

Molecular Dynamics of Neurotensin and Lysozyme Soft-Landing on Gold: Influence of the Molecular Projectile Velocity, Incidence Angle and Temperature

Samuel Bertolini* and Arnaud Delcorte



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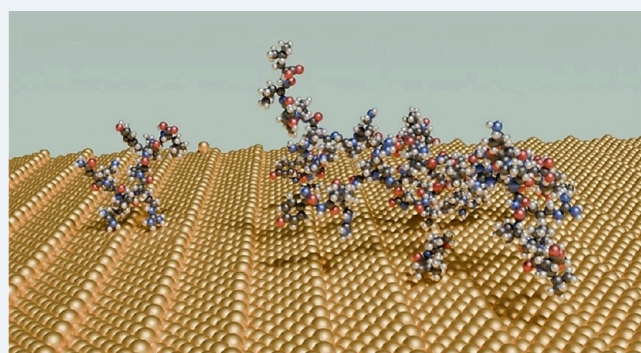


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ABSTRACT: Employing large argon cluster ion beams, the iBEAM technique has exhibited aptitude in transferring large intact biomolecules from a target to a collector surface in the vacuum, e.g., lysozyme and glucose oxidase, while preserving their bioactivity. Our molecular dynamics (MD) simulations described the desorption of intact lysozymes, glucose oxidase, and even lysozyme clusters comprising up to five units, thereby suggesting the potential soft desorption of heavy biomolecules and their molecular clusters. In turn, assuming their soft desorption, the present contribution models the landing of a single neurotensin cluster containing 5 neurotensin molecules or one lysozyme molecule onto a gold substrate using reactive MD. The parameter space, including incidence angle, collision velocity, and cluster/protein temperature, is systematically explored. Our simulations show that fragmentation increases with the rise of the velocity, collision angle toward the normal, and temperature. Also, after the collision, the backscattering phenomenon is predominantly influenced by varying the collision velocity but is less affected by the collision angle and temperature. Nonetheless, all molecular projectile parameters play a role in shaping the landing process on gold.



INTRODUCTION

Proteins present on surfaces facilitate desirable interactions with organic molecules, metallic ions, and living organisms, enabling applications in electrochemical sensing, hydrogen evolution reactions, and drug delivery systems. In electrochemical sensors, surface-bound proteins mediate redox reactions that generate a measurable potential difference between electrodes.¹ For instance, human telomerase reverse transcriptase in urine has been effectively detected using this mechanism.² Similarly, in hydrogen evolution reactions, bovine serum albumin adsorbed onto an electrode surface acts as an effective catalyst.³ Furthermore, drug delivery efficiency can be enhanced by modifying a drug's surface coating, improving its biocompatibility with target sites or prolonging its residence time in the body.⁴ These examples underscore the critical importance of controlled protein–surface interactions in advancing functional applications.

Protein deposition onto surfaces is typically achieved through solution dipping or casting, wherein adhesion forces are governed by electrostatic or van der Waals interactions between the protein and the substrate. However, weak intermolecular interactions among protein molecules influence their structural integrity during the drying process,^{5,6} often limiting film formation to a single monolayer and leading to gradual protein loss into the solvent.^{7,8} To overcome these

limitations, multilayer protein films can be fabricated by cross-linking proteins via ligand grafting or employing layer-by-layer deposition with polyelectrolytes.^{9–12}

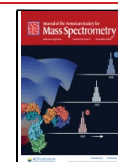
An alternative to solution processing is the use of vacuum-based techniques, which enable protein transfer via charging, electric field guidance, and ion soft or reactive landing onto a surface (preparative mass spectrometry). Among these methods, electrospray ionization (ESI) is the most conventional approach. In ESI, droplets containing proteins and solvent undergo evaporation, charging the protein molecules, typically in a vacuum, though ambient conditions are also feasible.^{13,14} Due to its ability to ionize large macromolecules, ESI has been widely employed in mass spectrometry and soft-landing applications.^{15,16} Another prominent technique is matrix-assisted laser desorption ionization (MALDI), which offers enhanced dimensional control and is similarly utilized for mass spectrometric analysis as well as soft and reactive landing.¹⁷ The soft-landing process requires low collision

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energy, whereas surface-induced dissociation (SID) occurs at higher energies, however, the resulting behavior also depends on the collision angle and the ion's stability.^{18,19}

Reactive landing is governed by the chemical reactivity of both the deposited ions and the surface collector. This process can be initiated through three primary mechanisms: (1) interactions with specific functional groups present on the surface, (2) fragmentation of ions upon landing followed by subsequent surface reactions, or (3) random formation of new bonds with molecules pre-existing on the substrate.^{20,21} Studies involving peptide deposition on self-assembled monolayers (SAMs) have confirmed the occurrence of reactive landing, though the efficiency of this process exhibits strong dependence on the peptide structure.²² The transition from reactive landing to dissociative collision can occur at relatively low collision energies, while larger molecules often remain intact. This phenomenon may be explained by energy dissipation through vibrational modes,^{23,24} or alternatively, we hypothesize that it may relate to a minimum activation energy threshold per atom.

For applications requiring multilayer construction with precise dimensional control, both soft and reactive landing techniques have proven effective.^{25,26} The iBEAM method, derived from secondary ion mass spectrometry (SIMS) principles, employs argon gas cluster ion beams (GCIB) to achieve soft desorption through low energy-per-atom impacts.^{27,28} This technique has successfully deposited bioactive proteins such as lysozyme and glucose oxidase while maintaining their native functionality.^{26,28} Further progress in fragmentation control may be achievable through cryogenic techniques adapted from SIMS methodology.^{29,30} Current research indicates that protein fragmentation during desorption exhibits correlation with three key parameters: organic film thickness, cluster size, and cluster velocity (or energy per atom, E/n).^{31,32}

Computational methods have been extensively employed to study surface phenomena, particularly in sputtering and desorption processes,^{33–36} as well as in investigations of soft and reactive landing on self-assembled monolayers (SAMs).^{37,38} Notably, the Reactive Force Field (ReaxFF) methodology^{49,50} and its recent algorithmic developments^{39–42} have enabled detailed investigations of polymer surface fragmentation during cluster collisions⁴³ and the sputtering dynamics of amino acids from bulk solids and graphite substrates using gas cluster ion beams (GCIB).^{44,45} In our previous work,⁴⁶ we employed computational simulations to examine the soft and reactive landing of lysozyme desorbed by argon GCIB onto rigid gold and hydrogen-terminated graphite collectors. These studies revealed the influence of protein structure, energy, and angle of collision, and the substrate nature, where the substrates were rigid. Building upon these findings, the present work systematically investigates the effects of velocity, impact angle, and temperature on lysozyme (1GXV)⁴⁷ and neurotensin sequence PLYENKPRRPYIL⁴⁸ interactions with gold, employing configurations representative of GCIB-assisted molecular transfer (iBEAM) but also similar to electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) based landing techniques. The iBEAM desorption technique generates hyperthermal protein species with flight characteristics that are fundamentally governed by two key parameters: (1) the physical properties of the molecular target substrate and (2) the incident argon gas cluster ion beam (GCIB) conditions.

Notably, the translational energy and thermal state of desorbed biomolecules exhibit a direct dependence on these parameters, while the collision angle can be precisely controlled through collector rotation. Motivated by this parallel control mechanism, for the different molecular vacuum deposition techniques, we systematically investigated the effects of varying collision velocity, impact angle, and temperature on desorption dynamics. Our analysis encompasses the complete spectrum of collision outcomes, from peptide/protein fragmentation and backscattering to the transition between surface-induced dissociation and soft-landing.

Computational Methods. Classical Molecular Dynamics. We previously investigated the landing of lysozyme proteins onto a rigid collector,⁴⁶ where the proteins' positions were obtained following argon cluster bombardment from a gold surface.³² In this study, we systematically examine the landing of a neurotensin cluster composed of five molecules (attracted by the Coulomb and van der Waals interaction), as well as a single lysozyme protein, which contains 5 water molecules confined, onto a gold surface. To achieve this, we modified the velocity, angle, and temperature of the protein or peptide cluster colliding from the same initial configuration. Specifically, we used collision velocities of 1, 2, 3, 3.5, 4, and 5 km/s; polar angles of 15°, 30°, 45°, 60°, 75°, and 90° (with respect to the surface); and temperatures of 300, 400, 500, 600, 700, 800, 900, 1000, and 1200 K.

To simulate the molecular dynamics of protein landing and fragmentation upon collision, we used the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS) code, applying reactive force fields (ReaxFF) within the framework of the electronegativity equalization method (EEM). The parameters for the proteins (C/H/O/N/S) were parametrized by Zhang et al., and we added the missing parameters of the gold atoms interacting with the protein (Au-X, where X is C/H/O/N/S) derived by Monti et al., thus combining ReaxFF force fields. By adding the Au parameters, some differences appear in the calculated atomic charges, when compared to the parameters used for Monti et al., as observed in Figure S1, although the charges tend to be generally similar.^{49,50} We conducted the simulations using a microcanonical ensemble (NVE) with a time step of 0.1 fs and a maximum simulation time of 500 ps. Periodic boundary conditions were applied in the directions parallel to the surface (XY), while the Z direction (perpendicular to the gold slab) was set as nonperiodic. Before the collision, the proteins and the gold slab were equilibrated at 300 K for 20 ps, separated and in vacuum, and no further relaxation was performed on the proteins, unless otherwise explicitly mentioned. From the relaxed protein structure, a new temperature was set by a random algorithm. The gold slab was created by cleaving an Fm3m gold crystal with a lattice parameter of 4.08 Å along the $\langle 543 \rangle$ direction, to contain step defects on the surface, also because gold collectors are used in the iBEAM technique, as well as silicon.⁵¹ The slab configuration included one frozen layer, one Langevin layer maintained at 300 K, and three free layers with a factor of 100 steps. While the thin layer approximation may result in a more rigid substrate compared to bulk gold, potentially enhancing the fragmentation propensity, we are confident that this effect is negligible in our system. This conclusion is supported by the minimal perturbation of the vibrational energy in the upper gold layers induced by collision propagation waves, as evidenced by our computational analysis. The final slab dimensions were 240 ×

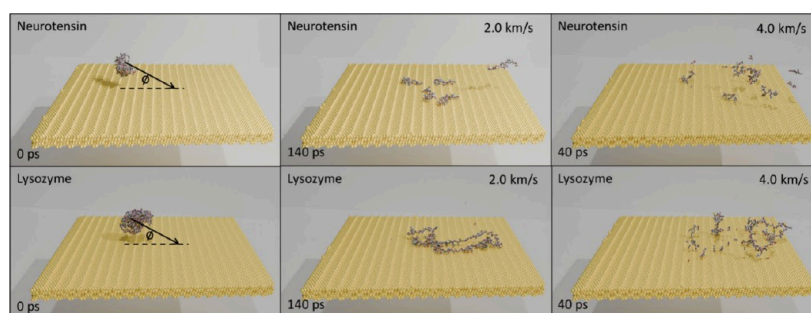


Figure 1. Initial and final configuration of the neurotensin cluster and lysozyme impinging on the gold target. Different collision velocities at 45° and 1000K represent the landing (2 km/s) and fragmentation (4 km/s) regimes for both biomolecular projectiles.

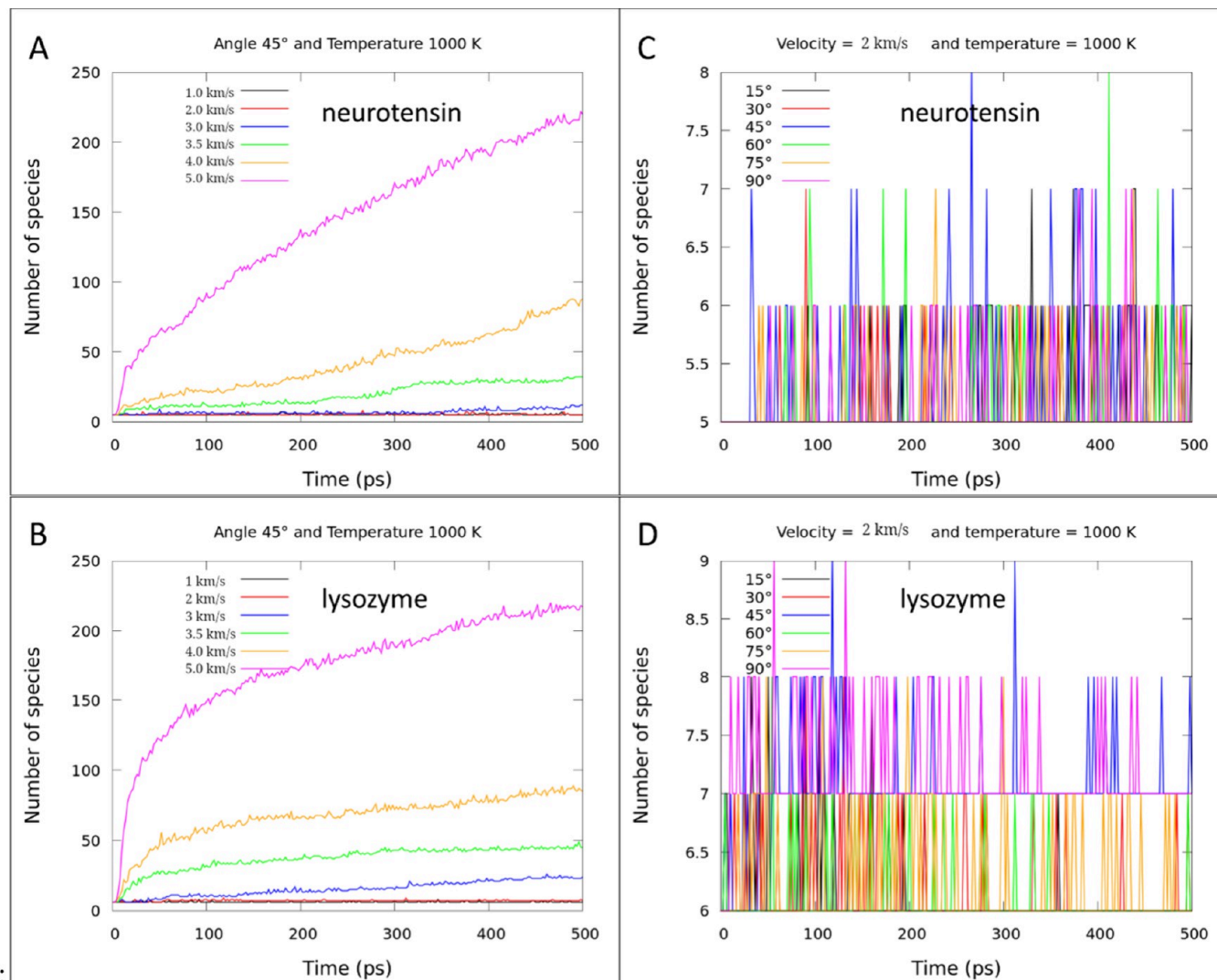


Figure 2. Time evolution of the number of fragment species created upon impact in different scenarios. Landing at constant temperature and angle, varying the collision velocity of (A) neurotensin and (B) lysozyme. Then the effect of changing the collision angle with respect to the surface in the soft landing regime is shown for (C) neurotensin and (D) lysozyme.

247 Å², and the initial configuration of the system prior to the collision is shown in Figure 1.

Comparison of DFT and LAMMPS. The DFT calculations were performed in Vienna Ab-initio Simulation Package (VASP)^{52,53} within the plane-wave basis set approach,^{54,55} gamma point sampling, 400 eV energy cutoff, and self-consistent electronic converger set to 10^{−4} eV and 10^{−3} eV/Å for energy and force, respectively. Electron–ion interactions

were modeled using PAW pseudopotentials^{56,57} from the VASP databases and 0.05 eV with Gaussian smearing.

To compare fragmentation in classical and quantum mechanics, we chose a peptide sequence (YES) to collide with a gold slab, performing the collision in a small model (Figure S2) using LAMMPS. From this, frames were selected, and a single-point calculation was used to determine the energy of each frame, conducted by both Density Functional

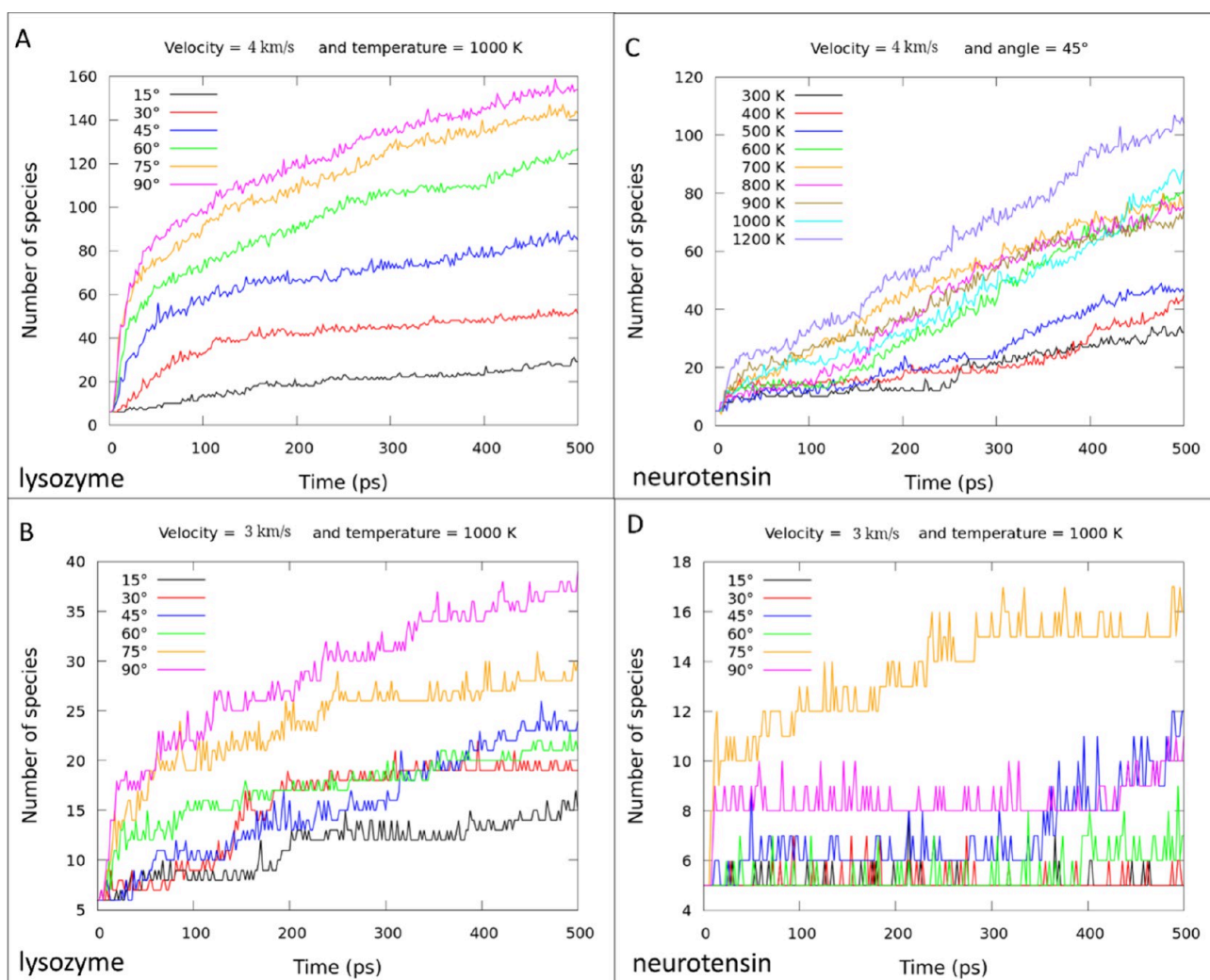


Figure 3. Time evolution of the number of fragment species after impact, for velocities close to and above the transition from soft landing to fragmentation (3.0 and 4.0 km/s). Landing is analyzed at constant temperature and different angles (A, B, and D), or at constant velocity of 4 km/s and angle of 45°, changing the temperature (C). Thus, lysozyme at 1000 K collides at (A) 4 km/s and (B) 3 km/s. (D) The neurotensin cluster collides at 1000 K and 3 km/s, for varying angles with respect to the surface.

Theory (DFT) and ReaxFF. The analysis shows that while ReaxFF tends to stabilize fragmentation products and lower energy barriers compared to DFT, both methods predict similar qualitative energetic profiles during the fragmentation process (Figure S2). This indicates that despite differences in absolute energies, ReaxFF effectively captures the basic fragmentation dynamics seen at the DFT level. Therefore, it will be used exclusively in this article.

RESULTS AND DISCUSSION

Fragmentation and Denaturation. The collision of a neurotensin cluster and a lysozyme with a gold surface can be categorized into two distinct regimes based on collision speed: soft landing at lower velocities or cluster separation (weak bond cleavage) and fragmentation (including covalent bond breaking) at higher velocities (Figure 1). The strong electrostatic interaction between the gold surface and the proteins or peptides facilitates their adhesion to the target surface, causing them to spread out in order to maximize the contact area between the gold and the biomolecules. As a result, at low velocity (2 km/s), lysozyme tends to denature upon landing, while the neurotensin molecules within the

cluster separate and lie flat on the surface. Proteins are expected to undergo denaturation on the gold surface, at least during the initial film formation. The degree of denaturation can be quantified by the change in the protein's surface area, calculated as the ratio of the final to the initial area (A_f/A_i) represented by the Connolly surface (the accessible surface area).⁵⁸ For neurotensin and lysozyme, these values are 1.79 and 1.97, respectively, indicating significant denaturation in both cases, with lysozyme showing a greater extent of denaturation due to its larger initial volume and mass compared with the neurotensin cluster. This happens because of the development of the Connolly surface of the peptide chains initially enclosed by the peripheral parts of the protein chains (larger volume/surface ratio).

In the fragmentation regime (4 km/s), fragments generated by the impact may be expelled from the system, while some remain on the surface. Hydrogen atoms can also penetrate the metal surface, forming dissociated hydrogens within the gold slab. Previous studies have observed hydrogen penetration into gold upon protein bombardment by argon cluster, and protein landing, where the hydrogen was removed from the protein to the bulk slab.^{31,32} The bond cleavage patterns observed in this

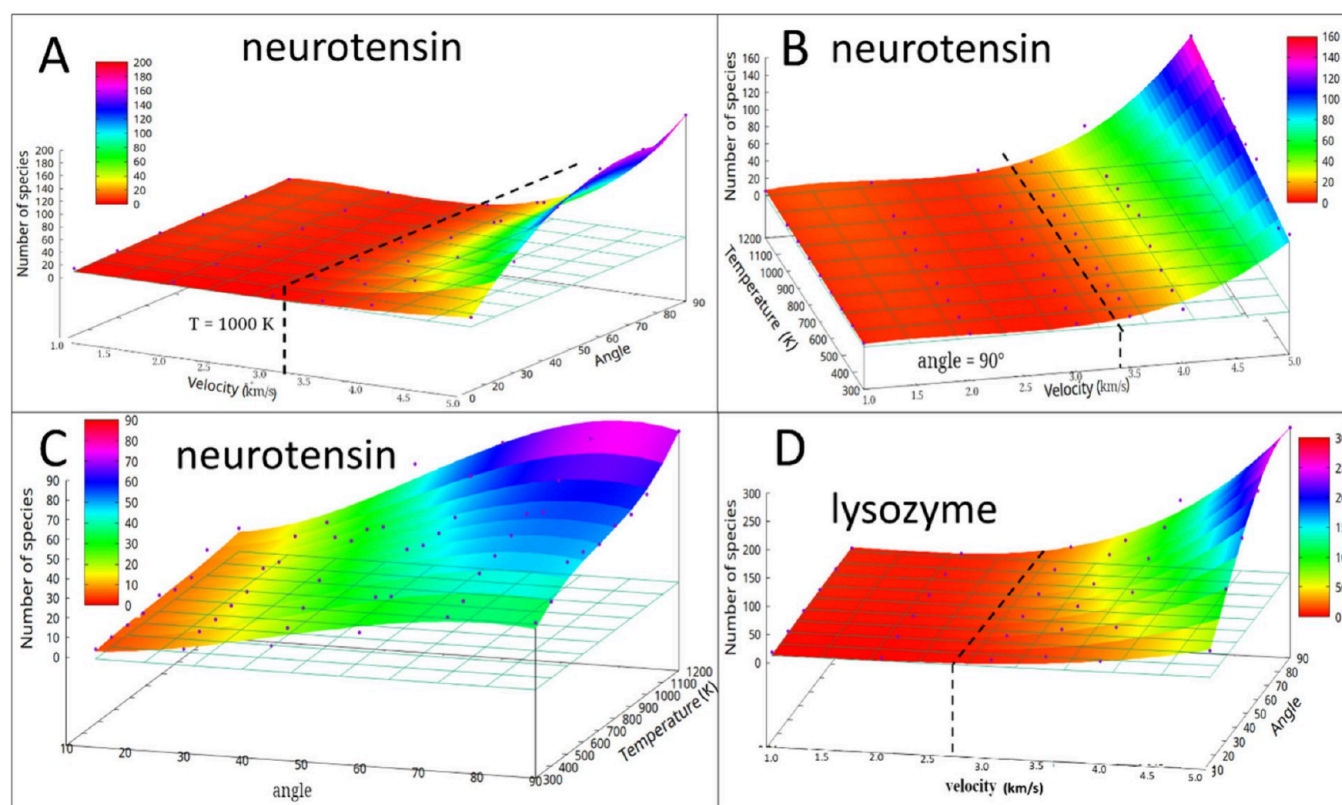


Figure 4. Isosurface of the number of species at 250 ps of simulation upon impact of a neurotensin cluster with the gold target: (A) at a constant temperature, changing the velocity and angle; (B) at a constant angle, modifying the temperature and velocity; (C) at a constant velocity (4 km/s), varying the angle and temperature. (D) Isosurface for the lysozyme changing the angle and velocity at a constant temperature. Purple points are input values, and the colored surface is a fit function.

investigation align with trends seen in earlier studies.⁴⁶ In surface-induced dissociation mass spectrometry, where protein fragmentation is induced by collisions with hard targets (e.g., gold) to detect ions,⁵⁹ repeated impacts may then lead to target degradation over time, due to hydrogen gas formation in the surface. Both soft landing and SID may involve protein or fragment backscattering, and these phenomena are influenced by specific collision parameters, including velocity, angle, and temperature.

First, we systematically analyzed the effect of the protein or peptide cluster velocities on the fragmentation (Figure 2A,B). Initially, the number of fragments produced after collision increases exponentially, then the fragmentation rate slows down, eventually tending to reach a plateau, at least for lysozyme. The number of fragments at a specific time also grows drastically as a function of collision velocity, regardless of the specific biomolecule impacting the target surface. However, fragmentation does not occur at lower velocities (Figure 2C,D), similar to the correlation between fragmentation and E/n observed in desorption of biofilms using argon cluster.^{31,32} Our results suggest that the transition to significant fragmentation could also be linked to the mass of the protein. For instance, neurotensin exhibits minimal fragmentation at velocities below 3 km/s, whereas lysozyme already undergoes a marked increase in fragmentation when it collides with the gold surface at the same velocity. The number of species normalized by the total mass is larger for the neurotensin cluster than that for lysozyme.

Under landing conditions where fragmentation occurs, the collision angle does affect the number of fragments produced

(Figure 3A,B,D). Fragmentation becomes dependent on the impact angle at intermediate velocities (~ 3 km/s) or higher. Generally, more pronounced fragmentation is observed at larger impact angles with the surface, particularly as the collision angle approaches the surface normal. This pattern is evident for both neurotensin clusters and lysozymes (Figure 3A,B,D), particularly at high velocity (Figure 3A). It is plausible that the velocity component perpendicular to the surface promotes fragmentation, while velocities parallel to the surface can transfer momentum more efficiently to fragments, which then backscatter from the target surface. Notably, our results differ from a previous study,⁴⁶ where reduced fragmentation of lysozyme was observed at angles closer to the normal surface. While this may seem contradictory, potentially collisions between the proteins while landing could affect the fragmentation in different angles, or stochastic effects were critically affecting the results (see *infra*). Here, we consider the statistical effects as the intrinsic randomness present in each simulation due to the distribution of velocity per atom to set the temperature, while a single collision was performed for each simulation.

At intermediate velocities (Figure 3B–D), fragmentation becomes prominent at larger angles, but additionally, stochastic effects are evident in the simulations. For neurotensin, at 3 km/s, a 45° angle results in a higher fragmentation ratio than a 60° angle, with maximum fragmentation occurring at 75° rather than 90° (Figure 3D). In contrast, for lysozyme at the same velocity, the greater mass induces fragmentation even at smaller angles, and the stochastic effects are less pronounced. For lysozyme, the highest fragmentation is

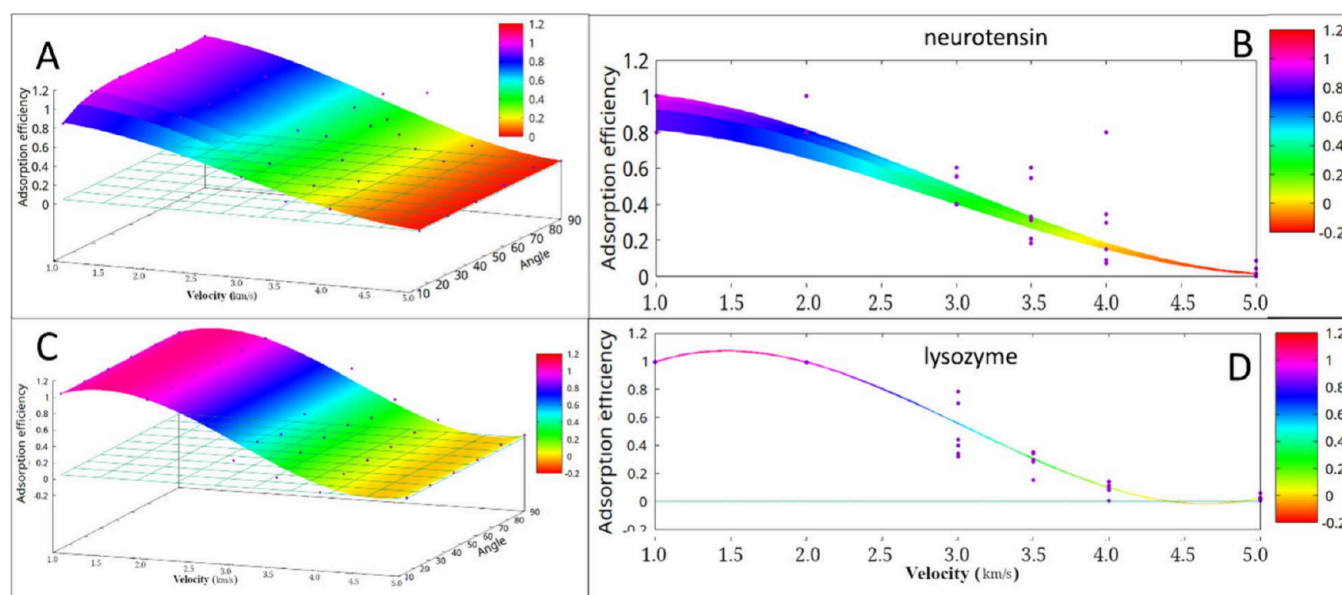


Figure 5. Adsorption efficiency obtained from the landed and backscattered mass, changing the velocity and angle of collision at a constant temperature (1000 K). (A) Isosurface and (B) profile of adsorption efficiency for neurotensin; and (C) Isosurface and (D) profile of adsorption efficiency for lysozyme.

observed at 90° (Figure 3B). At higher velocities (4 km/s), the stochastic effects diminish even for neurotensin. The initial temperature of the proteins also affects fragmentation, generally enhancing the number of fragment species (Figure 3C), where each species represents one molecule. However, stochastic fluctuations can still occur, as seen with neurotensin at a velocity of 3.5 km/s (Figure S3), where the highest temperature does not necessarily lead to the greatest fragmentation in the simulation.

As was previously considered, the velocity, angle, and temperature of the colliding protein all influence the fragmentation. However, our study analyzed these factors independently, without exploring their simultaneous interaction, as shown in Figure 4. Among these variables, collision velocity is the primary determinant of fragmentation, while angle and temperature have comparatively lesser effects. Furthermore, fragmentation appears to be initiated only after a minimum velocity threshold is reached, with this threshold varying based on the biomolecule's size but also the angle and temperature of collision. Consequently, lysozyme requires a lower minimum velocity to trigger fragmentation than the neurotensin cluster (Figure 4D). The fragmentation isosurfaces with respect to angle exhibit a curve-like pattern (Figure 4A–D), potentially following a sine or cosine function, while temperature isosurfaces tend to follow a more linear progression (Figure 4C,D). At higher velocities (4 km/s), variations in angle and temperature begin to influence fragmentation more significantly. For instance, at small angles (<30°), fragmentation is minimal or absent, but increases as the angle widens, even when the temperature remains constant (Figure 4). Similarly, the temperature amplifies the fragmentation process, provided that the angle and velocity are sufficient to induce fragmentation.

The Effect of the Time-of-Flight. In the previous simulations, relaxation was conducted at 300 K, and then the temperature was raised to a higher value without further equilibration. A complementary series of simulations was performed with a time of equilibrium at high temperature,

reflecting the effect of the molecule's time-of-flight toward the collector.

When the lysozyme is relaxed for at least 50 ps, there is a minimal change in conformation when comparing the relaxation at 300 and 1000 K, although, at higher temperatures, the protein gets completely dehydrated (Figure S4A,B). Nevertheless, the relaxation during the time-of-flight is enough to potentiate fragmentation for high temperature values such as 1000 K. This difference is observed when the collision against gold is done in the lysozyme relaxed during the time-of-flight. More fragments are generated when the lysozyme is relaxed under time-of-flight of 50 ps than at 300 K (Figure S4C), as observed by the number of fragments for 500, 800, and 1000 K, on different conditions of relaxation.

The difference scales proportionally to the difference between the proteins' temperatures and 300 K. The difference between the number of species during the collision, comparing the lysozyme relaxed at 300 K, and the relaxation considering the time-of-flight is seen in Figure S4D. It is evident that the time-of-flight becomes significant at temperatures above 800 K, where the difference between the number of fragments significantly changes comparing the two relaxation procedures, while at 700 K the differences are small. Nevertheless, our previous simulations indicate that the temperature of the proteins in the iBEAM method is typically below 800 K.³² Therefore, the effect of the time-of-flight can be neglected in the first approximation.

Sticking and Backscattering. When a protein collides with a surface, part of it may adhere to the surface, while another portion may be backscattered into the vacuum. Fragmentation can facilitate the backscattering of a protein or even individual molecules within a cluster, such as in the case of neurotensin. The adsorption efficiency (S_e) is calculated as the fraction of mass that adheres to the surface per impact ($S_e = m_{\text{landed}}/m_{\text{total}}$), and is primarily influenced by the collision velocity (Figure 5), with temperature and angle contributing statistically. In Figure 5, the mass landing does not discriminate the chemical configuration of the molecules, consequently

including different fragments or molecules. At low velocities, the molecules do not fragment and tend to stick to the surface; therefore, S_c is high. At high velocities, proteins tend to fragment into smaller pieces, which are more likely to backscatter as gas or short amino acid sequences. Additionally, the neurotensin adsorption efficiency curve tends to have larger variation as a function of angle than the lysozyme, due to the backscattering that occurs to some molecules in the neurotensin cluster at low velocities and low angles.

Backscattering is influenced by the nature of the molecular projectile itself, with our simulations indicating that lysozyme is more likely to adhere to the surface than neurotensin clusters, possibly due to differences in mass, size, and noncovalent interactions between neurotensin molecules. For instance, at a velocity of 2 km/s, all lysozymes stick to the gold surface, irrespective of the incidence angle, while about 20% of neurotensin backscatters. In neurotensin clusters, molecules located on the outer layers are more prone to backscattering than adsorption (Figure S5), which may be related to changes in attractive forces, moving from electrostatic (gold and peptide) to van der Waals interaction (covered gold and peptide) and the absence of strong binding force between the bottom and top neurotensin molecules in the same cluster.

One can expect a direct consequence of the molecule sticking to the substrate in SID mass spectrometry. Indeed, in the conditions of low protein fragmentation on a metal substrate (e.g., for the structural analysis of noncovalent clusters,⁵⁹ that is at rather low velocity, a high degree of sticking should be expected and the surface should be quickly covered by a molecular layer. Then, the interaction nature will change, and S_c may also be affected, as proteins would no longer collide directly with the metal but with adsorbed organic molecules. In methods such as iBEAM where proteins are transferred in a vacuum to a collector, our results indicate that the transferred amount should be strongly dependent on the velocity of the desorbed proteins.

Amino Acid Sequencing and Fragment Analysis.

Identifying and counting amino acids and analyzing their arrangement helps determine which ones are more prone to fragmentation and whether breaks occur in the main or side chains. Here we define the main chain as the continuous structure -NH-HCR-CO- of the amino acids and R as the side chain. For example, consider a hypothetical neurotensin sequence (PLYENKPRRPYIL), labeled according to the IUPAC-IUBMB standards. Any change in the number of amino acid pairs (sequence of 2 amino acids) indicates a break in the main chain, such as PLYENKPRRPYIL fragmenting into PLYENK and PRRPYIL, independently of the number of amino acid units changes or not. A side chain break occurs when a specific amino acid is altered without disrupting the overall sequence, such as PLYENKPRRPYIL becoming PLYENGPRRPYIL. In this case, the number of amino acid units and pairs remains unchanged, but the identity of a particular amino acid is modified. Thus, a single fragmentation on the side chain will vary the number of particular amino acids, possibly creating one and destroying another without necessarily modifying the number of amino acid units.

However, if the number of amino acid units changes, it signifies a discontinuity of the amino acid sequencing in the main chain, which could occur at the chain's termini, for instance, PLYENKPRRPYIL becoming PLYENKPRRPYI by removing a pair. Alternatively, the chain could break in the middle, removing two pairs, as seen when PLYENKPRRPYIL

becomes PLYEN and PRRPYIL with K being removed from the original amino acid. Lastly, a chain sequence break can occur internally without generating two distinct fragments. In this case, a new chain is formed, and a bridge (chemical bonds) between the two sequences exists, but it is no longer an amino acid, e.g., PLYENKPRRPYIL to PLYEN*PRRPYIL. In this example, two new chains belong to the same molecule; however, we are not analyzing here the number of species.

To clarify changes in the amino acid structure, we calculated the fractional change in the number of units and pairs from the start of the simulation, and we counted changes in each amino acid unit and pairs. Main chain breaks can be quantified by changes in the number of pairs over time as eq 1, once every single break on the pairs is a break in the main chain. Side chain breaks are based on variations in the number of units and the specific amino acids. For instance, if amino acid L changes to A, then there is no net change in the number of units. Side chain breaks can be expressed as eq 2:

$$B_{\text{main}} = n_{t_1}^{\text{pairs}} - n_{t_2}^{\text{pairs}} \quad (1)$$

$$B_{\text{side}} = \left[\left(\sum_i \left[\left| n_{t_1}^{\text{AA}_i} - n_{t_2}^{\text{AA}_i} \right| \right] \right) - (n_{t_1}^{\text{units}} - n_{t_2}^{\text{units}}) \right] / 2 \quad (2)$$

with $n_{t_1}^{\text{units}} = \sum_i n_{t_1}^{\text{AA}_i}$ and $n_{t_1}^{\text{pairs}} = \sum_i \langle \text{AA}_j, \text{AA}_k \rangle_{t_1}$.

Changes in the fractional units indicate overall fragmentation, while modifications in fractional pairs suggest alterations in the amino acid's main chain. The different fragmentation regimes can be expressed as in eq 3. Once an amino acid unit is destroyed, generating only one single pair change, as if the fragmentation is on the termini, then B_{regime} is 0.5. However, this contribution to the whole process can be neglected due to the small number of termini compared to the number of amino acids in the main chain. If the break is only in the side chain or there is no fragmentation, B_{regime} is 0. A break in the main chain can be divided into two regimes, separation and destruction. The separation regime consists of breaking the connection between two amino acids without destroying any amino acid, therefore reducing a single pair without affecting the number of units, giving B_{regime} equal to 1. While in the destructive regime, one single unit and two pairs disappear, resulting in $B_{\text{regime}} = 2$. Consequently, the higher the B_{regime} value, the more damage is produced in the main chain, and its values multiplies if there are simultaneous ruptures in the chain. If there are multiple units being separated or destroyed simultaneously, the higher the B_{regime} value at a specific time. Since the number of possible breaks is proportional to the molecular size, to better compare different proteins or peptides, the B_{regime} can be normalized by the number of initial amino acids contained in the system (initial units).

It is not clear if a specific amino acid sequence preferentially breaks, because it depends not only on the structure of the amino acid but also on the position of the AA in the protein chain and the collision conditions. For example, amino acids close to the beginning/ending of the chain tend to break more easily. Additionally, the sequences that follow an AA potentially can affect the fragmentation of a specific AA. Thus, further systematic investigation should take into account, also accounting for stochastic effects.

$$B_{\text{regime}} = (n_{t_1}^{\text{pairs}} - n_{t_2}^{\text{pairs}})^2 / (n_{t_1}^{\text{units}} - n_{t_2}^{\text{units}} + 1) \quad (3)$$

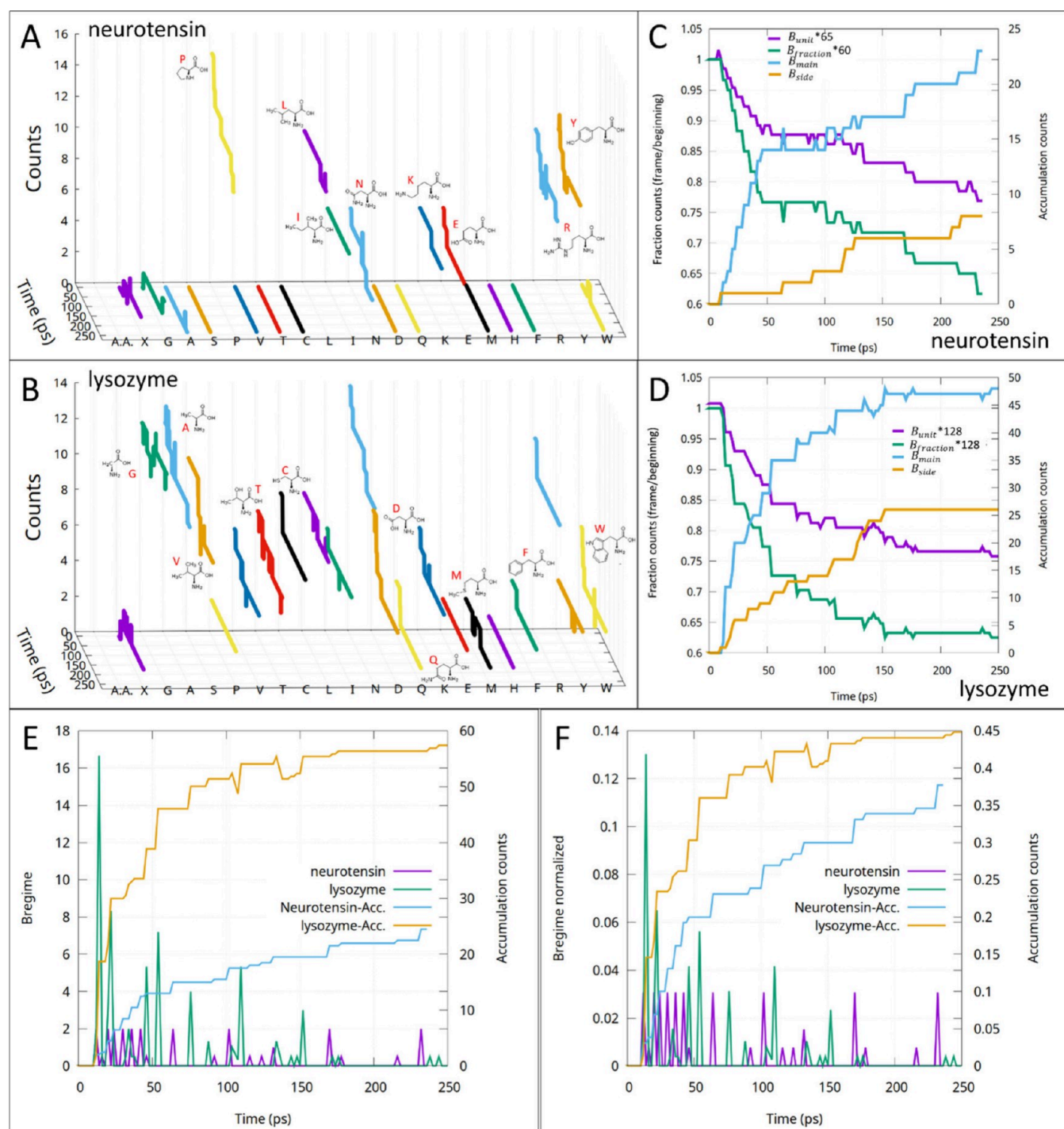


Figure 6. Counts of amino acid units in (A) neurotensin and (B) lysozyme. A fraction of the count from the initial configuration of the number of units and pairs, together with the accumulation counts of breaks in the protein's main (B_{main}) or side chain (B_{side}), counted for (C) neurotensin and (D) lysozyme. (E) Counts and cumulative value of B_{regime} of neurotensin and lysozyme, and (F) value B_{regime} normalized by mass.

The detailed fragmentation results based on the amino acid sequencing of the two types of molecules and the aforementioned indicators are presented in Figure 6. Aside from a few small amino acids (G and A), amino acid counts generally tend to decrease over time (Figure 6A,B). Both neurotensin and lysozyme exhibit a similar tendency to fragment within the chain, as reflected in their comparable unit/pair fraction ratios (Figure 6C,D). In absolute numbers, greater fragmentation of the main chain and side chains occurs in lysozyme, likely due to its larger size. Once the initial

number of units and pairs are normalized, the unit/pair fraction ratio reduces the effect of the mass, and both proteins display a similar behavior, with lysozyme showing a slightly more intense unit/pair fraction ratio, which could suggest a more intense reduction of amino acids amount. In parallel, side chain fragmentation is proportionally more pronounced in lysozyme than in neurotensin as shown by the orange versus blue curves in Figure 6C,D. B_{regime} gives a better idea of the whole fragmentation process (Figure 6E), once more amino acids are available to break and increase the number of the

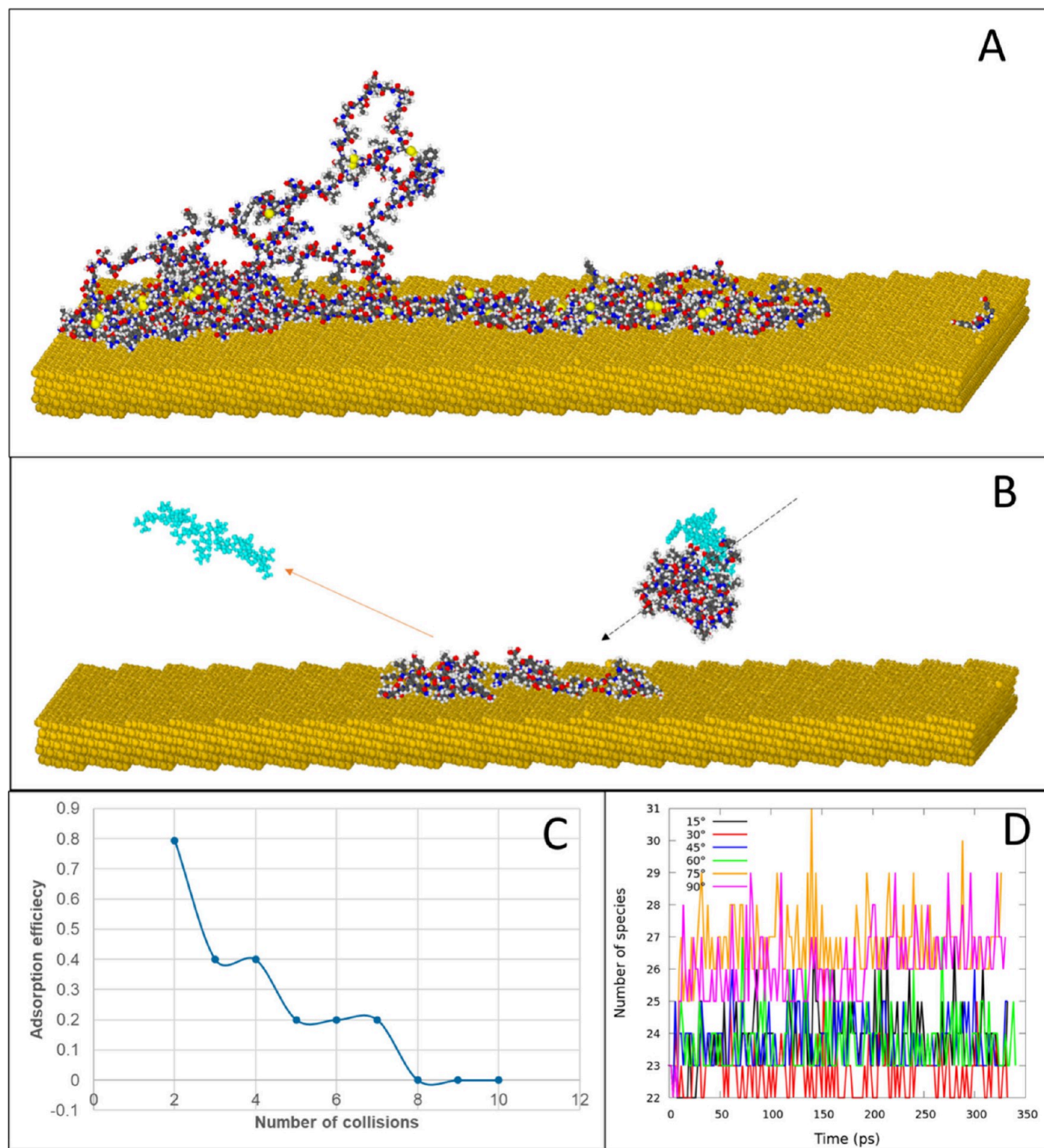


Figure 7. Multiple collisions of lysozyme and neurotensin clusters on a gold substrate. (A) Structure of lysozyme on gold after 10 ps of the 5th collision. (B) Structure of neurotensin on gold after 10 ps of the 5th collision, cyan color highlights a backscattered neurotensin. (C) Index of adsorption for neurotensin. (D) The 5th collision of a neurotensin cluster occurring at 3.5 km/s in different angles.

B_{regime} . Even when B_{regime} is normalized by the initial amount of units, lysozyme still shows more intense peaks (Figure 6F). Thus, we can consider that lysozyme has more fragmentation on the main chain than neurotensin, which could be due to its specific structural features or to the higher energy of impact when comparing the same velocity of collision.

Repeated Impacts and Accumulation. The deposition of a protein layer on a surface occurs through successive

protein collisions, leading to gradual accumulation until the desired thickness is attained. Upon initial contact, the first protein adheres to the gold surface, forming strong electrostatic interactions with surface atoms. Subsequent protein adsorption is primarily driven by van der Waals interactions or hydrogen bonds, in contrast to the electrostatic forces that dominate gold-protein interactions. To investigate this mechanism, we conducted additional collision simulations

under controlled conditions. The process was repeated at the same initial collision point to ensure consistency. Lysozyme adsorption was simulated over five sequential collisions (Figure 7A), while neurotensin clusters were subjected to ten collisions (Figure 7B). These simulations provide insight into the dynamic assembly of protein layers under defined physical parameters.

As successive lysozyme molecules accumulate, the initially two-dimensional adsorption pattern evolves into a distinct three-dimensional architecture (Figure 7A). This structural progression contrasts markedly with that of the flat monolayer observed following the initial collision event. The emerging three-dimensional configuration suggests progressive multi-layer formation mediated by protein–protein interactions, in addition to protein–surface binding.

The neurotensin cluster exhibits significantly lower surface adsorption efficiency compared to lysozyme. Our collision simulations reveal a distinct spatial dependence in adsorption behavior: peptides located at the cluster base demonstrate higher adsorption propensity, while those in upper regions show greater backscattering tendency (Figure 7B). This differential behavior likely stems from the absence of covalent linkages between neurotensin peptides, in contrast to lysozyme's unified polypeptide chain structure. Quantitative analysis shows that the adsorption efficiency per impact (S_c) decreases markedly during initial collisions (first and second impacts) at each impact (Figure 7C). After a certain number of collisions at 2 km/s, the cluster of neurotensin completely backscatters. These findings suggest two critical conditions for successful neurotensin layer deposition: (1) Optimal collision velocity must be sufficiently low to permit adsorption; (2) Impact angle must favor surface retention over scattering. Since the iBEAM deposition method provides neurotensin layers that grow rather efficiently with increasing ion dose, one must assume that the energy/velocity of the transferred molecules is sufficiently low to avoid predominant scattering even in the accumulation regime. In this respect, an interesting effect was observed in the experiments, namely that the ion-dose dependent thickness of layers of the peptide bradykinin (1060 Da) was increasing between 10 keV Ar_{5000}^+ (2 eV/atom) and Ar_{3000}^+ (3.3 eV/atom) and then decreasing drastically when going to Ar_{1500}^+ (6.6 eV/atom).^{25,26,28,60} Since it was shown experimentally that, between 1 and 10 eV/atom, there is correlation between the energy of the Ar beam and the kinetic energy (velocity) of the sputtered molecules,⁶¹ it is probable that the comparatively lower efficiency observed with the Ar_{1500}^+ beam was at least partly due to backscattering effects [54]. Analysis of the backscattering index for the second collision of the neurotensin cluster across varying angles, temperatures, and collision velocities (Figure S6) reveals that the index decreases for collisions below 3 km/s. Notably, values at 0.5 km/s and 1.0 km/s are comparable. In contrast, collision angle and temperature exhibit stochastic effects on the backscattering, as increases in these variables do not consistently correspond to either an increase or decrease in the index.

CONCLUSIONS

Molecular dynamics simulations reveal that neurotensin clusters and lysozyme exhibit distinct landing behaviors upon colliding with a gold target, influenced by the protein's collision velocity, angle, and temperature. At lower velocities, the proteins undergo soft landing deposition, while at higher

velocities, they enter a collision-induced fragmentation regime, resulting in fragmentation. Within this regime, more perpendicular collision angles and higher temperatures enhance fragmentation, the latter effect being more pronounced if a realistic time-of-flight is included in the simulations. The protein's size also plays a role; larger proteins, such as lysozyme, undergo more pronounced fragmentation, perhaps because of their greater kinetic energy upon impact or specific structure.

Collisions with gold cause denaturation of the initial landing molecules, spreading the proteins across the surface, which could reduce the bioactivity of the deposited overlayer (observed even at lower velocities). Using a molecular primer layer should reduce that effect, but our accumulation results indicate that it should be at the expense of a lower adsorption efficiency if molecules stay flat on the surface. In surface-induced dissociation mass spectrometry using a gold (or any other hard solid) target for fragmentation, the collision velocity can be controlled by adjusting the acceleration of a charged protein, thereby modulating fragmentation intensity. Additionally, controlling the collision angle by rotating the target surface should influence protein fragmentation in vacuum protein transfer techniques such as iBEAM, ESI, and MALDI.

In the particular case of the iBEAM method, the biomolecule's collision temperature and velocity may be affected by the argon cluster parameters and surface characteristics. For instance, we observe that in thinner layers the desorbed molecules tend to have higher velocities and temperature than in thicker layers, and consequently, higher fragmentation rates should also be observed upon landing. Also, larger argon cluster with smaller energy per atom (E/n) can desorb more softly clusters of proteins,^{31,32} thereby reducing the velocity and temperature during landing. The active sites of the transferred biomolecular film could potentially be better preserved by modifying the collision angle of the collector, reducing damage during the collision. Finally, in the cases of ESI and MALDI induced soft landing, the collision velocity of the biomolecular ions can be tuned to favor specific landing behaviors, going from soft and reactive landing to fragmentation when the collision's velocity is increased.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jasms.5c00174>.

Comparison between DFT and ReaxFF in the profile of energy during fragmentation, a comparison distribution of the charge between two different ReaxFF; effect of temperature over fragmentation and the relaxation temperature; highlight of neurotensin backscattering; and effect of temperature and collision angle on the backscattering of neurotensin (PDF)

AUTHOR INFORMATION

Corresponding Author

Samuel Bertolini – *Institute of Condensed Matter and Nanoscience, Université catholique de Louvain, 1348 Louvain-la-Neuve, Belgium*; orcid.org/0000-0003-0969-7142; Email: samuel.bertolini@uclouvain.be

Author

Arnaud Delcorte — Institute of Condensed Matter and Nanoscience, Université catholique de Louvain, 1348 Louvain-la-Neuve, Belgium; orcid.org/0000-0003-4127-8650

Complete contact information is available at:
<https://pubs.acs.org/10.1021/jasms.5c00174>

Notes

The authors declare no competing financial interest.

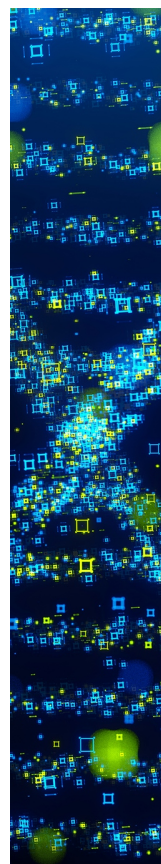
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