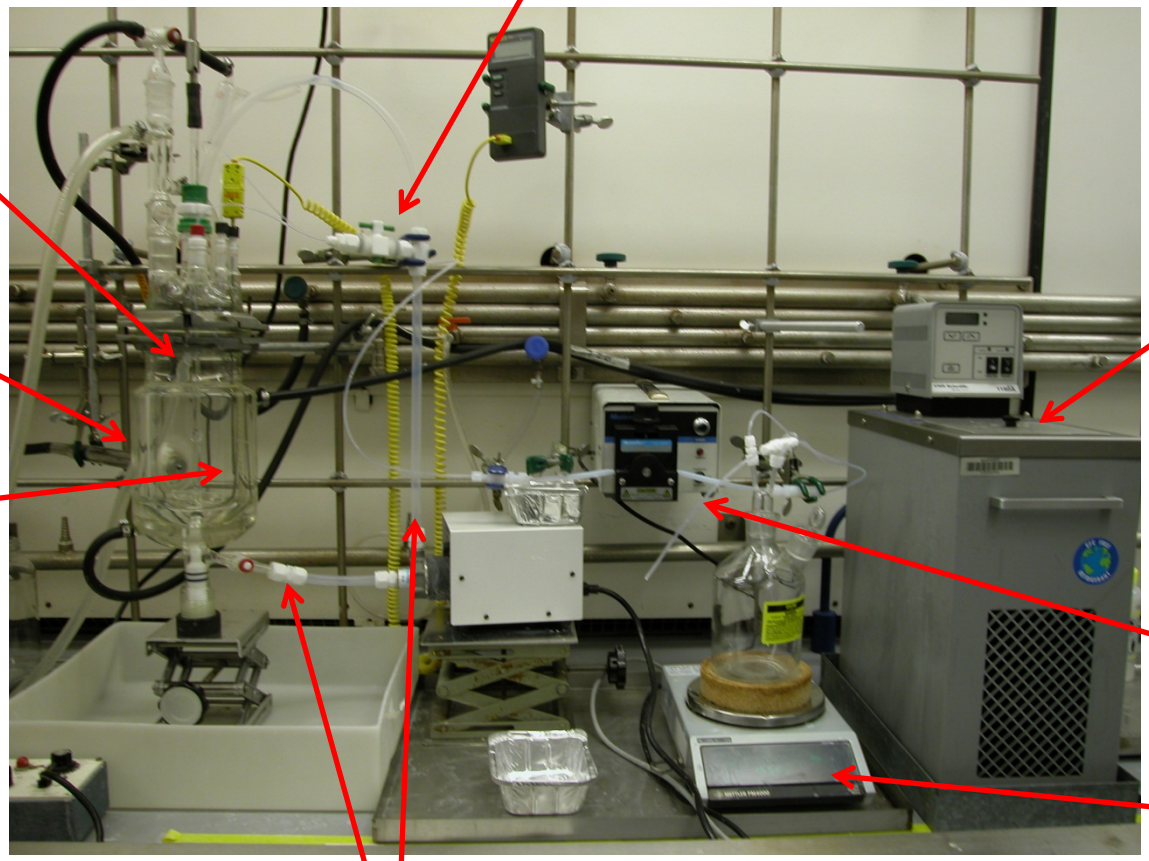
$$\frac{dC_P}{dt} = r_1 - r_n - r_g - \frac{C_P}{V}F$$

Formation of P

$$\frac{dC_{Ps}}{dt} = r_n + r_g - \frac{C_{Ps}}{V}F$$

Precipitation of P

Apparatus setup at DuPont

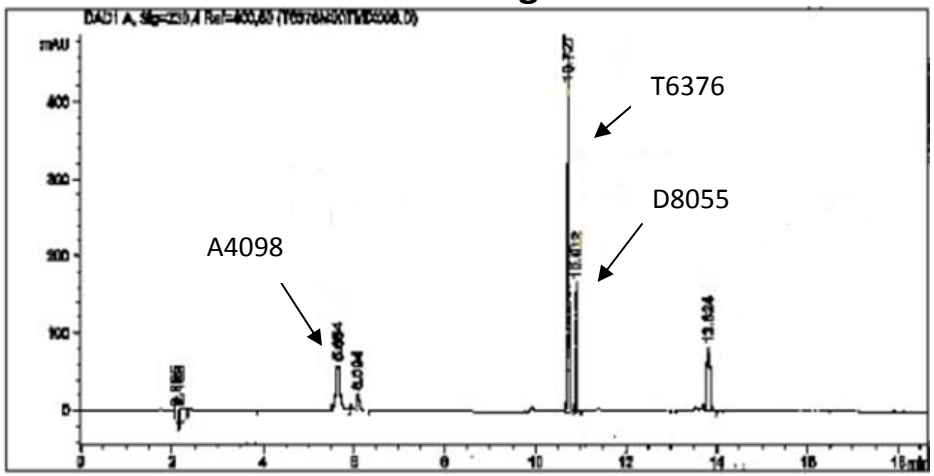


Experimental protocol

Description	Real Time	Target Time	Exp. Time	Spectra # B/A	Temp C	CMBSI R. wt. (g)	Total CMBSI Added (g)
No CMBSI 0% Reaction							
Started Collecting NIR Spectra	10:28 AM	5	0	2 ~ 12	79	470.42	-
Sampling Time	10:33 AM	4	5	12 ~ 20	79.6	470.42	-
25% of Coupling Rxn							
Pump On Time	10:37 AM	11	9	20 ~ 42	80	470.42	-
Pump Off Time	10:48 AM	-	20	42 ~ 82	79.6	354.95	115.47
Equilibrium Time	10:48 AM	20	20	-	-	-	-
Sampling Time	11:08 AM	2	40	82 ~ 86	80.7	354.95	115.47
50% of Coupling Rxn							
Pump On Time	11:10 AM	11	42	86 ~ 108	80.8	354.95	115.47
Pump Off Time	11:21 AM	-	53	108 ~ 148	81.1	238.44	231.98
Equilibrium Time	11:21 AM	20	53	-	-	-	-
Sampling Time	11:41 AM	2	73	148 ~ 152	82.8	238.44	231.98
75% Coupling Rxn							
Pump On Time	11:43 AM	11	76	152 ~ 174	82.5	238.44	231.98
Pump Off Time	11:54 AM	-	87	174 ~ 214	81.5	122.07	348.35
Equilibrium Time	11:54 AM	20	87	-	-	-	-
Sampling Time	12:14 PM	3	107	214 ~ 220	84.4	122.07	348.35
100% Coupling Rxn							
Pump On Time	12:17 PM	11	110	220 ~ 242	83.7	122.07	348.35
Pump Off Time	12:28 PM	-	121	242 ~ 282	81.8	15.9	454.52
Equilibrium Time	12:28 PM	20	121	-	-	-	-
Sampling Time	12:48 PM	4	141	282 ~ 290	83.3	15.9	454.52

High performance liquid chromatography

Chromatogram



Specifications

LC System	Agilent 1100 with DAD detector
LC Column	Zorbax Eclipse C-18 (25 cm x 4.6 mm, 5um)
Column Temp	40 C
Inj. Volume	10 uL
Flow Rate	1.5 mL/min
Detector Wv.	230 nm for A4098 and D8055, 270 nm for T6376
Retention Time	5.65 min (A4098), 10.73 min (T6376), 10.91 min (D8055)
Mobile Phase	Acetonitrile (Solvent B), pH 3 Water (Solvent A)

Gradient Method

Time (min)	Solvent B % (ACN)	Solvent A % (Water)
0	0	100
6	12	78
9	70	30
15	70	30
10 (Post Time)	0	100

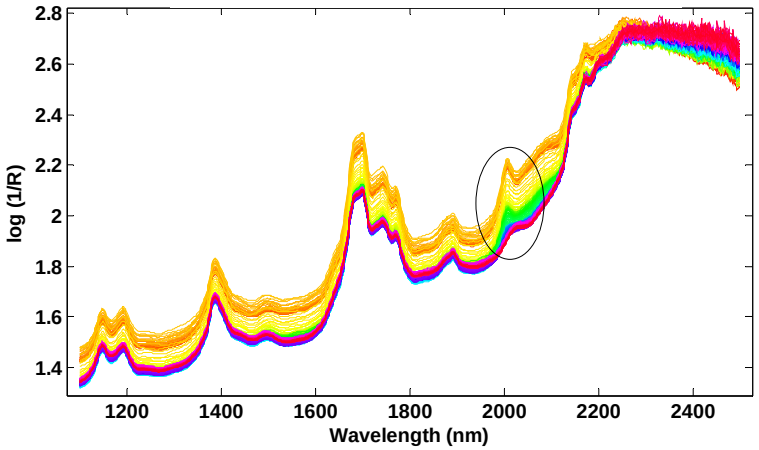
DuPont's HPLC methods Y6266.220.01.BE (Nov. 1, 2000), T6376.220.01.ES (Feb. 25, 1999), T6376.220.05.ES (Sep 21, 2004).

Comparison of two sampling methods

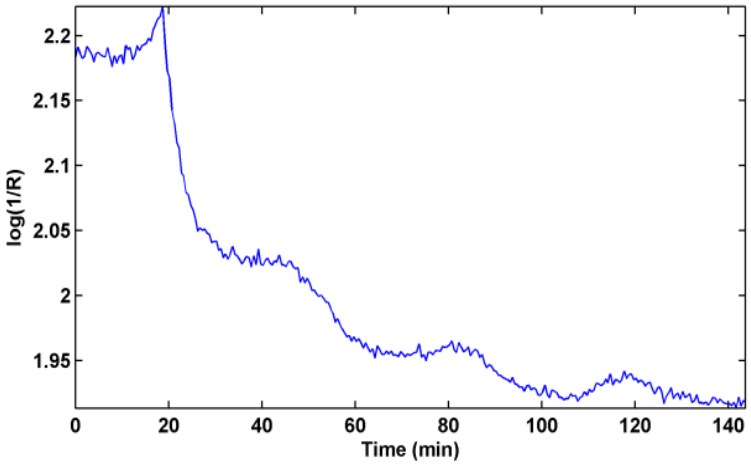
Sampling method (1)	Sampling method (2)
1. Transfer 20 µL out of 3 to 3.5 mL of the slurry sample (with a stir-bar) into a 25 mL glass vial. 2. Dilute the transferred amount with 20 mL of a 90% ACN and 10% IPA solution (Dilution Ratio 1:1000). 3. Sonicate for 10 min at 25°C.	1. Transfer 3 mL out of 3 to 3.5 mL of the slurry sample (without a stir-bar) into a 100 mL or 200 mL volumetric flask. 2. Dilute the transferred amount with 90% ACN and 10% IPA solution. 3. Sonicate for 15 min to 2 hours with a temperature between 25 to 60°C. 4. Transfer 333 µL out of the 100 mL volumetric flask or 666 µL out of the 200 mL volumetric flask into a 10 mL of volumetric flask. 5. Dilute the transferred amount with a 90% ACN and 10% IPA solution (Dilution Ratio 1:1000).

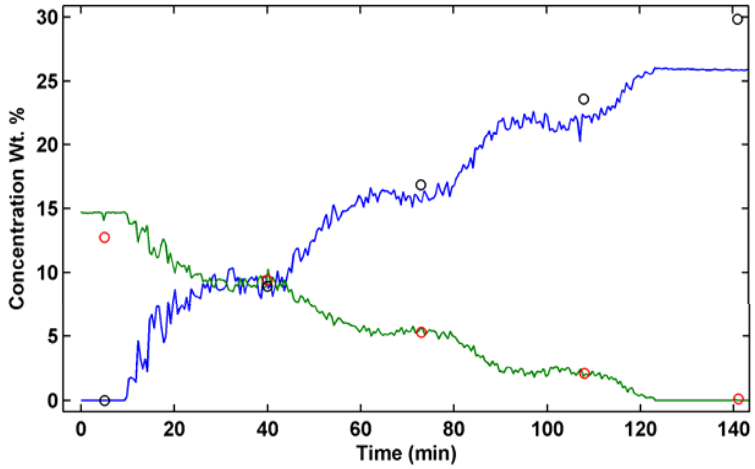
Slurry Sample #	A4098		D8055		T6376	
SS 1 – Average	9.42%	9.81%	0.30%	0.57%	8.95%	9.37%
SS 1 – STD	0.0773%	0.0460%	0.019%	0.057%	0.671%	0.450%
SS 2 – Average	5.31%	5.73%	0.29%	0.55%	16.85%	16.89%
SS 2 – STD	0.0879%	0.0577%	0.044%	0.038%	0.5666%	0.2788%
SS 3 – Average	2.08%	1.94%	0.30%	0.62%	23.60%	23.47%
SS 3 – STD	0.0192%	0.0319%	0.0077%	0.11%	0.1659%	0.7028%
SS 4 – Average	0.13%	0.70%	1.57%	0.46%	29.81%	25.53%
SS 4 - STD	0.10%	0.014%	0.0117%	0.014%	0.2247%	0.7819%
	3 mL	20 uL	3 mL	20 uL	3 mL	20 uL

Sulfonylurea coupling reaction (NIR)



At 2010 nm





Summary & future work

Project 1

(dissolution of salicylic acid)

- ATR UV-vis and NIR diffuse reflectance spectroscopy were used to monitor liquid and solid fractions of the dissolution of salicylic acid in a solvent mixture
- A power law equation was successfully used to model all six dissolution steps for the liquid phase, with k = 16.2759 $L^{n-1}/(mol^{n-1}min)$ and n = 1.7367
- Integrate NIR measurements into our model to validate and improve the estimated solid fraction
- Attempt to model the crystallization of salicylic acid

Project 2

(sulfonylurea coupling reaction)

- Fitting combined kinetic model to the batch reaction data to estimate the kinetic of the reaction, dissolution and crystallization
- Intentionally introduce perturbation into the batches and see if our monitoring method can quantify the degree of perturbation

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