JOINT INSTITUTE FOR NUCLEAR RESEARCH
Laboratory of Nuclear Problems

FINAL REPORT ON THE INTEREST PROGRAMME

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

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Abstract

Molecular Dynamics (MD) simulation serves as a deterministic computational microscope, bridging the gap between microscopic length and time scales and the macroscopic world of laboratory experiments. This report summarizes the comprehensive training received during the JINR INTEREST program. The curriculum covered the derivation of Newton's equations of motion for many-body systems, the parameterization of empirical force fields, and the application of periodic boundary conditions. In this Interest program, we have mainly focused on and studied DL_POLY and AMBER force fields.

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Introduction

Molecular Dynamics (MD) simulation has evolved into an indispensable tool in modern science, often described as a "computational microscope." It acts as a critical bridge connecting the microscopic length and time scales of atomic interactions with the macroscopic world of laboratory observations. “While experimental methods provide average macroscopic properties, MD simulations allow researchers to peer into the femtosecond-scale evolution of molecular systems, revealing the specific atomic motions that give rise to bulk phenomena such as diffusion, phase transitions, and protein folding.” (Tomobe et al., 2017)

At its core, MD is a deterministic technique that numerically solves Newton's classical equations of motion for a system of N interacting particles. By calculating the forces acting on every atom derived from potential energy functions (force fields), the method generates a trajectory that describes the positions and velocities of particles over time.

Objectives

The objectives of this project were to understand:

- The basic equations, potentials and simulation techniques.
- The computer code description for simulation of liquid model (Lenard-Jones potential).
- The use of selected general-purpose code for the simulation of ionic, polymeric and biochemical molecular systems.
- The theory of the basics of hybrid MD approach (classical quantum-chemistry potentials simulation methods).
- Molecular Dynamics test modeling.

Theoretical Framework

Equations of Motion

Molecular dynamics (MD) simulations rely on Newton’s equations of motion to describe the evolution of atomic and molecular systems over time. One of the cores of MD is the integration of Newton's second law for a system of N particles, originally expressed:

$$F_i = m_i a_i \qquad \textbf{Ecuación 1}$$

Where F_i is the force acting on an atom, m_i is the mass and a_i is the acceleration.
The Integrated form of the equation:

$$F_i(r_1 \dots r_N) = m_i \frac{d^2 r_i(t)}{dt^2} \qquad \textbf{Ecuación 2}$$

Where r_i indicates the atomic coordinates. Derived from the potential energy function U(r):

$$F_i = -\nabla_i U(r) \qquad \textbf{Ecuación 3}$$

Force Fields

In molecular dynamics, the "Force Field" (FF) represents the mathematical set of functions and parameters that describe the potential energy of a system of particles.

The total potential energy U_{total} is decomposed into intramolecular (bonded) and intermolecular (non-bonded) contributions

$$U_{total} = U_{bonded} + U_{non-bonded} \qquad \textbf{Ecuación 4}$$

Primarily constituted by the terms presented in equation #

$$U_{total} = U_{bond} + U_{angle} + U_{dihedral} + U_{VdW} + U_{Coulomb} \qquad \textbf{Ecuación 5}$$

For bonded interaction (Intramolecular), constrain the geometry of the molecule, modeling the covalent framework.

Bond Stretching (U_b): Modeled as a harmonic spring, this term penalizes deviations from the equilibrium bond length b_0. K_b represents the force constant (stiffness) of the bond.

$$U_{bond} = \frac{1}{2} \sum_{bonds} K_b \, (r - b_0)^2 \qquad \textbf{Ecuación 6}$$

Angle Bending (U_θ): Describes the energy required to distort the angle θ between three bonded atoms from its equilibrium value θ_0.

$$U_{angle} = \frac{1}{2} \sum_{angles} K_\theta \, (\theta - \theta_0)^2 \qquad \textbf{Ecuación 7}$$

Torsional Dihedrals (U_φ): This term governs conformational flexibility. Unlike bonds and angles, it is periodic and modeled using a cosine series. Where n is the periodicity (multiplicity) and δ is the phase shift.

$$U_{diheral} = \frac{1}{2} \sum_{diherals} K_{\varphi} [1 + cos(n\varphi - \delta)] \qquad \textbf{Ecuación 8}$$

For non-bonded interaction (Intermolecular), these terms describe interactions between atoms separated by more than three bonds or belonging to different molecules.

Van der Waals Interactions (U_{LJ}): Modeled via the Lennard-Jones (12-6) potential, which captures the balance between short-range Pauli repulsion and long-range London dispersion attraction. The r^{12} term represents the "hard core" repulsion due to overlapping electron orbitals (Pauli exclusion); while the r^6 term represents the attractive dispersion forces (induced dipole-dipole).

$$U_{LJ} = \sum_{i<j} 4_{\epsilon ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] \qquad \textbf{Ecuación 9}$$

An example of an MD simulation for Lennard-Jones system:

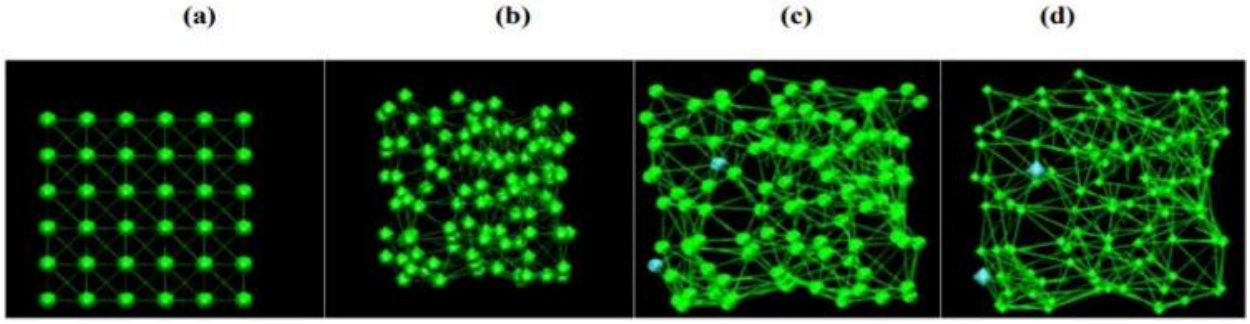

Figure 1: Sequential snapshots of the Lennard-Jones model configurations, where (a) t=0, (b) t=1, (c) t=10, (d) t=100 ps.

Electrostatic Interactions (U_{el}): Modeled by Coulomb's Law for point charges q. This is a long-range interaction that decays slowly (1/r), requiring advanced summation techniques (Ewald) for periodic systems. Where ϵ_0 is the vacuum permittivity and ϵ_r is the dielectric constant of the medium.

$$U_{el} = \sum_{i<j} \frac{q_i q_j}{4\pi\epsilon_0 \epsilon_r r_{ij}} \qquad \textbf{Ecuación 10}$$

These interactions are illustrated in Figure 1:

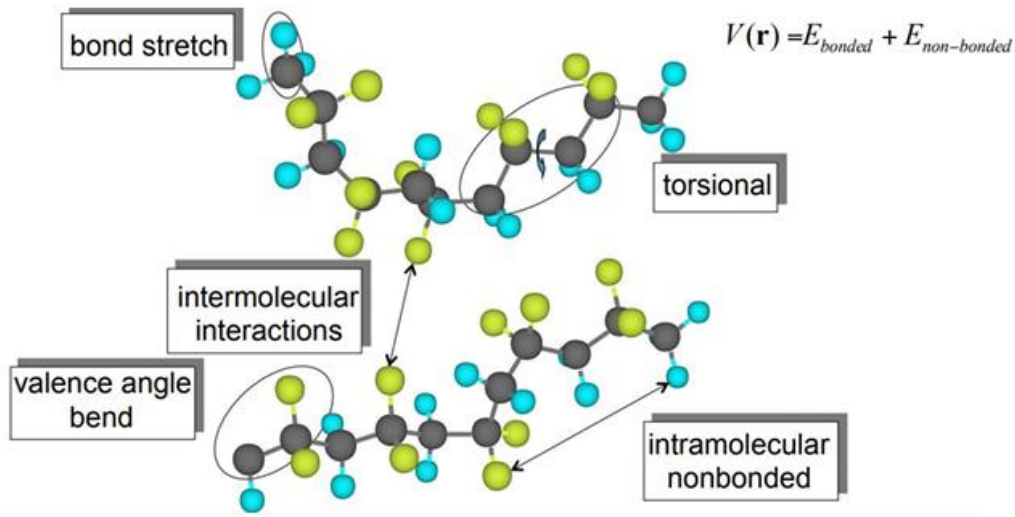

Figure 2: Different types of interactions

Temperature and Pressure controls

Temperature and pressure in MD are directly related to the kinetic energy and the volume of the system. To maintain a target temperature T_{ext}, the velocities of the particles must be adjusted. To simulate the pressure, the volume of the simulation box must fluctuate.

The Berendsen Thermostat (Weak Coupling) algorithm mimics a weak coupling to an external heat bath with temperature (T_{ext}). It corrects the system temperature (T) such that the deviation decays exponentially with a time constant τ_T. The scaling factor λ applied to velocities is defined as:

$$\lambda = \left[1 + \frac{\Delta T}{\tau_T}\left(\frac{T_{ext}}{T} - 1\right)\right]^{1/2} \qquad \textbf{Ecuación 11}$$

The Nosé-Hoover Thermostat (Extended System) is used in rigorous statistical sampling. This method introduces a "friction" coefficient σ(t) as an extra degree of freedom in the system's Hamiltonian. The modified equation of motion becomes:

$$\frac{d\sigma(t)}{dt} = \frac{f(t)}{m} - \sigma(t)v(t) \qquad \textbf{Ecuación 12}$$

The friction coefficient σ(t) itself evolves dynamically based on the difference between the instantaneous kinetic energy and the target temperature:

$$\frac{d\sigma(t)}{dt} = \frac{1}{\tau_T^2}\left(\frac{T}{T_{ext}} - 1\right) \qquad \textbf{Ecuación 13}$$

In the discrete finite-difference integration (used in DL_POLY code), this is realized as:

$$\sigma\left(t+\frac{\Delta T}{2}\right)=\sigma\left(t-\frac{\Delta T}{2}\right)+\frac{\Delta T}{\tau_T^2}\left(\frac{T}{T_{ext}}-1\right) \qquad \textbf{Ecuación 14}$$

This approach allows the system to fluctuate naturally, generating a correct canonical distribution.

Boundary Conditions

Boundary Conditions are mathematical constraints applied to the edges of the simulation box to resolve the problem of finite system size.

Since we can only simulate a limited number of atoms (typically 10^4 to 10^6) compared to macroscopic reality (10^{23}), simulating a system without boundary conditions would result in a cluster of atoms floating in a vacuum.

The simulation box (primary cell) is conceptually replicated infinitely in all three spatial dimensions (x, y, z) to form a lattice.

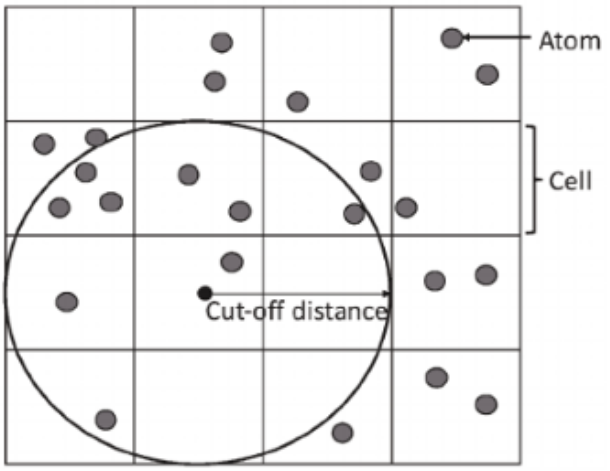

Figure 3: Periodic Boundary Conditions visualization.

When an atom moves out of the primary box through one face, its "image" simultaneously enters through the opposite face with the same velocity. This ensures the conservation of the number of particles (N) and mass within the system.

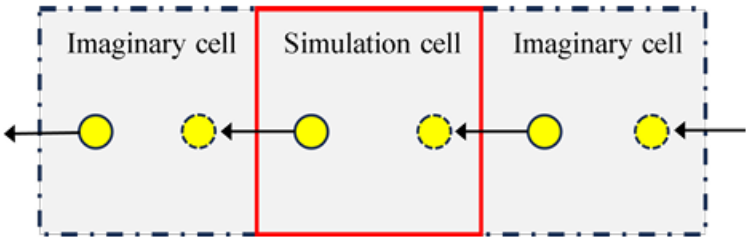

Figure 4: Particles movements through simulation cell.

Software and Methods

To bridge the gap between theoretical mechanics and observable phenomena, we utilized high-performance Molecular Dynamics (MD) engines. The choice of software is dictated by the nature of the system (e.g., biological macromolecules vs. ionic crystals) and the required force field compatibility.

DL_POLY

The primary tool utilized in this course was DL_POLY, a highly scalable general-purpose MD package developed at Daresbury Laboratory. It is particularly robust for simulating ionic structures, polymers, and materials science applications due to its flexible handling of boundary conditions and non-bonded potentials.

A distinct feature of DL_POLY is its rigid but clear file structure. A simulation is defined by three mandatory input files:

- CONFIG: Defines the initial state of the system. It contains the unit cell vectors (defining boundary conditions) and the initial atomic coordinates (x, y, z). It may also include initial velocities and forces if restarting a run.
- FIELD: Defines the force field topology and interaction parameters. Unlike biological packages that use automated topology builders, DL_POLY requires explicit definition of molecular species (masses, charges), bond potentials (harmonic, Morse), and non-bonded parameters (Lennard-Jones ϵ and σ).
- CONTROL: The "steering wheel" of the simulation. It specifies control variables such as the integration ensemble (NVT/NPT), temperature, pressure, time step (Δt), and the total number of steps. It also dictates the frequency of data dumping for analysis.

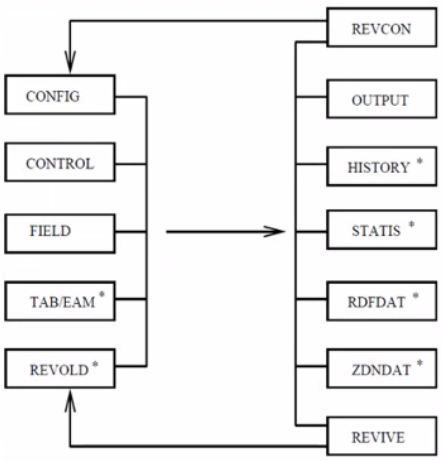

Figure 5: Input and output files for DL_POLY.

AMBER

For projects involving proteins and nucleic acids, we examined AMBER (Assisted Model Building with Energy Refinement). Unlike the material-agnostic DL_POLY, AMBER is tailored for biological macromolecules.

- Force Field Integration: AMBER natively implements force fields that are pre-parameterized for amino acids and nucleotides. This automation is handled by the LEaP module, which generates the topology and coordinate files from standard PDB structures.
- Solvation and Neutralization: The workflow involves explicit solvation (placing the protein in a box of TIP3P water) and adding counterions (Na^+/Cl^-) to neutralize the system charge, a critical step for calculating electrostatic energies correctly using Ewald summation.

Proposed Future Project

Modeling the Formation of the Glucose Analogue ^{18}F-FDG via Molecular Dynamics

This project aims to model the formation of the glucose analogue by simulating the crucial nucleophilic fluorination step where the fluoride-18 ion ($^{18}F^-$) attacks the precursor molecule.

Based on the work of "Interaction of Radiopharmaceuticals with Somatostatin Receptor 2 Revealed by Molecular Dynamics Simulations" (Gervasoni et al., 2023) we can see that MD simulations are used for real-present issues in the world of nuclear medicine.

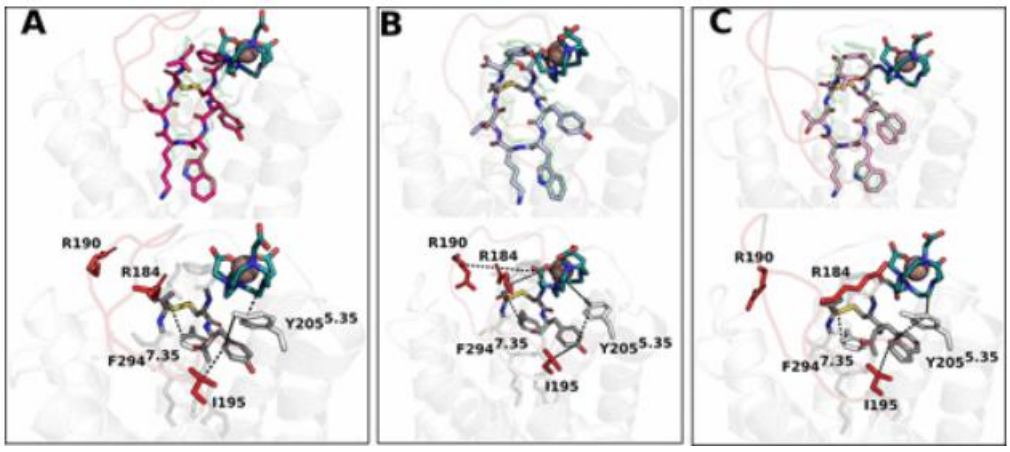

Figure 6: Representatives of the most populated conformational cluster extracted from MD trajectories for (A) 68Ga-DOTATOC, (B) 68Ga-DOTATATE, and (C) 68Ga-DOTANOC.

The objective remains focused on applying Molecular Dynamics (MD) and advanced computational chemistry explored in the course to a high-impact problem in Nuclear Medicine: optimizing the synthesis of the radiopharmaceutical 2-deoxy-2-(^{18}F)-fluoro-D-glucose (^{18}F-FDG). This project aims to model the formation of the glucose analogue by simulating the crucial

nucleophilic fluorination step where the fluoride-18 ion ($^{18}F^-$) attacks the precursor molecule. This research will elucidate the atomic-level mechanisms, solvent effects, and kinetic barriers that dictate the final product's yield and stereoselectivity.

Such detailed modeling provides a fundamental underpinning for improving synthetic protocols, directly contributing to the mission of advancing radioisotope applications at centers like JINR.

Conclusions

This course provided a comprehensive theoretical and practical foundation in Molecular Dynamics. We successfully navigated from the basic integration of Newton's laws for atomic fragments to the complex simulation of large molecular compounds.

Beyond the specific biological application, the computational strategies mastered here are directly transferable to the strategic interests of JINR. The ability to simulate collision cascades in DL_POLY is vital for analyzing radiation damage in nuclear waste immobilization materials. Furthermore, the accurate modeling of metal-ligand stability is a prerequisite for designing novel radiopharmaceuticals and chelators for nuclear medicine.

In summary, this project has confirmed that MD simulations are not merely illustrative tools but predictive engines capable of guiding experimental design, optimizing material properties, and unraveling the atomistic mechanisms of life and matter.

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