Single-Molecule Imaging with X-Ray Free-Electron Lasers: Dream or Reality?

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X-ray free-electron lasers (XFEL) are revolutionary photon sources, whose ultrashort, brilliant pulses are expected to allow single-molecule diffraction experiments providing structural information on the atomic length scale of nonperiodic objects. This ultimate goal, however, is currently hampered by several challenging questions basically concerning sample damage, Coulomb explosion, and the role of nonlinearity. By employing an original *ab initio* approach, we address these issues showing that XFEL-based single-molecule imaging will be only possible with a few-hundred long attosecond pulses, due to significant radiation damage and the formation of preferred multisoliton clusters which reshape the overall electronic density of the molecular system at the femtosecond scale.

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During the last years, the interest around x-ray free-electron lasers has increased enormously [1–12]. These facilities will generate the brightest x-ray pulses in the world, with atomic scale wavelength (> 0.05 nm) and maximum peak powers (0.1–0.5 TW) orders of magnitude beyond the current capabilities of synchrotron-based x-ray sources. Among the various challenges proposed, the possibility to perform single-molecule imaging has stirred particular interest [1,4,6,7,9,10,13,14]. The difficulties in determining the structure of proteins that cannot be crystallized, in fact, is one of the leading challenges for structural biology today, and the extremely brilliant, ultrashort, bursts of the XFEL have the potential to get around this problem. On one hand the XFEL pulse duration (femtoseconds), is the natural time scale of elementary atomic interactions and it is expected to open the study of the evolution of fundamental processes; on the other the XFEL could have the power to enable diffraction imaging of single molecules, thus overcoming conventional crystallography that works essentially through linear amplification [7,15]. However, to reach the ultimate goal of single-molecule imaging, things turn out to be very complicated, as the phenomenology arising from high intensity x-ray photon beam-matter interactions is not yet fully exploited. To date, the study of XFEL matter interaction is carried out with empirical models which treat electrons with very crude assumptions, ranging from simple rate equations to scattering cross sections, all of them derived in the framework of perturbative analysis of noninteracting systems subjected to low external excitations [16–20]. XFEL imaging, on the contrary, relies on the interplay between intense x-ray pulses and electron wave functions that, in turn, interact through nonlinear and extremely nonlocal (in space) functionals of the overall electron density [21]. An additional challenge to existing approaches also comes from the latest numerical results reported for the Linac Coherent Laser Source (LCLS) at Stanford [22], where the time structure of the XFEL pulse has been shown to be made of incoherent energy bursts—with mean time duration as short as 200 as—whose interaction with matter cannot be modeled without a first-principle theory. As a result, the frontier of atomic resolution imaging is still largely debated with the most problematic issues unsolved. Open questions include the photoionization and subsequent Coulomb explosion dynamics of a single molecule subjected to intense XFEL radiation (and, in particular, if it could survive long enough to allow the observation of a useful diffraction signal) [6], what is the sample far-field scattering pattern and if it encodes interference fringes with sufficiently high contrast to infer structural information on the material and, last but not least, what is the role of nonlinearity that, on the basis of recent theoretical calculations made on plasma models, is expected to affect the dynamics of high energy XFEL pulses [23].

In this Letter we aim to answer to these questions. On one hand, to define the basis for present and future research in XFEL science, we develop an *ab initio* model describing the nonlinear interaction of intense XFEL beams with matter; on the other, to address the above-mentioned open questions we realize an exceptionally large parallel numerical calculation (more than 15×10^6 computational hours) with the highly scalable code GZILLA—especially written and optimized for this problem—performing simulations with a variety of simple molecules. The main conclusion of this work is that, albeit some structural information is still retrievable in the femtosecond domain, accurate single-molecule imaging will be only possible in the subfemtosecond regime.

To derive a first-principle model of an ensemble of nonrelativistic electrons and nuclei under the presence of a time-dependent electromagnetic field [24], we resort to the quantum Hamiltonian $\hat{H}$:

$$\hat{H} = \int_V \frac{dV}{2} \frac{\mathbf{n}_n(\mathbf{p}_n - Ze\mathbf{A})^2}{m_n} + \frac{\mathbf{n}_e(\mathbf{p}_e + e\mathbf{A})^2}{m} + \epsilon_0(\nabla \times \mathbf{A})^2 + \mu_0(\partial\mathbf{A}/\partial t)^2, \quad (1)$$

with atomic nuclei (electrons) defined by the charge density operator $\mathbf{n}_n$ ($\mathbf{n}_e$), the momentum $\mathbf{p}_n$ ($\mathbf{p}_e$), the atomic number Z (elementary charge e) and mass m_n (m), while the electromagnetic (e.m.) field by the vector potential $\mathbf{A}$. Equations of motion are found through the application of the Poisson bracket operator and by employing density functional theory (DFT) [25], which provides a convenient framework for a full quantomechanical treatment of the many-body electron wave function (which in its original form is impossible to handle) [26]. It is worth to remark that in our model, at variance with previous theoretical and numerical studies, all the quantities (i.e., nuclei, electrons and e.m. field) are treated as dynamical variables evolving through the nonlinear set of equations arising from the Hamiltonian (1) itself. We observe that the application of DFT requires the representation of the interaction potential V_{xc} among electrons (see Eq. 6 of [26]). Our fundamental hypothesis, which will be verified by the following simulations, is an extremely fast atomic ionization (on the attosecond time scale), which will let the system behave as an electron plasma of cold atoms [23]. In this condition the interaction potential V_{xc} would be that of an electron gas, whose form is known analytically [27]. This expression is also the method of choice when studying atomic clusters under intense e.m. fields (see, e.g., Ch. 17 and 24 of [25]).

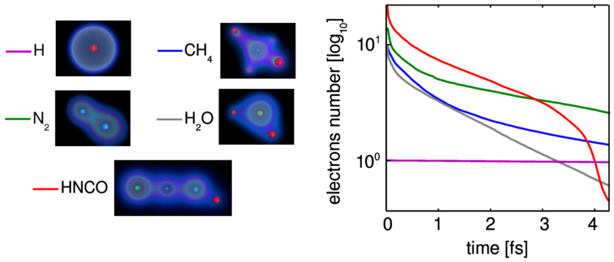

FIG. 1 (color online). (Left) Ground-state configurations for H, H_2O, CH_4, N_2, and HNCO; (Right) Number of "bounded" electrons versus time for molecules illuminated by a 100 nm-waist Gaussian beam of cw XFEL radiation with power $P = 150$ GW and wavelength $\lambda = 0.4$ nm.

In order to provide an adequate and experimentally interesting selection of molecules, we look at the four commonly found elements of organic chemistry (H,O,N,C) and study their stable configurations, ranging from the most elementary compound (hydrogen atom H, water H_2O, methane CH_4, nitrogen N_2) to the simplest combination involving all of them (isocyanic acid HNCO). The first series of *ab initio* simulations are devoted to study the key problem of sample radiation damage. At the input, we modeled a Gaussian spatial profile focused to 100 nm. To investigate the interplay between nonlinearity and geometry, we first considered a continuous (cw) excitation. Parameters for wavelength and power have been chosen from the SASE 3 configuration of the European XFEL ($\lambda = 0.4$ nm, power $P = 150$ GW). Figure 1 shows the photoionization of H, H_2O, CH_4, N_2 and HNCO, displaying the time evolution of the total number of electrons in the computational box (a cube of 1.5 nm side for N_2 and 1 nm for all the others). As seen in Fig. 1, the sample radiation damage is extremely high: with the only exception the H atom, large ionization occurs in a few of femtoseconds with the HNCO molecule exhibiting a radiation damage (percentage of electrons lost) of 98% after 4 fs, showing two different characteristic exponential ionization rates versus time. As a result, at the single femtosecond scale (much before a measurable Coulomb explosion of the nuclei), the dynamics is completely dominated by electrons shaking up; since the latter are the only source of scattered photons (nuclei, in fact, are too heavy to produce any appreciable scattering), any imaging-oriented XFEL application should be realized within ultrashort (≤ 1 fs) pulses. A second key observation comes from the different behavior of H, which indicates that nonlinearity, rather than geometry, outweighs the photoionization process. In fact, the internal electrons of H_2O and HNCO—whose wave functions have spatial extent comparable to those of H—escaped much before those of H (Fig. 1) thus showing the signature of a collective dynamics in the system evolution. Because of the high energy (and frequency) of the XFEL pulse, in fact, all the electron wave functions are practically free to interact, and in this situation the initial orbital geometry is expected to play a minor role being the dynamics ruled by electrons interactions. With this premises, a physical explanation of Fig. 1 can be drawn with the theory of solitons [28]. The electrons ground-state, in fact, being a solution of the time-dependent Khon-Sham equations (i.e., Eq. 6 of [26]) of the type $\psi_i \propto f(\mathbf{r})e^{i\omega t}$, can be regarded as a a set of solitary waves interacting through the V_{xc} functional, which constitutes a nonintegrable Kerr-like response (see Chap. 2 of [28]). With this type of nonlinearity, a general results is the formation of low energy clusters with a considerable amount of radiation emission, as soon as solitary waves are perturbed from their ground-state and forced to overlap (see, e.g., [29] in the context of nonlinear lattices). Therefore, when the XFEL pulse breaks in, it initiates a process of radiation emission that gets amplified by the system nonlinear response through the interaction among electronic solitary waves. It is clear that this mechanism does not play a role for hydrogen, which has just one electron, resulting in a much lower photoionization rate with respect to multielectronic atoms.

The most challenging (and unsolved) issue concerns the possibility of recording the far-field molecular interference image on a camera that will detect scattered photons within the whole duration of the x-ray pulse. To answer to this question, we performed a series of simulations collecting the far-field pattern [30], integrated in time as it would be done by a standard CCD, scattered by an HNCO molecule irradiated with an high energy XFEL pulse of Gaussian spatial distribution (100 nm spot-size) under different, ultrashort, pulse lengths. We begin by considering the XFEL short pulse operation, characterized by 2 fs pulses with peak powers of $P = 0.5$ TW at $\lambda = 0.15$ nm [22]. This regime allows a direct comparison with the XFEL technology accessible in the near future. The set of Figs. 2 and 3 provides a comprehensive analysis by showing the photoionization [Fig. 2(a)], the distance between the nuclei [Fig. 2(b)], the electron and nuclei dynamics and the angular far-field (supplemental movie 1 [26] and movie snapshots Fig. 3) time evolution of an HNCO molecule irradiated by a XFEL short pulse, constituted by a random series of Gaussian-shaped incoherent energy bursts, each of them with length of ≈ 200 [Fig. 2(a) dashed line]. As seen in Fig. 2(a), each XFEL energy burst pushes the HNCO ionization a step forward, appreciably damaging the molecule much before the arrival of the main pulse peak [Fig. 2(a), dashed line]. At the point of maximum XFEL intensity (≈ 1 fs), in fact, the HNCO molecule has lost three electrons; after the pulse peak, HNCO ionization proceeds at a slower rate and at the end the radiation damage reaches a value of 23%, with more than five electrons escaped from the molecule. Figure 3 illustrates the consequences of molecular damage on nuclei. In particular, the hydrogen atom is no longer bound to the structure (after 400 as) and initiates the process of Coulomb explosion. The nuclei pairs C–N and C–O, conversely, provide opposite dynamics: while the latter exhibit a tendency towards explosion, the former evolve with a constant bond length within the XFEL time window. In the framework of the previous nonlinear wave interpretation of the dynamics, such a different evolution is the hallmark of the generation of a robust multisoliton cluster, with a consequent spatial reshaping of the electron density due to the nonlinear mixing of C and N electron waves. The supplemental movie 1 [26]and Figs. 3(a)–3(d) provide a clear illustration of this process. At the beginning ($t = 0$ fs), the carbon atom shows no preferential coupling to either nitrogen or oxygen, as witnessed by the symmetric density distribution which equally affects C and N neighbors. However, as soon as the hydrogen atom looses its coupling to the structure [Fig. 3(c)], the situation dramatically changes: the carbon and nitrogen atoms interact and evolve towards a robust multisoliton cluster, as demonstrated by the strongly asymmetric density distribution which survives at the end of the XFEL pulse [Fig. 3(d)].

In conclusion, even by the use of short pulses and in the presence of negligible Coulomb explosion, the electronic radiation damage of molecular samples is still an issue: on one hand, it deprives the molecules of an appreciable number of electrons, on the other, it initiates a change of the electron density through the formation of preferred multisoliton clusters, which tend to oppose sample ionization. The net effect of these two different dynamics is a reshaping of the electron density which, in turn, leads to the inability to reconstruct the molecular structure from the far-field diffraction pattern. In other words, although the few femtosecond time scale is short enough to avoid a significant Coulombian explosion of the nuclei, the subfemtosecond (≈ 0.5 fs) electron density reshaping is still an issue for single-molecule imaging experiments. A general improvement is possible by moving to the attosecond domain, as expected on Fig. 2(a), which predicts considerably smaller radiation damage after the first energy burst (≈ 0.5 fs). Figure 4 summarizes the results of attosecond molecular diffraction: by employing a 400 as long ultrashort XFEL pulse, the far-field diffraction pattern shows

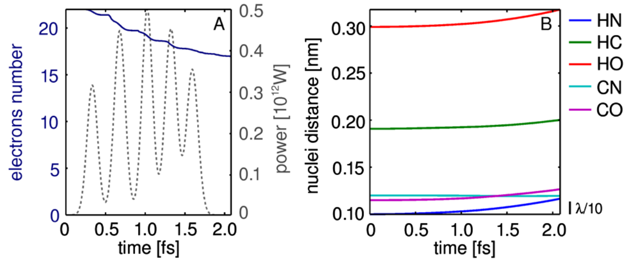

FIG. 2 (color online). Time evolution of electrons number [(a), solid lines] and nuclei distance (b) of HNCO irradiated by a random train of incoherent energy bursts of peak power $P = 500$ GW, wavelength $\lambda = 0.15$ nm and overall time length $T = 2$ fs [(a), dashed line].

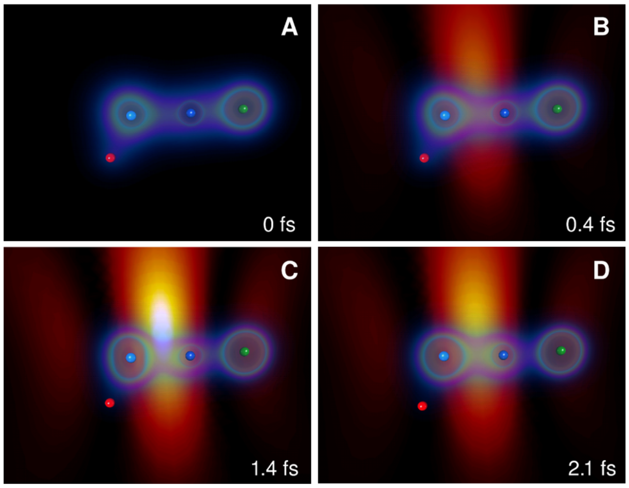

FIG. 3 (color online). (a)–(d) Far-field scattered angular pattern (red to yellow color map), nuclei position and electron density (blu to yellow colormap) time evolution of an HNCO molecule irradiated by a short XFEL pulse of 2 fs length, wavelength $\lambda = 0.15$ nm and peak power $P = 500$ GW [Fig. 2(a) dashed line].

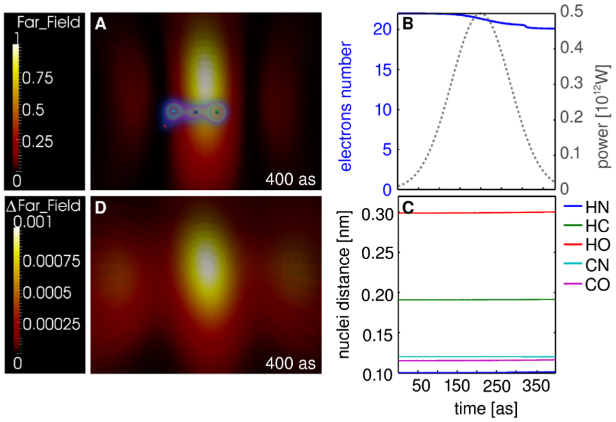

FIG. 4 (color online). (a) Angular far-field, nuclei position/electron density, (b) photoionization and (c) nuclei distance evolution of an HNCO molecule irradiated by a 400 as XFEL pulse of wavelength $\lambda = 0.15$ nm and peak power $P = 500$ GW (b), dashed line); (d) Image difference between the far field of (a) and the one generated by the ground state of HNCO in the absence of any radiation damage.

good fringe contrast [Fig. 4(a)], much superior to the pattern obtained in the fs regime [Fig. 3(d)], minimal radiation damage [8.5% as calculated from Fig. 4(b)] and no tendency toward nuclei explosion [Fig. 4(c)]. Figure 5D, showing the difference between the previous far-field diffraction pattern and the HNCO diffraction from the ground state (i.e., in the absence of any molecular damage), highlights the minimal effects of radiation damage in the attosecond diffraction regime [Figs. 4(a) and 4(d)]. The subfemtosecond domain, in other words, is sufficiently fast to minimize the nonlinear interaction dynamics of electron matter waves [Fig. 4(a)] and to maintain all the nuclei bonded together [Fig. 4(c)]. A computer reconstructed image from an attosecond diffraction pattern would therefore be a true representation of the original sample.

With the opening of LCLS and the collection of its initial experimental results, the XFEL has become a reality of unprecedented importance. In this Letter, we have derived an original and accurate description of XFEL beam interaction with matter, able to provide *ab initio* results and expected to settle the basis for present and future theoretical investigations in XFEL science. When applied to the one of the most promising applications of XFEL sources, our results predict that some work still needs to be done in order to reach the goal of single-molecule imaging and Angstrom scale microscopy, but we foresee that such frontiers may be just behind corner, especially in conjunction with the fast theoretical and experimental advances in the field of attosecond physics [12].

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