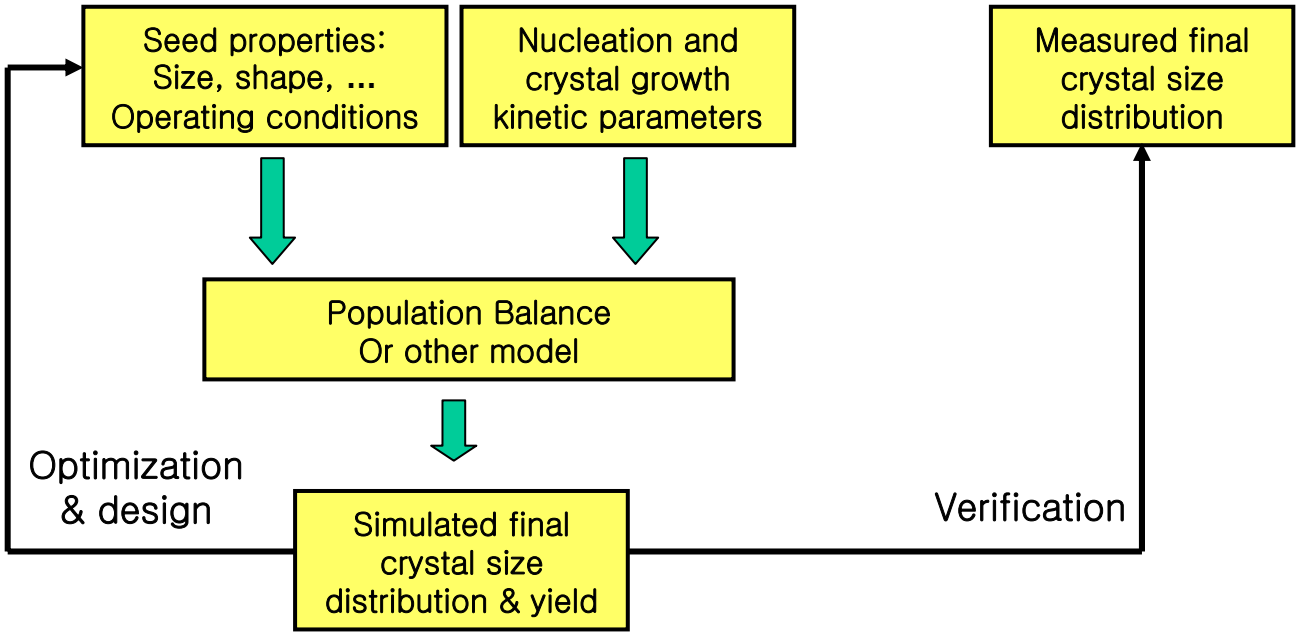
냉각 결정화 기술의 응용전략-2

고려대 화공생명공학과
양대륙

결정화공정의 모델링

결정화 모델의 구성 및 활용



Model for batch cooling crystallization

- **Model for the crystallizer**
  - **For modeling crystallization process, PBE is employed.**

$$\frac{\partial f(L,t)}{\partial t} = -\frac{\partial [G(L,t)\cdot f(L,t)]}{\partial L} \qquad f(0,t) = -\frac{B^0}{G\big|_{L=0}}$$

where, f is the population density of crystals, t is the time, L is the size of the particles, and G is the growth rate. (No breakage or agglomeration)

  - **The overall growth rate is given by**

$$G = k_g(T,L)\cdot \Delta c^g$$

where Δc is the difference of the concentration in the solution, c, and the saturation concentration c^*. And K_g is the growth kinetic parameter.

Model for batch cooling crystallization

- **The growth kinetic parameter, k_g**

$$k_g(T,L) = k_0 \exp\left(\frac{-E_g}{RT}\right)(1+k_1 L)^{k_2}$$

where, f is the population density of crystals, t is the time, L is the size of the particles, and G is the growth rate.

- **The mass balance**

$$\frac{dc}{dt} = -\rho \cdot k_v \frac{d\mu_3}{dt}$$

where, μ_3 is the third moment of the CSD

- **The third moment of the CSD**

$$\mu_3 = \int_0^\infty n \cdot L^3 dL$$

Model for batch cooling crystallization

- **The nucleation rate**

$$B^0 = k_b(T) \cdot \Delta c^{\beta}(T)$$

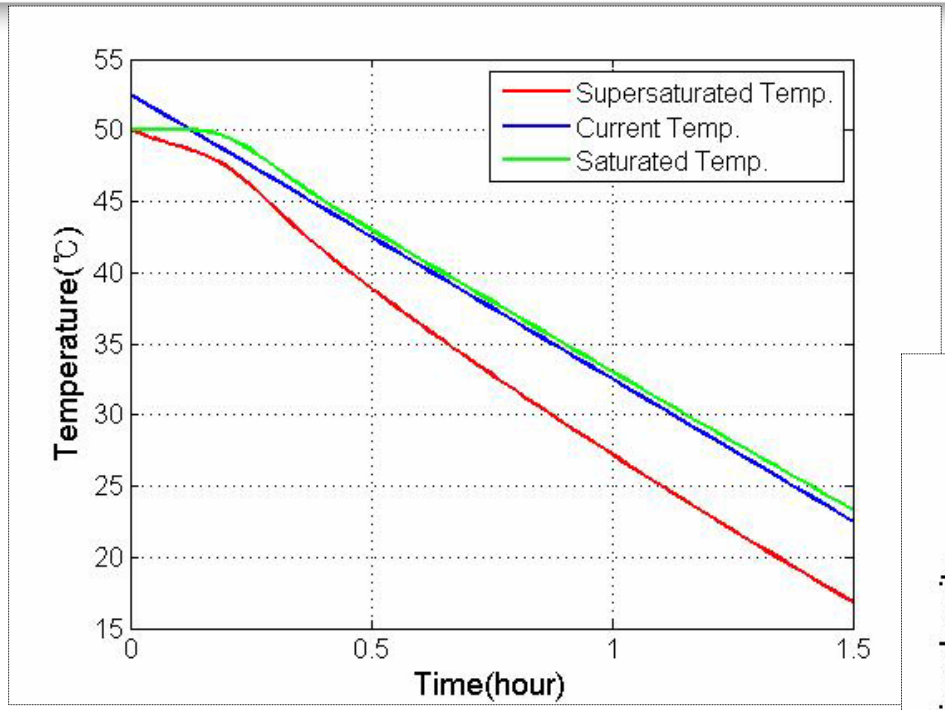
  - **The nucleation occurs if the metastable limit is violated.**
- **The population density of crystals is expressed as following equation,**
  - **The method which was suggested by Hu et al. [2] provides a means to reduce the PBE to a set of algebraic equations.**

$$f(L_i, t_{j+1}) \approx \frac{f(L_i, t_j)}{1 + \left.\frac{\partial G(L,t)}{\partial L}\right|_{L=L_i} \Delta t}$$

- $L_{i,j+1}$ **is given by**

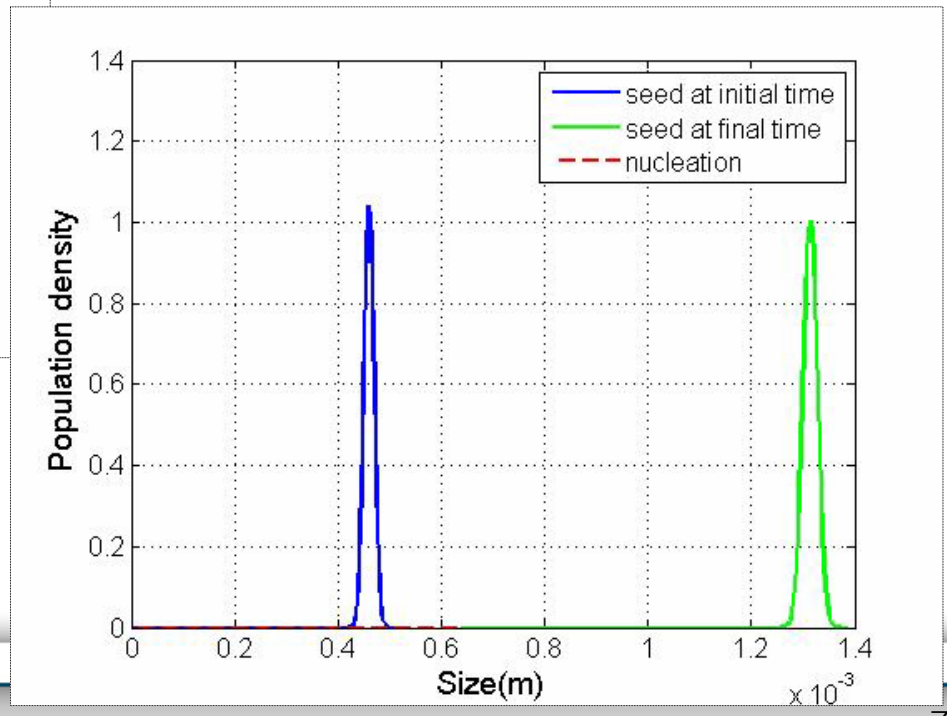
$$L_{i,j+1} \approx G(L_{i,j}, t_j)\Delta t + L_{i,j}$$

Simulation results of static MSL model with PBE



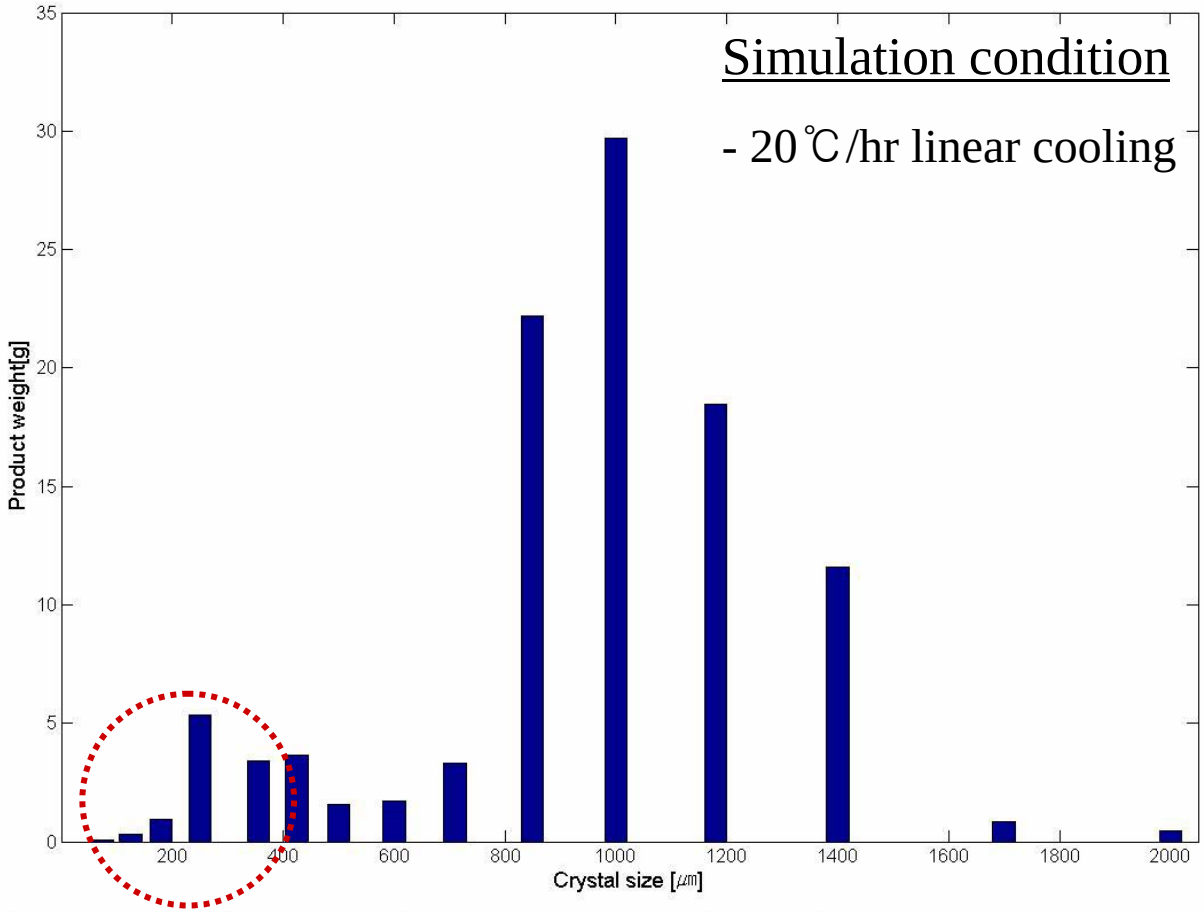
Simulation condition

- 20℃/hr linear cooling



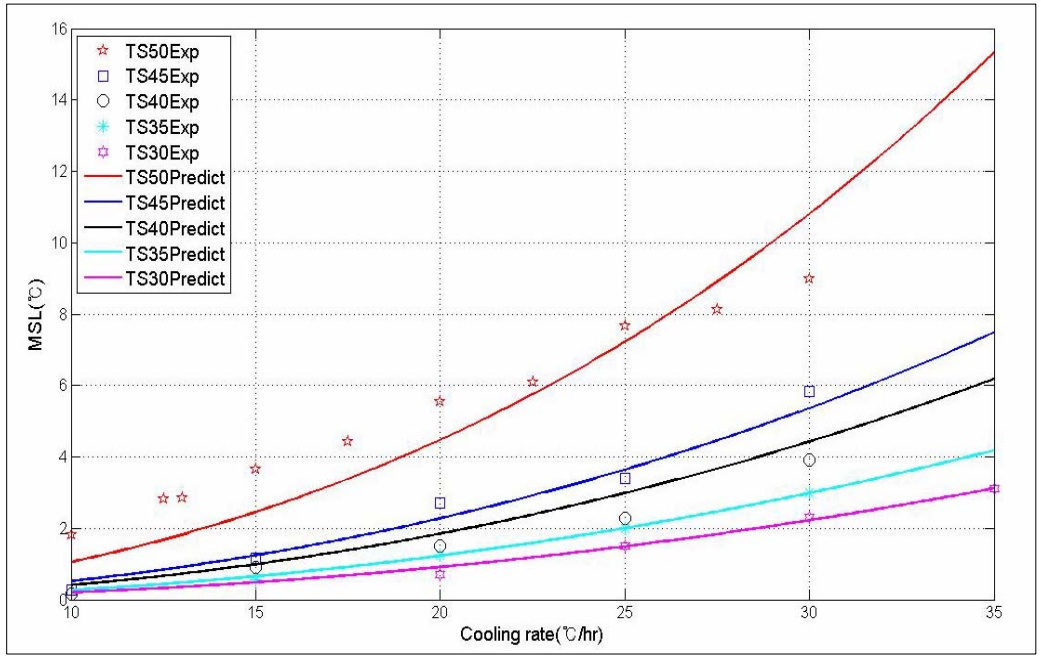
In this results nucleation are not happened.

Crystal size distribution of static MSL model (CV = 34%)



Nucleation are happened in experimental results.

Dynamic MSL model parameters

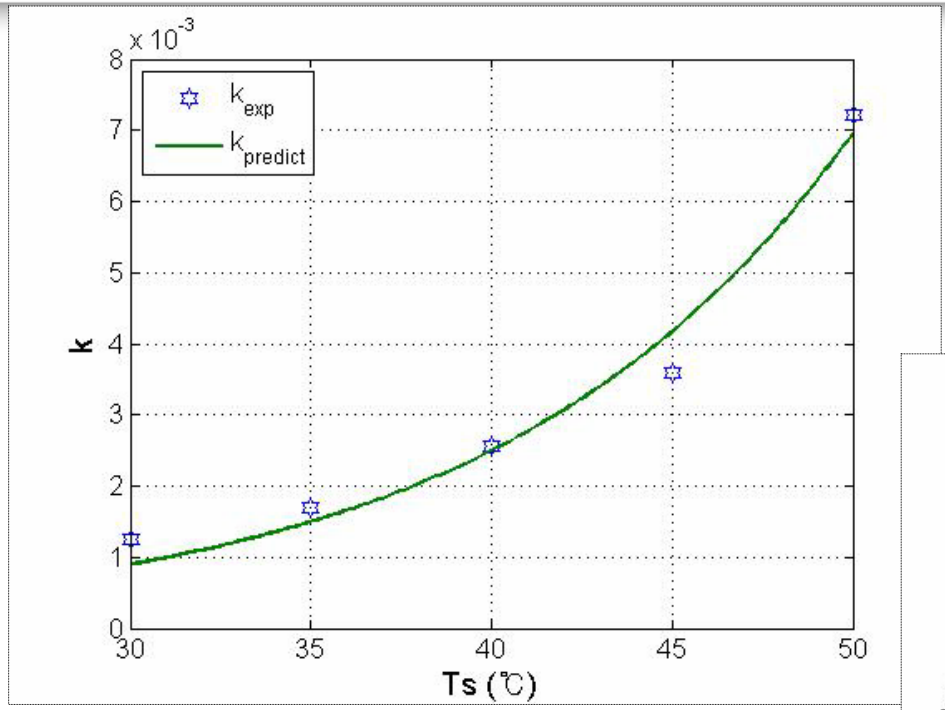


1.The parameter of MSL model are function of saturation temperature.

2.The value of parameter ‘p’ is fixed at 2.2 from experimental results.

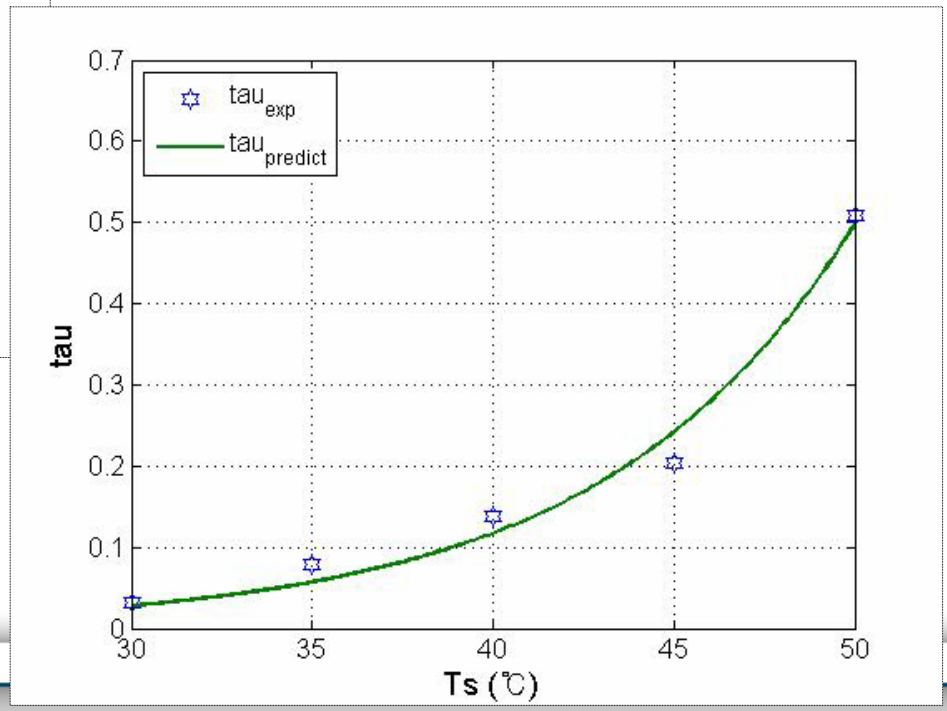
Saturation Temp.(℃)	k	tau
50	0.0067970	0.308611
45	0.0035823	0.203221
40	0.0025686	0.138270
35	0.0016849	0.0788168
30	0.0012498	0.0316436

Relation of model parameter & saturation temperature

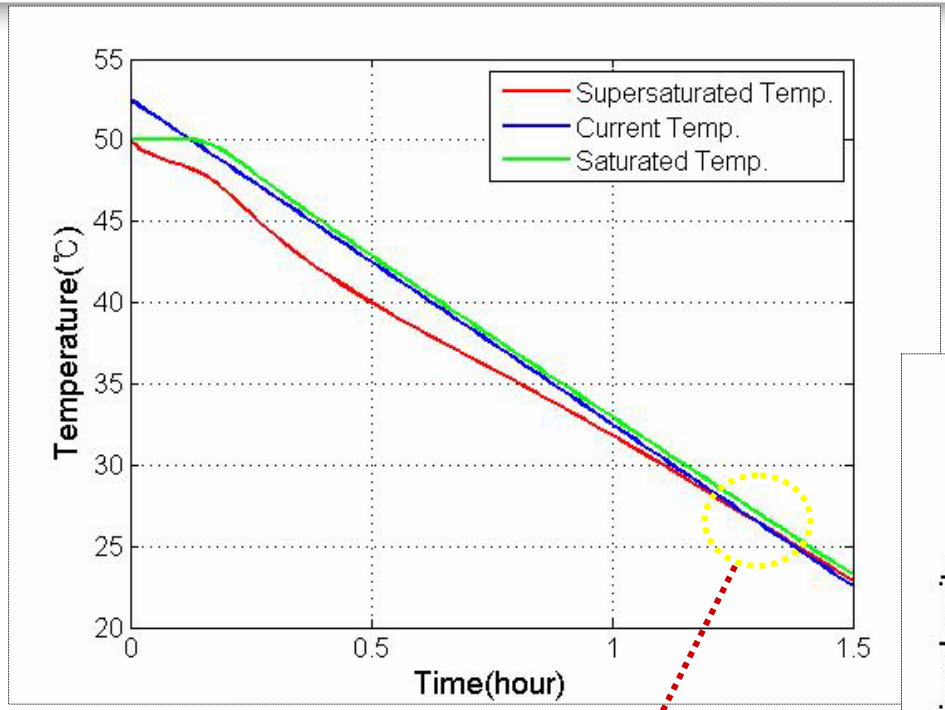


k = 5.346e-5*exp(9.628e-2*Ts)

tau = 3.278e-3*exp(9.120e-2*Ts)

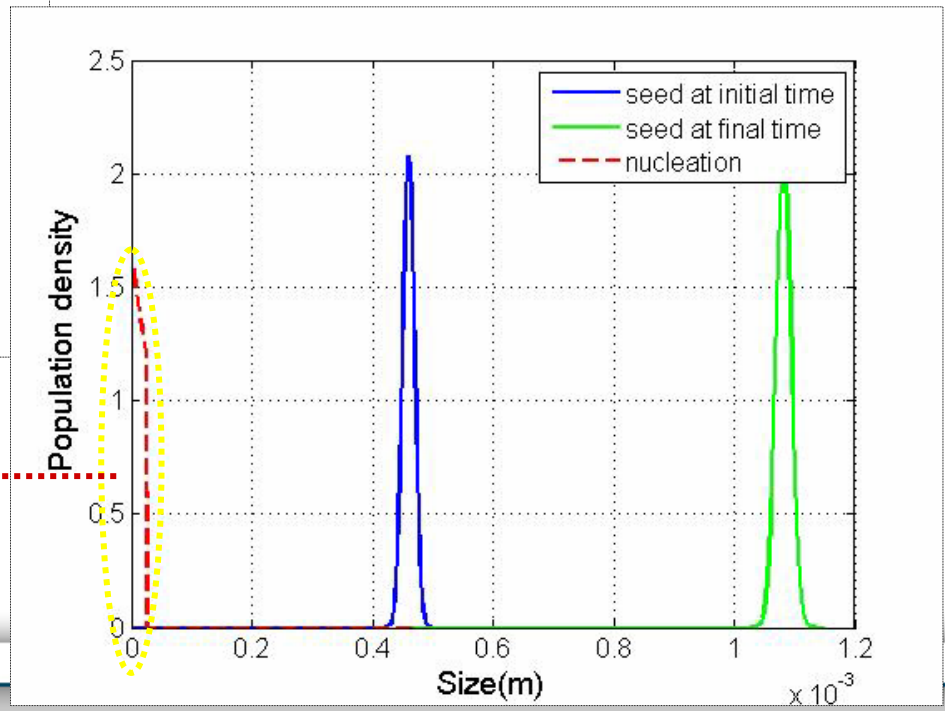


Simulation results of dynamic MSL model



Simulation condition

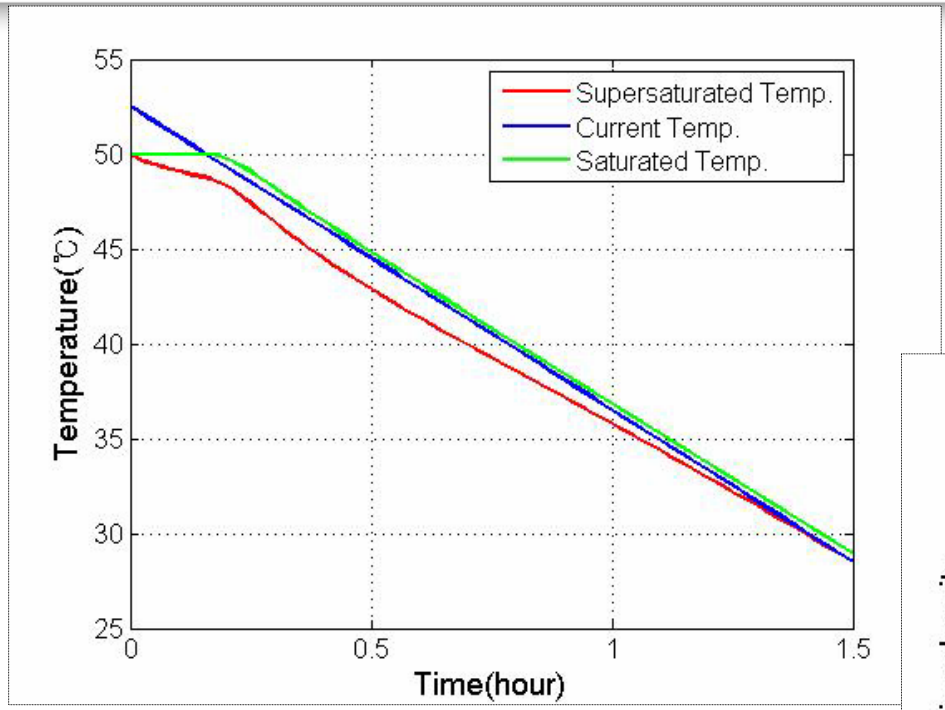
- 20℃/hr linear cooling



Nucleation are happened.

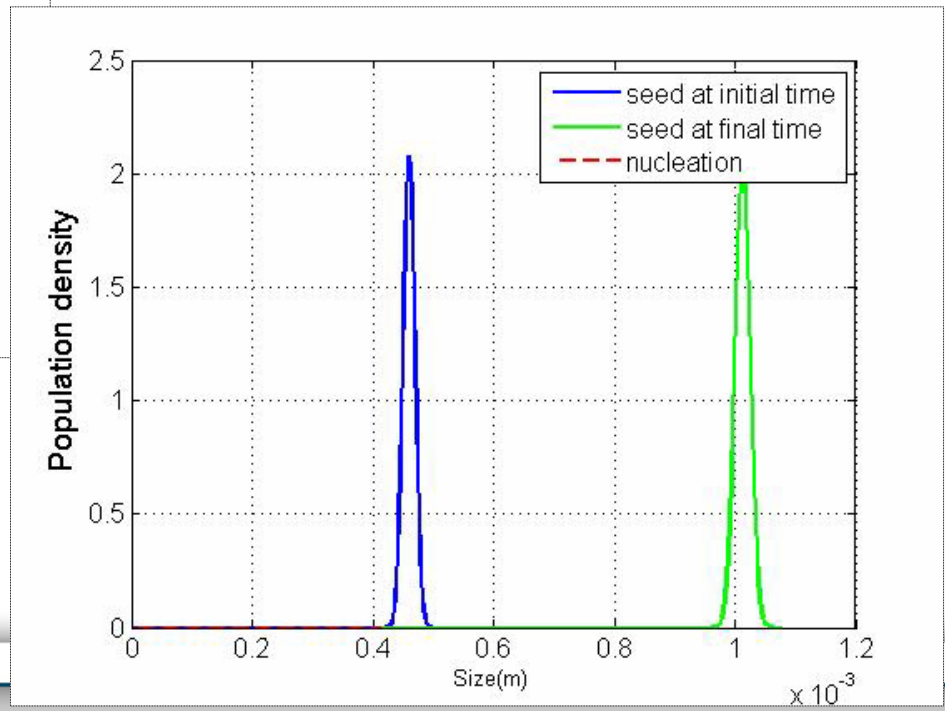
* So we can explain the experimental results of nucleation.

Simulation results of dynamic MSL model



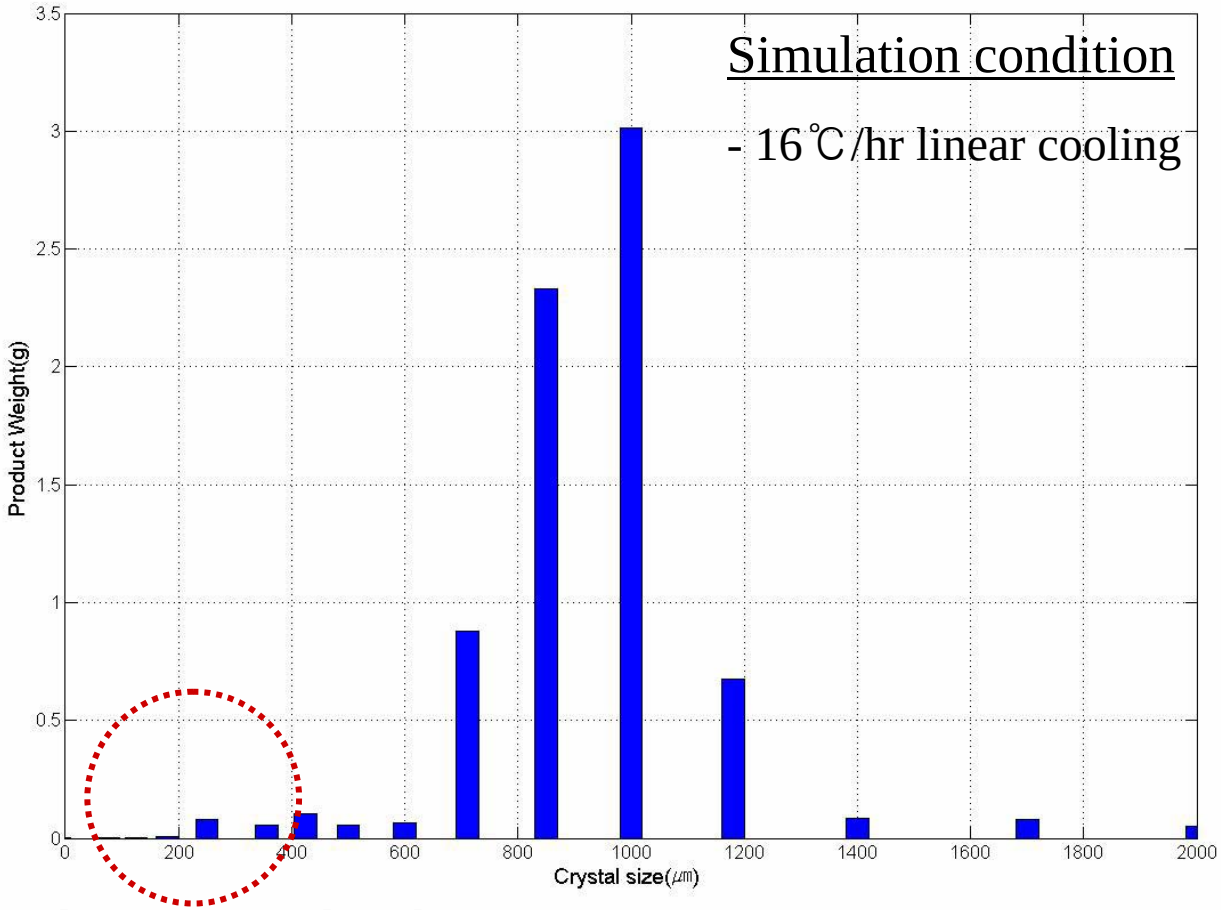
Simulation condition

- 16℃/hr linear cooling



In this results nucleation are not happened.

Crystal size distribution of dynamic MSL model (CV = 16%)

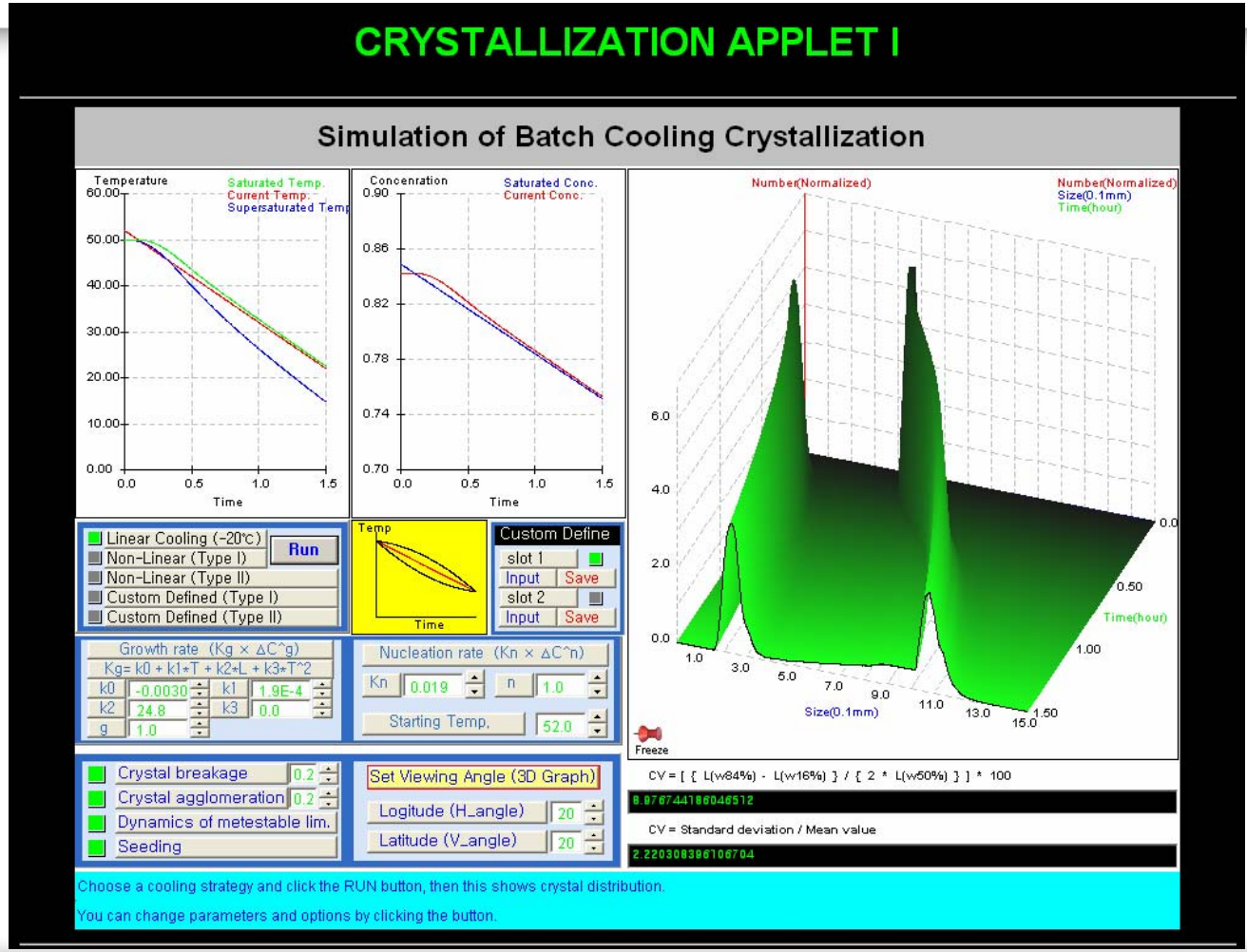


Nucleation are reduced.

Crystallization Applet

- **Crystallization applet**
  - Developed for enhancing the understandings of the crystallization behavior.
    - Effect of kinetic parameters
    - Effect of agglomeration and breakage
    - Effect of cooling strategy
  - Applet program
    - Platform independent
    - Java runtime is required
    - Interactive user interface
    - No user installation
    - Online/offline

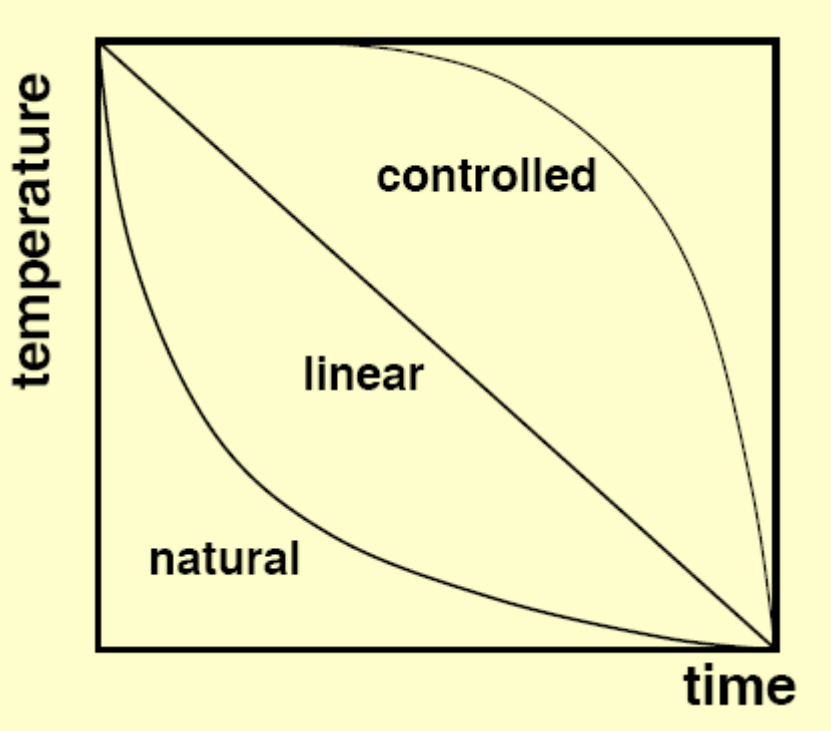
Crystallization Applet

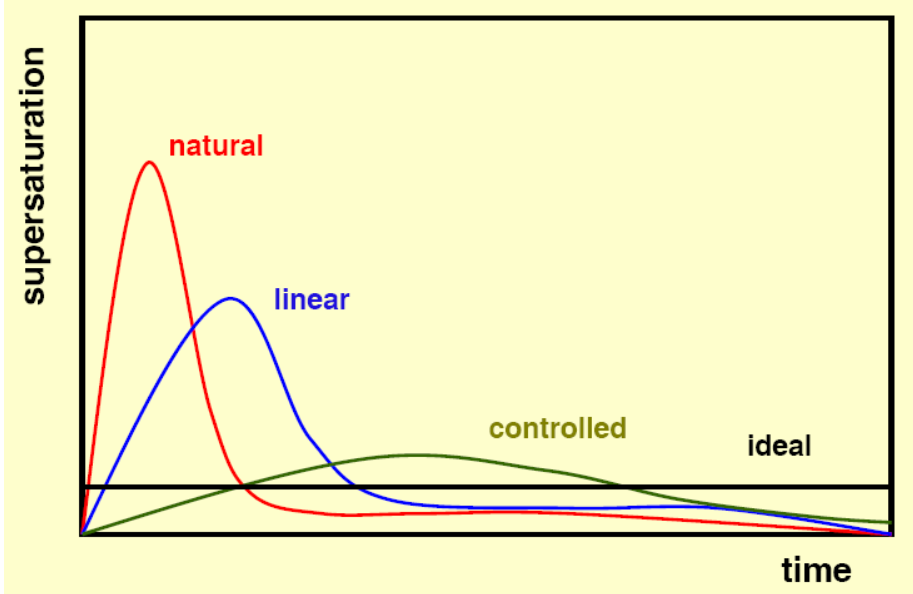


최적 냉각곡선의 도출

냉각결정화의 냉각 전략

- 기존 이론





Product parameter	Natural cooling No seeds	Contr. cooling No seeds	Contr. cooling Seeds
Weight mean size	168 µm	215 µm	287 µm
Number mean size	72 µm	70 µm	62 µm
Fines (%<100 µm)	6.8 %	4.7 %	5.0 %
CV (%) (w.m)	25 %	32 %	51 %
CV (%) (n.m)	89 %	102 %	110 %

* **Controlled cooling and seeding increases the weight mean size.**

* **The width of the distribution increases**

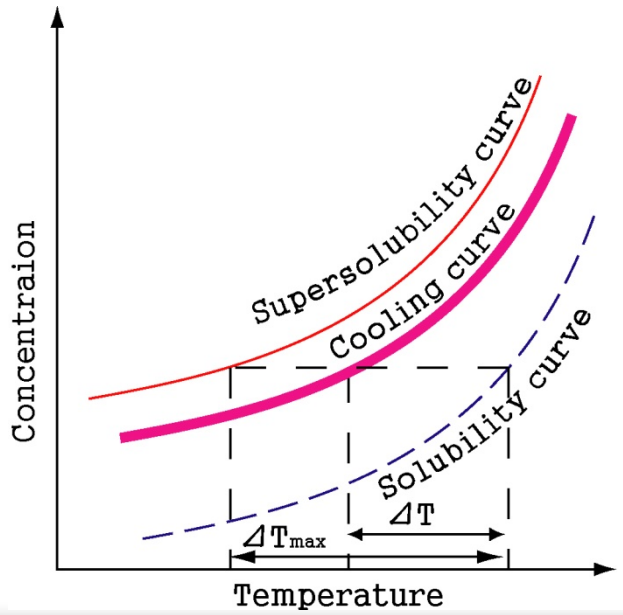
Optimal Cooling Strategy

- **Inside metastable region**

$$\Delta T_{\max} > \Delta T > 0$$

- **As possible as close to the metastable limit**
  - **The higher supersaturation makes the higher crystal growth rate.**
- **Desired supersaturation level (η_{des})**
  - **The nucleation should be prohibited.**
  - **Too close to the limit is dangerous.**
  - **Desired supersaturation level η_{des} <1.**

$$\eta = \frac{\Delta T}{\Delta T_{\max}}$$



- **Objective function for optimal cooling curve**
  - **Multi-step prediction is used.**
  - **Objective is maximizing mean crystal size.**
  - **Violation over desired supersaturation level η_{des} works as penalty.**

$$\min_{T(t_k)} -\omega_1 L(t_N) + (\eta - \eta_{des})^T W (\eta - \eta_{des})$$

$$\text{if } \eta_k - \eta_{des} < 0, \text{then } \eta_k - \eta_{des} = 0$$

$$\text{where } \eta = \frac{T^*(C) - T}{\Delta T_{\max}} = \frac{\Delta T}{\Delta T_{\max}}$$

Optimization based on Genetic Algorithm

- **Characteristics of genetic algorithm (GA)**
  - GA is a search technique used in computing to find exact or approximate solutions to optimization and search problems.
  - Genetic algorithms are categorized as global search heuristics.
  - Genetic algorithms are a particular class of evolutionary algorithms that use techniques inspired by evolutionary biology such as inheritance, mutation, selection, and crossover.
- **Advantages of GA**
  - The major advantage of GA is their flexibility and robustness as a global search method.
  - They do not need gradient information and make relatively few assumptions about the problem being solved.
  - They can deal with highly nonlinear problems and non-differentiable functions as well as functions with multiple local optima.

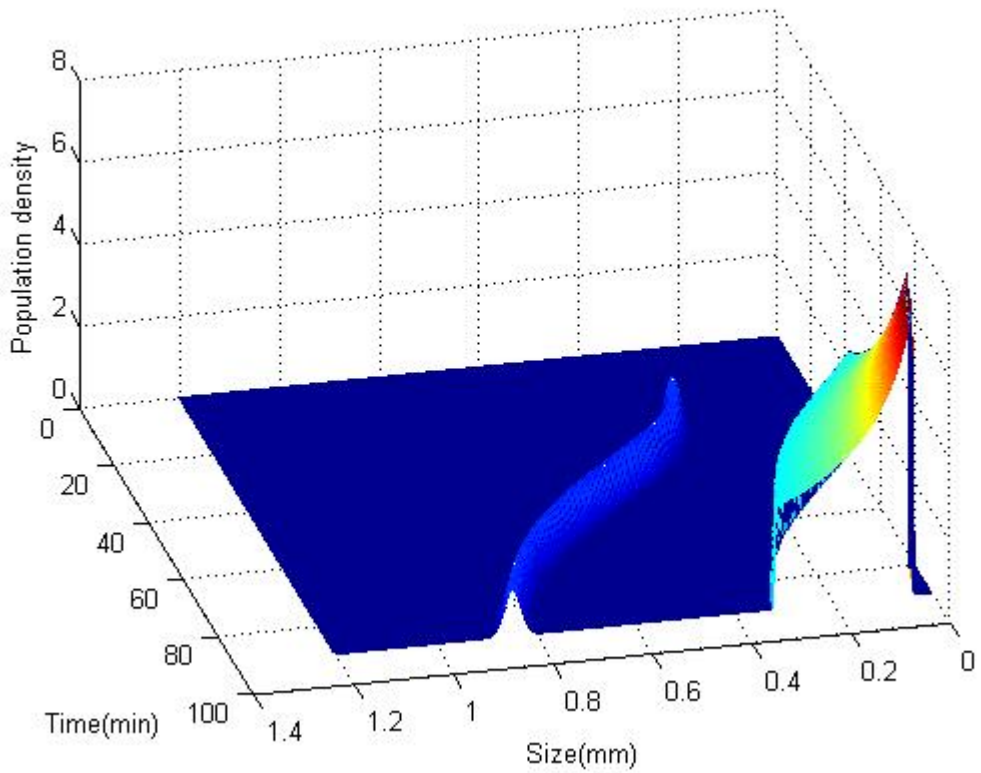
Optimization based on genetic algorithm

- **Fitness function**
  - **In order that the crystal growth rate is maximized while the nucleation rate is minimized, the operation should be close to MSL as possible and this problem can be formulated as an optimization problem.**
  - **The objective function can be chosen as a function of the third moments of the CSD.**
  - **For reality, cooling rate has upper and lower bound.**
  - **Operation time and termination temperature sets to be identical for all types of the cooling strategies.**

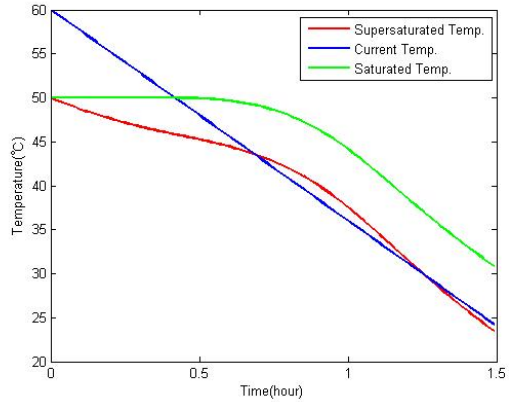
$$\min_{u(t)} \quad (\mu_3^n + w\frac{1}{\mu_3^s})$$

$$subject\ to \quad 0 \le u(t) \le 50$$

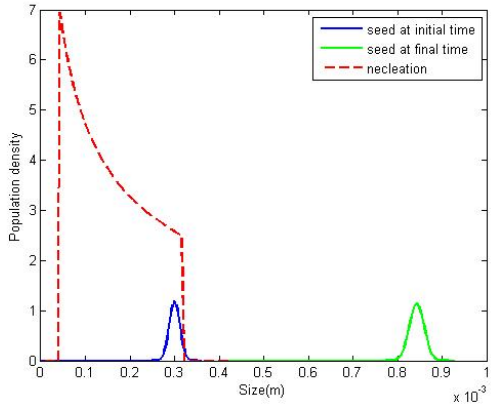
Simulation Results (Linear cooling)



(a)



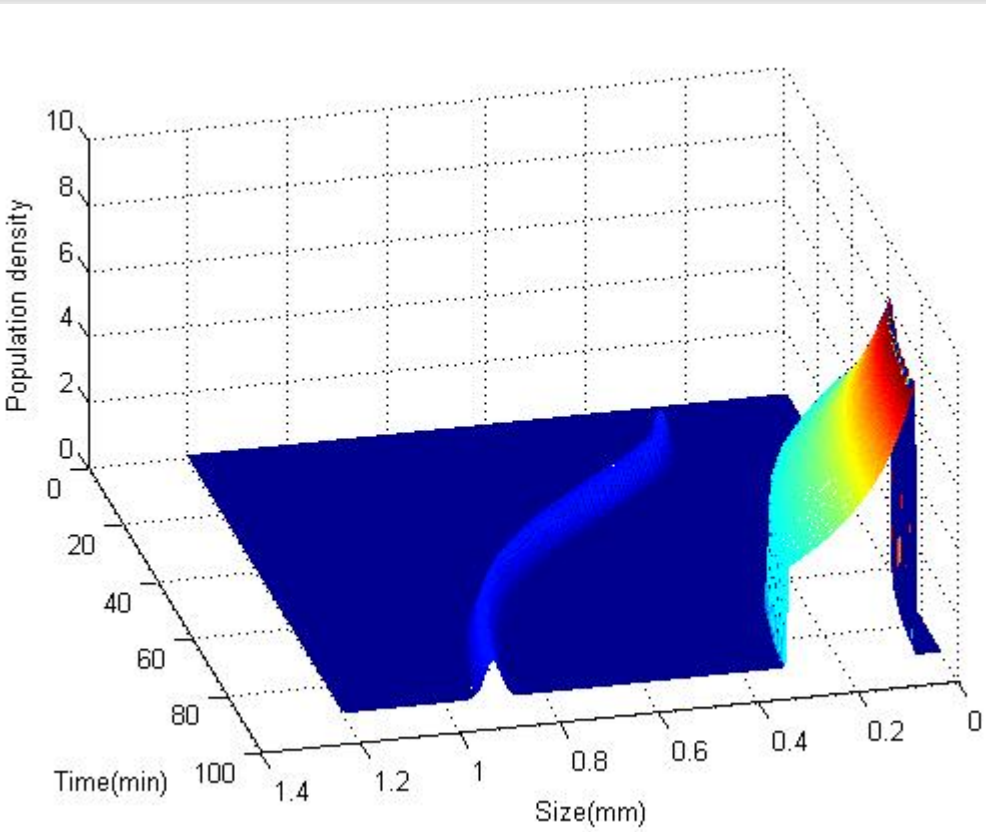
(b)



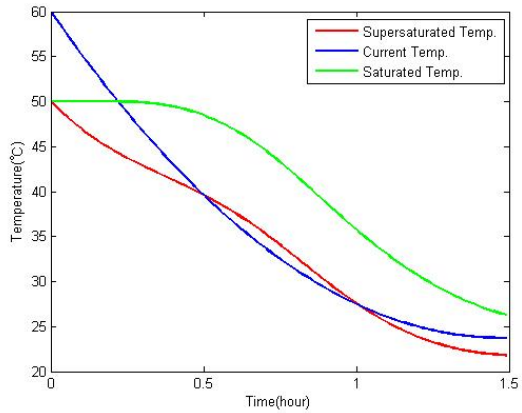
(c)

Fig 2. (a) Evolution of CSD for the linear cooling curve, (b) The linear cooling curve and metastable limit, (c) Seed and newly formed crystal size distribution

Simulation Results (Natural cooling)



(a)



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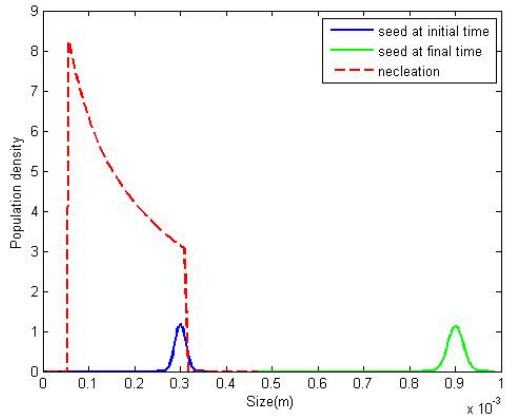
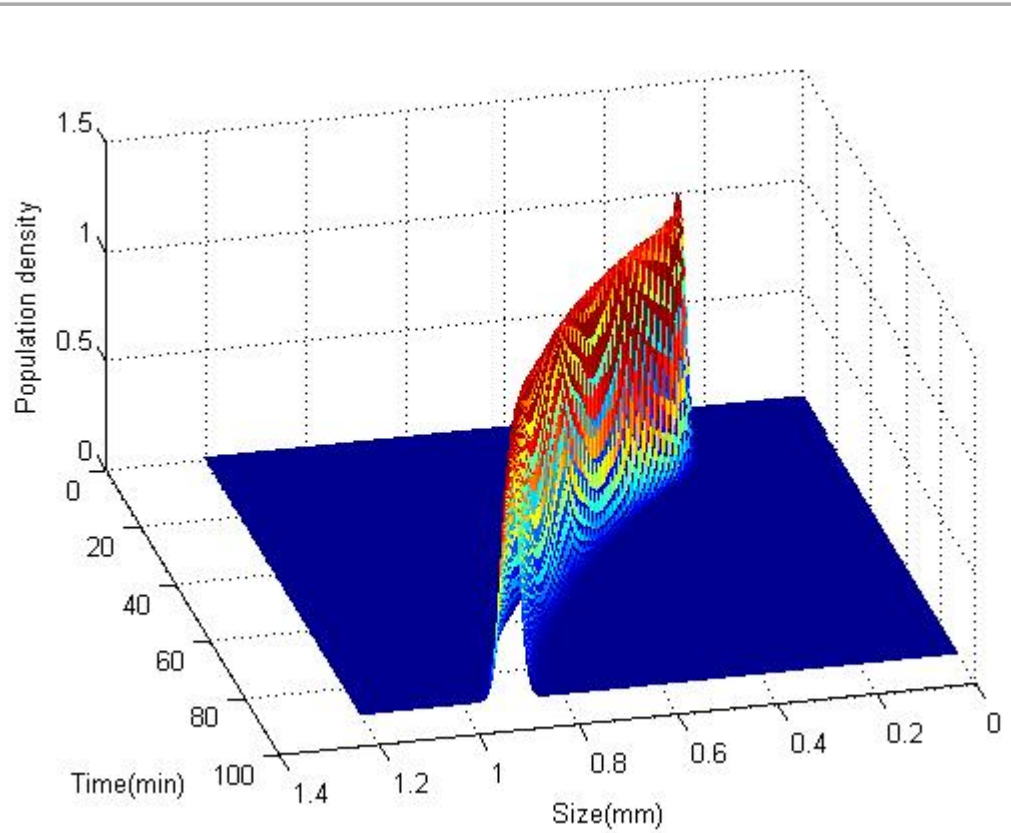


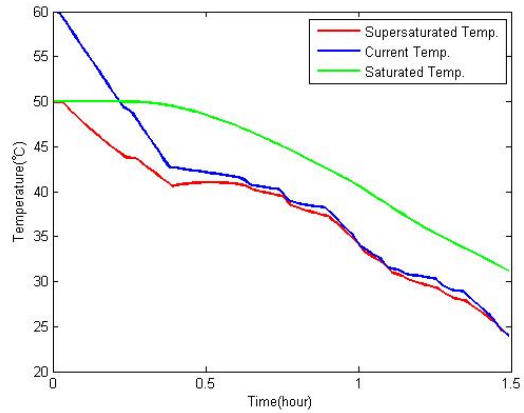
(c)

Fig 3. (a) Evolution of CSD for the natural cooling curve, (b) The natural cooling curve and metastable limit, (c) Seed and newly formed crystal size distribution

Simulation Results (Optimal cooling)



(a)



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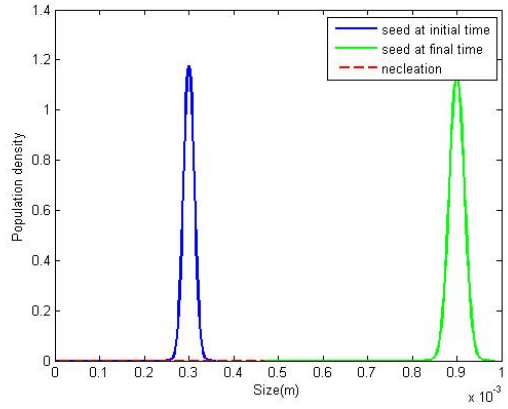


(c)

Fig 1. (a) Evolution of CSD for the optimal cooling curve, (b) The optimal cooling curve and metastable limit, (c) Seed and newly formed crystal size distribution

Results

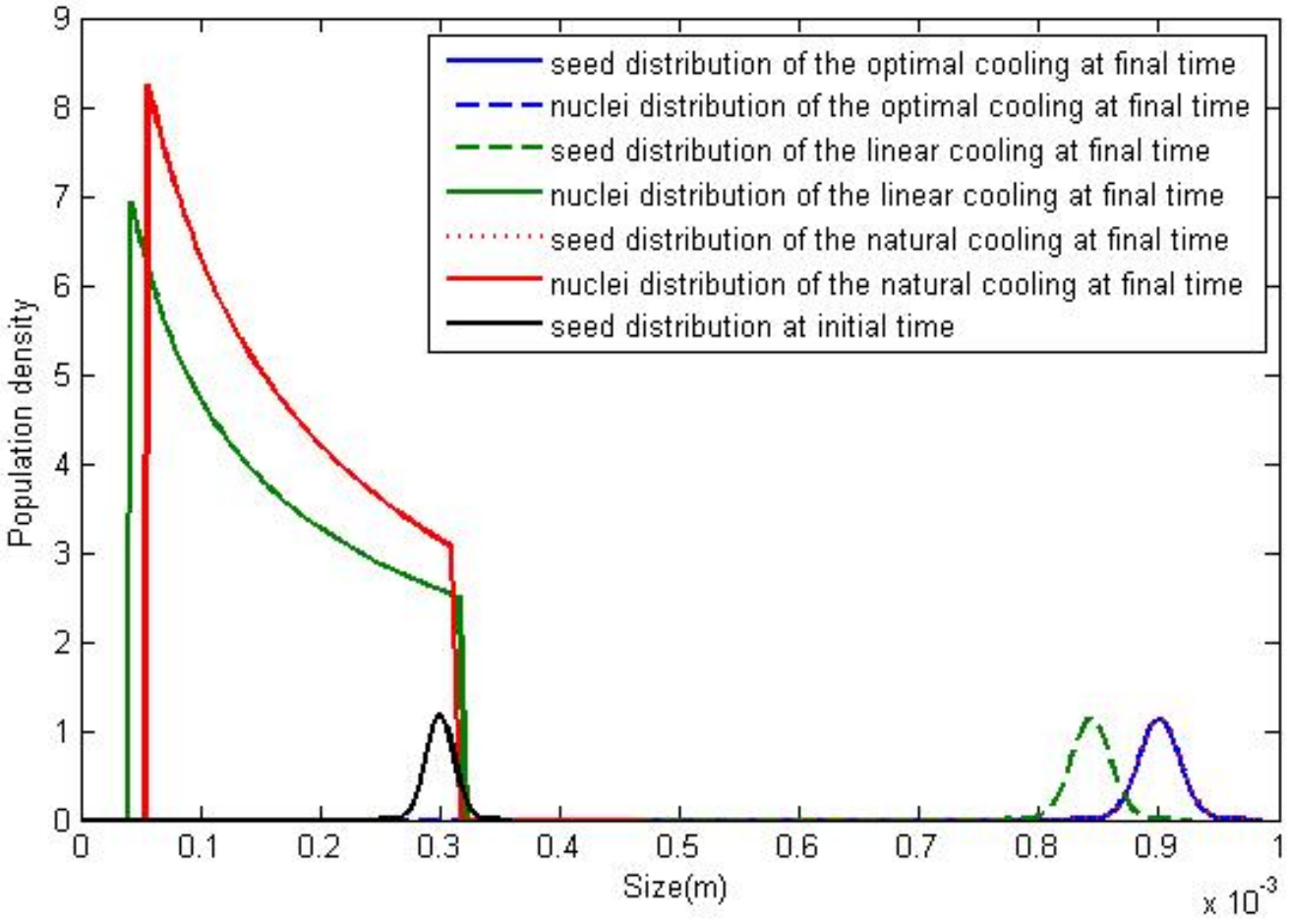
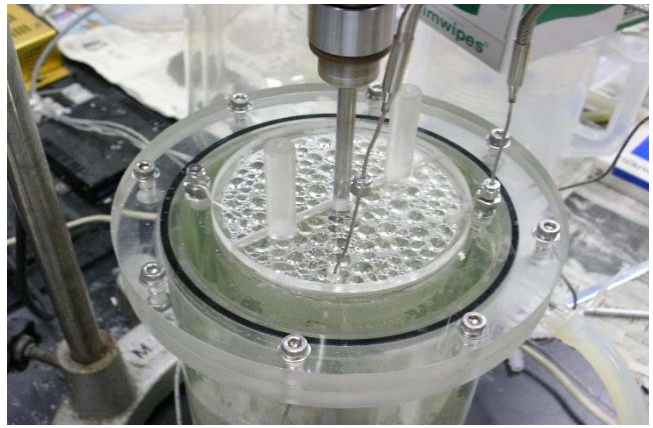
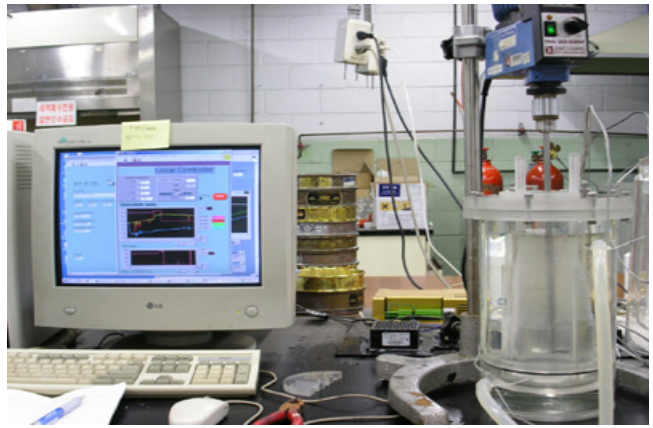


Fig 3. Comparison of three types of the cooling curve (optimal, linear, natural curve)

Example 1: Linear cooling

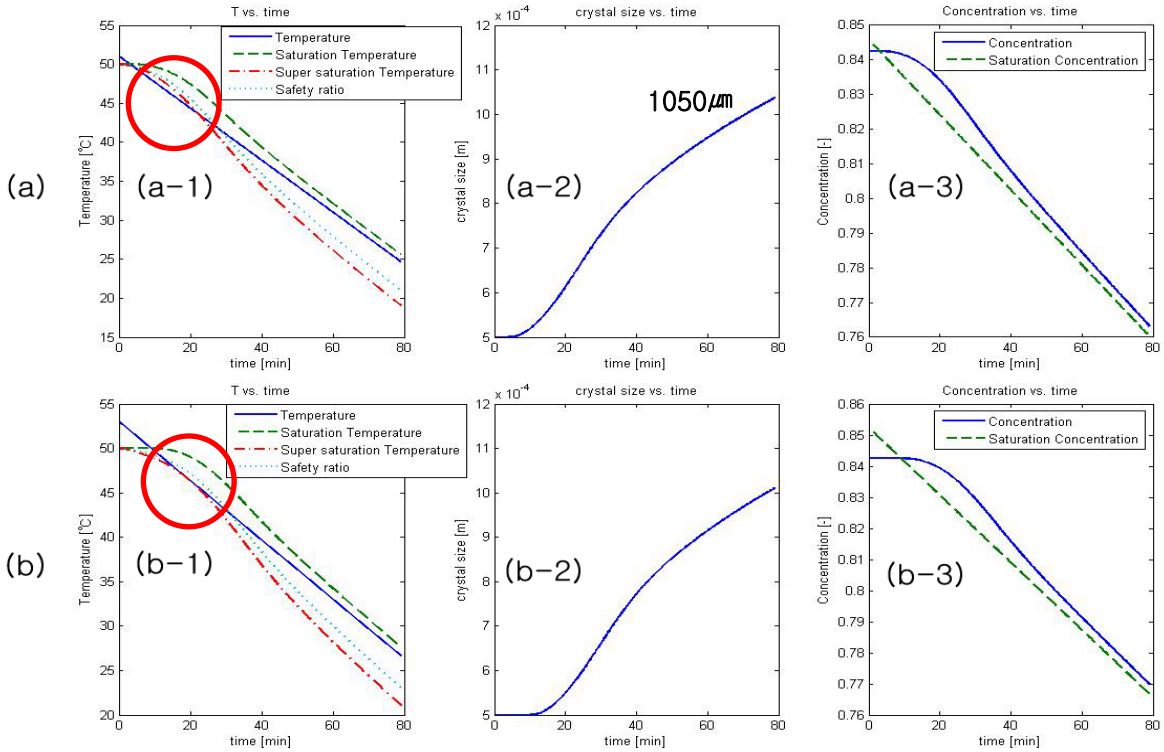
- **Experimental procedure**
  - ① **Making up solution.**
    - $(NH_4)_2SO_4$ – H_2O solution
    - Concentration : 0.8425(Ts=50℃)
  - ② **Keeping temperature as initial temperature for 1hr.**
    - RPM of agitator : 1000rpm
  - ③ **Starting cooling experiment**
  - ④ **Adding the seed crystal when reactor temperature cross over the saturation temperature**
    - Seed crystal size : 462.5㎛
    - Seed crystal weight : 10g
  - ⑤ **Filtering solution and drying the crystal**





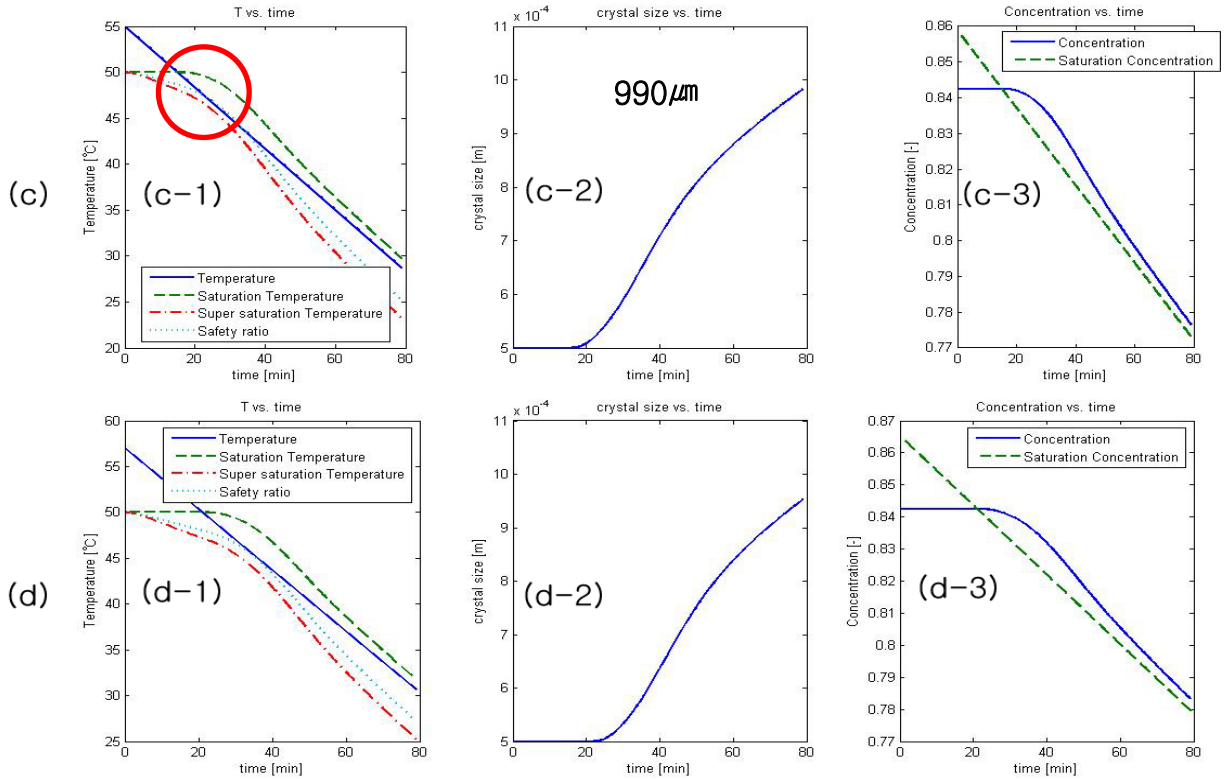
- **Estimating optimal initial temperature for linear cooling**
  - **Experimental condition**
    - **Solution concentration : 0.8425 [solute kg/ solvent kg] (T_s=50℃)**
    - **Cooling rate : 20℃/h**
    - **Processing time : 80 min.**
    - **initial temperature : 51℃, 53℃, 55℃, 57℃**
  - **Expected results**
    - **From 51℃**
      - ✓ **Crystal size : 1050 ㎛**
      - ✓ **Total weight : 92.61g**
      - ✓ **Broad crystal size distribution.**
    - **From 55℃**
      - ✓ **Crystal size : 990 ㎛**
      - ✓ **Total weight : 77.62g**
      - ✓ **Narrow crystal size distribution.**

- **Simulation results of linear cooling from 51℃ and 53℃**



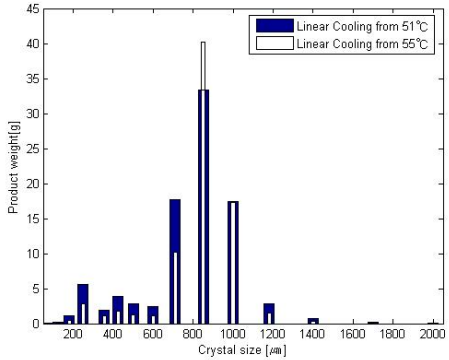
(a) Linear cooling from 51℃, (b) Linear cooling from 53℃

Simulation results of linear cooling from 55℃ and 57℃

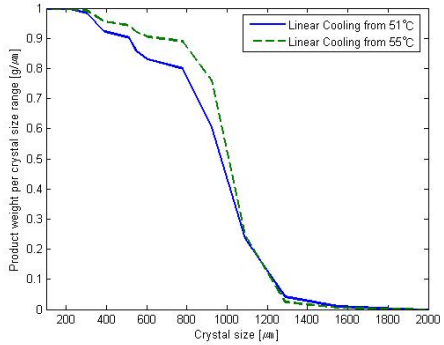


(c) Linear cooling from 55℃, (d) Linear cooling from 57℃

Results of Experiment 2-1



Crystal size distribution



Accumulated weight percent

	From 51℃	From 55℃
Mean crystal size (㎛)	971.81	1008.8
Total weight (g)	90.3235	78.3077
CV (%)	32.994	18.46

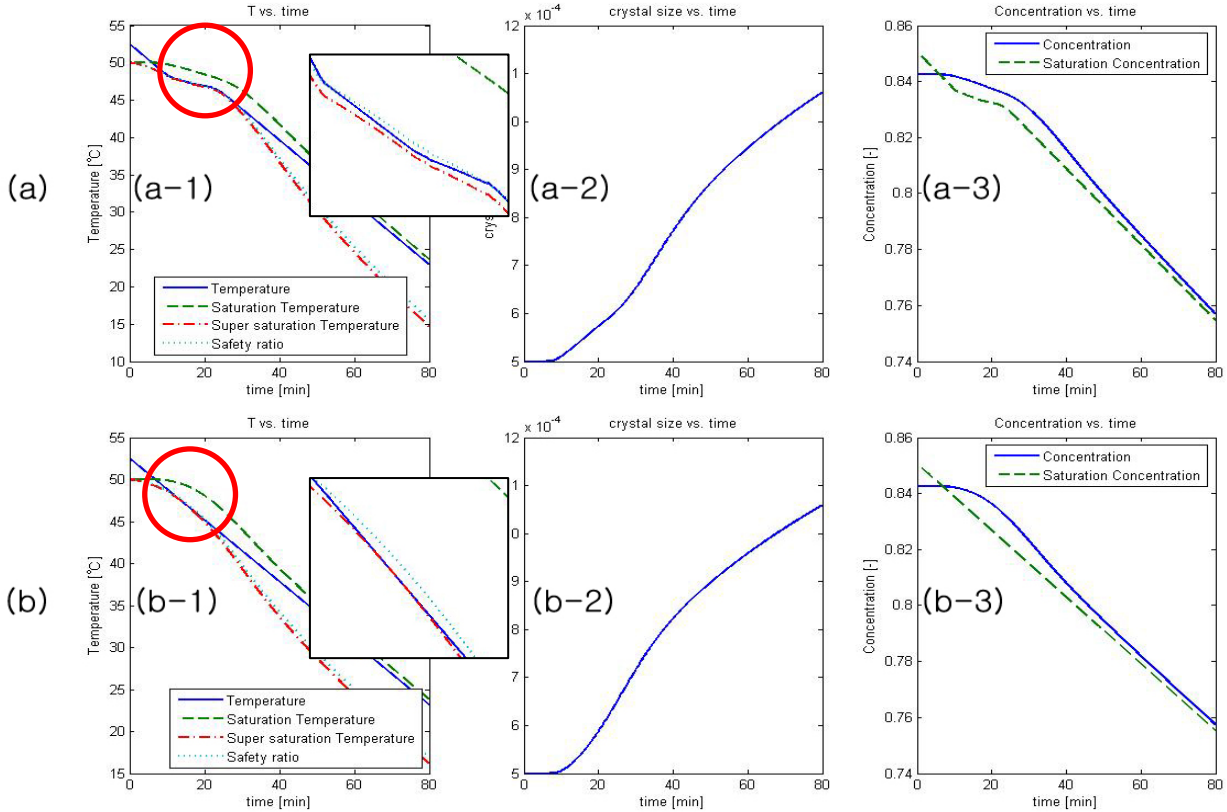
※ CV (Coefficient of variance) under the 20% Implies uniform size distribution.

$$CV = 100\left[\frac{L_{w_{84\%}} - L_{w_{16\%}}}{2L_{w_{50\%}}}\right]$$

Example 2: Linear vs. Optimal

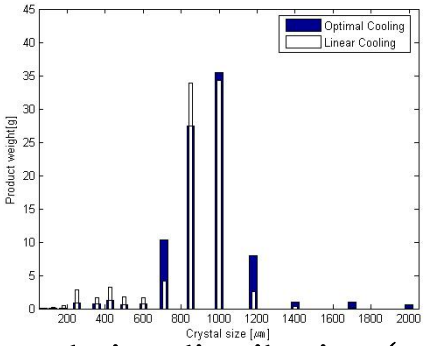
- **Optimal cooling Strategy**
  - **Experimental condition**
    - **Solution concentration : 0.8425 [solute kg/ solvent kg]**
    - **Processing time : 80 min.**
    - **Initial temperature : 52.5℃**
    - **Final temperature : 23℃**
    - **Cooling curve**
      - ✓ **Linear cooling : 22.125℃/h**
      - ✓ **Optimal cooling : by simulated data**
        - » Maximum cooling rate : 25℃/h
        - » Maximum heating rate : 5℃/h
  - **Expected results**
    - **Optimal cooling**
      - ✓ **Crystal size : 1050 ㎛**
      - ✓ **Total weight : 92.61g**
      - ✓ **Narrow crystal size distribution.**
    - **Linear cooling**
      - ✓ **Crystal size : 1050 ㎛**
      - ✓ **Total weight : 92.61g**
      - ✓ **Broad crystal size distribution.**

Simulation results of linear cooling and optimal cooling

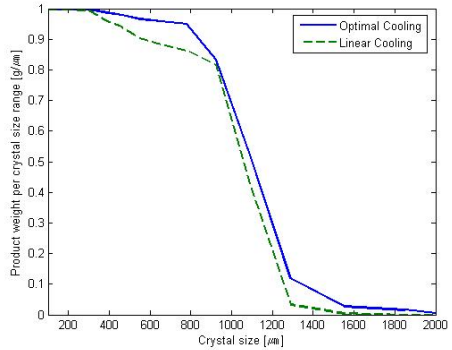


(a) Optimal cooling line, (b) Linear cooling line

Results of Experiment

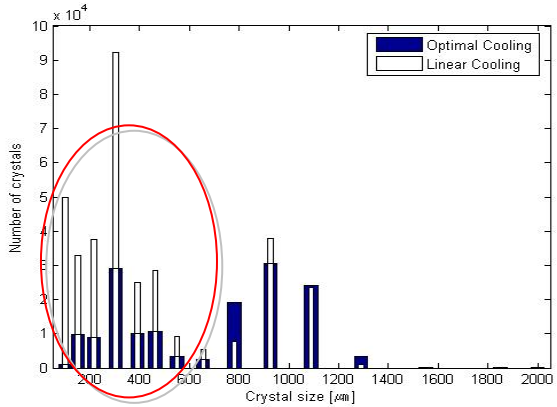


Crystal size distribution (weight)



Accumulated weight percent

	Optimal cooling	Linear cooling
Mean crystal size (㎛)	1101	1059.4
Total weight (g)	87.9859	87.0408
CV (%)	17.592	20.935



Crystal size distribution (Number of crystal)

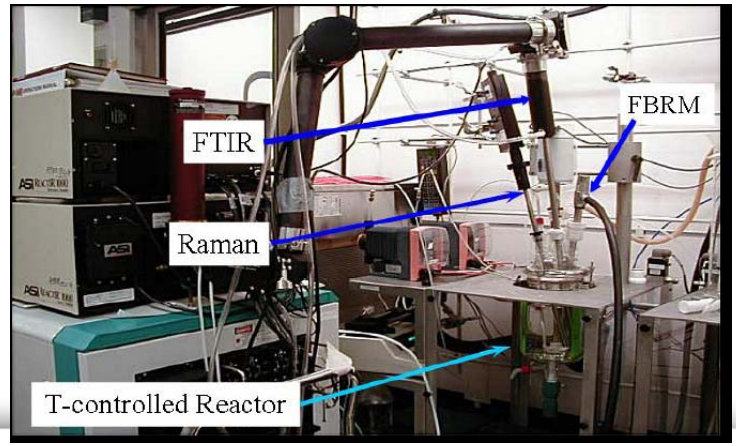
Process Analytical Technology (PAT)의 응용

PAT

- Process Analytical Technology (PAT)란?
  - 온라인 측정기를 이용한 결정화 운전 및 제어기술
  - PAT의 목적은 생산 공정을 이해하고 제어하기 위함.
- 왜 중요한가?
  - “Quality can not be tested into products; it has to be built in by design.” – FDA
    - 제품이 동일한 과정에 의해 생산되고 품질이 보증 되어야 함.
- PAT의 기대효과
  - 효율향상
  - 원가절감
  - 균일한 품질

- **PAT Tool의 기대효과**
  - **Multivariate data acquisition/analysis**
    - 중요 공정변수를 파악하기 위한 Design of Experiment
  - **Process analyzers**
    - Off-line, at-line, on-line, in-line, non-invasive
  - **Process endpoint monitoring and control**
    - 공정을 모니터링하고 원하는 조업조건에 유지
    - 최종 생산물에 대해 반응 또는 결정화 시간 대신 보다 명확한 물성을 이용한 결정 가능
  - **Continuous improvement/knowledge management**
    - 사후 관리 및 공정개선의 과학적 자료 축적

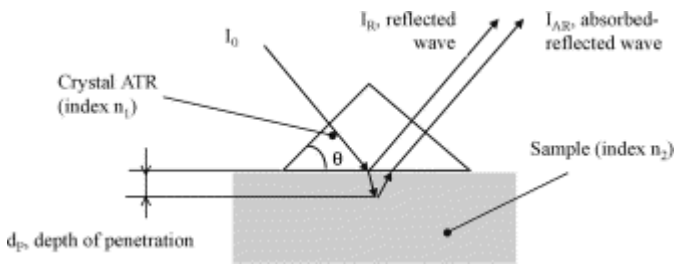
- **Process Analyzers**
  - 전통적인 측정 방법
    - Temperature, pressure, pH, turbidity, … probes
    - Mass flow meter
    - Volumetric gas uptake/evolution
  - 최근의 측정방법
    - *In situ* real-time (Operando) spectroscopy (midIR, NIR, UV-vis, Raman, acoustic)
    - *In situ* real-time particle analyzer (FBRM, PVM,…)
  - 미래에 나올 방법들
    - Advanced data management software package
    - Remotely controlled *in situ* real-time process sensors with high sensitivity
    - New process sensors (combo probe, diode laser frequency modulation spectroscopy,…)
    - …

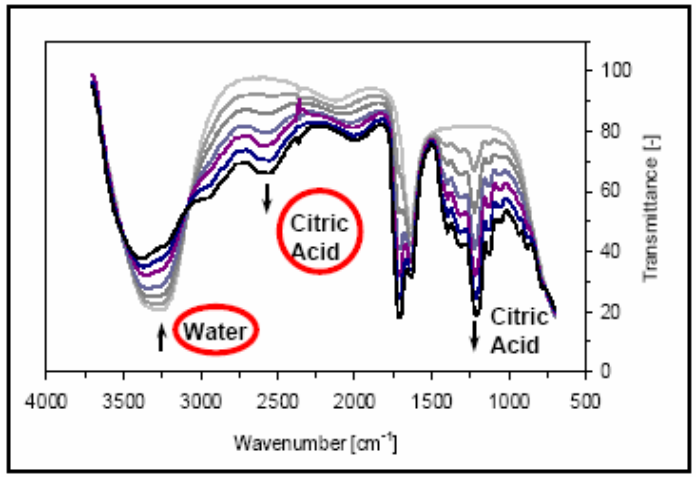


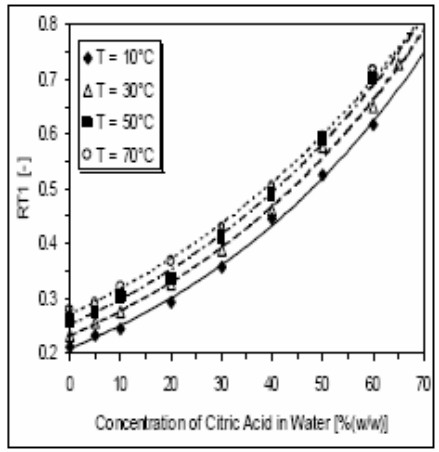
과포화도의 측정

Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectroscopy

- degree of supersaturation의 측정



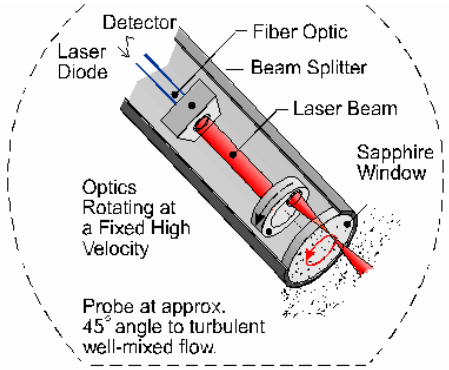


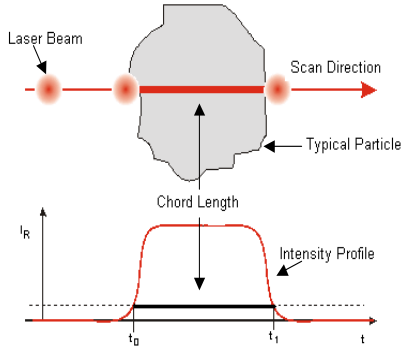


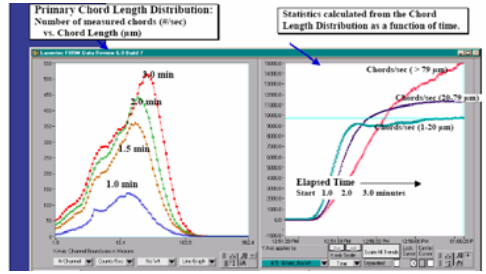
- 결정의 분포 측정
  - Conventional methods (Offline)
    - Sieving: 5-12500μm
    - Microscopy: 0.5-150μm
  - In-process Ultrasonic spectroscopy
    - 주파수가 1-150MHz 범위의 초음파가 1mm-5cm의 path를 통과하는 동안에 고체의 농도에 따라 초음파의 강도(intensity)가 변화하는 것을 측정
    - 결정 크기가 0.1μm-100μm 사이인 경우 30%-70% 사이의 solid 농도 측정
    - 온도별, 농도별 강도의 Attenuation에 따른 calibration 필요

In Situ Particle Size Analyzer (PSA)

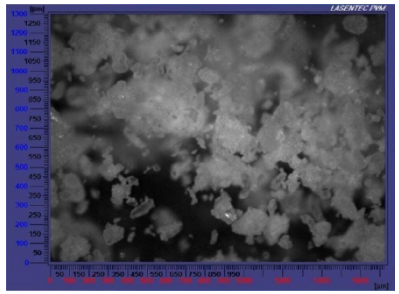
- Laser beam을 조사하여 반사되는 것을 측정해 입자의 수나 크기를 측정 (Focused Beam Reflectance Measurement, FBRM)
- 입자의 형태에 따라 어려운 calibration 필요
- 절대적 측정값보다는 상대적 변화의 측정에 적합

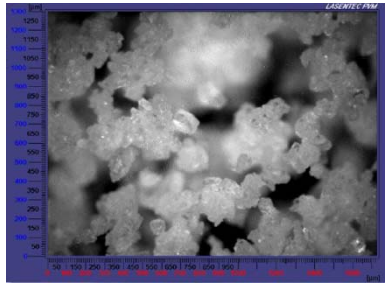


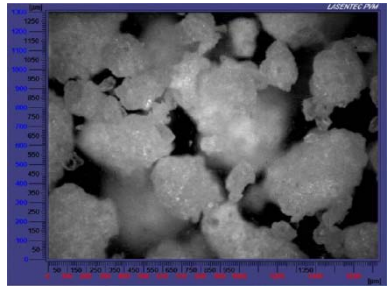




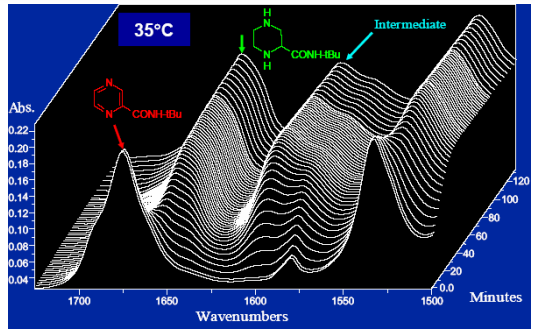
- In-process Video Microscopy (PVM)
  - 반응기 내의 한 지점에서 시간에 따른 결정 사진 capture
  - 결정의 크기나 모양의 변화, agglomeration, breakage등을 눈으로 확인
  - 자체적인 측정값을 내보내지 않음
  - *In situ* PSA와 같이 사용하는 것이 일반적
  - 예) 10분 간격으로 측정된 그림







결정구조 및 Morphology의 측정



- Raman spectroscopy
  - 결정 구조 측정
- In-process XRD (X-Ray Diffraction)
  - Polymorph에 따라 다른 위치에서 나타나는 X-ray 회절의 강도에 의해 polymorph의 농도 측정
- PVM
  - 반응기내의 결정에 대한 사진을 통해 결정

대표적 Example

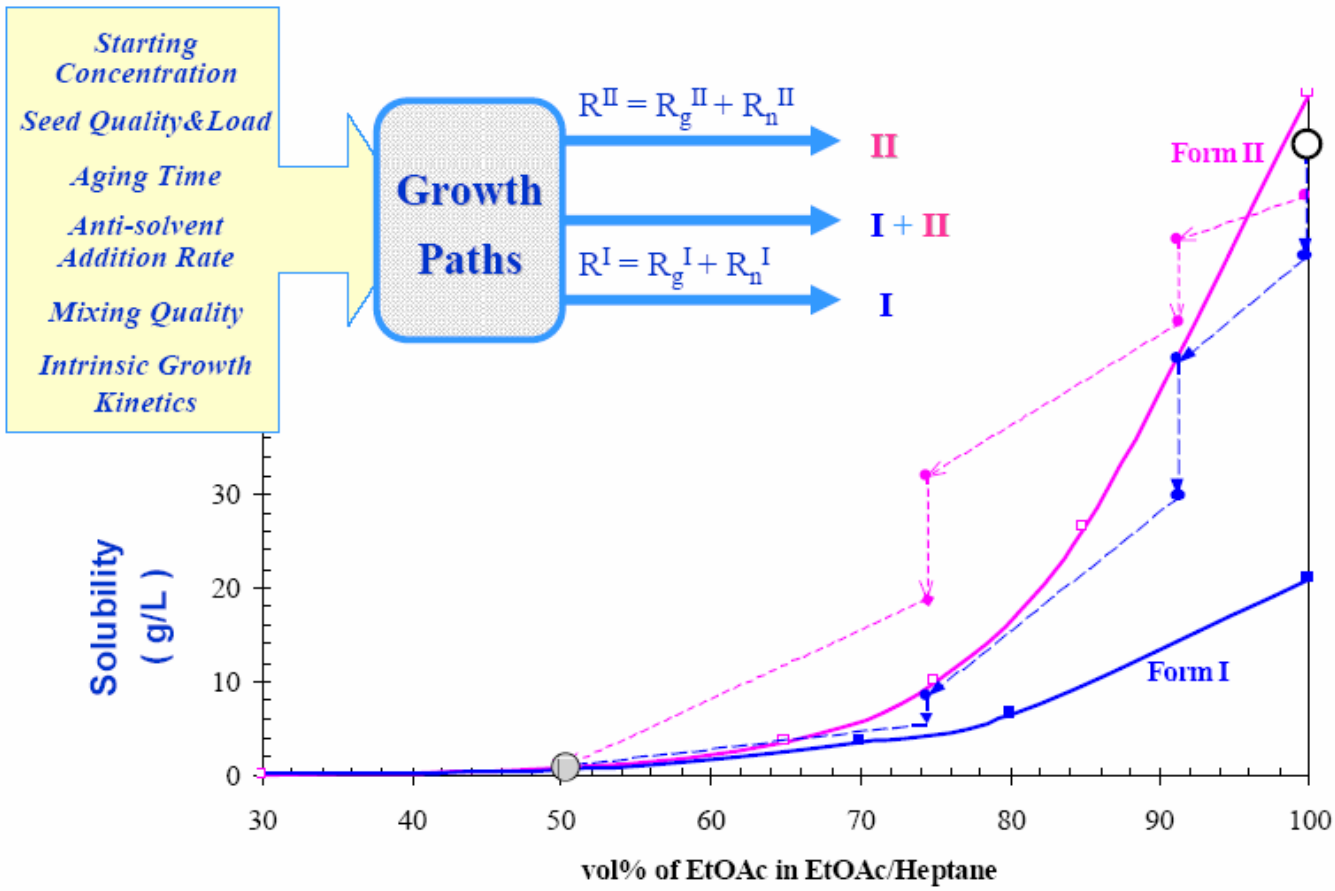
- **Polymorph 제어의 목적**
  - **순도**
    - 화학적 불순물 (reagents, by-products)
    - 잔류용매
    - solid forms (polymorphs, solvates, hydrates)
  - **물성**
    - 결정도와 결정구조
    - 결정의 morphology
    - crystal size distribution (CSD)
    - 결정 표면적, 밀도 등
    - 안정성
  - **생산성**
    - 수율
    - 생산시간 – crystallization, filtration, drying
    - 부피당 생산량 – g/L, kg/batch
    - 조업효율 – 인건비 등

(**출처**: J. Wang, C. Loose, J. Baxter, D. Cai, Y. Wang, J. Tom, and J. Lepore, "Growth promotion by H2O in organic solvent –selective isolation of a target polymorph," *J. of Crystal Growth*, 283, 469-478 (2005)

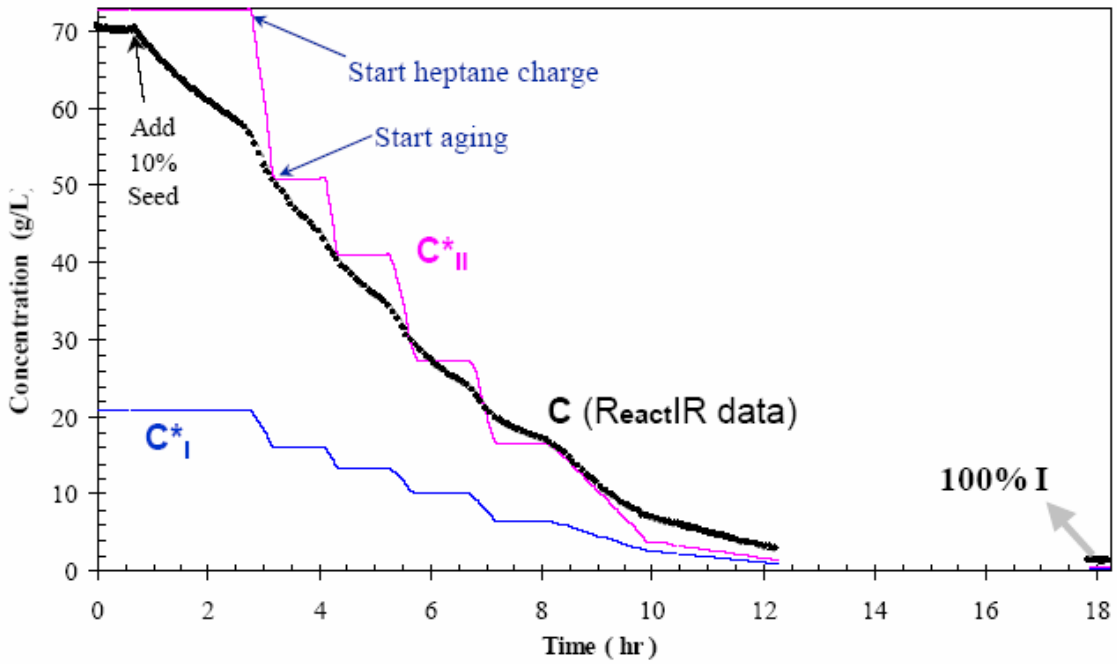
- **유효성분 (API)이 두가지 polymorphs 를 가짐**
  - Drowning-out에 의해 생산
  - Form I이 Form II보다 안정적

- **공정상 문제점**
  - 불가피한 Form II의 생성 (전형적으로 2~10%)
  - 매우 느린 Form I 성장속도 (기존 방법으로 18 시간 이상 소요)
  - 매우 느린 Form II에서 Form I로의 변환 속도 (특정용액에서 몇일 정도)
  - 40°C이상에서 분해 (낮은 온도에서 조업)
  - Form I 세척에 많은 세척수 필요 (<500 L/m2/hr)

- **공정개선의 주안점**
  - Form I의 선택적 성장을 위한 중요 파라미터의 파악
  - 순수한 Form I의 생산을 위한 강건하고 효율적인 공정의 설계

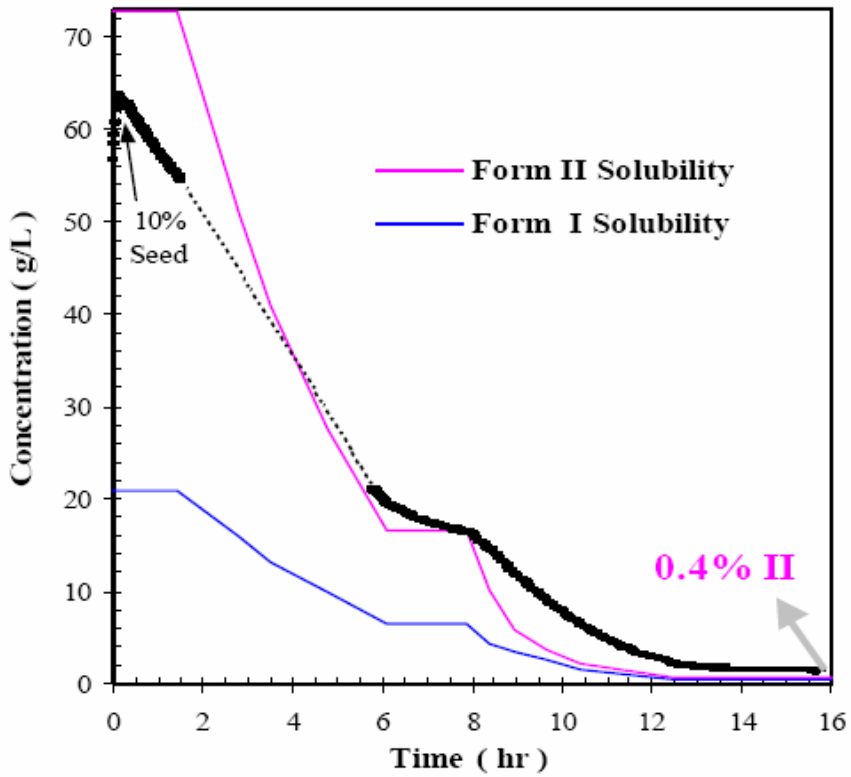

Starting Concentration
Seed Quality&Load
Aging Time
Anti-solvent Addition Rate
Mixing Quality
Intrinsic Growth Kinetics
Growth Paths
$R^{II} = R_g^{II} + R_n^{II}$
$R^{I} = R_g^{I} + R_n^{I}$
II
I + II
I
Form II
Form I
Solubility (g/L)
0
10
20
30
30
40
50
60
70
80
90
100
vol% of EtOAc in EtOAc/Heptane

Form I seed + controlled n-Heptane addition at 25°C



Control anti-solvent Addition Rate to maintain $C < C^*_{II}$

Narrow metastable zone of Form II

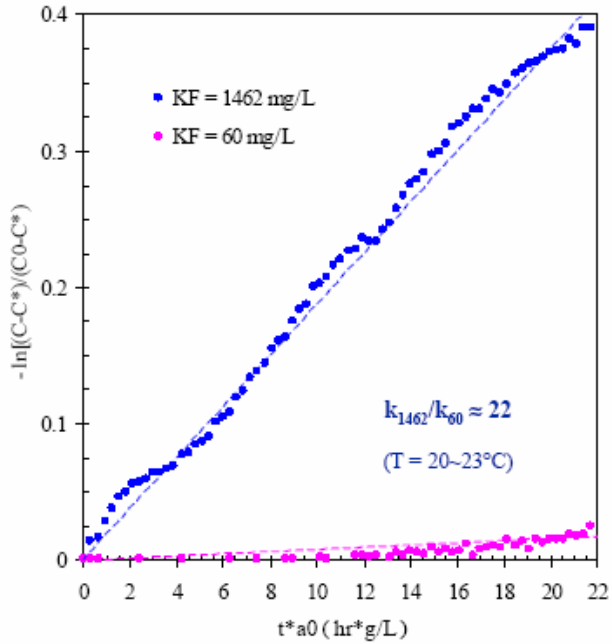


Problems:

- Poor robustness
- Long time cycle
- Low volume productivity

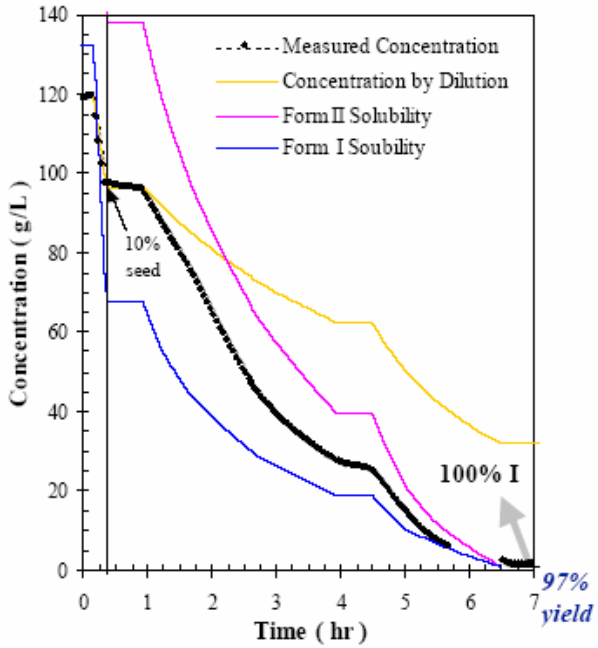
How to enhance the growth rate of Form I?

High C_{H2O} → high growth rate



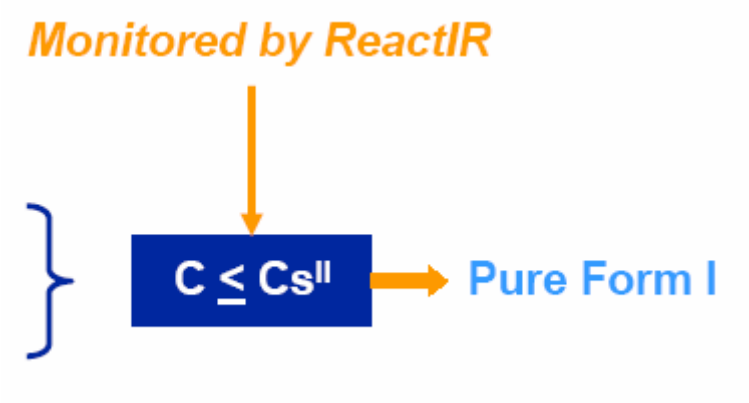
Effect of H_2O on ***k*** in 70:30 of (1IPA+10EtOAc): n-heptane at r.t., a_0=5.95g/L, ma≈30μm.

A highly efficient process with high C_{H2O}



A seeded batch isothermal rex in EtOAc (4840KF)/n-heptane system at 23°C.

- **관찰사항**
  - 중요 파라미터 도출
    - Anti-solvent addition rates
    - Solvent composition
    - Seed quality and loading



- **개선결과**
  - 확대된 순수한 Form I 생산 영역
  - Cycle time 단축 (2~4 hours vs. 18 hours)
  - 여과효율 향상 (~ 400 L/m²/hr vs. <500 L/m²/hr)
  - 단위부피당 생산성 향상 (~60 g/L vs. ~20 g/L)

Thank you!