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)

Supervisor:

Prof. Kholmirzo Kholmurodov

Student:

Mariya Zaneva, Bulgaria

Technical University of Sofia

3rd year student of Applied Physics and Computer Modelling

Participation period:

September 27 - October 22

Wave 5

CONTENTS

1. INTRODUCTION

Molecular Dynamics (MD) Simulation is an approach method that uses computer techniques to apprehend the dynamicity of biological molecules. By allowing atoms and molecules to interact for a certain period of time during the simulation, the method is able to analyze their physical movement and chemical interactions. It is one of the first simulation methods, and over the years, it has taken a the role of a powerful tool in physics, chemistry, and biology.

Computer simulations bring new insights into atomic change in the structure over a given period of time and can even be used to discover and design new molecules. They have altered the interplay between experiment and theory and serve as an important suffix to the lab experiments by saving time and cost.

There are two central families of MD methods - classical and quantum molecular dynamics simulations. In the "classical'' approach, molecules are treated as classical objects and answer to classical mechanics' laws. "Quantum" MD simulations take into account the quantum nature of chemical bonds.

2. THEORETICAL BACKGROUND

2.1. Atomic Force Field Model of Molecular Systems. Basic Equations and Potentials

In Molecular Dynamics Simulations, Newton's equations of motion are integrated numerically for typically 100-10000 particles, starting from an initial configuration - initial positions and velocities for all particles. The atomic force field describes physical systems as collection of atoms kept together by interatomic forces. The interaction law is specified by the potential $U(r_1, \ldots r_N)$, which represents the potential energy of N interacting atoms as a function of their positions $r_i = (x_i, y_i, z_i)$. The force acting upon the i^{th} atom is then determined:

(1) $$F_i = -\nabla_{r_i} U(r_1, \ldots, r_N)$$

Force Field can be understood as an empirical set of energy functions. It is typically the summation of bonded and non-bonded terms or covalent and non-covalent interactions among atoms and molecules.

A typical Force Field, used in the simulation of biosystems is expressed as **(2)**:

$$U(r_1,\ldots,r_N) = \sum_{bonds} \frac{a_i}{2}(l_i - l_{i0})^2 + \sum_{angles} \frac{b_i}{2}(\theta_i - \theta_{i0})^2 + \sum_{torsions} \frac{c_i}{2}[1 + cos(n\omega - \gamma_i)] + \sum_{atompairs} 4\epsilon_{ij}[(\frac{\sigma_{ij}}{r_{ij}})^{12} - (\frac{\sigma_{ij}}{r_{ij}})^6] + \sum_{atompairs} k\frac{q_i q_j}{r_{ij}}$$

The first two terms describe energies of deformations of the bond lengths and bond angles from their respective equilibrium values. The third term describes rotations around the chemical bond, which are characterized by periodic energy terms. The fourth term - van Der Waals repulsive and attractive interatomic forces in the form of the *Lennard-Jones 12-6 potential*. The last term describes the Coulomb electrostatic potential.

The solution of Newton's equations of motion gives the time evolution of a set of interacting particles:

(3)

$$F_i = m_i \frac{d^2 r_i(t)}{dt^2}$$

To solve the second-order differential equations the initial positions and velocities of the particles must be determined. The equations are discretized and solved numerically and the MD trajectories are defined by both position and velocity vectors - vectors $r_i(t)$ determine the changing in time positions, while the vectors $v_i(t)$ determine the kinetic energy and temperature in the system.

Kinetic energy can be given by the Maxwell-Boltzmann velocity distribution:

Maxwell-Boltzmann Velocity Distribution

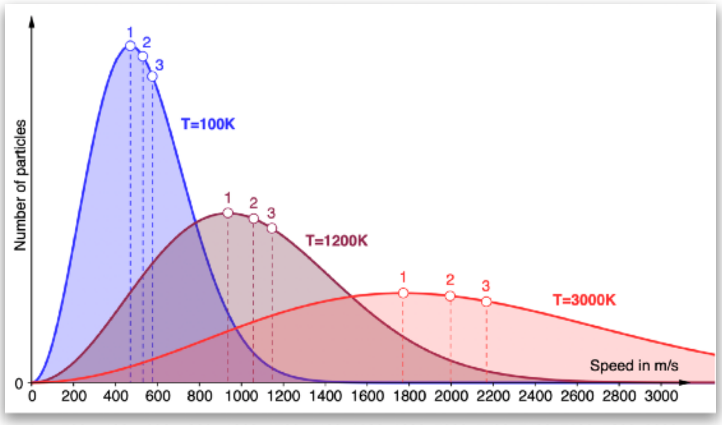


Fig. 1

Source: commons.wikimedia.org

(4)
$$E_k = \sum_{i=1}^{N} \frac{m v_i^2}{2} = \frac{3}{2} N k_b T$$

For the integration of Newton's equations of motion (Eq. 3), we can employ algorithms such as the *Verlet algorithm*. It is the most basic and widely used algorithm and its actually the two-third order Taylor Series expansion of the coordinate r_i of a particle at time $(t + \Delta t)$ and $(t - \Delta t)$:

(5)
$$r_i(t + \Delta t) \approx 2r_i(t) - r_i(t - \Delta t) + \frac{F_i(t)}{m_i} \Delta t^2$$

Some of the advantages of this algorithm are that it is self-starting, requires less computer memory, it is straightforward and the new positions are easily acquired from the previous ones.

Other examples of integration algorithms are *Euler algorithm, Leap Frog* algorithm and *Velocity Verlet schemes*, Beeman's algorithm, although the Euler algorithm is not time-reversible and suffers from a tremendous energy drift.

2.2 Electrostatics - Central Problem of MD Simulations. Periodic Boundary Conditions

New velocities v_{i+1} and positions r_{i+1} are found in the stepwise numerical integration procedure by computing the forces acting upon the atoms at each step. The force fields include long-range electrostatic and dispersion interactions and summation of order N^2 has to be performed to account for all non-bonded pairs. The complexity of the algorithm consists of calculating milions of Coulombic interactions for multibody systems at each time step. There are different techniques that can be implemented to deal with the problem. Because of limited computer memory only a finite sample of an infinite system can be represented in a computer method.

The "cut-off" method tapers the interaction potential over a predefined range of distances. It usually works well with the van Der Waals interactions, but the Coulombic forces are long-range.

The treatment of long-range forces is related to the choice of boundary conditions. The two common approaches are based on either *periodic boundary conditions* and Ewald method for lattice summations or on *spherical boundary conditions* and the reaction field method. The *Ewald summation* for Coulomb interaction is a correct approach taking into account periodicity. In the Ewald summation the electrostatic Coulomb potential is divided into two sums - in wave-number space and in real space.

Cut-off radius

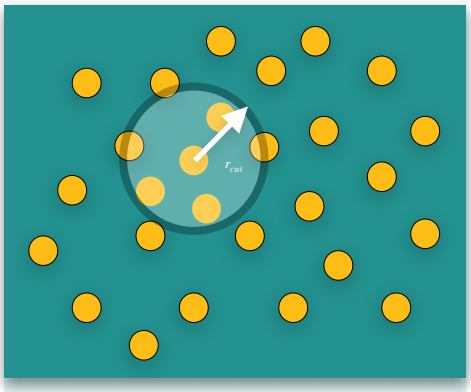
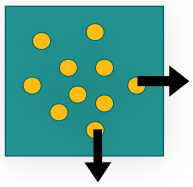


Fig. 2

Let's imagine that the simulation of a system is within a box-shaped container. There is a high possibility that a few particles leave the box, since we examine a dynamical fluid system.



In order to overcome the issue, we generate a replica of the box that covers it from all sides. Now, whenever a particle tries to move out from the central box another will enter its place with the same speed in order to maintain a balanced system.

Periodic boundary conditions enable a simulation to be performed using smaller number of particles in such a way that particles experience forces as if they are in bulk fluid.

Periodic Boundary Conditions

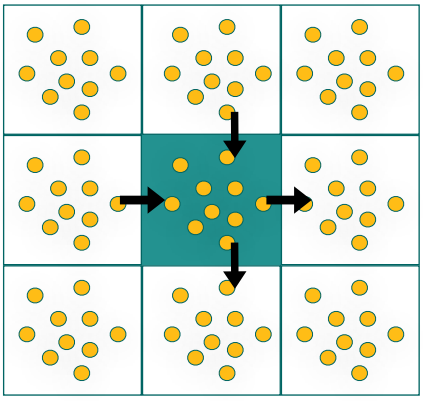


Fig. 3

2.3 Schrodinger Equation. Hybrid Molecular Dynamics

Quantum chemical methods of Molecular Dynamics are based on the $Schrödinger$ Equation:

(6)
$$i\hbar\frac{\partial}{\partial t}\Psi(r,t) = -\frac{\hbar^2}{2m}\nabla^2\Psi(r,t) + V(r)\Psi(r,t)$$

It is an equation that describes the evolution of the state Ψ of a quantum system in time. The Hamiltonian is the operator $\hat{H} = i\hbar\frac{\partial}{\partial t}$ in a stationary system , which can generally be expressed as:

(7)
$$\hat{H} = \hat{T} + \hat{V}$$

$\hat{T} = -\frac{\hbar^2}{2m}\Delta$ is the operator of the kinetic energy and $\hat{V}(r,t) = V(r,t)$ is the operator of interactions. When the second operator $\hat{V}$ doesn't depend on the time variable *t,* it is equal to the operator of potential energy $\hat{V}(r)$. In case of potential interactions the Hamiltonian is equal to the operator of the energy:

(8)
$$\hat{H}\Psi = \hat{E}\Psi$$

Using Dirac's notations, the $Schrödinger$ equation can also be written as:

(9) $$\hat{H}\,|\Psi> = i\hbar\frac{\partial}{\partial t}\,|\Psi>$$

Theoretically, the non-adiabatic coupling of electronic and nuclear dynamics is one of the most challenging problems of atomic many-body theory. The quantum approach for large systems is too complicated and time consuming. Generally, the dynamics is controlled by the van Der Waals and electrostatic interactions which are well described by the classical approach. The quantum chemistry interactions can be used only for small areas - for example, in the active center, where there is a quick formation of hydrogen bonds. In order to simplify the problem, the nuclear and electron motions can be separated using an adiabatic representation.

Adiabatic approximation refers to those solutions of the equation that make use of a time-scale separation between fast and slow degrees of freedom. Approximate solutions are then found as product states in the fast and slow degrees of freedom. One of the most fundamental and commonly used is the Born-Oppenheimer approximation. For a molecular system, the Hamiltonian can be written in terms of the kinetic energy of nuclei (N) and electrons (e) and the potential energy for the Coulomb interactions:

(10) $$\hat{H} = \hat{T}_e + \hat{T}_N + \hat{V}_{ee} + \hat{V}_{NN} + \hat{V}_{eN}$$

It assumes that the motion of electrons is much faster than nuclei due to their mass difference. This greatly simplifies the process of solving the $Schrödinger$ equation by fixing the position of the nuclei using a semiclassical approach and solving the equation for the electronic wavefunctions.

3. MD SIMULATIONS

The first force fields appeared in the 1960's, with the development of the molecular mechanics method and their goal was to predict molecular structures and vibrational spectra of isolated molecules. Since then the scope of research

has moved to deal with much more complex systems, more force fields were developed. Some popular force fields are CHARMM, AMBER and DL_POLY.

Chemistry at Harvard Macromolecular Mechanics (**CHARMM**) is the name of a widely used set of force fields for molecular dynamics, and the name for one of the oldest programs for MD associated with them. More advanced features include free energy perturbation (FEP), quasi-harmonic entropy estimation, correlation analysis and combined quantum, and QM/MM methods. Potential energy function of CHARMM22 force field:

$$V = \sum_{bonds} k_b(b - b_0)^2 + \sum_{angles} k_\theta(\theta - \theta_0)^2 + \sum_{dihedrals} k_\phi[1 + cos(n\phi - \delta)]$$
$$+ \sum_{impropers} k_\omega(\omega - \omega_0)^2 + \sum_{Urey-Bradley} k_u(u - u_0)^2$$
$$+ \sum_{nonbonded} \left(\epsilon \left[\left(\frac{R_{min_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{min_{ij}}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\epsilon r_{ij}} \right)$$

Assisted Model Building with Energy Refinement (**AMBER**) is a family of force fields for molecular dynamics of biomolecules and the name of the software package. The potential energy of the system is given as:

$$V(r^N) = \sum_{i \in \text{bonds}} k_{bi}(l_i - l_i^0)^2 + \sum_{i \in \text{angles}} k_{ai}(\theta_i - \theta_i^0)^2$$
$$+ \sum_{i \in \text{torsions}} \sum_n \frac{1}{2} V_i^n [1 + \cos(n\omega_i - \gamma_i)] + \sum_{j=1}^{N-1} \sum_{i=j+1}^{N} f_{ij} \left\{ \epsilon_{ij} \left[\left(\frac{r_{ij}^0}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{ij}^0}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right\}$$

DL_POLY is a general purpose classical molecular dynamics (MD) simulation software. It was developed at Daresbury Laboratory by I. T. Todorov and W. Smith in the for the molecular simulation community.

NAMD is a molecular dynamics program designed for high-performance simulations for large biological objects on CPU and GPU-based architectures. It is a multipurpose code that gathers algorithms to carry out simulations, using CHARMM, AMBER, OPLS and GROMOS biomolecular force fields. NAMD is useful for handling long-range electrostatics, controlling temperature, pressure, applying external potentials and hybrid QM/MM descriptions.

The Visual Molecular Dynamics (**VMD)** software will be used with **NAMD** in order to visualise the simulations.

3.1 Carbon Nanotubes - Theoretical Background

Carbon is the most versatile element in the periodic table. The carbon atom contains 6 electrons that are equally distributed between the 1s, 2s and 2p orbital. Due to the different hybridization capabilities of carbon, it exists in different allotropic forms from zero to three-dimension. Examples are Fullerene (0D), CNTs (1D), Graphene (graphite single layer, 2D) and Diamond (3D). In the last years, a lot of research has been done on carbon nanotubes (CNTs) and their contribution to the field of nanotechnology.

Carbon

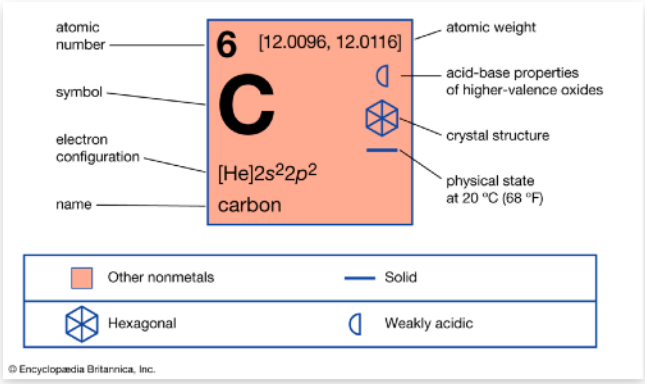


Fig. 4

Source: Encyclopaedia Britannica

Biomedical applications

The history of carbon nanotubes starts in the 1950s with the report of Radushkevich and Lukyanovich on hollow carbon nano-fibres with a diameter of 50nm. Due to the need of lighter materials with stronger characteristics, there was a lot of progress in the field. Carbon nanotubes were worldwide recognized after the discovery of multi-walled CNTs by Iijima in the year 1991.

Carbon nanotubes have many applications in biomedical sciences, gene therapy, biosensors and tissue engineering fields due to their mechanical, chemical, electrical, thermal and structural characteristics. Researchers over the years have also found applications in diagnostic devices, oncology radiation-based equipments, biosensor, drug delivery and drug discovery.

Sr. no.	CNT Nanomaterials	Biomolecules	Applications
	Poly (dimethyldiallylammonium chloride) (PDDA) modified GCE/SWC nanotubes.	Alcohol dehydrogenase	Ethanol bio-sensor
	Ionic liquid modified GCE/ Chitosan/Multi-walled CNT.	Cytochrome c	Hydrogen peroxide detector
	Chitosan/Multi-walled CNT.	Tramates versicolor heamoglobin	Biofuel cells O_2 biosensor
	Ionic liquid modified GCE/ Single-walled CNT.	Cytochrome c, Horseradish peroxidase, Myoglobin.	Biofuels, Biosensors
	Multi-walled CNTs-COOH or Multi-walled CNTs.	Canida rugosa lipase	Biocatalysis
	Chitosan modified GCE/poly (amidoamine)/Single – walled CNT.	Cytochrome c	Nitrite biosensor
	Modified boron-doped diamond electrode with CNT.	Carrena unicolor Laccase	
	Multiwalled CNT-COOH.	β-Glucosidase	Biocatalysis
	Nafion modified GCE/Multi-walled CNT-toluidine blue.	Horseradish peroxidise, Glucose oxidase	Glucose biosensor
	Silica modified GCE/Single-walled CNT.	Glucose oxidase	Glucose biosensor
	Sol-gel modified GCE/ Chitosan/Multi-walled CNT.	Horseradish peroxidise	Hydrogen peroxide detector
	Multi-walled CNT modified GCE.	Trametes hirsuta Laccase	Biofuel cells
	Chitosan modified glassy carbon electrode (GCE)/ Single-walled CNT.	Horseradish	Bioelectrochemical sensor

Fig.5

Source: [2]

3.2. MD Test Modelling

We will be investigating the permeation of water through nanotubes, as a model of transmembrane permeation of substrates through channels. A permeation event is defined as a water molecule entering from one end of a nanotube and leaving the other end, therefore traversing the entire length of the nanotube. A set of four nanotubes will be used and that will be our unit cell. Using periodic boundary conditions we will replicate the unit cell in the simulations.

We start by loading new molecule in VMD. The four nanotubes arranged in a membrane with water on both sides are visualized in [Fig. 6].

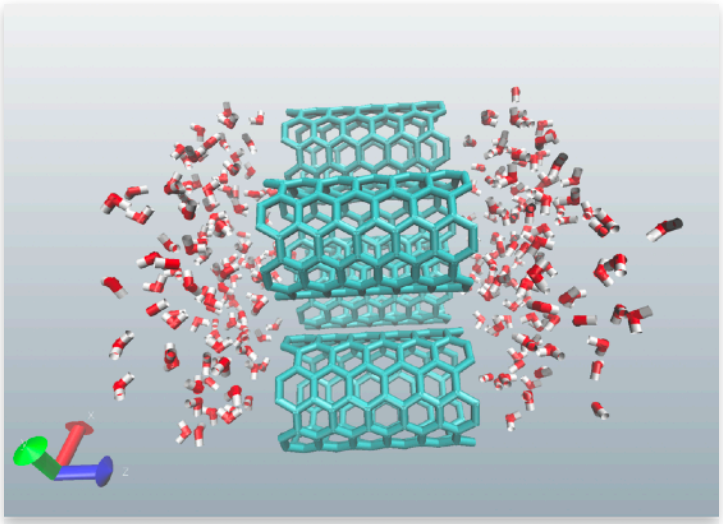


Fig. 6

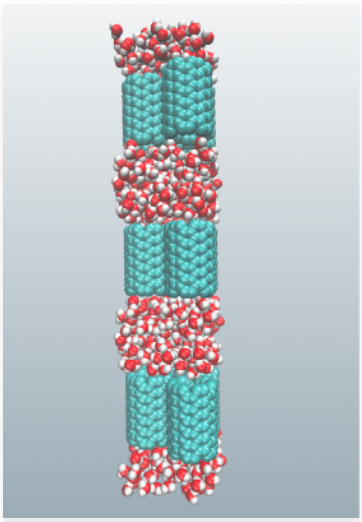


Fig. 8

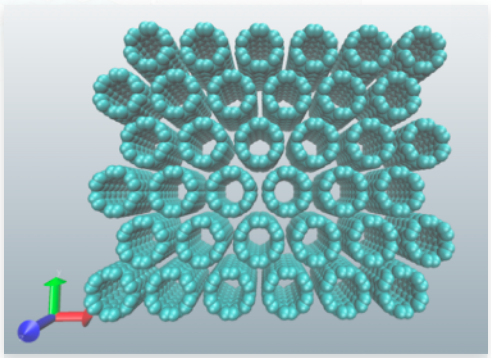


Fig. 7

The given dimensions of the unit cell are 24.07 by 20.85 by 34.00 $\dot{A}^3$. We use the commands to set the periodic cell dimensions to a (x), b (y) and c (z):

```
(mariya.zaneva) 5 % molinfo top set a 24.07
(mariya.zaneva) 6 % molinfo top set b 20.85
(mariya.zaneva) 7 % molinfo top set c 34
```

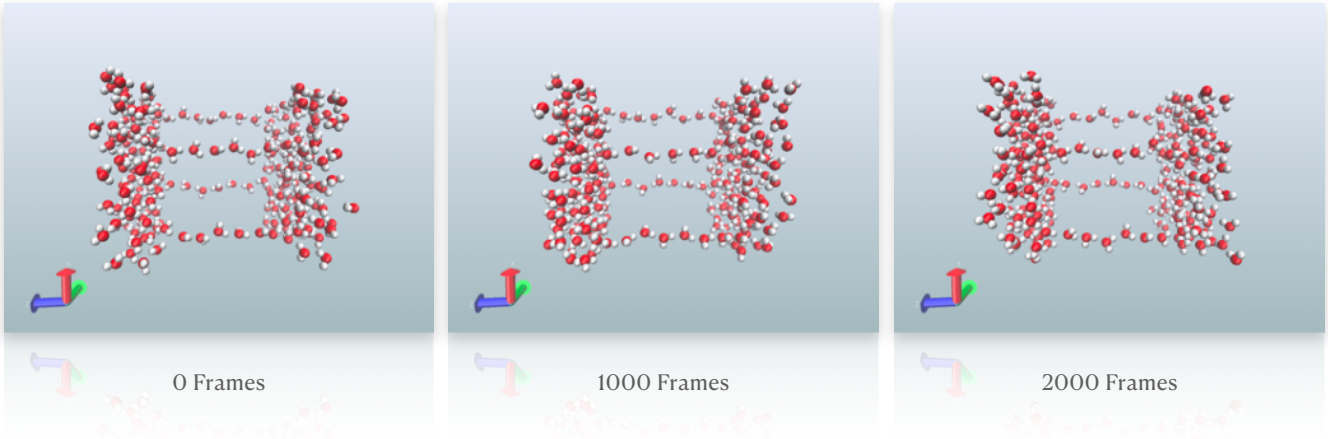
From the “Periodic tab” in the VMD software we can display more unit cells (X and Y) as shown in [Fig. 7]. Finally, we make the system periodic in Z - [Fig. 8].

We will simulate the water movement through the array of nanotubes under two different conditions. The first one will be free water diffusion in equilibrium and the second - directional water flow under a hydrostatic pressure difference. In order to simplify the calculations we take:

T = 300K,
V = const
Fixed carbon nanotubes and only observe the water molecules’ movement

Equilibrium Simulation:

We run a 3ns simulation with the calculated trajectories and velocities. We observe that water molecules in the same nanotube are aligned along the same direction and the orientation stays stable during the simulation. Let’s visualize only the water molecules:



By labelling some of the water molecules we can trace their movements during the simulation. We can see that the molecules do not pass one another in the nanotubes and there are permeation events rarely occur. We use a script file to analyze and give us the total number of permeation events:

*The total number of permeation events during 2500 frames in **+z** direction is: **23***
*The total number of permeation events during 2500 frames in **-z** direction is: **22***

We exclude the results from the first 500 frames, because we have no information which side (+z, -z) the molecules that were already in the nanotube have entered beforehand.

Simulation with induced pressure difference:

It is known that an osmotic pressure is equivalent to a hydrostatic pressure difference. By generating a hydrostatic pressure difference in the system, we can mimic experiments that study water channels. For example, there are experiments with graphene filters that use osmotic pressure difference to increase the water flow. We are

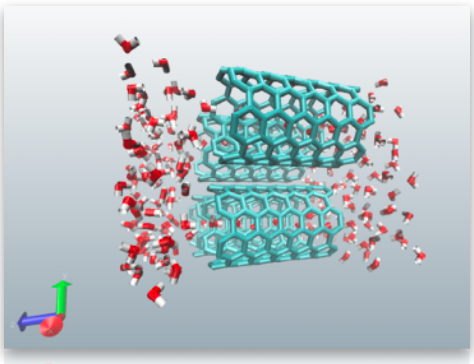


Fig. 9
Simulation with induced pressure difference

simulating a constant force along the z-direction on a layer of bulk water molecules. The induced pressure gradient results in a pressure difference on the two sides of the nanotubes. A constant force of 0.4 Kcal/mol/$\dot{A}$ along the +z direction is applied to a 5.4 $\dot{A}$ thick water layer. Through the 1ns simulation we can observe the directional water flow of the molecules. The net water flow is:

(nct) 13 % source flow.tcl
The net flow is 179.5 water molecules along +z

Modification of nanotubes:

We are going to assign a positive charge (+1e) to the center and two negative charges (-0.5e each) to the edges of the nanotubes. To visually represent the charges, we colour them by adding a CPK representation and Charge in the Colouring method in VMD:

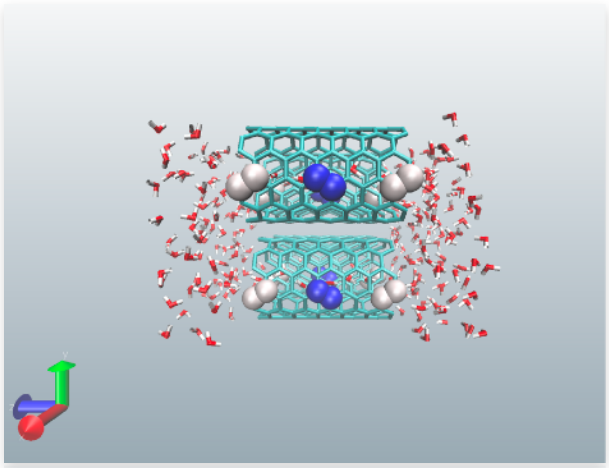


Fig. 10

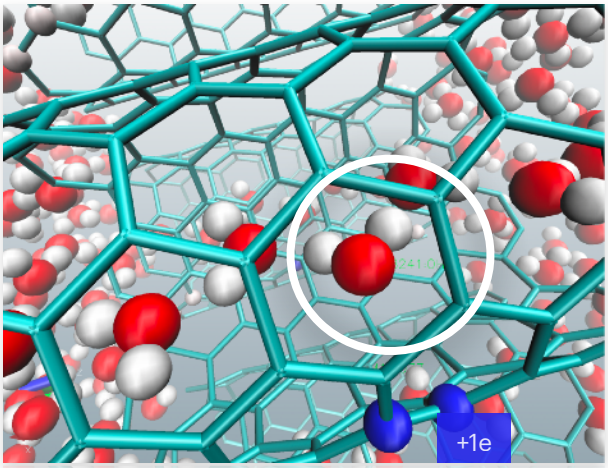


Fig. 11

We observe a very different water movement during the simulation. On figures [11] and [12] we can see the "bipolar" water orientation in the nanotubes. The interaction between the water (as shown in [Fig.11]) and the positive charge in the center of the nanotube doesn't let the molecule "escape".

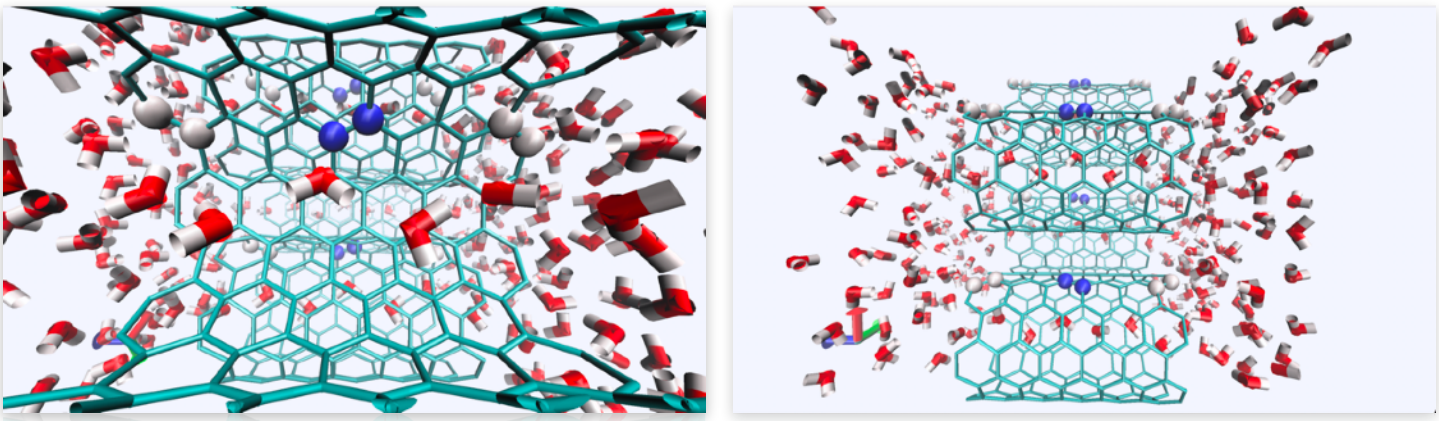


Fig. 12
Water orientation in modified nanotubes

We can calculate the water flow in the modified nanotube and see that it is very different, compared to the first two simulations:

(ntc) 14 % source flow.tcl
The net flow is 2.0 water molecules along +z

Therefore, the permeation property of the nanotubes can be altered by the introduction of charges in the system.

By modifying the **VdW** parameters from the CHARMM parameters file, we can also observe different results - we can increase or decrease water-nanotube interactions, or maximize the number of water molecules in the pore.

```
*
* This is a reduced version of the CHARMM22 parameter file for a
*   nanotube simulation in water
*
BONDS
!V(bond) = Kb(b - b0)**2
!
!atom type Kb          b0
CA   CA    305.000     1.3750
HT   HT      0.000     1.5139
OT   HT    450.000     0.9572
ANGLES
!V(angle) = Ktheta(Theta - Theta0)**2
!V(Urey-Bradley) = Kub(S - S0)**2
!
!atom types     Ktheta    Theta0   Kub     S0
CA   CA   CA    40.000    120.00   35.00   2.41620
HT   OT   HT    55.000    104.5200

DIHEDRALS
!V(dihedral) = Kchi(1 + cos(n(chi) - delta))
!
!atom types             Kchi    n   delta
CA   CA   CA   CA       3.1000  2   180.00

NONBONDED nbxmod  5 atom cdiel shift vatom vdistance vswitch
cutnb 14.0 ctofnb 12.0 ctonnb 10.0 eps 1.0 e14fac 1.0 wmin 1.5
!V(Lennard-Jones) = Eps,i,j[(Rmin,i,j/ri,j)**12 - 2(Rmin,i,j/ri,j)**6]
!
!atom  ignored    epsilon      Rmin/2
CA     0.000000  -0.070000     1.992400
HT     0.000000  -0.046000     0.224500
OT     0.000000  -0.152100     1.768200

HBOND CUTHB 0.5
END
```

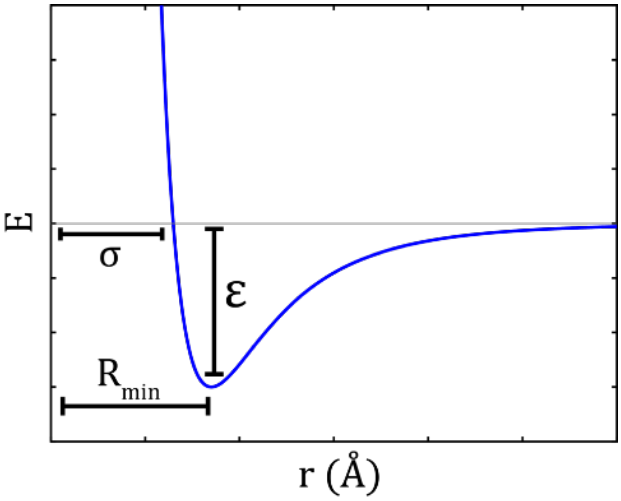


Fig. 13

Carbon nanotubes have some unique properties which can be utilized in the bio-medical fields such as gene delivery, drug delivery, and biosensors. Carbon nanotechnology can also be used as a filter, depending on the size of the carbon sheet and its properties. The material could also improve solar and energy storage, new supercapacitor batteries and electronic devices.

4. ACKNOWLEDGMENTS

I wish to express my deep gratitude to Professor Kholmirzo Kholmurodov for the information he provided us during lectures and discussions and for his invaluable assistance throughout this project. The acquired knowledge from the introductory course to Molecular Dynamics Simulations he presented would greatly benefit my studies and research for my future bachelor's thesis and master's program.

5. REFERENCES

1. Kholmurodov, K.T*, MD-Simulation in Chemical Research: From Atomic Fragments to Molecular Compound, 2011*

2. Ajay Thakur, Ruchi Bharti, Renu Sharma, *Carbon nanotubes: Types, synthesis, cytotoxicity and applications in biomedical, 2021*

3. Thijs J.H. Vlugt, Jan P.J.M. van der Eerden, Marjolein Dijkstra, Berend Smit, Daan Frenkel, *Introduction to Molecular Simulation and Statistical Thermodynamics, 2008*

4. Mohammad Sufian Badar, *Molecular Dynamics Simulations: Concept, Methods, Applications, 2020*

5. M.A. González, *Force fields and molecular dynamics simulations, 2011*

6. Jordi Cohen Fangqiang Zhu Emad Tajkhorshid, *Simulation of water permeation through nanotubes, 2012*

7. Jacob D Durrant, J Andrew McCammon, *Molecular Dynamics Simulations and Drug Discovery, 2011*

8. Jordan Muscatello, Frederike Jaeger, Omar K. Matar, and Erich A. Müller, *Optimizing Water Transport through Graphene-Based Membranes: Insights from Nonequilibrium Molecular Dynamics, 2016*

9. David J. Griffiths, *Introduction to Quantum Mechanics, 2005*