High-intensity phasing with x-ray free-electron lasers

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Collaboration

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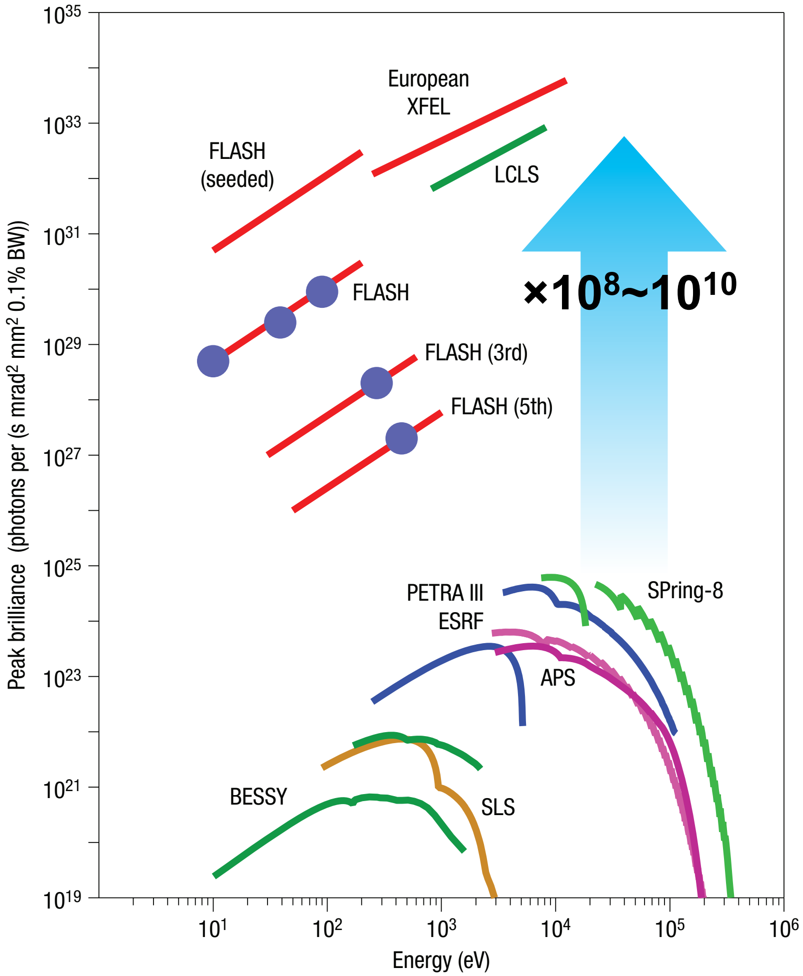
What is XFEL?

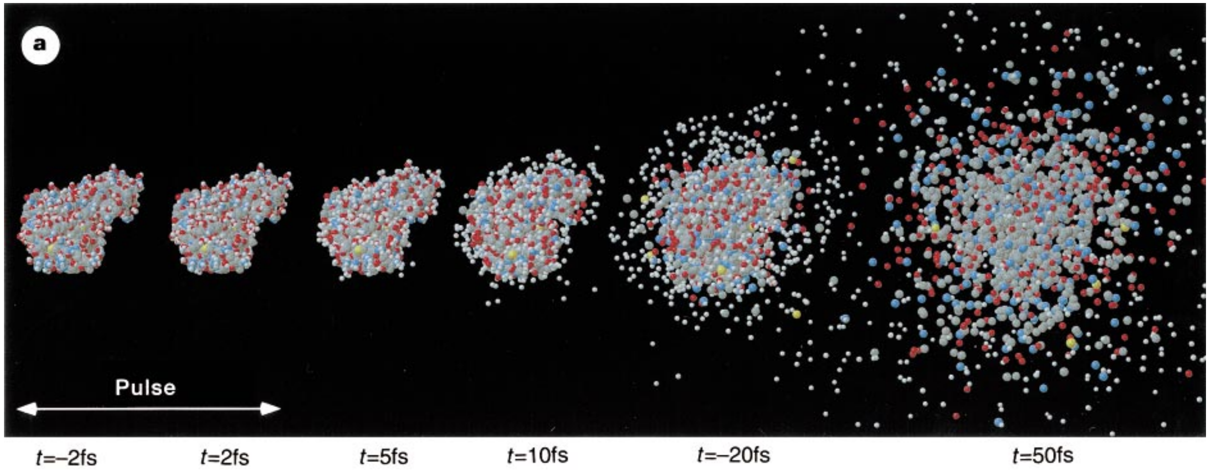
- XFEL: X-ray Free-Electron Laser
- *Ultraintense*
  - fluence: ~10^{13} photons/μm^2
  - peak intensity: ~10^{18} W/cm^2
- *Ultrafast*
  - pulse duration: femtoseconds or sub-fs
- Where?
  - FLASH at DESY, Germany (2004)
  - LCLS at SLAC, USA (2009)
  - SACLA at RIKEN, Japan (2011)
  - PAL XFEL at Pohang, Korea
  - European XFEL, Germany



Ackermann *et al.*, *Nature Photon.* **1**, 336 (2007).

Radiation damage by XFEL

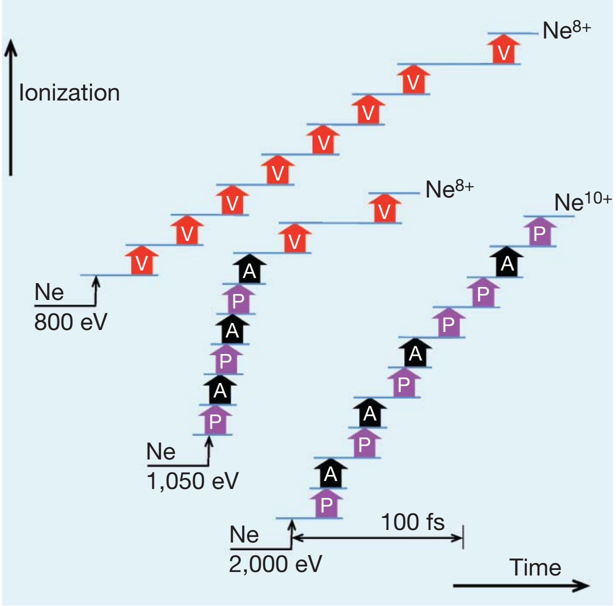
Coulomb explosion (nuclear damage)



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

Diffraction before destruction

Electronic damage

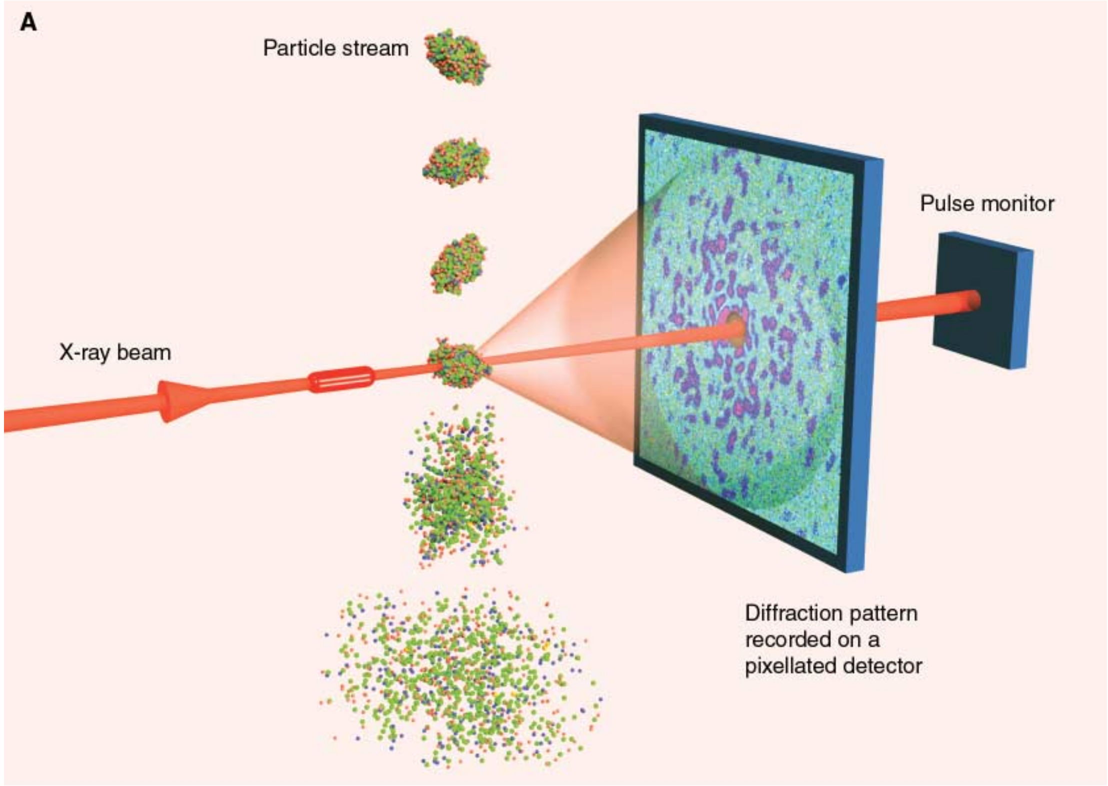


Young *et al.*, *Nature* **466**, 56 (2010).

Diffraction during ionization

Serial femtosecond crystallography (SFX)

- 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* or single molecules



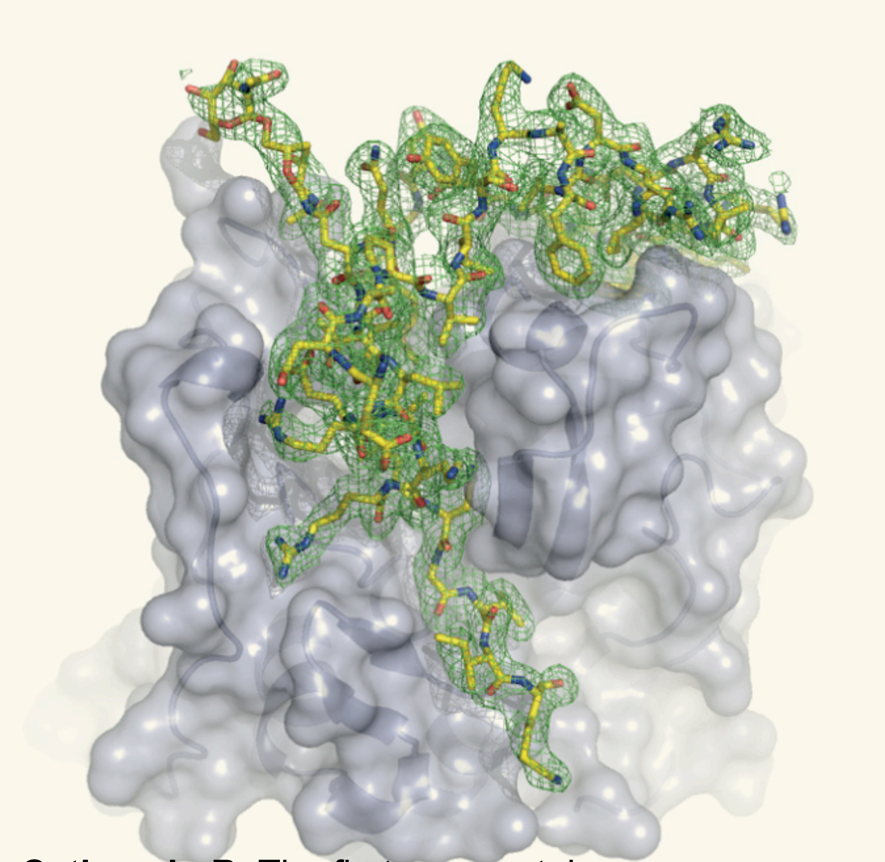
Gaffney & Chapman, *Science* **316**, 1444 (2007).

Phasing for XFEL experiments

- Femtosec. x-ray nanocrystallography: beyond proof-of-principle
- Mainly solved by molecular replacement

  e.g.) Redecke *et al.*, *Science* **339**, 227 (2013).
- SAD in the intermediate intensity regime (< the saturation fluence)

  Barends *et al.*, *Nature* **505**, 244 (2014).
- Need for *ab initio* phasing method at high x-ray intensity

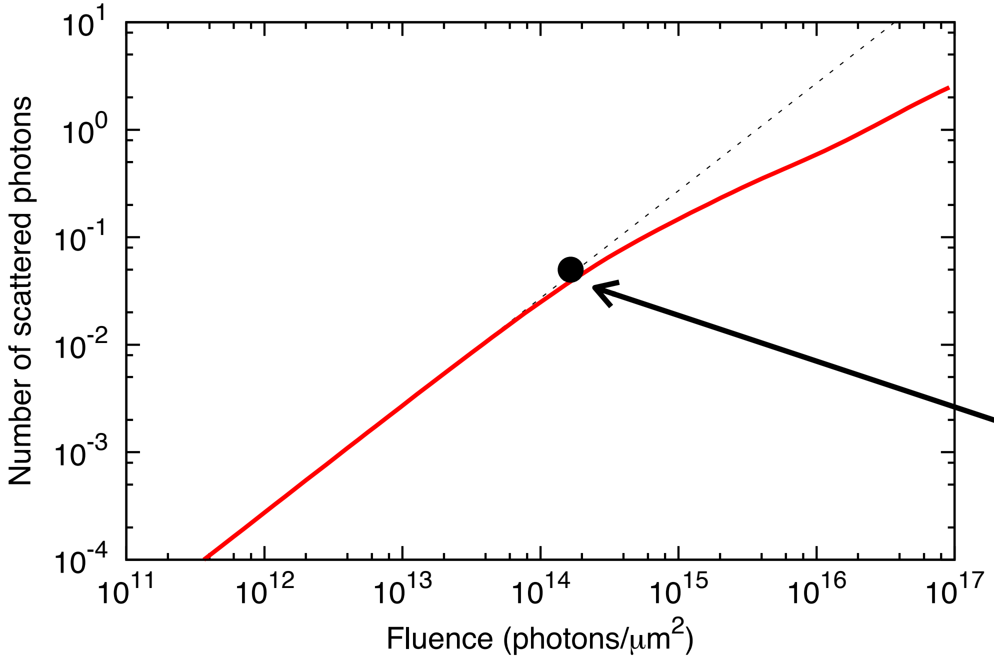


Cathepsin B: The first new protein structure determined by using XFEL

Picture taken from *Nature* **505**, 620 (2014).

What happens at high x-ray intensity?

- Fluence (photons/unit area) to saturate one-photon absorption



C @ 8 keV

σ_{abs} = 0.084 kbarns

⬇

prob. = $\sigma_{abs} \times F \sim 1$

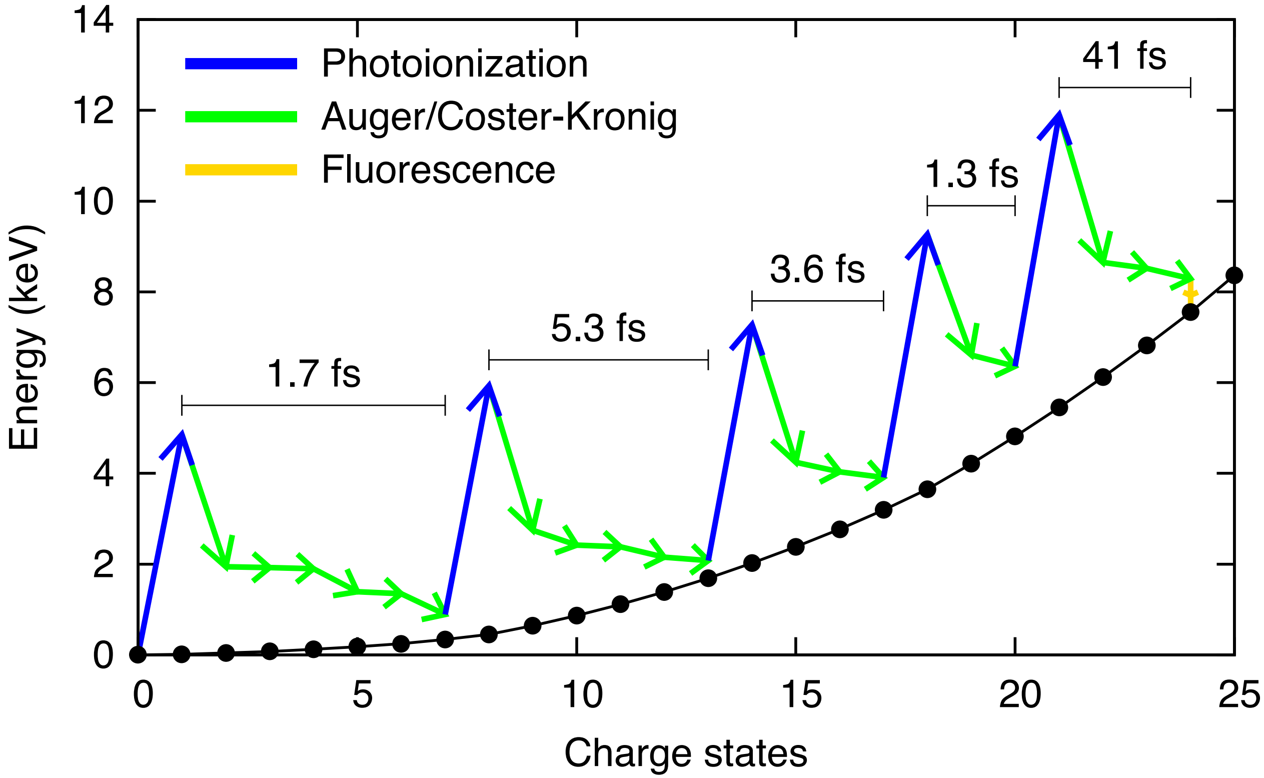
⬇

$F_{sat} = 1.2 \times 10^{14}$ ph/μm^2

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

- High x-ray intensity beyond one-photon absorption saturation
  - Synchrotron: at most one photon absorbed ➔ linear phenomena
  - XFEL: at least one photon absorbed ➔ nonlinear phenomena

Sequential multiphoton multiple ionization

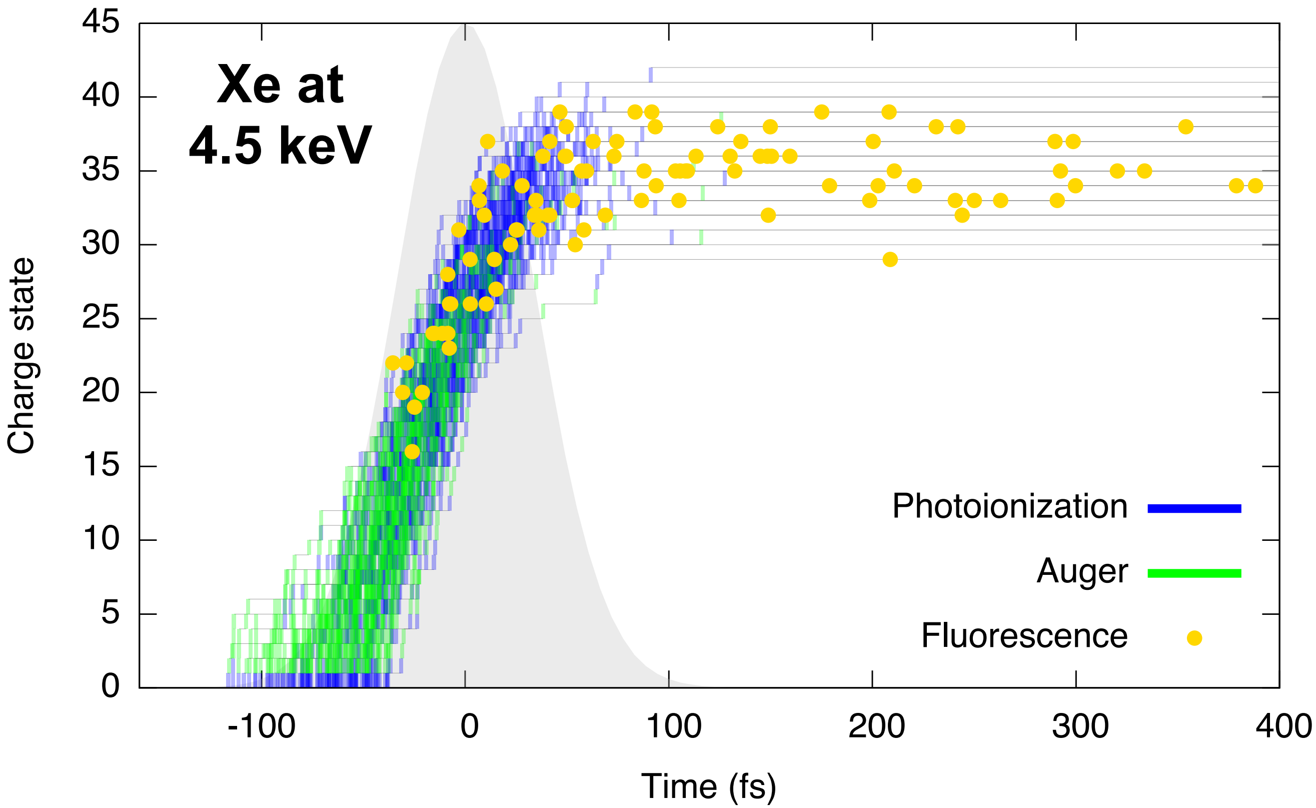


Xe @ 5.5 keV

Fukuzawa *et al.*, *Phys. Rev. Lett.* **110**, 173005 (2013).

- a sequence of photoionization, Auger decays, and fluorescences
- complicated multiphoton multiple ionization at high x-ray intensity

Complex inner-shell ionization dynamics

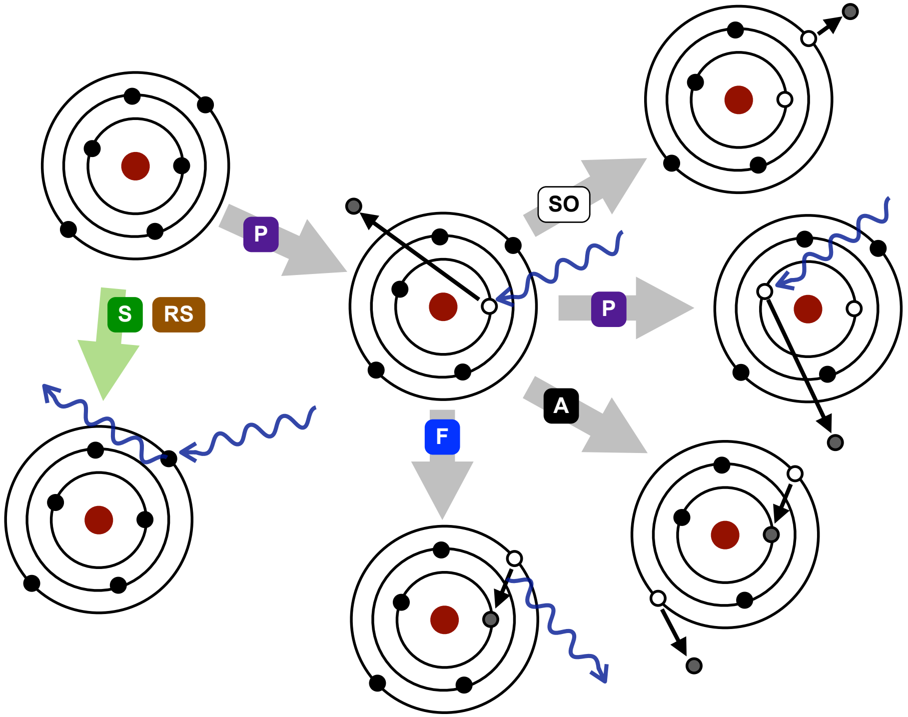


Son & Santra, *PRA* **85**, 063415 (2012).

- more than one million electronic states calculated
- more than 40 million x-ray-induced processes calculated
- conventional quantum chemistry codes not applicable

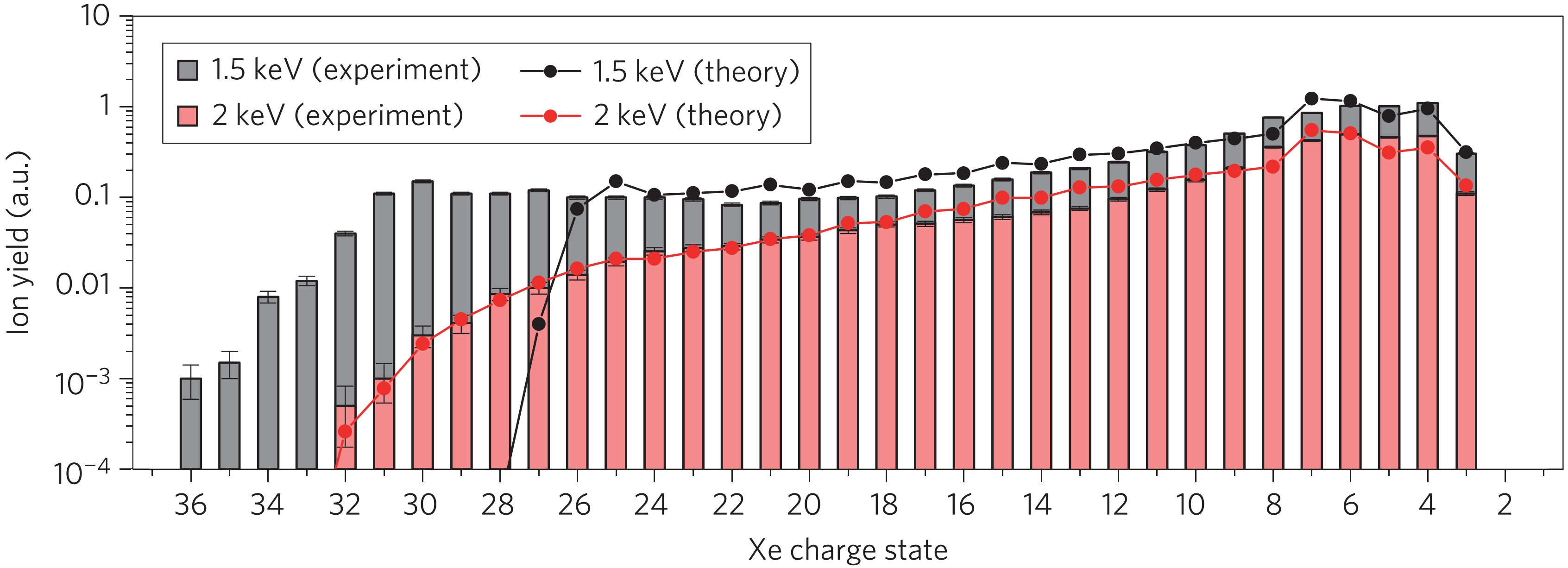
How to describe ionization dynamics?

- XATOM: describes dynamical behaviors of atoms interacting with XFEL pulses
- Uses the Hartree-Fock-Slater model
- Calculates all cross sections and rates of x-ray-induced processes for any given element / any given charge state / any given electronic configuration
- Solves coupled rate equations to simulate x-ray ionization dynamics



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

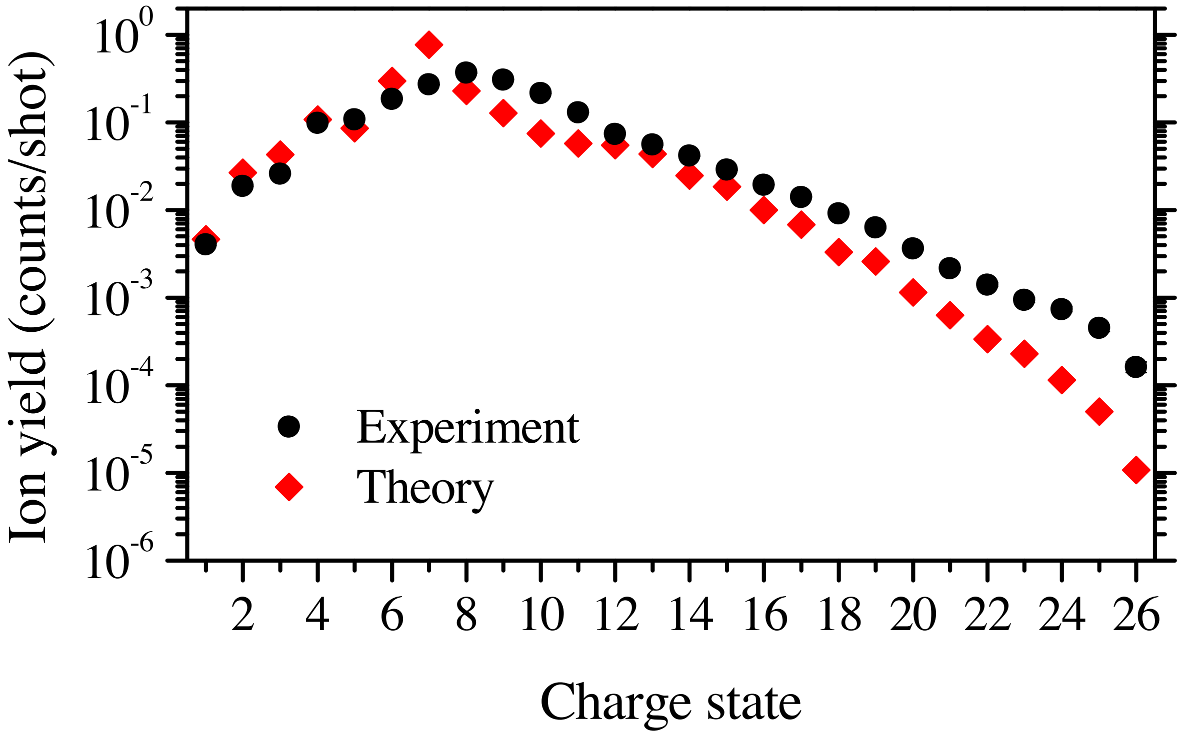
Xe at LCLS



Rudek *et al.*, *Nature Photon.* **6**, 858 (2012).

- Charge state distribution of Xe measured at LCLS
- At 2 keV: good agreement between experiment and theory
- At 1.5 keV: unprecedented high charge states (up to Xe^{36+}) in experiment
- Resonance-enabled ionization: may be suppressed by a narrow bandwidth

Xe at SACLA



Fukuzawa *et al.*, *Phys. Rev. Lett.* **110**, 173005 (2013).

- At 5.5 keV: deep inner-shell (*L*-shell) ionization dynamics
- Good agreement between experiment and theory
- Theoretical challenges: >20-million config. with >2-billion processes

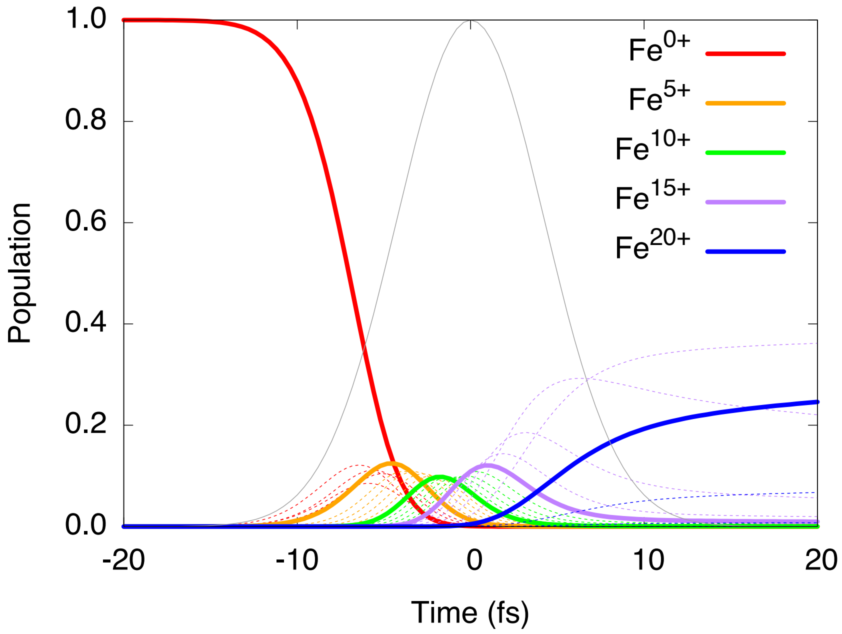
Electronic radiation damage

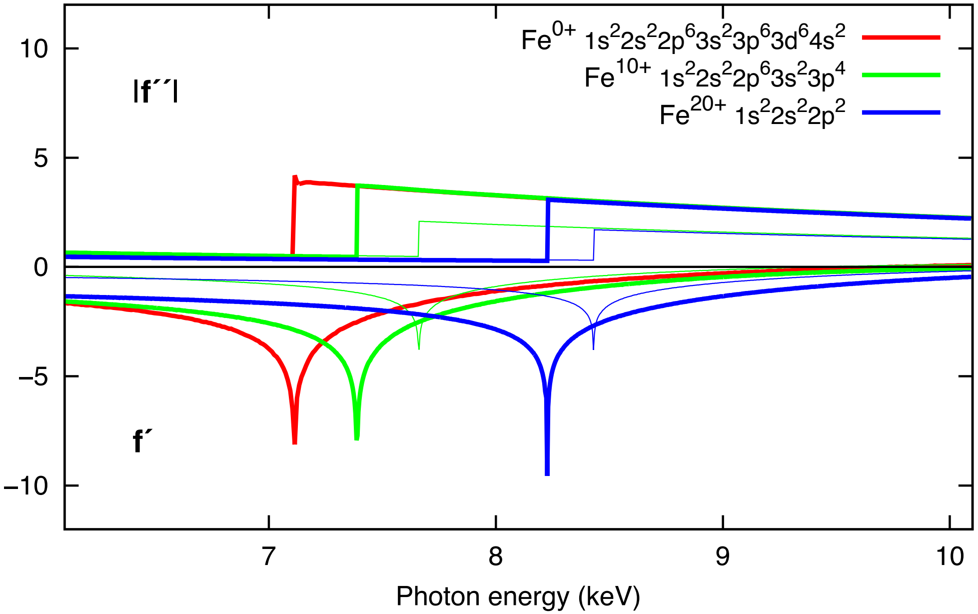
- Unavoidable at high x-ray intensity (time scale: ~femtoseconds)
- Can we reduce electronic radiation damage?
  - frustrated ionization: *higher* intensity, *less* ionization
  - seeded XFEL pulse: *narrower* bandwidth, *less* ionization
- Can we take benefits from electronic radiation damage?
  - understand ionization dynamics mechanism
  - heavy atoms at higher photon energies ➔ relevant for phasing
  - turn x-ray ionization into an advantage for phasing

Impact on anomalous scattering

- Extensive electronic rearrangements during one pulse
- Dramatic change of anomalous scattering for high charge states

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





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

Can we do MAD with XFELs?

- *Ab initio* phasing: MAD (multiwavelength anomalous diffraction)
- 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...?

Existence of a generalized Karle-Hendrickson equation
in the high-intensity regime

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

Scattering intensity including ionization

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

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

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

- All changes among N_H heavy atoms in a crystal are included.
- *P*: protein, *H*: heavy atoms; only heavy atoms scatter anomalously and undergo ionization 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

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

- MAD coefficients: $a(\mathbf{Q},\mathcal{F},\omega)$, $b(\mathbf{Q},\mathcal{F},\omega)$, $c(\mathbf{Q},\mathcal{F},\omega)$, and $\tilde{a}(\mathbf{Q},\mathcal{F},\omega)$

  → measured or calculated including electronic damage dynamics

- 3 unknowns: $\left|F_P^0(\mathbf{Q})\right|$, $\left|F_H^0(\mathbf{Q})\right|$, $\Delta\phi^0(\mathbf{Q})$ $\left[= \phi_P^0(\mathbf{Q}) - \phi_H^0(\mathbf{Q})\right]$

  → solvable with measurements at 3 different wavelengths.

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

MAD coefficients in generalized KH eq.

original KH equation

$$f_H(\omega) = f_H^0 + f'_H(\omega) + i f''_H(\omega)$$

$$a(\omega) = \frac{{f'_H}^2 + {f''_H}^2}{(f_H^0)^2}$$

$$b(\omega) = \frac{2 f'_H}{f_H^0}$$

$$c(\omega) = \frac{2 f''_H}{f_H^0}$$

$$\Rightarrow a = \frac{b^2 + c^2}{4}$$

Need to know *f’* and *f”*

generalized KH equation

$$\tilde{f}(\mathcal{F}, \omega, t) = \sum_{I_H} P_{I_H}(\mathcal{F}, \omega, t) f_{I_H}(\omega)$$

$$a(\mathcal{F}, \omega) = \frac{1}{\{f_H^0\}^2} \int_{-\infty}^{\infty} dt g(t) \sum_{I_H} P_{I_H}(\mathcal{F},\omega,t) \left| f_{I_H}(\omega) \right|^2$$

$$\tilde{a}(\mathcal{F}, \omega) = \frac{1}{\{f_H^0\}^2} \int_{-\infty}^{\infty} dt\, g(t) \left| \tilde{f}(\mathcal{F}, \omega, t) \right|^2$$

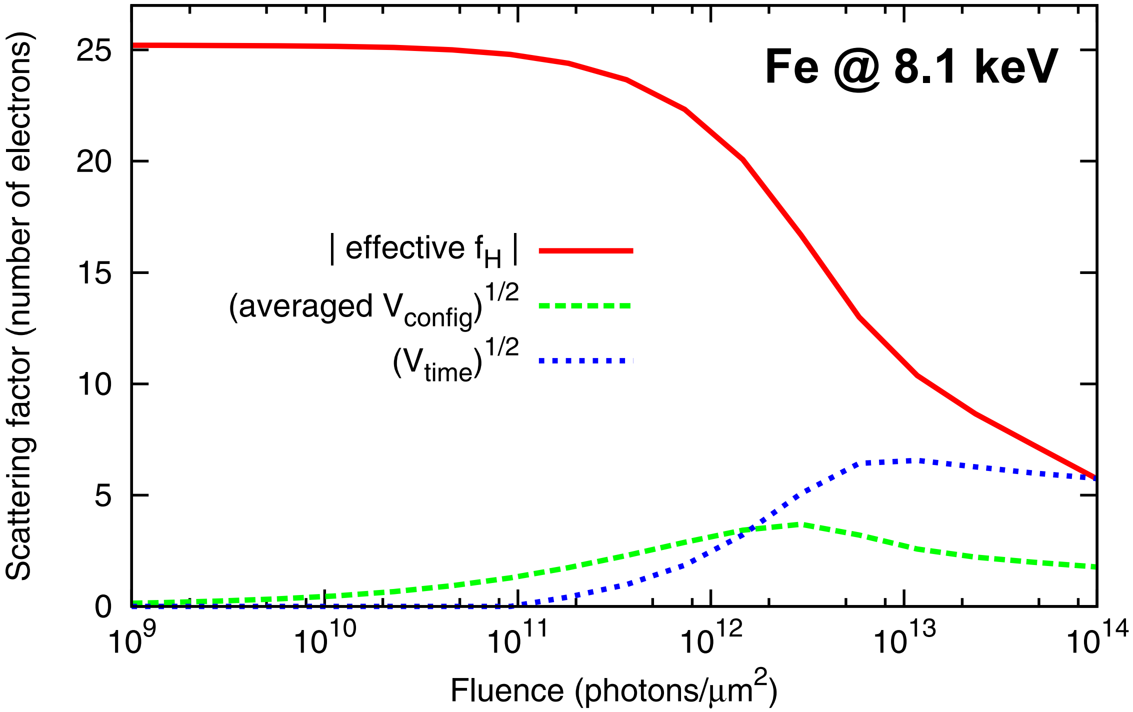
$$b(\mathcal{F}, \omega) = \frac{2}{f_H^0} \int_{-\infty}^{\infty} dt\, g(t)\, \mathrm{Re} \tilde{f}(\mathcal{F}, \omega, t)$$

$$c(\mathcal{F}, \omega) = \frac{2}{f_H^0} \int_{-\infty}^{\infty} dt\, g(t)\, \mathrm{Im} \tilde{f}(\mathcal{F}, \omega, t)$$

$$\Rightarrow a \neq \tilde{a} \text{ and } a \neq \frac{b^2 + c^2}{4} \text{ and } \tilde{a} \neq \frac{b^2 + c^2}{4}$$

Need to know *a*, *b*, *c*, and *ã*

Fluctuation at high x-ray intensity



$$\bar{f}_H(\mathcal{F},\omega) = \int_{-\infty}^{\infty} dt\, g(t)\, \tilde{f}(\mathcal{F},\omega,t)$$

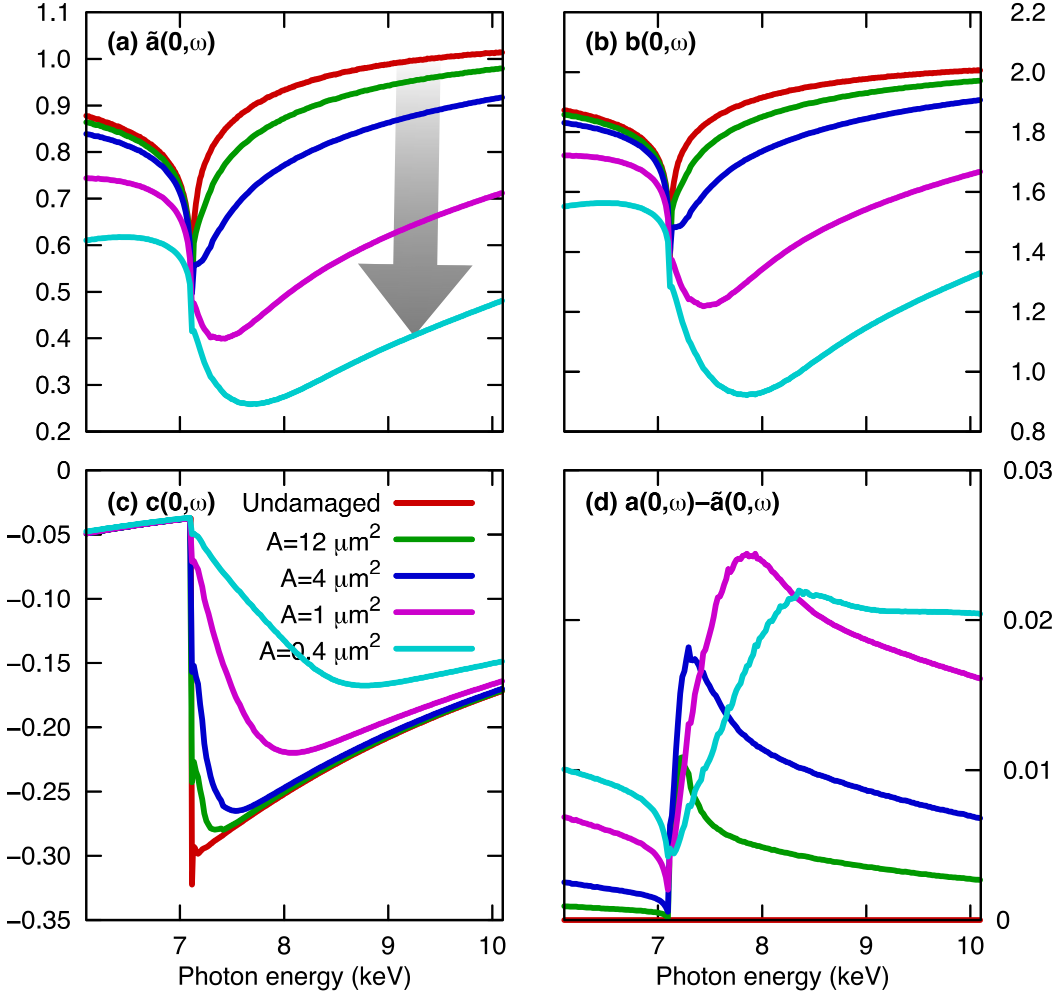
$$\bar{V}_{\text{config}} = |f_H^0|^2 (a - \tilde{a})$$

$$V_{\text{time}} = |f_H^0|^2 \left(\tilde{a} - \frac{b^2 + c^2}{4} \right)$$

$$\frac{dI}{d\Omega} = \mathcal{F} C(\Omega) \left[\left| F_P^0 + \bar{f}_H \sum_{j=1}^{N_H} e^{i\mathbf{Q}\cdot\mathbf{R}_j} \right|^2 + N_H \bar{V}_{\text{config}} + \left| \sum_{j=1}^{N_H} e^{i\mathbf{Q}\cdot\mathbf{R}_j} \right|^2 V_{\text{time}} \right]$$

Son, Chapman & Santra, *J. Phys. B* **46**, 164015 (2013).

Plotting of MAD coefficients



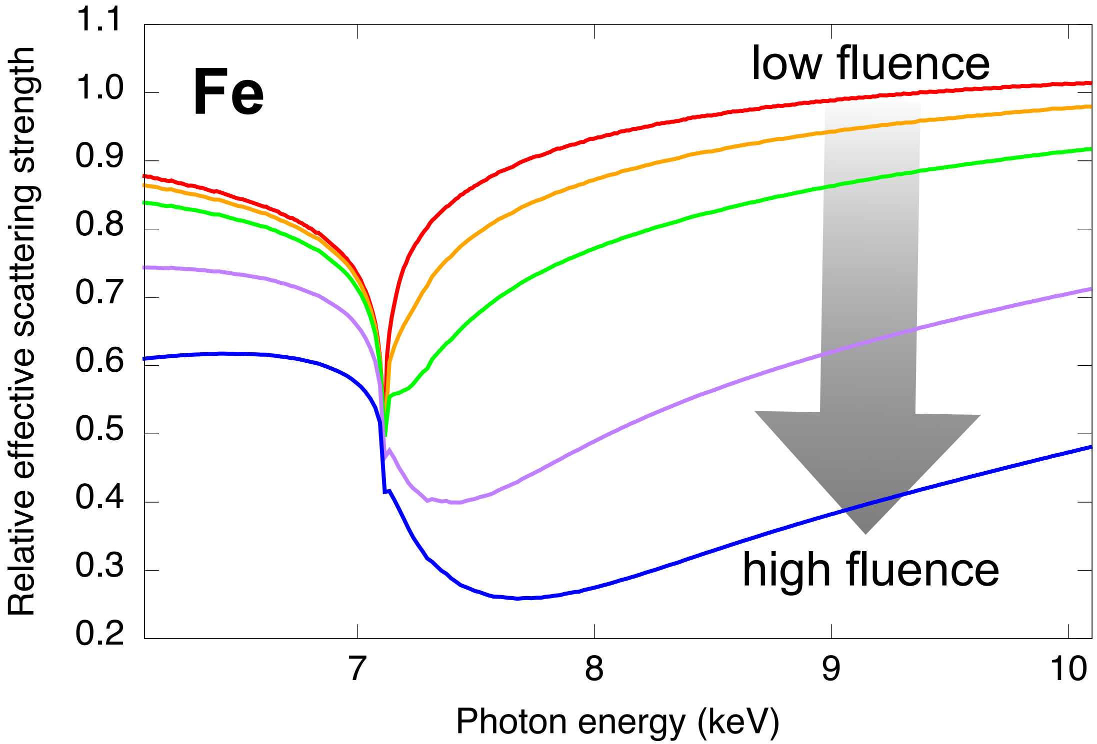
- calculated by XATOM
- different ionization mechanism before and after the edge
- contrast at different wavelengths
- anomalous scattering (MAD c coefficient) not completely eliminated
- bleaching effect as intensity increases

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

High-intensity phasing methods

- HI-MAD (high-intensity multi-wavelength anomalous diffraction)
  - generalized Karle-Hendrickson equation + MAD coefficients
- HI-SAD (high-intensity single-wavelength anomalous diffraction)
  - one dataset required — simple in measurement
- HI-RIP (high-intensity radiation-damage induced phasing)
  - two different fluences: undamaged and damaged
  - exploiting the bleaching effect of heavy atoms (HA)
- brand-new HIP: based on generalized Karle-Hendrickson equation
  - multi-fluence measurement at single wavelength
  - RIP-like: undamaged vs. damaged
  - SIR-like: HA-derivative vs. HA-free

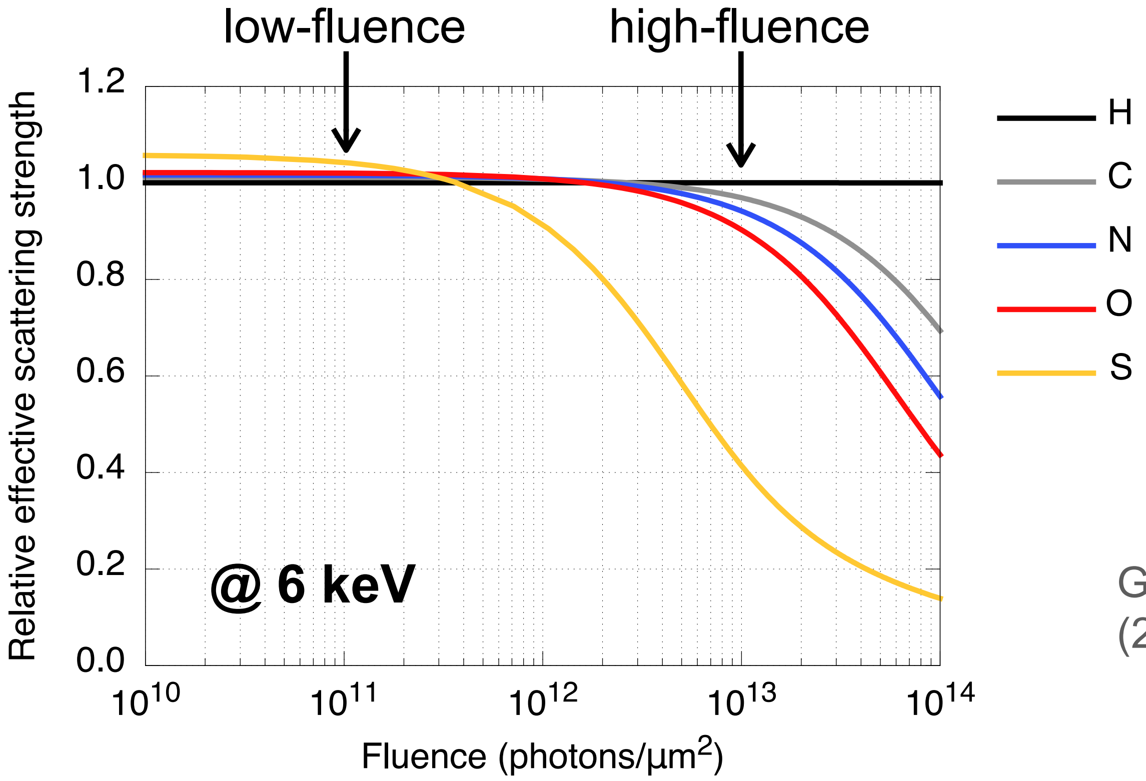
High-intensity MAD



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

- minimum deepened and edge broadened ➔ easy to choose wavelengths
- experimentally difficult to vary wavelengths, while keeping the same fluence

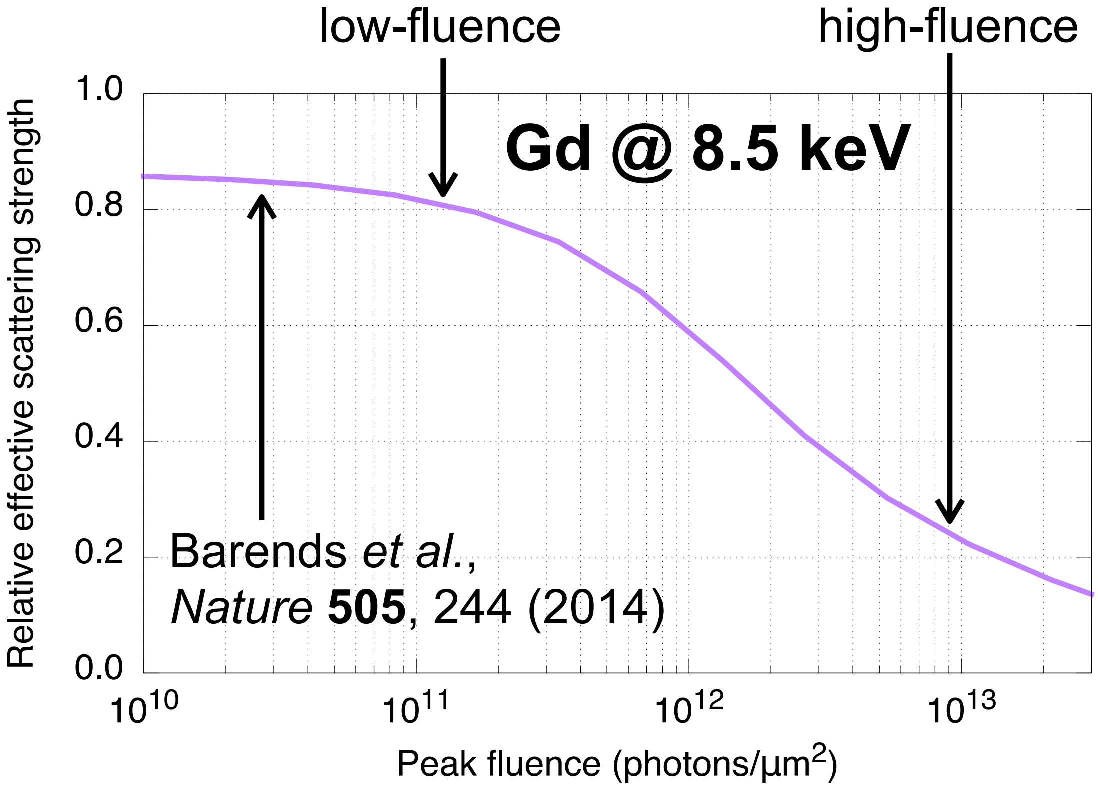
High-intensity RIP



Galli *et al.*, *J. Synch. Rad.* (2015, in press).

- exploiting selective ionization for S atoms at high x-ray intensity
- simulated datasets of Cathepsin B including ionization for all atoms
- phased by the RIP workflow (Max Nanao)

(High-intensity) SAD



experimental datasets of Gd-Lys measured at LCLS

Galli *et al.*, (submitted).

- phased by conventional SAD techniques
- tested at several fluences (LF: R_{free}=0.264, HF: R_{free}=0.457)
- Towards HI-SAD: need for generalized KH equation

Conclusion

- SFX with XFELs: revolutionary impact on structural biology
- Electronic radiation damage: unavoidable at high x-ray intensity
- XATOM describes multiphoton multiple ionization dynamics of individual atoms; tested by LCLS and SACLA experiments
- Generalized Karle–Hendrickson equation in extreme conditions of ionizing radiations: not only in phasing but also in refinement
- HIP: brand-new phasing only achievable at high x-ray intensity
  - high-intensity version of MAD, SAD, and RIP
- Novel phasing at high x-ray intensity: new opportunities for solving the phase problem in crystallography with XFELs

Acknowledgments

Xe at LCLS

- DESY, Germany: Daniel Rolles, Artem Rudenko (KSU), Benedikt Rudek (PTB)

Xe at SACLA

- Tohoku University, Japan: Kiyoshi Ueda, Hironobu Fukuzawa

HI-RIP and LCLS phasing experiments

- EMBL Grenoble, France: Max Nanao
- CFEL, DESY, Germany: Thomas White, Anton Barty
- Max Planck Institute for Medical Research, Heidelberg, Germany: Thomas Barends, Sabine Botha, Bruce Doak, Karol Nass, Robert Schoeman, Ilme Schlichting
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