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)

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Participation period:

26th February – 14th April, Wave 10

Dubna, 2024

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Abstract

Molecular modeling is one of the fastest spreading techniques in computational biology, which encompasses all the tasks from visualization, derivation, manipulation, and representation of the structures of molecules keeping in view the physical and chemical properties that depend on these structures. Molecular dynamic simulation is to predict the behavior of atoms and how they move as a time-dependent function, thereby providing the ultimate details concerning the atoms based on algorithms of physics that govern the interatomic interactions.

The tasks accomplished during INTEREST Program Project are:

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 hybrid MD approach (classical quantum-chemistry potentials simulation methods).

5: MD test modeling.

Project Aim

The course is an introduction to MD simulation and its object is to:

1. Delve into the basics of molecular dynamics simulation including the most important equations needed like Newtonian equations, potentials and force field and numerical integration methods.

2. Acquire theoretical knowledge about the diverse MD simulation software techniques.

3. Know about the efficacy and importance of MD simulation in several fields such as biological systems, chemical reactions, and material science that will help us in our future projects.

4. Acquaintance of several study cases such as:

    a. "Molecular dynamics simulations of valinomycin interactions with potassium and sodium ions in water solvent."
    b. "Molecular dynamics study of phase transformation of biphenyl molecule in an active solvent."
    c. "Molecular dynamics simulations of interactions of gold nanoclusters with a DNA fragment in hexagonal geometry."

Introduction

Molecular dynamics simulation is a computer calculation of the movement of all atoms in a molecule by solving Newtonian's equation of motion for all atoms.

Molecular dynamics (MD) simulations predict how every atom in a protein or other molecular system will move over time, based on a general model of the physics governing interatomic interactions.

These simulations offer predictive insights into the movement of atoms within complex molecular systems such as proteins, elucidating phenomena like conformational changes, ligand binding, and protein folding with remarkable temporal precision at the femtosecond scale. Moreover, they can anticipate atomic-level responses to perturbations like mutations, phosphorylation, or ligand interactions. [1].

To maintain numerical stability, the simulation employs short time steps, typically spanning only a few femtoseconds (10^{-15} s) each, considering that biologically significant events occur over nanosecond to microsecond timescales. Given the immense number of time steps and interatomic interactions involved, these simulations demand substantial computational resources.

Molecular Dynamics (MD) simulations are used across various scientific disciplines:

- **Chemical Physics:** Understanding molecular interactions and reactions.
- **Materials Science:** Studying material properties at the atomic level.
- **Biophysics:** Visualizing and analyzing the dynamic behavior of biomolecules.
- **Protein Study:** Investigating protein structure, function, stability, and interactions [2].
- **Drug Discovery**: Exploring protein conformations and aiding in homology modeling when crystal structures are not available [3, 4].

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Basic equations.

- *The conventional use of MD simulation is based on II Newton' law:*

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

$$\{\boldsymbol{r}_i, m_i, \boldsymbol{F}_i\}$$

$$\boldsymbol{r} = \{r_1, r_2, \dots, r_n\}; U(\boldsymbol{r})$$

$$\boldsymbol{F}_i(\boldsymbol{r}) = -\frac{\partial U(\boldsymbol{r})}{\partial \boldsymbol{r}_i}$$

$$m_i \frac{d^2 \boldsymbol{r}_i(t)}{dt^2} = \boldsymbol{F}_i\big(\boldsymbol{r}_i(t)\big) - \gamma_i m_i \frac{d\boldsymbol{r}_i(t)}{dt} + R_i(t)$$

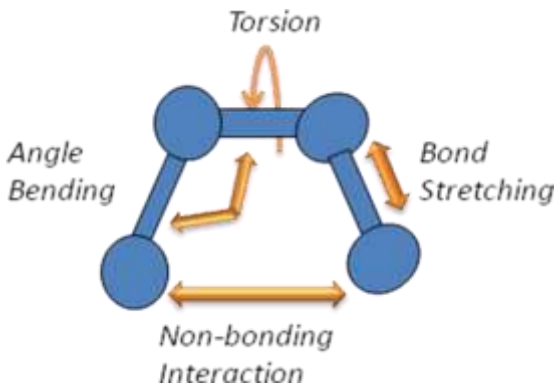


Fig.1. *Chemical bonds (bond stretching, angle bending, torsion) and non-bonding interaction.*

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

valence length potential,

$$U_b = \frac{1}{2}\sum_b K_b\,(r - b_0)^2$$

Valence angle potential,

$$U_\theta = \frac{1}{2}\sum_\theta K_\theta\,(\theta - \theta_0)^2$$

Torsion dihedral potential,

$$U_\varphi = \frac{1}{2}\sum_\varphi K_\varphi[\cos(n\varphi - \delta) + 1]$$

Van-der-Waals interaction potential (12-6 or Lennard-Jones (lj)):

$$U_{LJ} = \sum_{i,j}\left[\frac{A}{r_{ij}^{12}} - \frac{B}{r_{ij}^{6}}\right]$$

Electrostatics potential,

$$U_{el} = \sum_{i,j}\frac{q_i q_j}{\varepsilon r_{ij}}$$

Hydrogen bonding potential,

$$U_{HB} = \sum_{i,j}\left[\frac{A'}{r_{ij}^{12}} - \frac{B'}{r_{ij}^{10}}\right]$$

Lennard-Jones Potential.

- The Lennard-Jones (LJ) potential stands as a central element within Molecular Dynamics (MD) simulations, a pivotal computational approach employed in exploring atomistic phenomena spanning Chemistry, Physics, Biology, and Mechanics. Despite the extensive utilization of MD simulations, it's frequently disregarded that the conventional LJ potential relies on a century-old and somewhat arbitrary repulsion exponent[5].

- The Lennard-Jones (lj) or (12-6) potential looks like **Fig.2**. and **Table.1.**

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

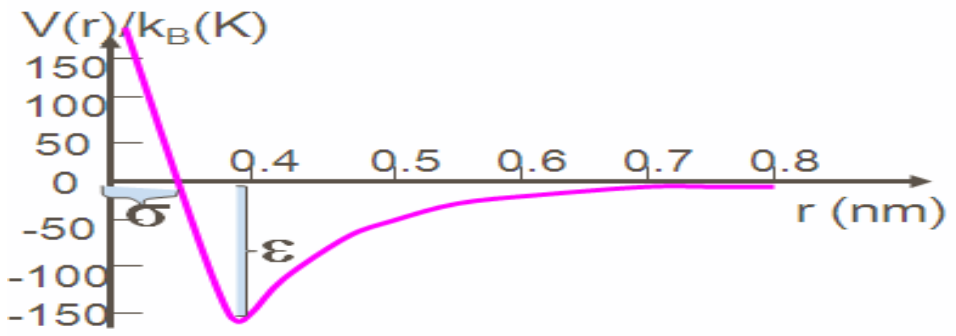


Fig.2. *The Lennard-Jones potential energy dependence on the atom-atomic distance.*

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

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**	**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**

The Lorentz-Berthelot mixing rule: $\sigma_{CS} = \frac{\sigma_{CC} + \sigma_{SS}}{2}$ $\varepsilon_{CS} = [\varepsilon_{CC} * \varepsilon_{SS}]^{1/2}$

MD Simulation Software.

- Several common software can be used in MD simulations [6] such as:

✓ **AMBER** (Assisted Model Building with Energy Refinement): A suite of biomolecular simulation programs that began in the late 1970s.

The term "Amber" refers to two things. First, it is a set of molecular mechanical force fields for the simulation of biomolecules (these force fields are in the public domain and are used in a variety of simulation programs). Second, it is a package of molecular simulation programs .

✓ **DL_POLY:** is a general purpose classical molecular dynamics (MD) simulation software developed at Daresbury Laboratory by I.T. Todorov, W. Smith, A.M. Elena, and others.

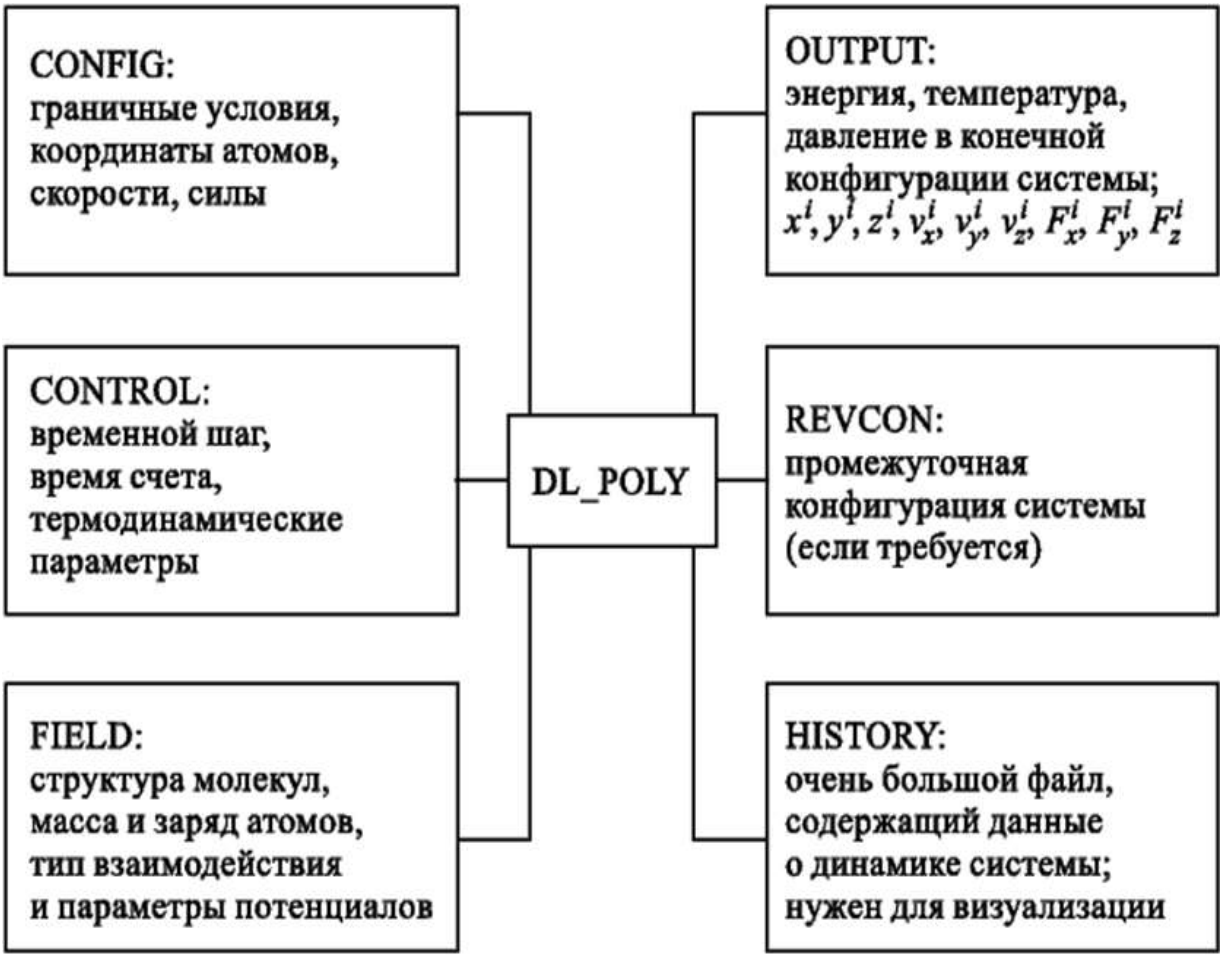
✓ **NAMD** (Nano-scale Molecular Dynamics): A parallel molecular dynamics code designed for high-performance simulation of large biomolecular systems.

✓ **GROMACS** (Groningen Machine for Chemical Simulation): A versatile package to perform molecular dynamics, i.e. simulate the Newtonian equations of motion for systems with hundreds to millions of particles.

✓ **LAMMPS** (Large-scale Atomic/Molecular Massively Parallel Simulator):
A classical molecular dynamics code with a focus on materials modeling.

✓ **CHARMM** (Chemistry at Harvard Macromolecular Mechanics) **:** A program widely used for macromolecular simulations, including energy minimization and molecular dynamics.

- *As previously mentioned, there are several simulation software used in MD simulations, but during our course we discussed DL_ POLY and AMBER in details.*



A flowchart scheme ➡ *input: CONFIG, CONTROL, FIELD; output: OUTPUT, REVCON, HISTORY.*

Case study

- *During the course we demonstrated the use of DL_POLY code in MD simulation of atomic and ionic structures, polymeric chains, and biomolecules. And now let's discuss a study case as an example* "Molecular dynamics simulation of valinomycin interactions with ions K^+ and Na^+ in water."

✓ ***Background***

- Valinomycin is a non-ribosomal peptide that was discovered from *Streptomyces fulvissimus* bacteria in 1955 [7]. Over the past more than six decades, it has received continuous attention due to its special chemical structure and broad biological activities [8]. In 1967, it was established that as a transporter, valinomycin catalyzes the exchange of K+ and H+ through a mitochondrial cell membrane, thereby causing no changes in the Na+ concentration . In biological membranes, there are several kinds of ionic pumps, which work at the expense of the free energy of ATP hydrolysis—a special Na+ /K+ -ATPase system of integrated proteins known as the sodium-potassium pump [7]. Valinomycin is an example of a protein that transports potassium ions as shown in **Fig.3**. Valinomycin has a macrocyclic (ring) structure as shown in **Fig.4.**

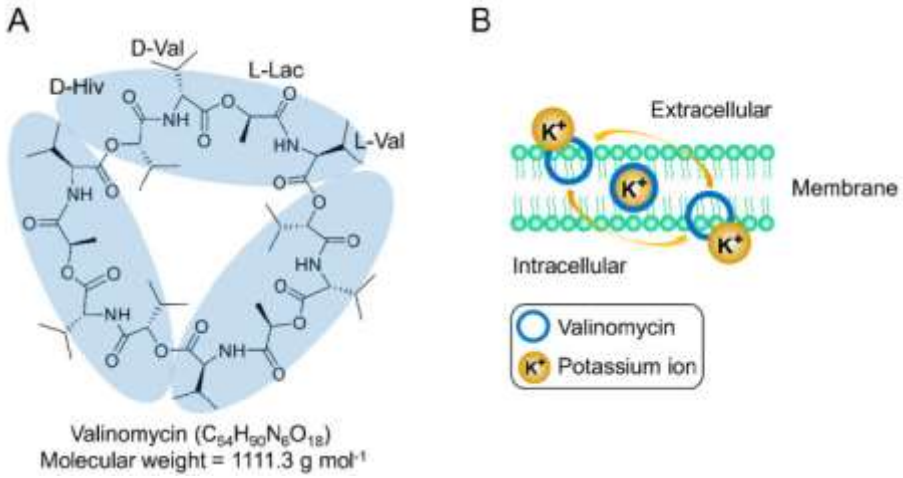


Fig.3. (**A**) Chemical structure of valinomycin and (**B**) valinomycin acts as a potassium-specific ionophore.

✓ ***Methodology***

-They used

(Truncated octahedron boundary conditions; 42,86 Å; *NVT* ensemble; integration time step 2 fs; *Shake* tolerance 10^{-8}; Water 1113×3=3339, potassium (sodium) ions 109).

(1) Periodic boundary conditions for all spatial axes; the geometry of the system configuration was a truncated octahedron with the side length of 42,86Å.

(2) Molecular dynamics (MD) simulations have been performed using the DL_POLY code, employed version 2.19 of the DL_POLY.

The configurational energy of the molecular model is represented as a sum of the energies of binding (Eval) and non-binding (Enb) interactions:

$$E = E_{val} + E_{nb}$$

The energy of valence (binding) interactions Eval is given by the following formula:

$$E_{val} = E_r + E_\theta + E_\varphi + E_{inv}$$

$$E_{nb} = E_{VDW} + E_{el} + E_{hb}$$

LJ-potential: $$U(r) = \left(\frac{A}{r^{12}}\right) - \left(\frac{B}{r^6}\right)$$

(A) *(B)*

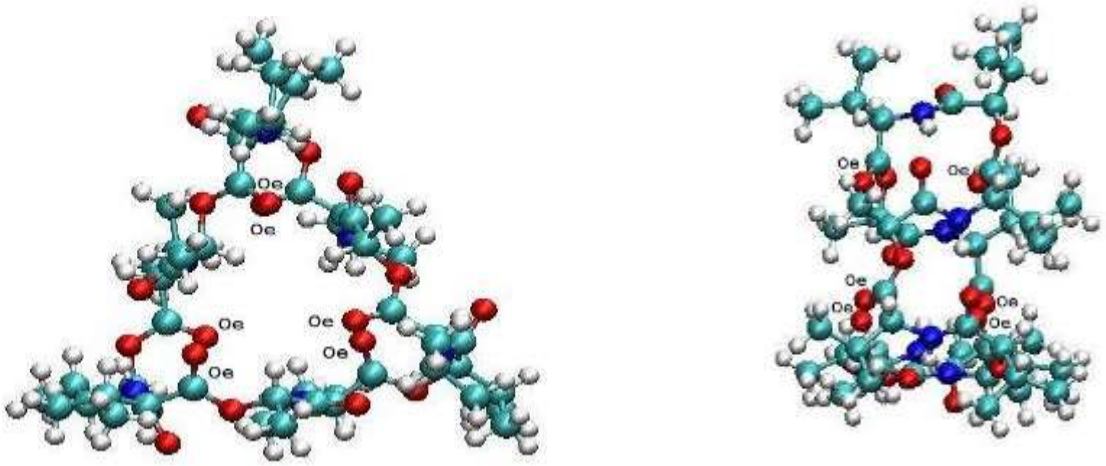


Fig.4*. Valinomycin configuration* ***(A)*** *– view on molecule surface,* ***(B)*** *– side view).*

Table 2. *Parameters of LJ (Lennard-Jones) potential.*

Atomic pair	**Potential**	**Functional form**	**Parameters**	**ε, kcal/mol**	**σ, Å**
C-C	*LJ*	$V(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$	**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

Lorentz-Berthelot combining rules:

$$\sigma_{CS} = \frac{\sigma_{CC} + \sigma_{SS}}{2} \quad , \quad \varepsilon_{CS} = \left[\varepsilon_{CC} * \varepsilon_{SS}\right]^{1/2}$$

Table 3. *Masses and charges for the system of valinomycin + $K^+(Na^+)$ + water.*

Atom	Mass number (in a.e.u)	Charge q (in |e|, proton)
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

✓ ***Results***

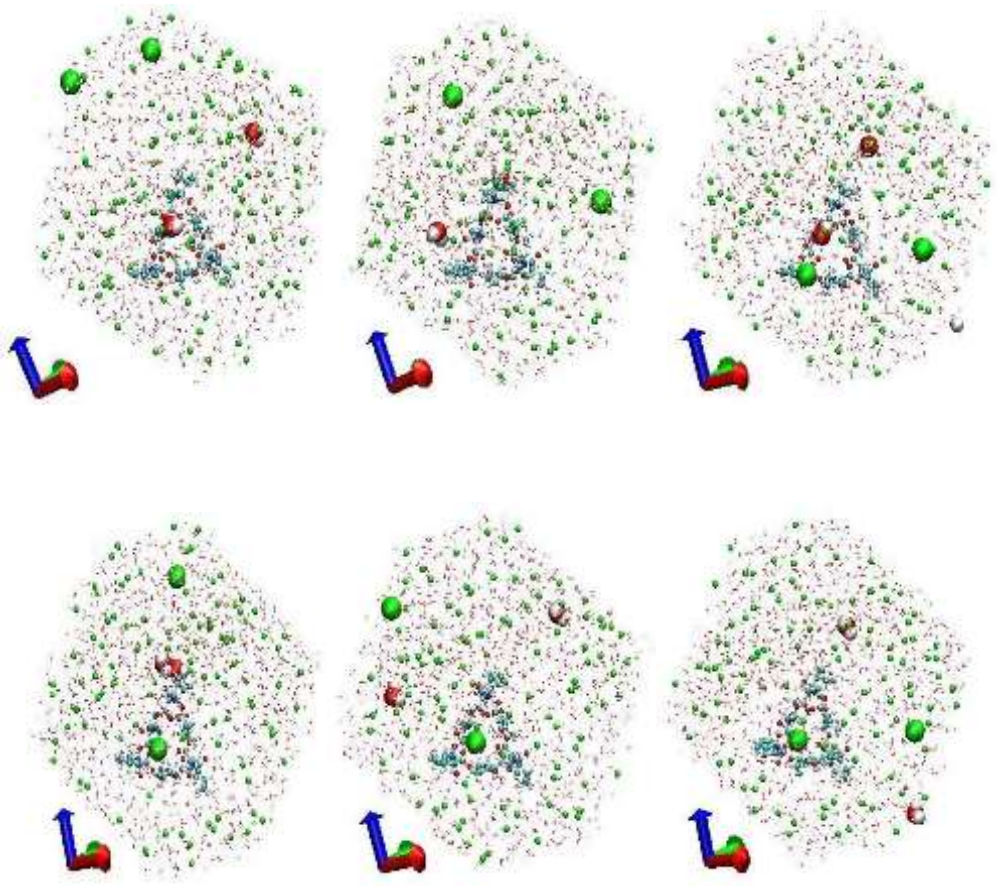
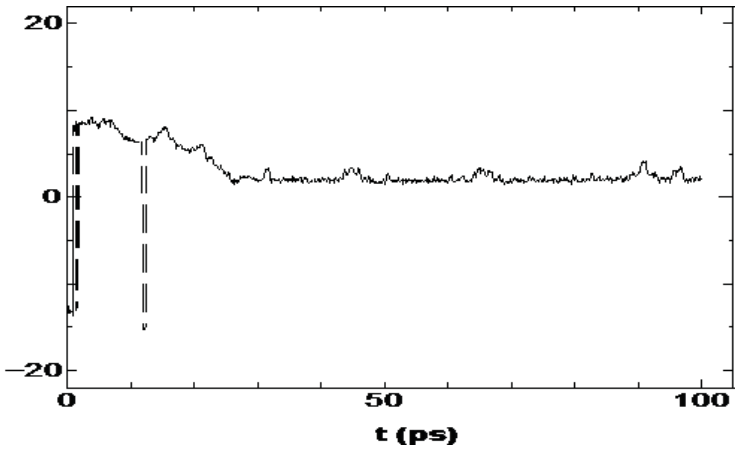
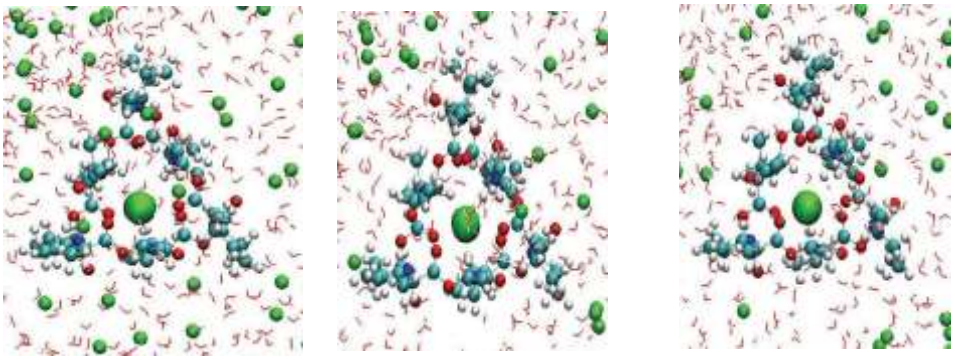


Fig.5. *Six sequential snapshots of valinomycin with potassium at t=0, 1, 2, 3, 5 and 10 ps (left to right, top to bottom).*



(a)



(b)

Fig.6. *A trajectory diagram of a potassium ion captured by a valinomycin molecule.*
(a). Three consequent configurations
(b). show the ion position inside the valinomycin localization cavity.

Conclusion

Molecular dynamics and molecular mechanics are commonly employed in tandem to attain the optimal conformer with the lowest energy state. This involves analyzing all potential conformations and their respective energies to determine the molecule's 3D shape accurately. Furthermore, it allows for a comprehensive examination of the molecule's electronic structure and polarizability while considering its binding energy when docking with a receptor or enzyme target, such as a drug candidate. Despite the need for cautious application, molecular modeling can offer valuable insights to biochemists, chemists and biologists engaged in medicinal research.

Future Scope

- MD simulations have a wide broad of applications not only in the field of biological science but in any field one can imagine ranging from physics, chemistry, biology to climatology and meteorology, video games, to film industries.

- As a medical biochemistry master's degree researcher interested in nanomedicine and cancer biology, I hope to use MD simulation technique in the field of drug discovery during my PhD studies.

- In short, simulations are used to determine the molecule's location to bind to its receptor and how it changes the binding strength and affinity of molecules that bind elsewhere. This information, along with other geometrical, physical, chemical, and thermodynamic properties, is used to alter the structure as many times as possible to design a drug that fulfills one's needs. Once this computational task is done, the experimental scientists take over, and after its testing and approval, clinical trials take place, and if it passes the clinical trial, the drug is ready to be launched in markets [2]. I will give an example of this later.

- Contemporary drug discovery processes start commonly with identifying and validating a biologically relevant target that can be modulated with drug molecules to prevent or cure a disease or alleviate symptoms of sickness **Fig.7**.

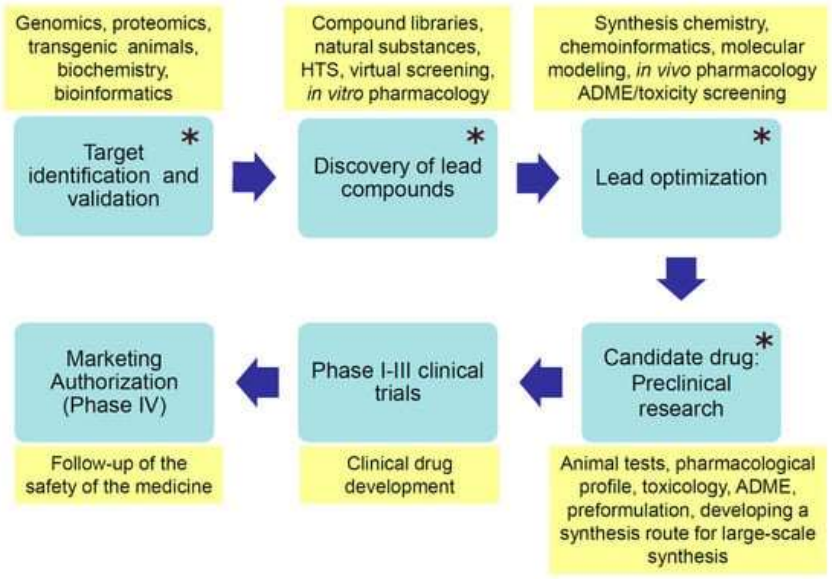


Fig.7. *Phases of modern drug development (blue boxes). The yellow boxes contain characteristic actions, methods, or tools used in the development phase. ADME—absorption, distribution, metabolism, and excretion; main steps of a drug in the body. Molecular dynamics simulations can be applied to facilitate research in the phases denoted with a star (*).*

RAS—Uncovering the Conformational Dynamics of a Challenging Anticancer Drug Target.

- RAS proteins function as intracellular molecular switches to control a wide variety of signal transduction pathways. All RAS proteins, including HRAS, NRAS, and KRAS represent the three most common RAS isoforms in humans, cycle between active and inactive states by binding to GTP and GDP. Active RAS interacts with multiple downstream effectors to drive cell growth and proliferation.
- Somatic mutations that impair hydrolysis of GTP to GDP stabilize RAS in its activated form, causing sustained proliferative signaling and oncogenesis.

- In fact, *RAS* genes are found mutated in nearly 30% of all cancers and are the primary drivers of many lethal cancers such as pancreatic, colon, and lung cancer [9]. Despite years of studies, however, pharmacologically targeting RAS has proved extremely tricky.

- An aspect of the biology of RAS and related G-proteins that is gaining increasing attention for its therapeutic prospect is their dynamic localization to and fluctuations at membrane surfaces. Unfortunately, both the process of membrane targeting, and the dynamics of the complex are difficult to study experimentally due to the resolution limit of current techniques. In contrast, the exponential growth in computational power over the last decade has begun to enable a detailed characterization of these phenomena using atomic-level molecular simulations.

- Invaluable insights have been gained into the dynamics of RAS in complex with biomimetic membranes using molecular dynamics (MD) simulations.

- For more than three decades, development of effective therapeutics to inhibit *RAS*-driven oncogenesis has eluded the field and RAS was thought to be 'undruggable'. However, a clinically approved mutant selective KRAS therapy is now within sight as the FDA has granted an allele-specific covalent inhibitor, AMG 510, Fast Track designation.

- AMG 510 binds to KRAS-G12C, the RAS mutant most commonly found in non-small-cell lung tumors. This successful inhibition of KRAS-G12C, has given hope that a range of mutant RAS allele-specific targeted therapies could become therapeutically tractable.

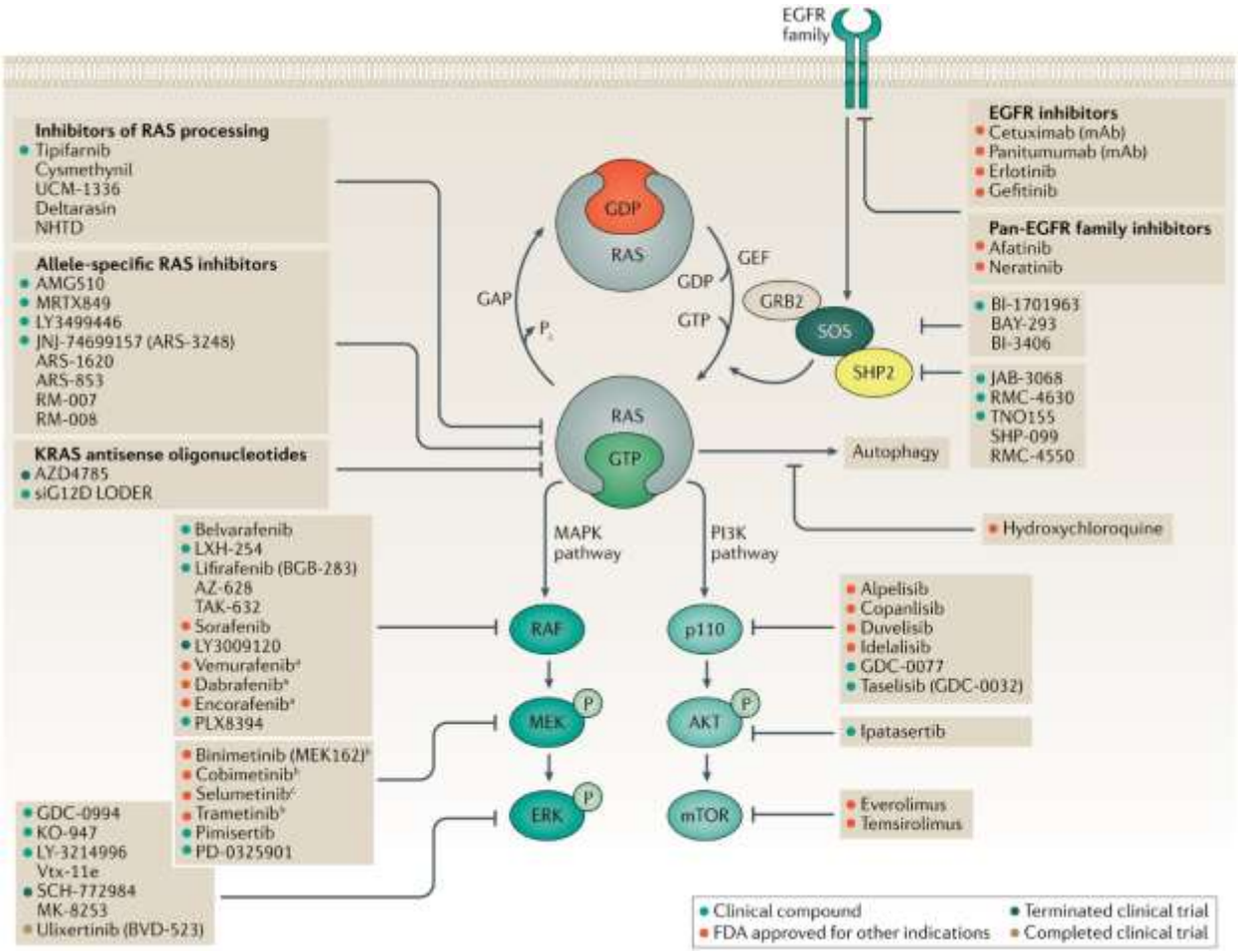


Fig.8. Clinical development of inhibitors for ***RAS***-mutant tumors.

- This is an exciting time to be at the forefront of 'drugging the undruggable' as there is new optimism that *RAS*-mutant cancers can be successfully treated.

- RAS proteins are the best characterized and most representative example of proteins that are targeted to membranes by lipid-based motifs, that's why I hope to work on this point in my future studies, especially when this MD simulation course shed the light on this research perspective and encouraged me to have a step forward to fulfill my objectives to apply and expand the knowledge of molecular dynamics simulations.

Acknowledgment

All thanks, gratitude, and respect to our Prof. Kholmirzo Kholmurodov for his dedication, commitment, and fruitful explanation during the course and for giving me this unique opportunity. Additionally, I would like to express my gratitude to the whole INTEREST Programme team at the Joint Institute for Nuclear Research for giving me this opportunity to learn, proceed and enhance my knowledge and skills.

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