Metadata needed for the full exploitation of diffuse scattering data from protein crystals

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ECM 29 Satellite Workshop on Metadata for Raw Data from X-ray Diffraction and Other Structural Techniques

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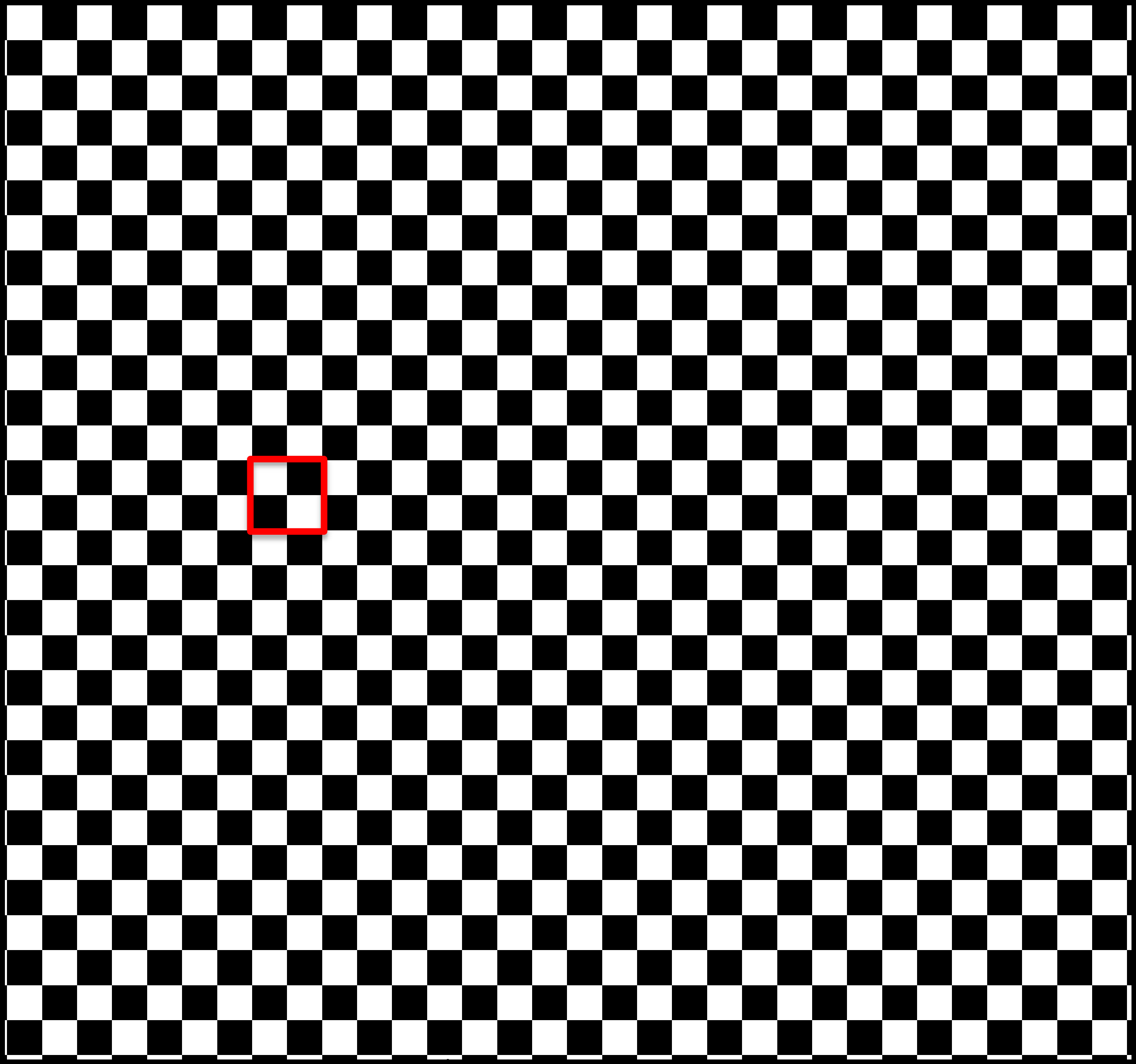
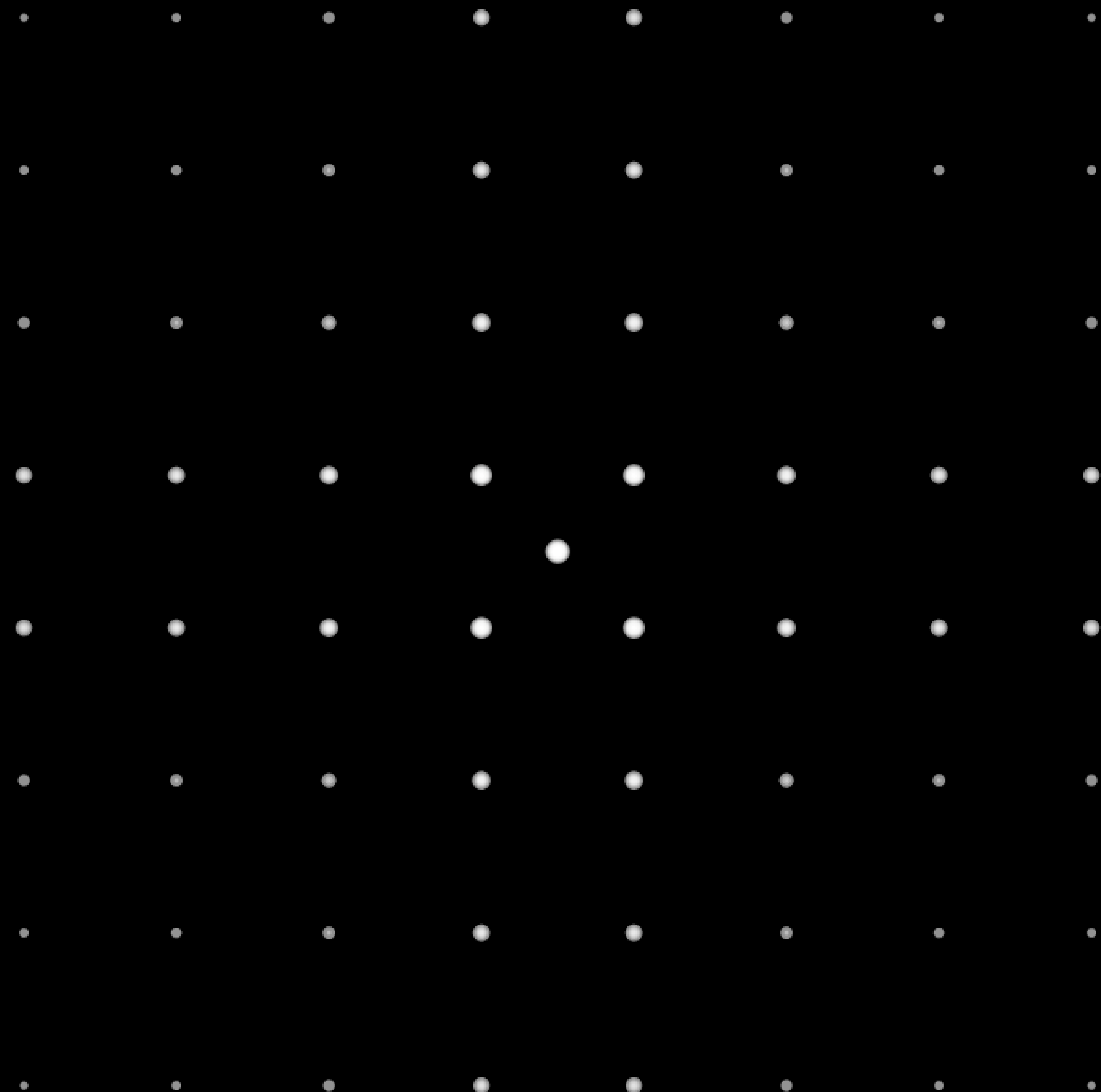
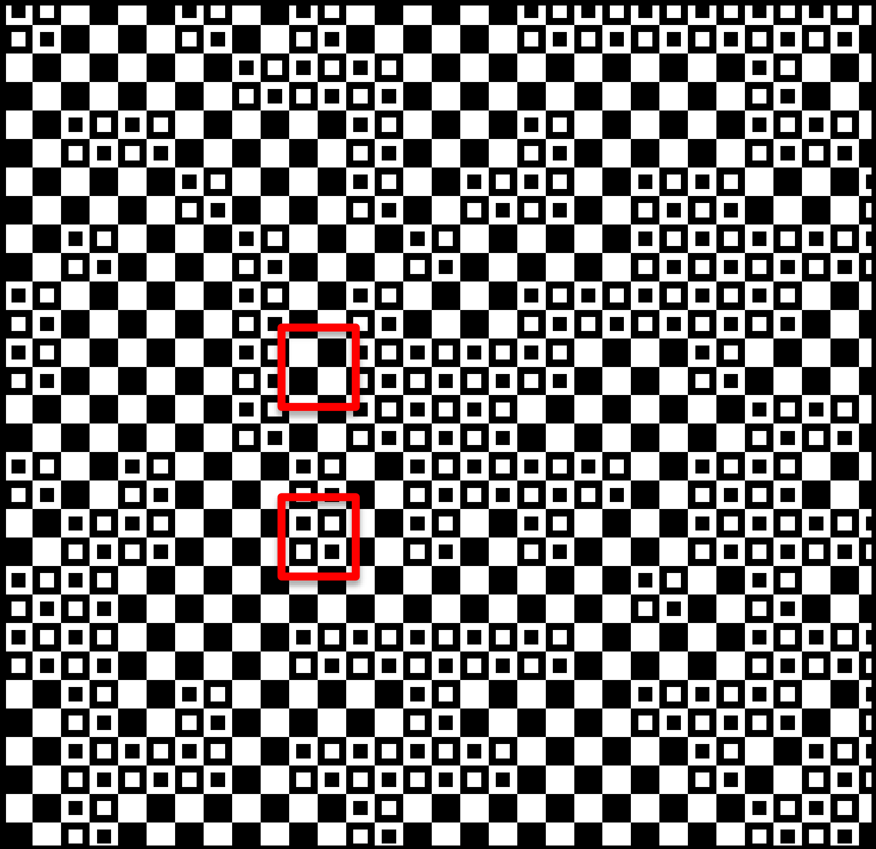
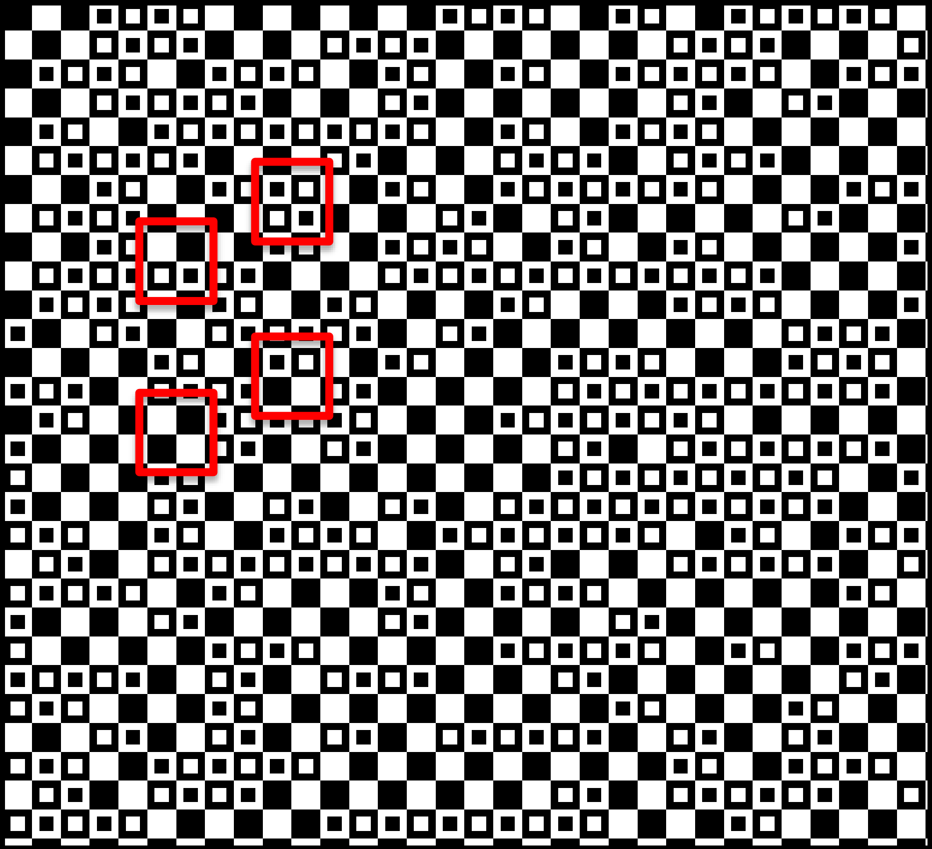
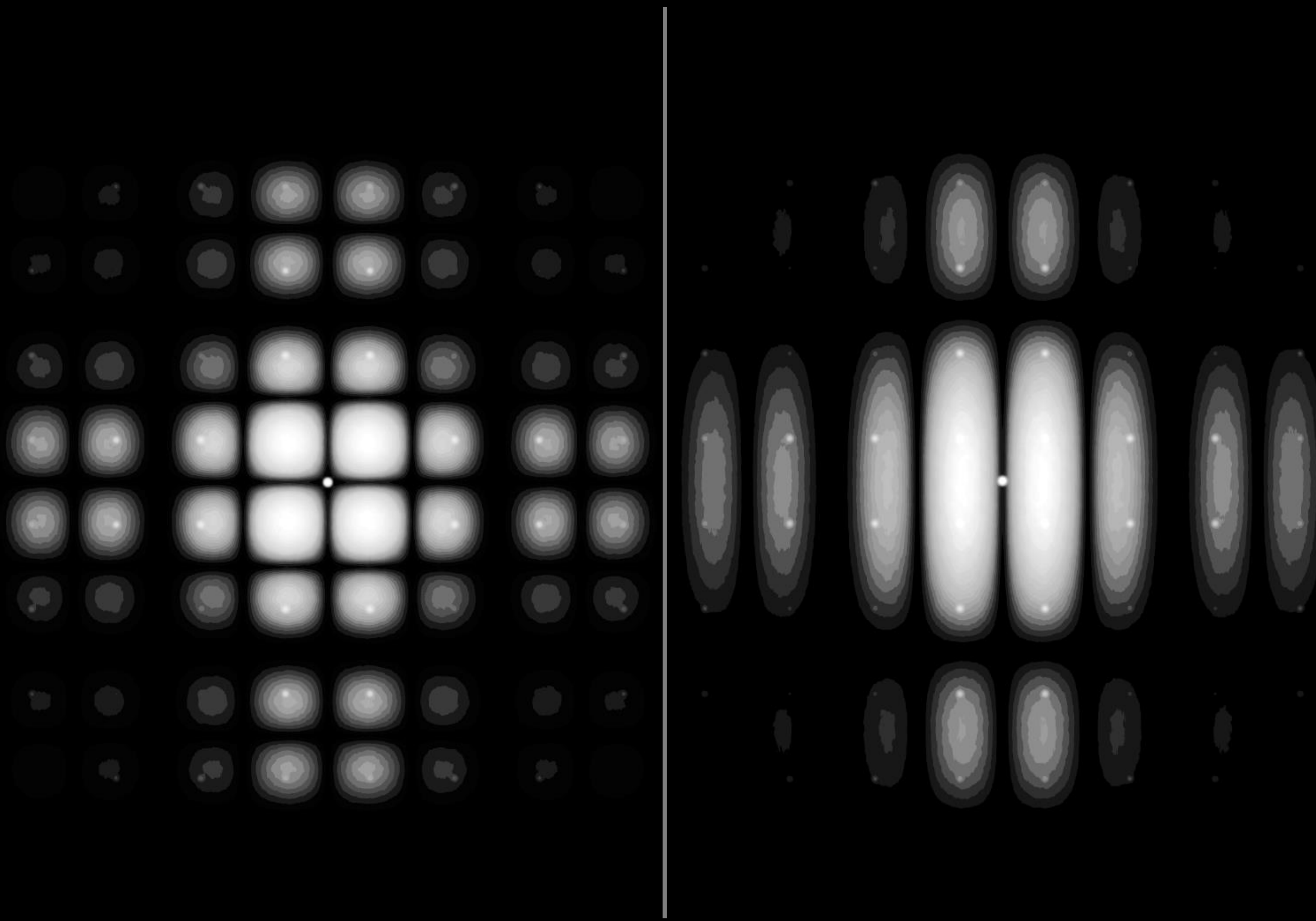
22-23 August 2015

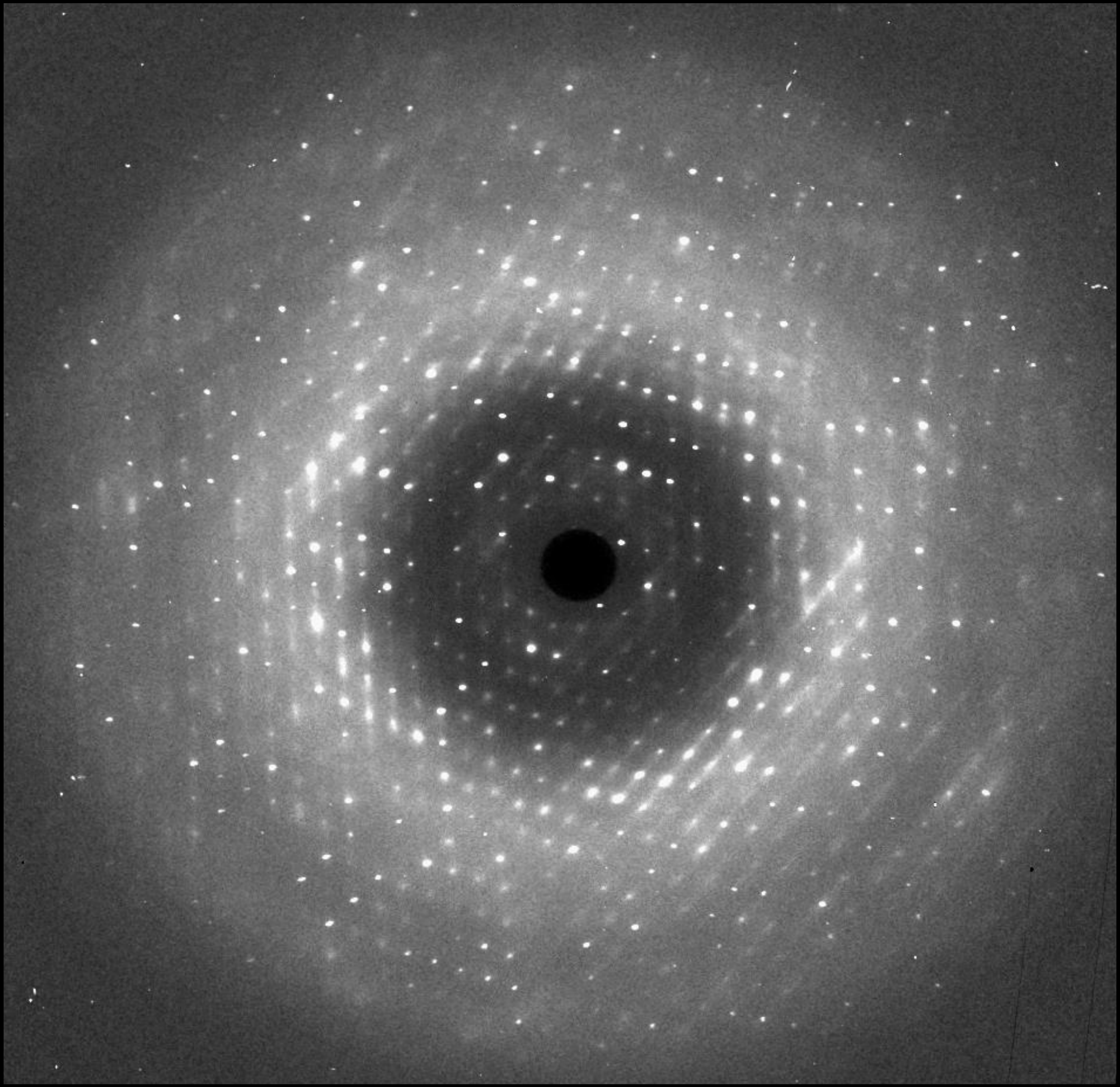












Diffuse X-Ray Scattering to Model Protein Motions

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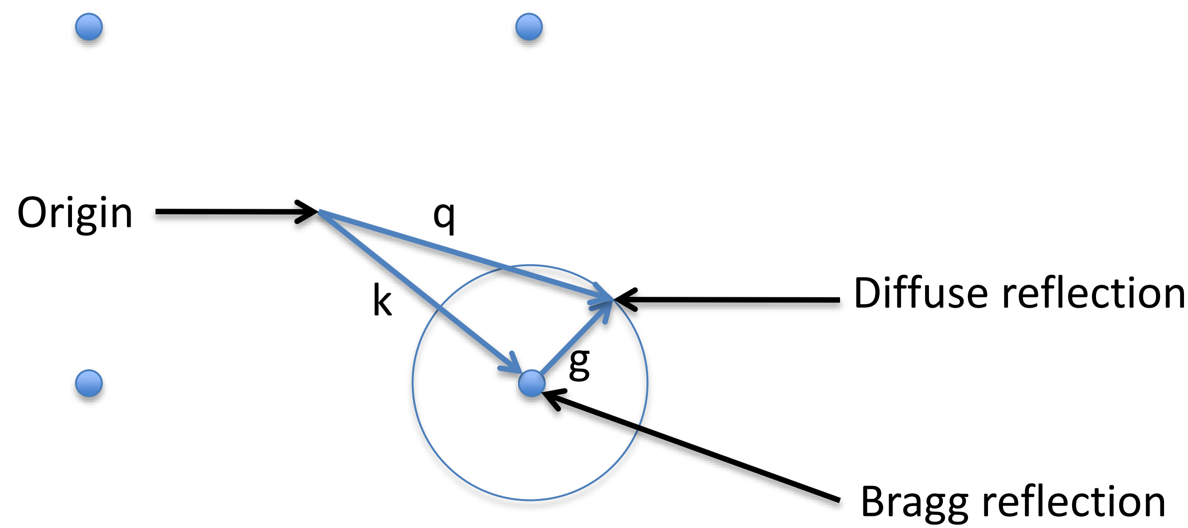
Problems in biology increasingly need models of protein flexibility to understand and control protein function. At the same time, as they improve, crystallographic methods are marching closer to the limits of what can be learned from Bragg data in isolation. It is thus inevitable that mainstream protein crystallography will turn to diffuse scattering to model protein motions and improve crystallographic models. The time is ripe to make it happen.

Structure **22** (2014) 182

Kathleen Lonsdale
Diffuse Scattering Pioneer

- 1924, student of Lawrence Bragg
- 1928, Solved benzene structure
  - Ended 60 year debate about flat aromatic ring
- 1942, **Champion of diffuse X-ray scattering**
- 1945, Fellow of Royal Society
  - One of first two women (along with Marjory Stephenson)
- 1956, Dame Commander of OBE
- 1966, First woman president of IUCr



$$I_D(\mathbf{q}) = \sum_{\mathbf{g},s} \left[I_0(\mathbf{q}+\mathbf{g}) + I_0(\mathbf{q}-\mathbf{g}) \right] \left| \mathbf{q} \cdot \mathbf{v}_s(\mathbf{g}) \right|^2$$

Born & Sarginson, 1941
James, 1948

Thermal Diffuse Scattering (TDS)

$$F = \sum_n f_n e^{i\mathbf{q}\cdot\mathbf{R}_n}$$

$$I(t) = |F|^2 = \sum_n \sum_m f_n f_m^* e^{i\mathbf{q}\cdot(\mathbf{R}_n - \mathbf{R}_m)}$$

$$I = \sum_n \sum_m \left[\left(\left\langle |f_n|^2 \right\rangle - |\langle f_n \rangle|^2 \right) \delta_{nm} + |\langle f_n \rangle|^2 \right] e^{i\mathbf{q}\cdot(\mathbf{R}_n - \mathbf{R}_m)}$$

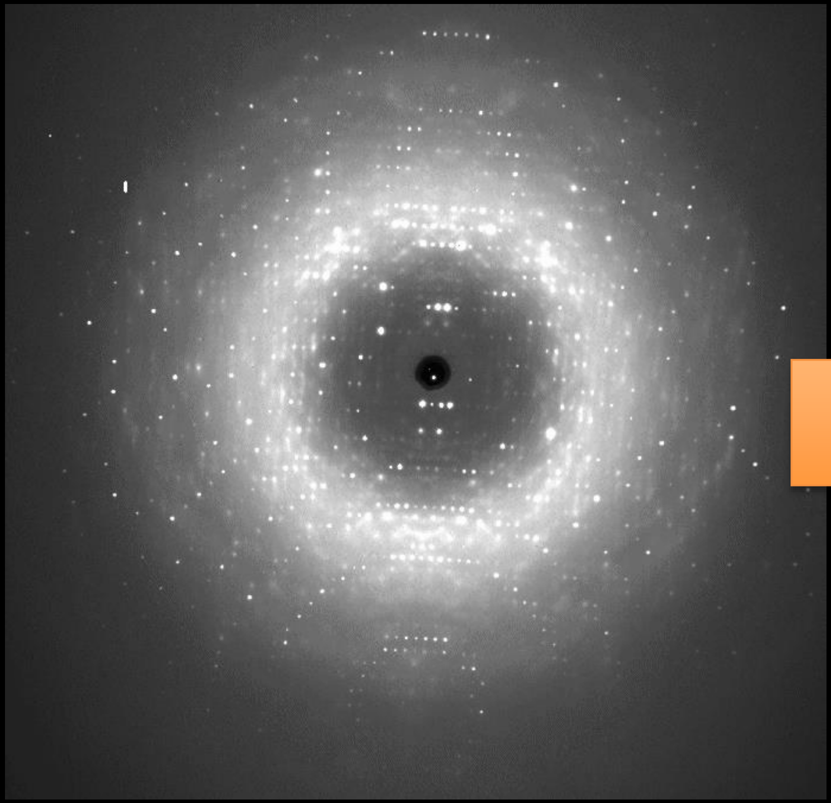
$$I = I_D + I_B$$

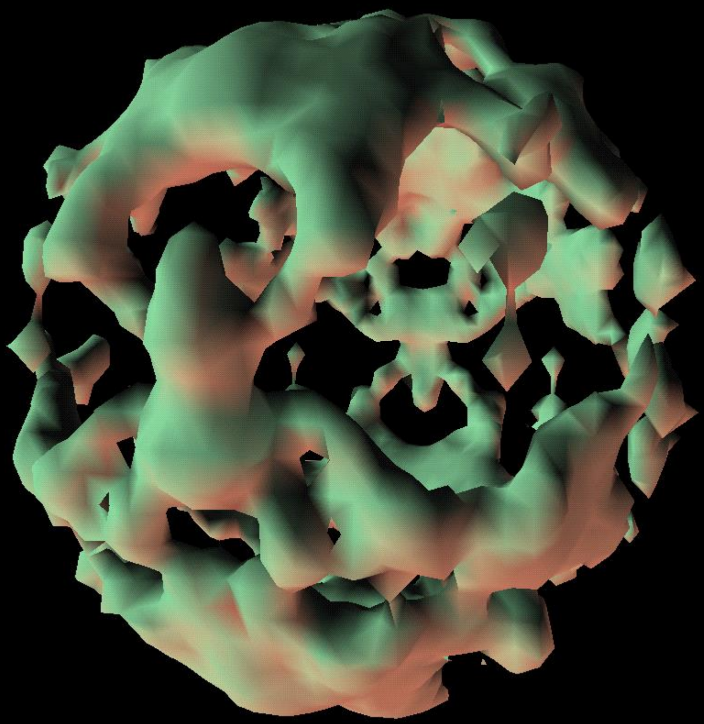
$$I_B = |\langle f \rangle|^2 \sum_n \sum_m e^{i\mathbf{q}\cdot(\mathbf{R}_n - \mathbf{R}_m)}$$

$$I_D(\mathbf{q}) = N\left(\left\langle \left| f_n - \langle f_n \rangle \right|^2 \right\rangle_n \right) \propto N \int d\mathbf{x} e^{i\mathbf{q}\cdot\mathbf{x}} \int d\mathbf{x}' \left\langle \Delta\rho_n(\mathbf{x}')\Delta\rho_n(\mathbf{x}' + \mathbf{x}) \right\rangle_n$$

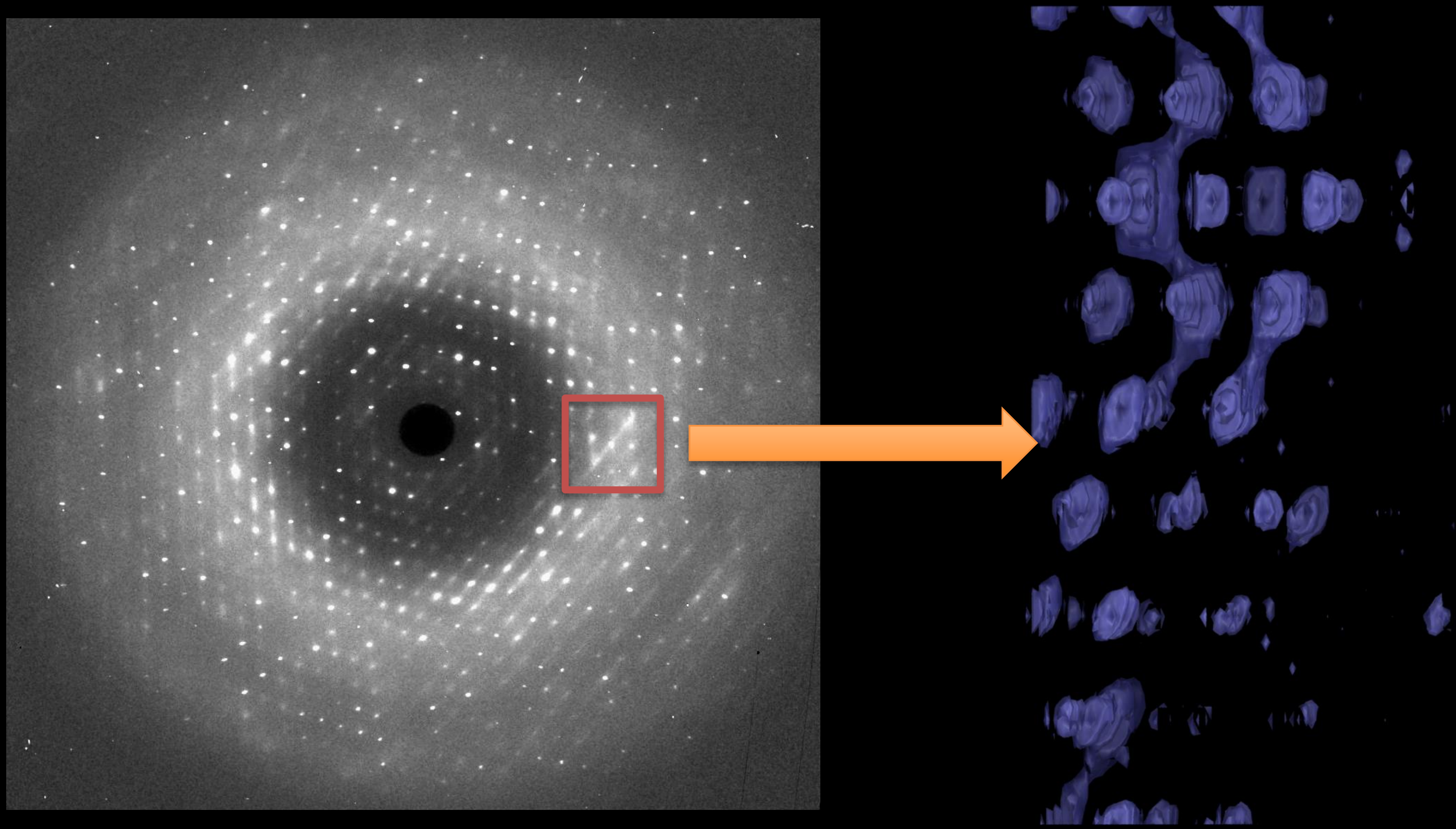
Sample using molecular dynamics simulations

Guinier 1956, 1963





Wall, 1996 (Ph.D. Thesis)
Wall, Ealick, and Gruner, *PNAS* 1997
Wall, *Methods Mol Biol* 2009
http://github.com/mewall/lunus



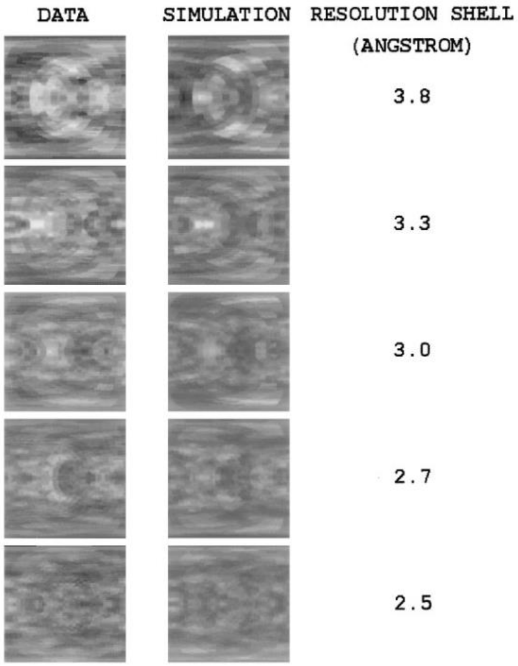
Wall, Clarage & Phillips, *Structure* 1997

$$I_D(\vec{q}) = (1 - e^{-\vec{q}\cdot\mathbf{U}\cdot\vec{q}})e^{-\vec{q}\cdot\mathbf{U}\cdot\vec{q}} I_0(\vec{q}) * \Gamma_{\mathbf{G}}(\vec{q})$$

$$\Gamma_{\mathbf{G}}(\vec{q}) = \frac{8\pi \det\|\mathbf{G}\|}{\left[1 + |\mathbf{G}\vec{q}|^2\right]^2}$$

Liquid-like motions
(Caspar et al)

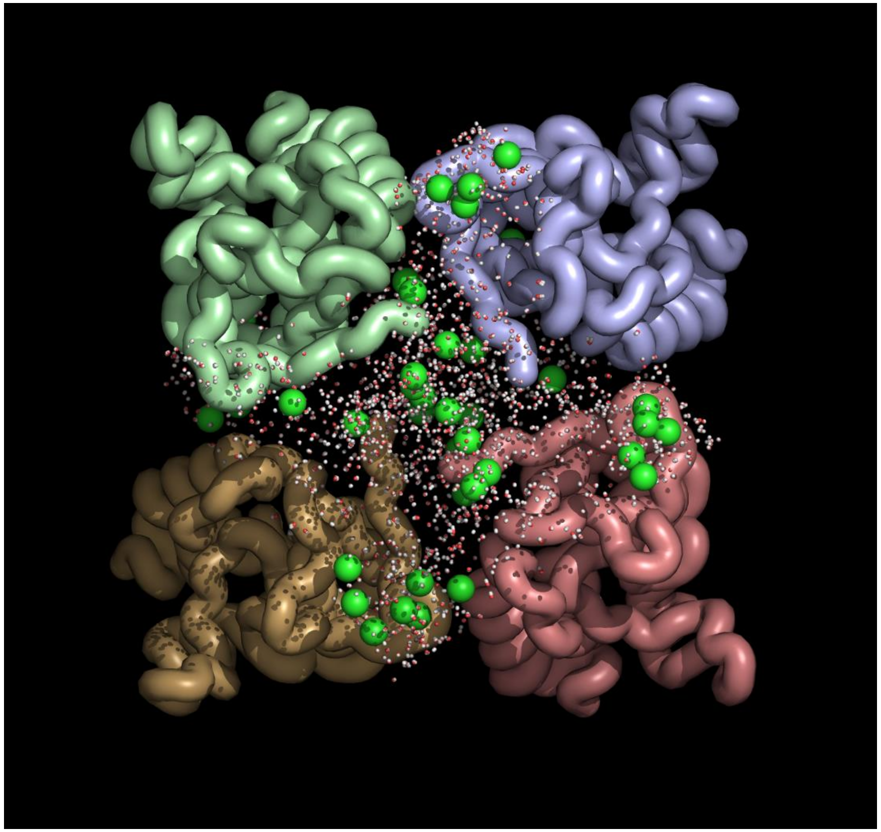
Snase: γ = 10 Å; σ = 0.36 Å
Calmodulin: γ = 4.8 Å; σ = 0.38 Å



$$\Gamma_{\mathbf{G}}(\vec{q}) = \frac{4\pi \det\|\mathbf{G}\|}{1 + |\mathbf{G}\vec{q}|^2}$$

Acoustic modes

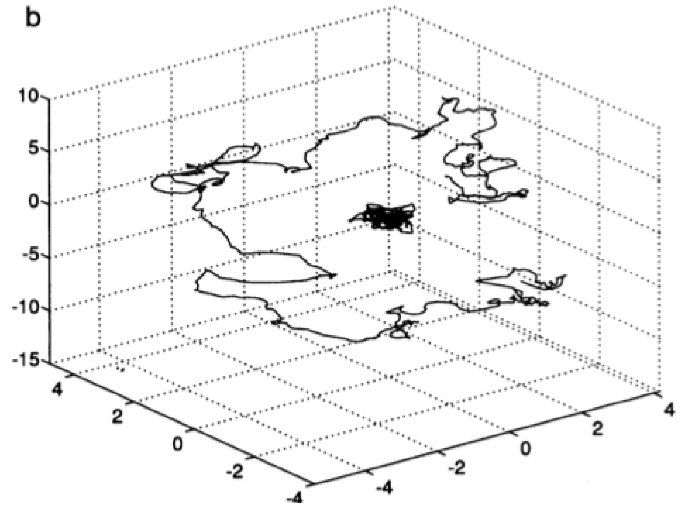
Correlations:	Displacements:
γ_1 = 50 Å	σ_1 = 0.0 Å
γ_2 = 135 Å	σ_2 = 0.4 Å
γ_3 = 85 Å	σ_3 = 0.0 Å



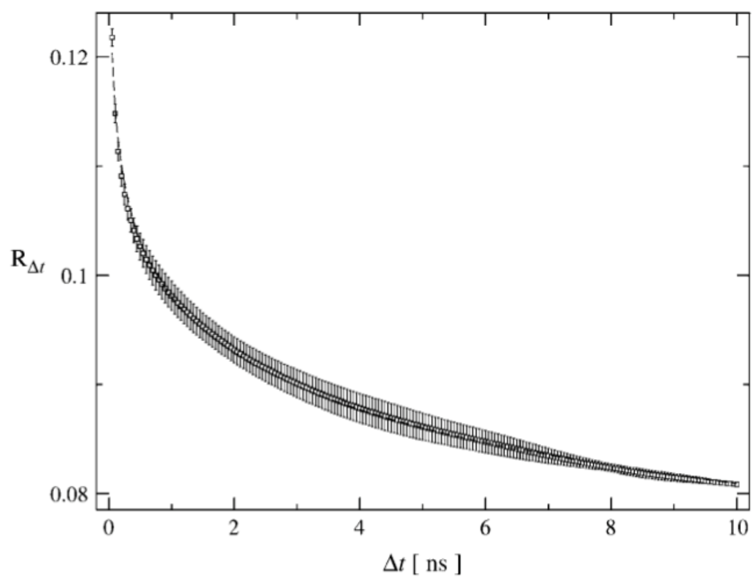
$$L = \frac{1}{2}\sum m_i \dot{\mathbf{R}}_i^2 - U\left(\mathbf{R}_1, \ldots, \mathbf{R}_N\right)$$

$$\frac{d}{dt}\left(\frac{\partial L}{\partial \dot{R}_k}\right) = -\frac{\partial L}{\partial R_k}$$

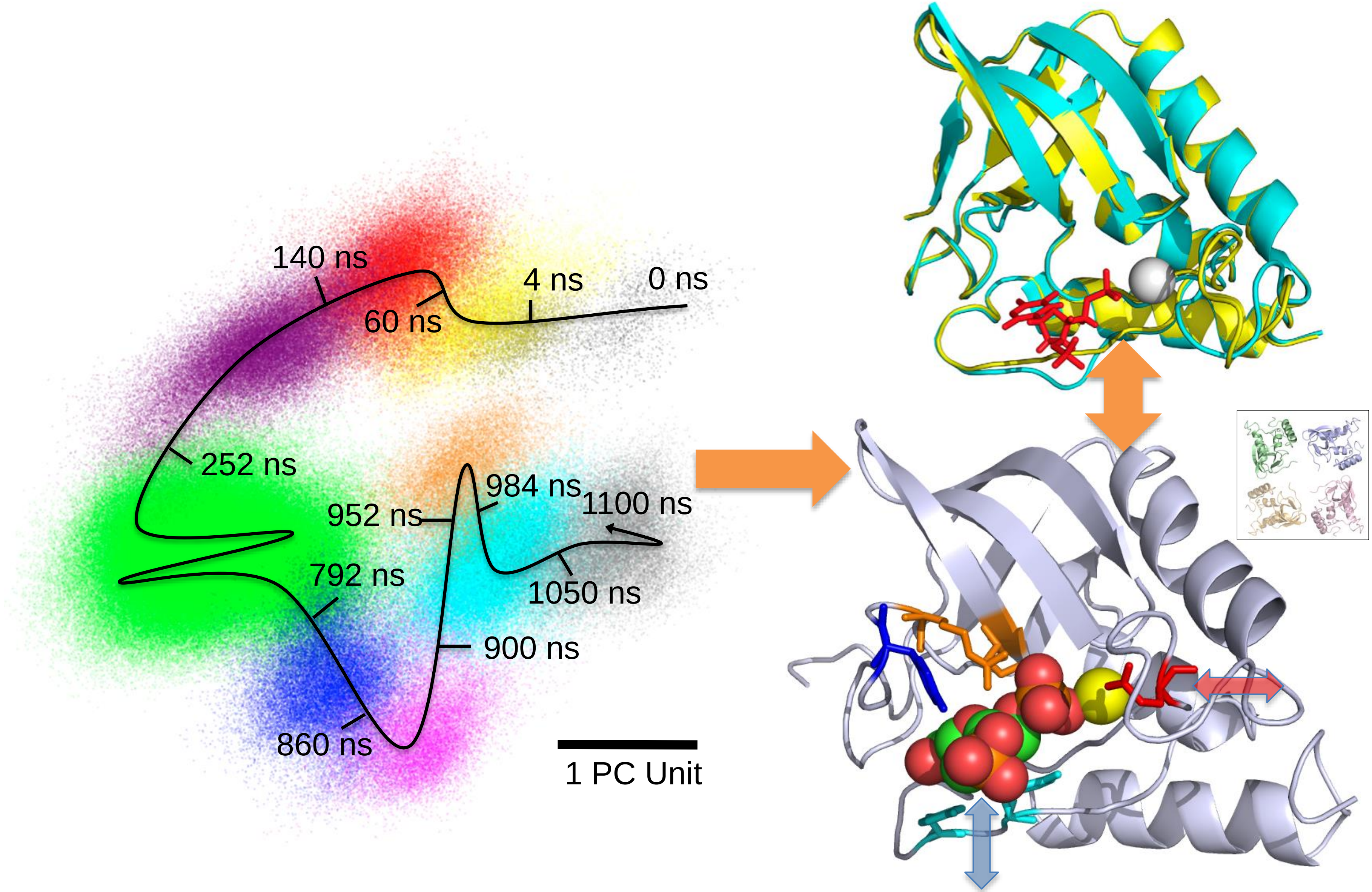
$$\mathbf{f}_i = m_i \ddot{\mathbf{R}}_i = -\frac{\partial U}{\partial \mathbf{R}_i}$$



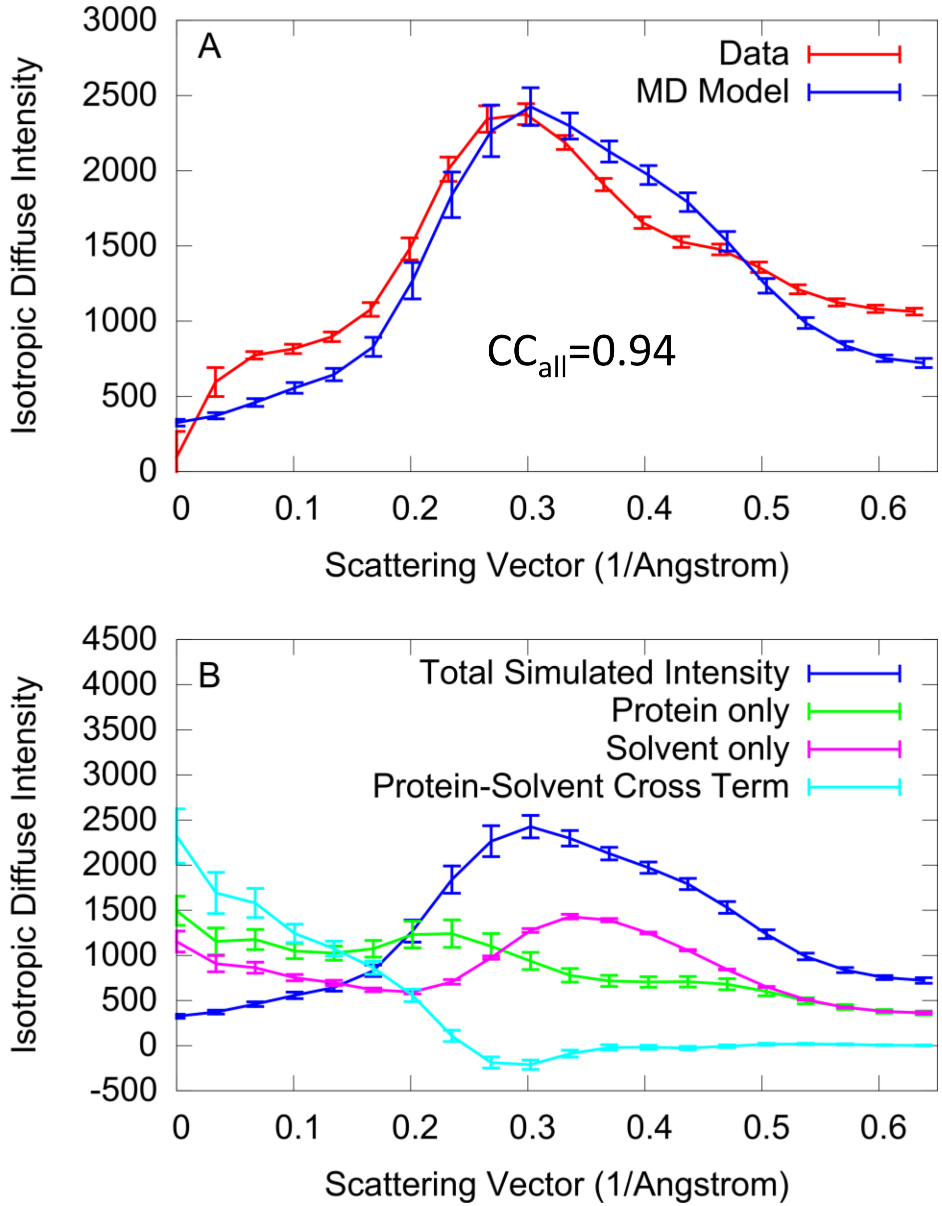
Clarage et al, *PNAS* 1995



Meinhold & Smith, *Biophys J* 2005

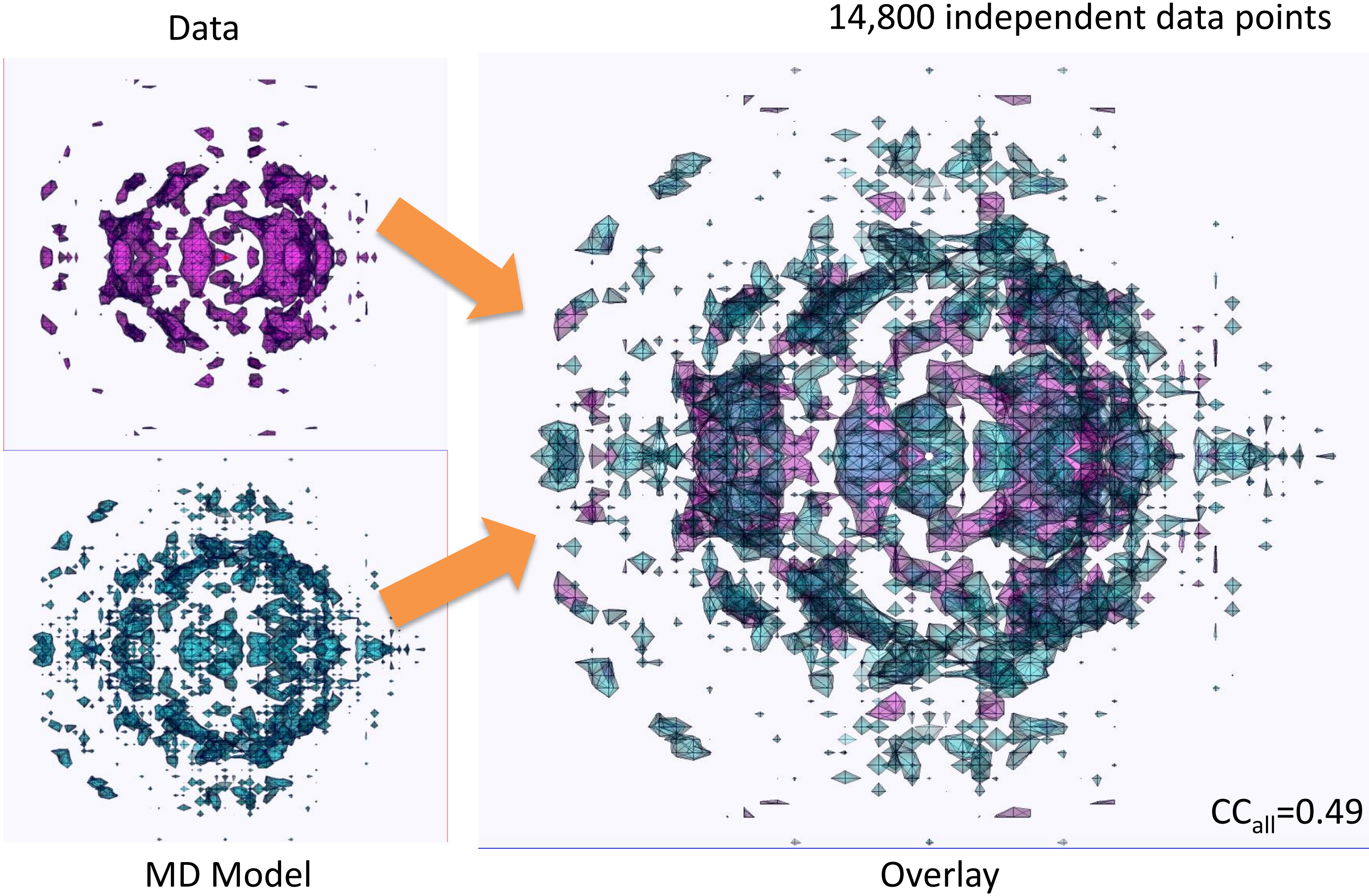


Wall et al, *PNAS* 2014



A
Data
MD Model
CC$_{all}$=0.94
Isotropic Diffuse Intensity
Scattering Vector (1/Angstrom)
B
Total Simulated Intensity
Protein only
Solvent only
Protein-Solvent Cross Term
Isotropic Diffuse Intensity
Scattering Vector (1/Angstrom)

14,800 independent data points

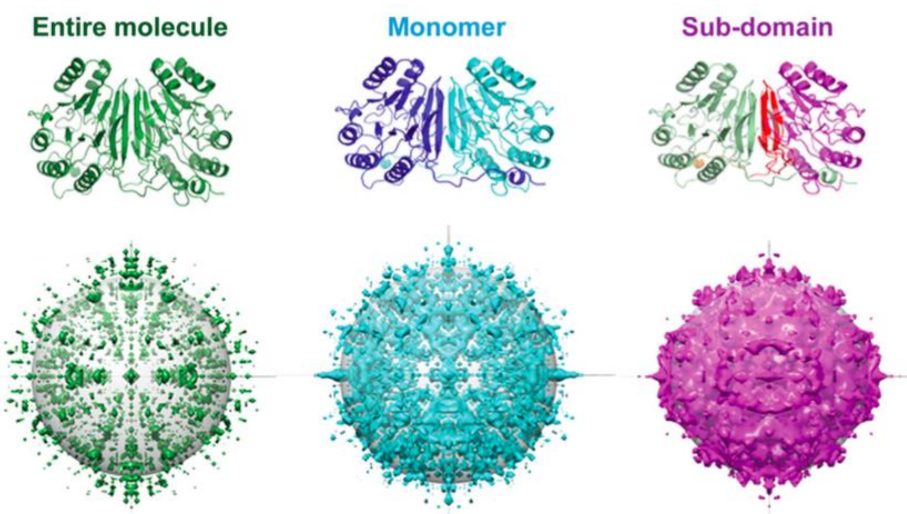


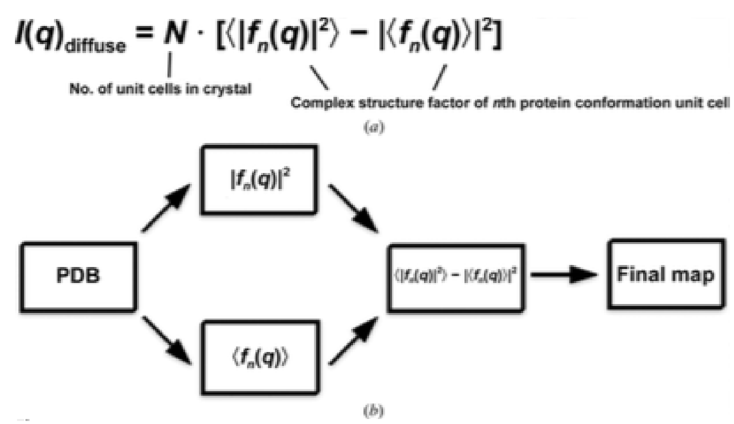
Overlay

Predicting X-ray diffuse scattering from translation–libration–screw structural ensembles

Andrew H. Van Benschoten,[a] Pavel V. Afonine,[b] Thomas C. Terwilliger,[c] Michael E. Wall,[d] Colin J. Jackson,[e] Nicholas K. Sauter,[b] Paul D. Adams,[b,f] Alexandre Urzhumtsev[g,h] and James S. Fraser[a*]

Acta Cryst. (2015). D**71**, 1657–1667





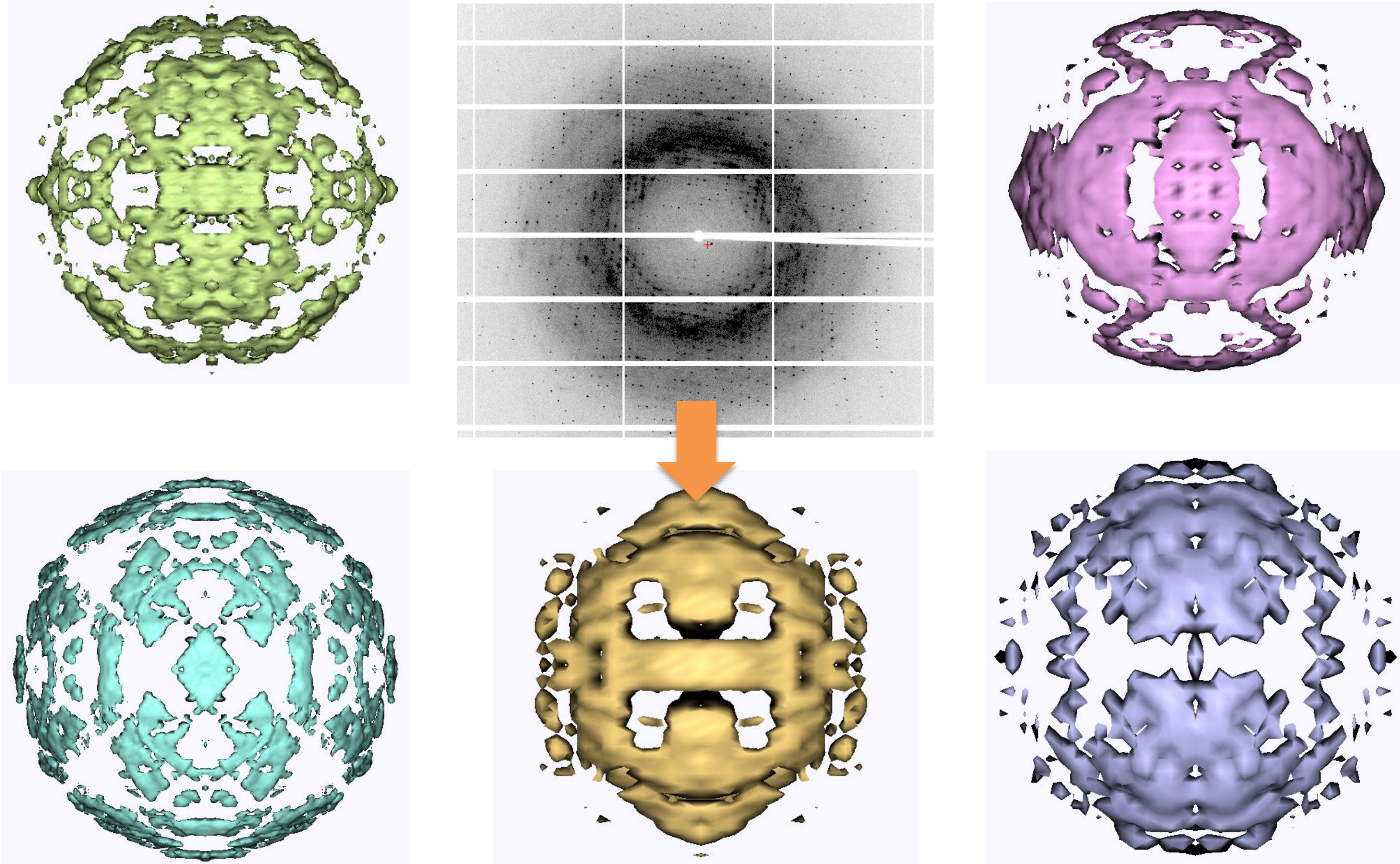


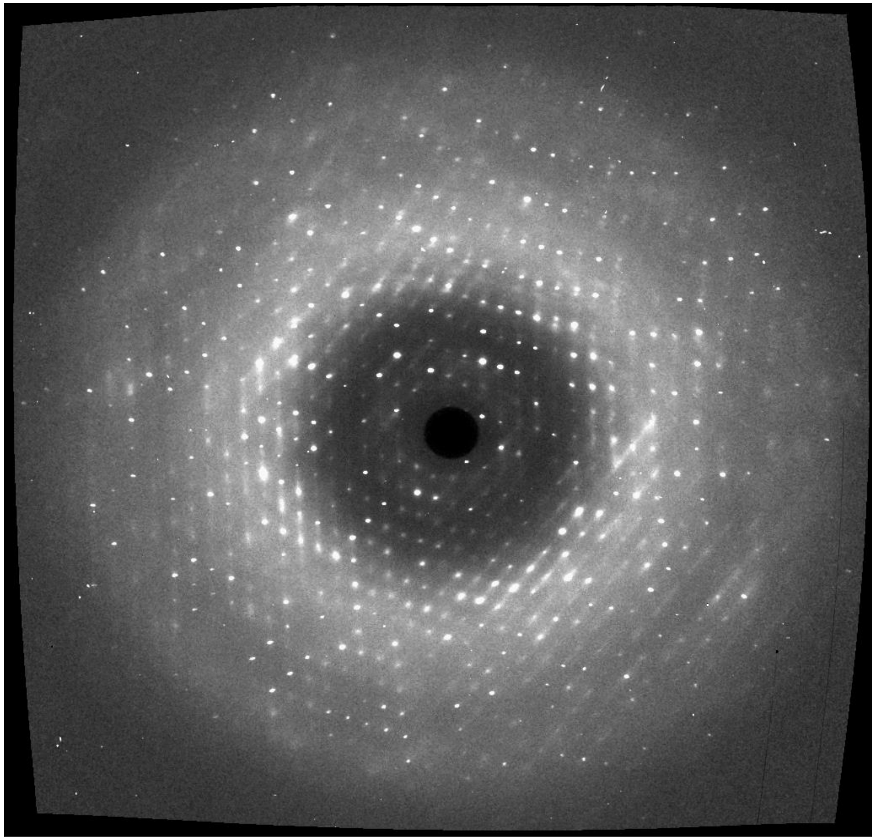
Image processing and scripts in Lunus (http://github.com/mewall/lunus)

DIALS indexing methods from Nicholas Sauter and Aaron Brewster, LBNL

Experiments of James Fraser and Others

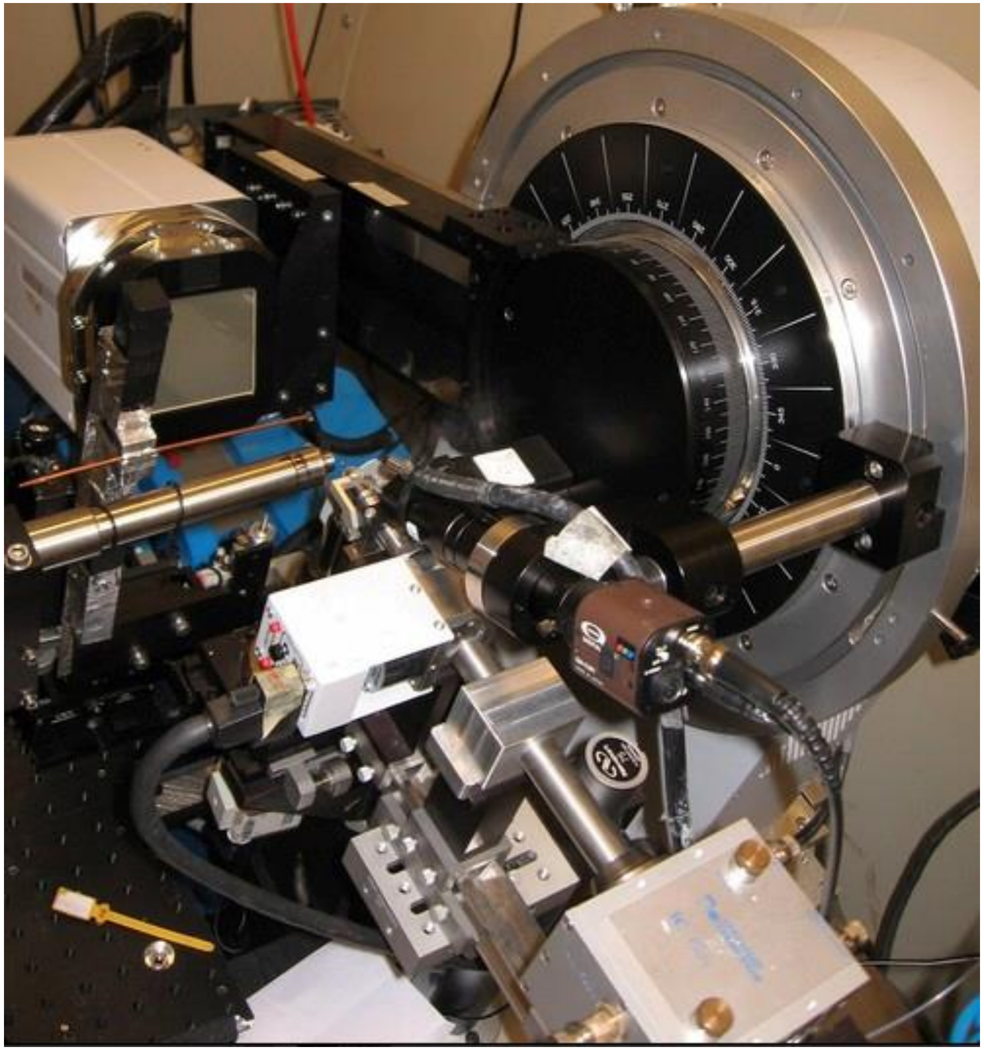
Raw Images

- No compression
- Simple layout of data
- Shared conventions for *r,c->x,y*
- Human-readable header
  - *i.e.* SMV or the like



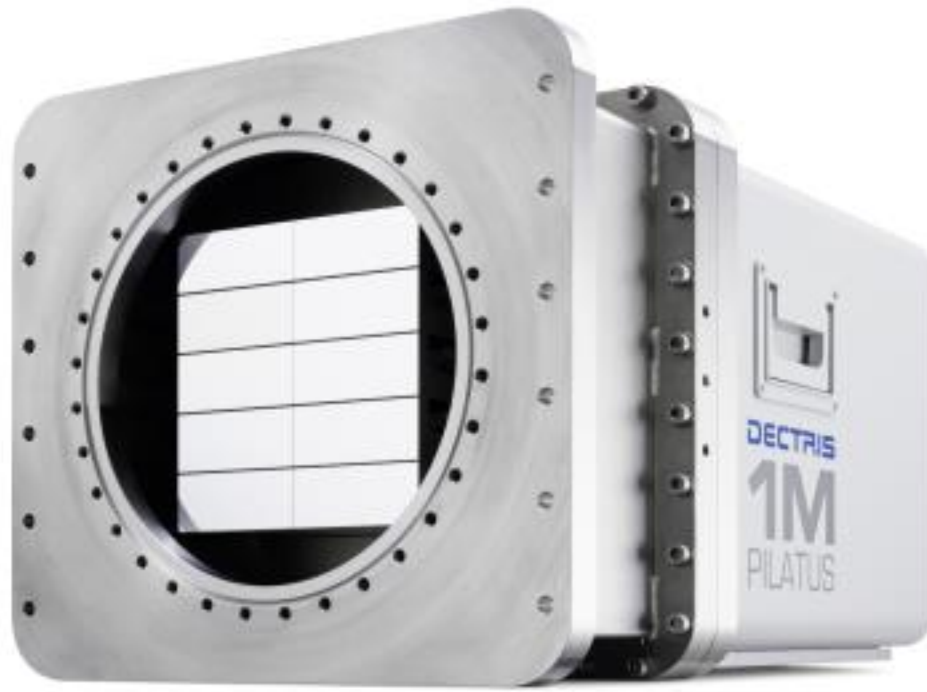
Beam Metadata

- Beam line
- Wavelength
  - Spectrum
- Polarization
  - Evidence
- Beam center
  - Evidence

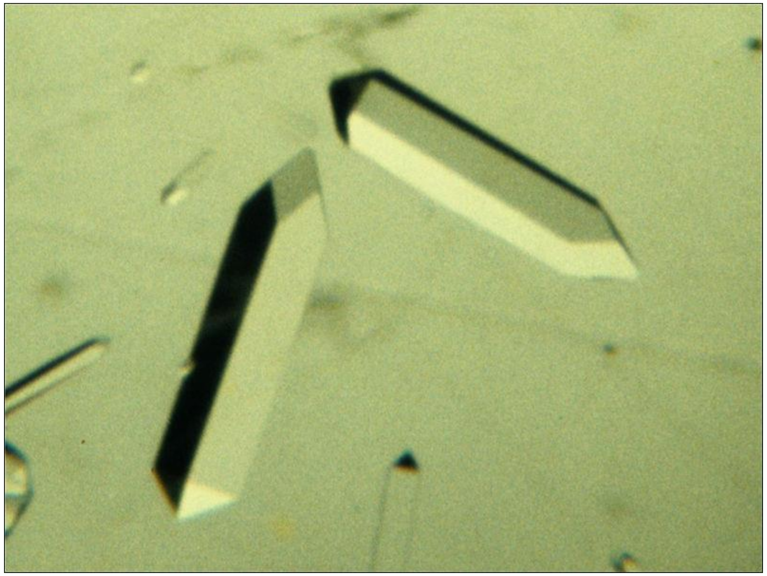


Detector Metadata

- Detector model
- Detailed operating mode
- Relation of ADU to X-ray counts
- Distance
  - Evidence
- Detector face rotation
  - Evidence
- Pixel size



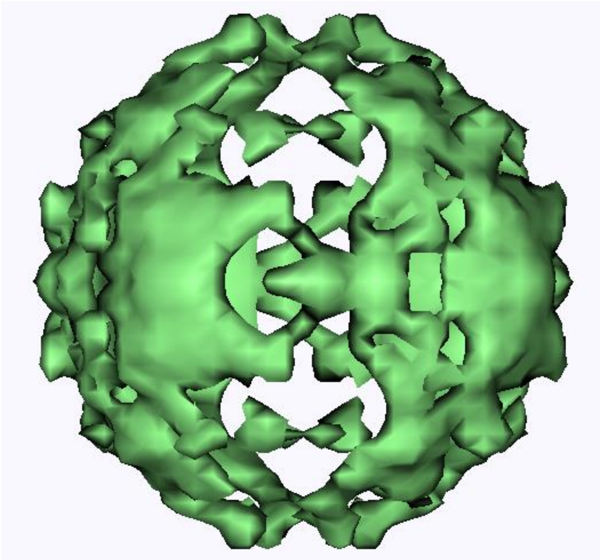
Crystal Metadata



- Space group
  - Evidence
- Unit cell
  - Evidence
- Chemical contents
- Light microscopy image for each exposure
  - Distinguish crystal from other scattering sources
  - Tomography model of specimen

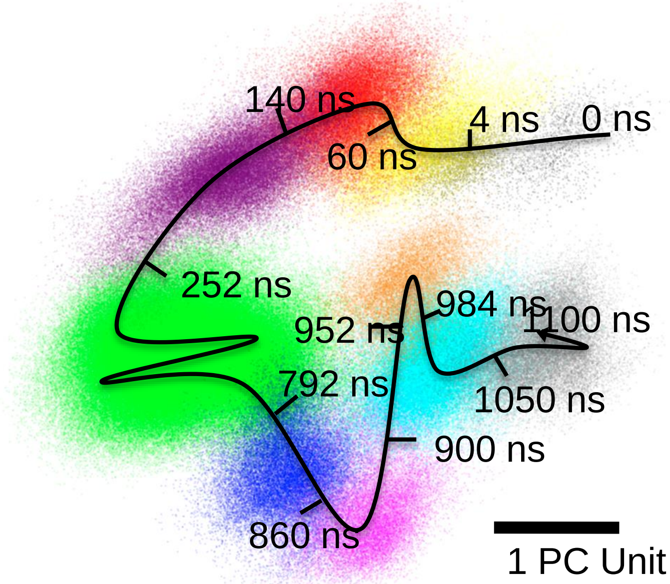
Integrated Diffuse Data Deposition

- *D*(*hkl*)
  - Fractional *hkl* possible
- Image processing parameters
  - Beam polarization
  - Solid-angle normalization
  - Bragg peak filtering
- Scale factors
- Frame-by-frame indexing information
- Flexible with respect to future needs for combined integration of Bragg and diffuse data

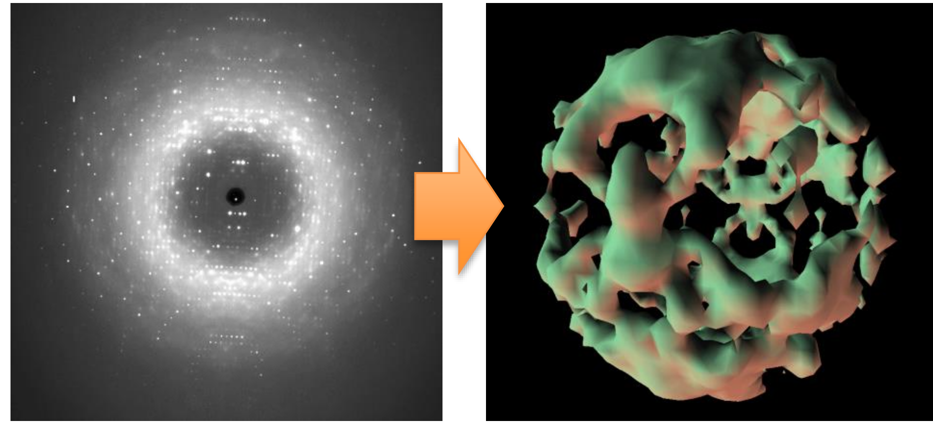


Diffuse Scattering Model Deposition

- Dynamical parameter values
  - Displacement correlations
  - Displacement amplitudes
  - Dispersion relation
- MD trajectories (large!)
- Calculated diffuse intensities



Acknowledgments



- Rice
  - George Phillips, Jr.
  - James Clarage (now at St Thomas)
- Cornell
  - Sol Gruner (formerly at Princeton)
  - Steven Ealick
  - CHESS staff
- FSU
  - Donald Caspar
- UCSF
  - James Fraser
  - Andrew Vanbenschoten
- LBNL
  - Paul Adams
  - Nicholas Sauter
  - Aaron Brewster
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  - Tom Terwilliger
- Global Phasing
  - Gérard Bricogne
- Funding
  - NSF, Welch Foundation, Keck Foundation, LANL LDRD
- ECM attendance
  - John Helliwell
  - Brian McMahon

Further Reading

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