Initial stages of crystallisation

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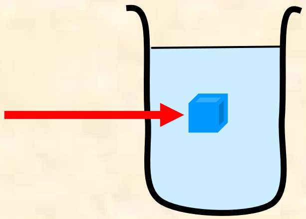


- Nucleation
  - subcritical clusters
  - laser-induced nucleation
- Chiral purification through crystal grinding
  - crystal size distribution

MID XFEL Workshop, 28-29 October 2009, ESRF

Classical nucleation theory

- Crystal nucleation not well understood
  - too fast
  - too few
  - too small
- Important
  - dictates crystalline form (polymorph)
    - pharmaceutical industry!
  - Ostwald's rule of stages
    - first least stable crystal is formed, later more stable
    - happens during nucleation

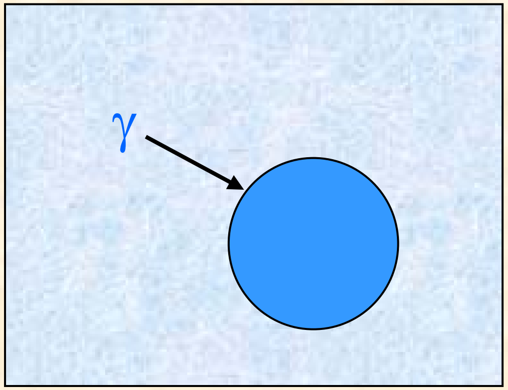
Nucleation

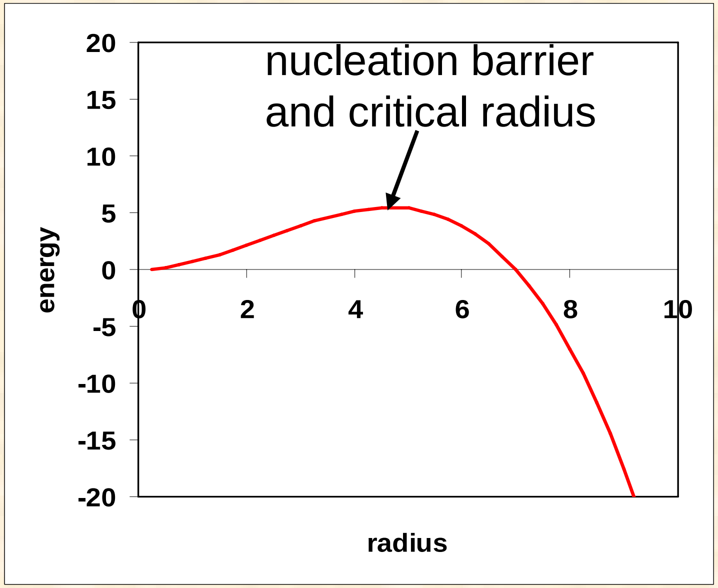
- dominated by surface/size effects
  - nucleation barrier
- classical nucleation theory
  - assume spherical nucleus, radius *r*
- driving force: $\Delta\mu$
  - surface free energy: γ
  - volume per growth unit: V_0
- Free energy:

$$G(r) = -\frac{\frac{3}{4}\pi r^3}{V_o}\Delta\mu + 4\pi r^2\gamma$$

bulk crystal: gain

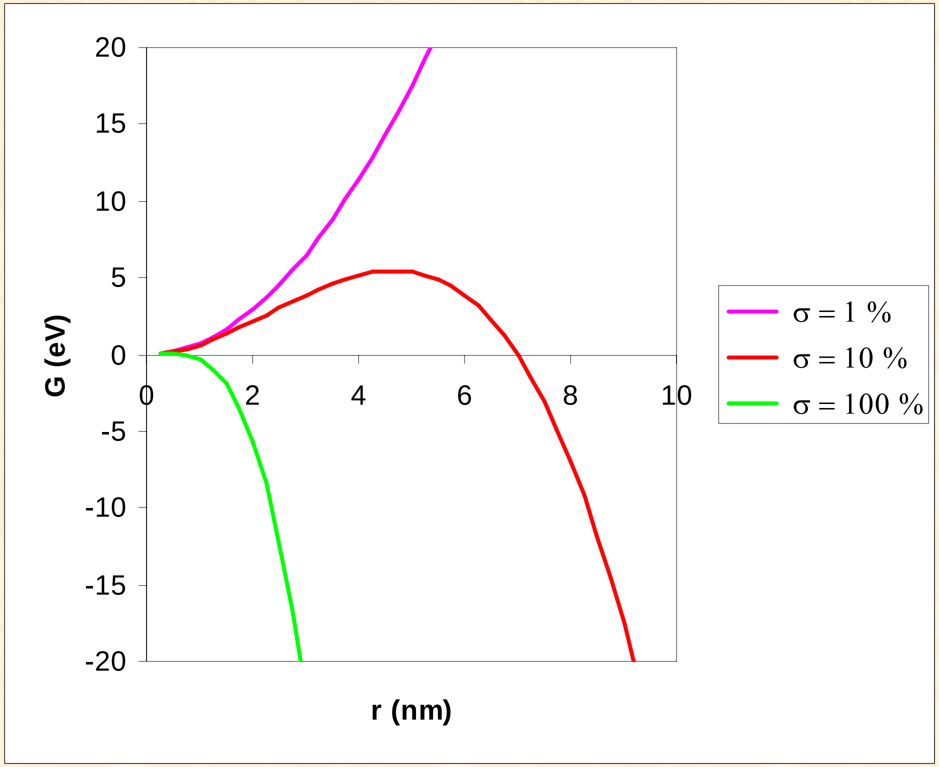
surface energy: loss





Effect of supersaturation σ

$$\Delta\mu = kT\ln\left(\frac{c}{c_{eq}}\right) = kT\sigma$$



- Probability of nucleation depends strongly on supersaturation
- Solution contains transient clusters below the critical size

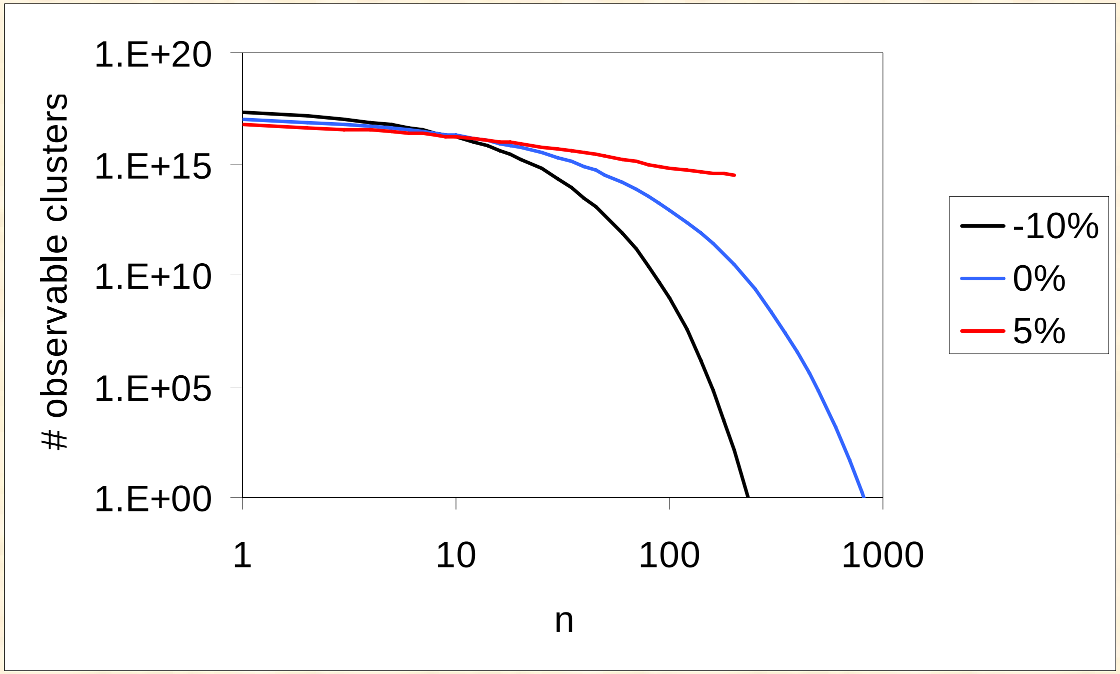
Observing nuclei

Two options

1. Watch actual nucleation event
   - rare
2. Watch transient precritical clusters
   - lots

Precritical clusters

- sample cell of 5 mm
- KCl
- critical cluster at σ = 5%, n^* = 220



Observable intensity

$$I_{peak} \approx (r_e n F)^2 \psi$$

- flux 10^{12} photons/pulse
  - after single pulse, cluster destroyed (?)
- n ~ 220
- F ~ 35

scattered photons in single pulse

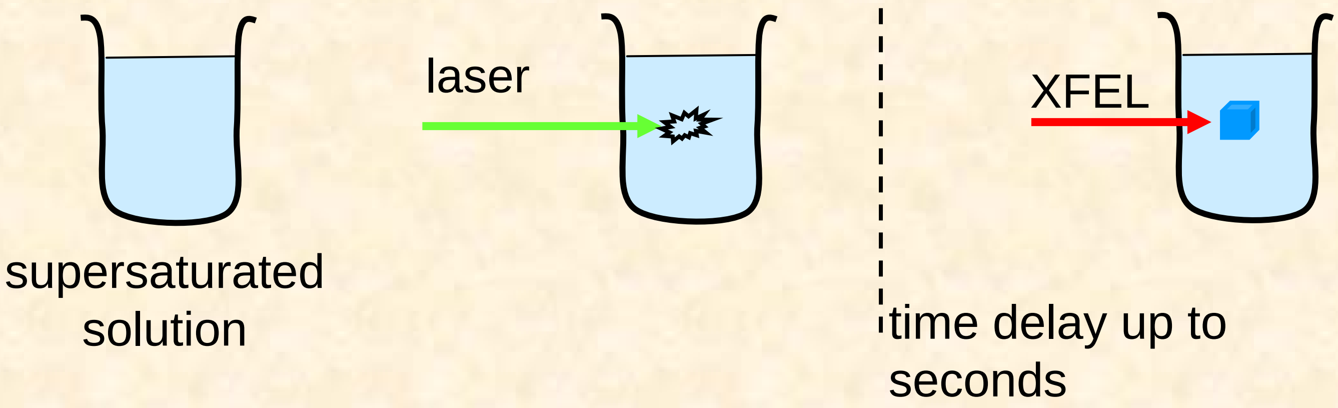
- 10 x 10 μm² beam: ~5
- 1 x 1 μm² beam: ~500
- 0.1 x 0.1 μm² beam: ~50,000 ← **OK?**

Beyond critical clusters

- Need larger cluster = growing nucleus
- How to find nucleus at the right time and the right place?
  - random
    - like winning the lottery
    - rapidly nucleating system will increase chances
  - many experiments are possible at rep-rate of XFEL
    - select only the successful ones
    - high-energy physics style

Laser-induced nucleation

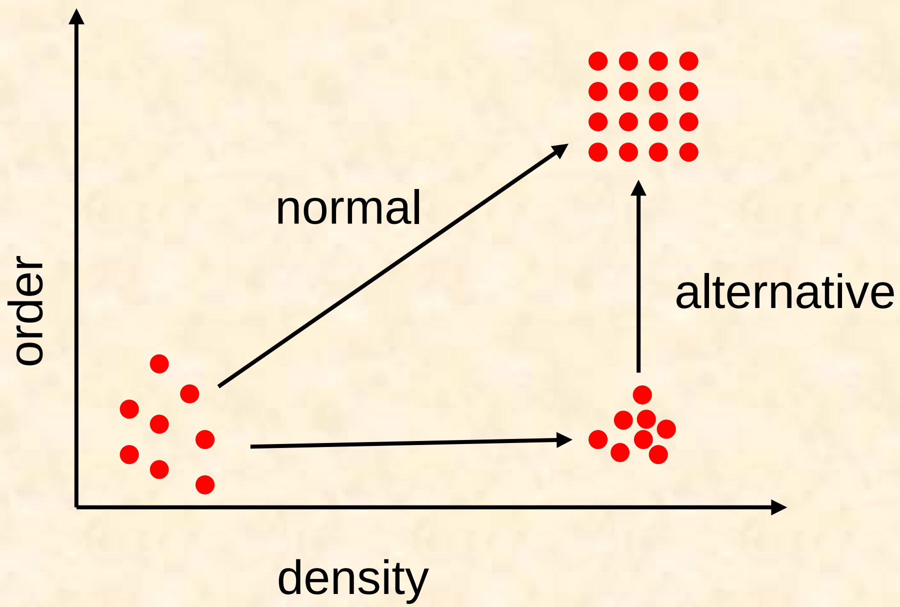
- Idea: use laser to induce nucleation
  - has been observed on e.g. KCl in single pulse
  - A.J. Alexander and P.J. Camp, Cryst. Growth & Design 9 (2009) 958.
  - ‘instantaneous’ (single pulse of 7 ns 1064 nm laser)
- Should produce growing nucleus at right time and place
- In situ: at least 12.4 keV



Intensity from nucleus

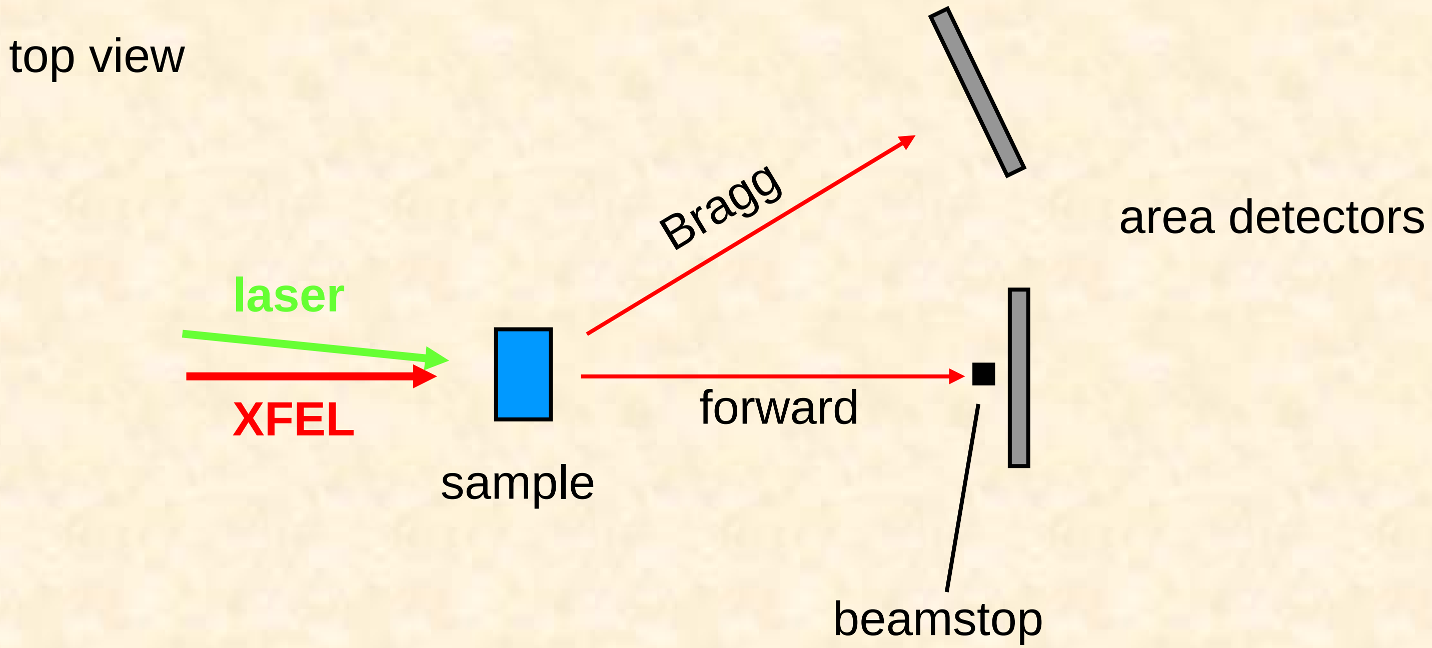
- Observe growing cluster after small time delay, 1 μm^2 beam
  - radius 10 nm; n = 58,000 — 3×10^7 photons/pulse
  - radius 50 nm; n = 7.3×10^6 — 5×10^{10} photons/pulse
- Many experiments needed
  - orientation of nucleus is random
- Determine
  - shape
  - crystallinity
    - Bragg scattering: crystalline part
    - forward scattering: high-density part
  - polymorph

Non-classical nucleation



- Two step mechanism
  - first density change
  - next crystalline order
- Again: Bragg + forward scattering

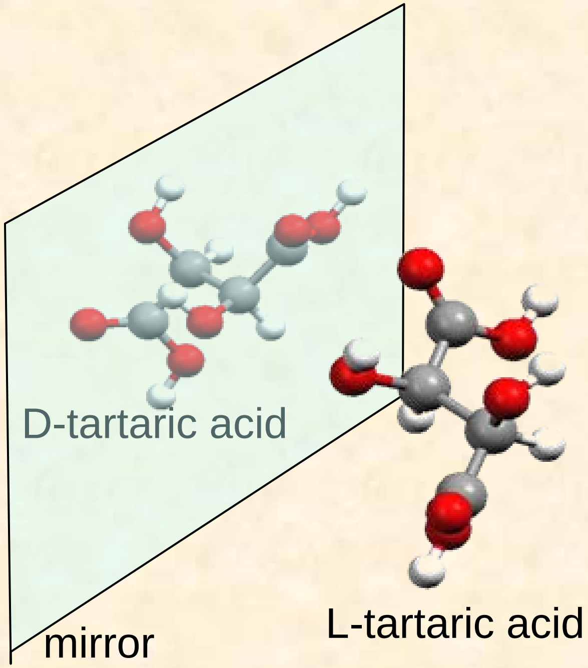
Experimental geometry



- single shot
  - system needs time to recover or move to fresh position

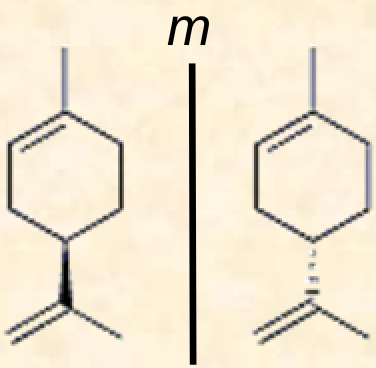
Chirality

- Many molecules have handedness
  - left/right
  - +/-
  - D/L
  - R/S (absolute configuration)
- Non-superimposable mirror images
- Enantiomers
- Chemical synthesis
  - usually racemic (50:50) mixture
- Natural amino acids
  - (almost all) left-handed
  - why?



Enantiomers

- In achiral environment
  - same physical properties (melting point, etc.)
- In chiral environment (human body)
  - very different properties
  - often important to select one enantiomer (drugs, thalidomide)

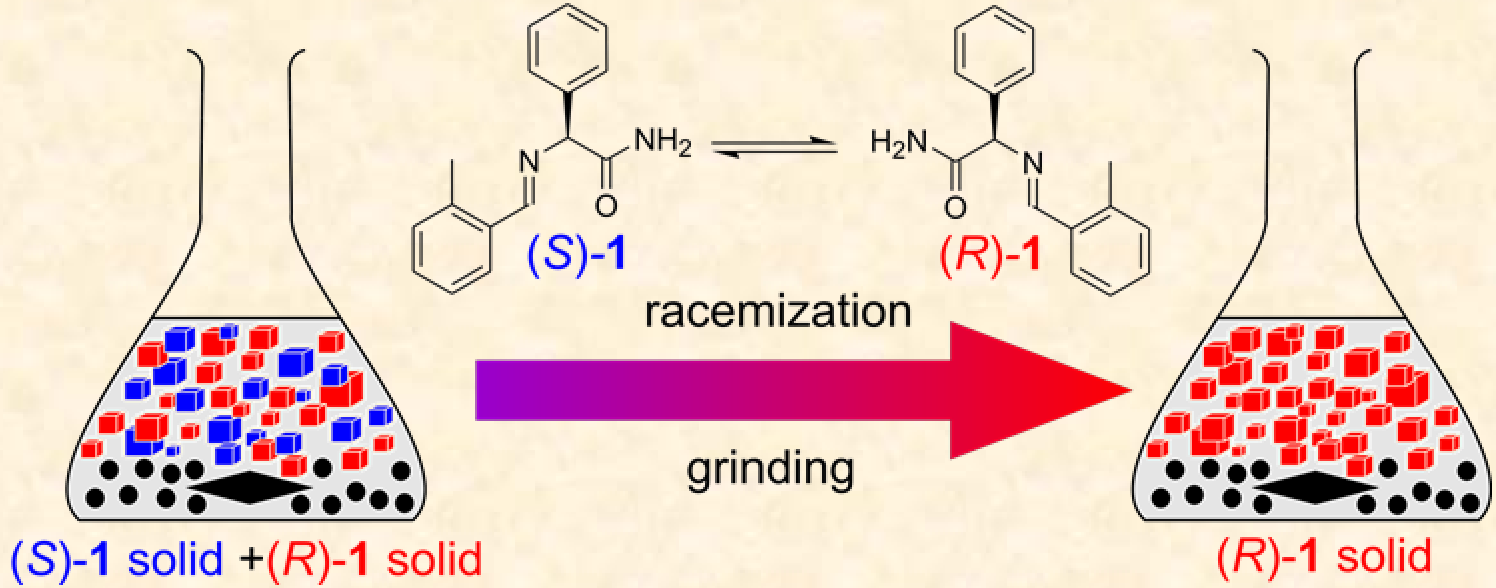


limonene

Chiral purification through crystal grinding

Model system

- *N*-(2-methylbenzylidene)-phenylglycine amide
- DBU as racemizing catalyst

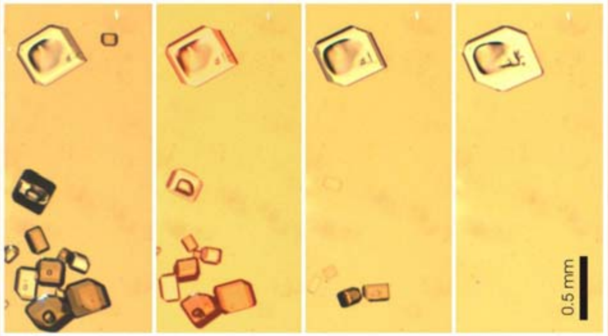


Wim Noorduin et al., J. Am. Chem. Soc. 130 (2008) 1158

Mechanism?

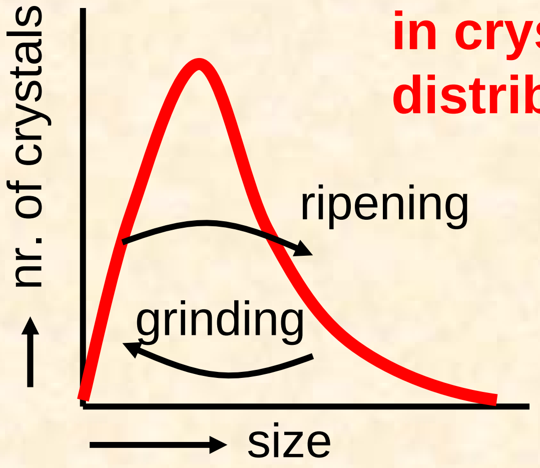
Attrition-enhanced Ostwald ripening

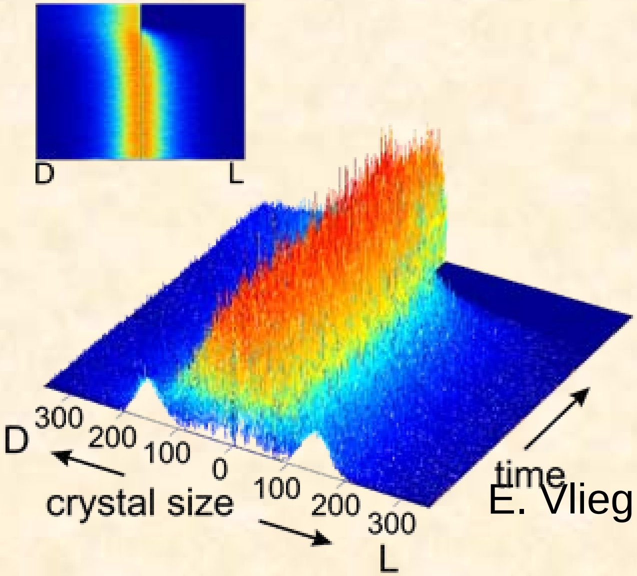
- Ostwald ripening
    - crystals get bigger
- Attrition
    - crystal get smaller



$NaClO_3$,
Wim Noorduin et al. Crystal Growth & Des. 8 (2008) 1675

Measure evolution in crystal size distribution

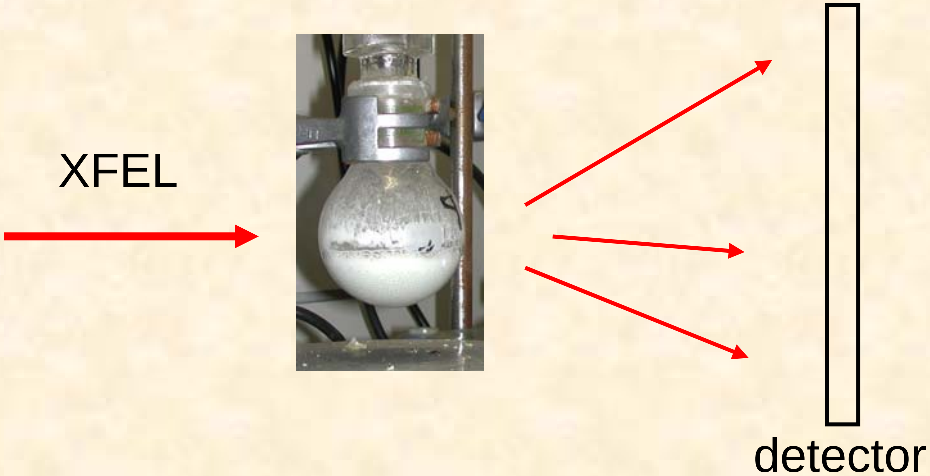




Crystal size distribution

- tens of thousands of crystals
- size from nm (dissolving) to ~10 μm
  - Smallest crystals are thought to play crucial role
    - direct incorporation
- ideally: distinguish between left and right

XFEL experiment



- Extract size and shape from coherent images along powder ring
  - large crystals: easy
  - small crystals (important!): difficult
- Accumulate statistics by several separated shots
  - give system some recovery time
- Watch evolution
  - hours time scale

Conclusion

- XFEL should make nucleation visible
- For in situ experiments, harder X-rays useful