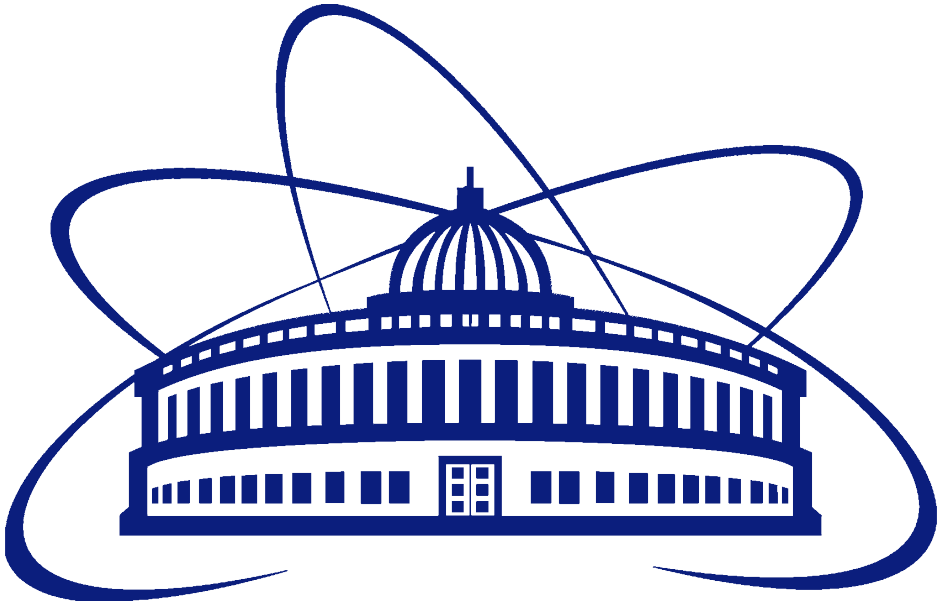

JOINT INSTITUTE FOR NUCLEAR RESEARCH

Final report on the interest programme

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

Wave 13: 20 October - 30 November, 2025

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November 27, 2025

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1 Abstract

Molecular Dynamics (MD) is a computational technique that enables atomistic exploration of structure, dynamics, and thermodynamic properties by integrating Newton's equations of motion for many-particle systems. This report summarizes the theoretical foundations, historical background, and practical implementation covered in the Molecular Dynamics Research course. Key components of MD force fields, potential energy functions, integration algorithms, periodic boundary conditions, and temperature- and pressure-control methods are presented concisely. Classical interatomic interactions, including bonded terms (bond stretching, angle bending, and torsional potentials) and non-bonded interactions (Lennard-Jones, Coulomb, and hydrogen-bond contributions), are described in relation to their impact on molecular behavior. Widely used force fields such as AMBER, CHARMM, OPLS, GROMOS, and COMPASS are reviewed, emphasizing their applicability to biomolecular and materials simulations. By integrating theoretical concepts with practical strategies, this report highlights how MD provides a framework for understanding the physicochemical determinants that shape molecular function and guide advanced simulation studies.

2 Course objectives

The objectives of the course *MOLECULAR DYNAMICS RESEARCH* are to explore:

1. The basic equations, potentials and simulation techniques;
2. The computer code description for simulation of 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 hybrod MD approach (classical quantum-chemistry potentials simulation methods);
5. MD test modeling.

3 Introduction

3.1 What is Molecular Dynamics (MD)?

Molecular Dynamics (MD) is a computational simulation technique in which the time evolution of a molecular system is obtained by numerically integrating Newton's equations of motion for all atoms, thereby generating trajectories that describe how positions and velocities change as a function of time.
Although conceptually straightforward, it has become one of the most versatile and influential approaches in science and engineering for examining the atomistic behavior of fluids and materials. Throughout its history, MD has been essential in validating theoretical descriptions of the fluid state, and more recently it has evolved into a practical tool for directly calculating physical properties of interest. Looking ahead, this synergy between theoretical development and simulation is expected to persist, enabling deeper insights into the nature of matter across increasingly broad temporal and spatial scales.

3.2 Historical Development

Brief Historical Overview of Molecular Dynamics Molecular Dynamics (MD) originated in the 1950s when electronic computers, initially built for wartime purposes, became accessible to scientists and enabled the numerical treatment of many-body systems. Alder and Wainwright performed the first MD calculations on hard-sphere gases, proving that statistical-mechanical problems could be tackled computationally. In the early 1970s the method was applied to more complex liquids; Rahman and Stillinger's 1971 simulation of water revealed a dynamic hydrogen-bond network and continuous molecular diffusion, overturning earlier static pictures of water structure. This success paved the way for biomolecular simulations, culminating in the first protein MD run (Karplus et.al., 1977) and ultimately contributing to the 2013 Nobel Prize in Chemistry awarded to Warshel, Levitt, and Karplus for multiscale modeling.
To reach longer time scales, constraint algorithms and multiple-time-step integrators were introduced, allowing larger integration steps while preserving accuracy. Thermodynamic ensemble sampling was expanded in the 1980s: Andersen's barostat (1980) enabled constant-pressure simulations, the Parrinello-Rahman method added cell-shape fluctuations, and Nosé–Hoover thermostats allowed canonical-ensemble sampling. The 1985 Car–Parrinello approach merged MD with density-functional theory, providing on-the-fly quantum forces and opening the door to bond forming/breaking events. Since the 1990s, exponential growth in computational power

and algorithmic refinements (enhanced-sampling, replica-exchange, metadynamics, multiscale QM/MM frameworks) have broadened MD's reach across physics, chemistry, and biophysics. Today MD is a mature, indispensable tool for interpreting experiments, designing materials, and probing molecular mechanisms across a wide range of time and length scales. [1]

4 Theoretical Background of MD Simulations

The fundamental premise of molecular dynamics is that atoms can be represented as classical particles under the Born–Oppenheimer approximation. Within this framework, the system's Hamiltonian depends solely on the positions and momenta of the atoms. The energetic interactions among them are described using potential functions—commonly referred to as force fields—whose complexity can vary widely. Some force fields are relatively simple and account only for repulsive atomic interactions, whereas others are highly sophisticated, capturing both intermolecular and intramolecular interactions with a high degree of accuracy. [2]
In a Molecular Dynamics simulation, we proceed in essentially the same way as in a real experiment. We begin by preparing the sample: we choose a model composed of N particles and integrate Newton's equations of motion until the system reaches a steady state where its properties no longer vary with time (that is, until it is equilibrated). Once equilibration is achieved, we carry out the actual measurements. Notably, many of the common errors encountered in computational experiments closely mirror those in laboratory experiments, such as improper sample preparation, measurements that are too short, irreversible changes occurring during the process, or mistakenly measuring a quantity other than the intended one. [3]
The most effective way to introduce Molecular Dynamics simulations is by examining a simple program. The example considered here is intentionally kept minimal so that it highlights the essential components of an MD simulation. Such a program is typically organized as follows [3]:

1. The parameters defining the simulation conditions, such as the initial temperature, number of particles, density and time step are read in.
2. The system is initialized by assigning starting positions and velocities to the particles.
3. The forces acting on all particles are calculated.
4. Newton's equations of motion are integrated. Together with the previous step, this forms the core of the simulation and is repeated until the desired simulation

time has been reached.

5. After the main loop finishes, averages of the computed observables are evaluated and printed, and the program terminates.

4.1 Newtonian Mechanics and Equations of Motion

Newtonian mechanics provides the fundamental physical basis for classical Molecular Dynamics (MD) simulations. In MD each atom i is treated as a point mass m_i whose trajectory $\mathbf{r}_i(t)$ is governed by Newton's second law:

$$m_i \frac{d^2\mathbf{r}(i)}{dt^2} = \mathbf{F}_i(\mathbf{r}) = -\frac{\partial U(\mathbf{r})}{\partial \mathbf{r}_i} \tag{1}$$

where $\mathbf{F}_i$ is the net force acting on the atom and $U(\mathbf{r})$ is the total potential energy expressed by a molecular mechanics force field. $U(\mathbf{r})$ is given by:

$$U(\mathbf{r}) = U_\mathrm{b} + U_\theta + U_\phi + U_{LJ} + U_\mathrm{el} + U_{HB} + \ldots \tag{2}$$

$$U(\mathbf{r}) = \frac{1}{2}k_b(r - r_0)^2 + \frac{1}{2}k_\theta(\theta - \theta_0)^2 + \frac{1}{2}\sum_\phi K_\phi[\cos(n\phi - \delta) + 1] + \ldots$$

$$\ldots + 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}} + \sum_{i,j}\left[\frac{A'}{r^{12}} - \frac{B'}{r^{10}}\right] + \ldots$$

The force field decomposes $U(\mathbf{r})$ into:

1. Bonded terms: bond stretching, angle bending, torsional rotations.
2. Non-bonded interactions: Electrostatics, Van-der-Waals and Hydrongen Bonding.

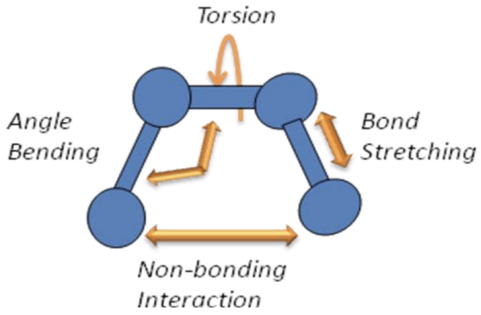
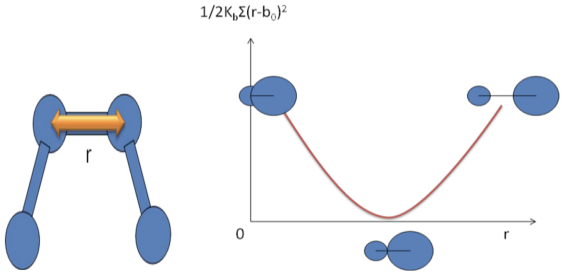


Figure 1: Chemical bonds (bond stretching, angle bending, torsion) and non-bonding interaction

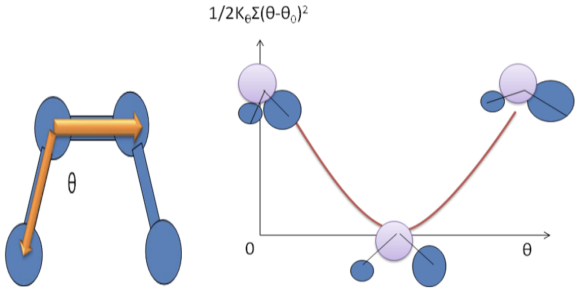
4.1.1 Bonded interactions

In a classical force field the bonded part of the potential energy is expressed as a sum of terms that depend on the internal geometry of the molecule. Typical contributions are:

- Bond-stretching (Valence length potential): Usually modeled with a harmonic spring: $U_{\mathrm{b}} = \frac{1}{2}k_b(r - r_0)^2$ where r is the instantaneous bond length and r_0 the equilibrium distance. Physically this term captures the restoring force that pulls a stretched or compressed bond back toward its equilibrium geometry, and it is accurate for small deviations around r_0 where the potential energy surface is approximately quadratic.

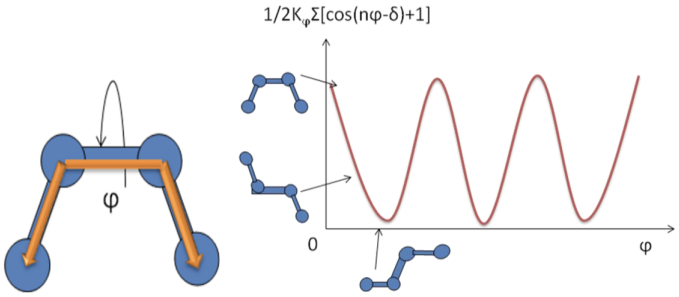


- Angle-bending (Valence angle potential): Also harmonic in the deviation of the bond angle θ from its equilibrium value θ_0: $U_\theta = \frac{1}{2}k_\theta(\theta - \theta_0)^2$. This term reflects the energetic penalty for bending the bond angle away from its preferred value, which originates from the overlap of atomic orbitals and the hybridization geometry of the central atom. As with bond stretching, the harmonic approximation holds for modest angular deviations and yields a parabolic energy well centred at θ_0.



- Torsional (dihedral) rotation: Described by a periodic Fourier series (often a cosine series) that captures the energy barrier for rotation about a bond: $U_\phi = \frac{1}{2}\sum_\phi K_\phi[\cos(n\phi - \delta) + 1]$, with ϕ the dihedral angle. This cosine series captures the energy barriers that arise from steric clashes, electronic conju-

gation, and orbital interactions as the molecule twists about the bond. The resulting potential is periodic, showing multiple minima and maxima that correspond to preferred rotamers (e.g., staggered, eclipsed) and to the energetic cost of moving between them.

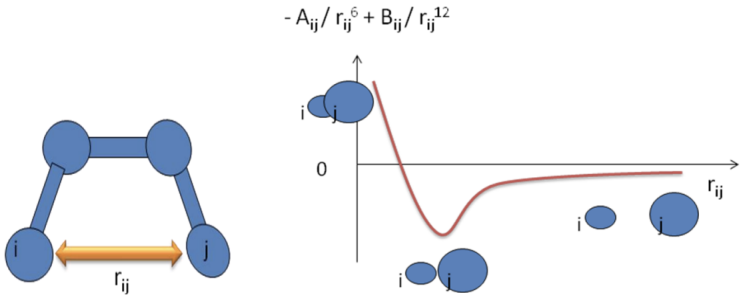


These three families of terms together define the covalent scaffold of the system and are evaluated at every MD step. The total bonded energy is the sum of all bond, angle and dihedral contributions, as outlined in standard molecular-mechanics force fields.

4.1.2 Non-bonded interactions

All atoms that are not directly linked by a covalent bond (or are separated by more than three bonds) interact through long-range van-der-Waals and electrostatic forces:

- Van-der-Waals (dispersion) forces are most commonly represented by the Lennard-Jones potential: $U_{\mathrm{LJ}}(r_{ij}) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right]$,where ε_{ij} and σ_{ij} are depth-of-well and size parameters for the atom pair (i, j). This interaction provides a simple physically grounded description of induced-dipole attraction and electron-cloud repulsion, enabling molecular-mechanics force fields to reproduce the balance between cohesion and steric exclusion that governs the structure and dynamics of condensed-phase molecular systems.



- Electrostatic interactions are described by the Coulomb law: $U_{\mathrm{el}}(r_{ij}) = \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}}$ with atomic partial charges q_i, q_j. The primary objective of MD when dealing with electrostatics is to obtain an accurate, efficiently computed representation of the long-range Coulomb forces that dominate the behavior of charged and polar systems. Because this interaction decays only as $1/r$, pairwise summation would be prohibitively expensive and would produce severe truncation artefacts if a simple distance cutoff were applied.Ewald summation or particle-mesh-Ewald (PME) methods are employed to treat periodic boundary conditions efficiently.
- Hydrogen-Bond Interaction: Is treated as a distinct term that complements the generic electrostatic and van-der-Waals contributions. The purpose is to capture the directionality and specific distance dependence of H-bonding, which are not fully described by simple pairwise Coulomb or Lennard-Jones terms. A common functional form is a short-range attractive-repulsive potential: $U_{\mathrm{HB}}(r) = \sum_{i,j}\left[\frac{A'}{r^{12}} - \frac{B'}{r^{10}}\right]$ where r is the donor–acceptor distance and the coefficients A' and B' are fitted to reproduce experimental or quantum-mechanical H-bond energies.

Van der Waals and Coulomb contributions are usually truncated at a cutoff distance r_{cut} (e.g., 10–12 Å) to limit the computational cost; forces beyond the cutoff are either ignored or treated analytically via long-range correction schemes.The total non-bonded energy is the sum over all eligible atom pairs of the Lennard-Jones and Coulomb terms, and it is evaluated after the bonded forces at each integration step. At each integration step the forces are evaluated from the current coordinates, and the equations of motion are integrated numerically. The most widely used algorithms are the Verlet family (standard Verlet, velocity-Verlet and leap-frog), which update positions and velocities using a finite-difference approximation of the second-order differential equation while preserving energy and momentum over long trajectories. The next step of MD, after giving force field potentials, is velocity generation: Initial atomic velocities are drawn from a Maxwell–Boltzmann distribution corresponding to the desired temperature, ensuring that the kinetic energy matches the target thermal ensemble. Maxwell distribution (the averages observable quantities in physics are expressed with):

$$f(v_x)dv_x = N(v_x)dv_x/N$$

$$f(v_x)dv_x = \frac{N(v_x)dv_x}{N} = \sqrt{\frac{m}{2\pi kT}}e^{-\left(\frac{mv_x^2}{2kT}\right)}dv_x$$

$$< A(v_x) > = \int_{-\infty}^{+\infty} A(v_x)f(v_x)dv_x$$

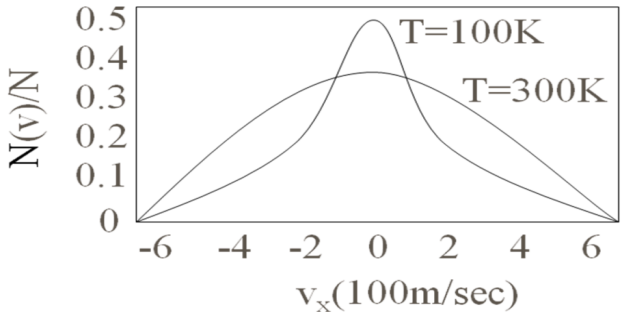


Figure 2: Graph of Maxwell velocity distribution depending on temperature.

To maintain a prescribed thermodynamic ensemble, additional terms are introduced into the equations of motion. For example, the Nosé–Hoover thermostat adds a friction variable that couples the system to a heat reservoir. The equation of motion with a heat exchanges (dissipation, friction):

$$\frac{d\boldsymbol{r}(t)}{dt} = \boldsymbol{v}(t) \quad \frac{d\boldsymbol{v}(t)}{dt} = \frac{\boldsymbol{f}(t)}{m} - \sigma(t)\boldsymbol{v}(t)$$

→ → (with add. eq. for friction coeff. $\sigma(t)$ →

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

Computer realization as discrete finite-difference algebraic equations for the Nose-Hoover thermostat:

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

$$\sigma(t) = \frac{1}{2}\left[\sigma\left(t - \frac{1}{2}\Delta t\right) + \sigma\left(t + \frac{1}{2}\Delta t\right)\right]$$

$$\boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right) = \boldsymbol{v}\left(t - \frac{1}{2}\Delta t\right) + \Delta t\left[\frac{\boldsymbol{f}(t)}{m} - \sigma(t)\boldsymbol{v}(t)\right]$$

$$\boldsymbol{v}(t) = \frac{1}{2}\left[\boldsymbol{v}\left(t - \frac{1}{2}\Delta t\right) + \boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right)\right]$$

$$\boldsymbol{r}(t + \Delta t) = \boldsymbol{r}(t) + \Delta t\, \boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right)$$

On the other hand, the Berendsen thermostat rescales velocities to control temperature. In this algorithm the equation of motion with a heat exchanges(dissipation, friction) is:

$$\sigma = \left[\!\left[1 + \frac{\Delta t}{\tau_T}\left(\frac{T}{T_{ext}} - 1\right)\right]\!\right]^{1/2}$$

$$\boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right) = \left[\!\left[\boldsymbol{v}\left(t - \frac{1}{2}\Delta t\right) + \Delta t \frac{\boldsymbol{f}(t)}{m}\right]\!\right]\sigma$$

$$\boldsymbol{v}(t) = \frac{1}{2}\left[\!\left[\boldsymbol{v}\left(t - \frac{1}{2}\Delta t\right) + \boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right)\right]\!\right]$$

$$\boldsymbol{r}(t + \Delta t) = \boldsymbol{r}(t) + \Delta t\, \boldsymbol{v}\left(t + \frac{1}{2}\Delta t\right)$$

Similarly, barostats such as Andersen's or Parrinello–Rahman's modify the equations of motion to allow volume (and cell shape) fluctuations, enabling constant-pressure simulations.In practice, the integration time step Δt is chosen to be a small fraction of the fastest vibrational period (typically 1–2 fs for bonds involving hydrogen). Constraint algorithms (e.g., SHAKE) are often employed to freeze high-frequency bond vibrations, which permits the use of larger Δt without compromising stability. By iteratively solving Newton's equations with these enhancements, MD generates a time-ordered series of atomic configurations trajectories from which structural, dynamical, and thermodynamic properties of the simulated system can be extracted.

4.2 The Force Field

AMBER, CHARMM, OPLS, and GROMOS are all classical, all-atom (or partly united-atom) molecular mechanics force fields designed primarily for biomolecules (proteins, nucleic acids, lipids, small organic molecules) in solution. They share a similar energy function: harmonic bonded terms for bonds and angles, periodic functions for dihedrals, plus non-bonded Lennard–Jones and Coulomb interactions.They are typically parameterized to reproduce structures and thermodynamic properties of biomolecular fragments and small molecules in aqueous solution.

1. AMBER
    - Scope and acronym: AMBER (Assisted Model Building with Energy Refinement) is both a family of force fields and a software package for biomolecular simulation.
    - Typical use: Widely applied to proteins, nucleic acids and other macromolecules in explicit or implicit water.

- Parameter sets: In modern simulations, protein parameters such as ff99SB ildn are common; this variant improves side-chain torsion potentials and is used, for example, in long MD simulations of membrane proteins like rhodopsin.

2. CHARMM

   - Scope and acronym: CHARMM (Chemistry at HARvard Macromolecular Mechanics) is both a program and a family of force fields for systems ranging from small molecules to large biomacromolecules, using various energy functions and models from quantum to fully classical potentials.
   - Biological force fields: CHARMM provides additive all-atom protein force fields specifically optimized to improve sampling of backbone and side-chain dihedral angles.
   - Role in interfaces: CHARMM parameters are often used as the biomolecular component when building combined force fields for protein–surface systems (e.g., CHARMM-based silica and mineral models, or GolP-CHARMM for proteins on gold).

3. OPLS (OPLS-AA)

   - Scope and acronym: OPLS stands for Optimized Potentials for Liquid Simulations; OPLS-AA is the all-atom variant.
   - Focus: OPLS-AA was developed and tested on conformational energetics and properties of organic liquids. 14 It is widely used for organic molecules and biomolecules in condensed phases.
   - Use in protein–surface studies: OPLS-AA is one of the major biomolecular force fields used for simulations of proteins and peptides in aqueous solution and has been combined with surface-specific parameters in protein–surface work.

4. GROMOS

   - Scope: GROMOS is another widely used biomolecular force field family, originally developed in conjunction with the GROMOS simulation package and later ported to other MD engines.
   - Focus: Like AMBER, CHARMM and OPLS-AA, GROMOS is parameterized for biomolecules in solution, with an energy function built from bonded terms plus non-bonded Lennard–Jones and Coulomb interactions.

- Typical use: It is commonly used for proteins, peptides and other biomolecular systems in explicit water, including work where biomolecular force fields are combined with separate surface models to study protein–surface interactions.

4.3 Periodic Boundary Conditions

Periodic boundary conditions are a computational strategy that mimics an infinite bulk system by replicating a finite simulation cell in all spatial directions. The central cell (the "real" system) is surrounded by identical images, and particles that cross a cell face re-enter from the opposite face, preserving continuity of the simulated material. PBC are used for:

1. Eliminate surface artefacts: A finite box with hard walls would introduce artificial interfaces that alter the thermodynamic properties of liquids, gases or solids. By tiling the box periodically, each particle experiences a homogeneous environment, allowing bulk properties (density, diffusion, pressure, etc.) to be measured without edge effects.
2. Reduce finite-size errors: The periodic replica effectively increases the system size without a proportional increase in the number of explicit atoms, improving the convergence of structural and energetic observables while keeping computational cost manageable.

Periodic boundary conditions provide a mathematically simple yet powerful way to embed a small, tractable simulation cell within an imagined infinite lattice. By enforcing continuity across cell faces, they remove surface artefacts, enable the use of standard long-range electrostatic methods (Ewald summation), and allow bulk thermodynamic properties to be extracted from modest system sizes. Proper selection of box dimensions, cutoff distances, and electrostatic algorithms, together with routine PBC checks, ensures that the periodic replica faithfully reproduces the intended physical environment.

4.4 MD Simulation of Lennard-Jones Systems

The LJ model describes non-bonded interactions with a simple functional form:

$$U_{\mathrm{LJ}}(r_{ij}) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] \tag{3}$$

where ε_{ij} sets the depth of the attractive well (dispersion) and σ_{ij} is the distance at which the potential crosses zero (size parameter). The r^{-12} term models the steep Pauli repulsion, while the r^{-6} term captures long-range dispersion.

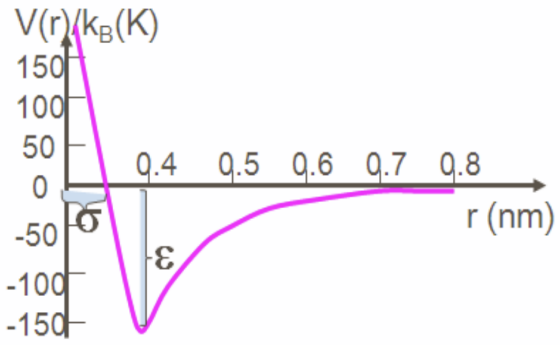


Figure 3: The Lennard-Jones potential energy dependence on the atom-atomic distance.

Typical Lennard-Jones parameters for elemental atoms are shown in Figure 4:

атом	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	0.272
S	183.0	0.352
Cl	173.5	0.335
Ar	119.8	0.341
Br	257.5	0.354
Kr	164.0	0.383

Figure 4: The LJ (Lennard-Jones) parameters of ϵ and σ for different atoms.

Molecular-dynamics simulation of Lennard-Jones systems offers a minimal yet powerful testbed for developing and benchmarking algorithms, thermostats, and analysis tools. By constructing an fcc lattice of 256 atoms, applying periodic boundary conditions, integrating the equations of motion with a standard velocity-Verlet scheme, and monitoring thermodynamic and structural observables (temperature, pressure, RDF, MSD), one can reproduce the well-known solid-to-liquid transition and quantify transport properties.The simplicity of the LJ potential, together with the availability of ready-to-use code snippets (e.g., the DL_POLY LJ-fluid routine) and clear visual benchmarks, makes LJ fluids an essential reference system for any practitioner of classical MD.

5 Applications and Future Work

5.1 Proposal: Using MD to Study Ion Selectivity

The ideas and methodologies outlined in this project lay the groundwork for employing Molecular Dynamics simulations on intricate biomolecular assemblies. Moving forward, the primary focus of this effort will be the creation and simulation of an ion-channel model to elucidate the molecular factors that govern ion selectivity. Ion channels are key controllers of cellular excitability and neuronal signaling, and even minor structural alterations can profoundly impact their functional behavior. Consequently, the capability to probe selectivity at atomic detail is a crucial advance for linking biophysical principles, physiological function, and computational modeling. Ion channels are essential components of neuronal and cellular signaling, and their ability to discriminate between different ions (such as Na^+, K^+, Ca^{2+}, or Cl^-) depends on highly specific structural and electrostatic features within the pore. By building a channel model and performing MD simulations under different ionic environments, I aim to characterize how variations in pore geometry, amino acid composition, and charge distribution influence permeation events and selectivity profiles.

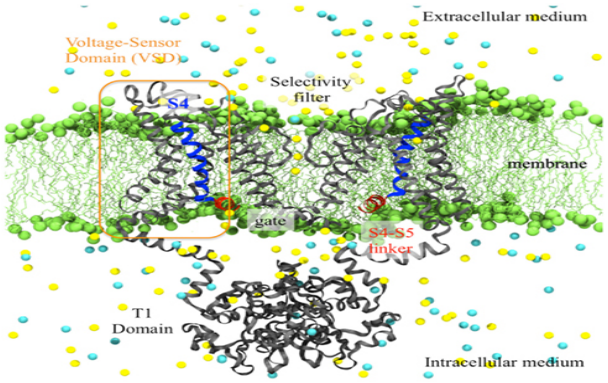


Figure 5: Side view of the activated Kv1.2 (derived from the X-ray crystal structure) embedded in its membrane environment. The entire channel is represented as gray ribbons while the highly charged S4 helix is highlighted in blue and the S4–S5 linker in red. The lipid head groups of the membrane (green) and the ions (K^+ in yellow and Cl^- in cyan) of the solution are represented as spheres. The water molecules are not shown for clarity.*Molecular Dynamics Simulations of Voltage-Gated Cation Channels: Insights on Voltage-Sensor Domain Function and Modulation. Frontiers In Pharmacology.*

Figure 5 illustrates a fully embedded ion channel within a lipid membrane, showing key structural regions such as the voltage-sensor domain, the selectivity filter, and the intracellular T1 domain. The system includes surrounding lipids, water molecules, and ions, representing a realistic biological environment. This type of

structural and dynamical representation is an example of the kind of molecular system I aim to reproduce through my simulations, allowing the detailed study of ion permeation and selectivity at the atomic level.

In my doctoral studies, this project will become a important line of research.By constructing an atomistic model of the channel and simulating its behavior under different ionic conditions, I will explore how pore geometry, charge distribution, hydration effects, and key amino acid residues contribute to selective permeation. These simulations will allow the characterization of binding sites, energy barriers, and local interactions that favor or hinder the passage of specific ions. Such insights are critical not only for understanding natural biological channels but also for interpreting pathological conditions in which channel selectivity is disrupted.

5.1.1 Metodology

I will make every simulation with GROMACS as the main MD platform. GROMACS offers fast, reliable algorithms for biomolecular systems, comprehensive tools for building models, and extensive analysis functions, making it ideal for ion-channel research. Its speed and versatility will enable precise modeling of the channel within a lipid bilayer, investigation of ion-permeation processes, and assessment of how structural characteristics affect selectivity.
I will employ the following steps to carry out the simulation:

1. **Ion Channel Model Construction:** Build an atomistic model of the ion channel using an available experimental structure or homology modeling tools.
2. **Membrane Embedding:** Insert the channel into a lipid bilayer using GROMACS tools or CHARMM-GUI to create a realistic membrane environment.
3. **System Solvation and Ionization:** Solvate the system with water molecules and add ions to neutralize the total charge and mimic physiological conditions.
4. **Force Field Selection:** Choose an appropriate biomolecular force field (e.g., CHARMM36, AMBER) to describe the interactions within the system.
5. **Energy Minimization:** Relax steric clashes and remove high-energy contacts to stabilize the initial configuration.
6. **Equilibration:** Perform NVT and NPT equilibration phases to allow the system to reach stable temperature, pressure, and density.
7. **Production MD Simulations** Run long-timescale simulations to capture the

structural and dynamical behavior of the channel under different ionic conditions.

8. **Trajectory Analysis** Analyze ion permeation events, pore geometry, hydration patterns, and structural fluctuations to characterize selectivity.

5.2 Future Directions

Future work will involve parameterizing the channel structure, embedding it in a lipid bilayer, solvating the system, and performing equilibrium and production simulations to extract structural and dynamical descriptors. Analyses such as potential of mean force (PMF) calculations, ion-density profiles, hydration-shell characterization, and root-mean-square fluctuations will be used to quantify selectivity and identify key determinants of ion preference. Ultimately, this project will contribute to a deeper understanding of selective transport in biological channels.

Acknowledgements

I would like to express my sincere gratitude to Dr. Kholmirzo Kholmurodov for his outstanding Molecular Dynamics course and his invaluable guidance throughout the learning process. His expertise and deep commitment to fostering scientific understanding have been fundamental to my development in MD simulating. I'm especially grateful for the insights he provided into the theoretical foundations and practical applications of MD, as well as for the engaging discussions that greatly enriched my perspective on the field.

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