Multiwavelength anomalous diffraction at high x-ray intensity

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HELMHOLTZ ASSOCIATION

Center for Free-Electron Laser Science
CFEL is a scientific cooperation of the three organizations:
DESY – Max Planck Society – University of Hamburg

Overview

> Why XFEL for nanocrystallography?

> Phase problem

> Electronic damage to heavy atoms

> MAD with XFEL: generalized Karle-Hendrickson equation

> MAD experiment at LCLS

> Conclusion

Acknowledgment

CFEL Theory Division

Robin Santra

CFEL Coherent Imaging Division

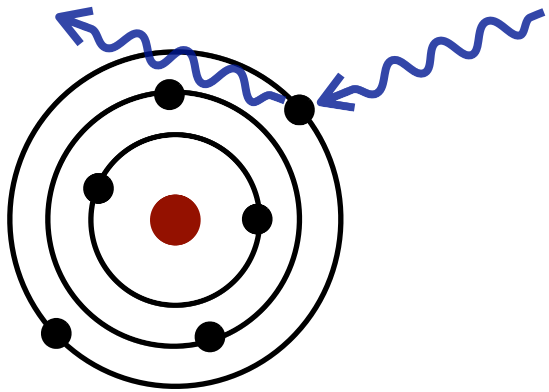
Henry Chapman

X-ray scattering

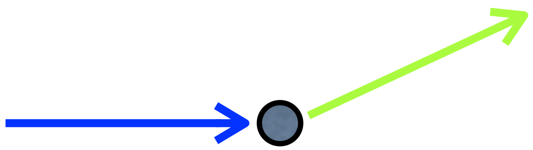
- Elastic x-ray scattering form factor

$$f^0(\mathbf{Q}) = \int d^3r \; \rho(\mathbf{r}) \; e^{i\mathbf{Q}\cdot\mathbf{r}}$$

$$\frac{d\sigma(\mathbf{Q})}{d\Omega} = \left(\frac{d\sigma}{d\Omega}\right)_T \left|f^0(\mathbf{Q})\right|^2$$

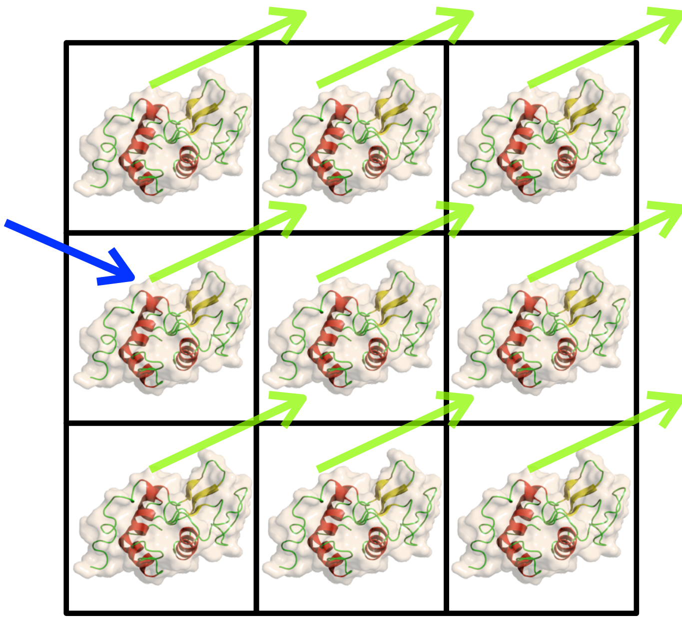


- Carbon at synchrotron radiation: 12 keV, 10^6 photons on 10μm × 10μm

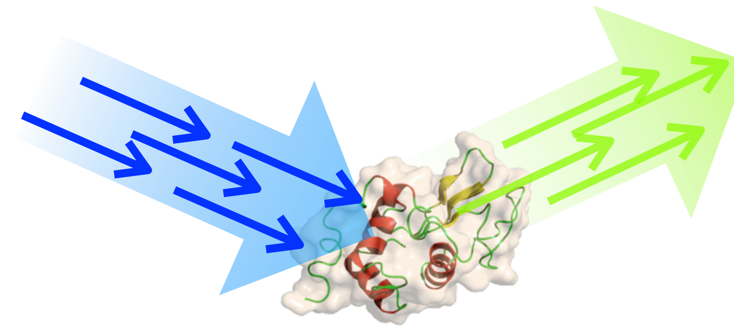


scattering
probability ~ 10^{-12}

Why X-ray free-electron laser



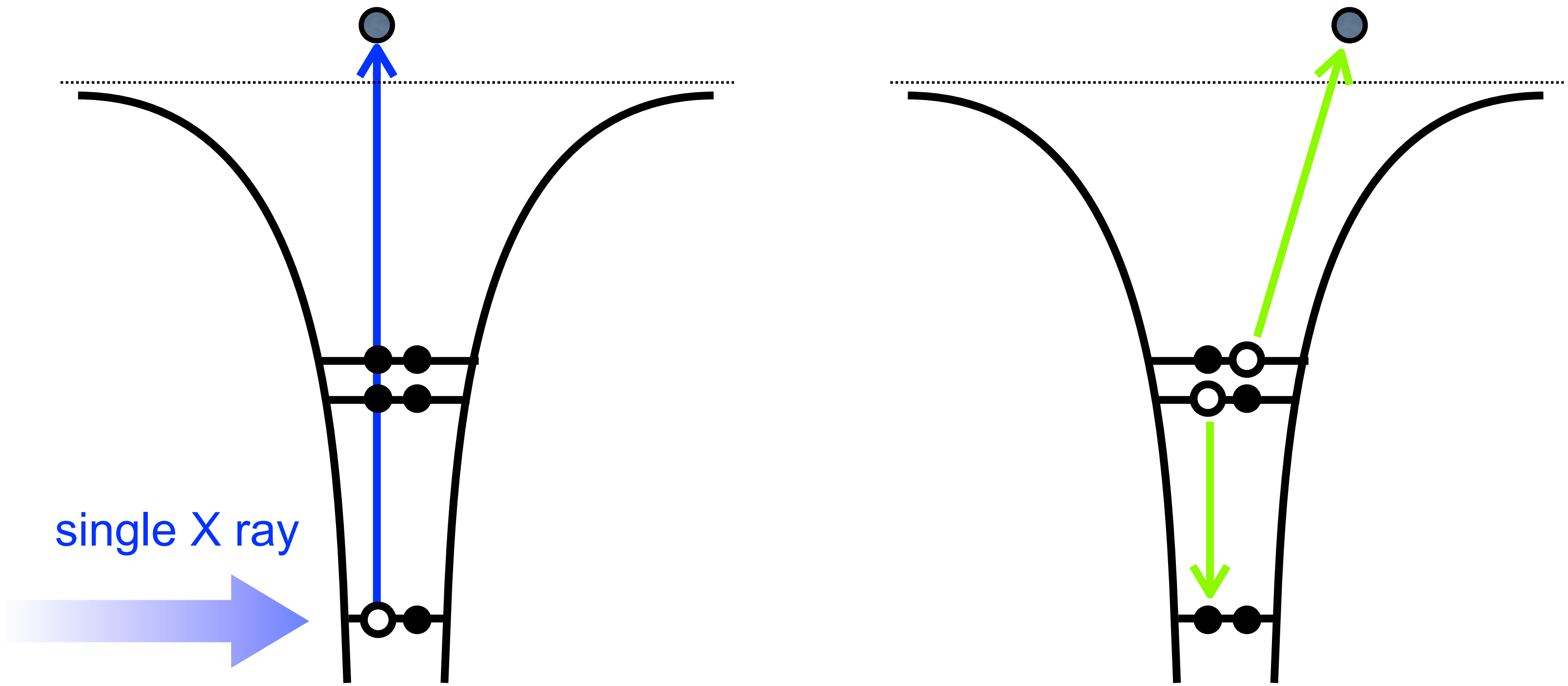
~10^8 molecules in
a µm-sized crystal



high x-ray fluence from XFEL
(×10^8~10^{10} more than
synchrotron radiation)

Typically $\sigma_{absorption} > \sigma_{scattering}$

Photoabsorption by X-rays



photoionization

$C \rightarrow C^{*+} + e^{-}$

Auger decay

$C^{*+} \rightarrow C^{++} + e^{-}$

XFEL: multiphoton multiple ionization expected!

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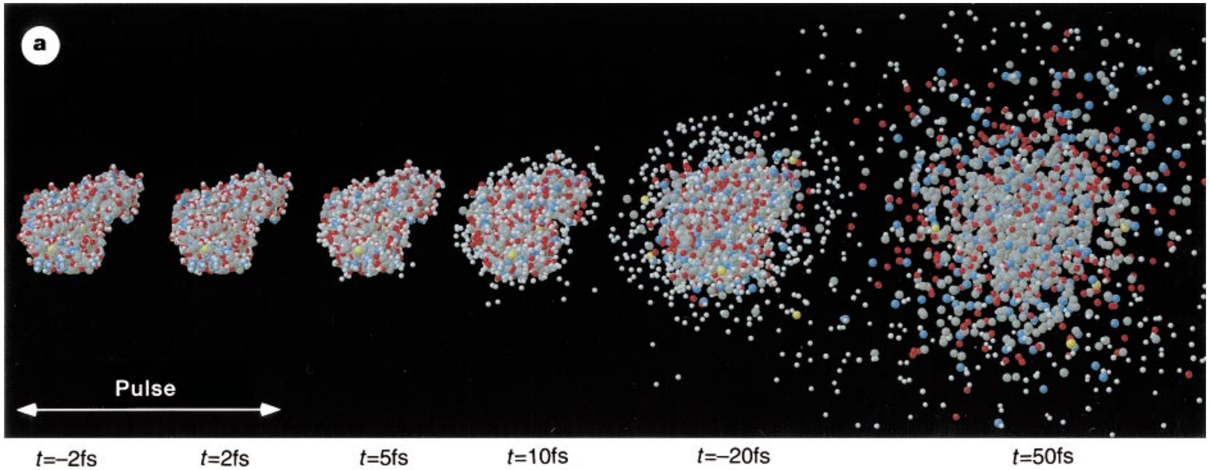
Radiation damage by XFEL

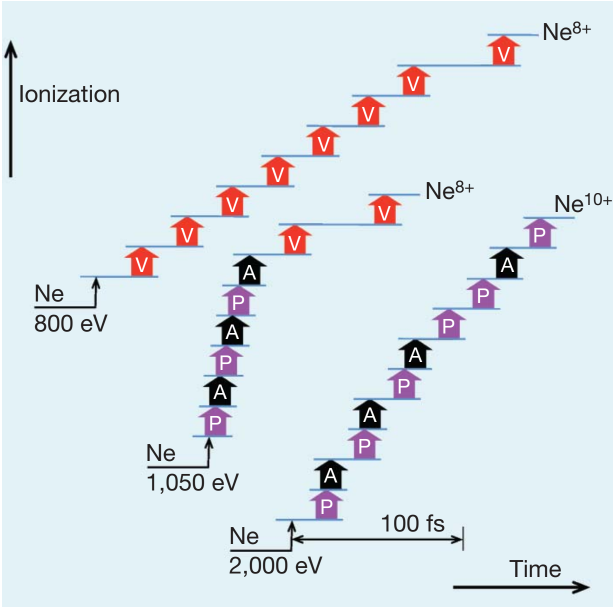
Coulomb explosion (nuclear damage)



Neutze *et al.*, *Nature* **406**, 752 (2000).

Diffraction before destruction

Electronic damage

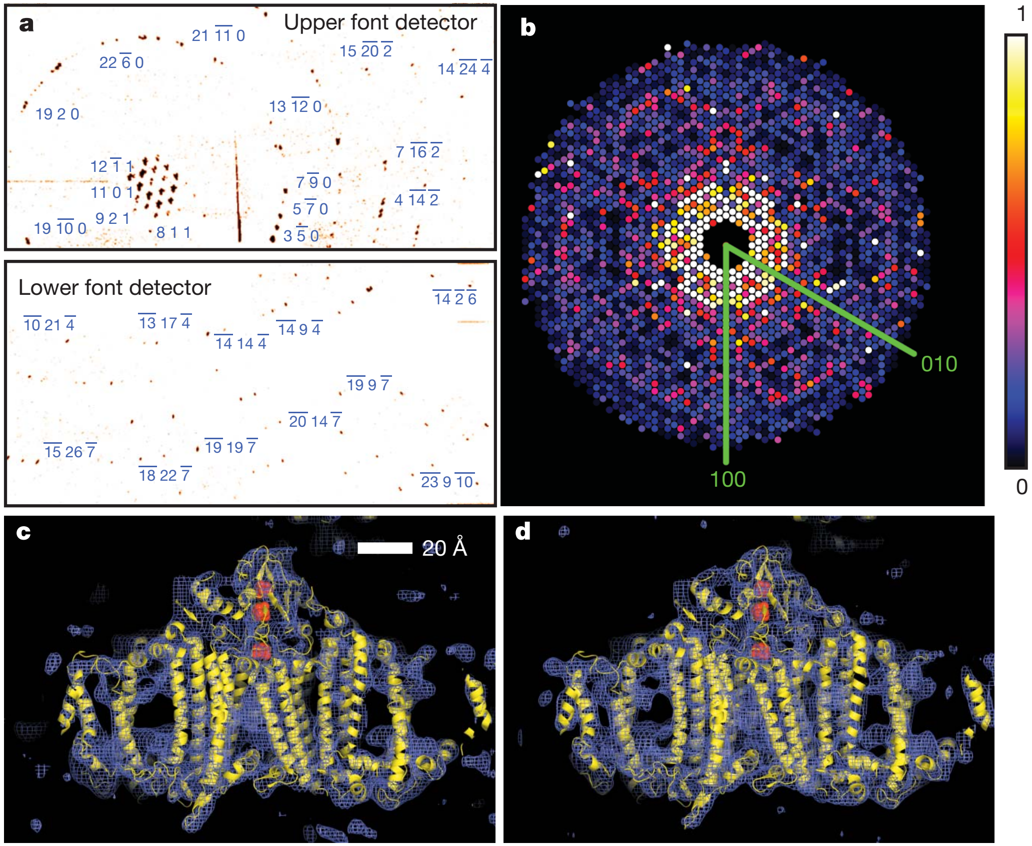


Young *et al.*, *Nature* **466**, 56 (2010).

Diffraction during ionization

Femtosecond X-ray nanocrystallography

- Growing high-quality crystals is one of major bottlenecks in x-ray crystallography.
- *Ultraintense* and *ultrafast* pulses from XFEL
- Enough signals from *nano-sized crystals* and single molecules
- Single-shot molecular imaging: revolutionary impact on structural biology



Chapman *et al.*, *Nature* **470**, 73 (2011).

- Photosystem I crystal size: 200 nm to 2 µm
- fluence: 10^{12} photons / 7×7 µm^2
- pulse duration: 10, 70, and 200 fs

Structural biology with XFEL

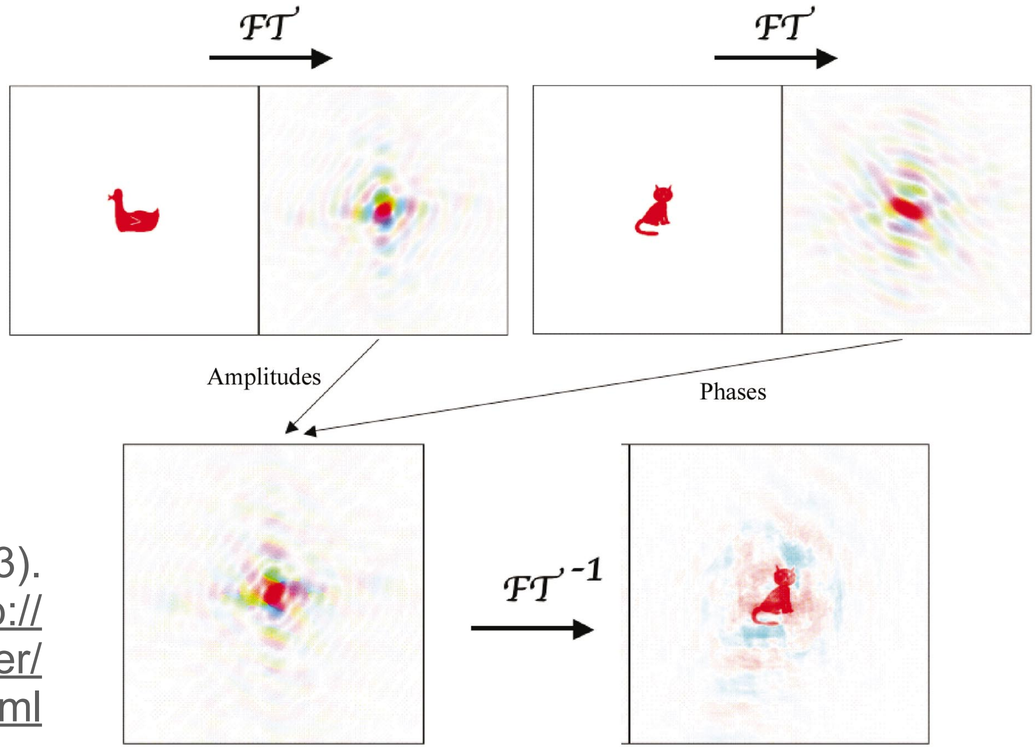
- Recent experiments
  - Chapman *et al.*, *Nature* **470**, 73 (2011).
  - Seibert *et al.*, *Nature* **470**, 78 (2011).
  - Barty *et al.*, *Nature Photon.* **6**, 35 (2012).
  - Boutet *et al.*, *Science* **337**, 362 (2012).
  - Koopmann *et al.*, *Nature Meth.* **9**, 259 (2012).
  - Johansson *et al.*, *Nature Meth.* **9**, 263 (2012).
- Reviews
  - Gaffney & Chapman, *Science* **316**, 1444 (2007).
  - Chapman & Nugent, *Nature Photon.* **4**, 833 (2010).
  - Mancuso, Yefanov & Vartanyants, *J. Biotechnol.* **149**, 229 (2010).
  - Schlichting & Miao, *Curr. Opin. Struct. Biol.* **22**, 613 (2012).
  - Neutze & Moffat, *Curr. Opin. Struct. Biol.* **22**, 651 (2012).

Phase problem

- Phase problem: a fundamental obstacle in constructing an electronic density map from x-ray diffraction

$$f^0(\mathbf{Q}) = \int d^3r\ \rho(\mathbf{r})\ e^{i\mathbf{Q}\cdot\mathbf{r}} = |f^0(\mathbf{Q})|\ e^{i\phi^0(\mathbf{Q})}$$

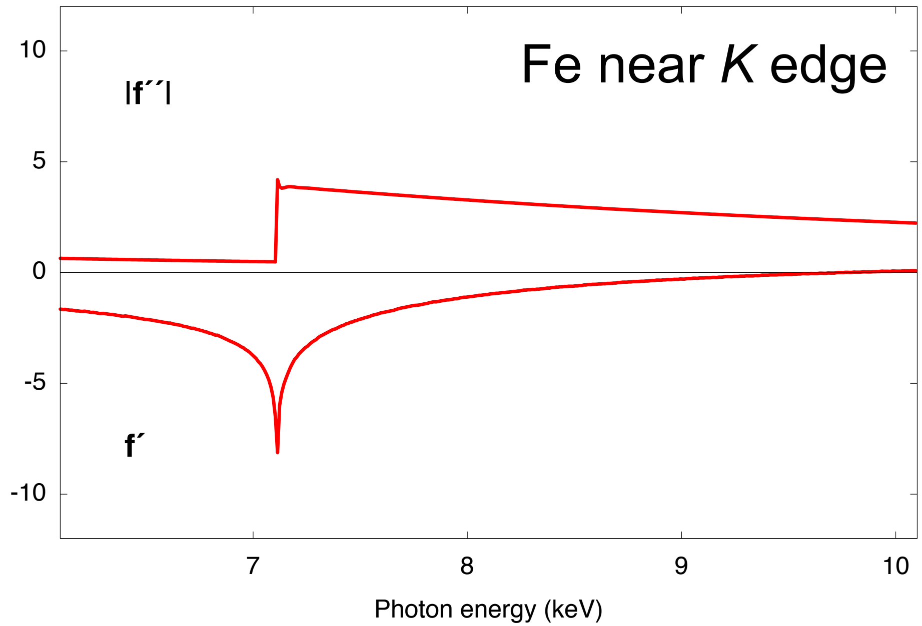
- Phases are essential for structural determination, but they are lost in measurement.



Taylor, *Acta Cryst.* **D59**, 1881 (2003).
Kevin Cowtan's Book of Fourier: http://www.ysbl.york.ac.uk/~cowtan/fourier/fourier.html

Multiwavelength Anomalous Diffraction

- Dispersion correction: $f(\mathbf{Q},\omega) = f^0(\mathbf{Q}) + f'(\omega) + if''(\omega)$

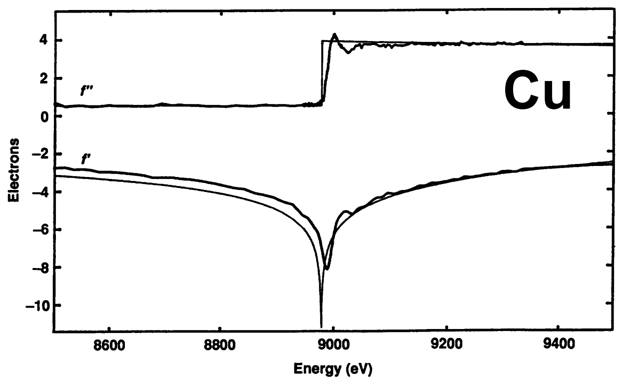


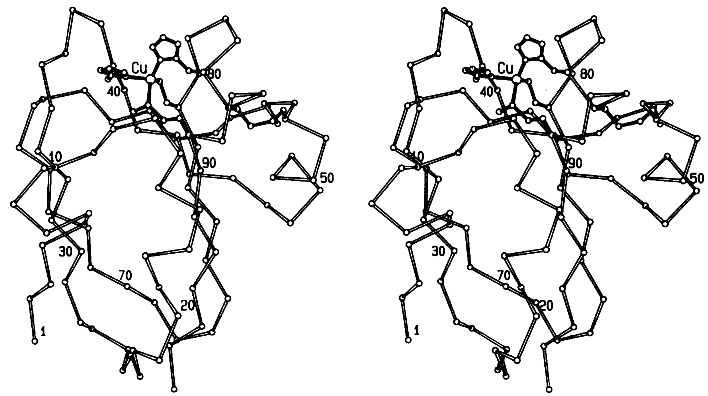
- MAD phasing: The Karle-Hendrickson equation provides a simple way for phasing from the contrast at two or more wavelengths.

Karle, *Int. J. Quant. Chem.* **18**, Suppl. S7, 357 (1980).
Hendrickson, *Trans. Am. Crystalgr. Assoc.* **21**, 11 (1985).

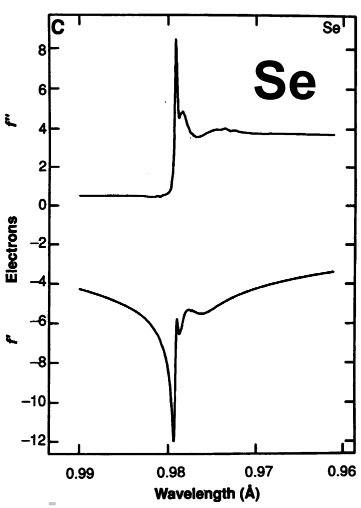
MAD with synchrotron radiation

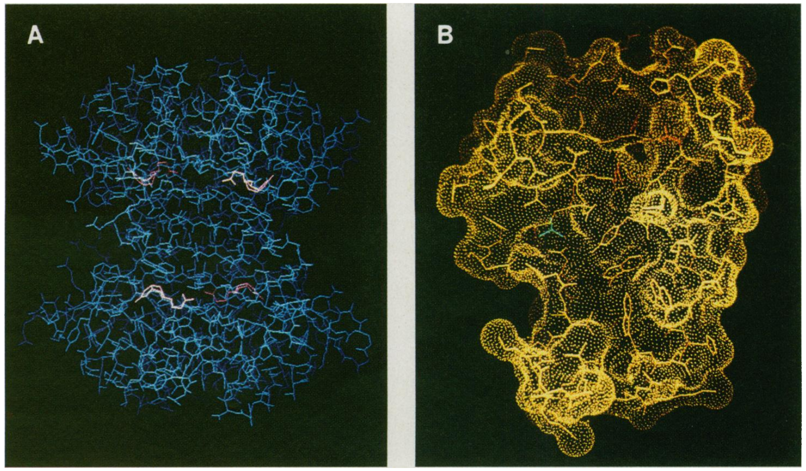
- MAD has been a well-established phasing method with synchrotron radiation since late 80's.





Cucumber basic blue protein
Guss *et al.*, *Science* **241**, 806 (1988).





A) Streptavidin
Hendrickson *et al.*, *PNAS* **86**, 2190 (1989).

B) Ribonuclease H
Yang *et al.*, *Science* **249**, 1398 (1990).

Picture taken from Hendrickson, *Science* **254**, 51 (1991).

New theory for new experiment

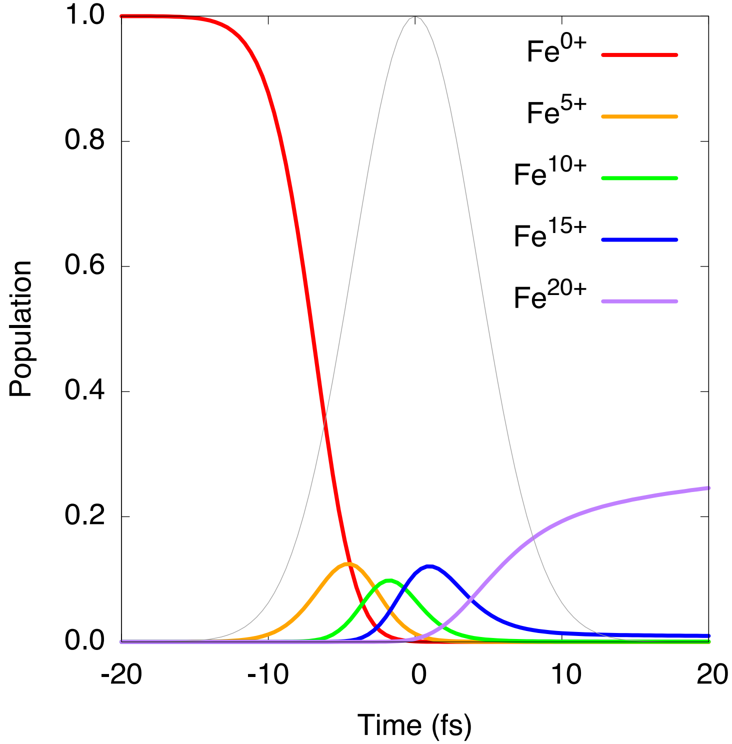
Can we use the MAD phasing with XFEL?

phase problem ➔ **MAD**

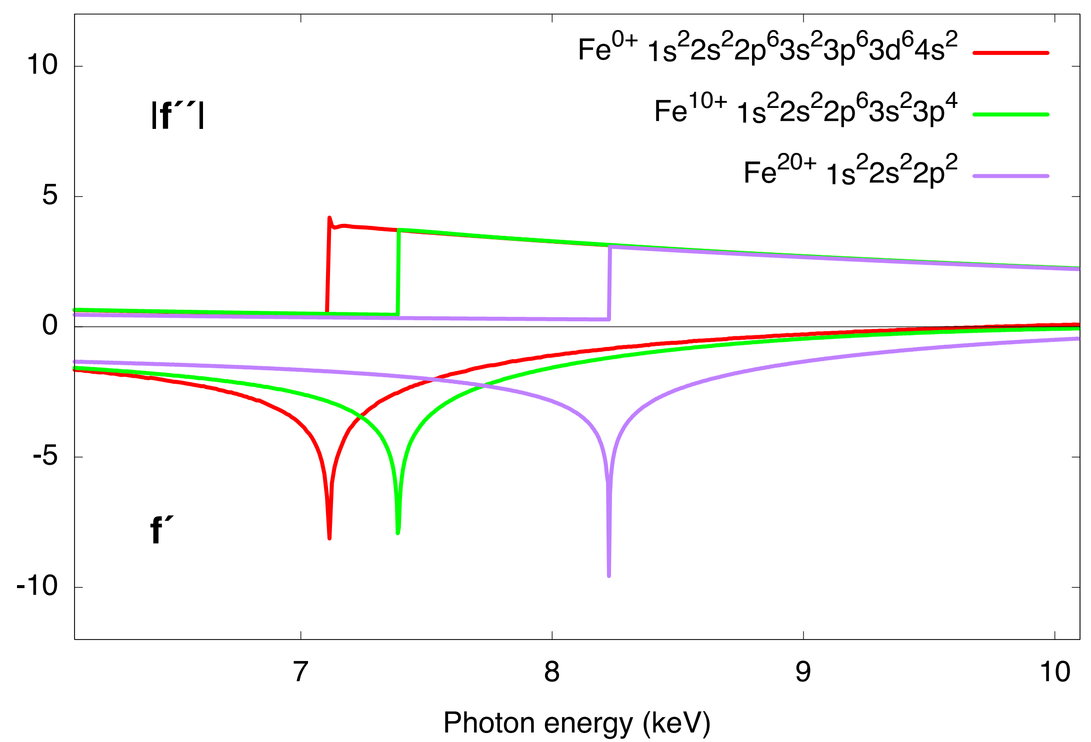
growing high-quality crystals ➔ **XFEL**

Electronic damage to heavy atoms

Population dynamics of Fe charge states during an XFEL pulse



Dispersion corrections of atomic form factors of Fe and its ions



(8 keV, 5×10^{12} photons/μm^2, 10 fs FWHM)

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

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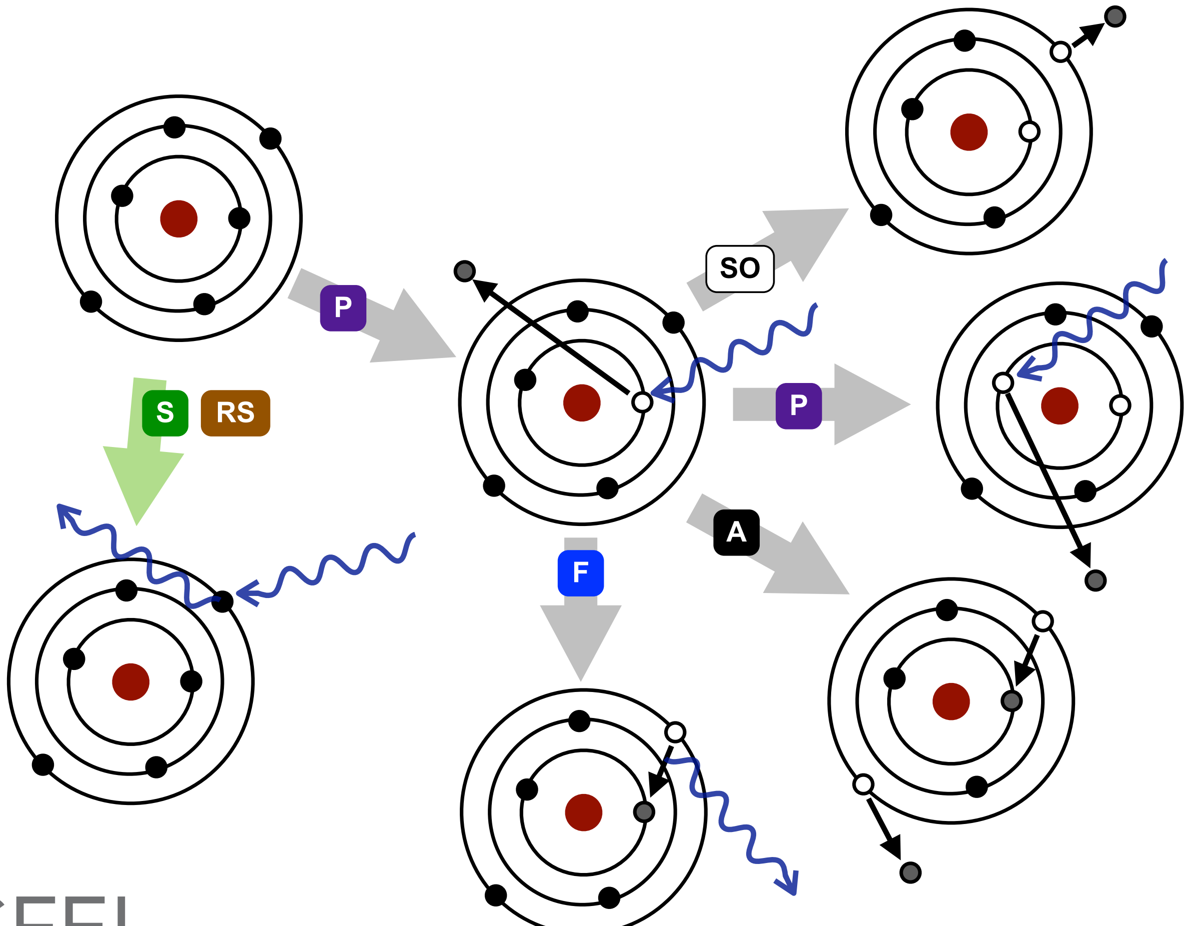
XATOM: x-ray and atomic physics toolkit

- X-ray-induced atomic processes for any given element and configuration
- Rate equation model to simulate ionization and relaxation dynamics



Son, Young & Santra, *Phys. Rev. A* **83**, 033402 (2011).

Prior speculations regarding MAD at XFEL

- Unavoidable electronic damage, especially to heavy atoms
- Dramatic change of anomalous scattering for high charge states
- Stochastic electronic damage to heavy atoms would destroy coherent scattering signals in nanocrystals
- MAD would not be an applicable route for phasing at XFEL...?

- We demonstrate the existence of a Karle-Hendrickson-type equation in the high-intensity regime.
- We show that MAD not only works, but also the extensive electronic rearrangements at high x-ray intensity provide a new path to phasing.

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

Scattering intensity including elec. damage

$$\frac{dI(\mathbf{Q},\omega)}{d\Omega} = \mathcal{F}C(\Omega)\int_{-\infty}^{\infty} dt\, g(t) \sum_{I} P_I(t) \left| F_P^0(\mathbf{Q}) + \sum_{j=1}^{N_H} f_{I_j}(\mathbf{Q},\omega) e^{i\mathbf{Q}\cdot\mathbf{R}_j} \right|^2$$

$$I = (I_1, I_2, \cdots I_{N_H}), \quad P_I(t) = \prod_{j=1}^{N_H} P_{I_j}(t)$$

$$f_{I_j}(\mathbf{Q},\omega) = f_{I_j}^0(\mathbf{Q}) + f_{I_j}'(\omega) + i f_{I_j}''(\omega)$$

- All changes among N_H heavy atoms are included.
- *P*: protein, *H*: heavy atoms; only heavy atoms scatter anomalously and undergo damage dynamics during an x-ray pulse.
- Heavy atoms are ionized independently.
- Only one species of heavy atoms is considered.

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

Generalized Karle-Hendrickson equation

$$\frac{dI(\mathbf{Q},\omega)}{d\Omega} = \mathcal{F}C(\Omega)\Big[\left|F_P^0(\mathbf{Q})\right|^2 + \left|F_H^0(\mathbf{Q})\right|^2\tilde{a}(\mathbf{Q},\omega) + \left|F_P^0(\mathbf{Q})\right|\left|F_H^0(\mathbf{Q})\right|b(\mathbf{Q},\omega)\cos\Delta\phi^0(\mathbf{Q}) + \left|F_P^0(\mathbf{Q})\right|\left|F_H^0(\mathbf{Q})\right|c(\mathbf{Q},\omega)\sin\Delta\phi^0(\mathbf{Q}) + N_H\left|f_H^0(\mathbf{Q})\right|^2\{a(\mathbf{Q},\omega)-\tilde{a}(\mathbf{Q},\omega)\}\Big]$$

- MAD coefficients: $a(\mathbf{Q},\omega)$, $b(\mathbf{Q},\omega)$, $c(\mathbf{Q},\omega)$, and $\tilde{a}(\mathbf{Q},\omega)$
  → measured or calculated with time evolution of config. populations
- 3 unknowns: $\left|F_P^0(\mathbf{Q})\right|$, $\left|F_H^0(\mathbf{Q})\right|$, $\Delta\phi^0(\mathbf{Q})$ $[=\phi_P^0(\mathbf{Q})-\phi_H^0(\mathbf{Q})]$
  → solvable with measurements at 3 different wavelengths.

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

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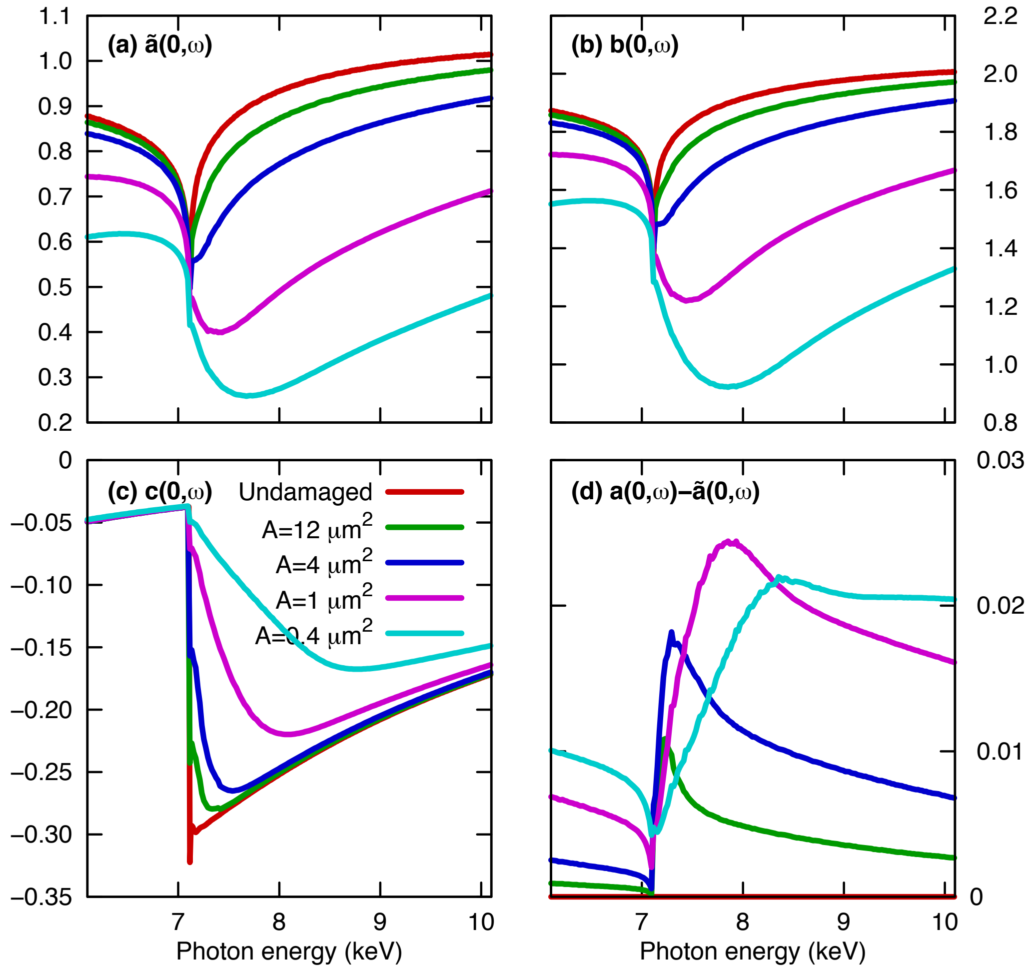
MAD coefficients

Fe in an x-ray pulse of 2×10[12] photons and 10 fs FWHM



- calculated by XATOM
- bleaching effect: minimum deepened and edge broadened
- **MAD works**: enhanced contrast at different wavelengths
- even easy to choose wavelengths

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

Alternative phasing method

- **SIR** (single isomorphic replacement): atomic replacement in sample preparation
- **RIP** (radiation-damage induced phasing): chemical rearrangement during the x-ray pulses
- **MAD** (multi-wavelength anomalous diffraction): $\Delta F_{\Delta\lambda}$
- **SAD** (single-wavelength anomalous diffraction): $\Delta F_{\pm}$

New phasing method: neither **SIR** nor **RIP**

Fluences rather than wavelengths: neither **MAD** nor **SAD**

Son, Chapman & Santra, *Phys. Rev. Lett.* **107**, 218102 (2011).

Huge collaboration around the world

- **CFEL Coherent Imaging, DESY, Germany**: Henry Chapman, Thomas White, Anton Barty, Kenneth Beyerlein, Karol Nass, Cornelius Gati, Daniel DePonte, Holger Fleckenstein, Richard Kirian, Mengning Liang, Richard Bean, Francesco Stellato, Lorenzo Galli, Carl Caleman, Oleksandr Yefanov, Chun Hong Yoon
- **CFEL Theory, DESY, Germany**: Robin Santra, Sang-Kil Son
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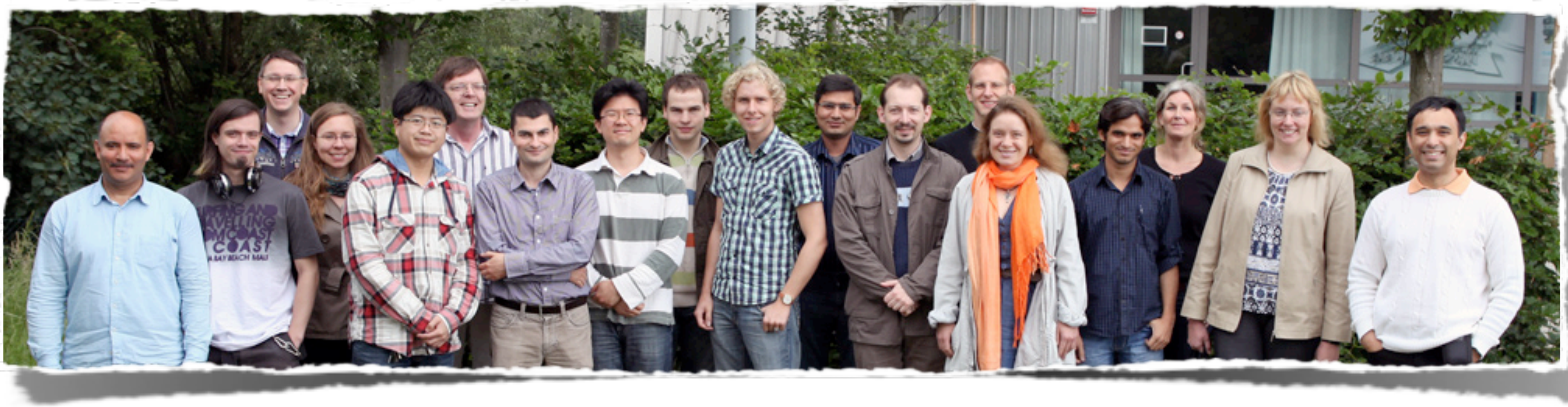
- **Univ. of Auckland, New Zealand**: Peter Metcalf
- **Univ. of Melbourne, Australia**: Andrew Martin

Conclusion

- MAD phasing method in extreme conditions of ionizing radiations
- Combination of ultrafast electronic dynamics at the atomic level and imaging of macromolecules by intense x-ray pulses
- Existence of a generalized Karle-Hendrickson equation for the MAD method at high x-ray intensity
- Bleaching effect on the scattering strength to be beneficial to the phasing method
- A new opportunity for solving the phase problem in femtosecond nanocrystallography with XFELs

➔ A breakthrough in structural biology

Acknowledgment: CFEL Theory Division



Ab Initio X-ray Physics

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Chemical Dynamics

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Pankaj Kumar Mishra

Modeling of Complex Systems

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Dr. Nikita Medvedev
Dr. Robert Thiele

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Take-home message

XFEL goes MAD.