냉각 결정화 기술의 응용전략-1

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서론

화학제품의 분류 (Pollak, 1993)

	Commodities	Fine chemicals	Specialty Chemicals
종류	Petrochemicals Basic chemicals Large-volume organics Monomers Commodity fibers Plastics	Advanced intermediates Building blocks Bulk drugs Bulk pesticides Active ingredients Bulk vitamins Amino acids Flavor and fragrance chemicals	Adhesives Diagnostics Disinfectants Electronic chemicals Food additives Mining chemicals Pesticides Pharmaceuticals Photographic chemicals Specialty polymers Water treatment chemicals
생산량	>10,000 ton/yr	1-10,000 ton/yr	<1 ton/yr
가격	<$2.5/kg	$2.5/kg-$100/kg	>$100/kg
특징	"what they are"	"what they are"	"What they can do"
수요처	Industry	Industry	Public

제품군에 따른 특징 (예)

Table 1. Comparison of Chemical Classes

Parameter	Commodities		Fine chemicals		Specialties
example	*o*-xylene	phthalic anhydride	3-amino-2-carboxy-4-chlorobenzophenone	2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide	chlorthalidone[a]
CAS Registry Number	[*95-47-6*]	[*85-44-9*]		[*77-36-1*]	[*77-36-1*]
molecular formula	C_8H_{10}	$C_8H_4O_3$	$C_{14}H_{10}NO_3Cl$	$C_{14}H_{11}ClN_2O_4S$	$C_{14}H_{11}ClN_2O_4S$
applications	>20	>10	1	1	1
price level, $/kg	0.50	1	10	100	1000
production, t/yr	2.5×10^6	$>1 \times 10^6$	100	100	100
producers	100	25	1	1	1
customers	100	50	1	captive	>> consumers
plant type[b]	D, C	D, C	M, B	M, B	F
manufacturing steps	1	2	5	10	1

[a]Also sold under the trade names Hydroton, Regroton, Igrolina, Igroton, and Renon.
[b]B is batch; C, continuous; D, dedicated; M, multipurpose; and F, formulation.

화학산업의 특징

Table 1. The chemical sector—main characteristics of the industries

Industry characteristics	Bulk chemicals	Fine chemicals	Speciality chemicals
Product life cycle[a]	Long	Moderate	Short/moderate
Product range (number of products)	00's	000's	0 000's
Product volumes[a]	>10 000 t/y	<10 000 t/y	Highly variable
Product prices[a]	<5 US$/kg	>5 US$/kg	>5 US$/kg
Product differentiation	None	Very low	High
Valued added	Low	High	High
Capital intensity	High	Moderate	Moderate/low
R&D focus	Process improvement	Process development	Application/product
Key success factors[b]			
—cost position	XXX	XX	X
—technical service	—	XX	XXX
—close links with the customer	—	XXX	XXX

[a] Typical examples—exceptions may apply.
[b] Relative importance: X low; XX, average; XXX, high importance.

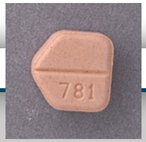
World most selling drugs

- *Source: IMS Health, a health care information company. Twelve months ending December 2005*

	Drug Name	Sales volume (billion $)	Annual Growth (%)	Usage	Producer
1	LIPITOR	12.9	6.4	High cholesterol	Pfizer
2	PLAVIX	5.9	16.0	Heart disease	Bristol-Myers Squibb & Sanofi-Aventis
3	NEXIUM	5.7	16.7	Heartburn	AstraZeneca
4	SERETIDE /ADVAIR	5.6	19.0	Asthma	GlaxoSmithKline

	Drug Name	Sales volume (billion $)	Annual Growth (%)	Usage	Producer
5	ZOCOR	5.3	−10.7	High cholesterol	Merck
6	NORVASC	5.0	2.5	High blood pressure	Pfizer
7	ZYPREXA	4.7	−6.8	Schizophrenia	Eli Lilly
8	RISPERDAL	4.0	12.6	Schizophrenia	Johnson & Johnson
9	PREVACID	4.0	0.9	Heartburn	Abbott Labs & Takeda Pharm
10	EFFECXOR	3.8	1.2	Depression	Wyeth





세계의 제약회사 (2004)

순위	회사명	국가	연간 매출 (MM$)	R&D 투자비 (MM$)	순이익 (MM$)	종업원수
1	Pfizer	USA	52,516	7,684	11,361	115,000
2	Johnson & Johnson	USA	47,348	5,203	8,509	109,900
3	GlaxoSmithKline	UK	37,318	5,204	7,886	100,619
4	Sanofi-Aventis	France	31,615	4,927	6,526	96,439
5	Novartis	Switzerland	28,247	4,207	5,767	81,392
6	Hoffmann-La Roche	Switzerland	25,163	4,098	5,344	64,703
7	Merck & Co.	USA	22,939	4,010	5,813	62,600
8	AstraZeneca	UK	21,427	3,803	3,813	64,200
9	Abbott Laboratories	USA	19,680	1,697	3,236	50,600
10	Bristol-Myers Squibb	USA	19,380	2,500	2,388	43,000

페니실린 정제공정의 예

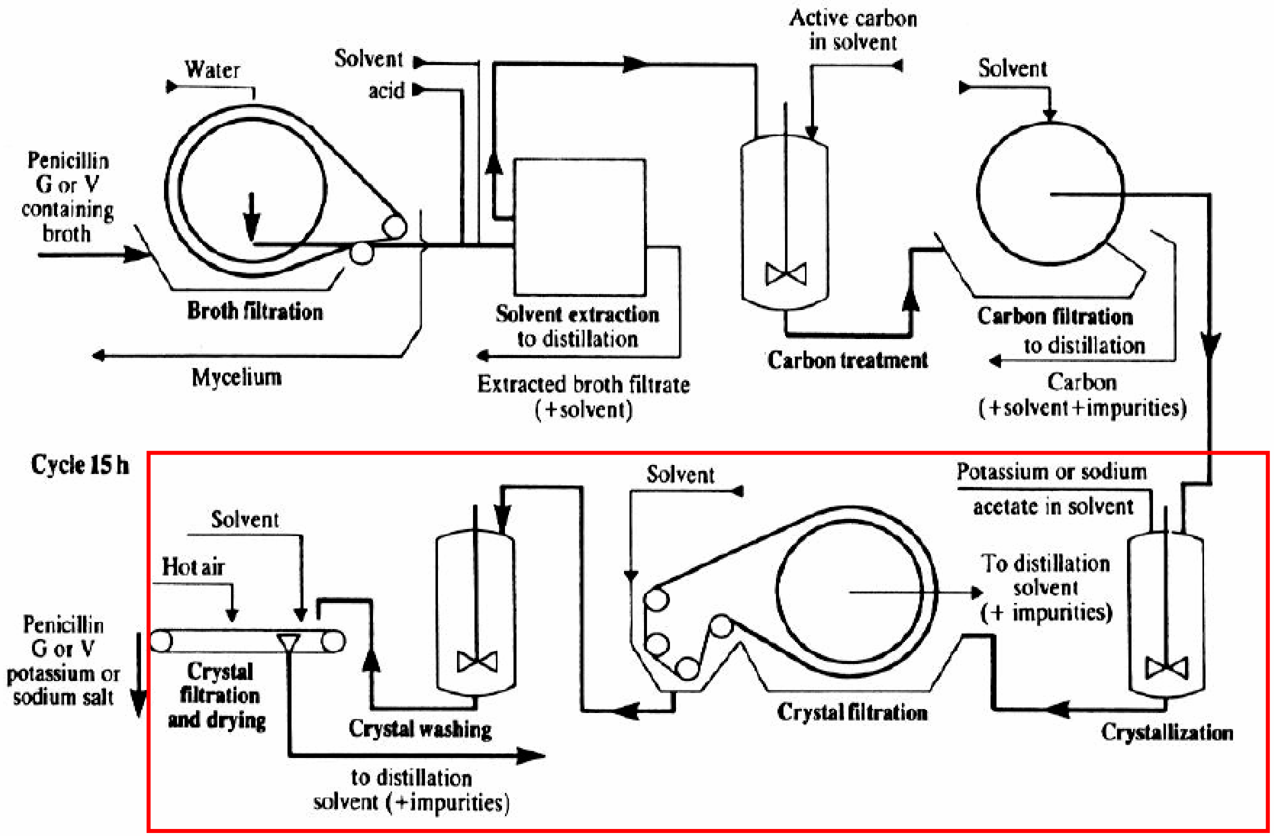
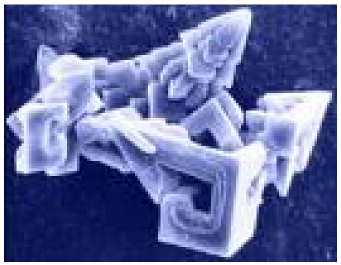


Fig. 3.7. Penicillin purification process of Gist-Brocades. (From Hersbach *et al.* 1984.)

- **결정화란 (Crystallization)**
  - 분리기술의 일종으로 액체 혹은 기체의 균일상으로부터 조작을 통하여 고체입자, 즉 결정(Crystal)을 얻는 과정

- **결정 (Crystal)**
  - 일정한 각도로 교차하는 평면이 대칭적으로 정렬된 특징적인 내부구조를 가진 고체물질
  - 이런 구조적 특징을 가지려면 분자가 한층 한층 쌓여가는 과정에 의해 생성되므로 결정의 성장이 상대적으로 느리게 진행된다.
  - 이때 결정의 모양은 결정을 구성하는 분자의 기본적인 구조에 의해 결정된다.



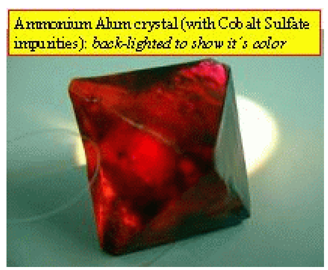


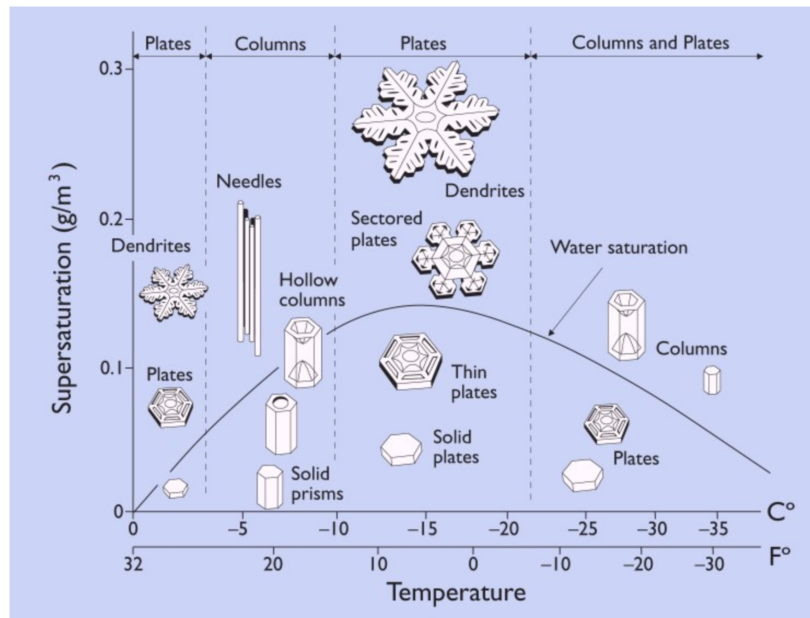


mineralminers.com

Potassium Ferricyanide crystal
deep red color

tiny Copper Sulfate seed crystals

Rochelle Salt crystal: *clear (no color)*

Ammonium Alum crystal (with Cobalt Sulfate impurities): *back-lighted to show it's color*



(출처: http://www.its.caltech.edu/~atomic/snowcrystals)

- 결정화가 일어나는 이유
  - 녹을 수 있는 정도(용해도, Solubility)보다 더 많은 용질이 용매에 녹아있을 때 (과포화, Supersaturation), 용질의 분자가 서로 결합하여 결정을 형성한다.

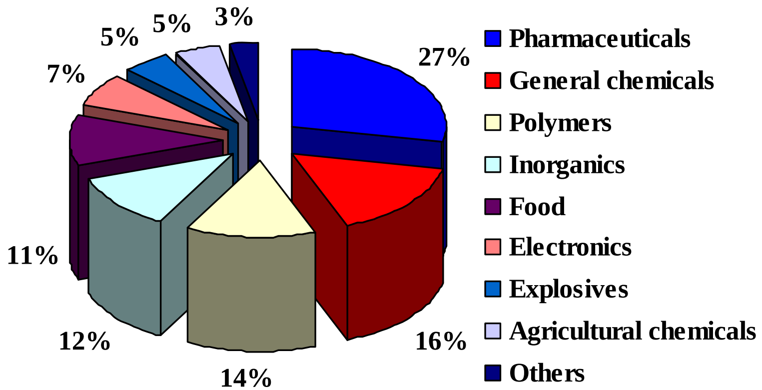
- 과포화의 원인
  - Temperature: 냉각, 용융
  - Concentration: 증발
  - Anti-solvent: Drowning-out
  - Additives: 염석
  - Pressure: 진공 (증발+냉각)
  - Reaction: 반응
  - Etc.

결정화의 장점

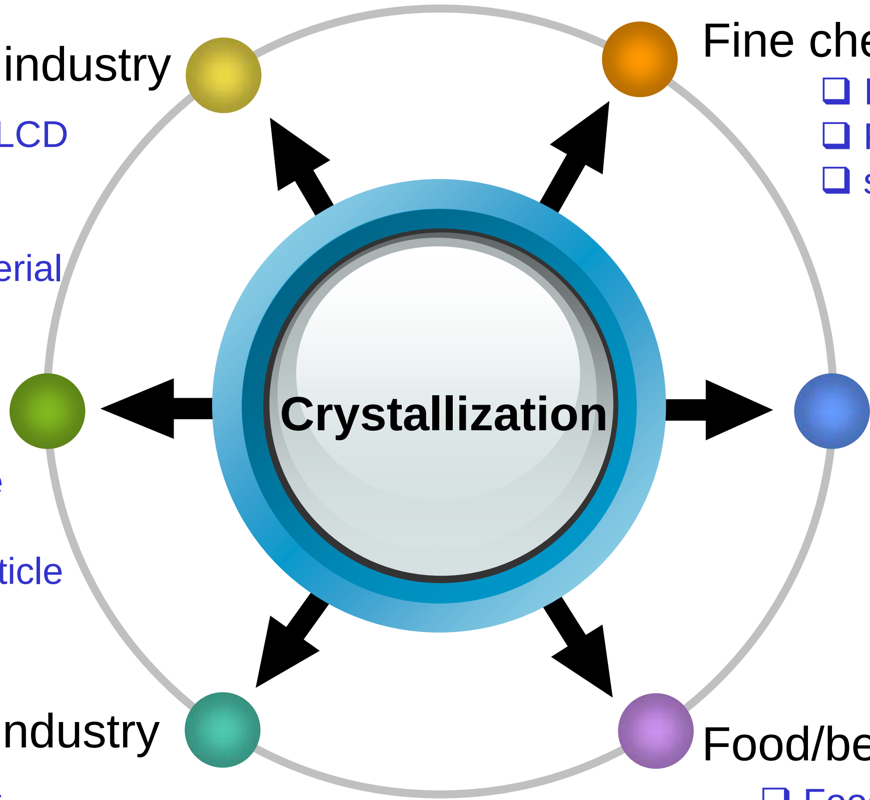
- 저 에너지 사용
  - 전통적인 분리공정에 비해 30~50% 정도의 에너지만 사용
- 단일공정
  - 공정의 구성이 간단하고 장비가 저렴
- 고순도 생성물

결정화의 산업적 중요성

- 화학산업의 많은 물질이 결정형태
  - 화학제품 중 60~90%가 결정형태
  - 정밀화학제품의 80%가 결정형태
- 화학산업에서 결정화가 포함된 공정이 최소 40%



결정화 관련산업



Semiconductor industry
- Photoactive material for LCD
- Organic EL separation
- CMP
- Nano luminescence material

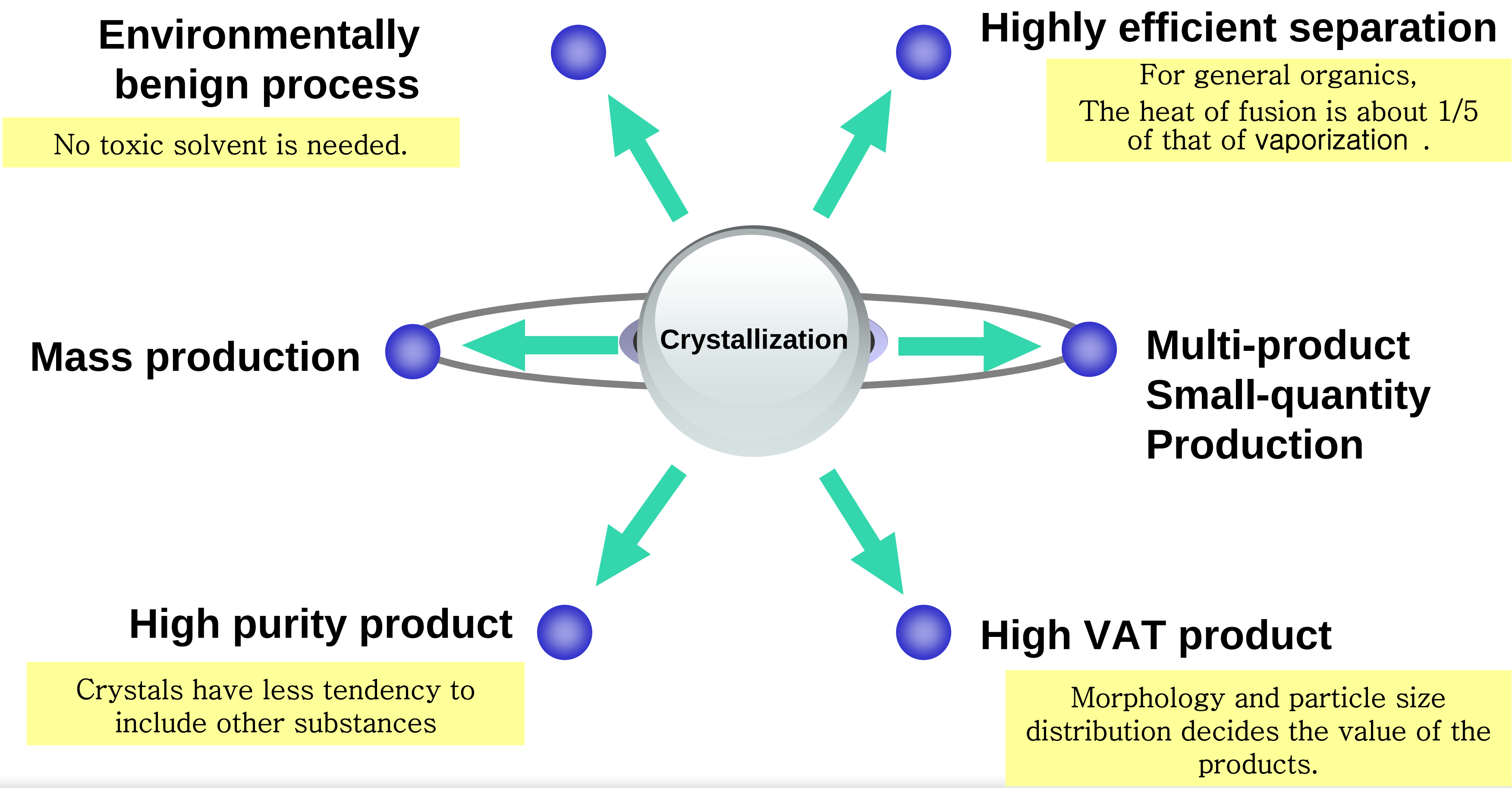
Fine chemical industry
- Intermediate separation
- Production of dye/ink
- surfactant separation

Pharm/medical
- Pharm. intermediate
- For drug delivery
- Functional nano particle

Petroleum industry
- Isomer separation
- Difficult mixture separation

Environmental Industry
- Waste treatment
- Valuable components recovery

Food/beverage industry
- Food additives production
- Amino acids production

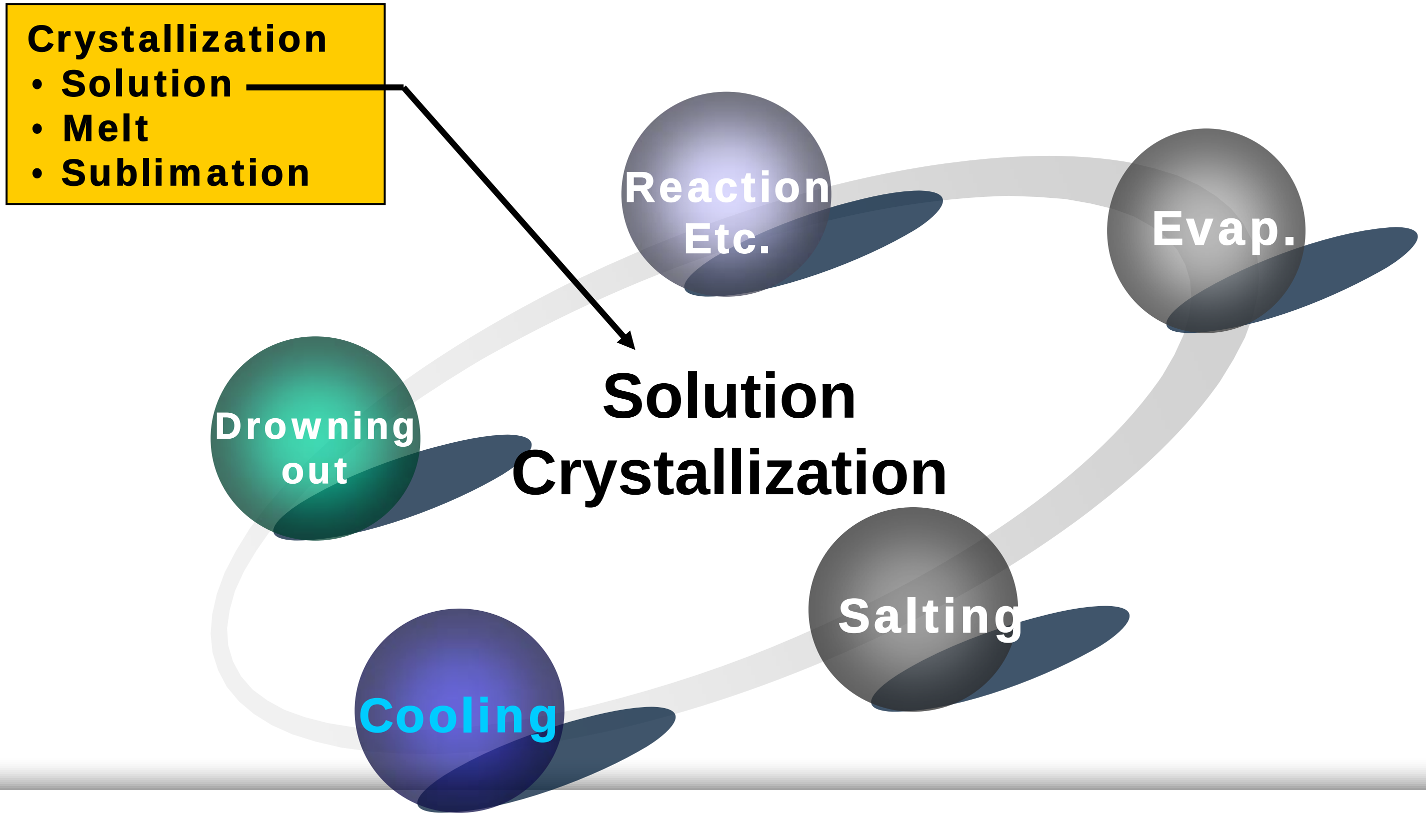

Environmentally benign process
No toxic solvent is needed.
Highly efficient separation
For general organics, The heat of fusion is about 1/5 of that of vaporization .
Crystallization
Mass production
Multi-product Small-quantity Production
High purity product
Crystals have less tendency to include other substances
High VAT product
Morphology and particle size distribution decides the value of the products.

증류와 결정화의 비교

Distillation	Crystallization
Phase equilibria	
Both liquid and vapor phases are totally miscible Liquid-vapor equilibrium Neither phase is pure Separation factor is moderate Ultra-high purity is difficult to achieve No theoretical limit on recovery	Liquid phase is totally miscible; solid phases are immiscible Solid-liquid equilibrium Solid phase is pure Partition coefficients are very high Ultra-high purity is easy to achieve Recovery is limited by SLE
Mass transfer kinetics	
High mass transfer rate in both VL phases Close approach to equilibrium Adiabatic contact assures phase equilibrium	Moderate mass transfer rate in liquid and zero in solid Slow approach to equilibrium Solid phase is not in equilibrium
Phase separability	
Viscosity in both phases is low Phase separation is rapid and complete Counter current contacting is quick and efficient	Liquid phase viscosity is moderate and solid phase rigid Phase separation is slow Counter current contacting is slow and inefficient

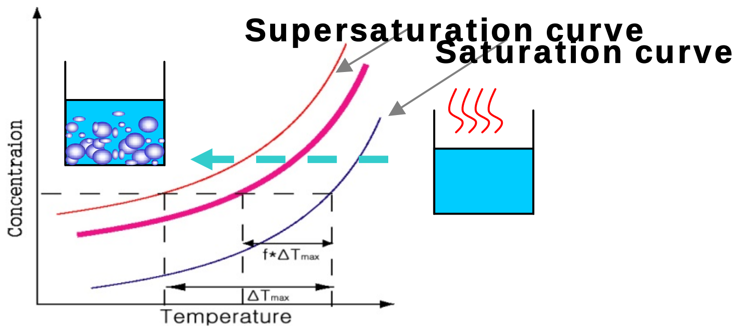
냉각결정화의 기본 이론

결정화의 분류


Crystallization
• Solution
• Melt
• Sublimation
Reaction
Etc.
Evap.
Drowning
out
Solution
Crystallization
Salting
Cooling

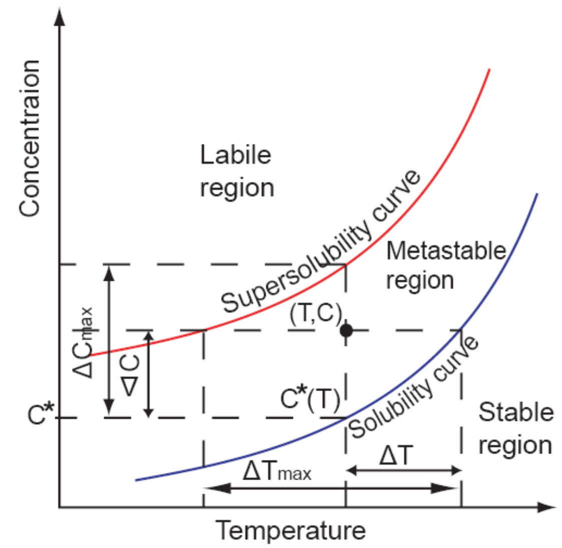
냉각결정화

- 용액을 온도를 변화시켜 과포화를 유도하여 결정을 생산
- 온도에 따른 용해도의 변화가 큰 물질에 대해 적용
- 초기 포화온도를 높일 수 없는 경우는 진공도 사용
  - 고순도이면서 균일한 분포의 생성물을 얻는데 유리
  - 정밀화학 및 반도체 공정에서 많이 사용
  - 품질요소: mean particle size, PSD, morphology, purity

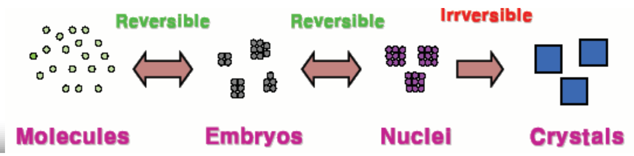


States of Solution

- 안정영역 (Stable region)
  - No crystallization or precipitation
  - Nuclei < critical size
  - Nuclei forms and melts in equilibrium
- 불안정영역 (Labile region)
  - Nuclei > critical size
  - Nuclei do not melt back to solution
  - Simultaneous
    - Nuclei formation
    - Crystal growth

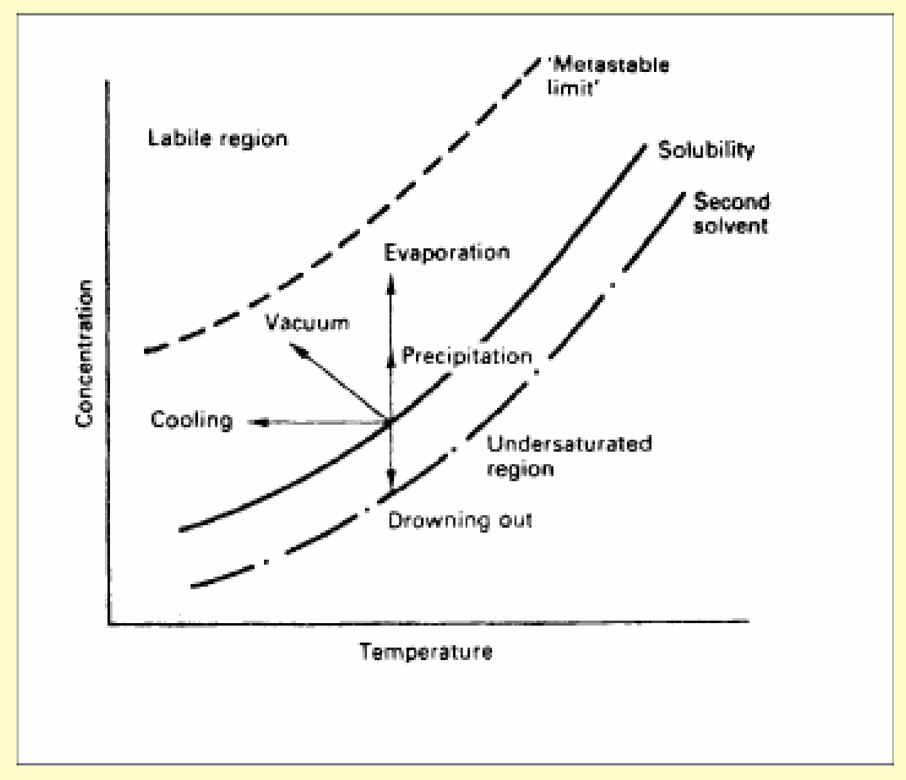


- 준안정영역 (Metastable region)
  - No nuclei (larger than critical size) formation
  - Only Crystal growth
  - Very important region for industrial crystallization
    - Controls the particle size distribution and mean particle size
    - Almost no by-product



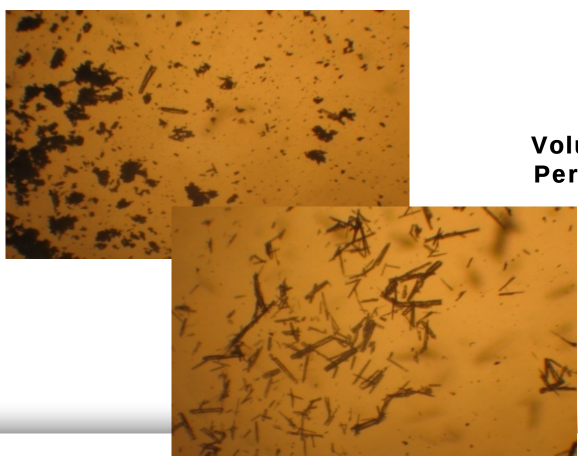
결정화의 상평형 이해

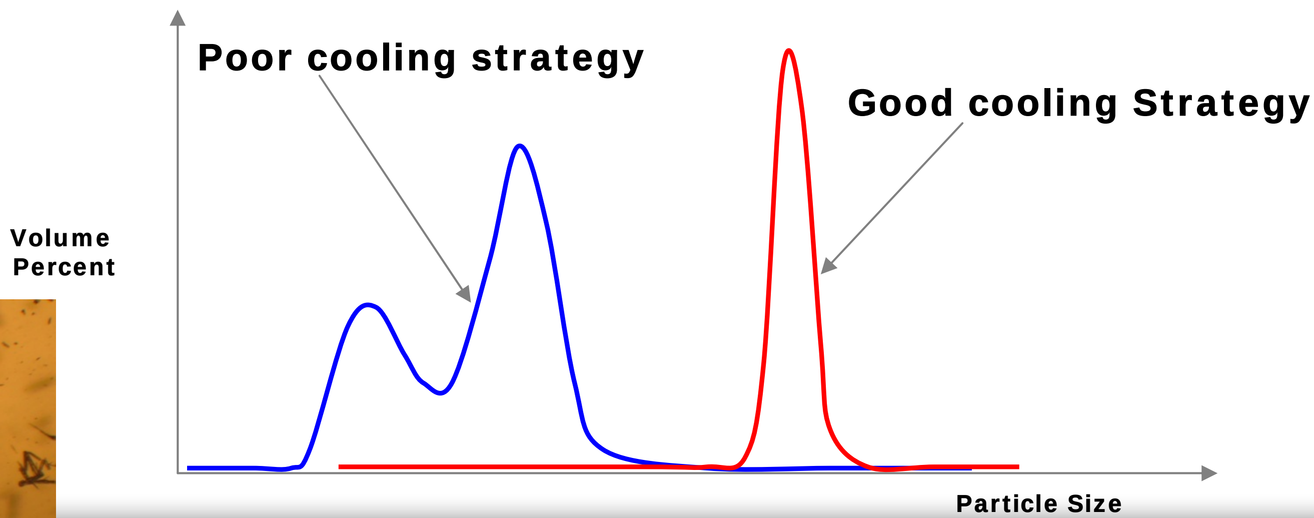
- Driving force
- 용액상태의 변화



결정화 조업조건의 중요성

- Inappropriate cooling strategy causes
  - Uneven particle size distribution
  - Smaller mean particle size
- Low purity and low product quality
- Requires time and energy for washing final product





Nucleation and Crystal Growth

- 핵생성 (Nucleation)
  - 일차핵생성 (Primary nucleation)
    - 균일 핵생성 (Homogeneous nucleation)
      - ✓ Solute molecule combines to produce embryos
    - 불균일 핵생성 (Heterogeneous nucleation)
      - ✓ Due to foreign nuclei which has lower surface energy
  - 이차핵생성 (Secondary nucleation)
    - Due to solute particles or Seeds
    - Apparent secondary nucleation
      - ✓ Small fragments washed from the surface of the seeds
    - True secondary nucleation
      - ✓ Current level of supersaturation is higher than the critical level for the solute particles present in solution
    - Contact secondary nucleation
      - ✓ Growing particle contacts with walls, stirrer, pump impeller, or other particle and generates residual solute particles
- 결정의 성장은 주로 degree of supersaturation에 의해 결정

Supersaturation

- Thermodynamically, solute in excess of solubility
  - Supersaturation = $\Delta\mu/RT$ where μ is chemical potential

- For practical use
  - $\Delta c = c - c^*$ or $S = c/c^*$ where c^* is saturation concentration
  - Supersaturation Δc is sometimes called "concentration driving force."

Crystallization Kinetics

- Nucleation rate: rate of formation of new crystal

$$\frac{dN}{dt} = B = k_N (\Delta c)^b \quad (\text{nuclei/sec} \cdot \text{m}^3)$$

  - Where b= order of nucleation
  - B=nucleation rate (rate of increase of crystal number)

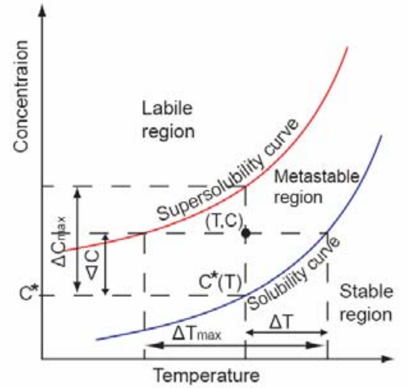
- Crystal growth: rate of increase of crystal dimension

$$\frac{dL}{dt} = G = k_G (\Delta c)^g \quad (\text{m/sec})$$

  - Where b= order of nucleation
  - B=nucleation rate (rate of increase of crystal number)

- Crystal agglomeration and breakage are also function of supersaturation

Metastable Zone Width



- 준안정영역에 관한 정보는 결정화 조업에 매우 중요
  - 균일한 PSD에 큰 영향
- Metastable zone width (MZW)
  - Maximum Allowable Undercooling (MAUC): $\Delta T_{max}(C)$
  - Maximum allowable supersaturation (MASS): $\Delta C_{max}(T)$
- 균일한 PSD를 위한 조업 조건
  - Driving force: $\Delta C = C - C^{*}(T)$ 또는 $\Delta T = T - T^{*}(C)$
  - 핵생성 조건: $\Delta C > \Delta C_{max}(T)$ 또는 $\Delta T > \Delta T_{max}(C)$
  - 결정성장은 ΔC나 ΔT (Driving force)가 클수록 빠름

준안정영역에 영향을 미치는 인자

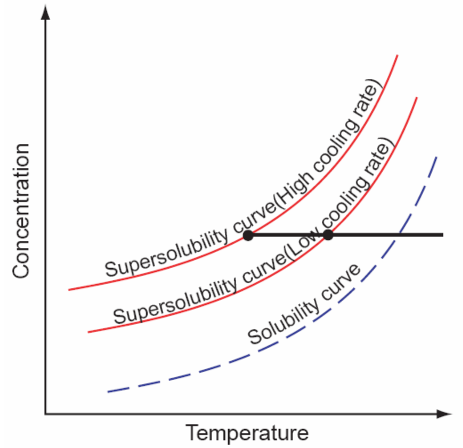
- 냉각속도
  - 일반적으로 냉각속도가 커질수록 MZW가 커짐
- Agitation
  - 교반속도가 너무 느린 영역에서는 변화 없음
  - 일반적으로 교반속도가 커질수록 MZW가 작아짐
- Additives
  - 종류에 따라 매우 달라짐
- Solution thermal history
  - 영향이 있음은 관찰되고 있으나 어떤 영향을 가지는지는 미지수

- **Existing Model for MZW**
  - **Nyvlt (1983)**

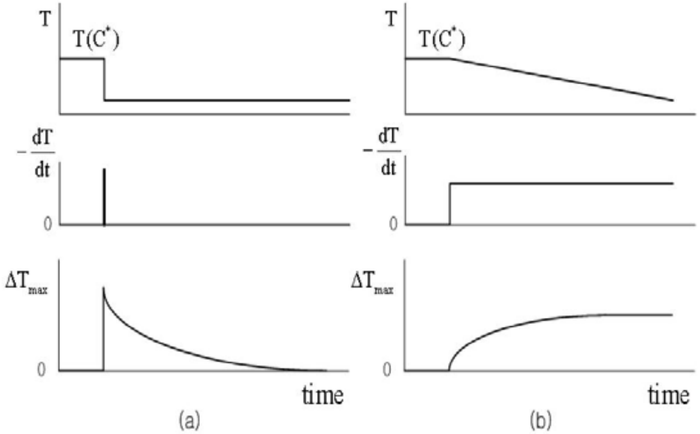
$$\log u = (m-1)\log\left(\frac{dc^*}{dT}\right) + \log k_n + m \log \Delta T_{\max}$$

  - **Cheong-Song Choi and Ik-Soo Kim (1991)**

$$\Delta C_{\max} = h_0 u^{h_1} + H_2 (T_0 - T)$$

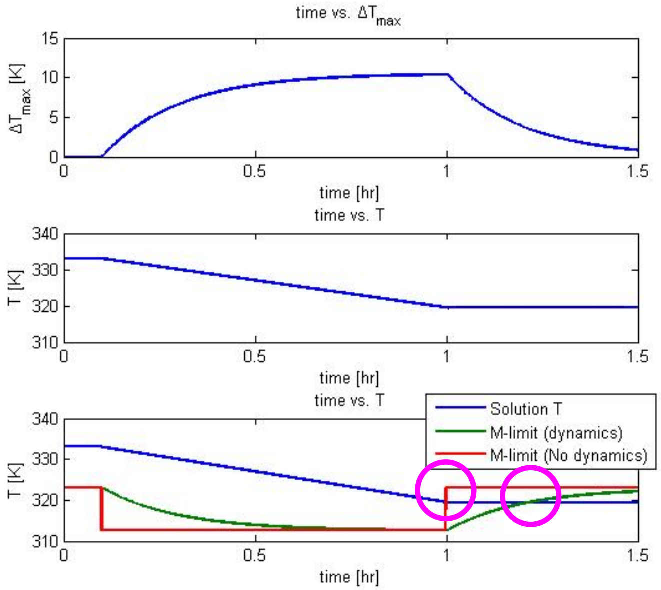


- **Weakness of previous approaches**
  - **MZW is considered as a Static property**
    - $\Delta T_{max} = k(u)^p$
  - **Cannot explain Induction time**
  - **Other unrealistic behavior**
    - **Cooling rate changes from nonzero to zero**
    - **Sudden start of cooling from equilibrium**



New approach

- MZW is not a static property.
- As cooling rate changes, the metastable limit is separated and converged to saturation curve asymptotically.
- Need to introduce dynamic concept.
  - Simple approach: 1^{st} or 2^{nd} order dynam
- Induction time can be explained.



Model for batch cooling crystallization

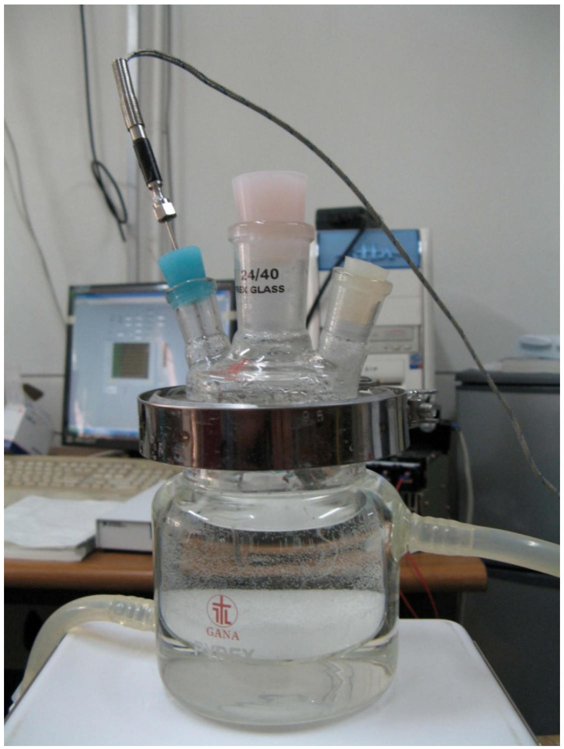
- The **dynamic model** of the metastable limit
  - To explain the dynamic behaviour of metastable limit, following 1st order dynamic model can be proposed.

$$\tau \frac{\Delta T_{\max}(t)}{dt} + \Delta T_{\max}(t) = ku(t)^p$$

Where, u is the cooling rate of the solution, and
Three parameters, k, p, and τ, are depend on saturation concentration.

  - This model has 1st order dynamics of supersaturation with nonlinear output to rate of driving force inducing supersaturation.

Experiments for defining dynamic model of metastable limit



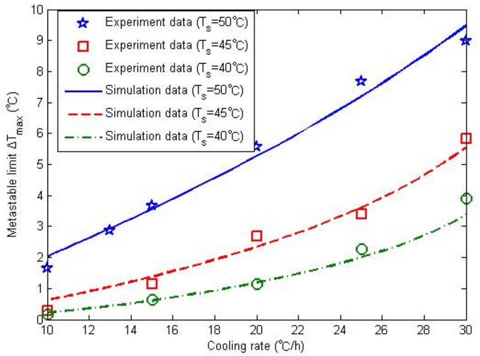
Reactor of nucleation experiment

- **Experimental procedure**
  1. **Making up solution.**
     - $(NH_4)_2SO_4$ – H_2O solution
  2. **Keeping temperature as initial temperature for 1hr.**
     - RPM of magnetic bar : 1100rpm (Max.)
  3. **Keeping temperature as initial temperature for 30min.**
     - RPM of magnetic bar : 400rpm
  4. **Starting cooling experiment**
  5. **Observing nucleation**
     - RPM of Strobo scope : 1400 rpm

Experiment 1-1

- **Finding out parameters for the dynamic model**
  - **Experimental conditions**
    - **Solution concentration (Saturation temperature)**
      - ✓ **0.8425(50℃), 0.8263(45℃), 0.8100(40℃)**
    - **Initial temperature : 10℃ higher than saturation temperature**
    - **Cooling rates : 30℃/h, 25℃/h, 20℃/h, 15℃/h, 10℃/h**
  - **Expected results**
    - **Parameters for dynamic model of metastable limit**
      - ✓ **k, p, τ**

Parameters for the metastable limit model



$$k = 4.545 e^{0.3195 T_s} \times 10^{-9}$$

$$p = 6.894 - 0.1015 T_s$$

$$\tau = 0.3682 + 0.03572 T_s$$

Estimated parameter from experiment 1-1.

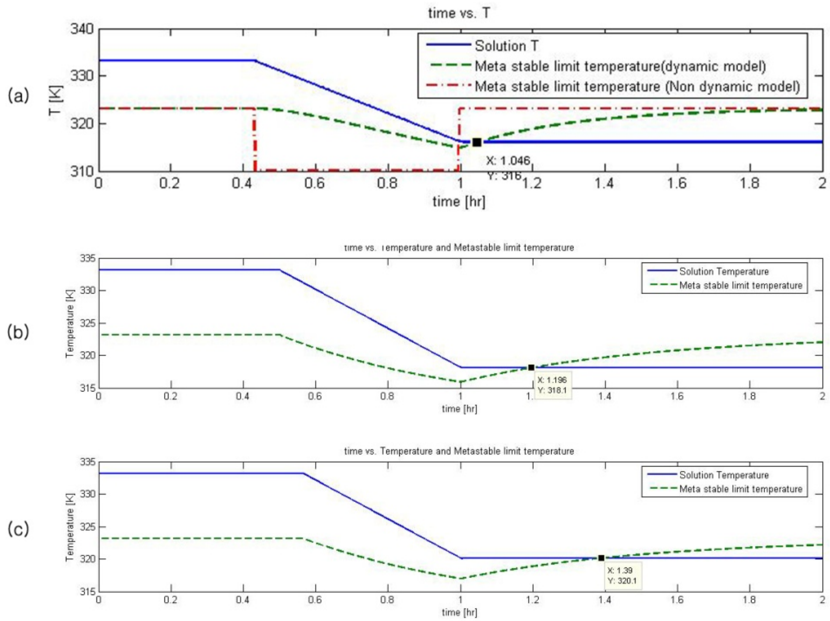
Concentration [solute kg/solvent kg]	Saturation temperature [℃]	k	p	τ
0.8425	50	0.0395	1.7976	0.5393
0.8263	45	0.0015	2.9413	0.4883
0.8100	40	0.0006	3.76	0.4720

Experiment 1-2

- **Verification of Proposition**
  - **Experimental condition**
    - **Solution concentration : 0.8425 [solute kg/ solvent kg] (T_s=50℃)**
    - **Initial temperature : 60℃ (10℃ higher than saturation temperature)**
    - **Cooling rate : 30℃/h**
    - **Keeping solution temperature at : 43℃, 45℃, 47℃**
  - **Expected results**
    - **Induction time is well predicted by the dynamic model**

Prediction of Nucleation time

Simulation result of experiment 1-2.



Results of experiment 1-2.

	Nucleation time (Experiment) [sec]	Nucleation time (Simulation) [sec]
(a)	149	165
(b)	740	705
(c)	1374	1404

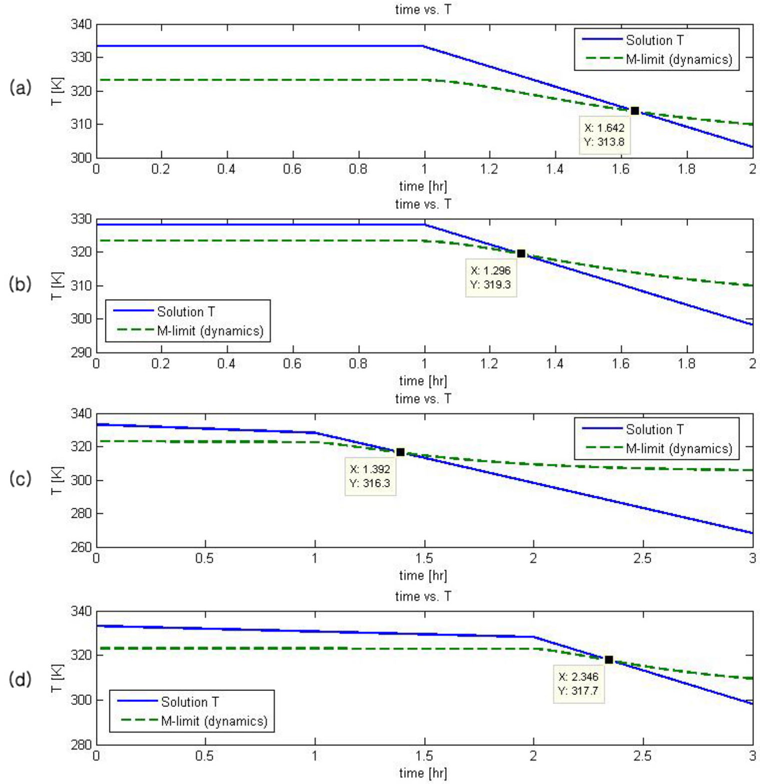
linear cooling of 30℃/h from 60℃ to (a) 43℃, (b) 45℃, (c) 47℃ and then hold

Experiment 1-3

- **Predicting the effect of thermal history**
  - **Experimental condition**
    - **Solution concentration : 0.8425 [solute kg/ solvent kg] (T_s=50℃)**
    - **Initial temperature : 55℃ (5℃ higher than saturation temperature)**
    - **Cooling rate : 30℃/h**
    - **Different thermal history**
      - ✓ **Linear cooling from 60℃ to 55℃. Cooling rate is 30 ℃/h**
      - ✓ **Keeping temperature as 55℃**
      - ✓ **Linear cooling from 60℃ to 55℃. Cooling rate is 5 ℃/h**
      - ✓ **Linear cooling from 60℃ to 55℃. Cooling rate is 2.5 ℃/h**
  - **Expected results**
    - **Thermo history is well predicted by dynamic model**

Prediction of Nucleation time for different thermal history

Simulation result of experiment 1-3.



Results of experiment 1-3.

Thermal history		Nucleation temp. (Experiment data) [℃]	Nucleation temp. (Simulation data) [℃]
Initial temp. [℃]	Cooling rate [℃/h]		
60	30	41.02	40.65
55	0	45.5	46.15
60	5	44	43.15
60	2.5	44.5	44.15

Thank you!