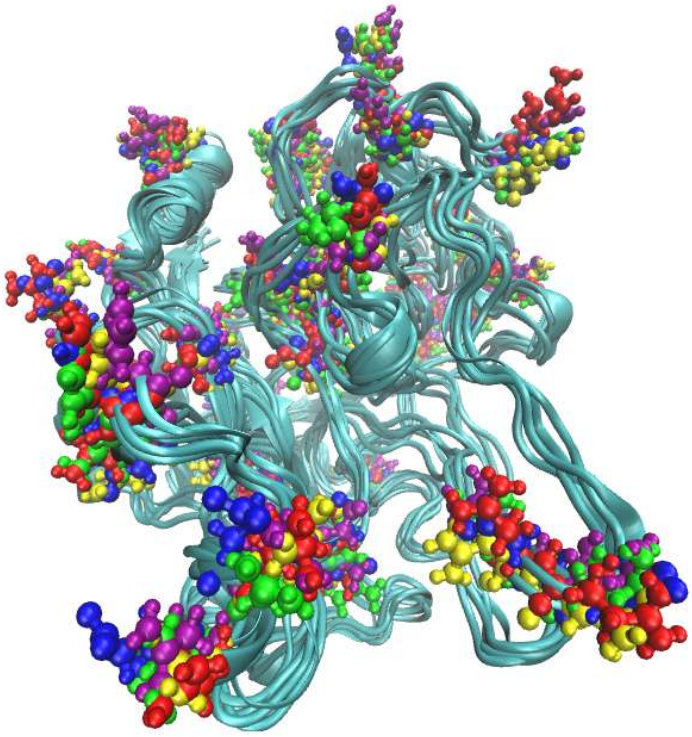
JOINT INSTITUTE FOR NUCLEAR RESEARCH

Frank Laboratory of Nuclear Physics

FINAL REPORT ON THE INTEREST PROGRAMME

MOLECULAR DYNAMICS SIMULATION RESEARCH (FROM ATOMIC FRAGMENTS TO MOLECULAR COMPOUND)



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Abstract

Molecular dynamics (MD) simulation serves as the bridge between the microscopic scales of length and time and the macrocosm of the laboratory. It is useful when actual life experiments are improbable and expensive. In this report, molecular dynamics is briefly discussed. Its basic equation and different force fields are discussed. The computer architecture of the MD-GRAPE-3 supercomputer is introduced. A study of the LENNARD JONES system and different MD simulation packages such as CHARMM, AMBER, NAMD & LAMMP, emphasizing *DL_POLY*, are presented. Molecular dynamics simulations of valinomycin interactions with potassium and sodium ions in water solvent is performed using Lennard -Jones potential and DL_POLY, and future research goals of MD are presented.

A. Introduction

Molecular dynamics was first developed in 1950s. Molecular dynamics (MD) modeling has become an effective tool for understanding biological systems down to the micrometer level with an accuracy comparable to experimental results at the subnanometer level. MD modeling has been an inevitable approach to creating mechanisms for understanding the dynamic behavior of macromolecules at the atomic level. In this review, along with a brief introduction to the basics of molecular dynamics modeling, we provide a description of recently developed advanced techniques, applications, and combinations of MD and other methods used with MD in the field of computational biology.[1]

We run computer simulations to understand the properties of a set of molecules in terms of their structure and the microscopic interactions between them. It complements existing experiments, allowing you to learn something new that you might not find otherwise. The two main product families for simulation technologies are molecular mechanics (MD) and Monte Carlo (MC). There is also a full range of hybrid technologies that combine these two functions. In this lecture, we will focus on MD. An obvious advantage of MD over MC is that it provides access to the dynamic properties of the system (transport coefficients, time-dependent response to disturbances, rheological properties and spectra).

Computer simulation serves as a bridge between the microscopic scales of length and time and the macrocosm of the laboratory. We make assumptions about intermolecular interactions and get "correct" predictions of bulk properties. Predictions are "accurate" in the sense that they can be as accurate as you want them to be, within the constraints of your computer's budget. At the same time, it can reveal details hidden behind mass measurements. For example, there is a relationship between the diffusion coefficient and the autocorrelation function of velocity (the former is easier to measure experimentally, the latter is much more difficult). In another sense, simulation serves as a bridge between theory and experiment. The theory can be tested by running a simulation using the same model. You can test your model against experimental results. Simulations that are difficult or impossible in a laboratory can also be done on a computer (for example, working at extreme temperatures or pressures).

Ultimately, we may want to make a direct comparison with experimental measurements for specific substances, in which case a good model of molecular interactions is needed. The goal of so-called ab initio molecular mechanics is to minimize the amount of tweaking and guesswork in this process. On the other hand, we may be interested in phenomena of a fairly general nature, or we may simply want to distinguish between good and bad theories. For this kind of purpose, you don't need to have a perfectly realistic molecular model. It may be very appropriate to include basic physics.[2]

B. Theoretical background

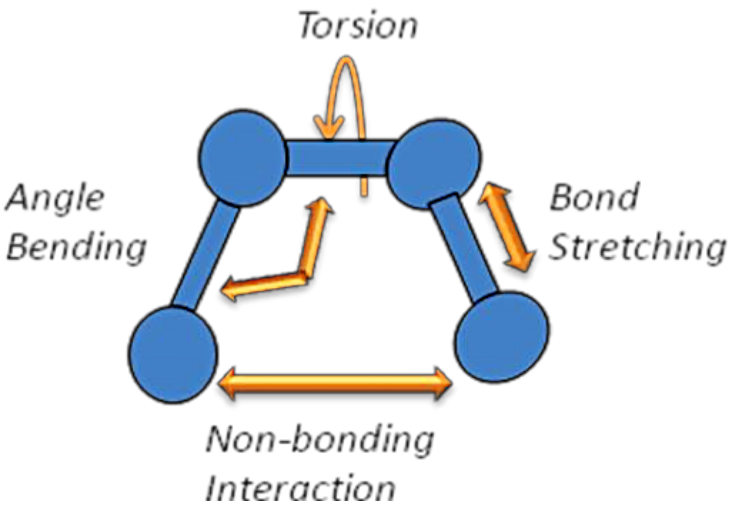
The basic equations and the force field potentials

Molecular dynamics of conventional use is based on II Newton' law:

$$m_i \frac{d^2 r_i(t)}{dt^2} = \boldsymbol{F_i}(\boldsymbol{r}), \quad i = 1,2,\dots n$$

$$F_i(r) = -\frac{\partial U(r)}{\partial r_i}$$

Any molecule is characterized by the presence of a bond stretching between two atoms, an angle bending of three atoms, and a fixed torsion of four atoms. In addition to chemical bonds, there is the participation of unbound van der Waals interactions (non-bonding interactions), and if the atoms also have a charge, also electrostatic forces, and potentials (Coulomb interactions). Then the potential energy:



$$U(r)=U_b+U_\Theta+U_\varphi+U_w+U_{Lj}+U_{el}+U_{HB}+\cdots$$

1. Valence Length potential: $U_b=\frac{1}{2}\Sigma_b K_b(r-b_0)^2$

2. Valence Angle Potential: $U_{\Theta} = \frac{1}{2}\Sigma_{\Theta} K_{\Theta} (\theta - \theta_0)^2$

3. Torsion Dihedral Potential: $U_{\varphi} = \frac{1}{2}\Sigma_{\varphi} K_{\varphi}[cos(n\varphi - \delta) + 1]^2$

4. Van der Waals Interaction Potential: $U_{\mathrm{Lj}} = \sum_{i,j}\left[\frac{A}{r_{ij}^{12}} - \frac{B}{r_{ij}^{6}}\right]$

5. Electrostatics Potential: $U_{\mathrm{el}} = \sum_{i,j}\left[\frac{q_i q_j}{\varepsilon r_{ij}}\right]$

6. Hydrogen Bonding Potential: $U_{\mathrm{HB}} = \sum_{i,j}\left[\frac{A'}{r_{ij}^{12}} - \frac{B'}{r_{ij}^{10}}\right]$

In molecular mechanics, the main functional forms of potential energy include bonding terms for the interactions of covalently bonded atoms, and nonbonding (also known as non-covalent) terms for describing long-range electrostatic and van der Waals forces.

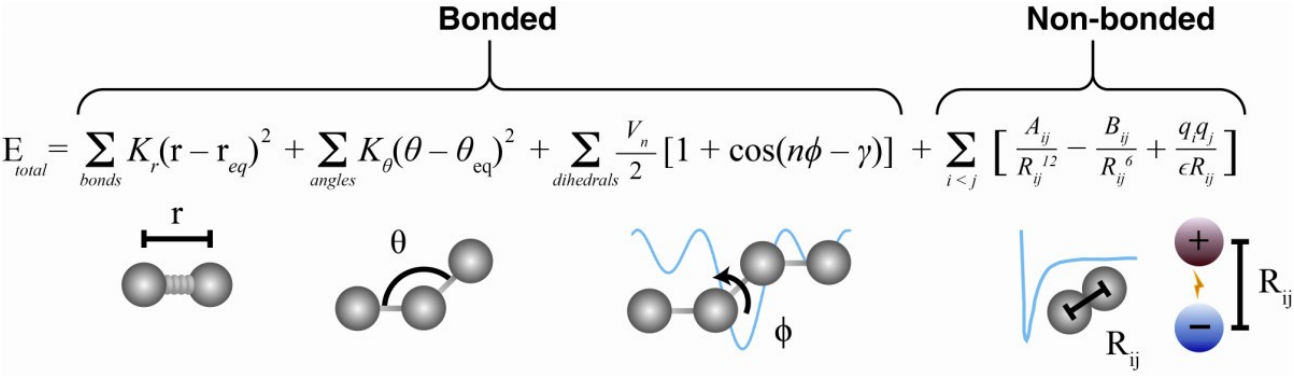


Figure 1. An example of an equation used to approximate the atomic forces that govern molecular movement.

Nuclear energy, which governs molecular motion, can be divided into energy due to interactions between chemically bonded atoms and energy due to interactions between unbonded atoms. Chemical bonds and atomic angles are modeled using simple springs, and dihedral angles (that is, rotations around bonds) are modeled using sinusoidal wave functions that approximate the energy difference between eclipses and zigzags. Uncoupled forces arise from van der Waals interactions modeled using Lennard-Jones dislocations and charged (electrostatic) interactions modeled using Coulomb's law.[4]

RIKEN MDGRAPE-3

MDGRAPE-3 is an ultra-high performance petascale supercomputer system developed by the Riken research institute in Japan. It is a special purpose system built for molecular dynamics simulations, especially protein structure prediction.

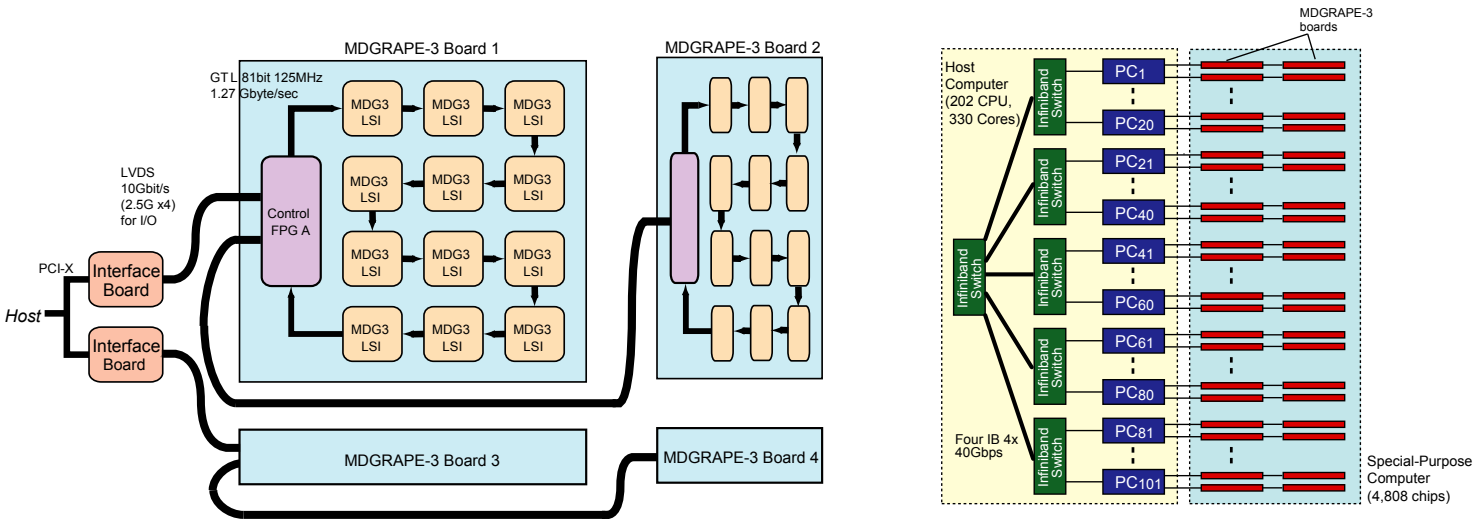


Figure 2. Block diagram of the MDGRAPE-3 board, which has 12 MDGRAPE-3 chips connected in a daisy- chain and an FPGA (left). Block diagram of the MDGRAPE-3 system, which is consisted of the PC cluster with 101 nodes and 402 MDGRAPE-3 boards (right). [6]

C. MD SIMULATION OF LENNARD-JONES SYSTEMS

The **Lennard-Jones potential** is an intermolecular pair potential. Among the intermolecular potentials, the Lennard-Jones potential is the potential that has been studied most extensively and most thoroughly. It is considered an archetype model for simple yet realistic intermolecular interactions.

The Lennard-Jones potential is the most widely used potential and is usually represented by the following equation:

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

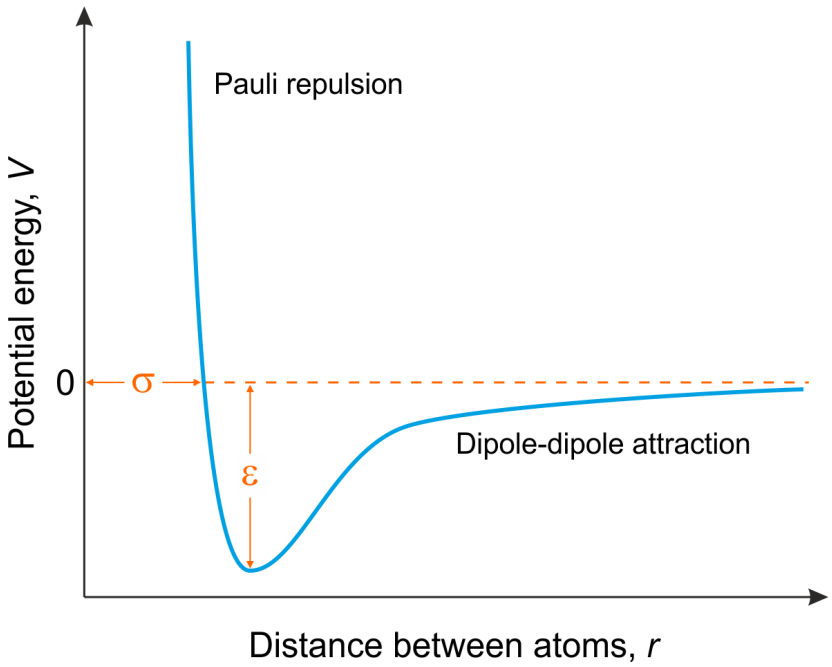


Figure 3. Graph of the Lennard- Jones potential function: Intermolecular potential energy as a function of the distance of a pair of particles.

Radial Distribution Function

The radial distribution function (RDF) denoted in equations by g(r) defines the probability of finding a particle at a distance r from another tagged particle. The RDF is strongly dependent on the type of matter so will vary greatly for solids, gases, and liquids. The average density at any point in a liquid is referred to as the bulk density, ρ=N/V. This density is always the same for a given liquid. The density of the liquid at a given distance of r from another molecule is referred to as the local density, ρ(r), and is dependent on the structure of the liquids. For N number of atoms and r_{ij} it is given by

$$\rho g(\boldsymbol{r}) = \frac{1}{N} < \sum_{i}^{N} \sum_{j \neq i}^{N} \delta\left[\boldsymbol{r} - \boldsymbol{r}_{ij}\right] >$$

Order Parameter

Function-parameter γ is widely used for distinguishing of the equilibrium states:

$$\gamma_x = \frac{1}{N} \sum cos\ (4\pi x_i / a)$$

$$\gamma_y = \frac{1}{N} \sum cos\left(\frac{4\pi y_i}{a}\right)$$

$$\gamma_z = \frac{1}{N} \sum cos\ (4\pi z_i / a)$$

$$\gamma = \frac{1}{3}[\gamma_x + \gamma_y + \gamma_z]$$

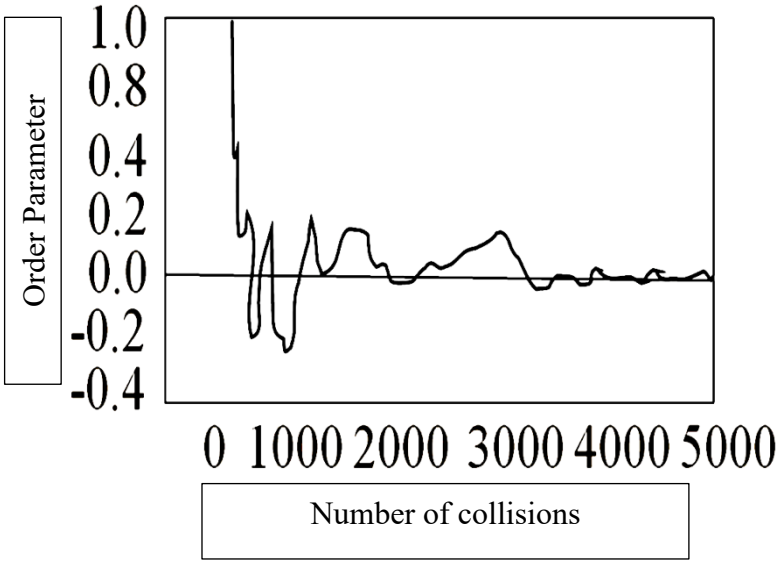


Figure 4. The order parameter γ dependency on the atomic collision number.

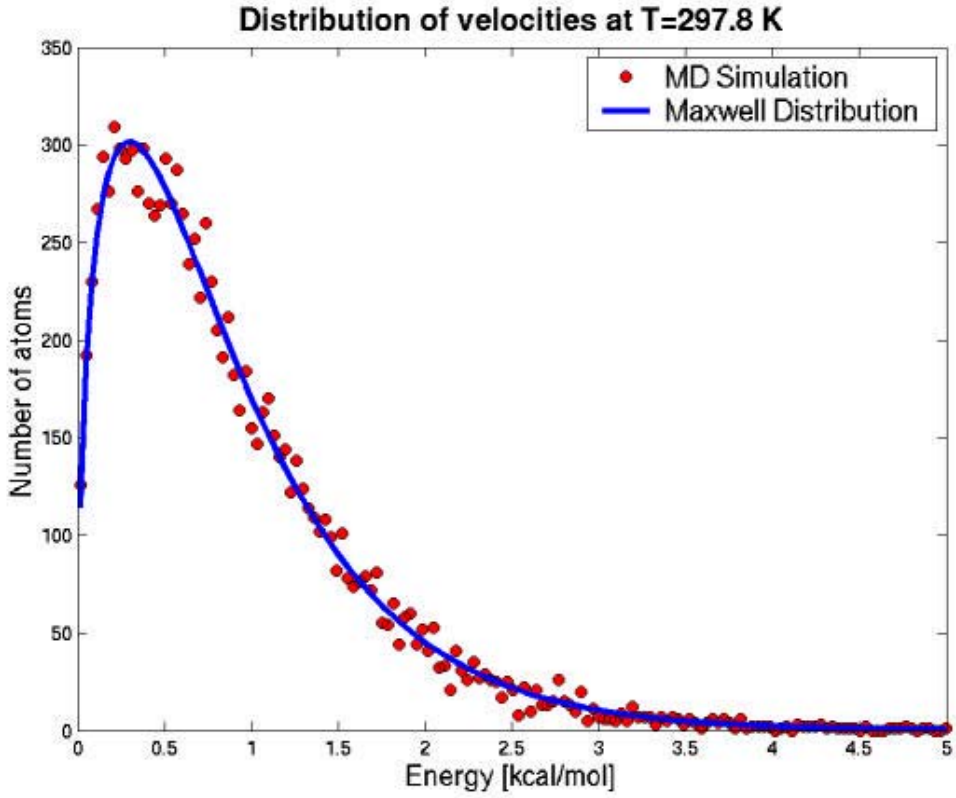
Boltzmann Distribution

The H–function or Boltzmann distribution is used for the monitoring of the equilibrium:

$$H_x(t) = \int_{-\infty}^{+\infty} f(v_x) ln f(v_x) dv_x$$

An NVT (temperature held constant) ensemble simulation at T=300K was terminated and continued as an NVE (energy constant) ensemble simulation. After an equilibration phase, the distribution of velocities from all atoms was determined (red) and fitted to the Maxwell velocity distribution (blue); the best fit corresponded to a temperature T=297.8 K.

$$f(\epsilon_k) = \frac{2}{\sqrt{\pi}} \frac{1}{(k_B T)^{\frac{3}{2}}} \sqrt{\epsilon_k} \exp\left(-\frac{\epsilon_k}{k_B T}\right)$$



D. Methods

Current generations of computers use parallel processing and accelerators to speed up processes. The most popular simulation codes (AMBER, CHARMM, GROMACS or NAMD) have long been compatible with the Message Passing Interface (MPI). When a large number of computational cores can be used at the same time, MPI can significantly reduce computation time. To take advantage of the locality of interactions, a common strategy is to distribute the system and model it across processors. This strategy is called spatial decomposition. You only need to simulate a small part of the system on each processor. The most efficient segmentation

is based on their position in space, not on a list of particles. Each processor processes the region of space in which the particles are located. Communication between processors is also reduced, because only processors that imitate neighboring regions need to exchange information. As already mentioned, the use of accelerators (mainly GPUs) has been a major breakthrough in simulation code. Originally designed for computer graphics, GPUs have evolved into fully programmable high performance general purpose processors and represent a major technological advancement for atomic machine motion. Much of the core MD code has already been prepared for the GPU, and MD code written specifically for the GPU (ACEMD) has also been developed. GPU-only simulation or in combination with MPI is currently the preferred strategy for high performance MD simulation. Surprisingly, simulation has been the most widely used use of HPC in the life sciences, but the increased performance and complexity of GPUs has led to greater use of personal workstations with similar performance.[3]

E. MD Simulation Packages

Use of selected universal codes for modeling ionic, polymeric and biochemical molecular systems.

Many features have been developed, optimized and tuned in general purpose packages such as DL_POLY, AMBER, CHARMM, NAMD etc. today in computer chemistry and nanotechnology applications. A distinctive feature of these programs is that they cover a wide range of molecular systems. From simple atomic structures to ionic systems, polymers and biochemical macromolecules.

Here is a list of some common codes for a universal MD simulation program that includes methods and algorithms from both classical and quantum chemistry.

1. **CHARMM** (Chemistry at Harvard Macromolecular Mechanics)

A molecular simulation program with broad application to many-particle systems with a comprehensive set of energy functions, a variety of enhanced sampling methods, and support for multi-scale techniques including QM/MM, MM/CG, and a range of implicit solvent models.

- CHARMM primarily targets biological systems including peptides, proteins, prosthetic groups, small molecule ligands, nucleic acids, lipids, and carbohydrates, as they occur in solution, crystals, and membrane environments. CHARMM also finds broad applications for inorganic materials with applications in materials design.
- CHARMM achieves high performance on a variety of platforms including parallel clusters and GPUs.
- CHARMM is actively maintained by a large group of developers led by Martin Karplus.[https://www.charmm.org//]

2. **AMBER (**Assisted Model Building with Energy Refinement**)** is a suite of biomolecular simulation programs. It began in the late 1970's originally developed by Peter Kollman's group at the University of California, San Francisco.

3. The DL_POLY Molecular Simulation Package

DL_POLY is a general-purpose classical molecular dynamics (MD) simulation software developed by IT at the Daresbury lab. Todorov, V. Smith, A.M. Elena and others.

Currently, only one version of the DL_POLY software, DL_POLY_4 (LGPL v3 release), has been developed and maintained by the UK academic community only. Previous versions of DL_POLY_2 (written by W. Smith, T. R. Forester, and I. T. Todorov) have been converted to DL_POLY_Classic and are available as open source on BSD.

The overall design of DL_POLY_4 provides scalable performance from single processor workstations to high performance parallel computers. It is provided as source code under license and can be compiled into serial application code using only a Fortran90 compiler, or into parallel application code if the MPI2 toolkit is available on the parallel machine. DL_POLY_4 provides a netCDF alternative (HDF5 library dependency) and fully parallel I/O for the default ASCII toolpath file.[5]

Force Field

The DL POLY 4 force field includes the following features:

1. All common forms of non-bonded atom-atom (van der Waals) potentials

2. Atom-atom (and site-site) coulombic potentials

3. Metal-metal (local density dependent) potentials

4. Tersoff (local density dependent) potentials (for hydro-carbons)

5. Three-body valence angle and hydrogen bond potentials

6. Four-body inversion potentials

7. Ion core-shell polarasation

8. Tether potentials

9. Chemical bond potentials

10. Valence angle potentials

11. Dihedral angle (and improper dihedral angle) potentials

12. Inversion angle potentials

13. External field potentials.

Boundary Conditions

DL POLY 4 will accommodate the following boundary conditions:

1. None, e.g. isolated molecules in vacuum

2. Cubic periodic boundaries

3. Orthorhombic periodic boundaries

4. Parallelepiped periodic boundaries

5. Slab (x,y periodic, z non-periodic).

4. LAMMPS[7]

Large-scale Atomic/Molecular Massively Parallel Simulator (**LAMMPS**) is a molecular dynamics program from Sandia National Laboratories. LAMMPS makes use of Message Passing Interface (MPI) for parallel communication and is free and open-source software, distributed under the terms of the GNU General Public License.

LAMMPS was originally developed under a Cooperative Research and Development Agreement (CRADA) between two laboratories from United States Department of Energy and three other laboratories from private sector firms.[1] As of 2016, it is maintained and distributed by researchers at the Sandia National Laboratories and Temple University.

On parallel computers, LAMMPS uses spatial-decomposition techniques to partition the simulation domain into small 3d sub-domains, one of which is assigned to each processor. Processors communicate and store *ghost* atom information for atoms that border their subdomain. LAMMPS is most efficient (in a parallel computing sense) for systems whose particles fill a 3D rectangular box with approximately uniform density.

LAMMPS also allows for coupled spin and molecular dynamics in an accelerated fashion[7]

5. NAMD[8,9]

Nanoscale Molecular Dynamics (**NAMD**, formerly **Not Another Molecular Dynamics Program**) is computer softwarefor molecular dynamics simulation, written using the Charm++ parallel programming model. It is noted for its parallel efficiency and is often used to simulate large systems (millions of atoms). It has been developed by the collaboration of the Theoretical and Computational Biophysics Group (TCB) and the Parallel Programming Laboratory (PPL) at the University of Illinois at Urbana–Champaign.

It was introduced in 1995 by Nelson *et al.* as a parallel molecular dynamics code enabling interactive simulation by linking to the visualization code VMD. NAMD has since matured, adding many features and scaling beyond 500,000 processor cores.

NAMD has an interface to quantum chemistry packages ORCA and MOPAC, as well as a scripted interface to many other quantum packages. Together with Visual Molecular Dynamics (VMD) and QwikMD, NAMD's interface provides access to hybrid QM/MM simulations in an integrated, comprehensive, customizable, and easy-to-use suite.[8,9,10]

Input files: CONFIG, CONTROL, FIELD

- **CONFIG**: The CONFIG file contains the dimensions of the unit cell, the key for periodic boundary conditions and the atomic labels, coordinates, velocities and forces.
- **CONTROL**: It Contains data about Temperature, Pressure, Step of Integration, Thermodynamic Parameters etc.
- **FIELD**: The FIELD file contains the force field information defining the nature of the molecular forces (structure, mass, charge, interaction potentials). This information

explicitly includes the topology of the system which sequence must be matched in the crystallographic description of the system in the CONFIG file.

- Output files: OUTPUT, REVCON, HISTORY
- **OUTPUT** : energy, temperature, pressure in the final configuration of the system;
- **REVCON**: intermediate system configuration and a restart configuration file – final.
- **HISTORY**: The HISTORY file is the dump file of atomic coordinates, velocities and forces containing system dynamics data, it is needed for visualization.

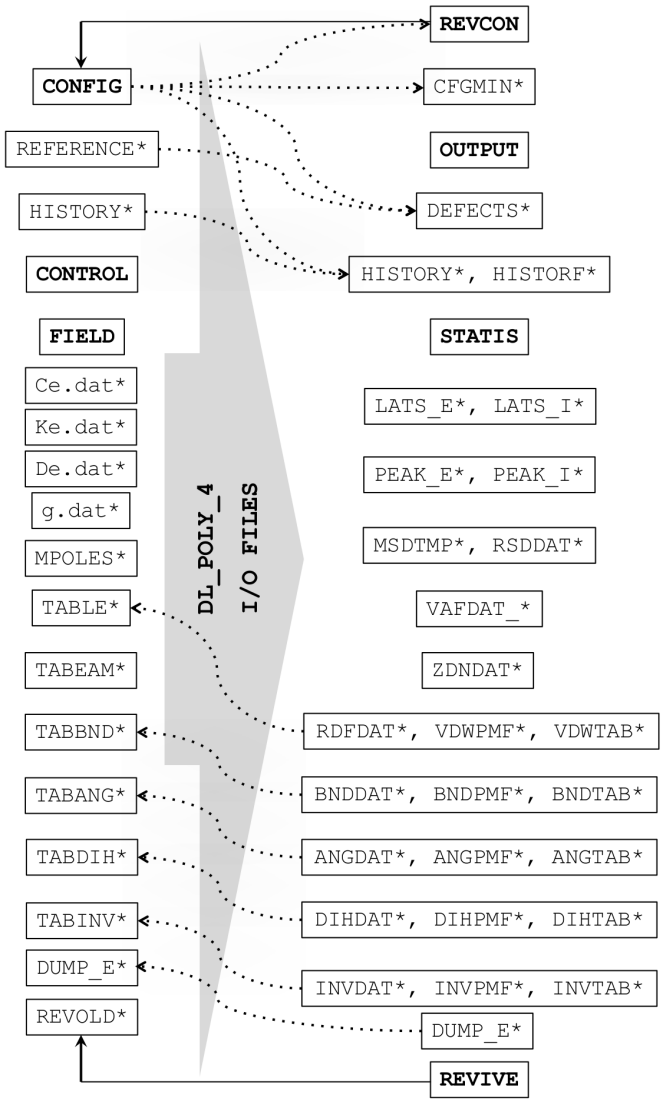


Figure 5. DL POLY 4 input (left) and output (right) files. Note: files marked with an asterisk are non-mandatory.

F. Molecular dynamics simulations of valinomycin interactions with potassium and sodium ions in water solvent[16]

Valinomycin (C54H90N6O18) is a naturally occurring dodecadecipeptide used as a potassium carrier and antibiotic. Valinomycin is derived from cells of several Streptomyces species. Notable is S. fulvissimus.

Valinomycin was first isolated from the *bacterium Streptomyces fulvissimus* in 1955. In 1967, it was confirmed that valinomycin as a carrier catalyses the exchange of K+ and H+ across the mitochondrial membrane without causing a change in Na+ concentration. Biological membranes have several types of ion pumps that work due to the free energy of ATP hydrolysis, a special Na + / K + -ATPase system of integral proteins, known as sodium-potassium pumps. Valinomycin is an example of a protein that transports potassium ions. Valinomycin has a macrocyclic (ring) structure as shown in FIG. 6 (a) and (b).

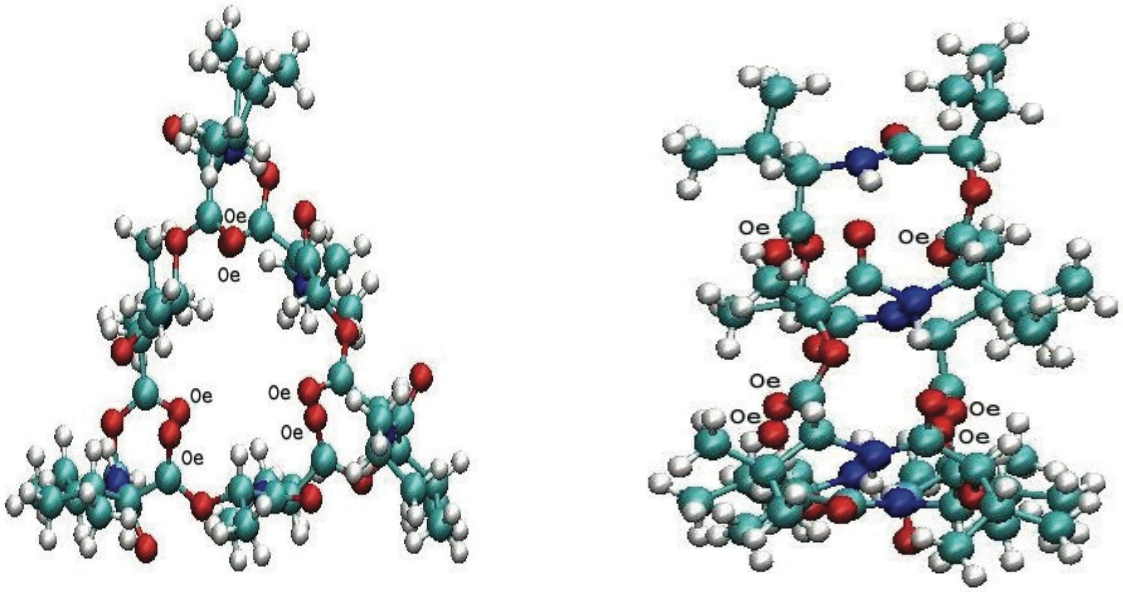


Figure 6. Composition of valinomycin. (a) molecular plane; (b) Side view. The colored spheres represent nitrogen (blue), carbon (blue), hydrogen (white), and oxygen (red) atoms. The six oxygen atoms capable of trapping external solvent ions are designated Oe.

Due to its chemical structure, valinomycin can form complexes with potassium ions trapped by molecules within the ring. On the other hand, valinomycin is readily soluble in the lipid phase of the membrane. The outer part is non-polar. Thus, valinomycin molecules located on the membrane surface capture potassium ions from the surrounding solvent. Potassium ions are then transported by valinomycin by diffusion across the membrane, and finally the ions are released from the solvent against the cell membrane. This creates an ion concentration gradient in the cell membrane. The potential relative to the cell perimeter varies from -70 mV to +50 mV. Translocations stimulate synaptic signalling required for biological function.

In this work, we aimed to measure the electric field strength (potential gradient) of a model system describing valinomycin as potassium (K+) and sodium (Na+) ions based on molecular dynamics (MD) simulations. The reaction field algorithm was used to calculate electrostatic interactions.

Molecular dynamics (MD) simulations have been performed using the DL_POLY code, which was developed by the molecular simulation group at the Daresbury Laboratory (England) with the support of the Research Council for Engineering and Physical Sciences.

The valinomycin molecule consists of 168 atoms; the number of K^+(Na^+) ions was 109. The water molecules were simulated as 3-site rigid bodies; the total number of water atoms was 3339 (1113 × 3).

Computer simulations were performed for a constant temperature of 300 K using the Nose – Hoover algorithm with the thermostat relaxation constant of 2 ps. For the van der Waals inter- actions, we have used the Lennard – Jones (LJ) potential. The interaction potential parameters and atomic masses and charges are shown in **Tables 1** and 2. The integra- tion of the equations of motion was performed using the Verle integration scheme in quaternion. The integration step was 2 fs (femtoseconds). The intermolecular che- mical bonds were estimated on the basis of the Shake algorithm to an accuracy of 10^{-8}.

Table 1. The Lennard – Jones (LJ) potential parameters for different atomic pairs.

Atomic pair	Potential	Functional form	Parameters	ε, kcal/mol	σ, Å
C-C	*LJ*	$U(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$	**ε, σ**	0.12	3.30
H-H	…	…	…	0.02	1.78
N-N	…	…	…	0.16	3.12
O-O	…	…	…	0.20	2.85
OS-OS	…	…	…	0.15	2.94
Oe-Oe	…	…	…	0.20	2.85
OW-OW	…	…	…	0.16	3.17
HW-HW	…	…	…	0.02	1.78
K-K	…	…	…	0.32	3.13
Na-Na	…	…	…	0.08	2.73

Table 2. The mass and charge values in the system of valinomycin + K^+(Na^+) ion + water.

Atom (md notation)	Mass m (m_e, a.m.u.)	Charge q (e, proton charge)
C	12.01	+0.47
H	1.00	+0.21
N	14.01	–0.40
O	16.00	–0.41
OS	16.00	–0.46
Oe	16.00	–0.41
OW	15.99	–0.82
HW	1.00	+0.41
K	39.10	+1.00
Na	23.00	+1.00

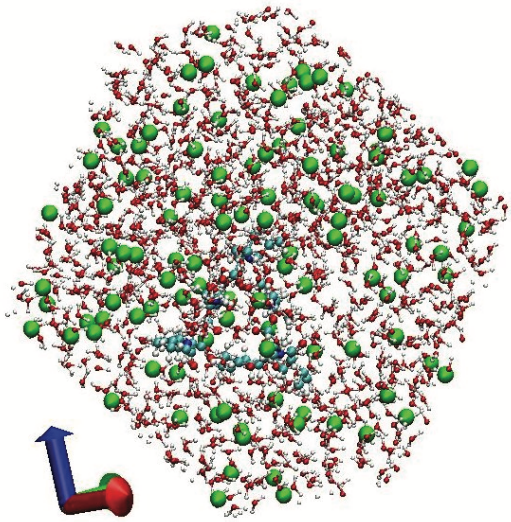


Figure 7. A valinomycin molecule (a triangular shape chain is in the center) surrounded by potassium ions (green spheres) and water molecules (red and white are oxygens and hydrogens, respectively).

G. RESULT

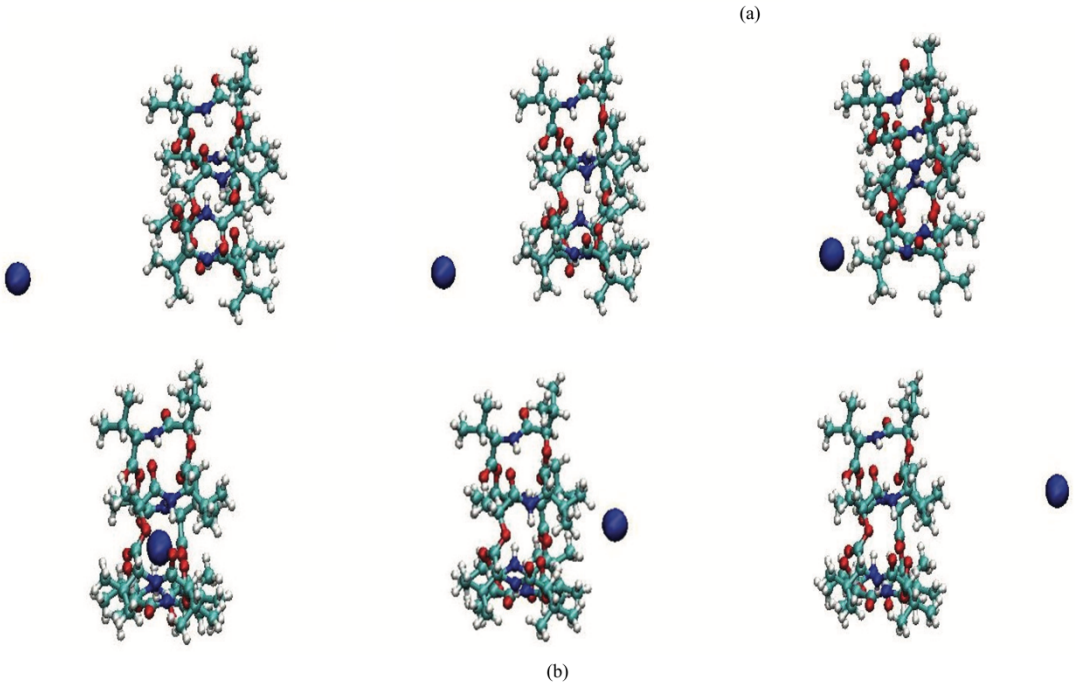


Figure 7.Six consequent configurations of valinomycin and a sodium ion penetrating into the cavity are shown (b). The snapshots correspond to the time moments of t = 0, 1, 2, 3, 5 and 10 ps (the electric field is directed from left to right).

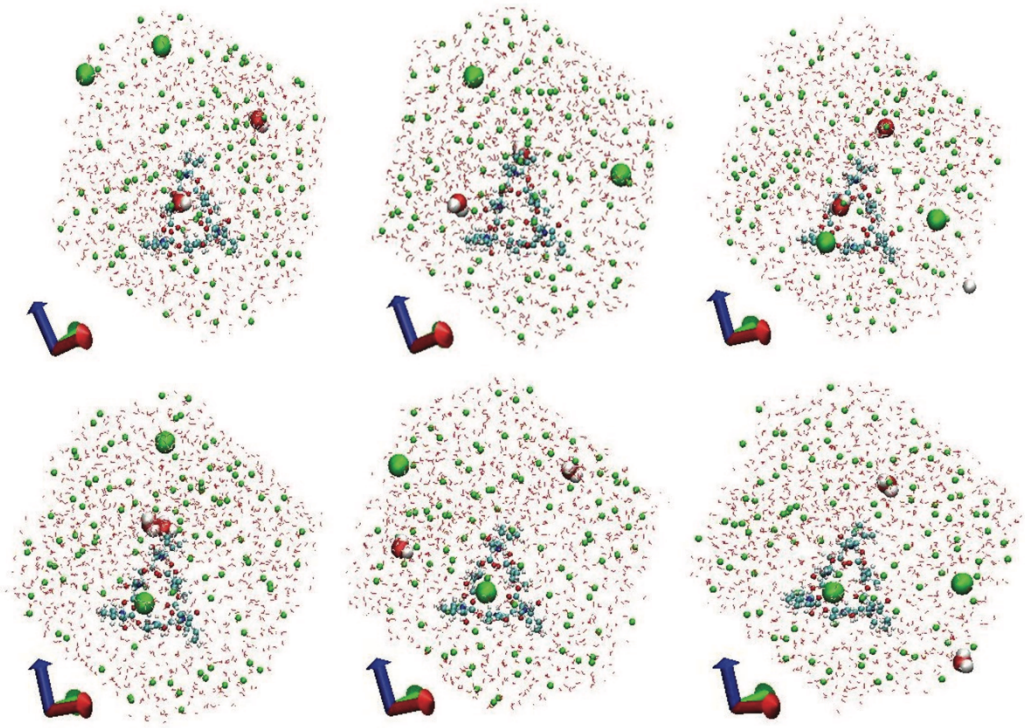


Figure 8. Six consequent configurations of valinomycin with potassium ions (green spheres). The snapshots correspond to the time moments of t = 0, 1, 2, 3, 5 and 10 ps (views from left to right and from top to bottom).

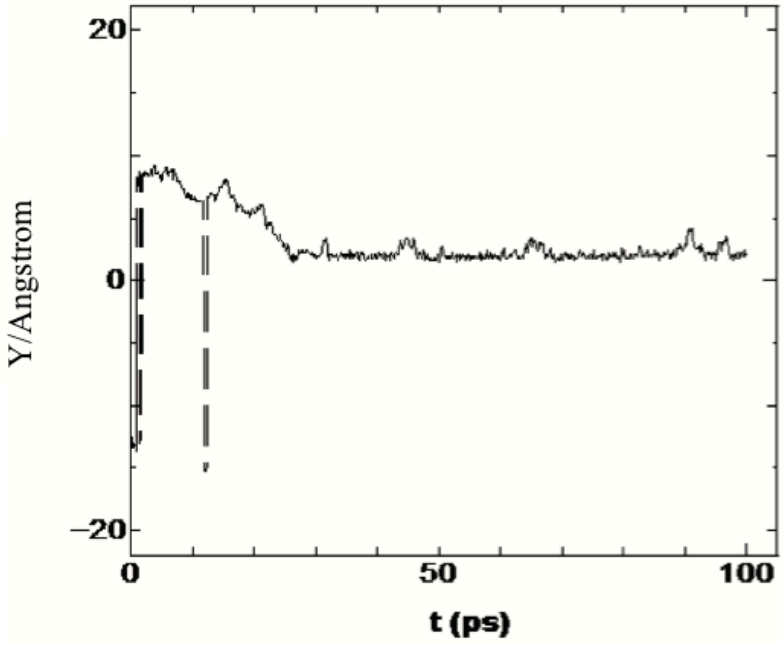


Figure 9. A trajectory diagram of a potassium ion captured by a valinomycin molecule

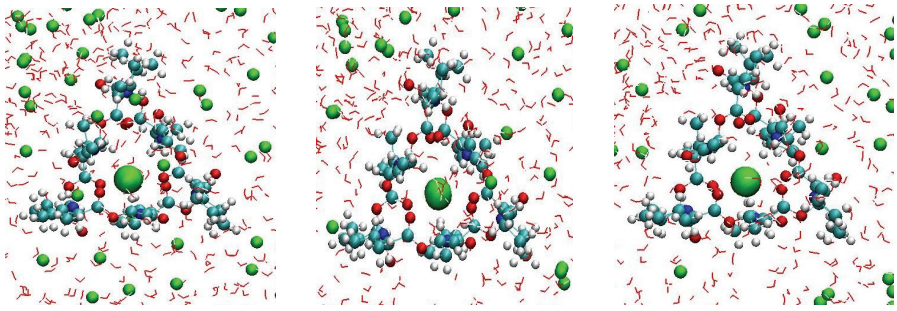


Figure 10.Three consequent configurations (b) show the ion position inside the valinomycin localization cavity.

H. Conclusion

MD Simulation has a history of more than 40 years. However, it was only in recent years that time boundaries have been set to make MD compatible with biological processes. Whereas our current normal simulation approaches the microsecond scale. We can effectively model the structural transformation or capturing of ligands. computer hardware improvements In particular, the use of the GPU and optimization improvements of the MD algorithm, including the coarse algorithm. It made us switch from a single structured analysis. which is the basis of molecular modeling as we know it. That is to say, when analyzing ensembles of form Structural groups represent much better true macromolecules. Because flexibility and dynamic properties are taken into account. (including all thermodynamic data) and facilitate agreement on experimental results. While the conceptual change is evident and the technology is advancing. But there is still a long way to go before biomolecular modeling. Creating a set of structures will become routine. There are tools that greatly simplify setting up macromolecular systems. and allow non-specialists to enter the world of modeling. Lack of optimized analytics tools And the difficulty of storing and transmitting the massive trajectories created is still a problem that must be solved. In any case, MD is already a valuable tool for understanding biology.

I. Future work

We are unable to simulate the brain to the last molecular detail. But proponents of simulation hope that uncovering the principles by which the brain works will enable some details to be generated by algorithms. For future research, I had chosen to perform MD modelling of brain neurons to the molecular level to get details, including the brain's extracellular interactions, and molecular-scale processes such as receptor binding. Molecular dynamics simulations can be used to investigate the internal motion of proteins, and how proteins interact with each other to modulate their activity.

Producing a biologically faithful simulation of the brain would require an almost limitless set of parameters but with Molecular dynamics there is still a hope that we can replicate the brain after getting full details about working of atoms at the smallest scale in brain which could open the doors for creating a brain with artificial electronics networks, mimicking the same behaviour.

J. Acknowledgement

I would like to express my sincere gratitude to my project supervisor**, Prof. Kholmirzo Kholmurodov**, for giving me the opportunity to do this project and providing invaluable guidance throughout this project. I am grateful for his support, constant encouragement and for sharing his knowledge and experience with me.

I would also like to thank the **JINR Interest Team** for their support and for this program that allows students from across the globe to utilize this opportunity and gain experience and knowledge.

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