JOINT INSTITUTE FOR NUCLEAR RESEARCH
Frank Laboratory of Neutron Physics

FINAL REPORT ON THE INTEREST PROGRAMME

INTRODUCTORY COURSE: MD-SIMULATION RESEARCH (FROM ATOMIC FRAGMENTS TO MOLECULAR COMPOUND)

Supervisor:
Prof Kholmirzo Kholmurodov

Student:
Baishakhi Sahoo
Institute of Chemical Technology,
Mumbai, India

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ABSTRACT

The theoretical underpinnings and several application fields of Molecular Dynamics (MD) simulation techniques are thoroughly examined in this research. The study starts with a summary of fundamental concepts, such as interatomic potentials, Newton's equations of motion, and force field elements including bond, angle, torsion, van der Waals, and electrostatic interactions. Important simulation techniques are covered, such as the use of periodic boundary conditions, ensemble types, and temporal integration algorithms. Specialised sections describe how MD is used to model biological systems using classical force fields like AMBER and CHARMM, polymer dynamics using Rouse, Zimm, and reptation models, and ionic systems with polarisable force fields. The structural shapes and application ranges of several force field families are briefly compared**.**

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1. Introduction

Molecular Dynamics (MD) simulation is a computational technique used to model the physical movements of atoms and molecules over time. It allows scientists and engineers to investigate the structural and dynamic behaviour of molecular systems under various conditions using the laws of classical mechanics. This course provided an introduction to the fundamental theories and practical applications of MD simulations. Through a combination of theoretical study and hands-on simulation exercises.[2]

1.1 History and Background

Not surprisingly, Monte Carlo (MC) and Molecular Dynamics (MD), the two most basic approaches to simulating condensed matter systems, originally appeared in the 1950s. Scientists in the US were given access to the first computers at this time, which had previously only been used for classified military research. The ability to do quick, automated computations was instantly thought to offer enormous potential for solving issues in statistical mechanics, for instance. Applications of the MD technique have been increasing since its original description was published by Alder and Wainright in 1957. Today, MD is a widely utilised research tool in fields like physics, chemistry, materials science, biology, and geology**.** The technique was primarily employed as a tool in statistical mechanics during the early years of MD, which spanned primarily the 1960s and 1970s. The most of the time, the emphasis was on basic, generic model systems like hard spheres or the Lennard-Jones fluid rather than attempting to model genuine systems. Learning about entire families of systems, such as simple liquids, was the main goal rather than answering questions about particular systems. Both the degree of specificity and the complexity of the models increased over time. For certain classes of systems, such as the CHARMM or AMBER force fields for organic and biological molecules, the ionic potentials for oxide materials, the embedded atom potentials for metals or the bond-order inspired potentials for covalent materials, empirical (i.e., derived from experimental information) models started to be developed.

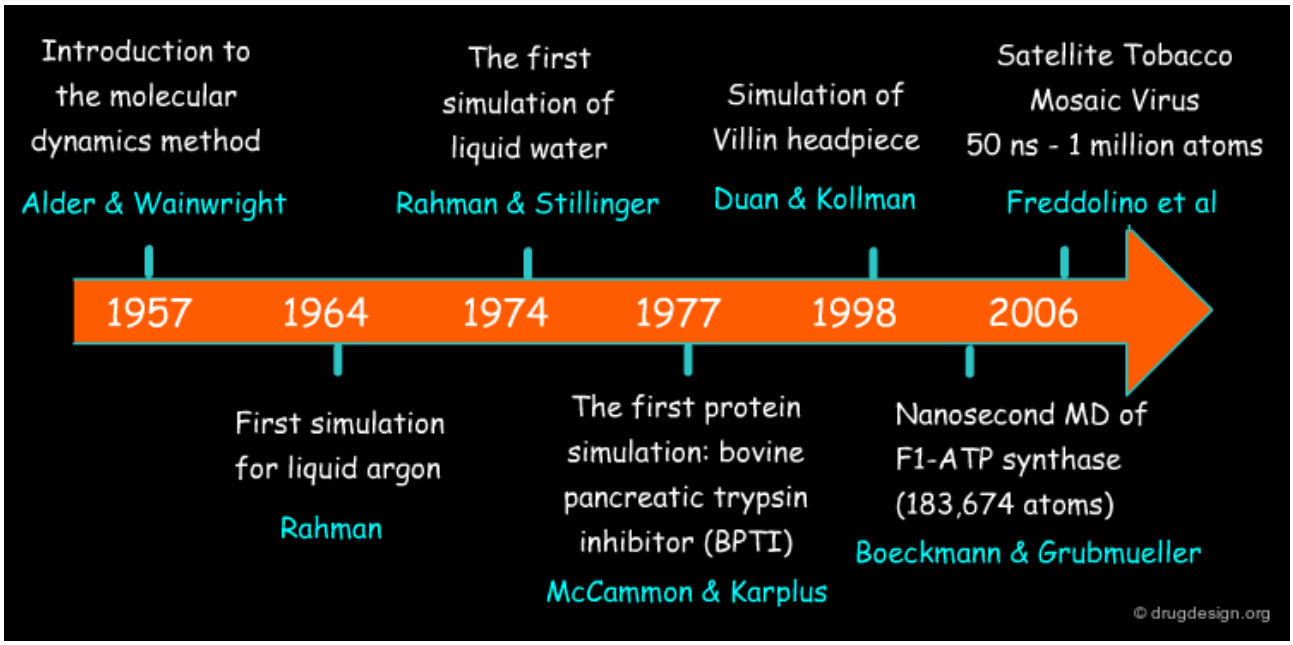

Figure 1. History of MD Simulation

1.2 Definition and Purpose of MD

Microscopic analysis techniques are required in the current era of nanotechnology in order to create new functional materials and look into physical events at the molecular level. These techniques take into account the constituent species of a system, including molecules and tiny particles. By examining these species' behavior, macroscopic and microscopic quantities of interest are determined. The Monte Carlo (MC) and molecular dynamics (MD) methods are examples of these techniques, which are referred to as "molecular simulation methods." Although MC approaches are quite effective for analyzing thermodynamic equilibrium, they are not appropriate for examining dynamic processes. While MD techniques are helpful for thermodynamic equilibrium, they are more beneficial when examining a system's dynamic dynamics in a state of one equilibrium.

The MD method's principle is simple and reasonable. In classical theory, Newton's laws of motion largely control how molecules move. MD simulations use the equations of motion to model particle motion on a computer. A computer is not required if a molecule moves only according to the principles of classical mechanics since mathematical calculations made with a pencil and paper may solve the molecule's motion. However, such mathematical analysis is not feasible because molecules in a system are many and interact with one another. Computer simulations thus become an effective tool for a microscopic investigation in this scenario.

Newton's equations of motion are numerically solved in Molecular Dynamics (MD) simulation, a computer technique that models the behaviour of systems at the atomic and molecular levels. The main goal of MD simulations is to comprehend the motion and interactions of atoms and molecules over time, offering in-depth information that is frequently unavailable through experimental methods. In order to forecast the structural, thermodynamic, and transport characteristics of materials and molecules under diverse circumstances, MD is essential. Through the use of potential energy functions to precisely depict interatomic interactions, MD enables scientists to investigate the time-dependent development of systems ranging from basic liquids to intricate biological macromolecules.

The capacity of MD to visualise real-time molecular processes at the nanoscale, such as chemical reactions, adsorption, folding, and diffusion, is one of its main benefits. This makes it a useful instrument in a number of domains, such as phase transitions, crystal formation, mechanical characteristics, etc. are all studied in material science. In chemical engineering, for fluid simulations, solubility research, and process optimisation. To investigate membrane dynamics, ligand binding, and protein folding using biophysics and biochemistry. In pharmaceutical sciences, for molecular docking and modelling of drug-target interactions. Furthermore, MD simulations are necessary to support experimental results and validate theoretical models. Before synthesis or trials, they offer a safe and economical means of testing theories and designing new materials or medications.

In conclusion, MD simulations are used to forecast system attributes, comprehend microscopic mechanisms, and improve scientific and industrial research in addition to simulating molecular behaviour.[3]

1.3 Course Objectives and Overview

This course, Molecular Dynamics Research, aimed to familiarise students with the basic ideas and methods of molecular dynamics (MD) simulations. It sought to give students a solid theoretical basis as well as real-world, hands-on experience with MD simulation implementation and molecular system modelling utilising computational tools. The goal of the course was to close the knowledge gap between theoretical ideas and practical applications in biological, chemical, and physical systems.

The following subjects and assignments were discussed during the course:
1) The basic equations, potentials and simulation techniques;
2) The computer code description for the simulation of the liquid model (Lenard-Jones potential);
3) The use of selected general-purpose code for the simulation of ionic, polymeric and biochemical molecular systems;
4) The theory of the basics of the hybrid MD approach (classical quantum-chemistry potentials simulation methods);
5) MD test modeling

The theoretical underpinnings, coding procedures, and simulation strategies covered in the course are compiled in this report. Additionally, it displays the outcomes of several test simulations conducted for 3D-structured biosensors.

2. Theory and Methodologies in Molecular Dynamics

The simulation of molecular dynamics (MD) is based on classical mechanics, which uses Newton's equations of motion to predict how atoms and molecules move. The theoretical underpinnings and methodology of MD simulations are described in this section. It covers interatomic potentials, fundamental equations of motion, and computational methods for modelling molecular systems.

2.1 Fundamental Equations, Potentials, and Simulation Techniques

Newton's second law of motion is the foundation of molecular dynamics (MD) simulations. The equation controlling each particle's motion in a system of n particles is as follows:

$$\boldsymbol{m_i \frac{d^2 r_i(t)}{dt^2} = F_i\left(r_i(t)\right) - \gamma_i m_i \frac{dr_i(t)}{dt} + R_i(t)}$$

Where:

- γ_i is the friction coefficient,
- $R_i(t)$ is a random force acting on the particle

Force fields, which contain words for a variety of physical interactions, are used to simulate the interactions between atoms in a molecular system. These interactions include:

- ✓ Stretching of bonds
- ✓ Bending an angle
- ✓ Torsional (dihedral) interactions
- ✓ Van der Waals and electrostatics are examples of non-bonded interactions

The total potential energy of the system can be expressed as a sum of different contributions:

$$\boldsymbol{U_{(r)} = U_b + U_\theta + U_\varphi + U_\omega + U_{LJ} + U_{el} + U_{HB} + \ldots\ldots\ldots}$$

Where,

(i) $\boldsymbol{U_b}$**(valence length potential)** $= \frac{1}{2}\sum_b K_b(r - b_0)^2$

It represents the energy that results from atoms' bonds being stretched or compressed from their equilibrium lengths. By penalising variations in bond lengths, it aids in the preservation of molecular structure.

(ii) U_θ **(valence angle potential)** $= \frac{1}{2}\sum_\theta K_\theta(\theta - \theta_0)^2$

It maintains the geometric integrity of molecules by accounting for the energy involved in variations from the ideal bond angles between three bonded atoms.

(iii) U_φ**(Torsion dihedral potential)** $= \frac{1}{2}\sum_\varphi K_\varphi[\cos(n\varphi - \delta) + 1]$

It is essential for managing conformational flexibility because it simulates the energy barrier involved in the rotation around a bond that joins two atoms in a dihedral configuration.

(iv) U_ω **(van der Waals interaction potential)**

It describes the weak, non-covalent interactions that occur between atoms as a result of induced dipoles; these interactions are important for preserving the structure and packing of molecules.

(v) U_{LJ} **(Lenard -Jones Potential)** $= \sum_{i,j}[\frac{A}{r_{ij}^{12}} - \frac{B}{r_{ij}^{6}}]$

Long-range attraction and short-range repulsion between unbonded particles are combined in this particular type of van der Waals potential.

(vi) U_{el} **(Electrostatic potential)** $= \sum_{i,j}\frac{q_i q_i}{\in r_{ij}}$

It is essential for simulating ionic and polar systems because it depicts the Coulombic interactions between charged atoms or molecules.

(vii) U_{HB} **(Hydrogen bonding potential)** $= \sum_{i,j}[\frac{A'}{r_{ij}^{12}} - \frac{B'}{r_{ij}^{10}}]$

It captures how hydrogen bonds, which are essential to the stability and structure of biomolecules, are directional and distance-dependent.[4]

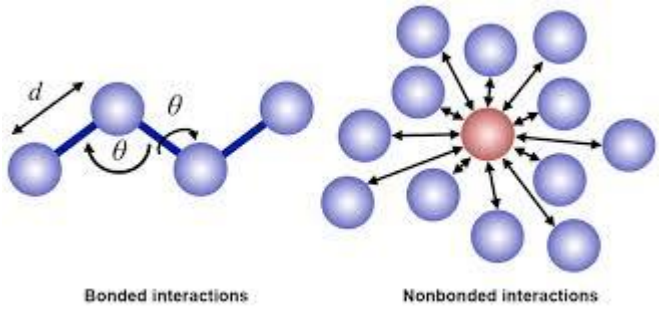

Figure 2. Different forces acting upon a molecule

Force field:

Polarisation effects are a component of advanced force fields that use models such as these to account for environment-induced charge redistribution.

- Variable charges
- oscillators of Drude (core–shell)
- Point dipoles that are induced

Although these techniques improve physical realism, they necessitate self-consistent computations at every time interval.

Popular force fields that are suited for various systems and parameterisation techniques are AMBER, CHARMM, OPLS, GROMOS, and COMPASS. Cross terms and anharmonic corrections are added by second-generation (Class II) force fields, whereas contemporary polarisable FFs (such as AMOEBA) provide better transferability at a higher computational cost.

AMBER: Designed for biomolecules like proteins and nucleic acids, AMBER uses fixed-charge models and is widely used for free energy and conformational studies.

CHARMM: A flexible force field for proteins, lipids, and nucleic acids, CHARMM includes cross-terms and is well-suited for membrane and large biomolecular simulations.

OPLS: Optimized for liquid-phase simulations, OPLS provides accurate thermodynamic properties for organic molecules and small drug-like compounds.

GROMOS: A united-atom force field tailored for proteins and aqueous systems, GROMOS is computationally efficient and commonly used with GROMACS.

COMPASS: A class II force field ideal for polymers and materials, COMPASS includes cross-coupling terms and is optimized for condensed-phase accuracy.

Choosing energy functions, fitting parameters to experimental or QM data, repeated optimisation, and validation against qualities not utilised in training are all steps in parameter development.

To sum up, force fields make large-scale MD simulations more effective, but they also need to be carefully selected and verified to guarantee physical accuracy in a variety of chemical conditions**.**[5][6]

Periodic boundary conditions (PBC) :

We frequently have to model systems with a huge number of atoms in Molecular Dynamics simulations. Periodic Boundary Conditions, or PBC, are used to handle this computationally. Atoms can exit one side of the simulation box and re-enter from the other side, according to PBC's assumption that the box is infinitely repeated in all directions. This lessens edge effects and replicates the behaviour of bulk materials. PBC introduces various approximations, particularly in non-periodic or disordered systems like liquids or amorphous solids, even though it aids in simulating an infinite system with a finite number of atoms. In certain situations, artificial periodicity may have a subtle impact on the outcomes. Under PBC, long-range interactions like electrostatics need special consideration. By dividing these interactions into short-range (real space) and long-range (reciprocal space) components, techniques such as the Ewald Summation are frequently employed. PBC is an effective technique for simulating bulk behaviour overall, but results should be carefully interpreted, especially when researching diffusion processes, flaws, or dislocations.

2.2 MD simulation of Lennard-jones systems

One of the most popular models for explaining how two neutral atoms or molecules interact is the Lennard-Jones (LJ) potential. It is a helpful approximation for simulating basic liquids and noble gases because it captures both the long-range attraction and short-range repulsive forces between particles. This section examines the behaviour of particles in a simple molecular system by implementing MD simulation using the LJ potential. This model is an essential first step in comprehending how particle trajectories change over time in an MD framework and how molecular interactions are represented.

A mathematical model known as the Lennard-Jones (LJ) potential uses the distance between two non-bonded atoms or molecules to describe how they interact. It is frequently used in simulations of gases, liquids, and soft matter systems and is particularly helpful in simulating van der Waals forces. The LJ potential is a fundamental component of Molecular Dynamics simulations because it strikes a balance between repulsive and attractive interactions using a straightforward but efficient functional form. Accurately simulating the physical behaviour of molecular systems at the atomic level requires an understanding of this potential.[7]

The Lenard-Jones (lj) looks like:

$$V(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

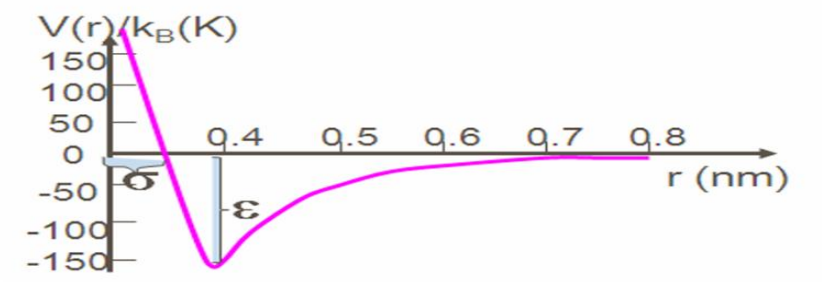

Figure 3. The Lennard-Jones potential energy dependence on the atom-atomic distance.

atom	ε/k_B (K)	σ (nm)
H	**8.6**	**0.281**
He	**10.2**	**0.228**
C	**51.2**	**0.335**
N	**37.3**	**0.331**
O	**61.6**	**0.295**
F	**52.8**	**0.283**
Ne	**47**	**0.272**
S	**183**	**0.352**
Cl	**173.5**	**0.335**
Ar	**119.8**	**0.341**
Br	**257.5**	**0.354**
Kr	**164.0**	**0.383**

Table 1. The LJ (Lennard-Jones)- parameters of ε and σ for different atom

Initial Setup in MD Simulations

An initial atomic configuration and velocities are needed to start an MD simulation. A flawless or minimally disrupted lattice is utilised for crystalline systems, while a less stable structure may progress towards equilibrium for liquids. Usually, velocities that correspond to the target temperature are chosen at random from the Maxwell-Boltzmann distribution. These can be changed to guarantee zero angular momentum and net momentum, avoiding rotation or system drift. A thermalisation (or equilibration) step is required since the original setup might not accurately reflect the desired temperature. In order to progressively obtain the target temperature, velocities are iteratively rescaled during this time. This artificial phase, which only serves to get the system ready for real simulation, is not included in the analysis of the results. How quickly the system forgets its starting condition and stabilises at the desired temperature determines how long it takes. [7]

2.3 Applications

2.3.1 MD Simulation for Ionic Molecular Systems

Strong Coulombic interactions and intricate local environments are characteristics of ionic molecular systems, including concentrated electrolytes and ionic liquids (ILs). These systems are frequently studied at the atomic scale using molecular dynamics (MD) simulations, which offer insights into transport, structure, and thermodynamic behaviour. However, because of the important role of induced polarisation, precisely modelling such systems is difficult.[1]

Nonpolarisable force fields, in which atomic charges are fixed and insensitive to the surrounding electrostatic environment, were used in early MD simulations. In highly ionic fluids, these models frequently fall short of reproducing important experimental observables, even while they perform very well in diluted solutions. Nonpolarisable force field simulations, for instance, frequently overestimate viscosity and underestimate ion diffusion coefficients, particularly at high salt concentrations. This is because polarisation effects—which are crucial in settings with strong local electric fields were left out.

Polarisable force fields have been developed to get around this restriction. The electronic distribution surrounding atoms can react dynamically to their environment thanks to these models. Common methods include:

- Atomic charges fluctuate according to electronegativity equalisation in fluctuating charge models;
- The electron cloud is depicted in classical Drude oscillator models as a massless charged particle that is connected to the nucleus via a harmonic spring;
- Atoms that interact with other dipoles and permanent charges are given mathematical dipoles in Induced Point Dipole Models.

At each MD step, the induced dipoles or charges must be solved for, and each of these models adds new components to the potential energy function. These techniques greatly enhance the prediction of characteristics like self-diffusion, ionic conductivity, and dielectric response, despite being computationally more costly. Mean-field approximations, like charge scaling or Lennard-Jones parameter adjustment, are employed when explicit polarisation is too expensive. For example, it has been demonstrated that lowering ionic charges to 70–80% of their nominal values enhances agreement with experimental results, but at the price of model transferability.

The system being studied and the trade-off between accuracy and computational expense determine which model is polarisable and which is not. Polarisation needs to be explicitly taken into account

in order to accurately simulate systems such as battery electrolytes, ionic liquids under confinement, or electrolyte–electrode interfaces.

2.3.2 MD Simulation for Polymeric Systems

Because they provide in-depth information on chain conformations, relaxation dynamics, and interactions, molecular dynamics (MD) simulations are crucial for examining the microscopic behaviour of polymers. The Zimm model (which includes hydrodynamic interactions) and the Rouse model (which ignores them) are frequently used to describe chain dynamics in diluted systems. The reptation model is used to represent curvilinear motion in a confined tube made of nearby chains in deep melts, where topological restrictions predominate. Because of mode conservation, standard microcanonical MD frequently has ergodicity problems in polymer systems. Langevin dynamics, which couples the system to a stochastic heat bath and efficiently screens hydrodynamic interactions, is frequently employed to address issue.[8]

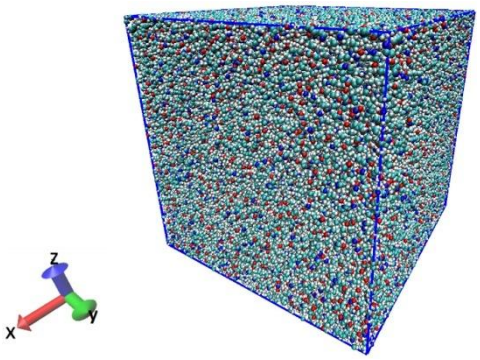

Figure 4. MD Simulation of polymers

2.3.3 MD Simulation for Biochemical Systems

Molecular Dynamics (MD) simulations are an essential tool for understanding the structure, energetics, and dynamics of biomolecules such as proteins, nucleic acids, and their complexes. Unlike static models derived from X-ray crystallography or limited-resolution NMR, MD simulations offer atomic-level resolution in space, time, and energy, enabling the study of biomolecular flexibility, conformational changes, and dynamic interactions.

Due to the complexity of biomolecules, MD simulations typically use classical force fields—such as GROMOS, AMBER, or CHARMM—employing effective interaction functions to model bond stretching, angle bending, dihedral torsions, and non-bonded interactions (Lennard-Jones and Coulombic terms). These force fields are parameterized using a combination of quantum mechanical data and experimental observations (e.g., crystal structures, solvation properties).

For proteins and nucleic acids, simulations are often performed in explicit water environments with periodic boundary conditions, allowing the use of realistic solvent models and electrostatic treatment via Ewald summation. Systems can be equilibrated using thermostats and barostats to maintain constant temperature and pressure conditions.

Key challenges include limited sampling due to short simulation times (typically <1 ns) and the difficulty of capturing slow conformational transitions. To overcome this, experimental constraints (e.g., NMR-derived distance bounds) can be incorporated into simulations via restraining potentials. This hybrid approach improves conformational accuracy and facilitates the interpretation of sparse or low-resolution experimental data.

Applications include:

- Modeling protein-ligand or protein-DNA interactions

- Investigating folding/unfolding mechanisms
- Evaluating mutation effects
- Estimating relative binding free energies via thermodynamic integration or perturbation methods

In summary, MD simulations serve as a powerful complement to experimental techniques in biochemistry, offering mechanistic insights and predictive capabilities that are otherwise inaccessible.[3][9][10]

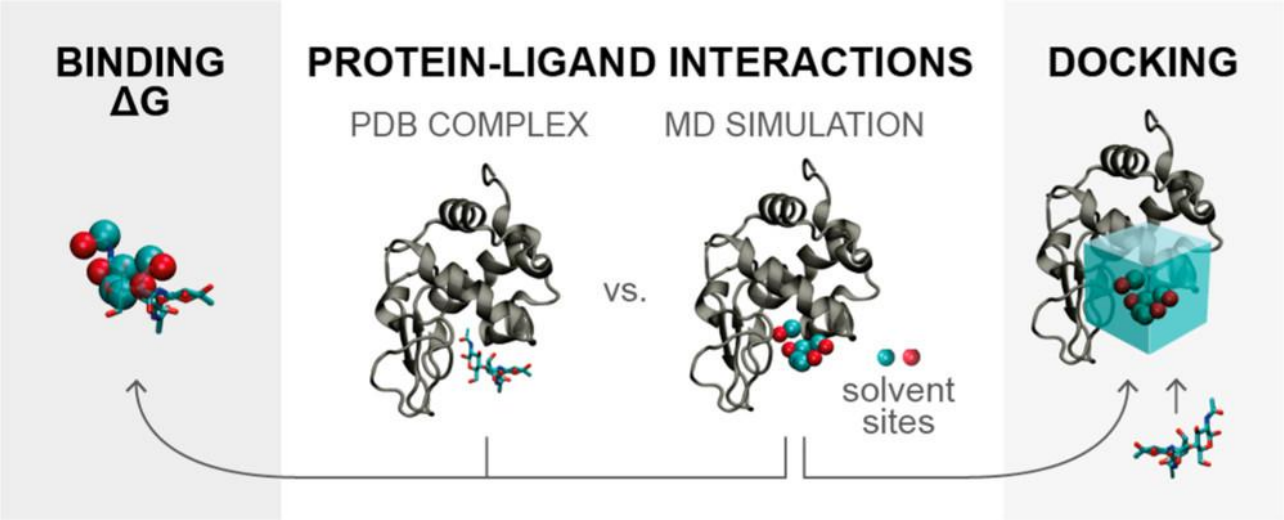

Figure 5. MD simulation preotein ligand interactions

3. Molecular Dynamics Simulation for 3D-Structured Biosensors from 2D Materials

Objective

By combining 2D materials into 3D structures, this effort seeks to improve electrochemical characteristics and create a biosensor. To help in sensor optimisation, molecular dynamics (MD) simulations will be used to examine charge transport, material stability, and molecular interactions.

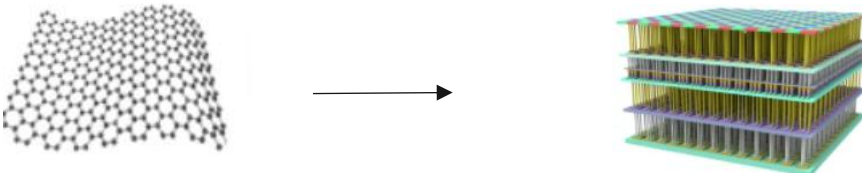

Figure 6. 3D arrangement of 2D Materials

2D Materials and Their 3D Arrangement

High conductivity, a huge surface area, and superior mechanical properties are characteristics of 2D materials such as graphene, MoS_2, and MXenes. However, electrochemical performance is limited by

their propensity to restack. These materials are perfect for biosensing applications because they improve charge transport, increase active sites, and improve ion diffusion when converted into 3D designs.

Significance in Biosensor Development

Electrochemical biosensors rely on charge transfer between the sensor surface and biomolecules. **3D-structured 2D materials improve:**

- **Sensitivity**: Higher surface area for biomolecule adsorption.
- **Charge Transport**: Enhanced electron mobility and reduced resistance.
- **Stability**: Better mechanical and electrochemical robustness for real-world applications.

Molecular Dynamics (MD) Simulation

MD is a computational technique that models **atomic-level interactions** over time. It helps:

- Predict **interlayer interactions** and stability of 3D structures.
- Analyze **charge transfer mechanisms** at the electrode-biomolecule interface.
- Study **adsorption and binding behavior** of target analytes on the sensor surface.

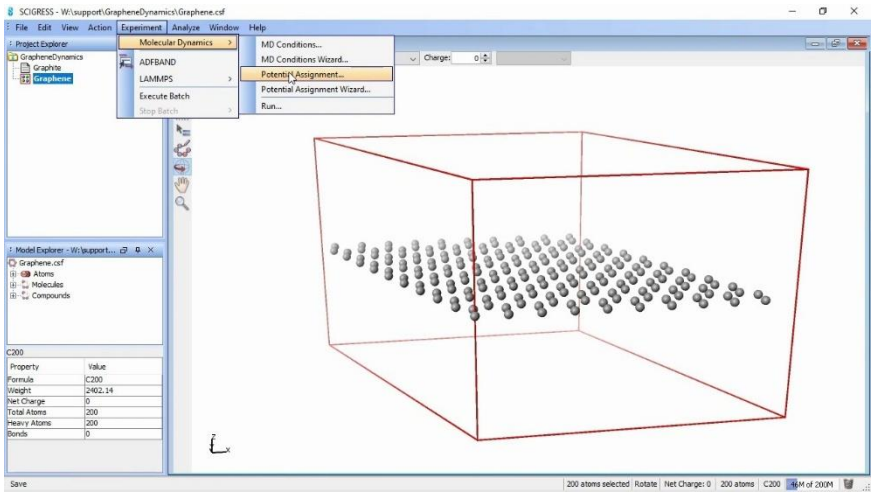

Figure 7. MD Simulation of Graphene

MD Simulation Workflow

1. **Material Modeling**: Construct 2D material models and simulate self-assembly into 3D structures.
2. **Electrochemical Analysis**: Study ion diffusion, charge transfer, and conductivity using MD-ReaxFF.
3. **Biomolecule Interaction**: Simulate analyte adsorption and reaction at the biosensor surface.

4. **Experimental Validation**: Compare MD results with **cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS)**.

Expected Outcomes

- Identification of the most stable **3D-structured 2D material** for biosensors.
- Insights into **electrochemical performance improvements** via MD.
- Optimization of **surface functionalization** to enhance biomolecule detection.
- Computational guidance for **experimental sensor design**.

Conclusion & Future Work

The performance of biosensors is considerably improved by 3D structures of 2D materials. MD simulations direct experimental advancements by offering vital insights regarding stability, charge transfer, and analyte interactions. Future research will concentrate on incorporating AI-driven material optimisation and realistic biosensing settings (pH fluctuations, solvent effects).

Acknowledgement

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