Overcoming the effect of radiation damage in biomolecular imaging

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This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract No. DE-AC52-07NA27344. LLNL-PRES-407734
Outline

I. XFEL-material interaction for biomolecules

II. Diffraction patterns of XFEL-irradiated biomolecules

III. Strategies for improving diffraction patterns

IV. Summary and conclusions
Diffraction image single biological molecules with ultrashort pulses before the absorbed energy has time to alter the structure

Particle injection

CCD collecting diffraction pattern


XFEL output:
8 keV,
< 70 fs,
2x10^{12} photons
in 100 nm spot

Combine 10^5-10^7 measurements

Classification → Averaging → Orientation → Reconstruction

Alternative to classification: Alignment and detecting ion fragments
Processes in XFEL - material interaction

- Processes in low-Z materials during the pulse:
  - Photoionization
  - Auger relaxation
  - Electron impact ionization
  - Electron equilibration
  - Three-body recombination
  - Electron-ion coupling
  - (Recombination)

- Fast electrons escape the molecule and charge it up
- Electrons may be trapped
  (first secondaries, then Auger e-, then photo e-)
- Molecule expands due to Coulomb and hydrodynamic forces
High-field effects

• Multi-photon ionization and excitation (e.g. above-threshold ionization, high-harmonic generation etc) are well known phenomena in the optical and (recently) EUV regime.
• In the x-ray regime, inner-shell phenomena dominate.
• Currently, little is known about multi-photon inner shell processes.

• With a 100 fs pulse and 100 nm focus, we are not in the strong-field regime yet (Keldysh parameter $\gamma \sim 10$, assuming a flat-top pulse profile), but tighter focus or shorter pulses could lead to $\gamma < 1$.

• Our current models do not include high-field effects.
  => We will need to investigate under which conditions this is justified, and improve our models accordingly.

• In charged nanoparticles, the strong quasi-static electric field can lead to tunneling ionization
Models to describe XFEL - material interactions

- Large systems can be described by a continuum model (typical range of 8 keV photo electrons is ~ 1µm)

- Smaller systems can be described by molecular dynamics simulations
  - We are developing an MD capability for LCLS so simulate up to $10^8$ particles

- Intermediate size systems are difficult to model
  - We used a continuum model for large molecules by treating long-range photo electrons separately from the rest of the molecule
Continuum model for XFEL-induced dynamics in single particles and clusters

- Previous models have been limited to small system sizes
- Our two-fluid hydrodynamic model for large systems assumes that
  - Sample is initially a homogeneous continuum
  - Sample has spherical symmetry
  - Separate free electrons and ions fluids interact by the Coulomb force
  - Rate equations describe the ionization of each atomic species
- We do not assume local charge neutrality

“real” molecule

Continuum model

Hau-Riege et al.,
PRE 69, 051906 (2004),
PRE 71, 061919 (2005),
PRL 98, 198302 (2007),
PRE 77, 041902 (2008)
Example: Dynamics of Anthrax Lethal Factor

R=50Å, τ=40fs, fluence=6x10^{12} photons/100nm diameter

- Collisional ionization is dominant initially
- Heavier atoms get ionized faster
- Captured photoelectrons accelerate ionization
• Higher-charged outer layers explode faster than inner layers
• Inner part of molecule is more strongly ionized
Atomistic model for XFEL-induced dynamics in single particles and clusters

- Continuum model does not describe single-atom effects (e.g. escape of H)
- We are developing a massively-parallel MD code to study XFEL-material interactions (based on our hot-dense radiative plasmas code (Glosli, Hau-Riege, et al., PRE 78, 025401 (2008)))
- Includes relevant physics that is known today and allows studying LCLS-relevant sizes (> $10^8$ atoms)

Example: Protein with 93,102 atoms
XFEL diffraction pattern of biomolecules

• Diffraction pattern degrades due to
  • Atomic motion
  • Stochastic atomic ionization
  • Quasi-free electrons

• Diffraction pattern is influenced by
  • Ionization state of molecules
  • Coherence properties of the LCLS beam
  • Distribution of bound and quasi-free electrons
Effect of ionization x-ray material interaction

• Since absorption occurs predominantly through photoionization, the ionization state can easily be accounted for by correcting the cross sections.

• Scattering strongly depends on the subshell ionization state since the atomic form factor is the Fourier transform of the electron density:

\[ q = 4\pi \frac{\sin \theta}{\lambda} \]

**Details of ionization states influences the diffraction pattern**

Hau-Riege, PRA 76, 042511 (2007)
Effect of the limited temporal coherence of the LCLS beam

Coherence time ~ maximum time delay of two beams scattered into the highest resolution part of the diffraction pattern

Scattering factor for a single SASE spike (Gaussian-shaped):

\[
F(\vec{q}, t_0) = \int_V \rho(\vec{r}) e^{i\vec{r} \cdot \vec{q}} e^{-\frac{(t_0 - \vec{r} \cdot \vec{q}/\omega)^2}{4\sigma^2}} dV
\]

Diffraction pattern is the incoherent sum of multiple SASE spikes.

At LCLS at 8 keV, the particles have to be smaller than 500 nm to achieve atomic resolution

Effect of radiation damage is surprisingly minor

Contribution of the later part of the pulse to the diffraction pattern is smaller since

1.) Atomic ionization increases with time, and ionized atoms have less scattering power.
2.) Atomic motion increases with time, and the degraded diffraction pattern changes quickly in time, so that its contribution is averaged out
   • For a given fluence, short pulses are preferable

Ionization damage averages out…
Ionization damage is surprisingly minor and can be corrected for

1.) Need statistical information about the ionization process:

   (i) For the case of mono-atomic ionization-damaged particles, a perfect correction (“repair”) of pulse- and shot-averaged diffraction pattern is possible!

   (ii) For the case of a more generic particle, partial “repair” of the diffraction pattern is possible

   Works for
   • stationary atoms
   • randomly-ionized atoms (on average spatially homogeneous)

2.) Can be applied blindly even when atoms move and ionization is not spatially homogeneous

The good news is that we do not have to know the details of the ionization process.

Hau-Riege et al., PRL 98, 198302 (2007)

10/9/08
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Using a tamper to reduce expansion dynamics
Encapsulating the molecule with a sacrificial layer reduces damage

without tamper

charged layer

neutralized hot core

with tamper

tamper e.g. H$_2$O

Hau-Riege et al., PRL 98, 198302 (2007)
Effect of tamper

• A tamper leads to a radially more homogeneous ionization of the molecule
  - Advantageous for “repair” of patterns

• A tamper reduces the radial atomic motion but does not necessarily reduce the amount of ionization damage
  - It possibly reduces ionization since it fosters recombination
  - It possibly accelerates ionization by capturing photo-electrons earlier in the pulse
Combining biomolecular tamper with repair methods of diffraction patterns: Anthrax lethal factor

Repair Tamper & repair

Distortion of diffraction pattern

<table>
<thead>
<tr>
<th>Number of Diffraction Patterns</th>
<th>Repair</th>
<th>Tamper &amp; Repair</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>-1.6%</td>
<td>-2.4%</td>
</tr>
<tr>
<td>10</td>
<td>-11.1%</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>-18.0%</td>
</tr>
</tbody>
</table>

\[ \text{C}_{0.31}\text{H}_{0.52}\text{N}_{0.08}\text{O}_{0.09}\text{S}_{0.01}, \]
\[ D=80\text{A}, 40\text{A tamper, 10fs pulse,} \]
\[ 3\times10^{12} \text{photons/100nm} \]

Diffraction pattern of damaged molecule can be substantially “repaired”!
Pulse lengths > 50 fs are acceptable!
Planned FLASH experiment to demonstrate tamper concept

- Using our holographic pump-probe setup, we will demonstrate the hydrodynamic aspect of a Si tamper.

![Diagram showing the hydrodynamic aspect of a Si tamper with reference object.](image)

**Femtosecond time-delay X-ray holography**

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Conclusions

Demonstrating atomic-resolution diffraction imaging of biomolecules and nanostructures will require

• Classification under non-ideal conditions
  • Alternatively molecular alignment or determination of molecular orientation from explosion fragments
• Image reconstruction under non-ideal conditions
• Modification of particles upon injection

We need a multi-scale model to describe LCLS-material interaction to guide experiments