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Invited Comment

Perspectives for quantum interference with biomolecules and biomolecular clusters

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Abstract
Modern quantum optics encompasses a wide field of phenomena that are either related to the discrete quantum nature of light, the quantum wave nature of matter or light–matter interactions. We here discuss new perspectives for quantum optics with biological nanoparticles. We focus in particular on the prospects of matter-wave interferometry with amino acids, nucleotides, polypeptides or DNA strands. We motivate the challenge of preparing these objects in a 'biomimetic' environment and argue that hydrated molecular beam sources are promising tools for quantum-assisted metrology. The method exploits the high sensitivity of matter-wave interference fringes to dephasing and shifts in the presence of external perturbations to access and determine molecular properties.

Keywords: matter waves, biomolecular quantum optics, quantum assisted metrology

(Some figures may appear in colour only in the online journal)

1. Matter-wave interferometry: from the foundations of physics to biomolecule metrology

The wave-particle duality is often seen as the basis of modern quantum mechanics since our best non-relativistic description of nature, the Schrödinger equation, was strongly inspired by wave mechanics even before Louis de Broglie's hypothesis [1] was experimentally confirmed [2, 3]. Matter-wave physics has become an essential part of modern physics and the basis for fast evolving technologies using electrons, neutrons, atoms and even complex molecules as quantum probes.

The *wave nature of electrons* rules atomic, molecular and condensed matter physics as well as chemistry in a rather obvious way because it influences all interatomic bonds. Also biology is affected by matter-wave phenomena on the small scale, when enzymatic activities are driven by electron [4, 5] and proton tunneling [6] or when the energy transport in light harvesting complexes depends on exciton coherence over single-digit nanometer distances [7, 8].

Diffraction of neutrons became a powerful tool for condensed matter research [9] and neutrons were the first neutral quantum particles to serve in matter-wave interferometers for tests of fundamental quantum physics [10, 11].

Atom diffraction was seen as early as in 1930 by Estermann and Stern [12] but atom optics became a research field only 50 years later [13–20]. With the advent of laser cooling [21–23] the field has rapidly grown and *quantum degenerate atomic gases* [24, 25] are nowadays used around the world, also in advanced matter-wave sensors [26, 27]. Several research groups are currently developing atom interferometry into a reliable technology for ultra-sensitive force measurements [28–31] with applications in geodesy, prospection of

natural resources, inertial navigation and tests of quantum physics at the interface to general relativity [32, 33] and cosmology [34].

Diffraction and interference of *small molecules* began with the surface diffraction of H_2 in 1930 [12]. In the mid-90s diffraction of small helium clusters [35], Mach–Zehnder interferometry of Na_2 [36] or Ramsey–Bordé interferometry of I_2 [37] and SF_6 [16] opened new avenues for molecular quantum optics. Recently, it even became possible to prepare Bose–Einstein condensates of diatomic molecules [38, 39].

Considering this progress, it is natural to ask how to extend quantum optics to ever more massive and complex objects [40]. In response to this challenge the first diffraction of C_{60} fullerenes [41] triggered the development of new interferometer schemes [42–44], advanced diffraction elements [45–47] and new detection methods [48–50] for *matter-wave interferometry with macromolecules*. A plenitude of recent experiments demonstrated the wave nature of more than two dozens of different organic molecules and molecular clusters, with masses ranging between 300 and beyond 10 000 amu [51], and de Broglie wavelengths of $\lambda_{dB} = 0.3$–5 pm. The transverse coherence typically covers several hundred nanometers over coherence times up to the millisecond scale. This suggests that the capability of modern experiments has reached a state where interferometry with biologically relevant nanomaterials is becoming feasible, including for instance vitamins and amino acids, peptides, proteins, nucleotides or RNA/DNA strands.

2. Motivation of quantum interferometry with biologically relevant molecules

We see a five-fold motivation for quantum coherence experiments with biological nanoparticles:

2.1. The intellectual challenge

Since we have seen quantum interference with complex organic molecules, the question arises if we can use similar techniques for matter of biological relevance, maybe even on objects that carry the code for self-replication. If that can be done, what are the prospects for the delocalization of quantum systems that are capable of sustaining life on the microscale? This question was taken to the extreme in Erwin Schrö-dinger's thought experiment of a cat in a quantum super-position of being dead and alive.

Matter-wave interferometry with biomolecules mimics Schrödinger's cat, when we replace the state of 'dead-and-alive' by the state of a molecule being 'left-and-right' in an interferometer with macroscopically distinct arms. One might argue that the delocalization of a composite system differs from Schrödinger's thought experiment by the lack of entanglement. The cat analogy is, however, justified for N atoms strongly tied into a single molecule: When they coherently pass a double slit, they realize a mode entangled with the vacuum $|\psi \propto |N_L\rangle|0_R\rangle + |0_L\rangle|N_R\rangle$, i.e. a coherent superposition of two situations, where all N atoms of the same

molecule are passing the left while the right opening remains empty and vice versa. It has been a matter of debate whether such single-particle states should be identified with entanglement. One may however argue, that these states can in principle be mapped onto an entangled two-particle state, which can be used in tests of Bell's inequalities [52] and macrorealism [53, 54]—even if the practical implementation of this feat still represents a substantial challenge.

The cat experiment can be approximated by a many-body system of high mass, high internal complexity, elevated temperature and eventually biological functionality. These criteria are increasingly well fulfilled by amino acids ($m \leqslant 2 \times 10^2$ amu) and vitamins ($m < 10^3$ amu), polypeptides and short DNA strands ($3 \times 10^2 - 6 \times 10^3$ amu), proteins ($10^4 - 10^6$ amu) and long RNA or DNA sequences up to viroids and plasmids ($m > 10^5$ amu), leading to viruses ($m \sim 10^6 - 10^7$ amu) and eventually bacteria ($m > 10^8$ amu) or bigger entities.

2.2. Nanotechnology made by nature

Even 90 years after the formulation of Schrödinger's quantum mechanics it is still a matter of debate, whether the apparent absence of quantum superposition in our macroworld is sufficiently explained by quantum decoherence [55–60]. Other hypotheses suggest amending the theoretical description by nonlinear terms, which are often associated with spontaneous [61–63] or gravitationally induced wave function collapse [64–66]. Quantum interference experiments with very massive particles are a viable approach to test such ideas [40, 67–69]. However, they often require freely propagating neutral particles beams and generating them has remained a challenge until today. We propose to exploit nature's capability in assembling and preselecting functional units such as proteins or DNA with an amazing accuracy and reproducibility, also for quantum optics experiments. The transfer of these units into sufficiently intense molecular beams is one of the key challenges of such studies and the present work describes in particular progress and perspectives around this question.

2.3. Decoherence

Matter-wave physics even with viruses or bacteria would not necessarily address the role of quantum mechanics 'in biology' because living objects usually interact with their environment. In living organisms this seems to restrict matter delocalization to sub-nanometer and sub-nanosecond time scales [8]. Quantum optics may, however, reveal insights into the role of conformation and structure of biomolecules for their coupling to the environment. The interaction between a quantum particle and its environment is one of the principle path-ways to classical appearances. Even though emission or collision processes must also be described by quantum physics, their sheer number in a complex many-body system and the impossibility to track them all in an experiment, may effectively wash out all phases that distinguish quantum from classical phenomena [55, 59, 60, 70]. In comparison to homogeneous nanoparticles or clusters, biomolecules are
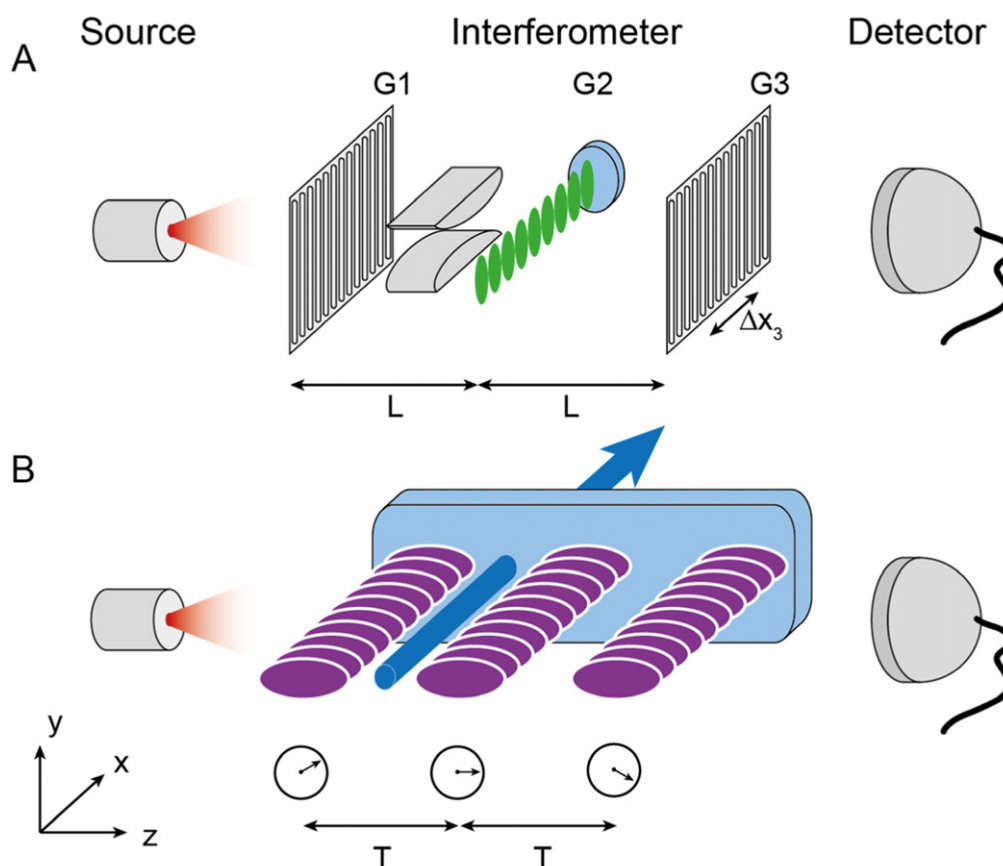
Figure 1. Prospects for quantum interference-assisted molecule metrology. (A) The Kapitza–Dirac–Talbot–Lau interferometer [43] consists of three gratings with a fixed mutual distance L. It has been successfully applied to numerous organic molecules, also in quantum-assisted metrology [68, 79]. (B) OTIMA interferometry [44] uses three retro-reflected nanosecond pulsed photo-depletion gratings to realize three absorptive masks that remove molecules from the antinodes of the grating. The pulsed nature of the grating structure allows suppressing various dispersive phase shifts and opens a window to time-resolved metrology. In both cases, metrology relies on the fact that matter-wave physics leads to the formation of molecular density patterns on the nanoscale. Interaction of the delocalized molecules with electric, magnetic and optical fields or collisions with directed atoms and molecules will shift these fringes. This is depicted in (A) by a deflector electrode and by a running light wave in (B). The high sensitivity of these instruments derives from the fact that even minuscule perturbations—as for instance imparted by single photons interacting with single molecules—shift the matter-wave fringes by an amount that is readily resolved.

complex many-body systems with a broad range of electric, magnetic, optical and structural properties that render quantum decoherence studies intriguing.

2.4. Interference-assisted measurements of (bio)molecular properties

Modern interferometers [68] (figure 1) generate nanoscale fringes of molecules. As the position of these molecular 'rulers' can be shifted by external perturbations and because fringe shifts can be read with nanometer accuracy, matter-wave interferometers are sensitive tools for molecule metrology. Their classical analogs, i.e. three-grating deflectometers have been successfully used in gravimetry before [71]. The position sensitivity of such classical instruments increases with decreasing grating period. When the grating period becomes smaller than $d = \sqrt{\lambda_{dB} L}$, and the distance L between two gratings is comparable to the Talbot length, such instruments natively operate in the quantum regime. Similarly, deflectometers in the time domain that use three pulsed photo-depletion gratings, become genuine quantum devices

as soon as the pulse separation time is comparable with the Talbot time $T \geqslant d^2 m / h$. Both conditions, in position space and in the time domain, ensure that the molecular coherence function is delocalized by more than one grating period of the second grating.

2.5. Interference-assisted metrology in a biomimetic environment

In all molecule interference experiments to date, the quantum particles have been isolated in a high vacuum to protect them from position-resolving interactions with their environment [70]. We here suggest packaging biomolecules in their own microcosmos, pictorially speaking to provide a 'natural habitat' for Schrödinger's cat. We ask in particular whether biomolecules can experience quantum delocalization while being immersed in a biomimetic environment, i.e. while being multiply hydrated in a small water cluster. This is of particular interest for quantum-assisted measurements on molecules of biological relevance where the addition of water may allow to

elucidate the influence of the solvent on conformation, folding or spectral properties.

In the following we sketch recent experimental progress and a conceivable roadmap towards quantum experiments with biomolecules in a biomimetic environment. We note that the technological challenges for molecules up to about $m < 3000$ amu are different from those around $m \simeq 10^4 - 10^5$ amu. The lower mass range is already accessible using vaporization into a noble gas and VUV photoionization [72]. In this mass range, precision experiments are particularly relevant because they can be compared with advanced computational studies. In contrast to that, molecular beam methods for neutral high-mass proteins and DNA strands, as required for high-contrast matter-wave interferometry, are still at an early experimental stage.

Section 3 introduces the Vienna molecule interferometers and their use in quantum-assisted metrology. Section 4 discusses open challenges in the physical chemistry of amino acids and polypeptides and identifies a number of intriguing questions that shall become accessible in molecule interferometry. Section 5 demonstrates the feasibility of sources that can deliver biomolecules of interest in a high vacuum environment under conditions compatible with current matter-wave interferometers—also with the potential for hydration. Section 6 concludes, with an additional perspective on interference experiments with high-mass biomolecules.

3. State of the art and perspectives in quantum-assisted molecule deflectometry

Quantum-assisted molecule metrology is based on the idea that matter-wave interferometry can transform extended molecular beams into a nanoscale patterns. Shifts of this fringe pattern in the presence of external fields can be probed by sampling the molecular beam with an absorptive mask of commensurate period [73] or even be seen using nanoscale imaging [49].

The interferometers at the University of Vienna consist of three gratings positioned in a near-field arrangement, named after Henry F. Talbot and Ernst Lau. It was first proposed [74, 75] and implemented for atoms [76, 77] by John Clauser and realized in our group for macromolecules in different variations: first as Talbot–Lau interferometer with three mechanical gratings (TLI) [42, 78], as *Kapitza–Dirac–Talbot–Lau interferometer* (KDTLI) with a central phase grating [43, 73] and recently as *optical time-domain matter-wave interferometer* (OTIMA) with three optical gratings [44]. All three variants contain three periodic structures (see figure 1) to prepare spatial molecular coherence (G1), to impose quantum diffraction (G2) and to probe the emerging molecular interference pattern (G3).

Even for initially incoherent molecular beams, each slit in G1 confines the molecular location to an extent that the ensuing momentum uncertainty spreads the coherence function over at least one grating period in G2. For that to happen, G1 needs to be absorptive, which can be realized by a

nanomechanical mask (KDTLI) or by using a photo-depletion grating (OTIMA) [46, 79].

In figure 1 and due to our present interest in biomolecules we limit our discussion to the KDTLI and OTIMA design, where G2 is realized as a standing light wave. When the molecules arrive at the second grating each molecule is delocalized and interacts with more than one antinode of G2.

The subsequent free evolution of the wave function leads to the formation of a periodic pattern of the molecular density, i.e. a set of interference fringes which can be sampled in comparison with the transmission mask G3 [43]. The fringe spacing is $d \simeq 79$ nm (in OTIMA) and $d \simeq 266$ nm (in KDTLI) and can be resolved with an accuracy that is primarily determined by signal-to-noise, in practice to better than 5% of the grating period. Both of these instruments can be operated with de Broglie wavelengths down to about 3×10^{-13} m in their current setting in the Vienna laboratories. This corresponds for instance to the value of the 15 amino acid polypeptide gramicidin D or a DNA strand with three base pairs ($m \simeq 1800$ amu) entrained in a cold supersonic noble gas jet at $600 \, \text{m s}^{-1}$.

Higher masses and more complex biomolecules will become accessible if the beam is slow [80] or the interferometer is stretched. Narrower fringe periods can be achieved when the gratings are positioned in a fractional Talbot order [81] and when the grating slit width is reduced to a small fraction of the grating period.

Measurable fringe shifts may already be imposed by subtle external perturbations: non-polar or floppy polar molecules of electric susceptibility $\chi_{\text{el}} = \alpha + \langle d_x^2 \rangle / k_B T$ will experience a lateral force $F_x \propto \chi_{el}(\boldsymbol{E} \cdot \nabla) E_x$ that depends on the internal molecular structure—characterized by the polarizability α, the projected dipole moment d_x and the microcanonic molecular temperature T—as well as the local electric field $\boldsymbol{E}$ [82, 83].

Molecular matter-wave interferometers have already provided new information on electrical, optical and structural properties [82–89]. Similar applications are envisaged in the presence of magnetic fields for molecules with magnetic dipole moments or aromatic compounds with high magnetic susceptibility. Even the momentum recoil imparted by the absorption of a single photon onto a fraction of all molecules will change the interference pattern measurably [85, 90]. Combining these elements may also enable new studies on photo-isomerization and photochemistry of biomolecules, also in a hydrated environment.

4. Prospects for interference-assisted metrology on hydrated biomolecules

The influence of hydration on the structure and dynamics of biomolecules in the gas phase has recently attracted much attention in biophysical chemistry [91–96]. The addition of water molecules to amino acids or peptides enables studies on the transition between molecular structures in the gas phase and in solution. How many water molecules are needed to cause that transition depends on many details [97–99].

The addition of water can also stabilize non-canonical tautomers of single nucleic bases [100–102]. This mechanism has been discussed as a source of spontaneous mutations in DNA [103]. The effect of hydration on the conformation space of flexible molecules has been studied for amino acids [104, 105], neurotransmitters [106–108], sugars [109–111], and oligonucleotides [112–114]: it may reduce the number of conformations even down to a single conformer [106] but it may enable new conformations, too [115].

Hydration effects in the folding of small peptides have been investigated using infrared spectroscopy [113, 116, 117] and for larger peptides structural transitions in the gas phase are often inferred from the number of absorbed water molecules and collision cross sections [93]. Solvation may also have a strong influence on the electronic structure of amino acids [118] and the excited state dynamics of DNA bases depend critically on solvation [119, 120]. We here discuss how to address some of these questions also in matter-wave interferometry.

4.1. Molecular beam deflection

Early work in physical chemistry has shown the power of classical deflectometry in the analysis of oligopeptides [121–124]. This idea can be extended to quantum deflectometry, which is less invasive because it can operate with higher spatial resolution and weaker electric fields. This is for instance interesting for studies of the transition between alpha-helices, beta-sheets and random coils in alanine-rich peptides, where the stability depends on the applied electric field and the internal temperature [125, 126]. Such peptides form stable helices in the liquid phase, but their gas phase structure still requires elucidation. The addition of water molecules may foster the transition to the helix and water molecules between different binding sites may restrict the number of conformations to a single one. This stabilization of a specific conformer in water will influence the measurement of the molecule's electric dipole moment and become visible in interferometric deflection studies.

4.2. Single-photon recoil spectroscopy

For various molecules of biological relevance, the electronic structure is little known when they are isolated in the gas phase. It is not easily accessed by conventional methods, especially when the absorption cross sections are small. In such cases, the absorption of a single-photon by only a fraction of all molecules in the beam already modifies the interference fringes and thus reveals the absorption cross sections. This interference-assisted absorption measurement has already been demonstrated to work for very dilute molecular samples and it is even applicable to particles that do not fluoresce [85, 90]. Such measurements have the potential to identify states and transition strengths eventually also in systems that undergo fast internal relaxation processes.

The conformational state of gas phase biomolecules is usually characterized by vibrational or rotational spectroscopy [127] which sheds light on the molecule's surrounding,
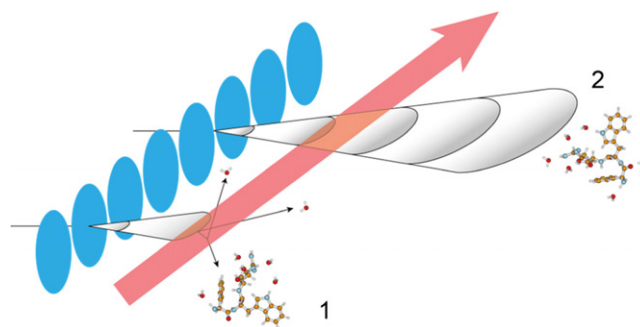

Figure 2. Proposed beam splitter based on the dissociation of biomolecular water clusters. Clusters which pass by the antinodes of the standing light wave can be electronically excited by a single UV photon (1) while those which move through a node remain in their electronic ground state (2). An intense running wave IR laser beam can selectively induce the dissociation of excited state molecules when it is sufficiently far-detuned with respect to the vibrational frequencies of the electronic ground state.

solvation or conformation. We suggest that IR spectroscopy can also be realized in matter-wave interferometry, if the transverse delocalization of the wave function is comparable to the IR wavelength.

4.3. Perspectives for a dehydrating matter-wave beam splitter

The single-photon-induced removal of one or several H_2O molecules from a hydrated compound may also become the basis for a diffraction grating, as shown in figure 2. It would act in close analogy to the photo-induced fragmentation grating, which has recently been experimentally demonstrated for weakly bound van der Waals clusters [47]. It can be useful in cases where other single-photon effects fail to deplete the molecular beam [44]. This may prove beneficial for experiments with polypeptides and oligonucleotides, only few of which have so far been successfully photo-ionized at accessible laser wavelengths above 157 nm [128].

The photo-depletion process may be triggered or completed by a single UV or VUV photon. For large particles with high heat capacity we propose that sufficient heat can be provided in a two-stage process, where the absorption of a single photon in the antinode of a UV laser grating transfers each molecule to an electronically excited state where it may be heated by an intense infrared running wave. The fragmentation of excited state molecules in CO_2 laser light has recently been successfully demonstrated [129]. Position selectivity can be achieved if the absorption cross sections of the vibrationally cold ground state and the hotter excited state differ by more than two orders of magnitude. Since water molecules are bound by hydrogen bonds, they should be emitted and cool the molecule before it breaks any covalent bond. Dehydration shall therefore be explored as a potentially effective beam depletion mechanism—and therefore potentially general matter-wave beam splitter. This requires that the fragmentation recoil removes the depleted molecules from a molecular beam that is typically collimated to about one milliradian.
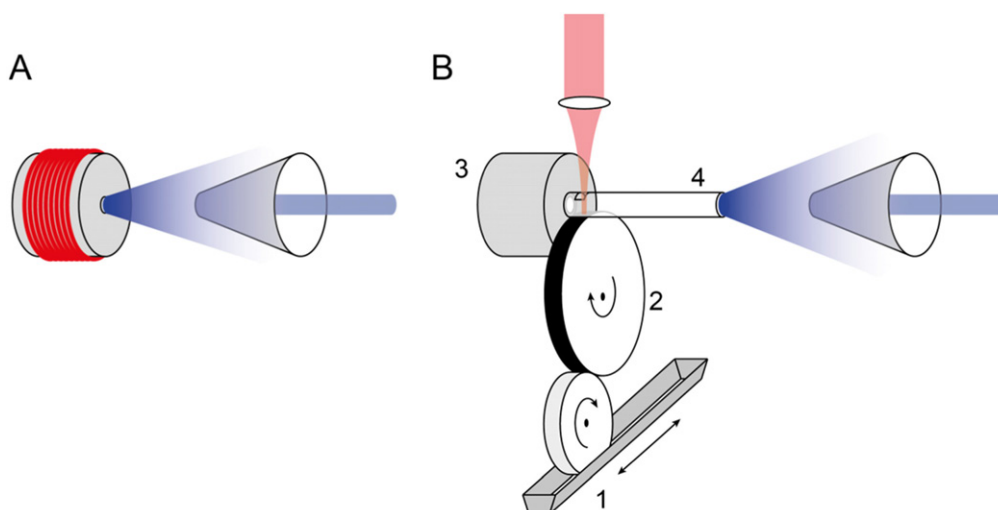
Figure 3. Molecular beam sources. (A) Small biomolecules can be evaporated thermally and co-expanded in a supersonic noble gas jet. This leads to well-directed beams with high forward velocities and temperatures low enough for efficient clustering of biomolecules and water adsorbates. (B) For less volatile particles, such as polypeptides or proteins the interaction with the heating source needs to be kept short. Nanosecond laser desorption into the supersonic jet proves powerful in getting such species isolated and as small clusters into a directed molecular beam: The transfer from the sample supply slide (1) to the desorption wheel (2) is made via a soft felt wheel. The glassy carbon wheel (2) turns at about 1 Hz to expose a fresh sample spot for every laser shot. The desorbed molecules are injected into a noble gas beam emerging from a cold pulsed valve (3). The molecules are cooled in the gas expansion and form clusters with water inside a 40 mm long collision channel (4).

4.4. Dehydration decoherence?

In all these envisaged experiments the combined system of a molecule and its water adducts must remain stable during its transit through the interferometer. The thermal evaporation of a single water molecule would be sufficient to lose the molecule from the beam or to encode which-path information and decoherence. In practice, however, the reemission of water even from room temperature molecules is restricted to the sub-nanosecond scale and thus only possible in the source region [130]. At later times, the evaporation rate is governed by the absorption of blackbody radiation. ESI studies found [131] rates of 0.05–0.1 Hz, which is well compatible with the expected coherence times for protein interferometry (10^{-4}–10^{-2} s).

5. Cold beams of biomolecules and biomolecular clusters

5.1. Seeded jet expansion sources

In order to prepare matter-wave assisted metrology experiments, we are particularly interested in intense sources for biomolecules in the mass range of up to 3000 amu. While thermal sources are still suitable for some small biomolecules, most of all larger biomolecules tend to fragment upon extended heating. This can be circumvented by short-pulse laser desorption. As shown in figure 3, we here explore both methods and couple them to the adiabatic expansion of a noble gas, which provides the required cooling to keep the molecules intact and to allow for the formation of peptide–water clusters, too.

In figure 3(A) the molecules are heated inside the small capsule sealed onto an Even-Lavie valve [132]. A 20 μs long gas jet expands into high vacuum to form a molecular beam that has enabled OTIMA interferometry with clusters of anthracene [44], hexafluorobenzene and vanillin [47]. We here extend the source to the use of hydrated biomolecular clusters and show in figure 4(a) that $(\text{Vanillin})_n$ $(\text{H}_2\text{O})_m$ clusters can readily be generated, at least up to the double pentamer.

In order to extend the mass range to large polypeptides we use pulsed laser desorption (1064 nm) [122, 133, 134] from a glassy carbon wheel, as shown in figure 3(B). The wheel can be continuously coated in high vacuum with any biomolecule of interest [135]. The excess desorption energy is removed in fast collisions with the expanding noble gas, where the molecules are pushed to velocities up to 600 m s^{-1} by room temperature argon atoms. State of the art molecule interferometry is currently compatible with de Broglie wavelengths down to $\lambda_{dB} = 0.3$ pm. The adiabatic cooling is therefore still compatible with particles up to 2000 amu at room temperature or up to 4000 amu in cryogenic gases. This covers peptides in the range of 8–15 amino acids, such as for instance the family of linear gramicidins, indolicidin, bradykinin and others.

The time-of flight mass spectra of clusters of tryptophan (Trp) and indolicidin are shown in figures 4(b) and (d). The peptides and amino acid clusters are detected by single-photon ionization using light of a fluorine laser emitting at 157 nm. Such vacuum ultraviolet radiation is well-suited for tryptophan-rich polypeptides, since among all 20 natural amino acids only some conformers of tryptophan exhibit an ionization energy of less than 7.89 eV.
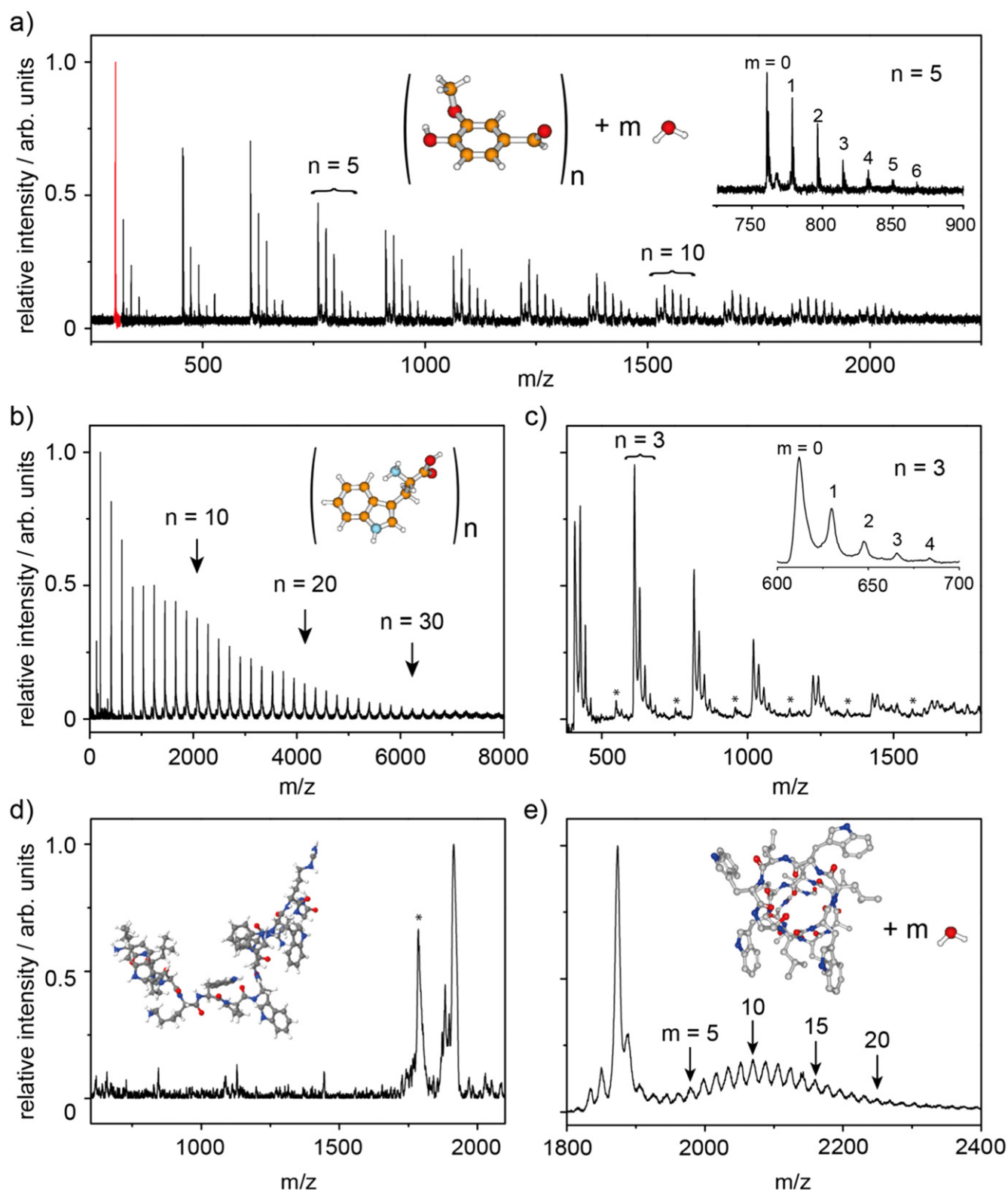
Figure 4. (a) Hydrated clusters of vanillin, generated in free supersonic noble gas expansion. Here the intensity of the pure $n = 2$ cluster drawn in red is artificially reduced by a factor of 0.5. The inset shows up to the $m = 5$ water cluster. (b) Pure tryptophan clusters (Trp_n, $n = 1–30$) and (c) their respective water clusters ($Trp_n(H_2O)_m$) can be prepared by thin-film laser desorption into a noble gas jet. The inset in (c) illustrates this for the $n = 3$, $m = 0–4$ cluster. The same method is capable of producing beams of polypeptide monomers and their water clusters as shown for (d) indolicidin [136] and (e) multiply hydrated gramicidin D [137]. The asterisks in (c) and (d) denote spurious sample fragments and impurities.

Water clusters can be formed by mixing the polypeptide with water in a collision channel. We find that water clusters up to the H_2O pentamer are well seeded. Tryptophan is easily decorated by up to the water pentamer figure 4(c), as required for the studies proposed in section 4. The 15-amino acid peptide gramicidin can be coated with more than 20 water molecules, as shown in figure 4(e).

5.2. Size-selected water clusters in interferometry?

Seeded gas expansion sources are powerful tools, as they deliver rather intense and directed molecular beams. However, they generate clusters only with statistical control over the number of water adducts. Although standard mass detectors could easily detect the attachment of a single water molecule, water can also be detached in parallel to the ionization process in the mass detector itself. The detection laser scrambles the mass distribution if the deposition of excess energy leads to the evaporation of water molecules. This effect can be minimized and in some cases eliminated by single-photon or resonantly enhanced multi-photon ionization [138].

Differentiating between the sources of fragmentation—in the source, in free flight or in the detector—is a general challenge of physical chemistry. Matter-wave interferometry may help in clarifying these questions, as long as the number of decay pathways is small [87]. Since modern interferometers can accept a broad distribution of wavelengths one can then, therefore, still deduce information about the difference between hydrated and anhydrated particle.

Hydrated beams are well compatible with electric or magnetic deflectometry in conservative fields.

Photo-induced dehydration needs, however, to be considered in recoil spectroscopy because the absorption process results in heating and possibly subsequent fragmentation/dehydration. For small molecules or multi-photon spectroscopy this can be a decoherence mechanism if the absorbing molecules remain in the detected molecular beam. However, such decoherence may also be exploited as a spectroscopic signature, if one can reference the spectroscopy signal to the molecular interference pattern in the absence of the exciting light. Finally for large molecules, the heat capacity and density of states are expected to become sufficiently large for fast internal energy relaxation processes to dominate over dehydration.

6. Perspectives for quantum optics with high-mass biomolecules

Our discussion so far was focused on challenges and promises with biomolecules up to about 3000 amu. In this mass range, sources have become practically available and they will soon enable new experiments at the interface between quantum optics and biophysical chemistry. For proteins or DNA strands in the mass range of 10^4–10^5 amu, pulsed laser desorption is still a viable launching method, but if we aim at de Broglie wavelengths above 10^{-13} m and lasting coherence we also require low internal temperatures (below 80 K) and low

velocities (several $10 \, \mathrm{m \, s^{-1}}$). This goal may be achieved by advanced buffer gas cooling methods [139, 140] but it is still an experimental challenge.

Alternatively, one may consider singly charged ions as precursor particles. Charged particles are also easily manipulated and guided using ion optics. While matrix-assisted laser desorption ionization produces pulsed beams of dominantly singly charged particles, electrospray ionization (ESI) generates continuous beams of highly charged species. Charge reduction techniques [141] then need to be combined with continuous quadrupole mass filtering to generate a monodisperse ion beam. Mass-selectivity in the source is particularly important when the detector lacks this capability in favor of much higher sensitivity. This is for instance the case in single molecule fluorescence detection [49].

Cold, slow and even hydrated particles may be generated in reactions with a cold buffer gas. The exploration of this as well as the subsequent neutralization still requires future studies, but photo-detachment is a promising candidate for soft neutralization in many cases.

Many developments in the field are very challenging and potentially very rewarding. Existing matter-wave interferometers are already capable of operating with organic molecules composed of more than 800 atoms. Quantum optics with biomolecules is now about to generalize this capability to a new class of particles to shed new light on fundamental questions of physics and to prepare advanced measurements at the interface to biophysical chemistry.

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