PPXRD-14

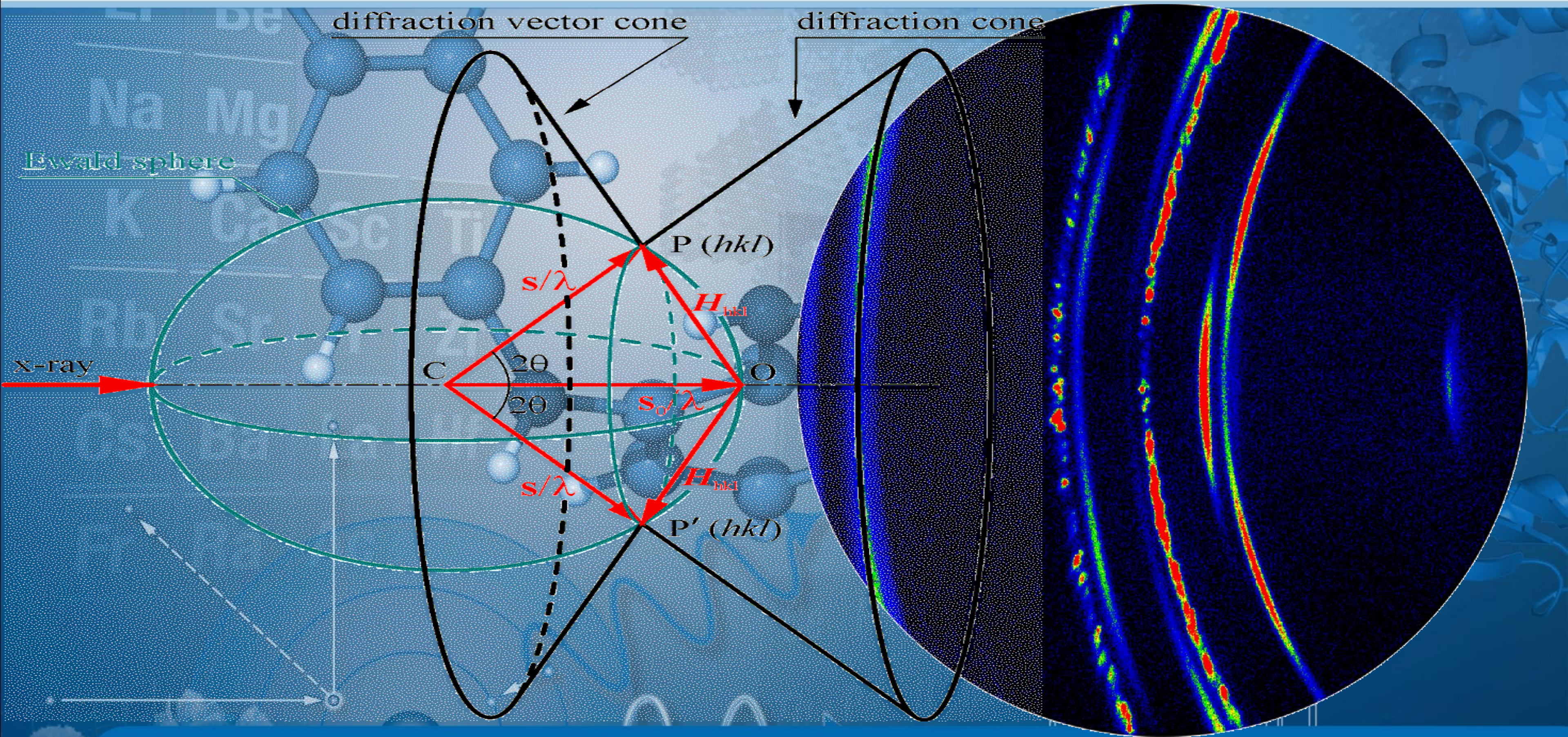
Pharmaceutical Powder X-ray Diffraction Symposium

6-9 June 2016

Fort Myers, Florida, U.S.A.

Instrumentation and Applications of XRD^2 for Pharmaceutics

Bob He, Bruker AXS



This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

Sponsored by The International Centre for Diffraction Data

ICDD
International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd ICDD Website - www.icdd.com

X-ray Applications for typical pharmaceutical samples

XRD & XRD^2	Single Crystal	Several Grains	Powder	Finished Product	Solutions
Qualitative Phase ID	✓Φ⊕	✓Φ⊕	✓Φ	✓Φ	✓Φ
Quantitative Rietveld analysis			✓		
Quantitative analysis with standards		✓	✓	✓	
X-ray movie, Non-Ambient	✓Φ	✓Φ	✓Φ	✓Φ	✓Φ
Structure solution, Indexing	✓Φ		✓		
Microdiffraction/ Mapping		✓Φ⊕	✓Φ⊕	✓Φ⊕	
Shape analysis			✓Φ	✓Φ	✓Φ
HTS	✓Φ⊕	✓Φ⊕	✓Φ⊕		
Grain-Size det.		✓Φ	✓Φ		
%Crystallinity		✓Φ⊕	✓Φ⊕	✓Φ⊕	✓Φ⊕

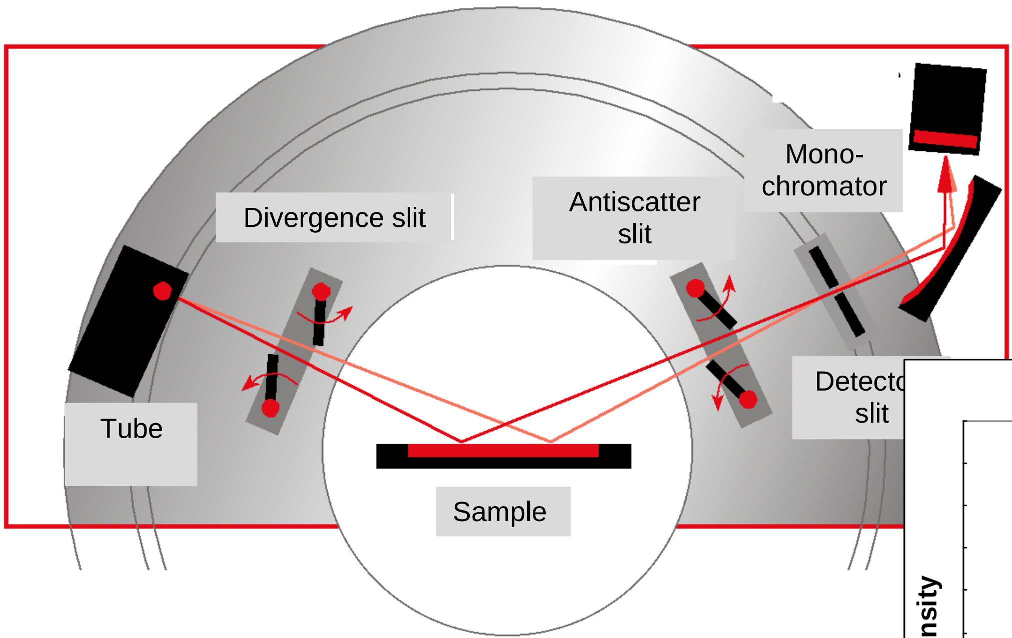
✓- can be performed by either XRD or XRD^2

Φ – better with XRD^2

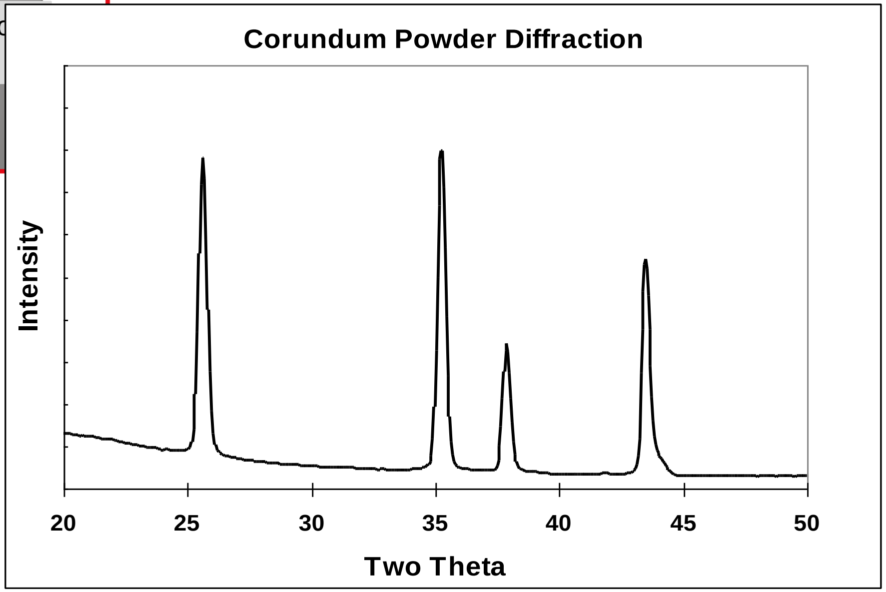
⊕ - accept performance and accurate results only with XRD^2

Basic Concept – XRD^2

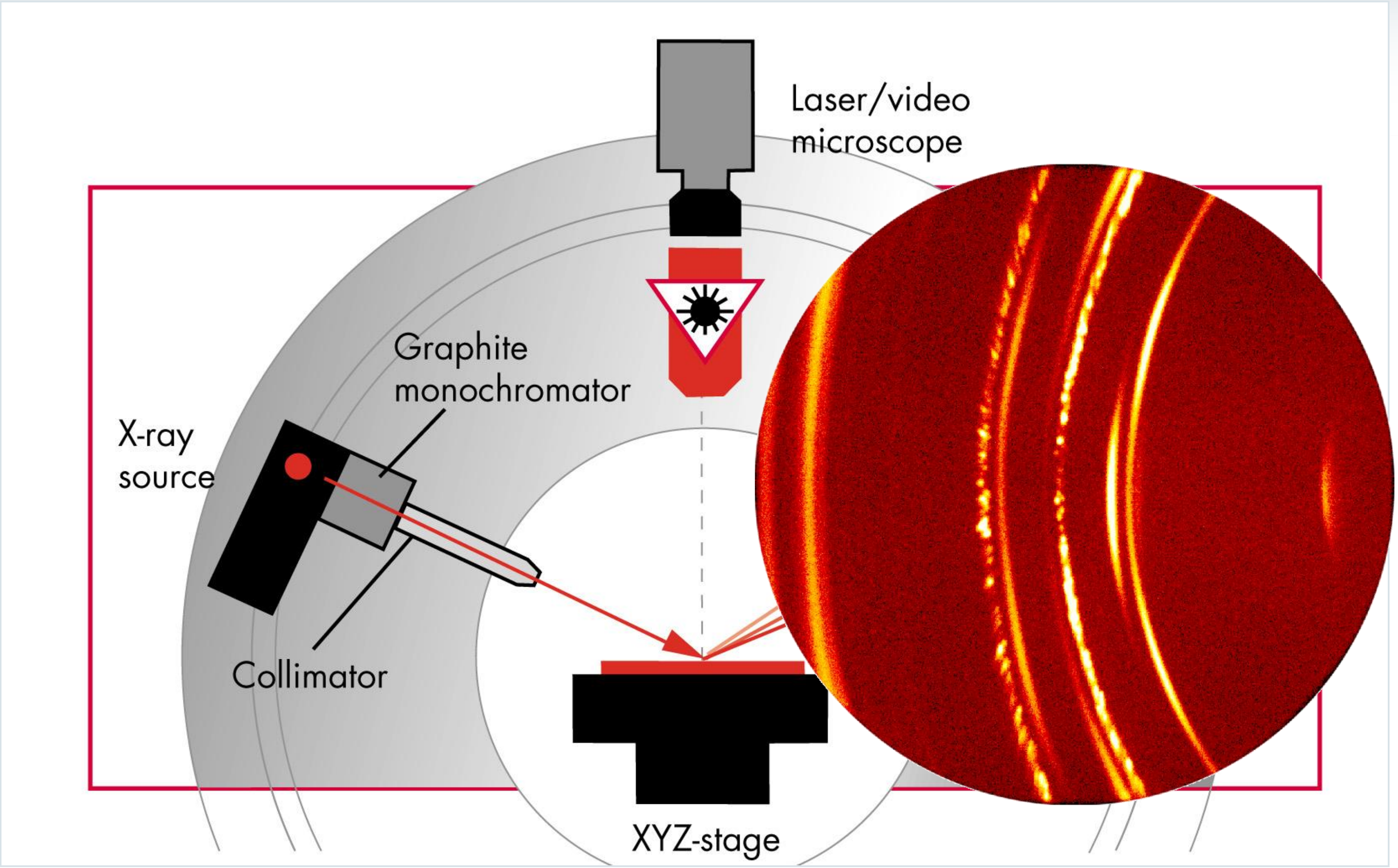
Conventional X-ray Diffractometer



- Bragg-Brentano Geometry.
- Scanning over 2θ range to collect XRD pattern.

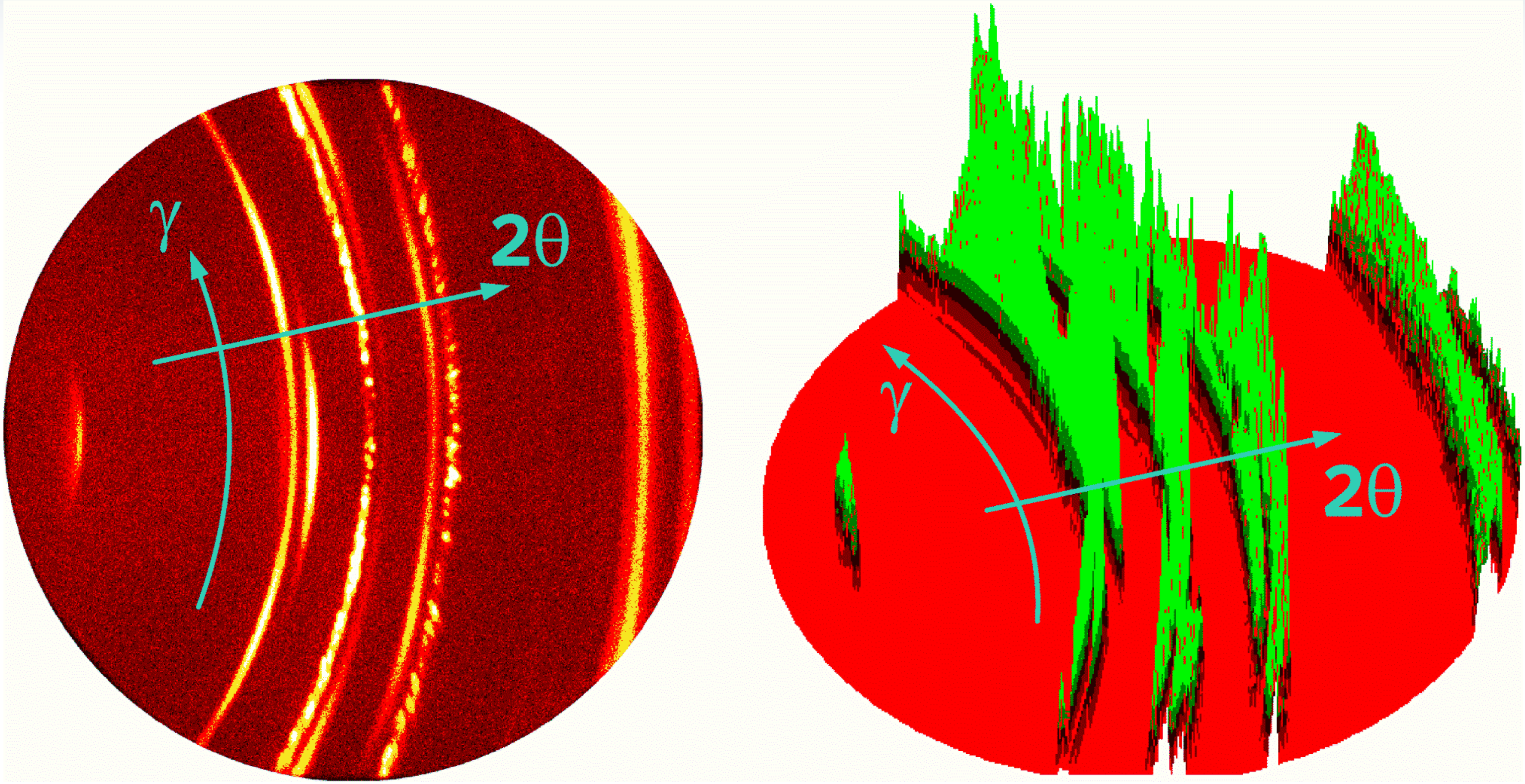


XRD^2: Two-dimensional X-ray Diffraction



XRD^2: Single Frame from Battery Anode Collected with Vantec-500 Detector

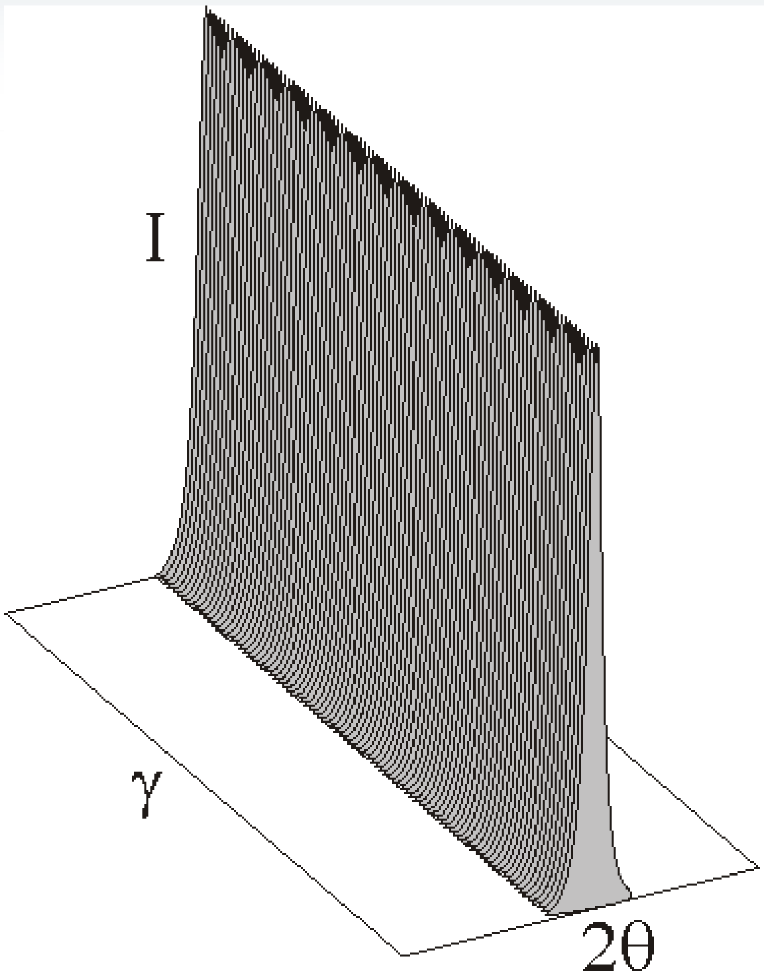
BRUKER



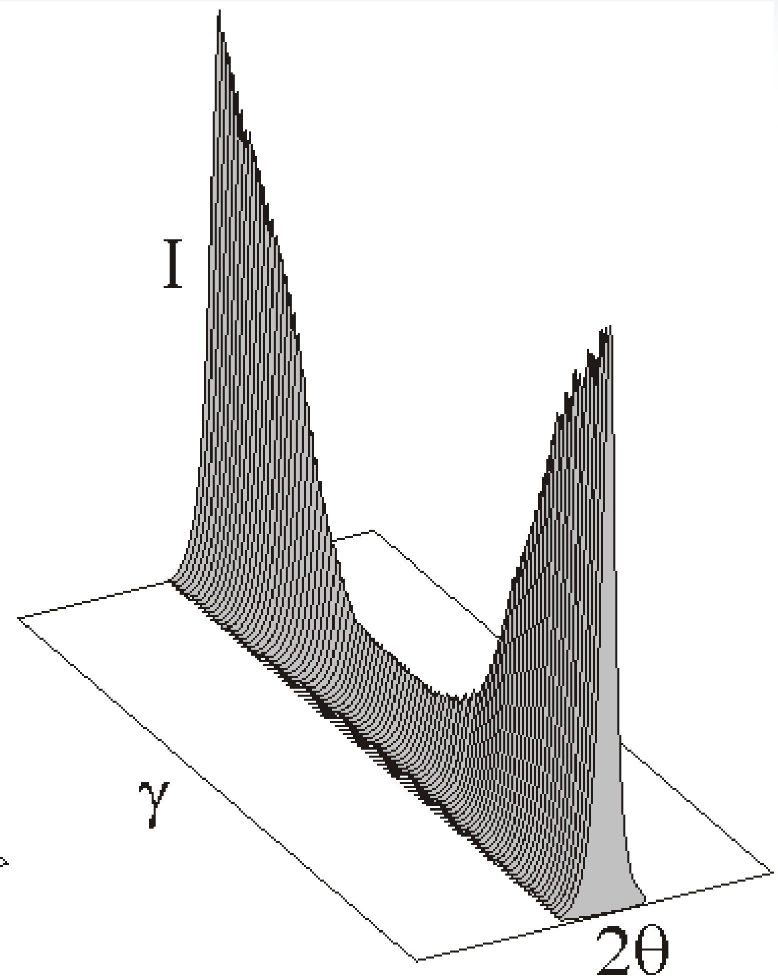
- 2θ coverage: 70° at 8 cm detector distance
- Contains information on phase, stress, texture and grain size

XRD²: 2D pattern in I on γ-2θ coordinates

Powder

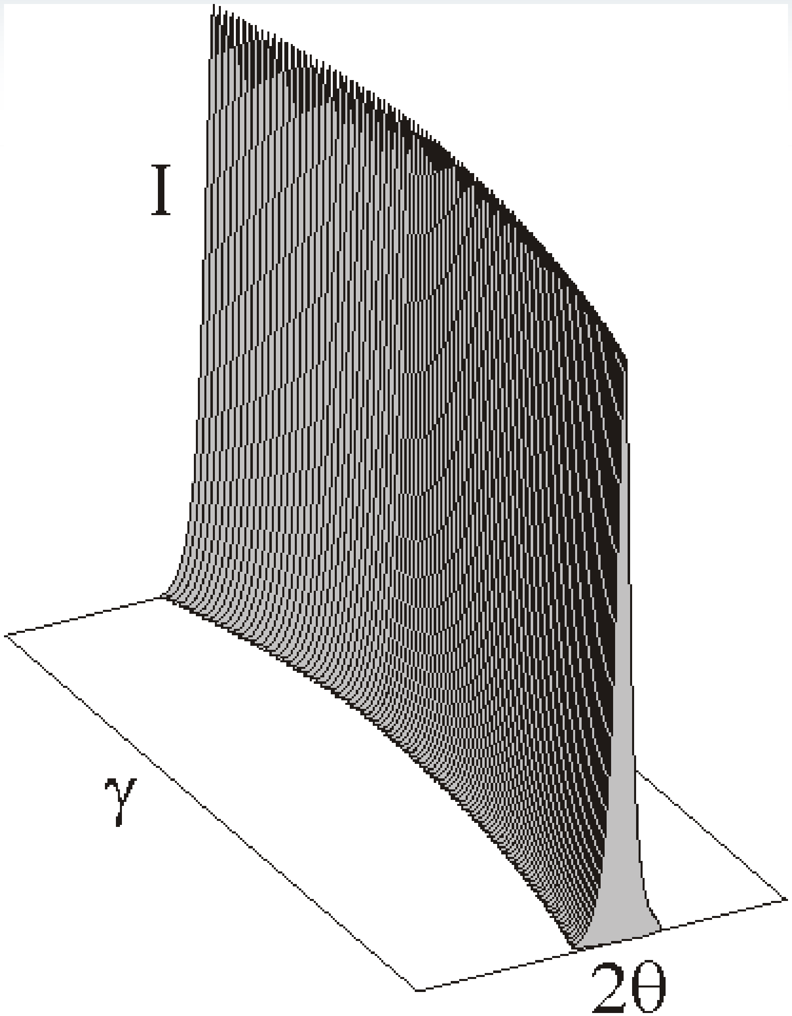


Texture

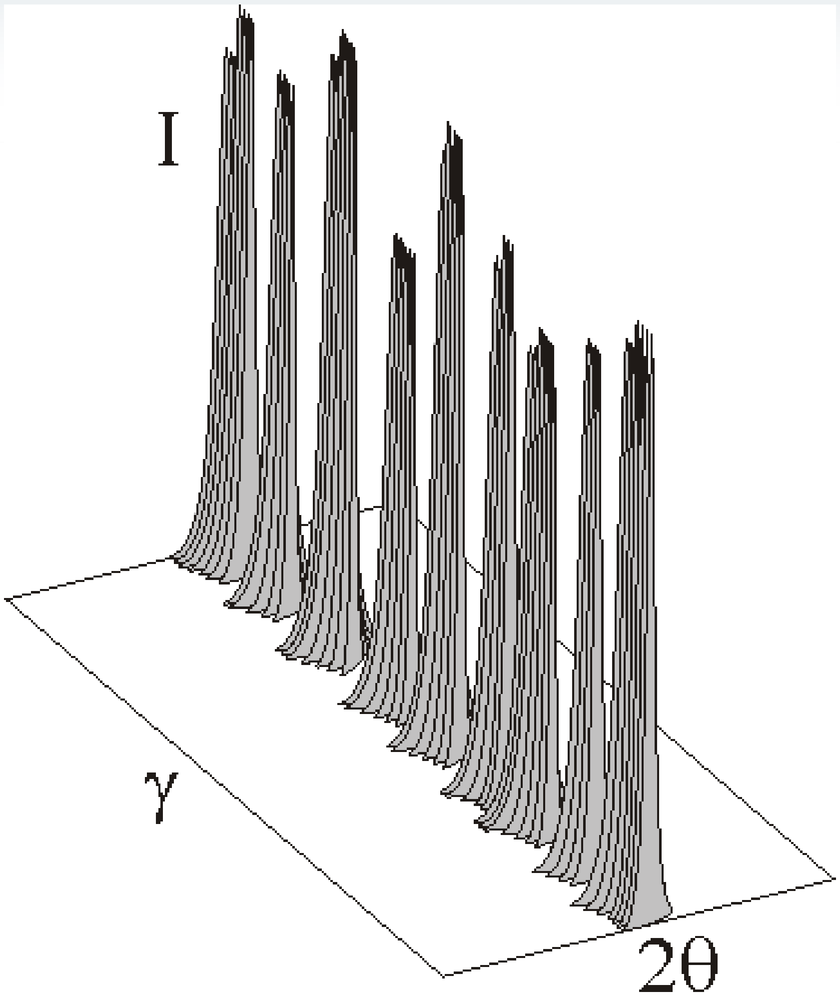


XRD²: 2D pattern in I on γ-2θ coordinates

Stress



Large grains



Fundamental Equations and Diffraction Vector Approach

XRD²: Diffraction Vector as a Function of 2θ and γ

Laue equations with 3 lattice axes:

$$\boldsymbol{a}\cdot(\boldsymbol{s}-\boldsymbol{s}_0)=h\lambda$$

$$\boldsymbol{b}\cdot(\boldsymbol{s}-\boldsymbol{s}_0)=k\lambda$$

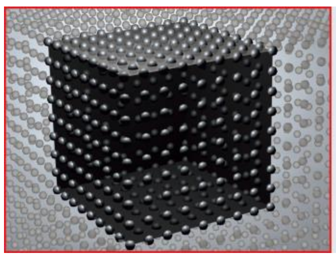
$$\boldsymbol{c}\cdot(\boldsymbol{s}-\boldsymbol{s}_0)=l\lambda$$

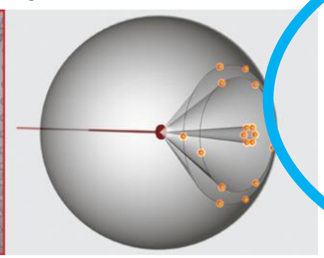
The magnitude of the vector

$$\left|\frac{\mathbf{s}-\mathbf{s}_0}{\lambda}\right|=\frac{2\sin\theta}{\lambda}=\left|\mathbf{H}_{hkl}\right|=\frac{1}{\boldsymbol{d}_{hkl}}$$

Leads to Bragg law:

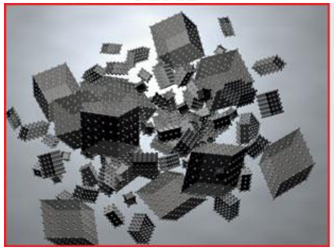
$$2\boldsymbol{d}_{hkl}\sin\theta=\lambda$$

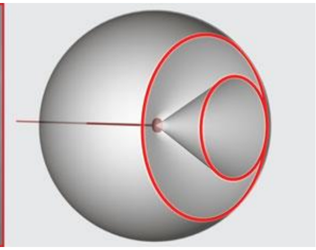


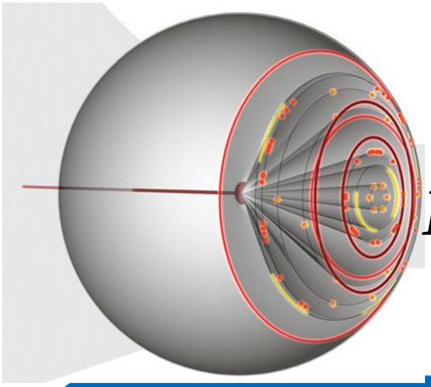


Diffraction condition in vector

$$\frac{\mathbf{s}-\mathbf{s}_0}{\lambda}=\mathbf{H}_{hkl}$$

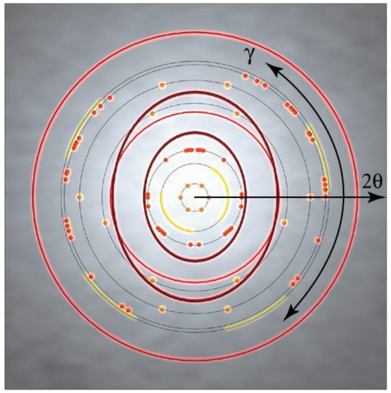






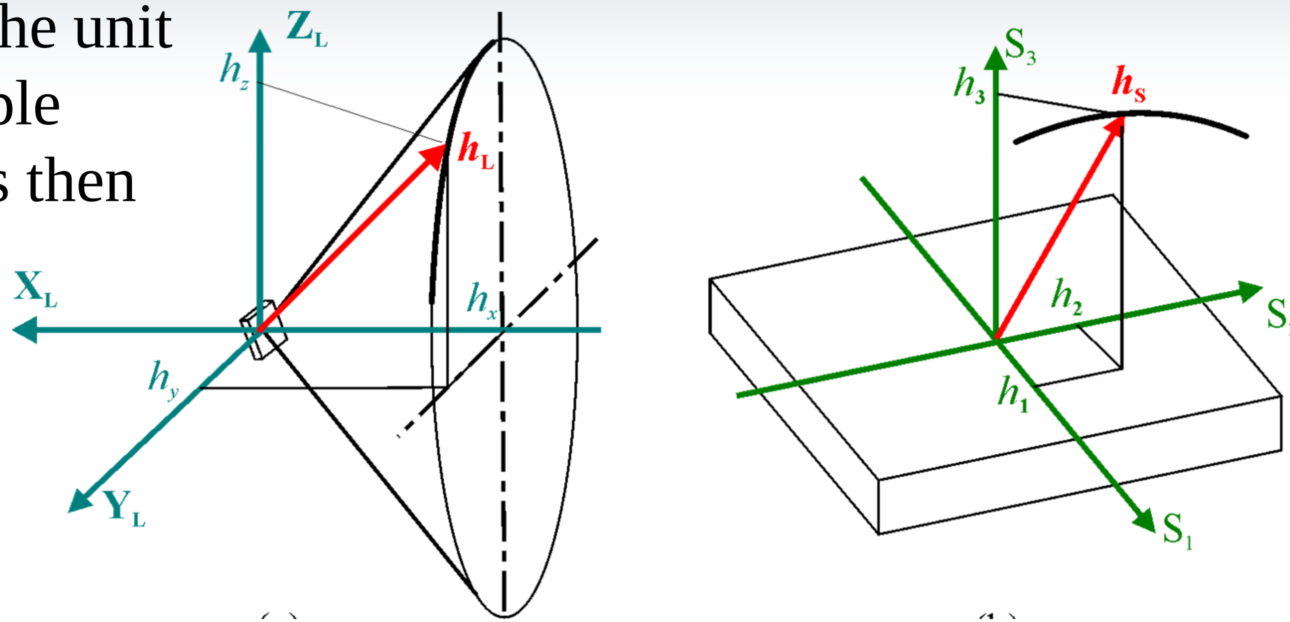
Introduce γ for XRD²:

$$\boldsymbol{H}=\frac{\boldsymbol{s}-\boldsymbol{s}_0}{\lambda}=\frac{1}{\lambda}\begin{bmatrix}\cos 2\theta-1\\ -\sin 2\theta\sin\gamma\\ -\sin 2\theta\cos\gamma\end{bmatrix}$$



XRD^2: Sample Space and Unit Diffraction Vector

The components of the unit vector $\boldsymbol{h}_S$ in the sample coordinates $\mathbf{S_1S_2S_3}$ is then given by



$$\begin{bmatrix} h_1 \\ h_2 \\ h_3 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} h_x \\ h_y \\ h_z \end{bmatrix}$$

Or

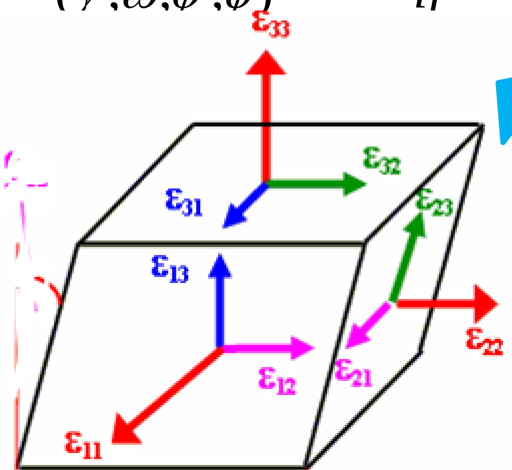
in expanded form for Eulerian geometry:

$$\begin{aligned} h_1 &= \sin\theta(\sin\phi\sin\psi\sin\omega + \cos\phi\cos\omega) + \cos\theta\cos\gamma\sin\phi\cos\psi \\ &\quad - \cos\theta\sin\gamma(\sin\phi\sin\psi\cos\omega - \cos\phi\sin\omega) \\ h_2 &= -\sin\theta(\cos\phi\sin\psi\sin\omega - \sin\phi\cos\omega) - \cos\theta\cos\gamma\cos\phi\cos\psi \\ &\quad + \cos\theta\sin\gamma(\cos\phi\sin\psi\cos\omega + \sin\phi\sin\omega) \\ h_3 &= \sin\theta\cos\psi\sin\omega - \cos\theta\sin\gamma\cos\psi\cos\omega - \cos\theta\cos\gamma\sin\psi \end{aligned}$$

XRD²: Diffraction Vector as a Function of γ

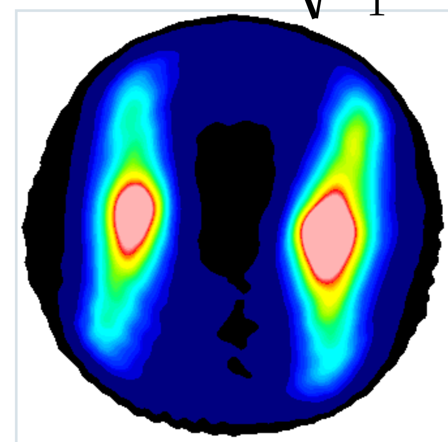
Stress and strain:

$$\varepsilon_{(\gamma,\omega,\psi,\phi)} = \varepsilon_{ij} \cdot h_i \cdot h_j$$



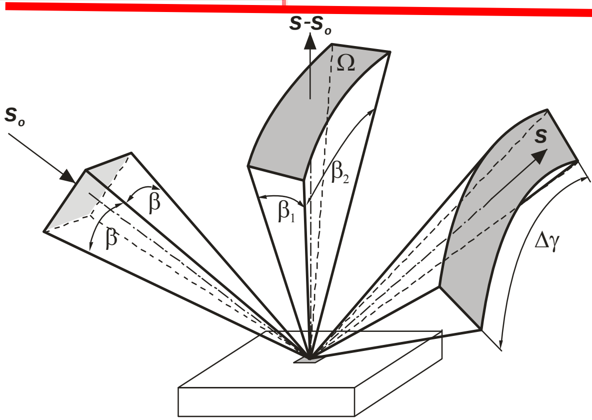
Texture (pole-figure):

$$\alpha = \sin^{-1}|h_3|,\ \beta = \pm\cos^{-1}\frac{h_1}{\sqrt{h_1^2 + h_2^2}}$$



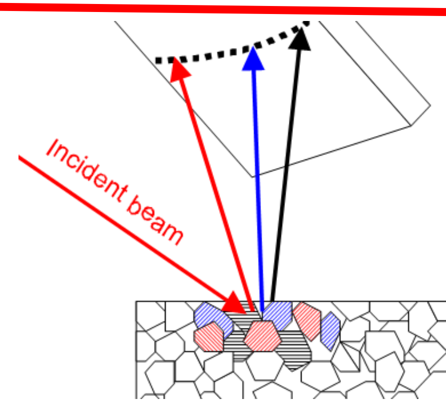
Unit vector:

$$\mathbf{h}_L = \begin{bmatrix} h_x \\ h_y \\ h_z \end{bmatrix} \qquad \mathbf{h}_s = \begin{bmatrix} h_1 \\ h_2 \\ h_3 \end{bmatrix}$$



Crystal size:

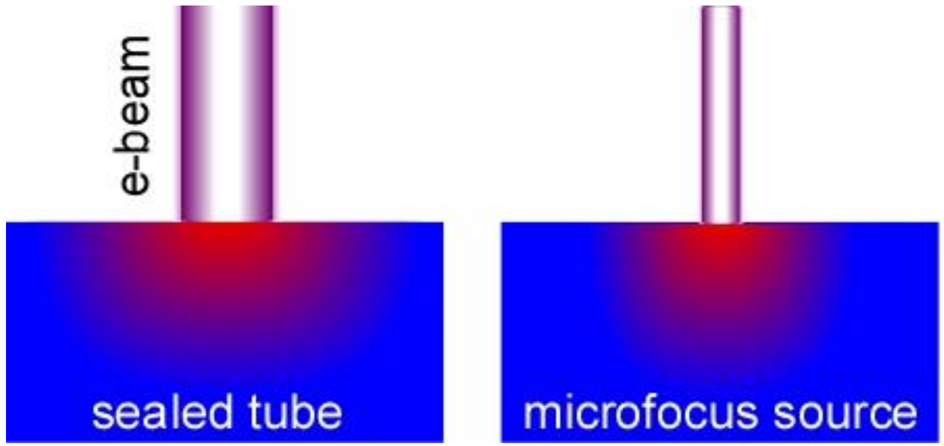
$$N_s = p_{hkl} \cdot \frac{Vf_i}{v_i} \cdot \frac{\Omega}{4\pi}$$



Sources & Optics

How to make brighter source I: Microfocus sources

- Brightness (***B***) is proportional to power loading (***p***)
- >99% power turns to heat and needs to be removed
- Power loading is higher for *smaller spot focus*



$$\boldsymbol{p}_{\max} = \frac{2\boldsymbol{\kappa}\left(\boldsymbol{T}_m - \boldsymbol{T}_0\right)}{\boldsymbol{r}\sqrt{\boldsymbol{\pi}\ln(2)}}$$

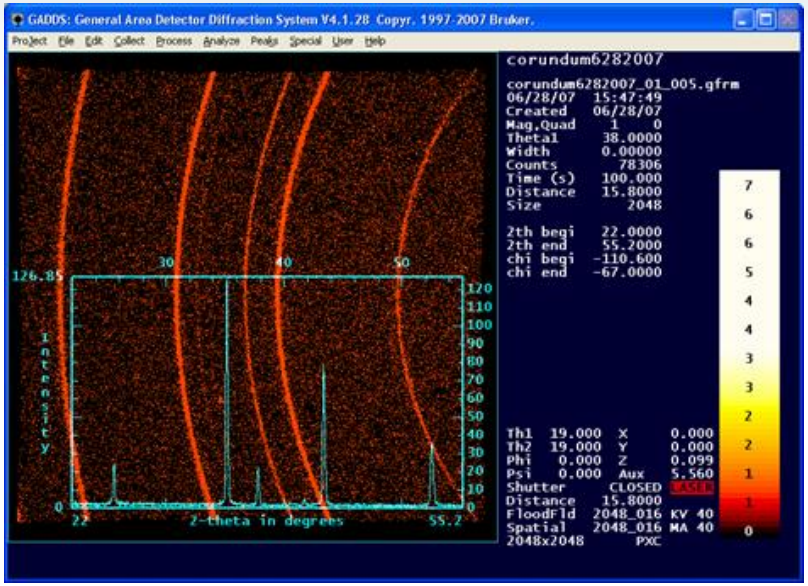
- Large spot
- Quasi-one dimensional heat flow limits power loading

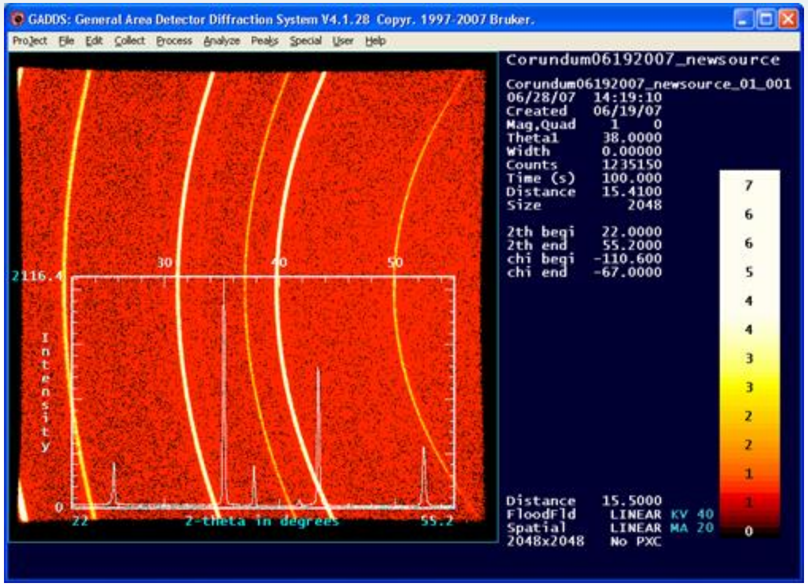
- Small spot
- Two dimensional heat flow (more efficient cooling)
- Relative performance improved by 10 times

IμS microfocus source

- Intensity $3x10^{10}$ X-rays/mm^2-sec (Cu Kα)
  - 8 times higher than conventional 5.4 kW rotating anode
- Typical lifetime >5 years
  - High reliability
  - 3 year warranty
  - >300 installed
- Air-cooled
- Available in Cr, Cu, Mo, Ag

IμS & VÅNTEC-2000 vs. Classic Set-up
Corundum Comparison

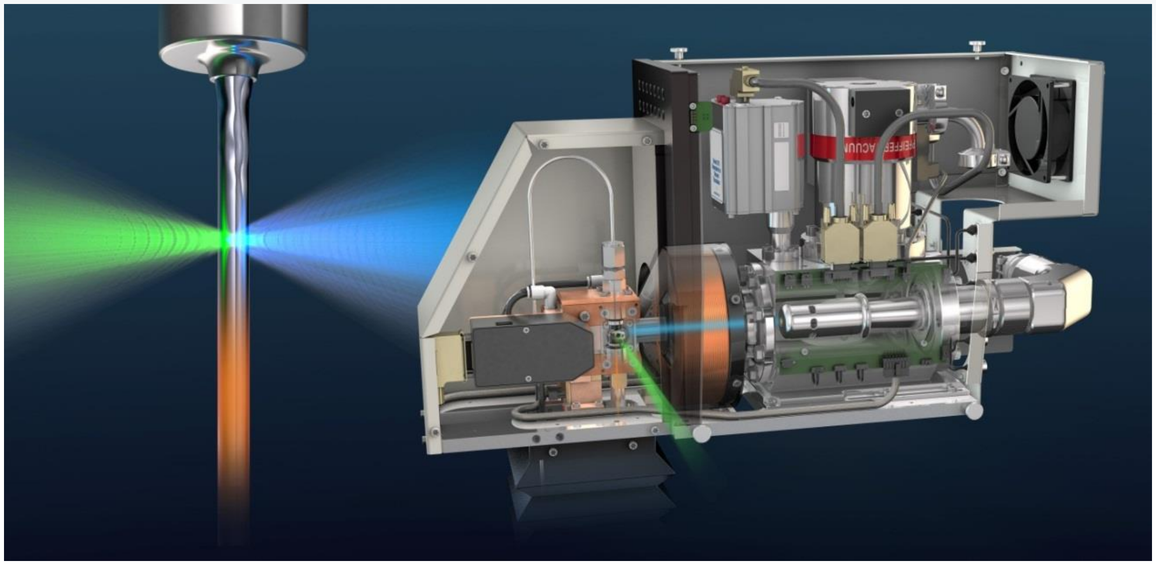


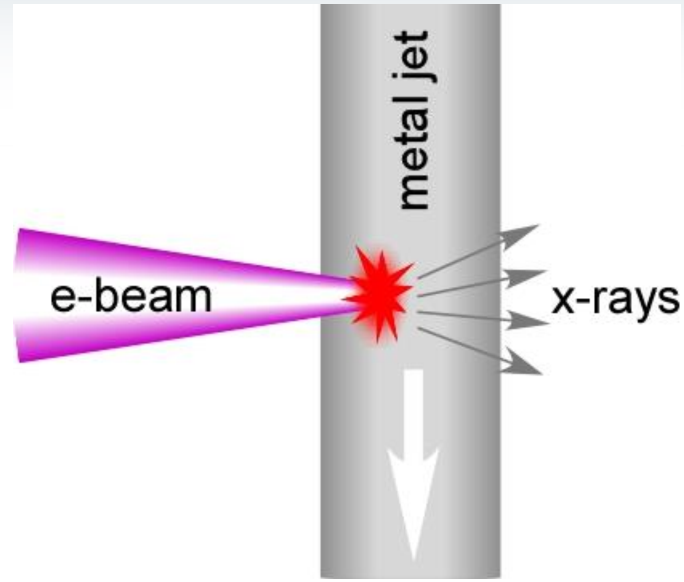


Sealed Tube with Göbel Mirror	Microsource (IμS)™
45kV, 40mA, (1800 W)	45kV, 0.650mA, (30 W)
0.3mm collimator	0.3mm collimator
total counts: 78K	**total counts: 1235K**

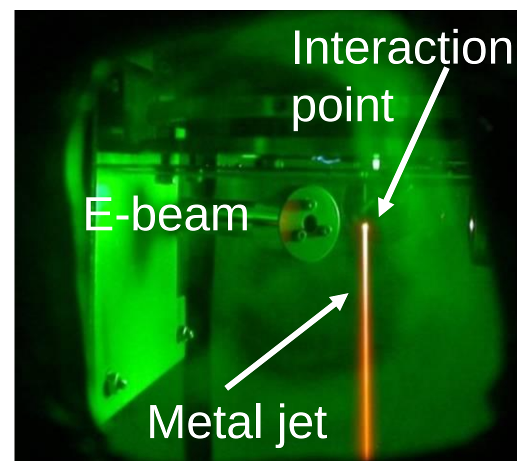
Intensity: 15.8x; Efficiency: 948x !

NEW: Liquid metal sources

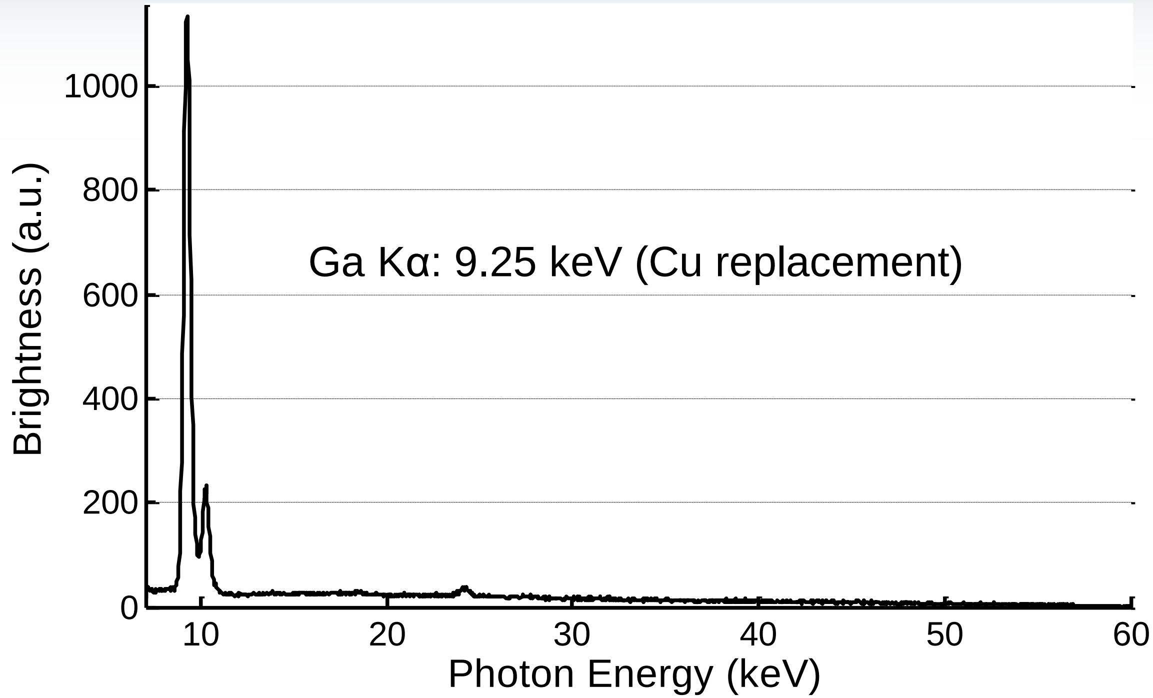




- High-speed liquid-metal-jet anode
- Anode is regenerative
- No longer limited by melting
- >500 kW/mm^2 e-beam power density
  - Rotating anode limited to maximum 50 kW/mm^2



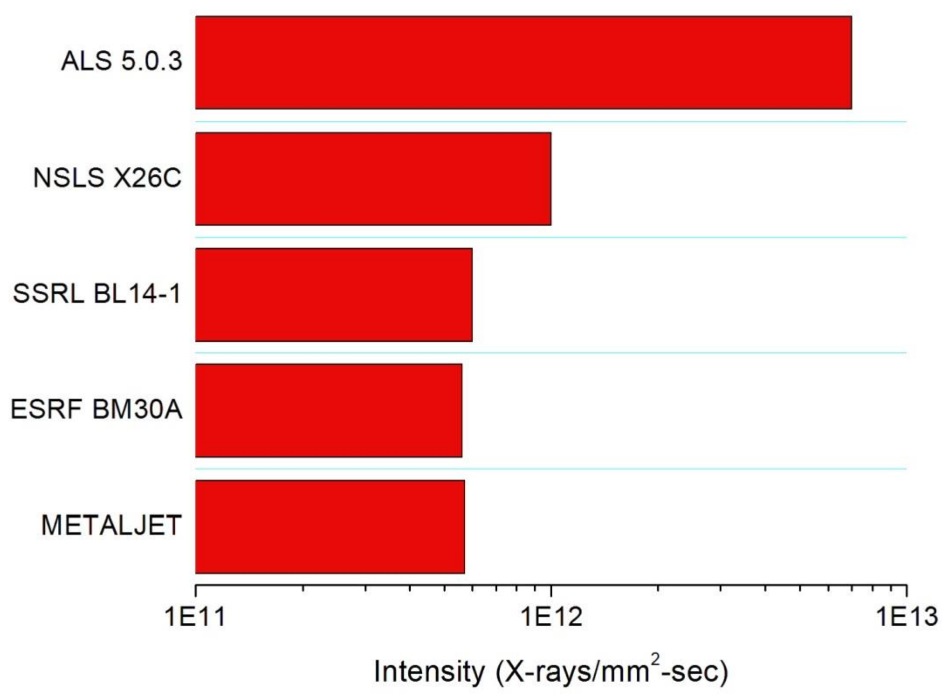
Source Spectrum and Brightness



Spot size [µm, FWHM]	**Voltage** [kV]	**Power** [W]	**Ga Kα Brightness** [Photons/(s × mm^2 × mrad^2 × line]
5	60	50	1.5×10^{11}
10	60	100	7.6×10^{10}
20	60	200	3.8×10^{10}

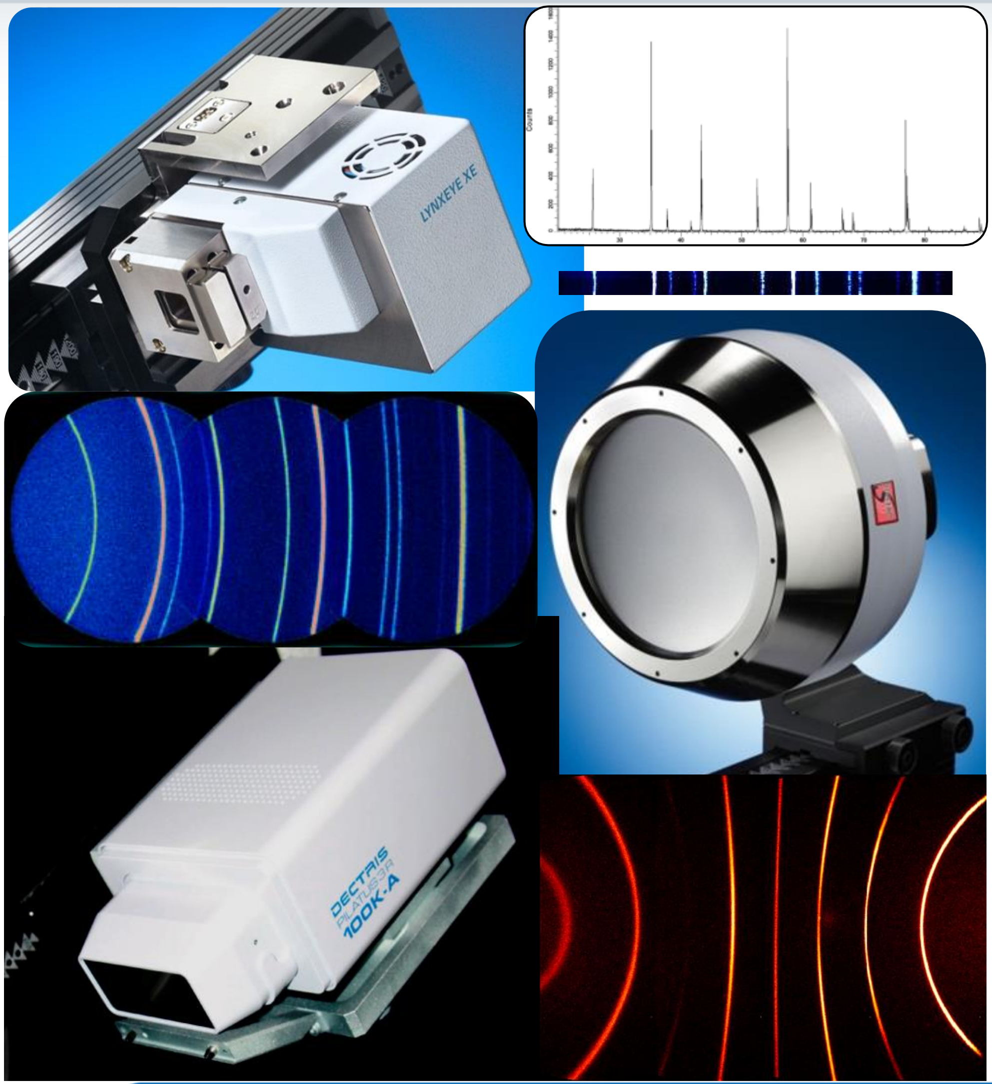
So, is it possible to put a synchrotron beamline on a table top?

- Yes, at least the equivalent of a typical present generation bending magnet beamline



Detector

Choice of Detectors: 0D/1D/2D



LYNXEYE XE

- Silicon strip technology
- Best Energy Discriminator of any 1D detector
- 0D, 1D and 2D modes
- Ideal detector for random powders and RSMs
- No Maintenance

VANTEC 500

- Detector with the Largest Active Area
- Radiation Hard
  - Can take the direct beam and strong reflections
- No Maintenance

PILATUS3 R 100K-A

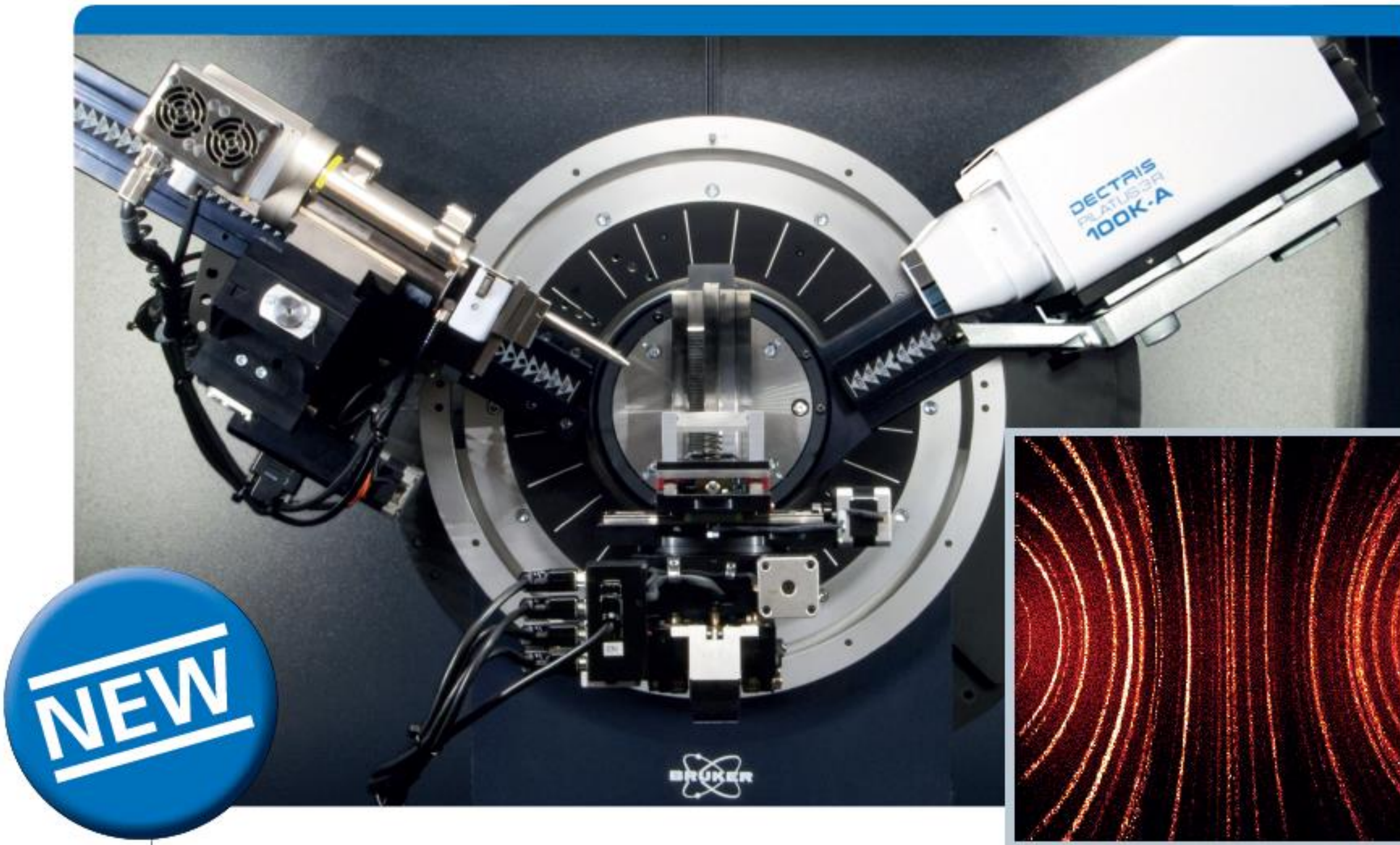
- Hybrid Photon Counting (HPC) technology
- High count rate capability
- Sensitivity: Co, Cu + hard radiation (Mo, Ag)
- Active area: 83,8 x 33,5 (2.807) mm2No Maintenance
- Pixel size: 172µm (195 x 487 pixel)

VÅNTEC-500 – Outperforms all previous gaseous detectors.

- Large active area: 140 mm in dia.
- Frame size:
  2048 x 2048 pixels
  1024 x 1024 pixels
  512 x 512 pixels
- Pixel size:
  68 μm x 68 μm
  136 μm x 136 μm
  272 μm x 272 μm
- High sensitivity: 80% DQE for Cu
- High max linear count rate:
  0.9 Mcps – global;
  160 kcps/reflection -local
- Low background noise:
  $<10^{-5}$ cps/pix
- Maintenance-free:
  no re-gassing

D8 DISCOVER with PILATUS3 R 100K-A

2D HPC Technology for Your Lab Instrument

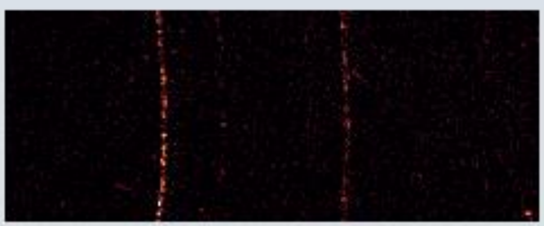


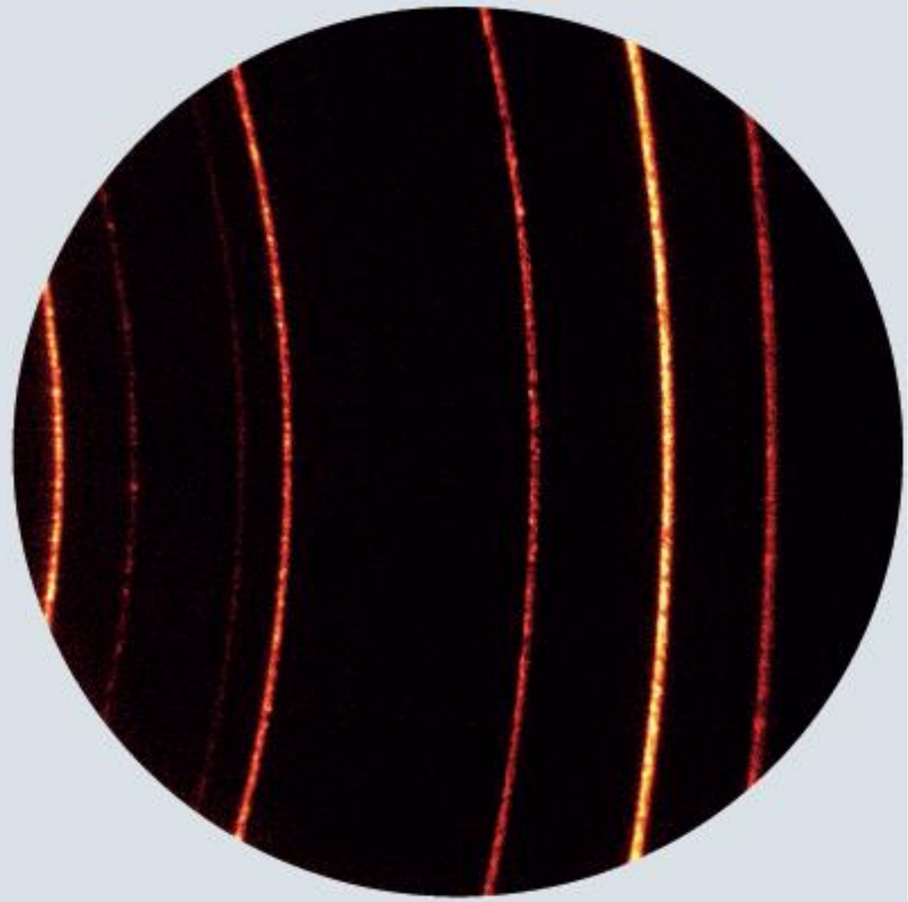
XRD^2 : Detector Orientation: γ-optimized *vs*. 2θ optimized

XRD² : Choice of Detectors: Active Area and Orientation

PILATUS3 R 100K-A

VÅNTEC-500



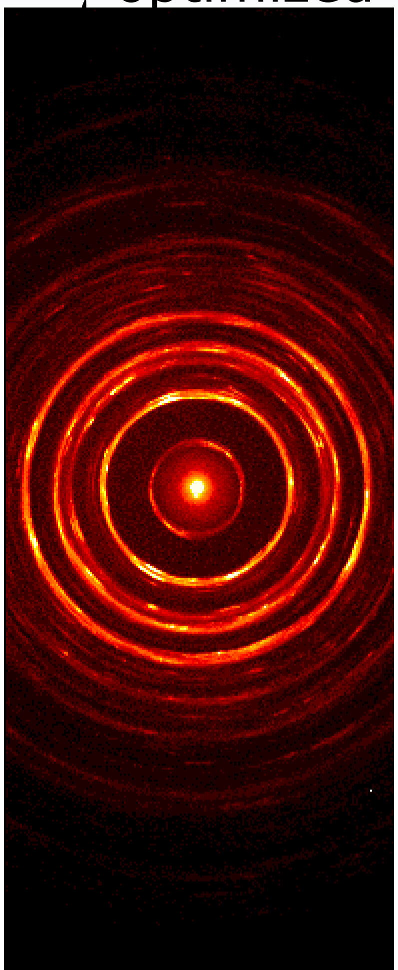


NIST 1976 (corundum) data collected at sample-to-detector distance of 20 cm.

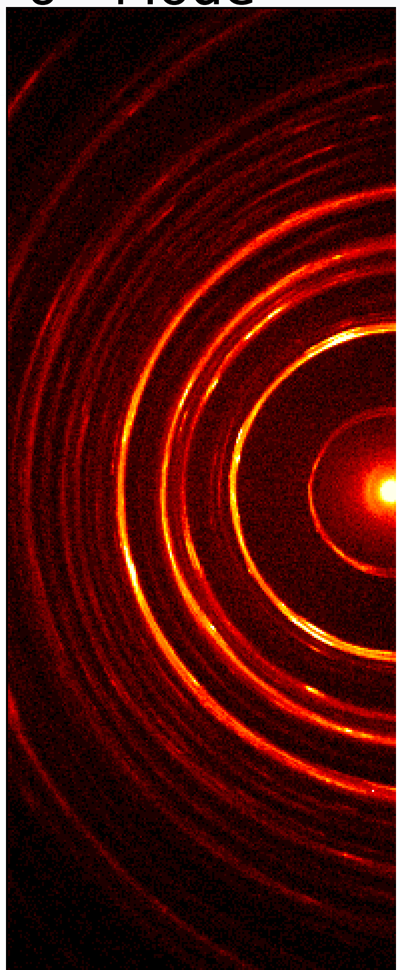
Left: PILATUS3 R 100K-A (2Theta-optimized Mode)
Middle: PILATUS3 R 100K-A (Gamma-optimized Mode)
Right: VÅNTEC-500

XRD^2 : Detector Orientation and Distance: frames collected with Aspirin

γ optimized – 0° Mode

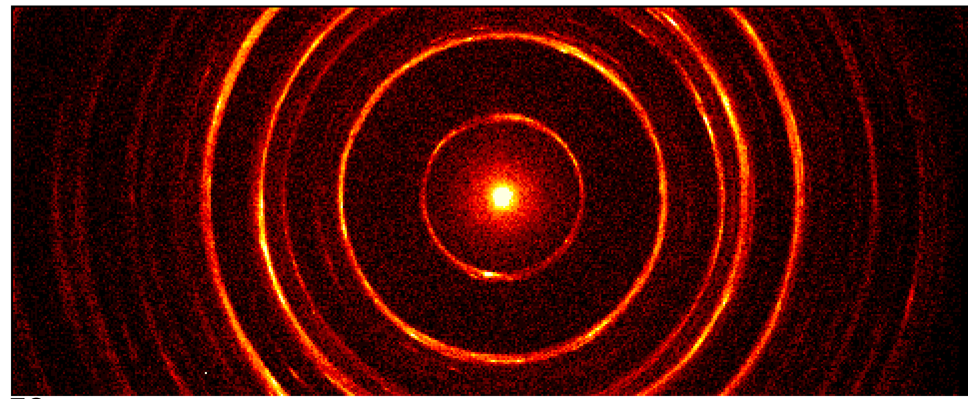


30 mm

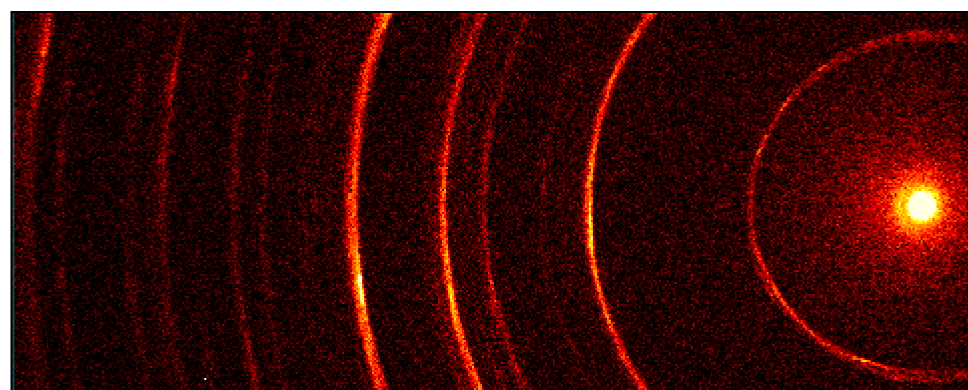


50 mm & offset 19deg

2θ optimized – 90° Mode



50 mm



10 mm & 20 deg off

Sample Stage & System Configuration

XRD² : Sample Stages for Various Application

Centric Eulerian Cradle

- Most versatile stage on the market
- Ψ, φ, **<u>X, Y</u>** and Z are always mounted

Universal Motion Concept Stages

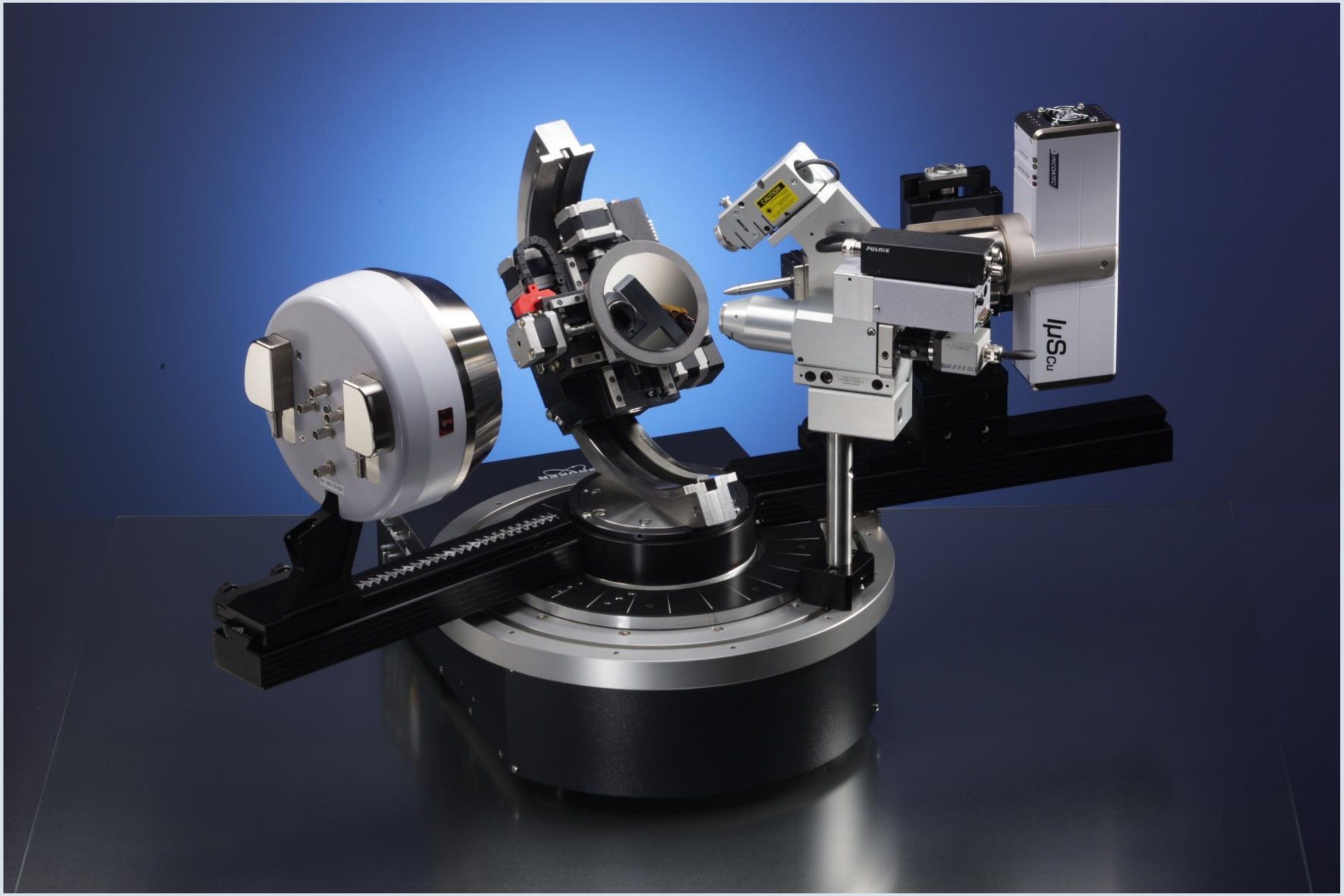
- Sits in front of the goniometer
  - Allows more weight and travel
- UMC 1516
  - Ψ, φ, X, Y and Z
- UMC 150 HTS
  - Designed for Reflection and Transmission
  - 96 well plates
  - X, Y and Z

Accessory Attachments

  - Attach directly to the XY table
  - Standard Powder Adapter (included)
  - Dome Temperature stages
  - Capillary Attachment
  - Wafer Chucks

Horizontal System

Horizontal th-2th, CEC

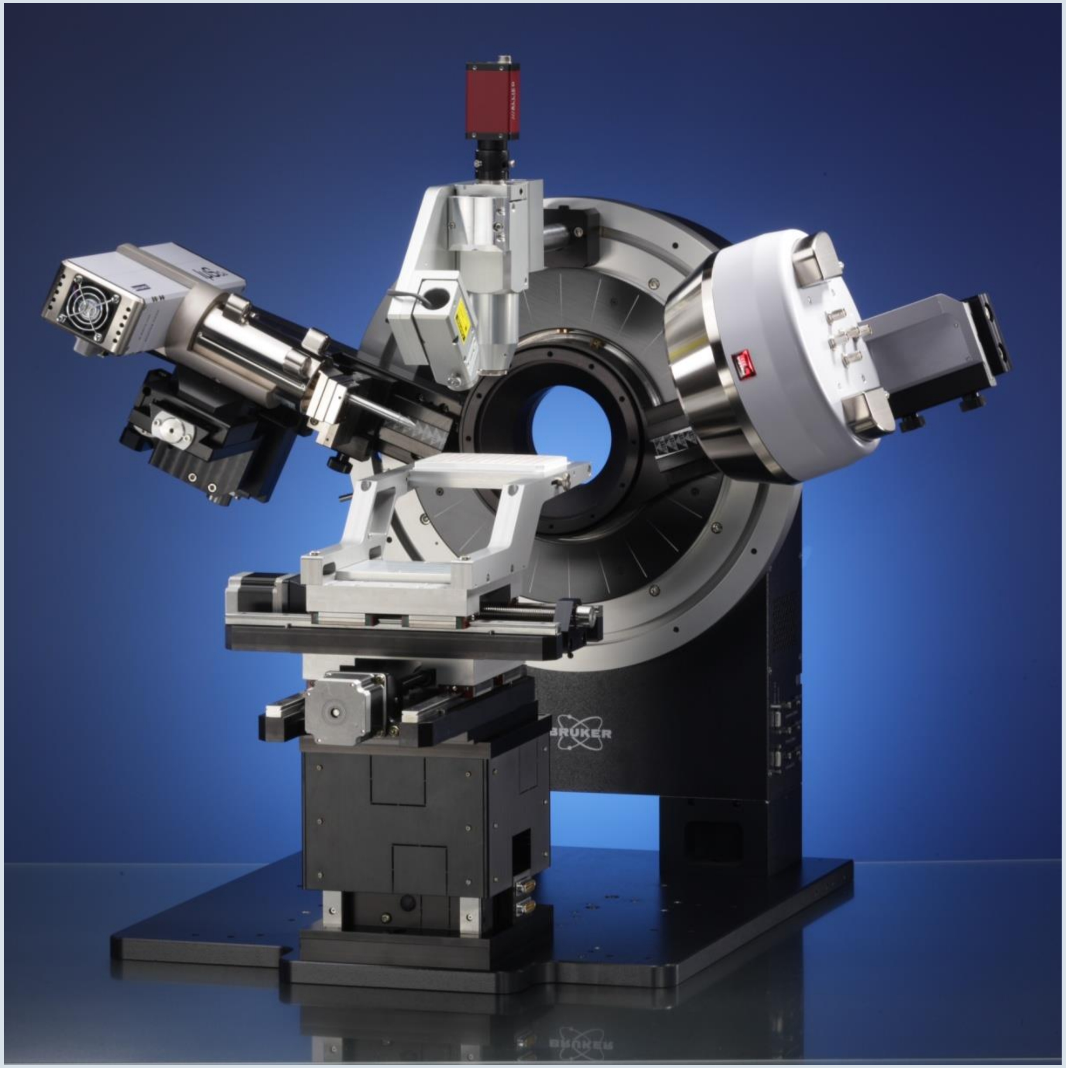


No barrier between 0D/1D/2D

Vertical theta-theta, CEC for microdiffraction/stress/texture

High-throughput Screening (HTS)

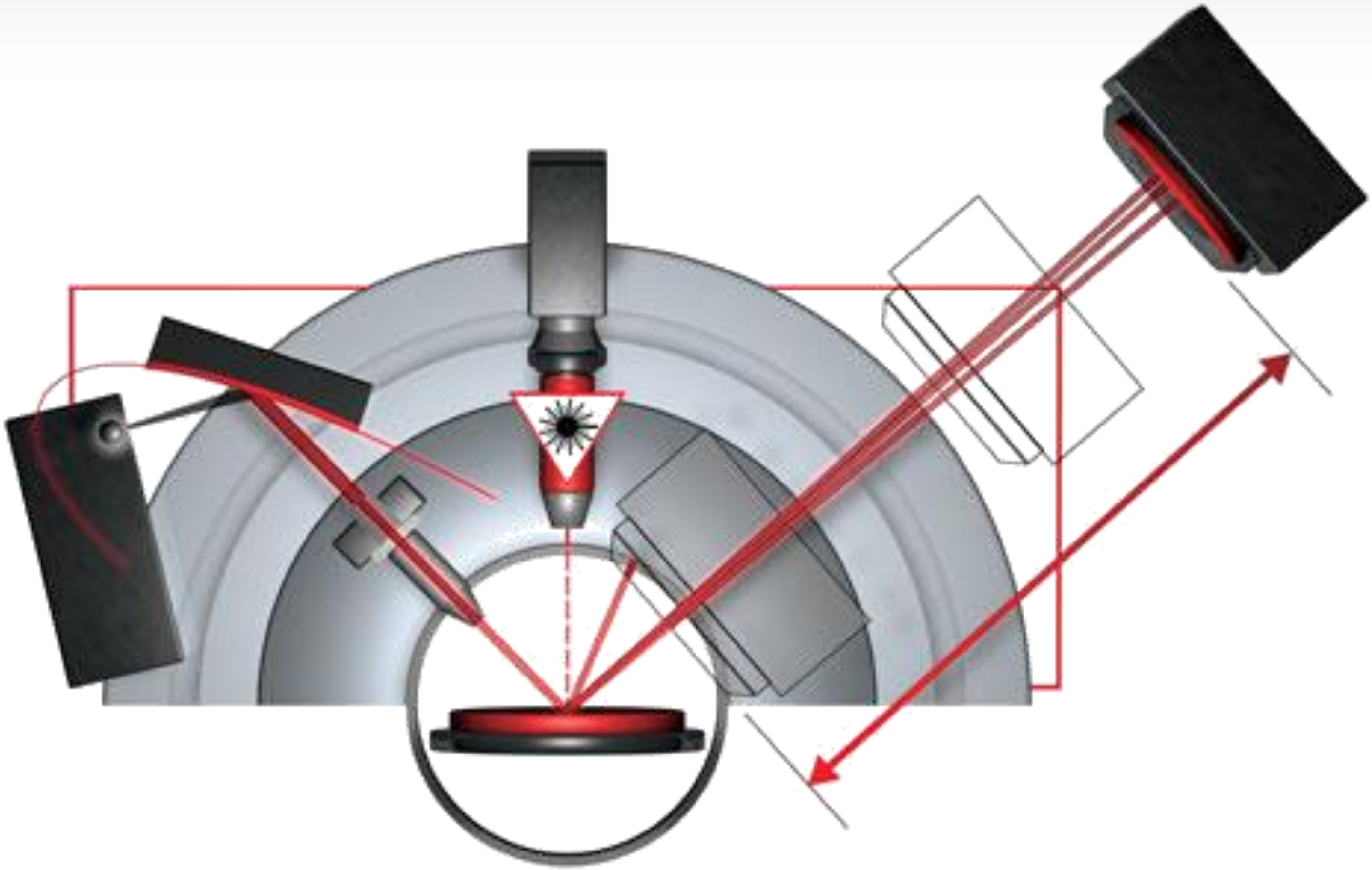
Vertical theta-theta, Reflection/Transmission



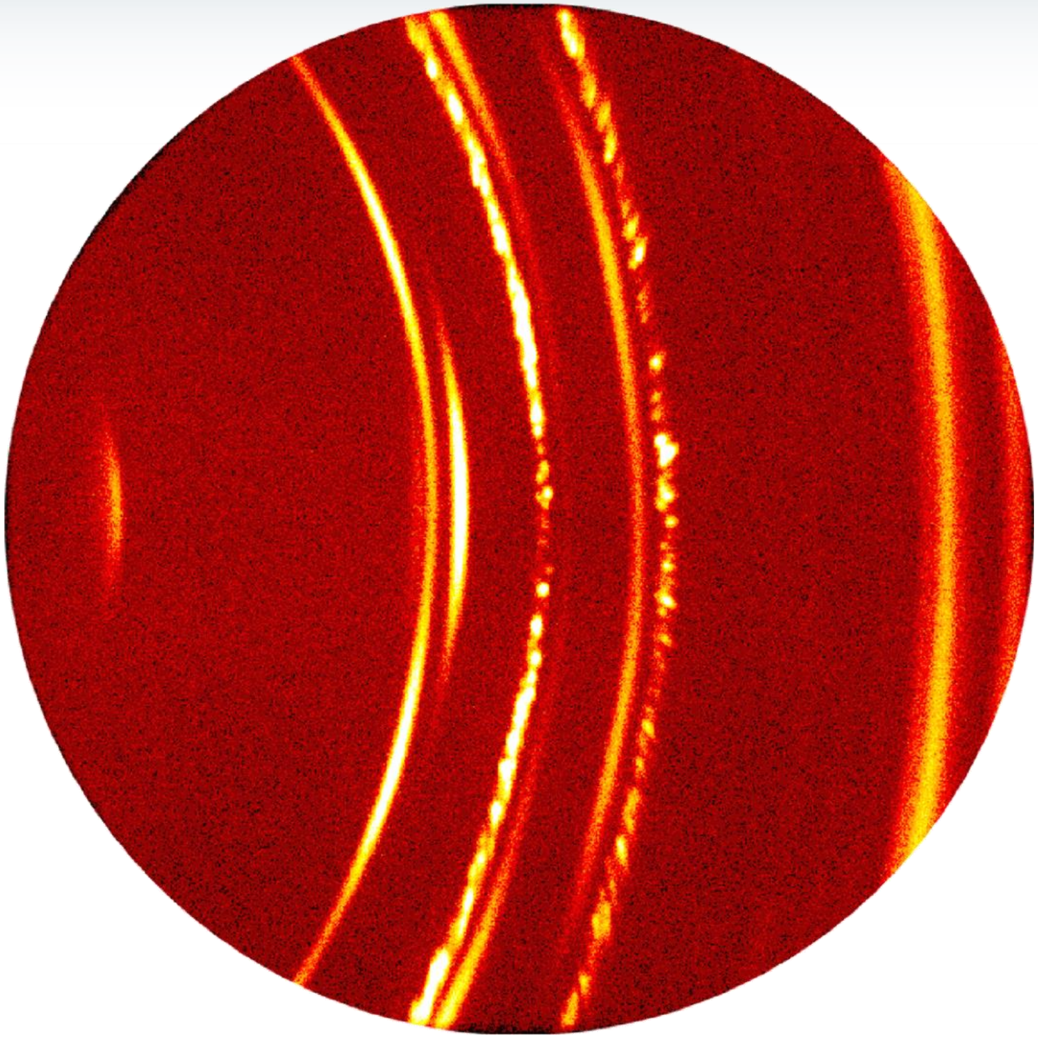
D8 DISCOVER
High Throughput Screening

Phase Identification

XRD^2: Phase ID Measurement Geometry



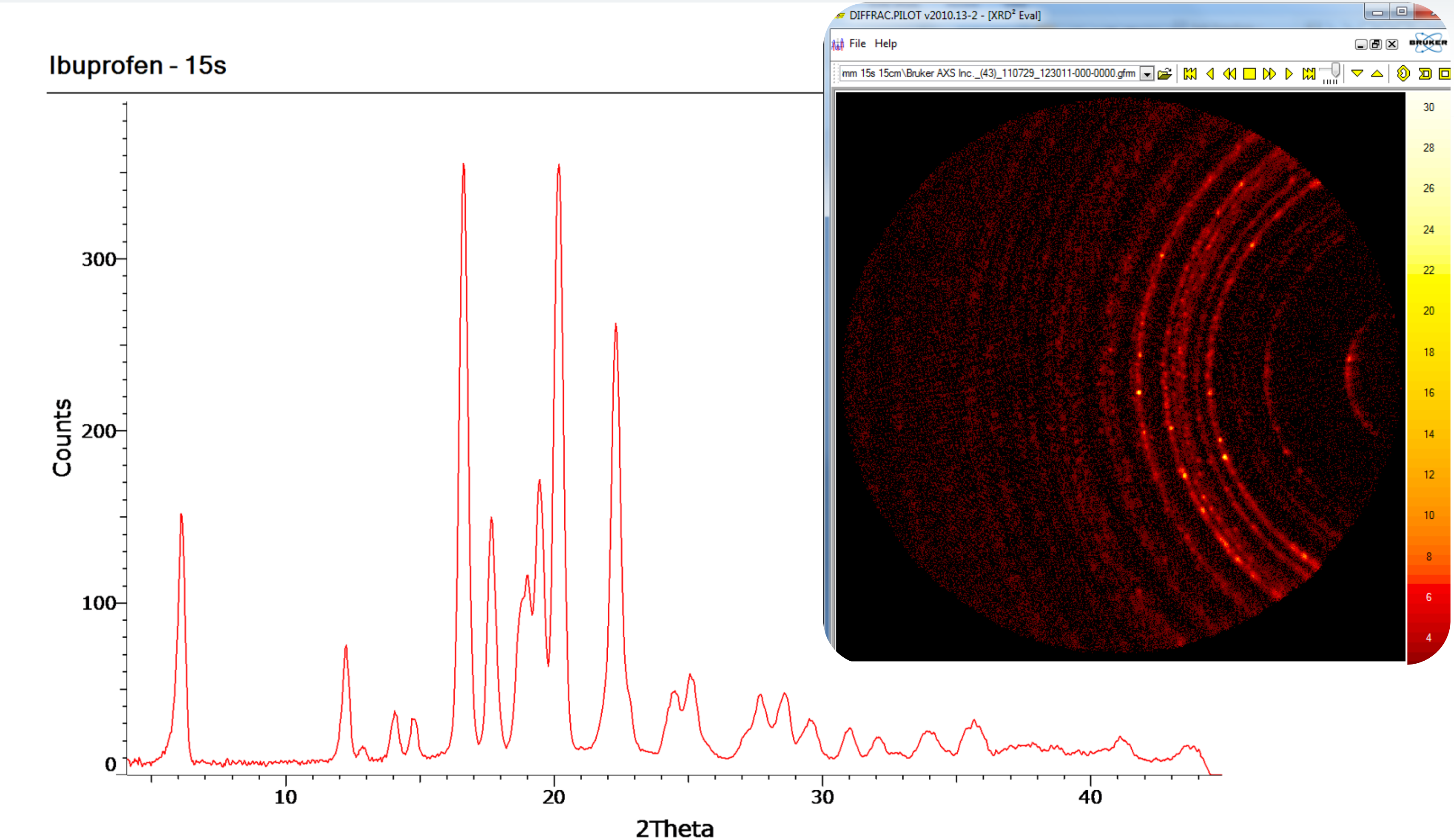
XRD^2: Single Frame Covering All



- Multilayer battery anode.
- 2θ coverage: 70° at 8 cm detector distance
- A single frame showing information on phase, stress, texture and grain size
- 2D detector is essential for In-situ measurement

Ibuprofen
Integrated to 1-D data

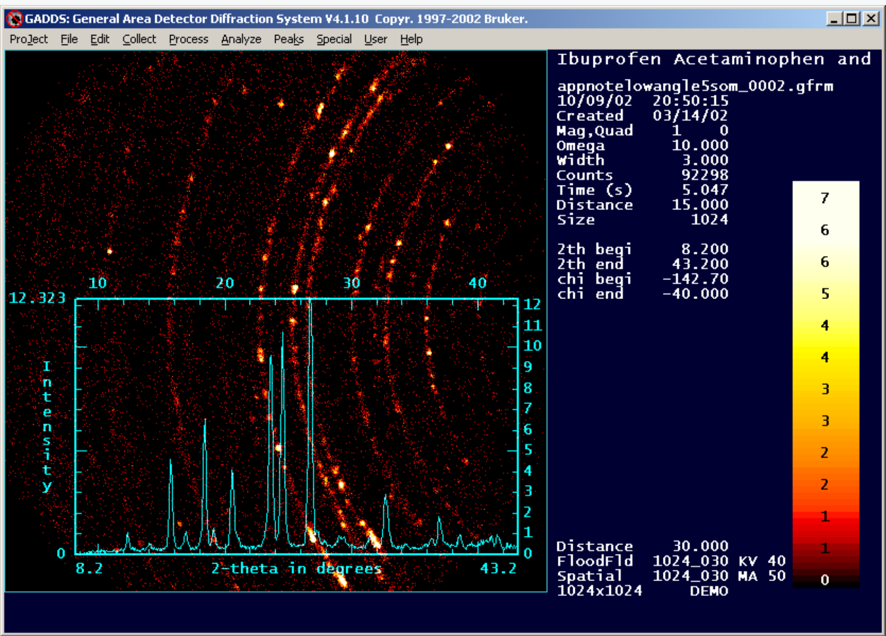
t	Dist	Beam
15 s	15cm	300 µm



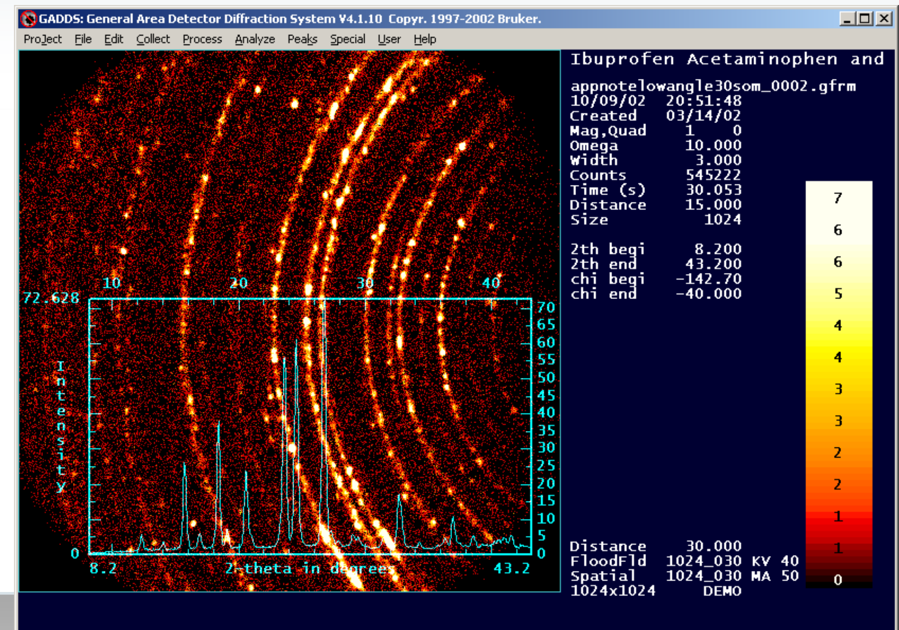
XRD^2: Data Collection:

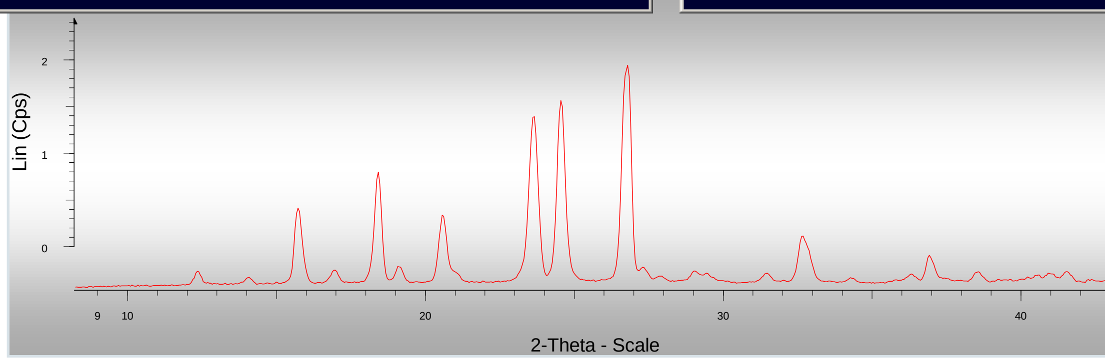
Acetaminophen powder

5 second data collection

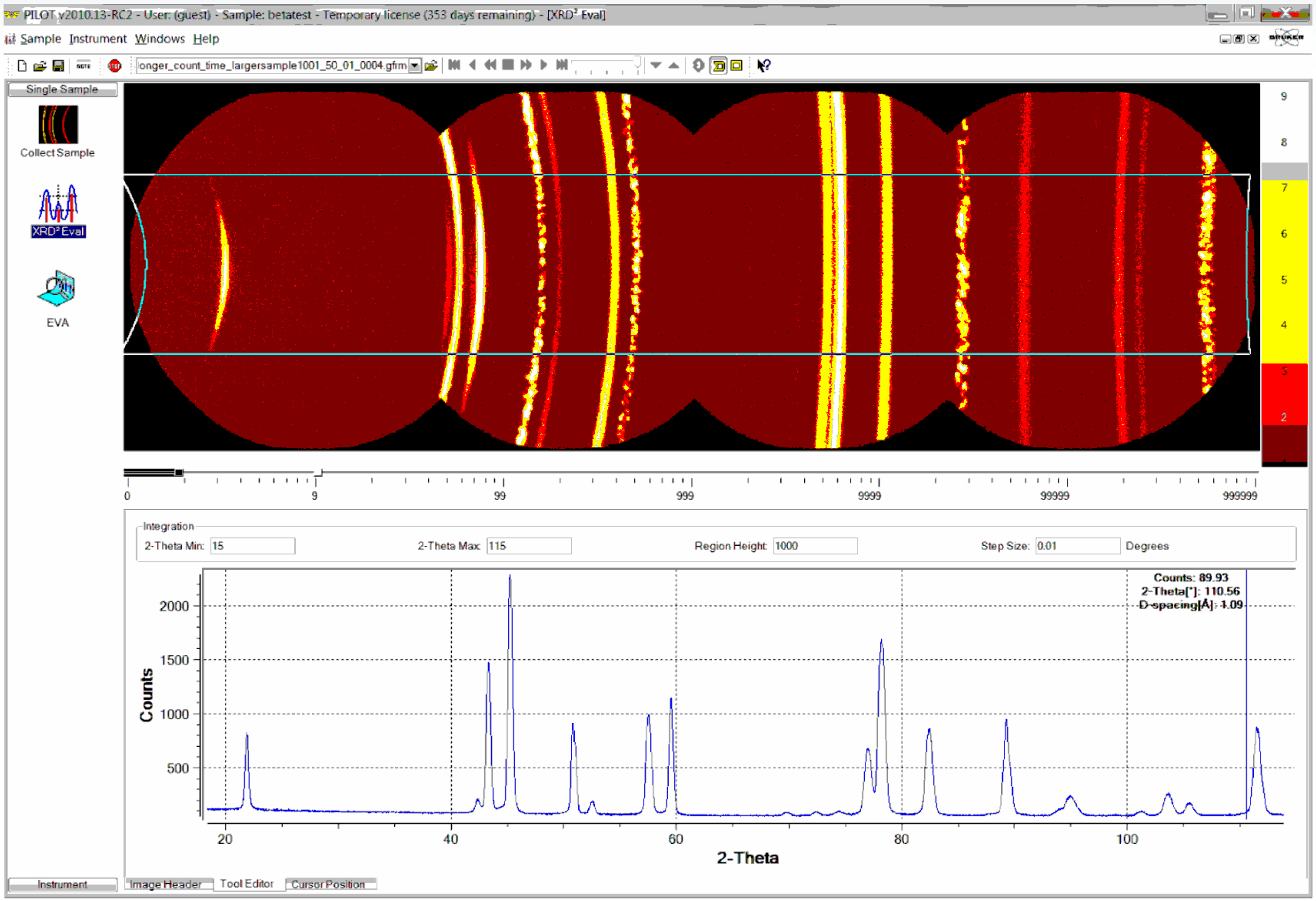


30 second data collection



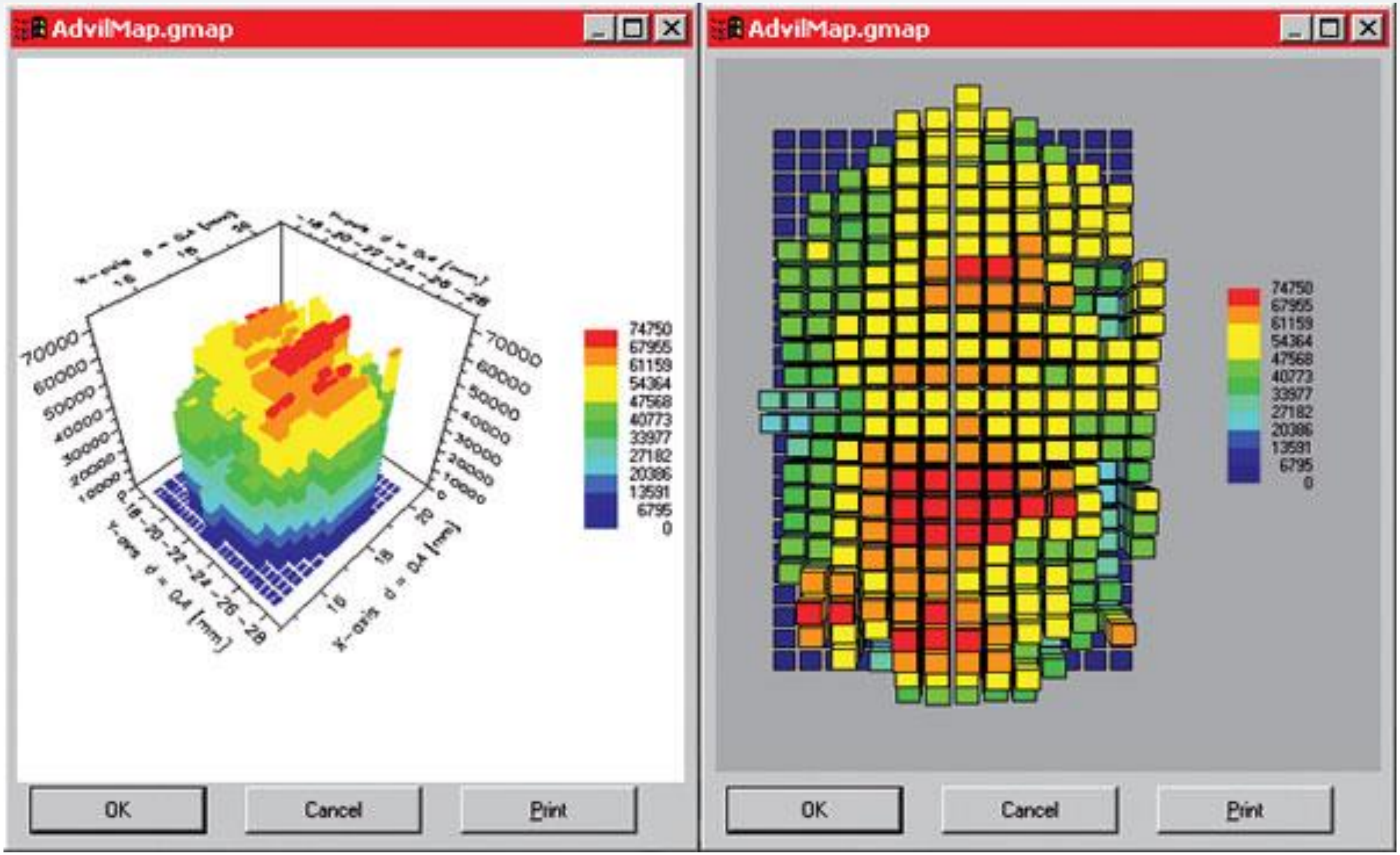


XRD²: Frame Merge and Integration



- 4 frames at 20 cm
- Merged frames 2θ coverage: 100°
- Integrated profile for phase ID search/match

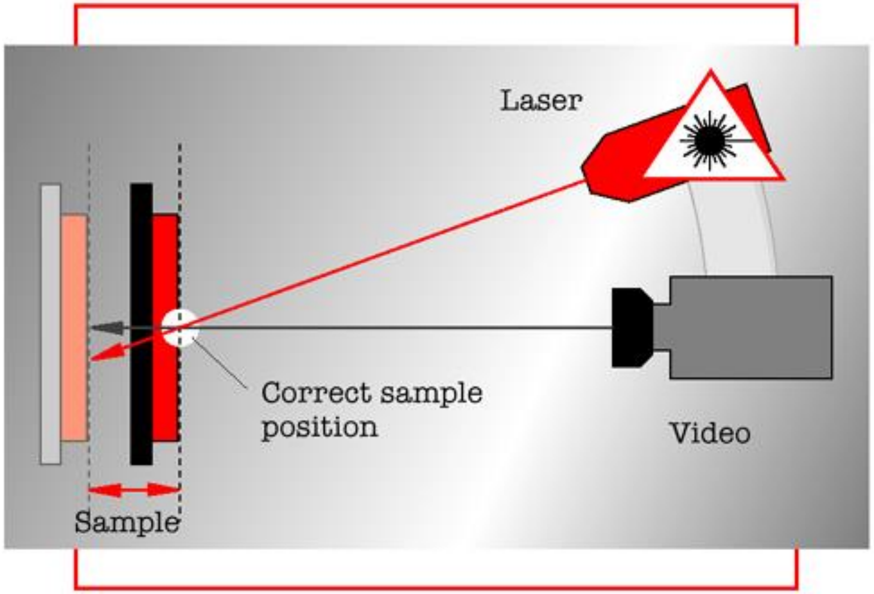
XRD²: Mapping: API Distribution in a Pill

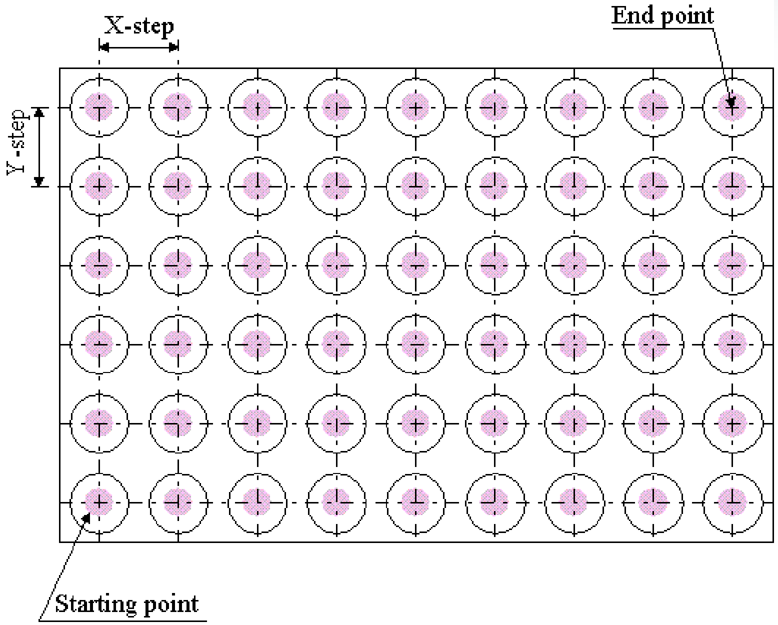


XRD²: High throughput screening

Laser/video sample alignment

Easy and accurate sample positioning without touching the sample surface

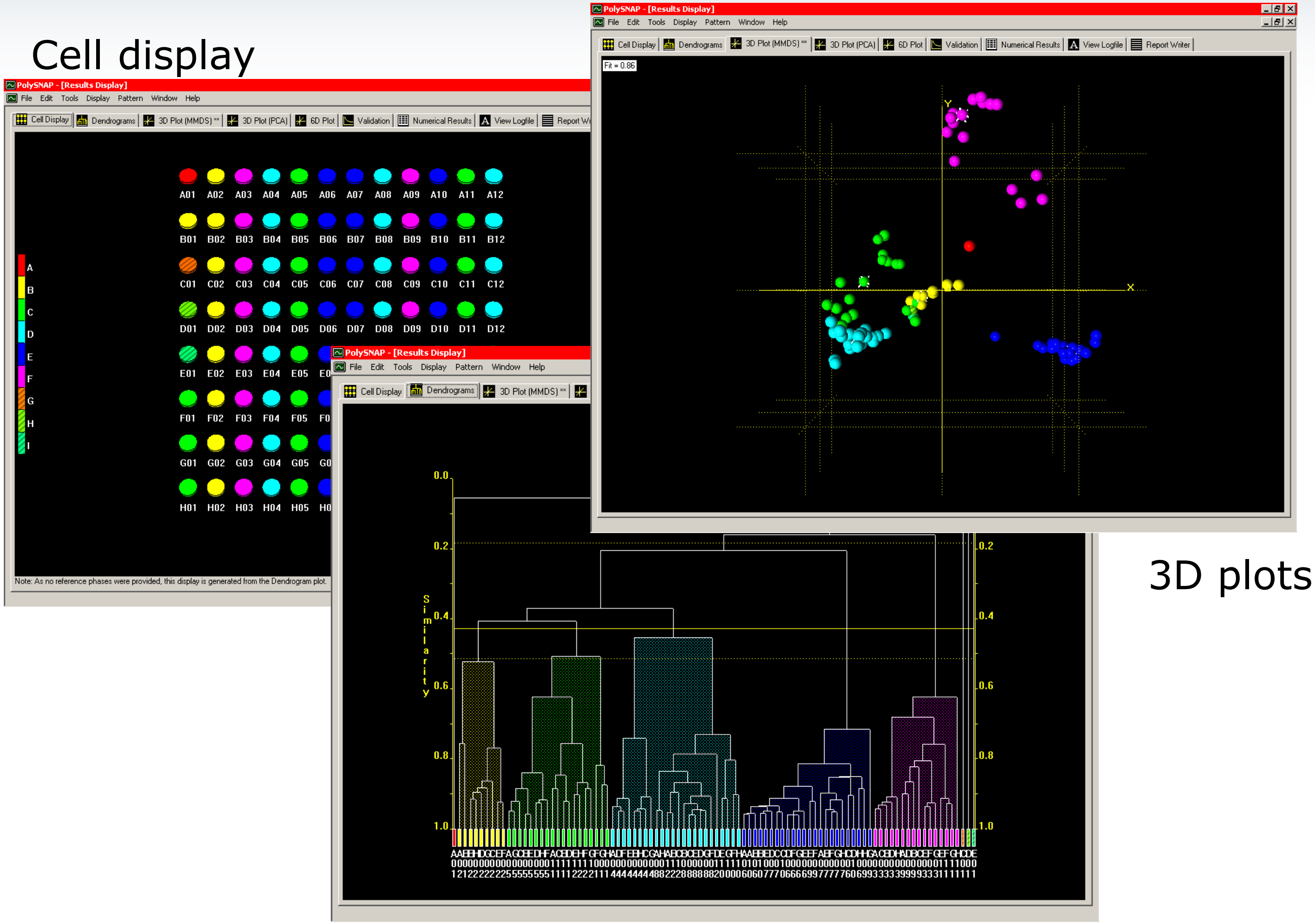




Video image of each material library spot can be automatically stored during data scan

PolySNAP for Combined Analysis:
Correlation among XRD, Raman and other probes

Cell display



3D plots

Dendrogram

Particle/Crystal Size

XRD²: Crystal Size by γ profile analysis: Organic glass for food & drugs

Food

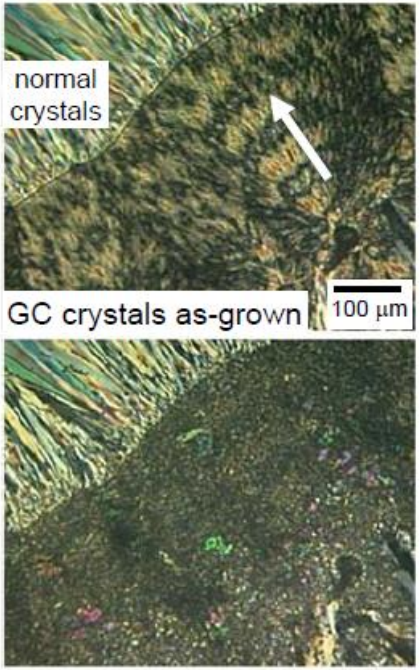
Bio-preservation

In sugar glasses

In amber

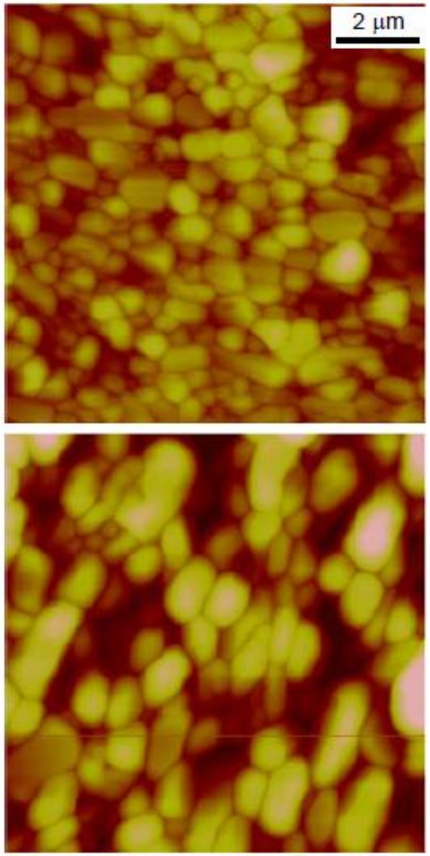
Annealing of GC crystals

LM



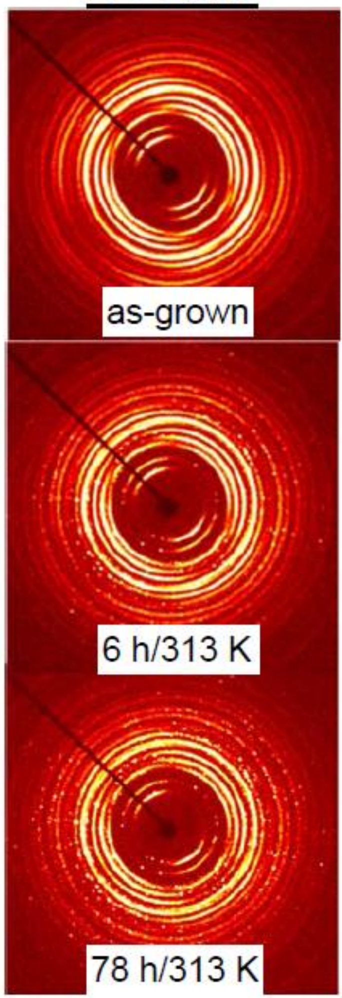
50 min/313 K

AFM



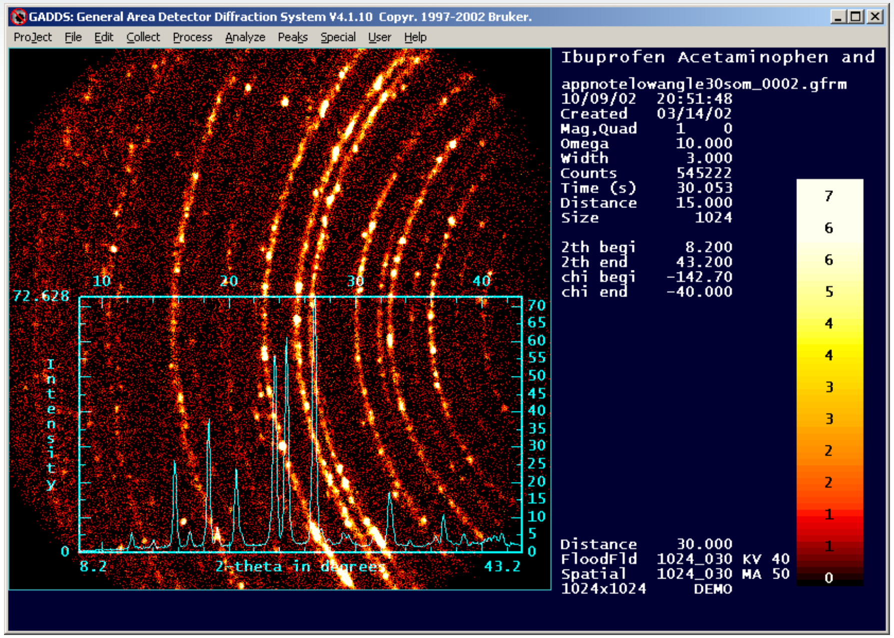
30 min/313 K

2D XRD



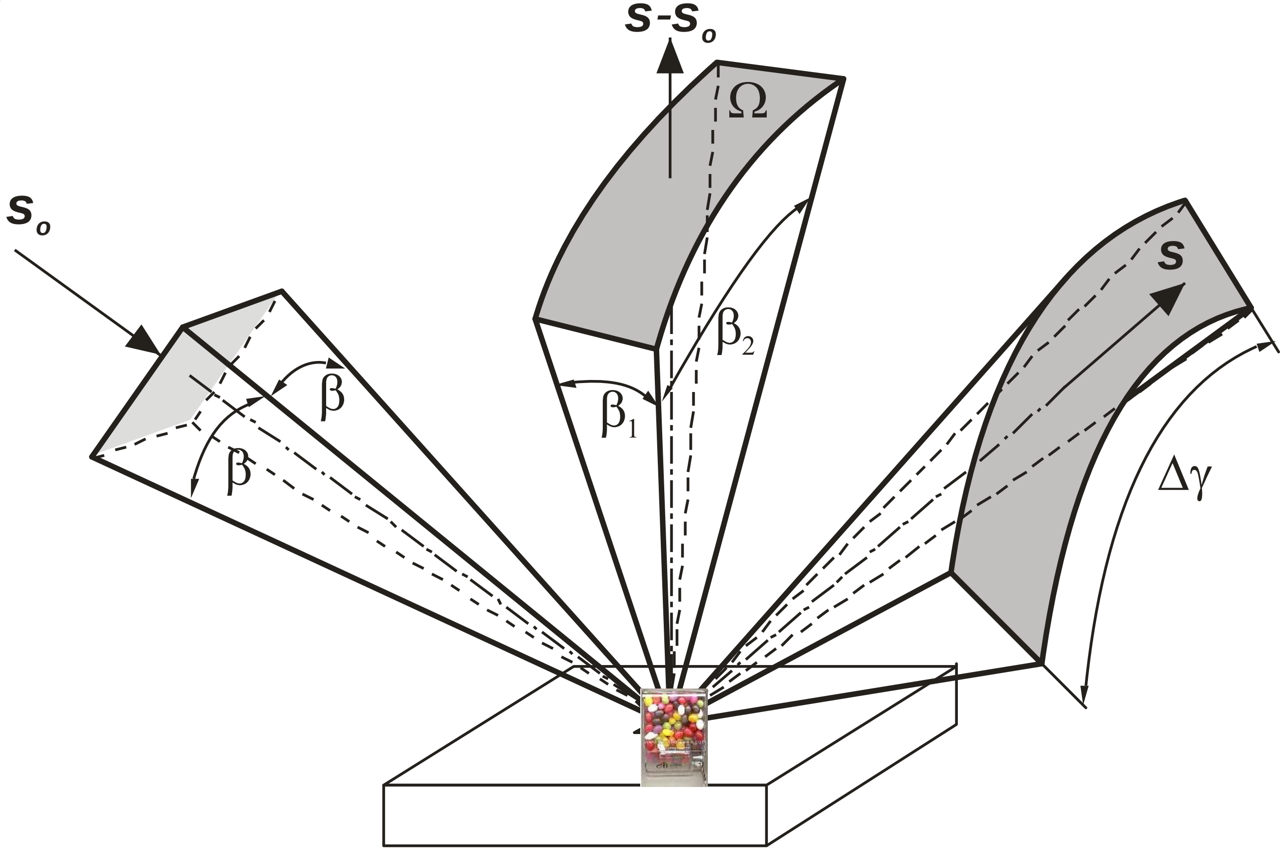
*Courtesy of Prof. Lian Yu, U. of Wisconsin - Madison

XRD²: Data Collection:
Acetaminophen powder



- The spotty diffraction ring is due to the large crystallites compared to the sampling volume (beam size).
- The number of spots on the ring is determined by crystallite size, instrumental window (γ-range), multiplicity of the crystal plane, and effective diffraction volume.
- The size of jelly beans and candy bin determines how many you can fill.

XRD^2: Particle size measurement by γ profile analysis:



For XRD^2, the instrumental window Ω is given by

$$\Omega = \beta_1 \beta_2 = 2\beta \arcsin[\cos\theta \sin(\Delta\gamma / 2)]$$

XRD^2: Particle size measurement by γ profile analysis:

For XRD^2 in reflection mode, the crystallite size is given by

$$d = k\left\{\frac{p_{hkl} b^2 \arcsin[\cos\theta \sin(\Delta\gamma/2)]}{2\mu N_s}\right\}^{1/3}$$

where μ is the linear absorption coefficient

For transmission mode with the incident beam perpendicular to the sample surface, the crystallite size is given by

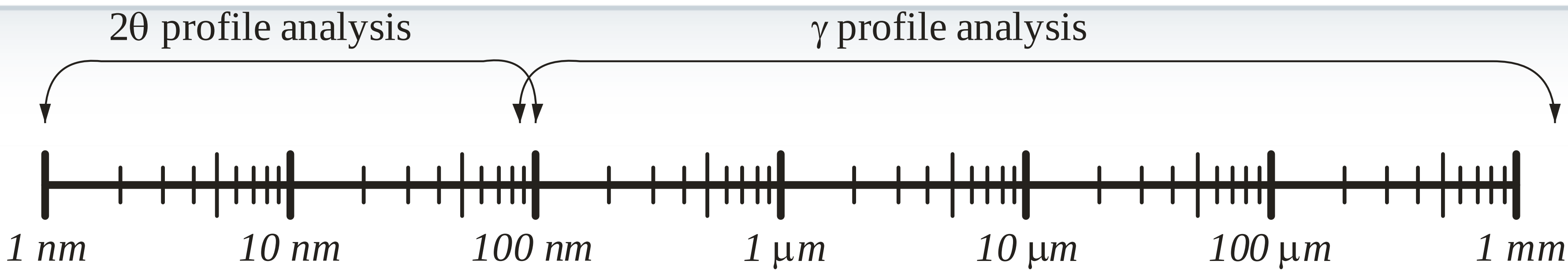
$$d = k\left\{\frac{p_{hkl_i} b^2 t \arcsin[\cos\theta \sin(\Delta\gamma/2)]}{N_s}\right\}^{1/3}$$

where t is the sample thickness.

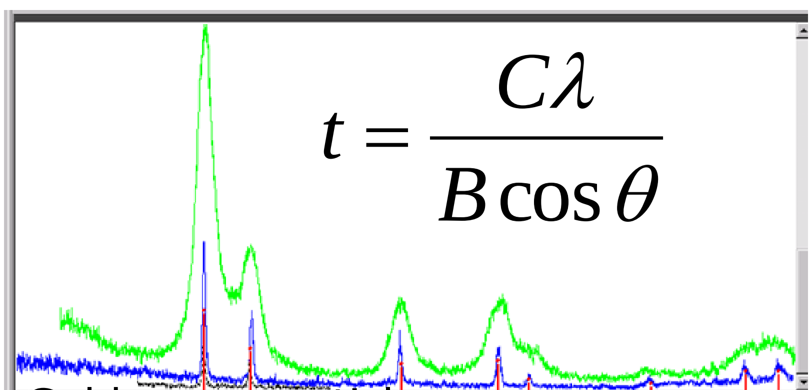
k is the instrument calibration factor or can be calculated from:

$k = \left(\frac{3\beta}{4\pi}\right)^{1/3}$ if the instrument broadening in 2θ direction is known.

XRD^2: Particle Size Analysis

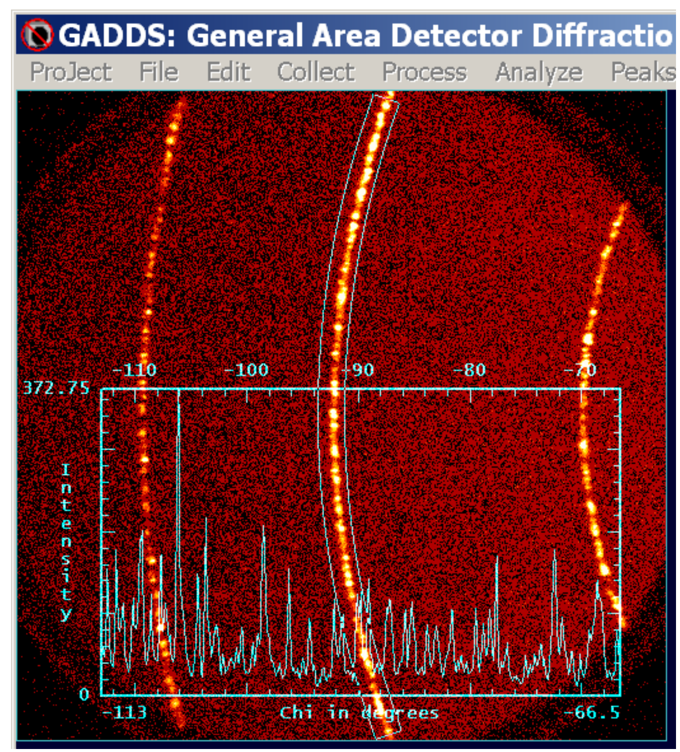


Scherrer equation:



$$t = \frac{C\lambda}{B\cos\theta}$$

Gold nano-particle



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