In situ Measurement and Characterization of Crystal Growth by X-ray Diffraction

Crystallization Monitoring – a QbD tool

Detlef Beckers,
Klaus Bethke,
PANalytical B.V.
The Netherlands

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- Motivation
- Experimental set-up
- *In situ* monitoring of DL-Alanine crystal growth
- Crystal morphology investigation by CT

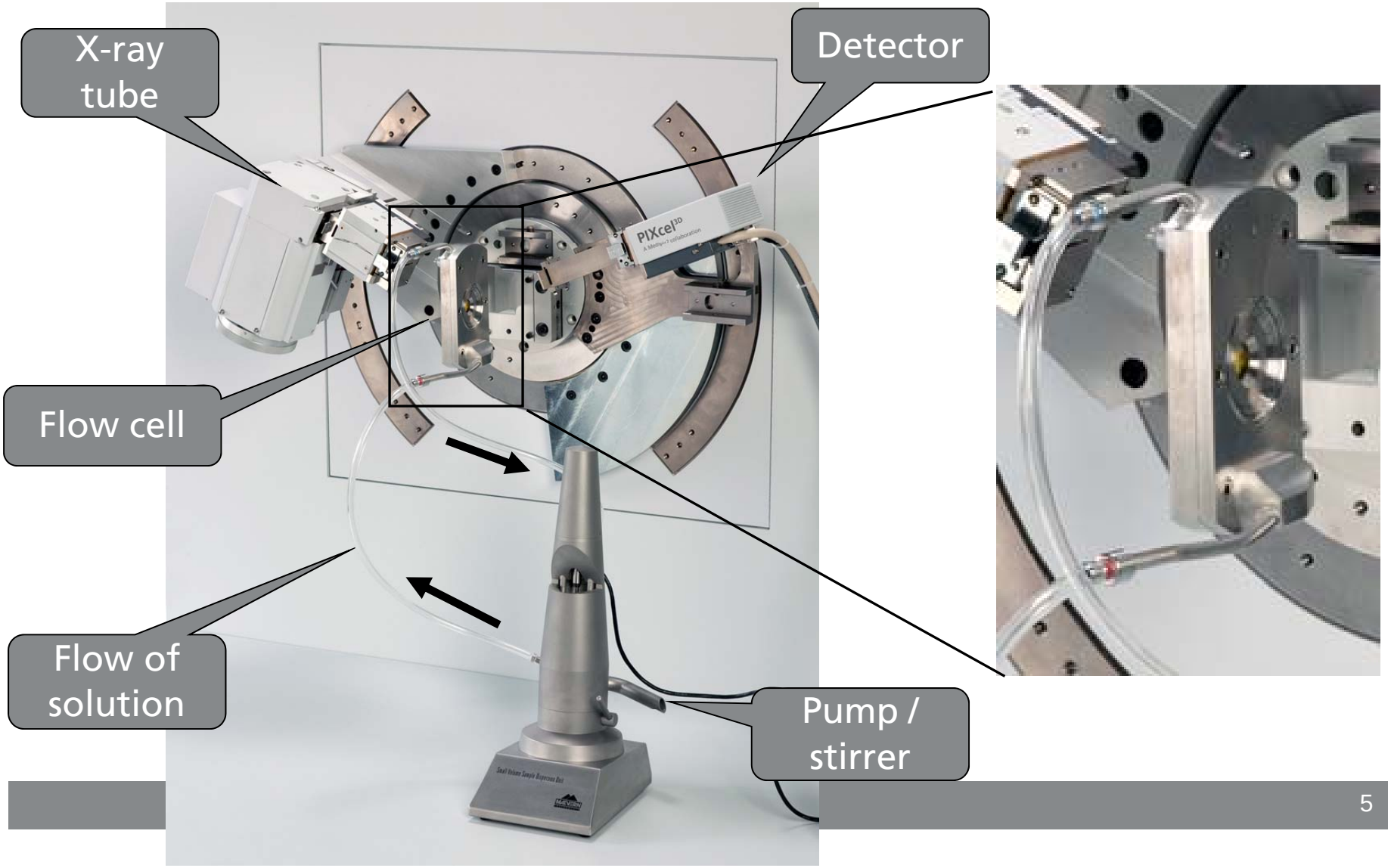
Crystallization monitoring: a key industry requirement

- Crystallization is always a key aspect of pharmaceutical manufacturing and development:
  - Significant impact on the efficiency and profitability of the overall process
  - Over 90% of all pharmaceutical products contain active ingredients produced in crystalline form
  - Undetected fluctuations in the crystallization process can alter the crystal structure or stability, affecting the safety and the bioavailability of the product.
  - Failure to meet product specifications incurs significant costs

Industry need for on-line monitoring

- Monitoring of crystallization processes both in research and scale-up is essential for a **QbD** (Quality by design) approach and to develop **"PAT"** solutions
  - Process Analytical Technology (PAT) is the design and control of manufacturing processes through real-time measurements with the goal of ensuring final product quality
- **Paramaters to control**: crystal size distributions, polymorph formation and intermediates, impurity-crystal interactions, morphology (shape)
- Current monitor techniques:
  - NIR, Raman: polymorphs
  - FTIR: solution concentration

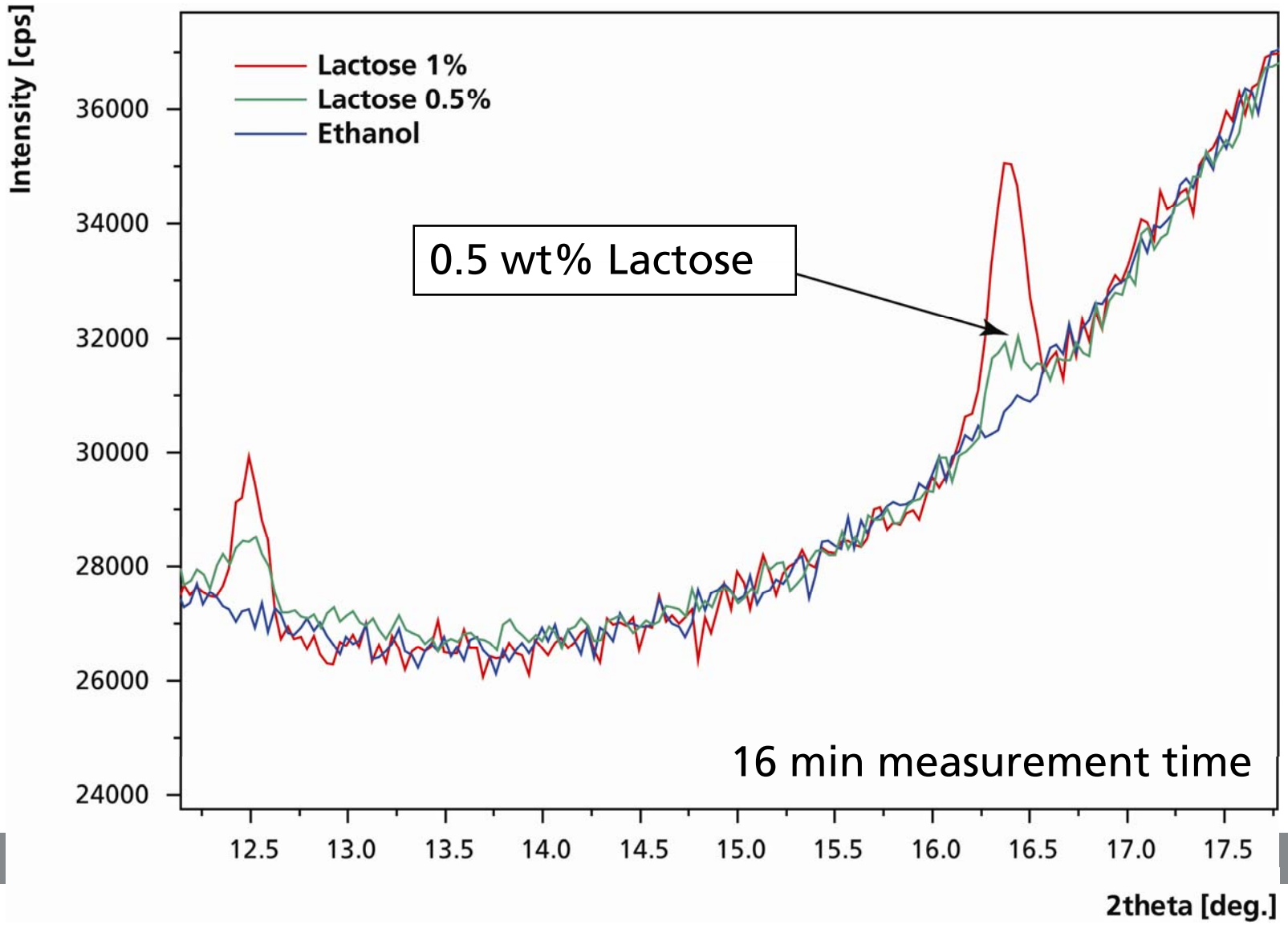
Experimental – set-up



Applications for *in situ* studies

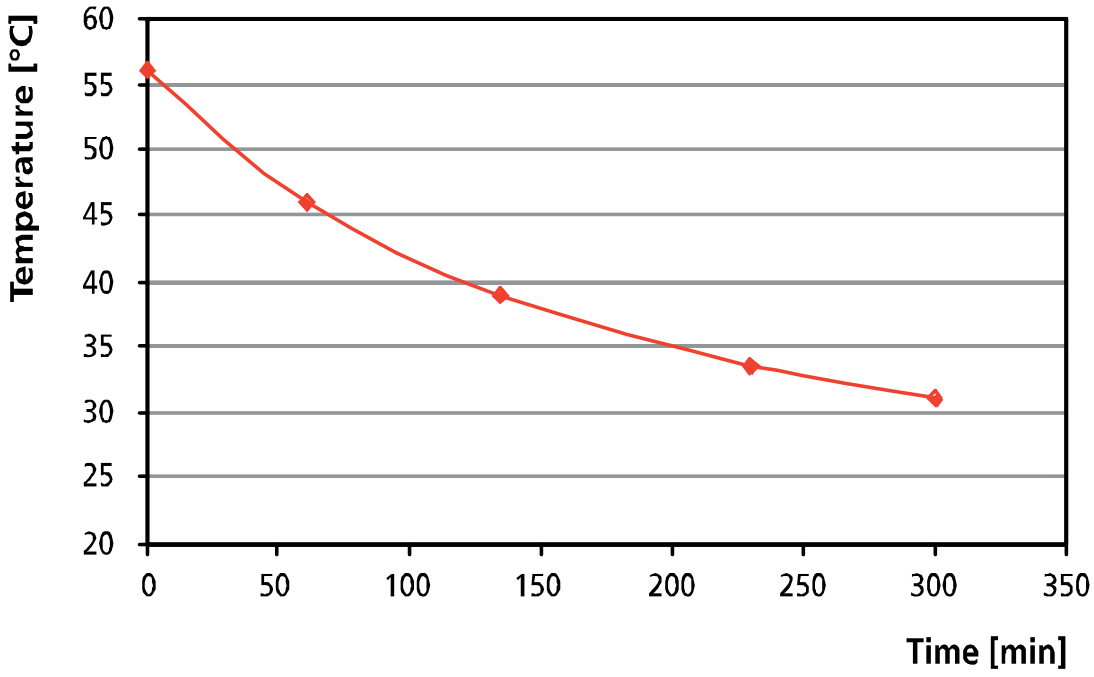
- Crystallization from supersaturated solutions: e.g. investigation of intermediates (polymorphs) and hemi-hydrates during the crystallization process
- Solvent / anti-solvent reactions (e.g. in cleaning processes , re-crystallization)
- Parameter optimization in the crystallization process (pH, (anti-)solvent concentration, etc…)
- Small angle X-ray scattering (SAXS) studies of early crystallization stages or nano particles
- Scale-up investigation

Sensitivity test - Lactose in ethanol



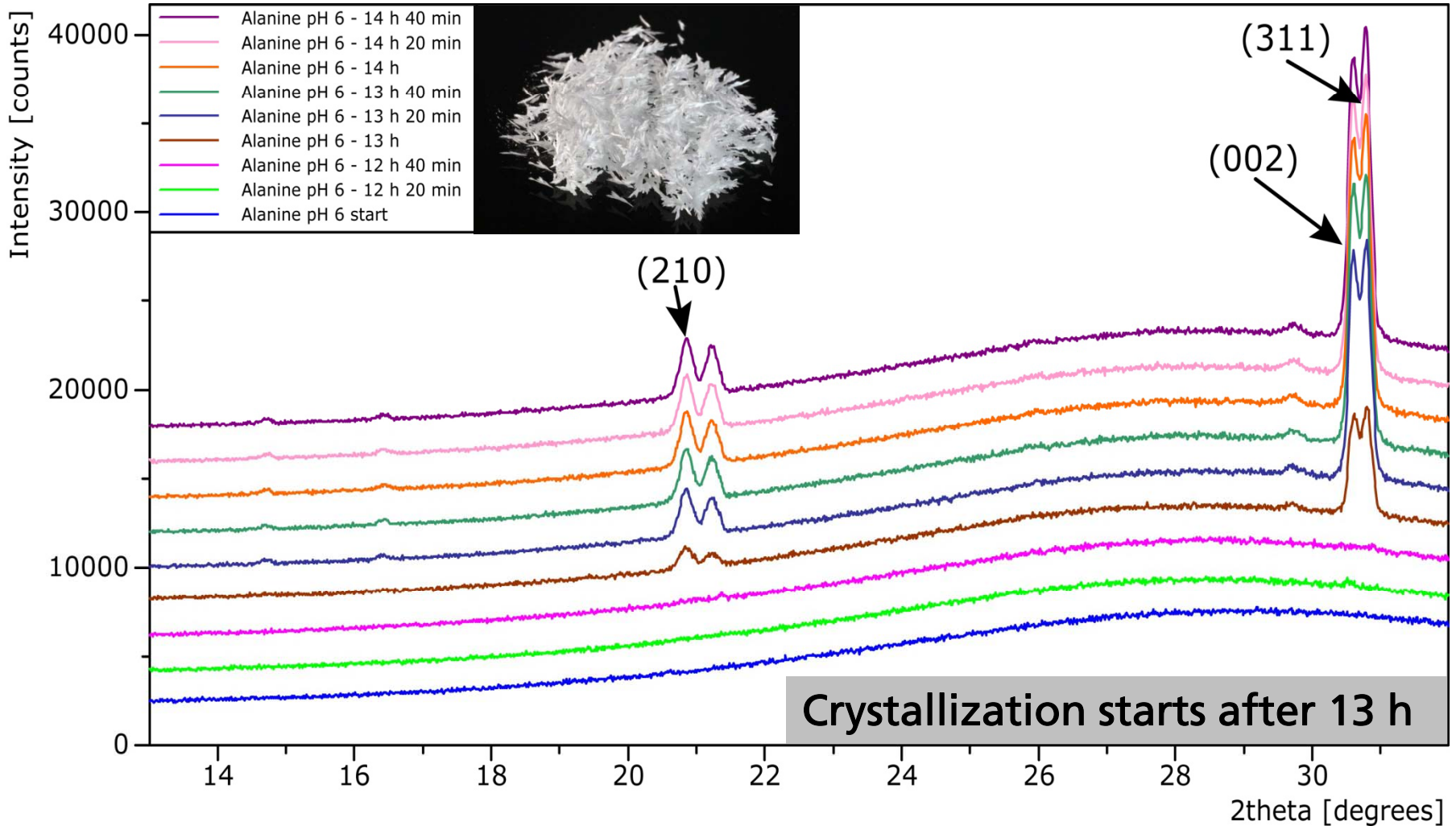
Experimental: DL-Alanine crystallization

- 24.5 g DL-Alanine ($C_3H_7NO_2$) dissolved in 100ml water at 56°C and cooled down
  - Normal pH (~6.1)
  - pH 9.5
  - pH 3.5

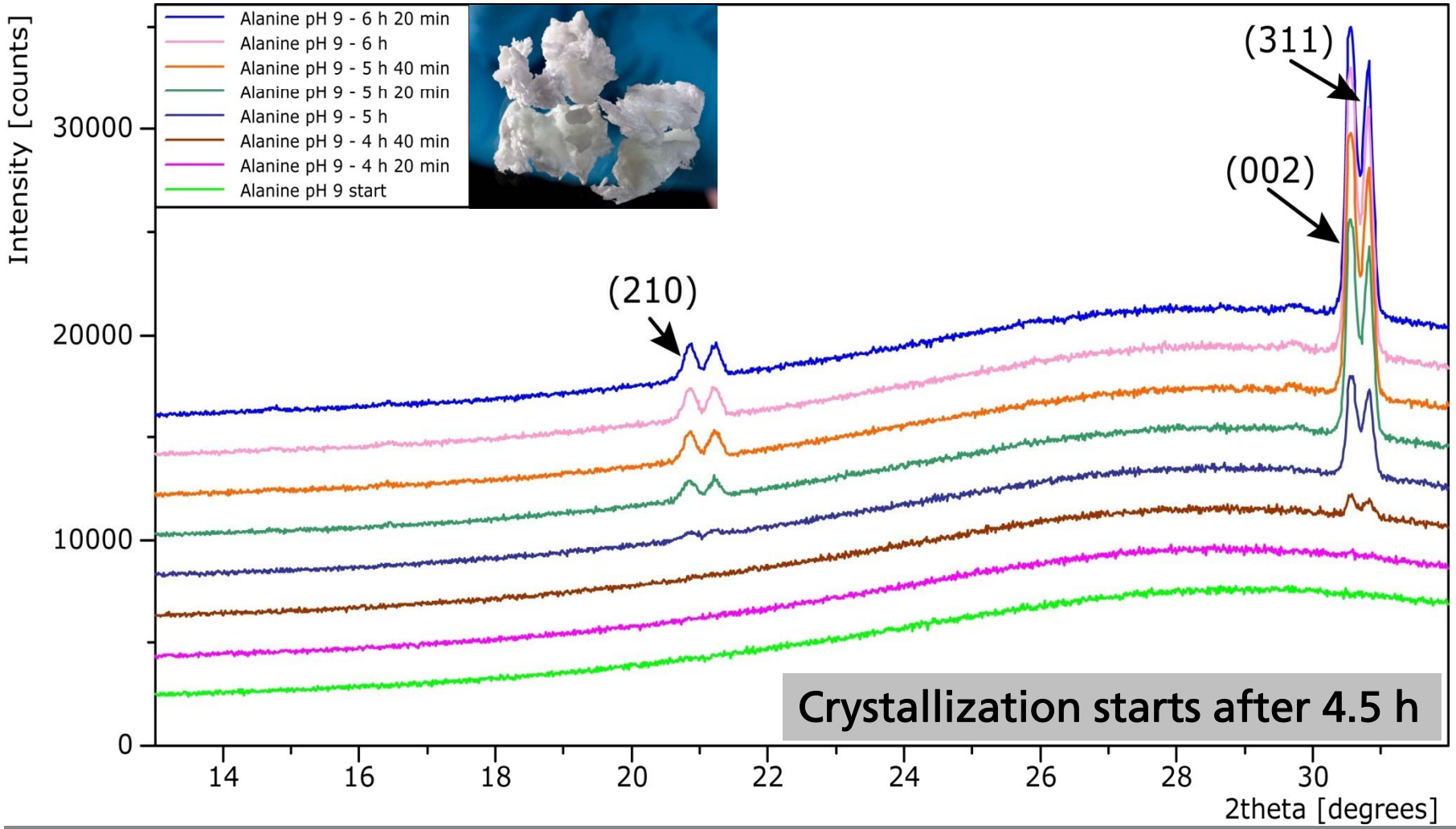


Orthorhombic,
needle-like morphology,
main growth along c-axis

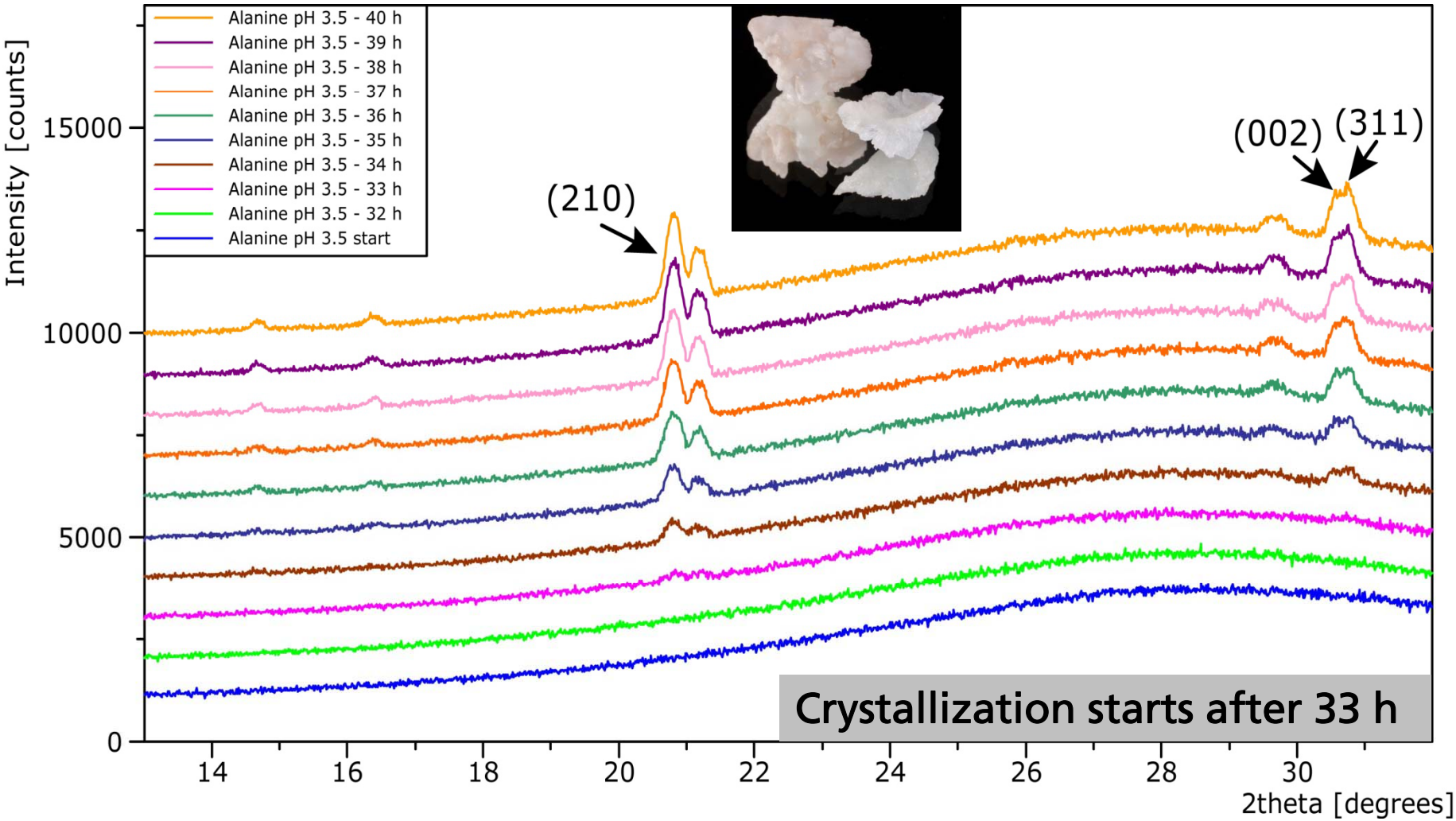
DL-Alanine crystallization at pH = 6.1



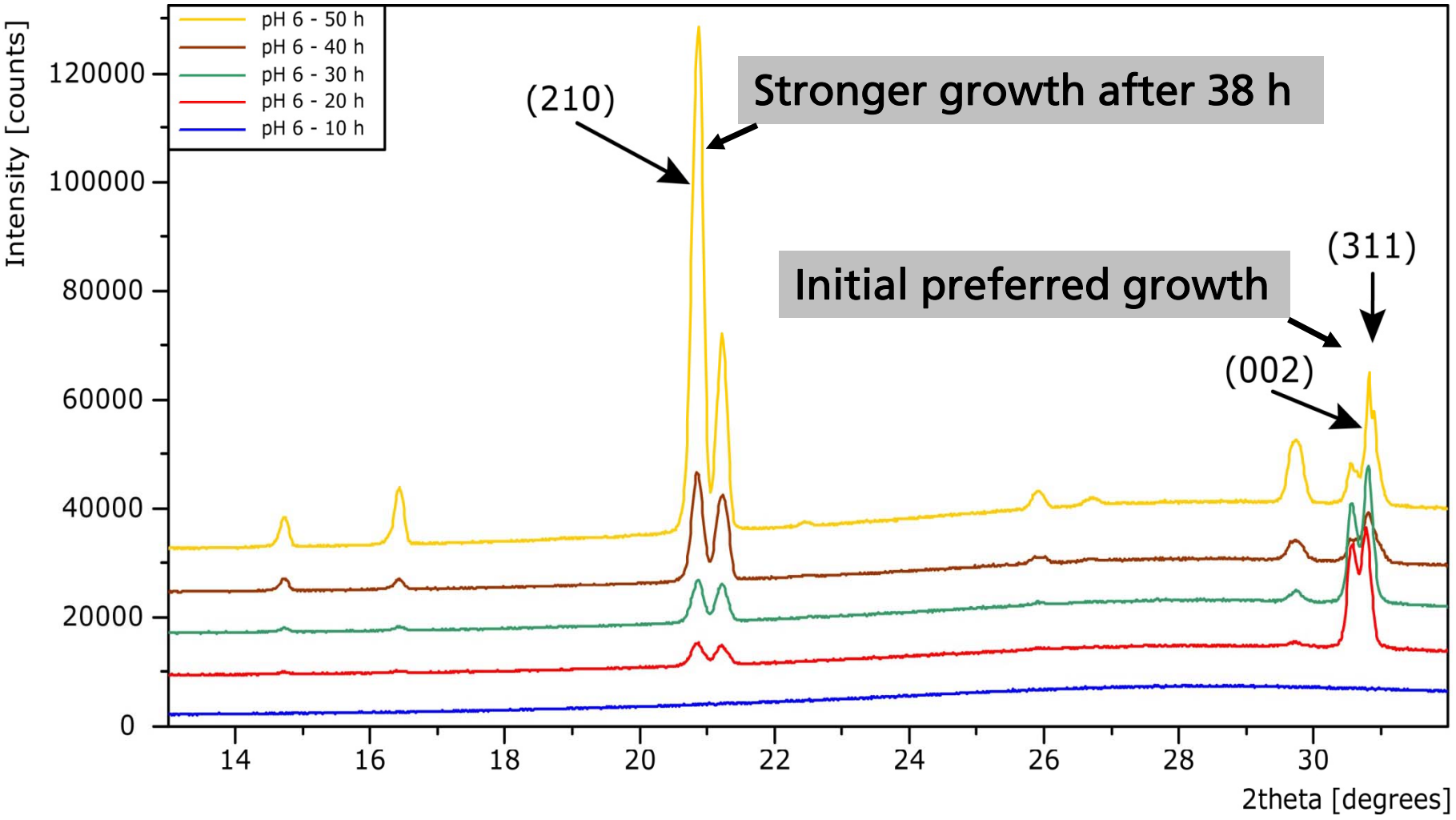
DL-Alanine crystallization at pH = 9.5



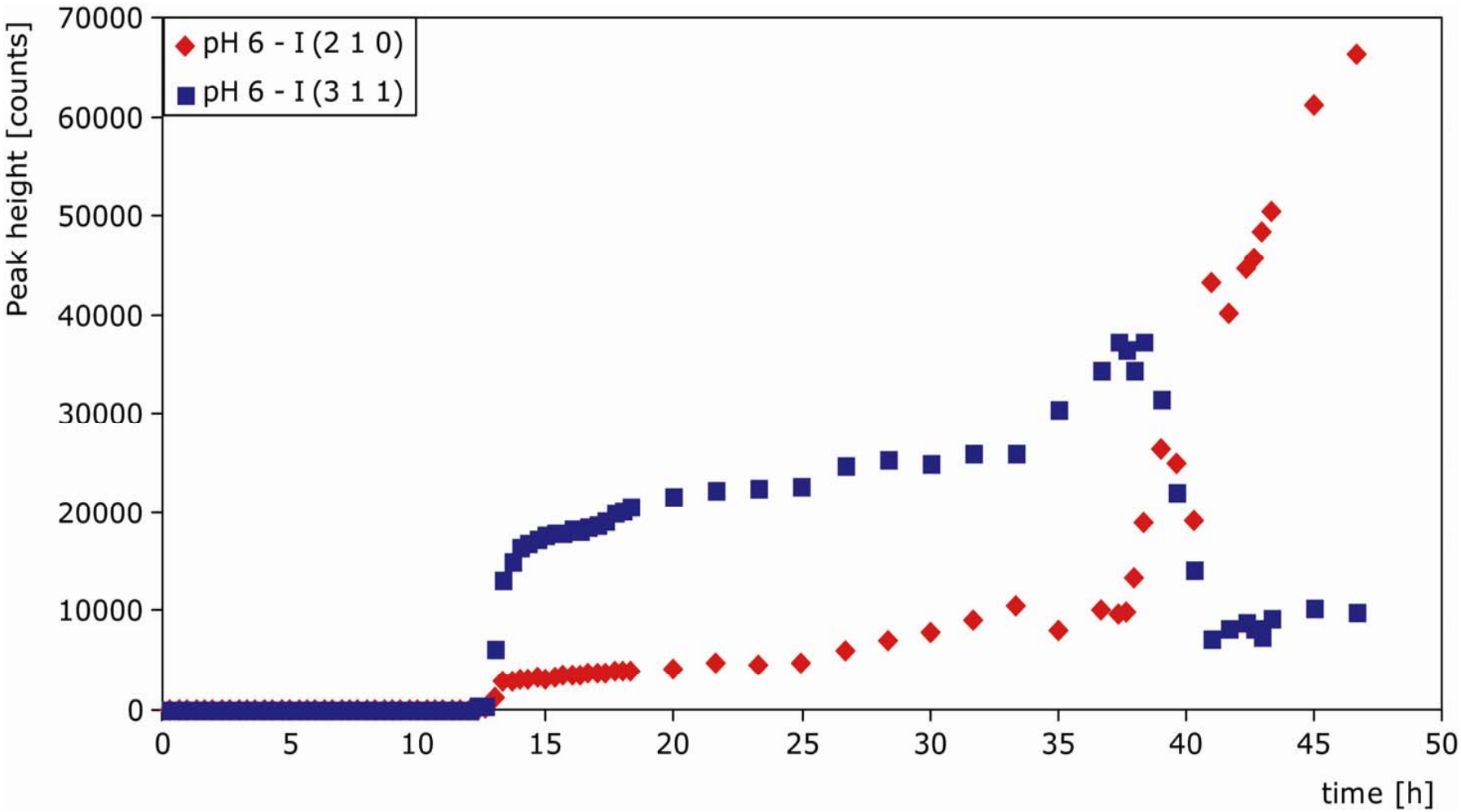
DL-Alanine crystallization at pH = 3.5



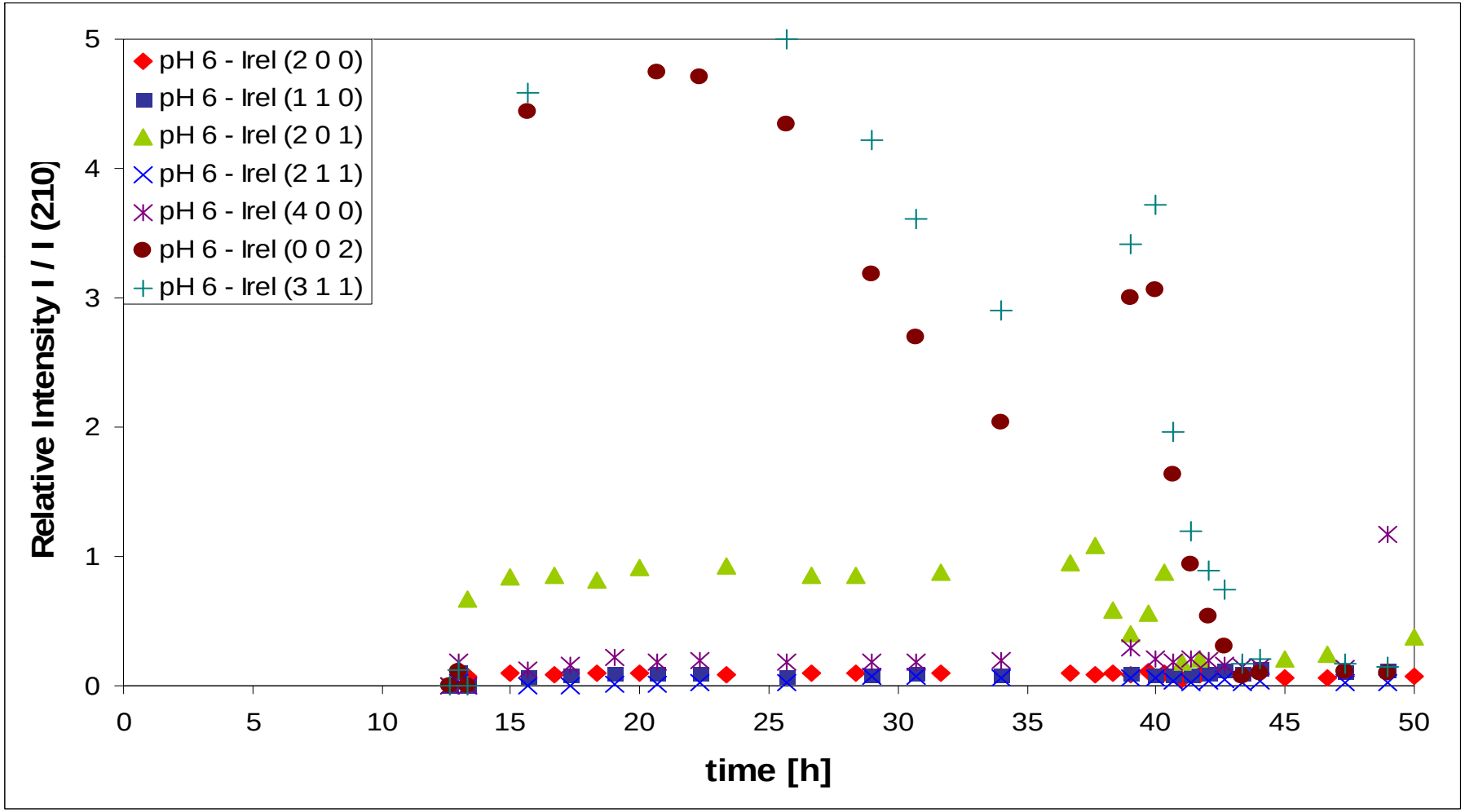
DL-Alanine crystallization at pH = 6.1



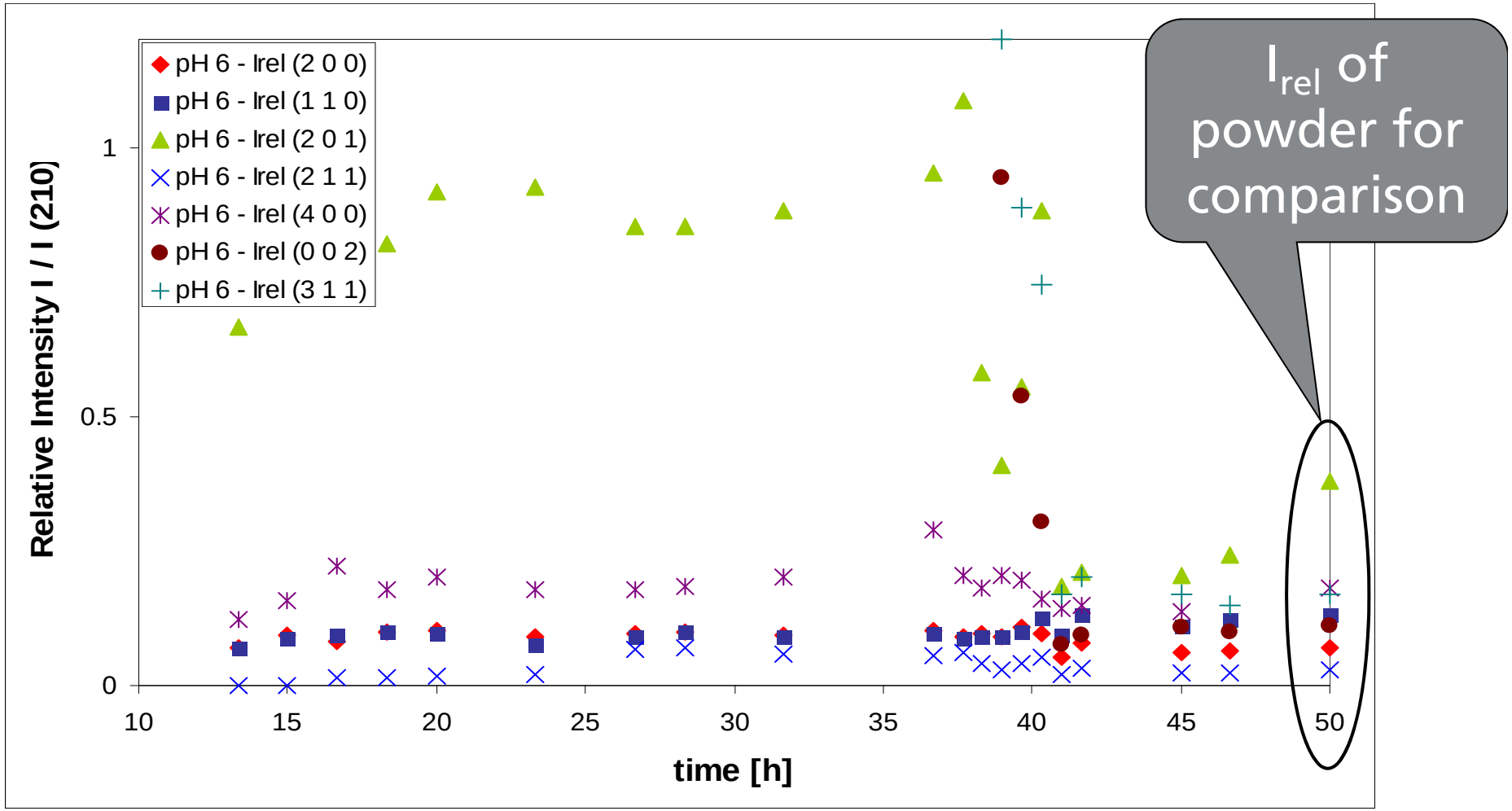
DL-Alanine crystallization at pH = 6.1



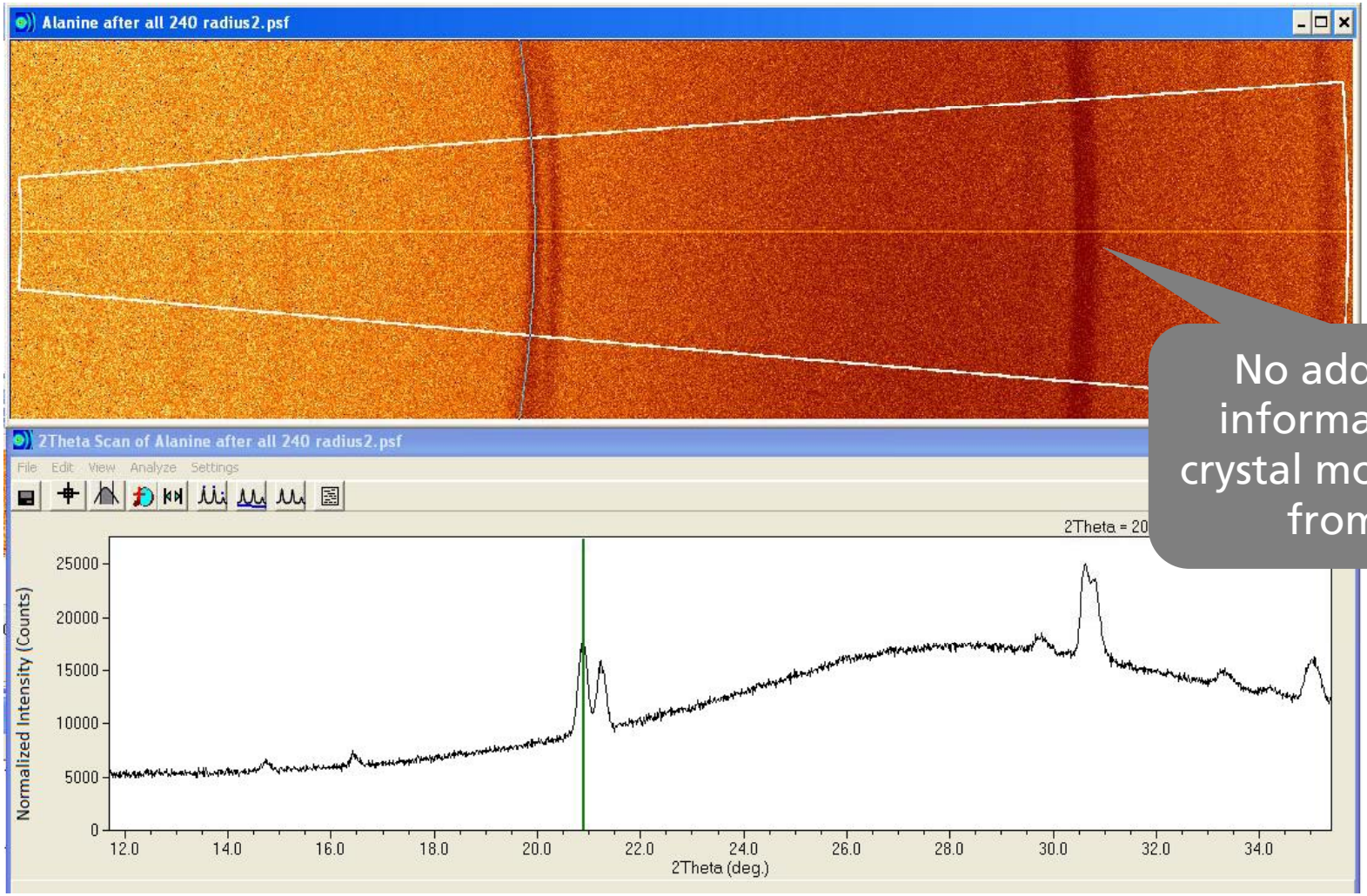
DL-Alanine crystallization at pH = 6.1



DL-Alanine crystallization at pH = 6.1

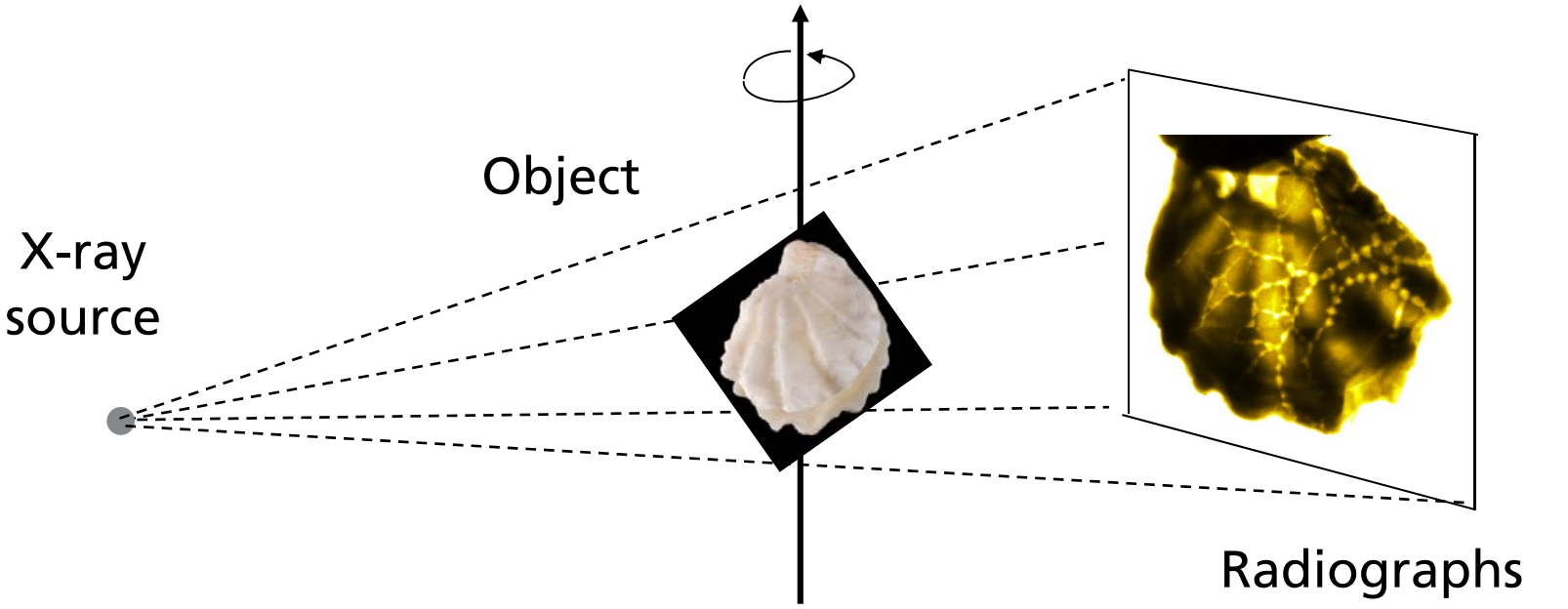


DL-Alanine crystallization at pH = 6.1 – 2D data

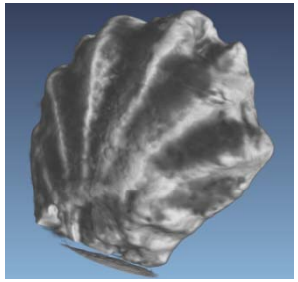


No additional information on crystal morphology from 2D

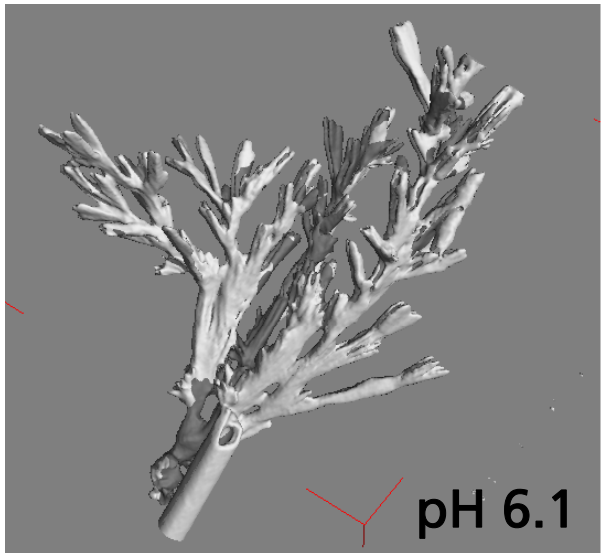
X-ray tomography - principle

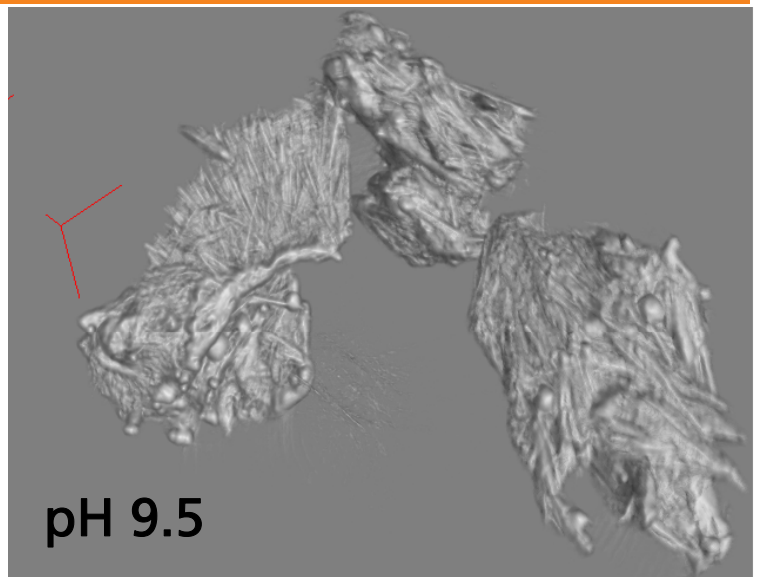


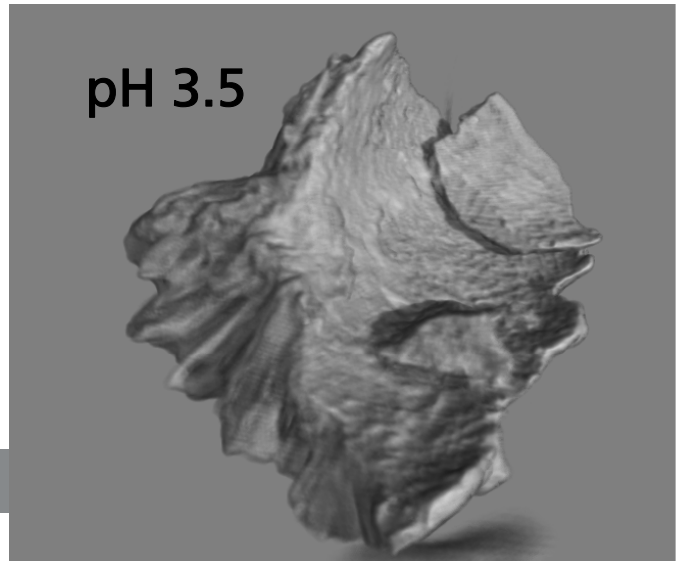
Volume reconstruction ⇒



DL-Alanine: different crystal shapes (“morphology”)







Conclusions 1 – DL-Alanine crystrallization

- Different crystallization conditions show distinct differences in crystallization initiation and crystal morphology.
- At pH = 6.1 and pH = 9.5, first crystallization is most pronounced by the (002) and (311) reflections. Only much later followed by fast growth of the (210) reflection.

Conclusions 2 - DL-Alanine crystrallization

- Crystallization at pH = 6.1 solution starts after 13 h, whereas at pH = 9.5 first crystals are formed much faster (4 h).
  At pH = 3.5 crystallization is very slow (start after 33 h).
- pH = 6.1; pH = 9.5: peaks become much sharper in the course of the crystallization, indicating increasingly larger crystals.
- In the slow crystallizing condition at pH = 3.5, the crystal morphology is less pronounced - broad peaks point towards smaller crystallites.

Outlook - Ludox® TM-50 silica nanoparticles