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Nanoplastics and Biostructures: Exploring the Capabilities of MD Computer Simulations

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Abstract
Micro- and nanoplastics (MNPs) represent a class of emerging contaminants whose diminutive dimensions, extensive surface area, and chemical resilience facilitate intimate interactions with biomacromolecules. Owing to their ability to traverse biological barriers, MNPs accumulate in tissues and directly engage proteins, nucleic acids, and lipid assemblies, thereby perturbing structure and function. Nanoplastics, in particular, adsorb onto protein surfaces, disrupt secondary and tertiary conformations, and partition within lipid bilayers. Molecular dynamics (MD) simulations provide atomistic insight into these processes–adsorption, corona formation, membrane insertion, and conformational modulation-complementing *in vitro*, *in vivo*, and epidemiological investigations. Current knowledge on MNP-induced alterations of protein architecture and membrane integrity is synthesized, integrating toxicological data, biophysical measurements, and MD results. A streamlined MD workflow is presented for nanoplastic–protein and nanoplastic–membrane systems, outlining key structural, thermodynamic, and dynamical observables (e.g., protein RMSD, membrane order parameters, surface coverage, interaction energies) that correlate with experimental endpoints such as enzymatic inhibition, membrane leakage, oxidative stress, and inflammation. Finally, conceptual and methodological challenges in linking atomistic mechanisms to adverse outcome pathways and risk assessment are discussed.

Keywords: nanoplastics; molecular dynamics; computer simulations; protein corona; lipid bilayer; biomolecular interactions; toxicology

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1 Introduction

Plastic production has grown to hundreds of millions of tons per year, with a substantial fraction entering aquatic and terrestrial ecosystems as waste [2]. Weathering, mechanical abrasion, and (bio)chemical degradation fragment bulk polymers into microplastics (< 5 mm) and eventually nanoplastics (1-100 nm) [2]. Their small size facilitates long-range transport, cellular uptake, and translocation across physiological barriers including intestinal epithelium, gills, and the blood-brain barrier [2, 1, 10].

At nanoscale dimensions, plastic particles exhibit behavior reminiscent of engineered nanomaterials, including high specific surface area, strong adsorption of biomolecules, and size- and surface-dependent toxicity [2, 1]. Experimental studies have shown that nanoplastics can be internalized by diverse cell types, accumulate in tissues, perturb metabolic and signaling pathways, and induce oxidative stress, inflammation, and neurotoxicity [2, 1]. At the same time, *in vivo* concentrations and exposure regimes often differ from those used in laboratory tests, leading to uncertainty in environmental and human health risk assessment [2, 1].

A critical open question is how MNPs perturb the structure and function of specific biomolecules and assemblies, such as enzymes, structural proteins, lipid bilayers, nucleic acids, and protein complexes. Nanoplastics can form protein coronas that modulate cellular uptake [13, 14, 15, 16, 17], bind directly to protein surfaces and alter secondary structure [3], or dissolve into lipid bilayers and modify membrane organization and dynamics [4, 9, 11]. Addressing these questions requires integration of toxicology, biophysics, and molecular simulation.

Molecular dynamics simulations are uniquely suited to resolve the nanoscale and molecular mechanisms of MNP-biomolecule interactions, as demonstrated in recent MD studies of nanoplastic-membrane systems and nanoplastic-protein model systems [3, 4]. Their theoretical foundations and algorithmic details are described extensively elsewhere [5, 6, 7, 12]. In parallel, adverse outcome pathway (AOP) frameworks, originally developed for traditional toxicants, are being adapted to micro- and nanoplastics to provide mechanistic links from molecular initiating events (MIEs), such as reactive oxygen species (ROS) generation or membrane perturbation, to organism- and population-level adverse outcomes [1].

The aims of this article are therefore four-fold:

1. To summarize the current experimental and computational evidence for the effects of micro- and nanoplastics on protein structure and other biological molecules [2, 3, 4, 1].
2. To introduce MD methodology in this context, emphasizing system construction, force-field selection, and sampling strategies for nanoplastic-biomolecule systems [5, 6, 7, 12, 4].
3. To propose and illustrate a concrete set of test MD simulations for nanoplastic-protein and nanoplastic-membrane interactions, including practical observables and their interpretation.
4. To review which physical quantities can be extracted from MD trajectories and how they relate to experimentally relevant toxicity endpoints and AOP concepts [1].

2 Micro and nano plastics in Biological Systems

2.1 Sources, sizes, and environmental occurrence

Macro-scale plastic waste in oceans, freshwaters, soils, and sediments gradually fragments into micro- and nanoplastics via combined action of photodegradation, thermal oxidation, mechanical abrasion, and biodegradation [2]. Microplastics originate both from primary sources (e.g. cosmetic microbeads, industrial pellets) and secondary fragmentation, while nanoplastics arise predominantly as secondary particles, though some commercial nanoplastic applications exist [2]. The dominant commodity polymers include polystyrene (PS), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC), and polyethylene terephthalate (PET) [2].

Nanoplastics are difficult to detect and quantify in environmental matrices due to their small size, low mass, and interference from natural colloids [2]. Consequently, estimates of environmental concentrations remain uncertain, complicating the extrapolation of laboratory toxicity data to real-world scenarios [2]. Standardization of sampling, isolation, and analytical protocols for nanoscale plastic particles remains an active area of research [2].

2.2 Uptake, translocation, and bioaccumulation

In aquatic organisms, PS and PMMA nanoplastics have been shown to be ingested by invertebrates (e.g. daphnids, rotifers, copepods, mussels) and vertebrates (e.g. fish), distribute to tissues including gills, liver, and gonads, and even cross the blood-brain barrier [2, 1]. In some cases, nanoplastics are transferred along food chains (algae → zooplankton → fish), affecting feeding behavior and lipid metabolism in higher trophic levels [2].

In mammalian models and *in vitro* intestinal models, PS and PET nanoplastics can cross epithelial barriers with low but non-negligible bioavailability, enter the circulation, and reach secondary organs [2, 1]. Surface chemistry (e.g. amine vs. carboxyl functionalization) and size strongly influence uptake, intracellular trafficking, and toxicity [2, 1]. These observations confirm that nanoplastics can reach cellular and subcellular compartments where direct molecular interactions with proteins, membranes, and nucleic acids become possible [10].

2.3 General toxicological endpoints

Across species, frequently reported endpoints of MNP exposure include:

- Oxidative stress (increased ROS, altered antioxidant enzyme activities; impaired redox homeostasis) [1].

- Inflammation (cytokine induction, immune cell activation, tissue infiltration and damage) [1].
- Neurotoxicity (acetylcholinesterase inhibition, altered neurotransmitter levels, behavioral changes such as reduced locomotion and altered feeding) [2, 1].
- Growth inhibition, developmental delays, reproductive toxicity, and altered energy metabolism in multiple taxa [2, 1].

AOP-based analyses highlight ROS generation as a central MIE for both micro- and nanoplastics, with oxidative stress and inflammatory signaling as key events leading to growth inhibition, behavioral changes, and other adverse outcomes [1]. For nanoplastics in particular, the high surface-to-volume ratio and capacity to cross cellular membranes amplify the importance of these molecular events [1].

3 Direct effects on proteins and other biomolecules

3.1 Adsorption and protein corona formation

When nanoplastics enter biological fluids, they rapidly adsorb proteins and other biomolecules, forming a "protein corona" that defines the biological identity of the particle and strongly influences cellular uptake and downstream responses [2, 1]. Coronas on PS nanoplastics can include plasma proteins, lipoproteins, complement factors, and pattern-recognition molecules, altering immune recognition, transport properties, and biodistribution [2, 1, 10].

From a structural perspective, adsorption can:

- Partially unfold proteins or shift conformational equilibria between folded, misfolded, and intermediate states [9].
- Mask or expose functional motifs (e.g. receptor-binding domains, catalytic residues).
- Promote protein-protein crosslinking or aggregation at the plastic surface, with potential amyloid-like behavior in some cases.

These effects depend strongly on surface chemistry, curvature, and heterogeneity of the nanoplastic, variables that can be systematically explored with all atom and/or coarse-grained MD simulations [5, 7].

3.2 Nanoplastics and secondary structure in model peptides

Atomistic MD simulations have begun to clarify how nanoplastics perturb secondary structure in model peptides. Hollóczki and co-workers investigated the interaction of plastic nanoparticles (including PS-like and nylon-6,6 particles) with helical peptides and tryptophan zipper motifs using explicit-solvent MD and structural analysis [3]. Ramachandran plots and secondary-structure assignments revealed that adsorption to

polymer nanoparticle surfaces can alter α-helix and β-hairpin stability, shifting dihedral angle distributions relative to neat aqueous solution [3]. Hydrophobic side chains showed strong affinity for hydrophobic plastic surfaces, and adsorption changed the local backbone conformational landscape, with potential implications for misfolding or aggregation [3, 9].

In classical backbone dihedral-angle space, conformational preferences can be described by a probability density $p(\phi, \psi)$, from which a conformational free-energy surface

$$F(\phi, \psi) = -k_{\mathrm{B}} T \ln p(\phi, \psi)$$

can be derived [5, 6, 9]. Here k_{B} is the Boltzmann constant, T the absolute temperature, and $p(\phi, \psi)$ the normalized probability of observing a given pair of dihedral angles. Nanoplastic-induced shifts in $p(\phi, \psi)$ therefore correspond to changes in the free-energy landscape of peptide secondary structure [9, 18].

These simulations demonstrate that even simple hydrophobic nanoplastics can influence the free-energy landscape of peptide secondary structure, particularly for motifs with large hydrophobic exposure or marginal stability [3, 9, 8].

3.3 Nanoplastics and membrane proteins

Many membrane proteins rely on specific lipid environments and membrane physical properties (thickness, curvature, lateral pressure profile) for proper folding, dynamics, and function [11, 10]. Any nanoplastic-induced perturbation of the bilayer may therefore secondarily alter membrane protein structure and activity. MD simulations of polyethylene nanoplastics in phosphatidylcholine bilayers show that nanoparticles dissolve into the hydrophobic core, disintegrating into single polymer chains that significantly increase bilayer thickness, alter lipid tail conformations, and enhance lateral lipid diffusion [4].

Bilayer thickness d_{bilayer} is commonly defined as the average distance between phosphorus atoms in opposing lipid leaflets [11]:

$$d_{\mathrm{bilayer}} = \left\langle z_{\mathrm{P}}^{(\mathrm{upper})} - z_{\mathrm{P}}^{(\mathrm{lower})} \right\rangle,$$

where $z_{\mathrm{P}}^{(\mathrm{upper})}$ and $z_{\mathrm{P}}^{(\mathrm{lower})}$ are the instantaneous z-coordinates of headgroup phosphorus atoms in the upper and lower leaflet, and $\langle\rangle$ denotes a time and molecule average. Hollóczki and Gehrke observed an increase of ~ 1.1 nm ($\sim 27\%$) in d_{bilayer} upon incorporation of PE nanoplastics into a POPC bilayer [4].

Lipid tail ordering is often quantified via the deuterium order parameter

$$S_{\mathrm{CD}} = \frac{1}{2} \left\langle 3 \cos^2 \theta - 1 \right\rangle,$$

where θ is the angle between the C-D (or C-H) bond vector and the bilayer normal. Increased S_{CD} corresponds to more ordered, extended hydrocarbon chains. Nanoplastic-

induced changes in S_{CD} provide a direct measure of how polymer incorporation modifies chain conformations [4].

These physicochemical changes can in principle:

- Shift helix tilt and rotation for transmembrane segments.
- Alter oligomerization equilibria of membrane protein complexes.
- Perturb gating, transport, or signaling processes that depend sensitively on membrane mechanics and thickness [11, 10].

While detailed MD studies of explicit membrane proteins in the presence of nanoplastics remain scarce, the membrane-centric results strongly suggest that MNPs can indirectly affect membrane protein structure and function via bilayer remodeling [4, 11, 1].

3.4 Other biomolecules: nucleic acids and carbohydrates

Direct MD work on nanoplastic-nucleic acid interactions is limited, but by analogy to carbon nanomaterials and other hydrophobic nanoparticles, one can anticipate base stacking interactions with hydrophobic surfaces and potential destabilization of local DNA/RNA structure, especially in unpaired or loop regions [7, 1]. Carbohydrate-rich structures such as mucins or glycosaminoglycans can adsorb onto charged nanoplastics, influencing corona composition, colloidal stability, and diffusion in mucus or extracellular matrix [1, 10]. Explicit simulation of these systems would require specialized force fields and longer timescales, but the conceptual framework is similar: MNPs reshape local conformational ensembles via non-specific hydrophobic and electrostatic interactions [5, 12].

4 Molecular dynamics methodology for nanoplastic-biomolecule systems

4.1 General MD framework

Classical MD integrates Newton's equations of motion for all atoms in a system, given a potential energy function (force field) that encodes bonded and non-bonded interactions [5, 6, 7]. For a system of N atoms with coordinates $\mathbf{r}_i$ and masses m_i, the equations of motion are

$$m_i \frac{\mathrm{d}^2\mathbf{r}_i}{\mathrm{d}t^2} = \mathbf{F}_i(\mathbf{r}_1, \ldots, \mathbf{r}_N) = -\nabla_{\mathbf{r}_i} U(\mathbf{r}_1, \ldots, \mathbf{r}_N),$$

where U is the potential energy and $\mathbf{F}_i$ the force acting on atom i [5, 6]. In practice, these equations are integrated numerically with algorithms such as the velocity Verlet scheme with a timestep Δt (typically 1-2 fs for all-atom biomolecular simulations) [5, 6].

For nanoplastic-biomolecule systems, typical choices include all-atom or united-atom force fields for proteins and lipids (e.g. AMBER, CHARMM, OPLS, GROMOS)

combined with polymer models for commodity plastics parameterized to reproduce structural and thermodynamic properties [7, 3, 4]. Explicit solvent (e.g. SPC/E or TIP3P water with ions) is usually employed to capture hydration and screening effects [5, 7, 4].

Periodic boundary conditions and particle-mesh Ewald (PME) electrostatics are standard for treating long-range interactions [5, 6]. Temperature and pressure control (e.g. Nosé-Hoover thermostat, Langevin thermostat, Parrinello-Rahman or Langevin piston barostat) maintain near-physiological conditions [5, 7].

The direct output of an MD simulation consists of the time-dependent positions and velocities of every atom in the system, collectively referred to as the trajectory. This trajectory is typically stored at regular intervals (e.g. every picosecond) and serves as the primary raw data from which all physical observables—such as RMSD, secondary structure content, diffusion coefficients, and interaction energies—are computed during post-processing. The trajectory thus provides a complete microscopic record of the system's evolution, enabling detailed analysis of structural transformations, binding events, and dynamic fluctuations that occur during the simulation.

Current all-atom MD simulations of nanoplastic–biomolecule systems are typically limited to timescales of tens to hundreds of nanoseconds and system sizes of hundreds of thousands to a few million atoms. These constraints arise from the computational cost of evaluating forces at each timestep and integrating equations of motion for all particles. Nevertheless, even within these limits, MD simulations can capture critical molecular events—such as initial protein adsorption, partial helix unfolding, nanoplastic insertion into lipid bilayers, and the onset of membrane remodeling—that provide valuable mechanistic insight into how nanoplastics perturb the structure and function of biological molecules.

4.2 Representing nanoplastics

Nanoplastics can be represented on a spectrum from coarse-grained beads to detailed atomistic models of polymer chains [7, 3, 4]. For PE and PS, united-atom descriptions have been successfully used to simulate plastic nanoparticles and chains in aqueous and lipid environments [3, 4]. Two common representations are:

- **Globular nanoparticles**: approximately spherical aggregates of multiple entangled polymer chains at a given diameter (e.g. 5 nm), representing a particulate nanoplastic [3].
- **Disentangled chains**: multiple linear polymer chains dispersed or partially aggregated within a medium, representing nanoplastics that have penetrated and reconfigured within a biomolecular assembly [4].

The choice depends on the biological question (e.g. initial adsorption vs. long-term incorporation and dissolution).

4.3 System construction: proteins and membranes

For protein-nanoplastic simulations, a typical protocol is [5, 7]:

1. Choose a protein of interest (e.g. small α-helical peptide, enzyme with known plastic binding, membrane protein).
2. Obtain or build an equilibrated structure in water (and membrane if applicable).
3. Place a nanoplastic particle or polymer chains at a defined distance and orientation relative to the protein, with sufficient solvent and ions to reproduce the desired ionic strength.
4. Perform energy minimization, gradual heating, and equilibration with positional restraints before production runs.

For membrane systems, Hollóczki and Gehrke constructed large POPC bilayers ($\sim$ 2300 lipids) with a PE nanoparticle embedded as a transmembrane object and conducted extensive equilibration and 200 ns production runs, complemented by systems with disentangled chains between lipid leaflets and appropriate control systems [4]. Similar strategies can be applied to mixed-lipid bilayers, cholesterol-rich membranes, or organelle-like compositions [11].

4.4 Sampling considerations and enhanced methods

Timescales for protein adsorption, partial unfolding, and membrane remodeling can exceed hundreds of nanoseconds [3, 4]. Where necessary, enhanced sampling methods (e.g. metadynamics, umbrella sampling, replica-exchange MD) can accelerate exploration of rare events such as insertion, desorption, or large conformational transitions [12]. Reaction coordinates might include:

- Distance between protein center of mass and nanoplastic.
- Polymer insertion depth into a membrane (measured along the bilayer normal).
- Backbone RMSD and fraction of native contacts Q for specific secondary-structure elements.

The potential of mean force (PMF) $W(z)$ for nanoplastic insertion along coordinate z (e.g. depth in a bilayer) can be obtained from umbrella sampling as [12]

$$W(z) = -k_{\mathrm{B}}T \ln P(z) + C,$$

where $P(z)$ is the unbiased probability distribution and C an arbitrary constant. The PMF quantifies the free-energy cost or gain associated with moving the particle along z.

4.5 MD simulation workflow

For clarity, Figure 1 shows a simplified flow diagram of a typical MD simulation workflow as used for nanoplastic-biomolecule systems. This algorithmic view emphasizes that nanoplastic-specific models enter primarily in the system-definition stage (structures, force field) and in the analysis stage (choice of observables directly linked to toxicological endpoints [5, 7, 1]).

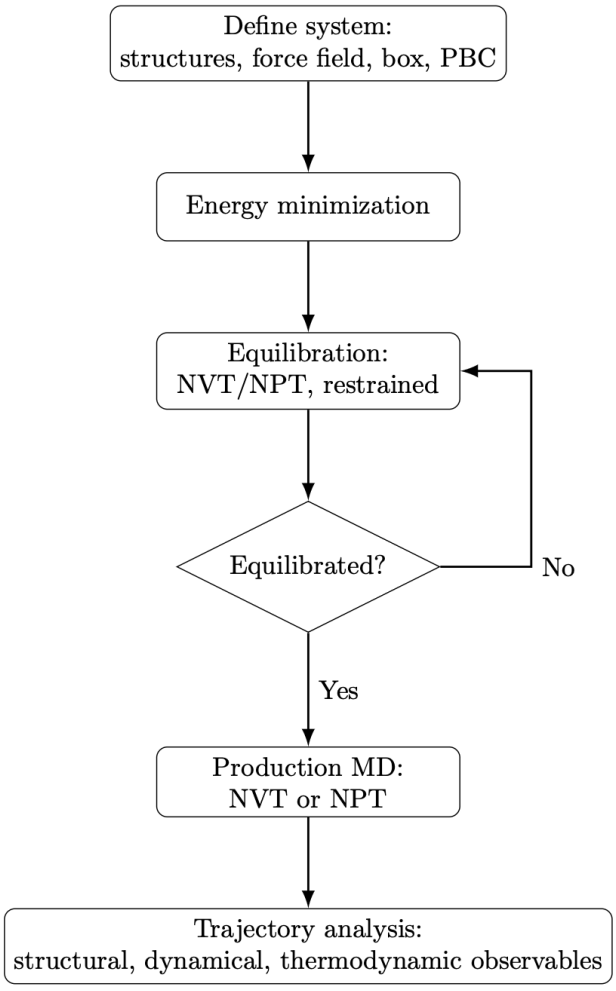

Fig. 1: Simplified flow diagram of a molecular dynamics simulation workflow for nanoplastic-biomolecule systems [5, 6].

5 Example simulations

5.1 Nanoplastic-model protein adsorption

5.1.1 System design

A minimal, yet informative setup includes:

- **Protein**: a small α-helical peptide (e.g. 10-20 residues) or a β-hairpin motif such as a tryptophan zipper, previously used to study nanoplastic-protein interactions [3, 9].
- **Nanoplastic**: a $\sim$ 5 nm PS or nylon-6,6 nanoparticle modeled as entangled chains; optionally variants with different surface chemistries (neutral, carboxylated, aminated).
- **Solvent**: explicit water with physiological ionic strength (e.g. 0.15 mole per liter NaCl).

Multiple initial configurations (e.g. different orientations and distances) should be simulated to assess variability and convergence [5, 6].

5.1.2 Observables and mathematical definitions

From these trajectories, one can compute the following characteristics.

(1) Secondary structure content

The time-dependent fraction $f_\alpha(t)$ of residues in α-helical conformation can be monitored using DSSP or similar algorithms [9]. An overall average fraction

$$\bar{f_\alpha} = \frac{1}{T}\int_0^T f_\alpha(t)\,\mathrm{d}t$$

allows comparison between the free peptide and the peptide adsorbed on the nanoplastic surface. Analogous expressions can be defined for β-sheet or coil content [9].

(2) Backbone RMSD and RMSF

The root-mean-square deviation (RMSD) of backbone atoms from a reference structure (e.g. initial or average structure) is defined as [5, 7]

$$\mathrm{RMSD}(t) = \sqrt{\frac{1}{N_{\mathrm{bb}}}\sum_{i=1}^{N_{\mathrm{bb}}} \left\|\mathbf{r}_i(t) - \mathbf{r}_i^{\mathrm{ref}}\right\|^2},$$

where N_{bb} is the number of backbone atoms, $\mathbf{r}_i(t)$ their positions at time t, and $\mathbf{r}_i^{\mathrm{ref}}$ the reference positions. Residue-wise flexibility can be captured by the root-mean-square fluctuation (RMSF)

$$\mathrm{RMSF}_i = \sqrt{\left\langle \|\mathbf{r}_i(t) - \langle \mathbf{r}_i \rangle\|^2 \right\rangle_t},$$

where $\langle \mathbf{r}_i \rangle$ is the time-averaged position of atom i [6].

(3) Protein-plastic contact number

A simple measure of contact between protein and nanoplastic is

$$N_{\mathrm{c}}(t) = \sum_{i \in \mathrm{prot}} \sum_{j \in \mathrm{plast}} H\left(r_{\mathrm{c}} - \left\|\mathbf{r}_i(t) - \mathbf{r}_j(t)\right\|\right),$$

where H is the Heaviside step function, r_{c} a cutoff (e.g. 0.4 nm), and the sums run over protein and plastic atoms, respectively [5]. Averaging $N_{\mathrm{c}}(t)$ over time and decomposing by residue type provides insight into binding interfaces.

(4) Interaction energies

The non-bonded interaction energy $E_{\mathrm{int}}(t)$ between protein and nanoplastic can be decomposed as [7]

$$E_{\mathrm{int}}(t) = E_{\mathrm{Coul}}(t) + E_{\mathrm{LJ}}(t),$$

where E_{Coul} and E_{LJ} are Coulombic and Lennard-Jones contributions. These can be further decomposed by residue or side-chain class to identify hydrophobic or electrostatic "hotspots" of binding.

5.2 Nanoplastic-lipid bilayer simulations

5.2.1 System design

Following Hollóczki and Gehrke, one can construct [4, 11]:

- A POPC or mixed-lipid bilayer in saline solution.
- A globular PE nanoparticle (5 nm diameter) embedded as a transmembrane object.
- A companion system where the same total number of monomers are arranged as disentangled chains between the leaflets.
- A control bilayer without plastic.

These systems enable direct comparison of structural and dynamical metrics across conditions.

5.2.2 Observables and mathematical definitions

Key membrane observables include the following characteristics.

(1) Bilayer thickness and area per lipid

As defined above, the bilayer thickness is

$$d_{\text{bilayer}} = \left\langle z_{\text{P}}^{(\text{upper})} - z_{\text{P}}^{(\text{lower})} \right\rangle,$$

and the area per lipid A_{lipid} in a rectangular box of dimensions $L_x \times L_y \times L_z$ is [11]

$$A_{\text{lipid}} = \frac{L_x L_y}{N_{\text{lipid,leaflet}}},$$

where $N_{\text{lipid,leaflet}}$ is the number of lipids per leaflet. Nanoplastic incorporation tends to increase d_{bilayer} and decrease A_{lipid} compared to a neat bilayer [4].

(2) Tail order parameters

For each C-H bond along the lipid tails, the deuterium order parameter

$$S_{\text{CD}} = \frac{1}{2} \left\langle 3\cos^2\theta - 1 \right\rangle$$

quantifies chain ordering, where θ is the angle between the bond vector and bilayer normal [11]. A shift toward more positive S_{CD} indicates greater alignment and chain extension. Nanoplastic-induced changes in S_{CD} directly reflect modifications in membrane mechanical properties [4].

(3) Lateral diffusion coefficient

The lateral diffusion coefficient D of lipid molecules in the bilayer plane can be extracted from the two-dimensional mean-square displacement (MSD) [11, 6]

$$\text{MSD}(t) = \left\langle \left\| \mathbf{r}_{\parallel}(t_0 + t) - \mathbf{r}_{\parallel}(t_0) \right\|^2 \right\rangle_{t_0},$$

where $\mathbf{r}_{\parallel}$ is the 2D position (projection onto xy plane). For sufficiently long times in the diffusive regime,

$$\text{MSD}(t) \approx 4Dt,$$

so that D can be estimated from the slope of $\text{MSD}(t)$ vs. t. Hollóczki and Gehrke observed an increase in D in the presence of PE nanoplastics [4].

(4) Surface coverage and interfacial areas

Using Voronoi tessellation-based domain analysis, one can compute the total nanoplastic surface area A_{tot} and its partition into interfaces with lipids $A_{\text{plast-lip}}$, water $A_{\text{plast-wat}}$, and other plastic atoms [3, 4]. A simple measure of surface coverage by lipids is

$$\theta_{\text{lip}} = \frac{A_{\text{plast-lip}}}{A_{\text{tot}}}.$$

An increase in θ_{lip} over time reflects progressive embedding of nanoplastic material into the bilayer [4].

6 Physical quantities from MD and their interpretation

Table 1 summarizes representative quantities obtainable from MD trajectories in this context, along with their physical meaning and relevance.

In the context of proteins and peptides, the key structural observables extracted from MD trajectories - such as the time-dependent secondary structure content, Ramachandran angle distributions, root-mean-square deviation (RMSD), and root-mean-square fluctuation (RMSF) - are directly linked to how specific segments of the polypeptide chain become ordered, loosened, or partially unfolded in the presence of nanoplastics [9, 10]. First, the evolution of the secondary structure content (e.g. the fraction of residues in α-helical or β-sheet conformation) quantifies the stability of individual motifs under different environmental conditions [9]. If a peptide or protein maintains a high and nearly constant average helical fraction $\bar{f}_\alpha$ in aqueous solution, while $\bar{f}_\alpha$ decreases significantly in the presence of nanoplastics, this indicates that the particles promote local helix unfolding. In structural terms, adsorption of nanoplastics to hydrophobic faces of a helix may stabilize alternative side-chain orientations and backbone hydrogen-bond patterns, thereby shifting the equilibrium toward more disordered or coil-like states [3, 9]. Conversely, an increase in the fraction of coil structure in specific sequence segments signals that these regions lose their native secondary structure and become more flexible and extended [9, 10].

Second, Ramachandran plots and the associated conformational free energy surface $F(\phi, \psi)$ provide a microscopic view of backbone conformational changes [9, 18]. Shifts of the dominant populations in (ϕ, ψ) space away from regions typical for α-helical conformations (around $\phi \approx -60°, \psi \approx -45°$) toward regions associated with β-structures or disordered states indicate that the peptide backbone rotates around the C_α-N and C_α-C bonds and adopts alternative conformations [9]. In the presence of nanoplastics, such shifts can arise because interactions with the plastic surface stabilize particular side-chain orientations or backbone hydrogen-bonding patterns, thereby altering the location of the free-energy minima in (ϕ, ψ) space and moving the system toward misfolded or partially unfolded conformations [3, 4].

Global measures such as RMSD with respect to a reference structure report how far the entire protein deviates from its initial or experimentally determined conforma-

Table 1: Representative MD observables for nanoplastic-biomolecule systems.

Quantity	**Definition / MD evaluation**	**What it reveals**	**Relevance in nanoplastic context**
Secondary structure content	Fraction of residues in α, β, 3_{10}, π, coil via DSSP or similar [9]	Stability of helices, sheets, turns	Adsorption-induced helix or sheet destabilization linked to loss of protein function or misfolding [8, 3].
Ramachandran distributions	2D histograms of ϕ, ψ dihedrals and free energy $F(\phi, \psi)$ [9]	Allowed vs. disfavored backbone conformations	Shifts in backbone ensembles near plastic surface vs. bulk indicate structural perturbation [3].
RMSD / RMSF	Deviation from reference structure and residue-wise fluctuations [5, 6]	Global and local flexibility	Increased fluctuations near binding sites may correlate with activity loss or gain.
Protein-plastic contact number	Number of atoms or residues within a cutoff distance from plastic [5]	Binding interface size and composition	Identifies hydrophobic patches driving adsorption and potential hotspots for structural change.
Bilayer thickness	Average leaflet separation (P-P distance) [11]	Membrane stretching or thinning	Nanoplastic-induced thickening observed for PE in POPC, with implications for membrane protein function [4].
Area per lipid	Box area divided by number of lipids per leaflet [11]	Lateral packing density	Decrease upon plastic incorporation indicates denser packing and possible permeability changes [4].
Tail order parameters	$S_{\mathrm{CD}} = \frac{1}{2}\langle 3\cos^2\theta - 1\rangle$ per tail segment [11]	Chain ordering and fluidity	Changes reflect altered mechanical properties and diffusion barriers [4].
Lateral diffusion coefficient	Slope of MSD vs. time in 2D, $\mathrm{MSD}(t) \approx 4Dt$ [6, 11]	Membrane fluidity	Increased diffusion in presence of plastic suggests modified viscosity and domain dynamics [4].
Interaction energies	Non-bonded energies between plastic and biomolecules [7]	Binding strength, driving forces	Decomposition by residue or lipid species indicates specificity of nanoplastic-biomolecule contacts.
Surface coverage and interfacial areas	Voronoi tessellation on molecular surfaces [3, 4]	How much plastic surface contacts lipids vs. water	Demonstrates dissolution of nanoplastics into membranes and entanglement with lipids [3, 4].

tion [5, 6, 7]. A gradual increase of RMSD that reaches a plateau at a moderate value typically reflects relaxation toward a thermally equilibrated conformation in the given environment, whereas a pronounced growth of RMSD and large fluctuations suggest transitions to alternative, structurally distinct states [5]. In the context of nanoplastic exposure, a substantial and persistent increase of RMSD for a functional helix or domain relative to the control simulation in water would be indicative of destabilization of that structural element, potentially compromising its biological role [9, 8]. Complementarily, residue-resolved RMSF quantifies local flexibility along the sequence, allowing

one to identify regions that become either more mobile or more rigid [6]. An increase in RMSF for residues in contact with the nanoplastic surface points to enhanced local mobility, suggesting frequent transitions between folded and partially unfolded substates, whereas a decrease in RMSF may signal that the protein segment becomes "locked" against the plastic surface in a single, adsorbed conformation [3, 4]. Together, these observables translate changes in the microscopic conformational ensemble into quantitative descriptors of structural destabilization, local unfolding, or rigidification triggered by nanoplastics.

For lipid bilayers, the set of observables described above - including the bilayer thickness d_{bilayer}, the area per lipid A_{lipid}, the deuterium order parameter S_{CD}, and the lateral diffusion coefficient D - captures how nanoplastics alter lipid packing, chain extension, membrane fluidity, and mechanical properties [11]. In particular, thickening of the bilayer accompanied by a decrease in A_{lipid} corresponds to a state in which the hydrocarbon chains are more extended and lipids are packed more densely in the plane of the membrane [11]. This situation has been observed in simulations where polyethylene-like nanoplastics dissolve into the hydrophobic core and disintegrate into individual chains, effectively acting as "spacers" that push lipid tails into more elongated conformations and increase the distance between opposing leaflets [4]. From the point of view of membrane structure, such changes can modulate the hydrophobic mismatch between lipids and embedded membrane proteins, shift helix tilt angles, and modify the energetic cost of pore or defect formation [11, 10].

The deuterium order parameter S_{CD} provides a more local, segment-resolved measure of chain extension and orientational order [11]. More positive values of S_{CD} indicate that the corresponding C-H (or C-D) bonds are preferentially aligned with the bilayer normal, which is characteristic of straighter, more ordered hydrocarbon chains; values closer to zero indicate increased conformational disorder and a higher population of gauche states along the chain. An overall increase in S_{CD} in the presence of nanoplastics therefore reflects a shift toward more ordered and extended lipid tails, consistent with membrane thickening and a more "gel-like" state of the bilayer core [4, 11]. Conversely, a decrease in S_{CD} would imply increased chain bending and a more fluid, disordered membrane. By quantifying these changes, MD simulations provide a direct microscopic link between nanoplastic-induced alterations at the level of individual lipid chains and macroscopic membrane properties such as rigidity, permeability, and domain formation [11, 1].

The lateral diffusion coefficient D characterizes the translational mobility of lipids in the membrane plane and is a sensitive indicator of membrane fluidity [6, 11]. If incorporation of nanoplastic chains into the bilayer core increases D relative to a control system, this suggests that local packing interactions between neighboring lipids are weakened or reorganized, facilitating lateral rearrangements and potentially leading to the formation of heterogeneous microdomains with distinct dynamical properties [4, 11]. Conversely, a decrease in D indicates that the membrane becomes more viscous and laterally constrained, which could hinder the diffusion and oligomerization of membrane proteins, and thereby affect signaling processes that rely on lateral organization [11, 10]. In combination with d_{bilayer}, A_{lipid}, and S_{CD}, the diffusion coefficient thus completes a coherent picture of how nanoplastics reshape the membrane landscape at both structural and dynamical levels.

Finally, interaction energies between nanoplastics and biomolecules, together with the number and nature of contacts at the interface, illuminate how specific molecular interactions drive the structural changes discussed above [7, 5]. A strongly stabilizing interaction energy between nanoplastics and proteins, combined with a high number of hydrophobic contacts, indicates the formation of a persistent adsorption interface, often involving exposure of otherwise buried hydrophobic side chains and "flattening" of helices or loops against the plastic surface [3, 4]. In membrane systems, favorable interaction energies between nanoplastic chains and lipid tails, accompanied by extensive polymer-lipid contacts, signal dissolution of the nanoplastics into the hydrophobic core and entanglement with lipid acyl chains [4]. These energetic and contact-based descriptors therefore bridge geometric observables (secondary structure content, bilayer thickness, order parameters) with a mechanistic understanding of the driving forces underlying nanoplastic-induced structural perturbations [7, 5].

Taken together, the physical quantities computed from MD trajectories - geometric, energetic, and dynamical - provide a consistent and quantitative language for describing how nanoplastics alter the conformational ensembles of proteins and peptides, reshape lipid bilayers, and modify the interactions that govern biomolecular structure and function [9, 11, 4, 1]. They thus form a crucial link between atomistic mechanisms and experimentally observed toxicological endpoints, such as loss of enzymatic activity, membrane leakage, oxidative stress, and inflammation [2, 1].

7 Nanoplastics, oxidative stress, and adverse outcome pathways

Hu and Palić systematically reviewed micro- and nanoplastic-induced oxidative and inflammatory events and mapped reported endpoints onto existing AOPs [1]. Across diverse organisms and models, ROS generation emerged as a common MIE, followed by oxidative stress, activation of MAPK and Nrf2 pathways, lipid peroxidation, DNA damage, mitochondrial dysfunction, lysosomal disruption, apoptosis, and inflammation [1].

From an MD perspective, several of these events relate directly or indirectly to structural and dynamical changes in proteins and membranes:

- **Membrane perturbation**: altered bilayer properties can affect mitochondrial inner membrane function, promoting ROS production and initiating ROS-induced ROS-release cascades [1, 11].
- **Lysosomal integrity**: nanoplastic accumulation and membrane disruption can compromise lysosomal membranes, releasing hydrolytic enzymes and further exacerbating oxidative damage [1].
- **Enzyme inactivation**: structural changes in antioxidant enzymes or signaling proteins may impair detoxification and repair pathways, amplifying oxidative stress [9, 10].

AOP-based schematics for micro- and nanoplastics indicate that from an ecological perspective, ROS-driven cascades ultimately lead to growth inhibition, behavioral changes, and reproductive impairment, while from a human-health perspective, apop-

tosis and chronic inflammation emerge as probable outcomes, although detailed AOPs remain incomplete [1].

8 Perspectives, challenges, and future directions

Despite rapid progress, significant gaps remain in our understanding of how micro- and nanoplastics perturb biomolecular structure and function:

- Experimental toxicology often uses high doses and simplified exposure scenarios that may not reflect environmental conditions [2, 1].
- The diversity of plastic types, sizes, shapes, and surface chemistries complicates generalization from model particles (often pristine PS) to environmental nanoplastic mixtures [2].
- Environmentally aged nanoplastics, with modified surfaces and adsorbed contaminants, likely interact differently with biomolecules than pristine laboratory particles [2, 1].
- Comprehensive MD studies of realistic systems (e.g. mixed coronas on heterogeneous nanoplastics interacting with multi-domain proteins or complex membranes) are computationally demanding [3, 4, 5].

Nonetheless, MD can play a central role in bridging molecular-level mechanisms with higher-level toxicological outcomes by:

- Systematically exploring structure-activity relationships for different polymer chemistries, sizes, and functionalizations using standardized sets of observables such as those listed in Table 1 [5, 6].
- Quantifying how specific nanoplastics perturb known protein motifs (e.g. α-helices, β-hairpins, catalytic loops) or membrane properties and mapping these perturbations to MIEs and KEs in AOP frameworks [1, 9, 11].
- Providing mechanistic hypotheses to guide targeted experiments and refine AOPs, including predictions of size- and surface-charge dependence of ROS generation, membrane damage, and enzyme inactivation [1, 12].

Future work should prioritize integration of MD with high-resolution biophysical experiments (e.g. NMR, cryo-EM, advanced fluorescence), realistic exposure scenarios, and multi-scale modeling that connects nanoscale events to cellular and organismal responses [9, 10, 4, 1]. As analytical methods for detecting and characterizing environmental nanoplastics continue to improve, it will become increasingly feasible to simulate realistic nanoplastic-biomolecule systems with parameters directly informed by field data [2].

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