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MOLECULAR DYNAMICS SIMULATIONS: EXPLORING THE TEMPORAL EVOLUTION OF COMPLEX SYSTEMS FOR THERMODYNAMIC AND BIOLOGICAL INSIGHTS

Prakash R[a]*, Joanna Nicole D'souza [b], Maryanne Varghese [c], Sarah Philip [d]

[a] Department of Mathematics, RV College of Engineering, Bengaluru 560059, Karnataka, India
[b, c, d] Department of Biotechnology, RV College of Engineering, Bengaluru 560059, Karnataka, India
Corresponding author: prakashr@rvce.edu.in

Abstract:

Molecular dynamics (MD) simulations offer a powerful computational approach to track the precise temporal evolution of systems under defined conditions, such as specific temperature or pressure. By leveraging statistical mechanics, these simulations provide comprehensive insights into thermodynamic properties and dynamic behaviors. Beyond thermodynamics, MD simulations enable detailed exploration of chemical reaction mechanisms and other time-dependent processes, including diffusion. Particularly, in the context of biomaterials, MD simulations facilitate a deeper understanding of structure-activity relationships and aid in the rationalization of biological applications, making them an indispensable tool in the study of complex and extensive systems.

Keywords: Biomolecules, Molecular dynamics, Boundary conditions, MD trajectory, Radial distribution functions.

1.0 Introduction

Understanding the characteristics of biomaterials at the microscopic level is a difficult endeavor due to the intricacy of the several physicochemical interactions that influence their activity. For example, bioactive implants used for bone repair or replacement are often inorganic materials (glasses, ceramics, or a suitable mix) that may interact and integrate with a biological environment (1-3). A variety of interactions between the synthetic material and the living body occur at the same time, dynamically modifying the material-tissue interface until the implant is either firmly anchored to the tissue by strong chemical bonds, or has completely dissolved after completing its task (for example, after releasing a drug or an antibacterial agent in-situ) [2].

Surface-analytical experimental techniques can reveal macroscopic effects and processes at the interface between an implant and its biological environment, sometimes with very good time and space resolution, providing an explicit measurement of the different responses of specific biomaterials in realistic conditions [4]. To gain a better understanding of how biomaterials work, one must examine processes that occur on a "atomistic" scale (that is, interatomic separations as small as 0.1 nm and a time resolution of 10 6 s or less): unfortunately, even the most powerful experimental methods cannot achieve this resolution. Computer

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simulations offer a direct path to investigating the structural and dynamical features of atom assemblies, making them an excellent tool for probing the properties of biomaterials at the atomic level.

In particular, with the advent of powerful supercomputers and the availability of parallel simulation codes optimized to make the most of the unprecedented computational power available, we can now conduct accurate and reliable computer experiments of systems and processes that were previously impractical. The molecular dynamics (MD) method is now the most widely used strategy for modelling relatively large and complicated systems with atomistic precision, such as periodic solids, liquids, and biomolecules in solution ([5] - [8]).

An MD simulation offers a succession of "snapshots" of the system at various points in time: this trajectory replicates the system's natural temporal development under defined operational circumstances, such as room temperature and air pressure. As we will see in the coming sections, an MD trajectory not only gives us access to the thermodynamic parameters of the system, but it also allows us to look at dynamical processes that are controlled by the simulation's limited temperature.

On the one hand, classical MD using predefined force fields can be used to investigate biological system and materials containing up to millions of atoms for time lengths up to the microsecond scale, with an accuracy which is completely and exclusively determined by the force field adopted. On the other hand, ab-initio (AI) MD can be used to tackle systems that are intrinsically difficult or impossible to treat with classical MD and predefined potentials, such as those involving chemical reactions, breaking and formation of chemical bonds, and in general electronic effects which can hardly be incorporated in a classical interatomic potential ([6], [9], [10]).

2.0 The Molecular Dynamics Method:

All molecular dynamics techniques include the numerical integration of the classical equations of motion for a system with N atoms or interaction sites:

$$F_i = m_i a_i;\ F_i = -\frac{\partial V}{\partial r_i},\ i = 1, 2, ..., N \qquad (1)$$

where the index i runs from 1 to N; r_i and a_i are the position and acceleration vectors of atom i, m_i is the atomic mass, F_i is the total force acting on i, and $V = V(r_1, \ldots, r_N)$ is the potential function. The latter is the key ingredient of an MD simulation: once V has been defined, eq. 1 allows us to propagate an initial configuration $\Gamma(0) = \{R(t = 0); P(t = 0)\}$, where $R = \{r_1, \ldots, r_N\}$ and $P = \{p_1, \ldots, p_N\}$ are the set of individual positions ri and momenta pi , respectively, along discrete subsequent time points Δt, separated by the time step Δt.

The proper time step (t) for an MD run depends on the quickest motions that characterise the system, such as high-frequency vibrations: t should be brief enough to limit errors in the (finite-difference) integration of these fast motions, avoiding an unnecessary short t that will only waste computer resources.

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2.1 Statistical Ensemble:

A single configuration (or microstate) Γ of our N-particle system is represented by the 6N components of the {R} and {P} position and momentum vectors; the set of all the possible Γ = {R; P} microstates are named phase space.

A standard MD simulation of Nrun time steps will produce a trajectory {Γ (0), Γ (Δt), Γ (2Δt), … …, Γ (NrunΔt)} in phase space, which is the sequence of Nrun successive instantaneous configurations visited by the system during its dynamical evolution.

The individual configurations of an MD trajectory are all unique and different from each other, they belong to a common constant energy portion of the phase space. The collection of all microstates sharing the same total energy (or some other macroscopic quantity) is the statistical ensemble.

2.3 Periodic Boundary Conditions:

No matter how large the number of atoms N in the simulated system is, it will always be much smaller than the number of atoms (of the order of the Avogadro number, ~ 6×10^{23}) in a real, macroscopic sample.

The most immediate consequence is that the ratio of the number of atoms found at the boundary and in the bulk of the system will be much higher in the simulated than in the real system: everything would be surface.

The common solution to remove this artifact in MD simulations is to apply periodic boundary conditions (PBC) to a central box containing the system: the box is replicated infinitely along each direction, such that a particle leaving the central box will be mirrored by the image of the same particle in the adjacent box, which will enter the box from the opposite side. In this way, boundaries are completely removed and every atom in the central box is embedded in a bulk-like environment ([11], [21]).

2.4 Calculating Structural and Dynamical Properties:

The extremely detailed description of an MD trajectory can be processed to obtain measurable thermodynamic properties of a system. However, in most cases, it is this highly detailed description, and its correspondingly high space and time resolution, which make MD simulations an invaluable tool, providing a unique route to investigate structural and dynamical properties which are not easily measurable with standard experimental techniques.

For instance, radial distribution functions (RDF) are a powerful tool to analyze the atomistic structure of liquids and solids: these functions show maxima at the typical interatomic distances which characterize the system.

The individual contributions of specific atomic pairs to the total radial distribution function of disordered solids and liquids are hard to identify in the experimental RDF obtained from diffraction experiments, and advanced techniques are often needed to separate the individual patterns.

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On the contrary, the straightforward postprocessing analysis of an MD trajectory can easily provide each individual contribution to the total RDF, thus enormously helping the assignment of the peaks in the experimental curve, and the interpretation of the underlying atomic structure.

In fact, it is quite straightforward to calculate partial RDFs from an MD trajectory, simply by focusing on the distance rAB separating all atoms of species A and B during the trajectory: the partial A-B RDF(r) is the probability of finding an A-B pair separated by r, relative to a homogeneous (random) distribution of A and B:

$$RDF_{AB}(r) = \frac{\left\langle \frac{1}{N_A} \sum_{i=1}^{N_A} \sum_{j=1}^{N_B} \delta\left(r - r_{ij}\right) \right\rangle}{\rho_{AB}^{hom}(r)} \qquad (2)$$

where the <…> brackets denote a time average, N_A and N_B are the total number of atoms of species A and B, respectively, and the ideal density of a corresponding homogeneous system is at the denominator, whereas the numerator is essentially the cumulative (running) coordination number of species B found in a sphere of radius r centered on atom A.

2.5 Classical MD: The potential function:

In MD simulations, the nuclei move in the potential energy surface V (R). For most systems, it is not possible or practical to obtain V (R) through ab-initio energy minimizations.

In classical MD, one selects an analytical potential function suitable for the system under study before starting the simulation, and then calculates the forces as analytical gradients of this potential function. The interatomic potential function for classical MD is typically written as a sum of different terms, each one representing a different kind of interaction. For instance, short-range, non-bonded interactions can be described through a term of the form:

$$V^{N_B}(R) = \sum_i \sum_{j>i} v(r_{ij}) \qquad (3)$$

where the double sum runs over all different pairs of atoms and v (r_{ij}) is the pair potential, representing the contribution of the individual interaction of atom i with atom j.

For systems dominated by covalent interactions, such as organic species and biomolecules, many force fields complement the nonbonded interaction terms with additional terms, more suited to represent the individual bonds and functional groups.

In this case, the potential function can be made dependent not only of the bonding distance between pairs of atoms, but also on the bending angle between groups of three atoms and on the dihedral (torsion) angle involving chains of four atoms:

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$$V^{\text{bonded}}(\mathrm{R}) = \sum_{\substack{\text{bonds}\\ \text{i - j}}} k_{ij}\left(r_{ij} - r_{ij}^{0}\right)^2 + \sum_{\substack{\text{angles}\\ \text{i - j - k}}} k_{ijk}\left(\theta_{ijk} - \theta_{ijk}^{0}\right)^2 + \sum_{\substack{\text{dihedrals}\\ \text{i - j - k - l}}} k_{ijkl}\left(\phi_{ijkl} - \phi_{ijkl}^{0}\right)^2 \qquad (4)$$

Amongst all the potential parameters, a particularly critical choice in calculations employing empirical potentials involves the atomic charges qi , which affect the calculation of long-range electrostatic forces: whereas in some cases it is possible to adopt formal ionic charges, many standard forcefields employ partial (fractional) charges, for instance obtained from quantum mechanical calculations, which may provide a more accurate representation of the actual charge on average surrounding an atom in a partially covalent.

2.6 Potential Parameters:

Having selected a suitable analytical form, the selection of appropriate parameters is the most critical task in building a model potential for MD simulations.

Because each individual interaction term requires specific parameters, which are different for bonds, angles, dihedral, van der Waals, and electrostatic interactions involving different pairs or groups of atoms, it is easy to see that the number of potential parameters needed to start the simulation can be quite substantial, for multicomponent systems [20].

Different strategies can be followed to obtain the set of parameters: one can variationally identify the best combination of parameters which, when used in the potential, yields a model which reproduces experimental or ab-initio properties of systems related to the one under study [12].

For instance, cell parameters, elastic constants and phonon frequencies of crystalline structures, obtained from experimental data or from ab-initio calculations, can all be used to parameterize a potential aimed at modeling solid, amorphous and liquid phases.

3.0 AB-INITIO Molecular Dynamics (AIMD):

All issues related to the transferability of the potential are removed if the interatomic forces are calculated “on-the-fly” from first principles, that is through a rigorous quantum-mechanical approach for each new configuration visited along the MD trajectory [17].

This is the spirit of ab-initio MD (AIMD): whereas the nuclei still move following the classical equations of motion 18.1, their motion is now controlled by highly accurate ab-initio forces. Because the calculation of ab-initio forces involves an explicit optimization of the electronic structure at each time step, this enormously increases the computational requirements of AIMD [18].

In 1985, Car and Parrinello devised a method to advance the nuclear positions using ab-initio forces, but without the need of repeating an explicit, self-consistent electronic minimization at each time step ([13], [14]).

This remarkable goal was achieved by introducing the electrons as additional (fictitious) dynamical degrees of freedom, which led to a set of coupled differential equations for the (real) motion of nuclei and that (fictitious) of the electrons [19].

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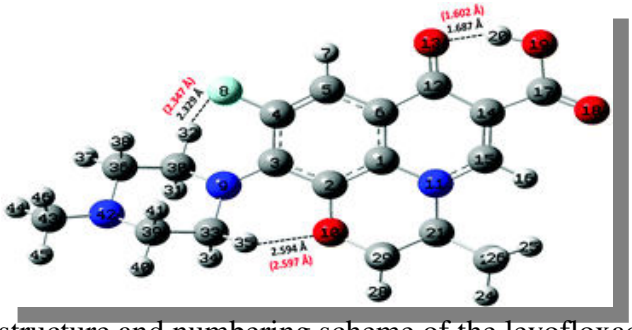
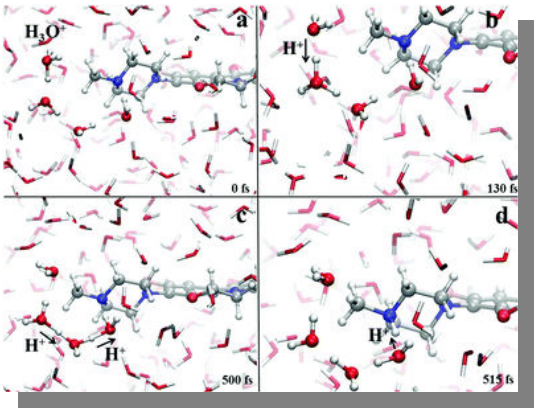
3.1 AIMD: Case Study

In this study, the software package CP2K was used to perform Car–Parrinello-like molecular dynamics (CPMD) simulations of levofloxacin solvated in aqueous solutions [15].

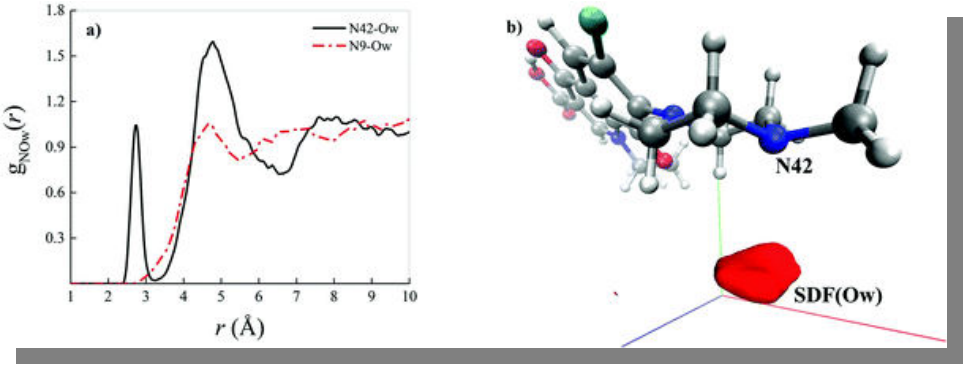
A numerical sample composed of one levofloxacin and 253 water molecules (i.e., 814 atoms) was placed in a cubic simulation box with an edge equal to 20.21 Å under periodic boundary conditions. Such a molecular configuration was then equilibrated by means of first-principles molecular dynamics for 5 ps, after which an accumulation run 50 ps-long initiated [16].



Ground-state structure and numbering scheme of the levofloxacin molecule



Protonation mechanism of levofloxacin giving rise to the protonated levofloxacin HL form. Red, white, grey and blue spheres represent the oxygen, hydrogen, carbon and nitrogen atoms, respectively. Proton transfer events are marked with a black arrow heading toward the acceptor species.



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(a) Radial distribution function (RDF) between the nitrogen atom of levofloxacin labeled as N42 and the oxygen atoms of the solvating aqueous environment (black solid curve) and the RDF between the nitrogen atom of levofloxacin labelled as N9 and the oxygen atoms of the surrounding water molecules (red dashed-dotted curve) as determined from CPMD simulations.
(b) Spatial distribution function (SDF) of the oxygen atoms (Ow) of the surrounding water molecules taking as a reference the levofloxacin nitrogen atom N42.

4.0 Conclusion and Future scope

The molecular dynamics approach is a potent form of computer simulation that gives access to the precise temporal development (trajectory) of a system under specific parameters, such as a specific temperature or pressure. Statistical mechanics methods may be used to examine the system's whole trajectory in order to derive thermodynamic values and dynamical characteristics. In addition, the mechanism of chemical reactions and other time-dependent processes, such as diffusion, can be elucidated in great detail. MD simulations are a useful tool for understanding structure-activity correlations and rationalizing biological applications when used to mimic extensive and complicated systems, such as biomaterials.
For many physiologically significant systems, it is now possible to follow fast processes—those happening in less than a millisecond—at atomic precision using molecular dynamics simulations. These simulations seem to be in a position to have a considerable influence on how new medications are discovered, maybe even changing the drug discovery process itself.

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