Classical Molecular Dynamics Simulation of Lysozyme

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Qcourse 570-1

Proteins

- Proteins are complex macromolecules formed from 20 different types of amino acids.
- The functionality of protein is an emergent property of the 3D spatial arrangements of these amino acids.
- This implies, the amino acids that are sequentially far apart can be found closer in proximity giving rise to the chemical and physical nature of the protein itself.
- The spatial arrangement of atoms in proteins is known as conformation.
- The conformations available for a given set of parameters/conditions are most stable ones.
- Therefore, understanding/predicting the 3D nature of proteins is of paramount importance.

Proteins

- We now have experimental 3D structures of 120,000 proteins, with resolution of about 0.5 to 2-3 A, still only a small fraction.
- 3D structures can be predicted using theoretical method like molecular modeling techniques which is a key aspect of computational structural biology.
- Proteins show various functionalities, such as antibody, messenger/transport, storage, enzyme catalysis etc.
- Proteins in their native forms are not static.
- There is a need for the protein to be dynamic. The various conformations reflect the fact that they are performing different functions.
- They undergo folding-unfolding processes while exhibiting biological functions and interacting with other molecules.
- Molecular pictures of protein, interpreting different experimental data, are highly significant for drug design and other aspects of biotechnology.

Searching Conformational Space

- To characterize molecular mechanism of proteins, it is essential to study the dynamics of the structure.

- **Energy Minimization:** macromolecule with a physical model an energy function has to be constructed, which assigns a potential energy value of different configuration particles
- In general, one is interested in min V(x), the lowest energy conformation of the PES.
- Different algorithms such as steepest descent, conjugate gradient, Newton-Raphson are used to locate the global minimum in the energy landscape.

- Only a small fraction of conformational space could be explored and not the whole PES.

- EM is used for resolve steric hindrance, predict experimental structure determination.

Searching Conformational Space

- **Molecular Dynamics:** The most widely used approach to search the conformational space of protein.

- Relies on Newton's equation of motion. Successive configurations of the proteins are generated by integrating Newton's laws of motion.

- The resultant trajectory specifies how the position and velocity of the constituent particles evolve.

- Various thermodynamic properties such as entropy, enthalpy, heat capacity etc. can be calculated from the trajectory.

- Structure – Functional relation problem in biochemistry is now mapped to geometry – conformation problem.

Tutorial Example, Lysozyme

- **Software Used:** GROMACS, (GROningen MAchine for Chemical Simulations), Netherlands

Input files required for energy minimization and MD simulation

1) Molecular structure file (.pdb, .gro)

.gro - gromos structure file, contains both coordinates and velocities

.pdb - contains coordinates, downloadable from RSC PDB

2) Topology file: Contains complete description of all the interactions of the system i.e. force field parameter

3) Molecular dynamics parameter file (.mdp): Details of MDS like time step, total no. of steps, temperature, pressure.

4) .itp file: '*include topology file*' information used to restrain the positions of heavy atoms, and useful top

Tutorial Example, Lysozyme

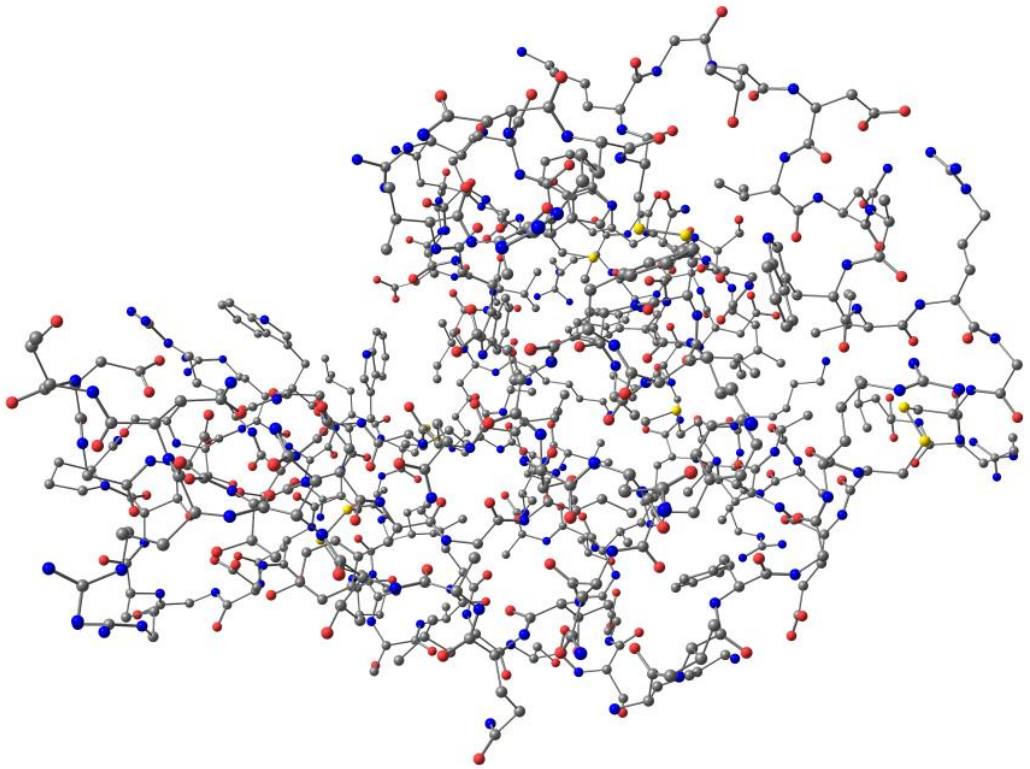
- **Lysozyme** is an antimicrobial enzyme produced by animals that forms part of the immune system.

- Lysozyme is abundant in secretions including tears, saliva, human milk, and mucus.

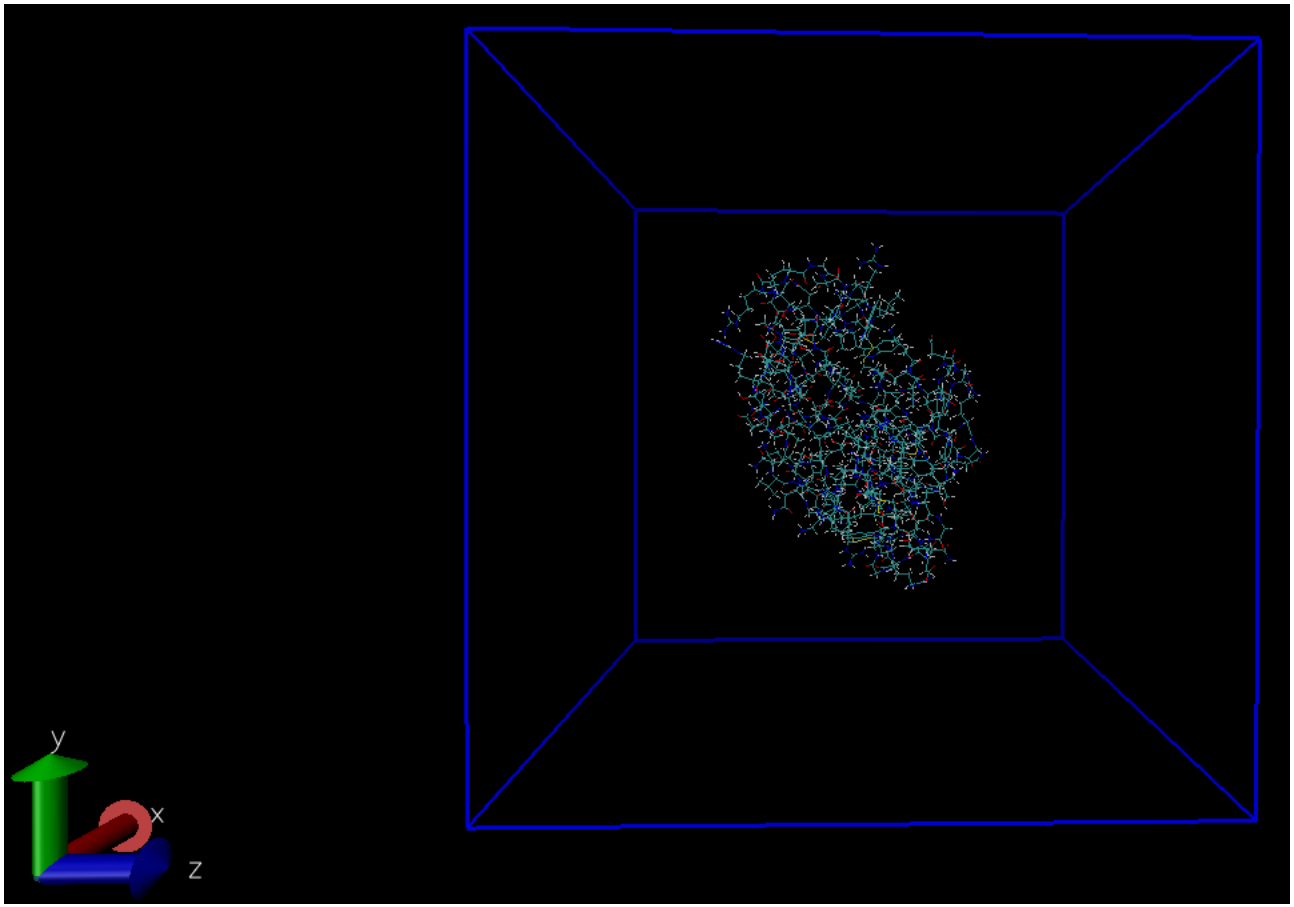
- 1aki.pdb , no. of atoms = 1097
- **Steps:**
- **Preparing initial state**
    1. Generate protein topology
    2. Add box and solvation
    3. Add ions to the solvated system
- **Interaction potential**
    1. Energy minimization
- **Particle dynamics**
    1. Equilibrating system
    2. MD run

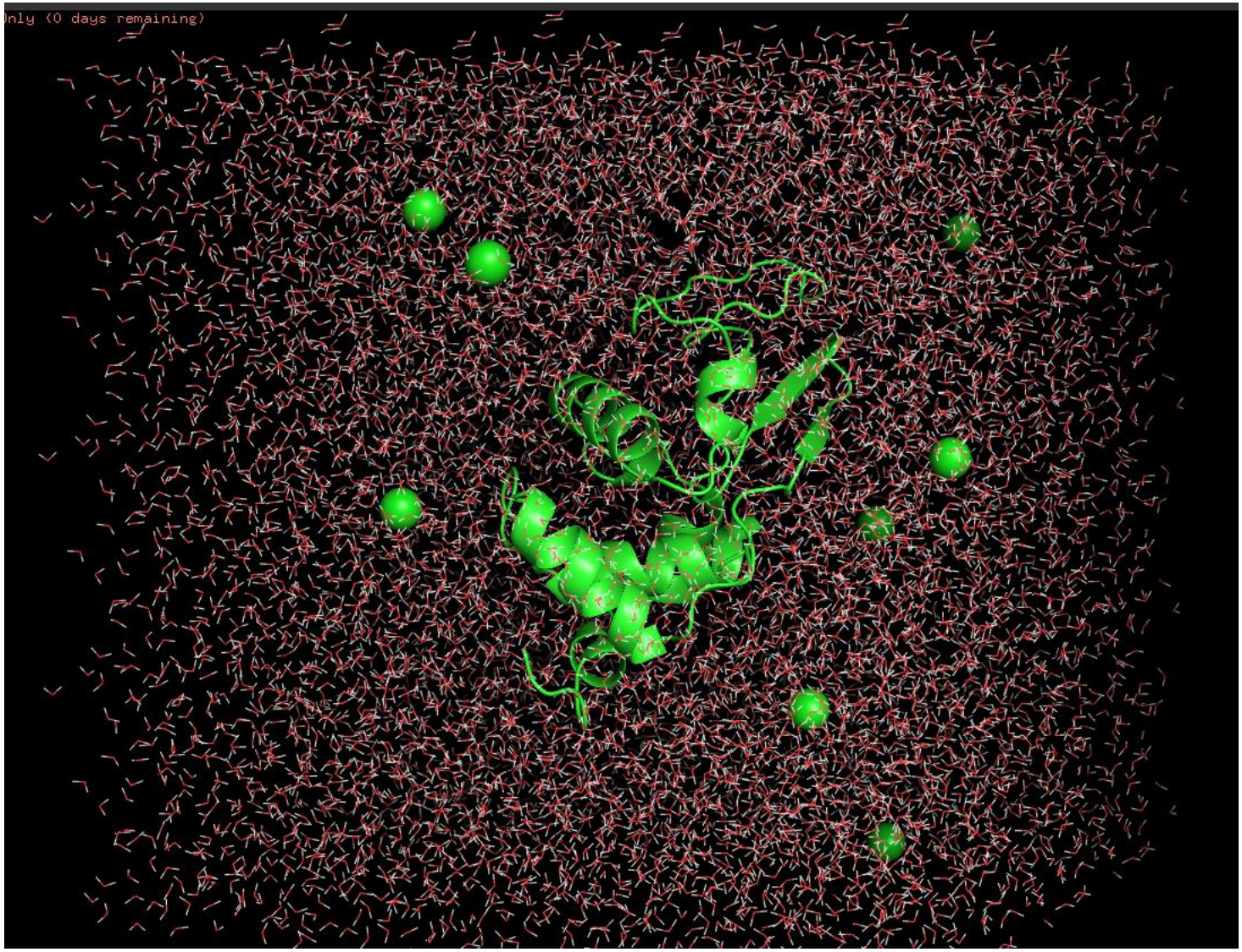
Tutorial Example, Lysozyme

- Toplogy (.top) file was created using OPLS (Optimized Potentials for Liquid Simulations) AA (All Atom) FF



Snapshot

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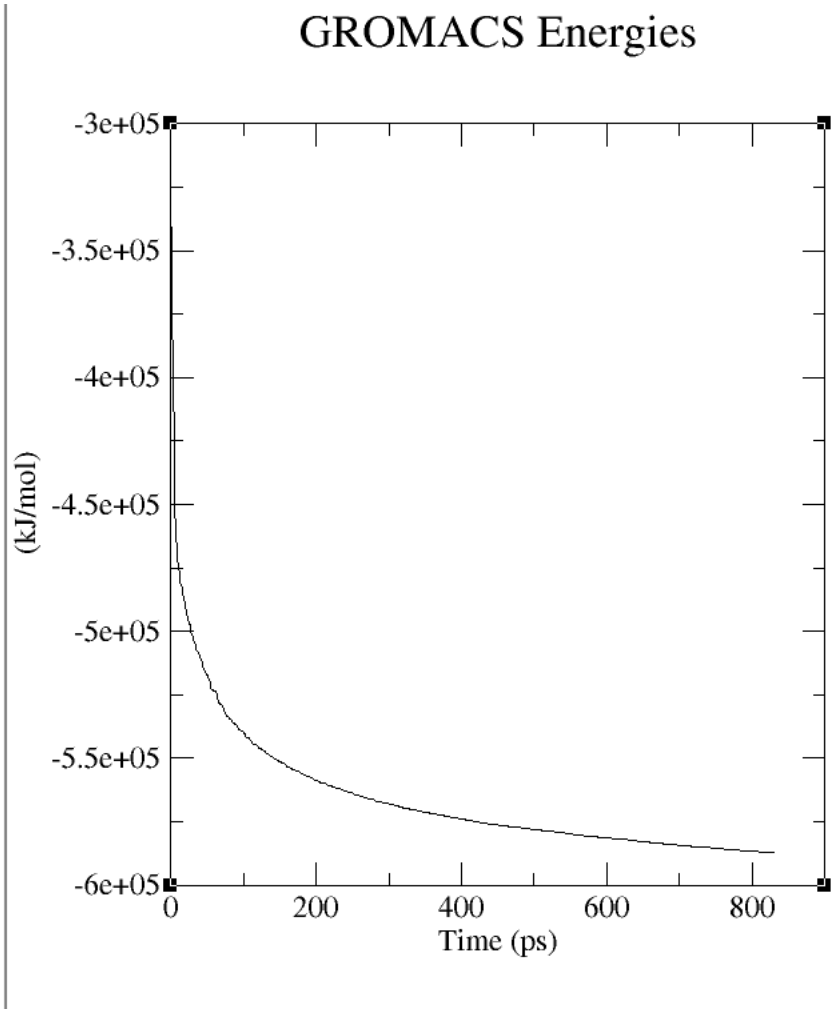


-587245.44 J/mol

Equilibration of the System

- Energy minimization step assures reasonably optimized structure for further evaluation.
- Before doing molecular dynamics simulation, the system (solute+ solvent/lysozyme + water) needs to be equilibrated.
- This procedure ensures the optimization of solvent in presence of the solute.
- The equilibration is carried out for the temperature and pressure that we would like to do the experiment at. Usually, 300K and 1 atm pressure
- Achieving the right temperature ensures proper orientation of solute and solvent.
- Achieving the right pressure ensures the proper density of the system.

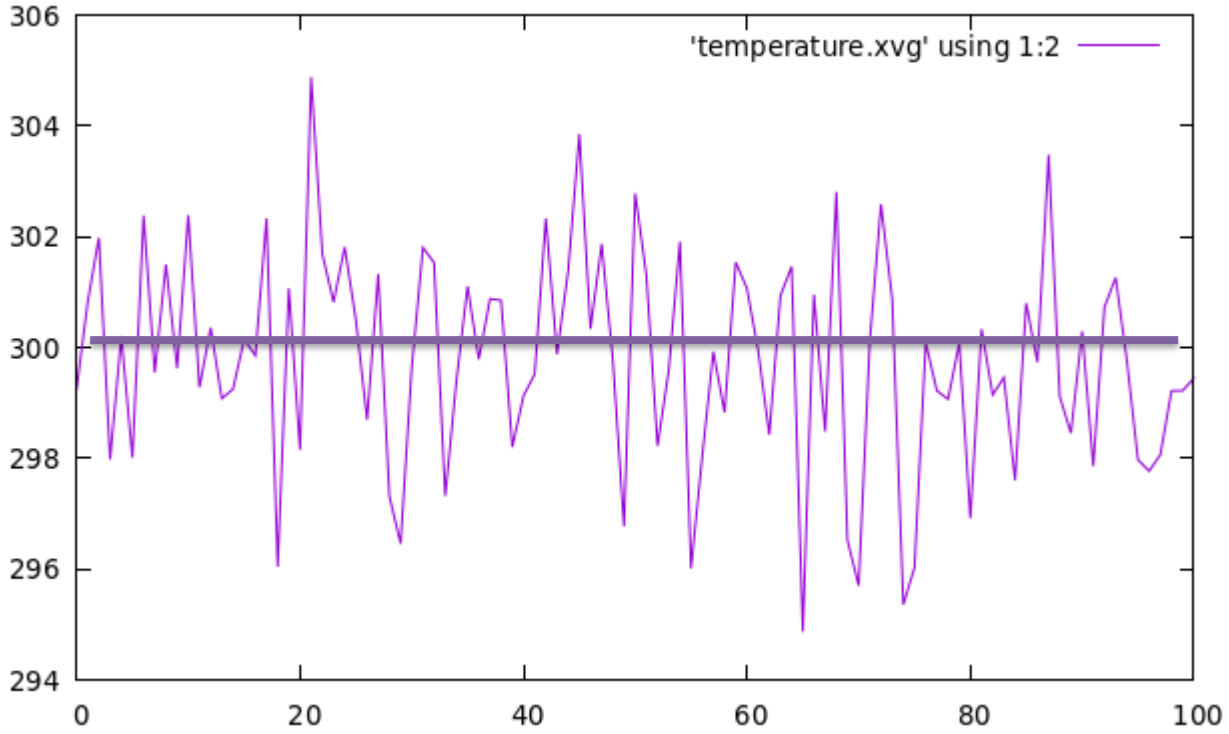
Equilibration of the System - NVT

- In the first stage of equilibration , the system is considered in the *NVT* ensemble.

  N – no. of particles, **V – Volume** , T – Temperature are constant

- Also known as isothermal-isochoric or canonical ensemble

- The temperature reaches the plateau at 300 K (desired value)



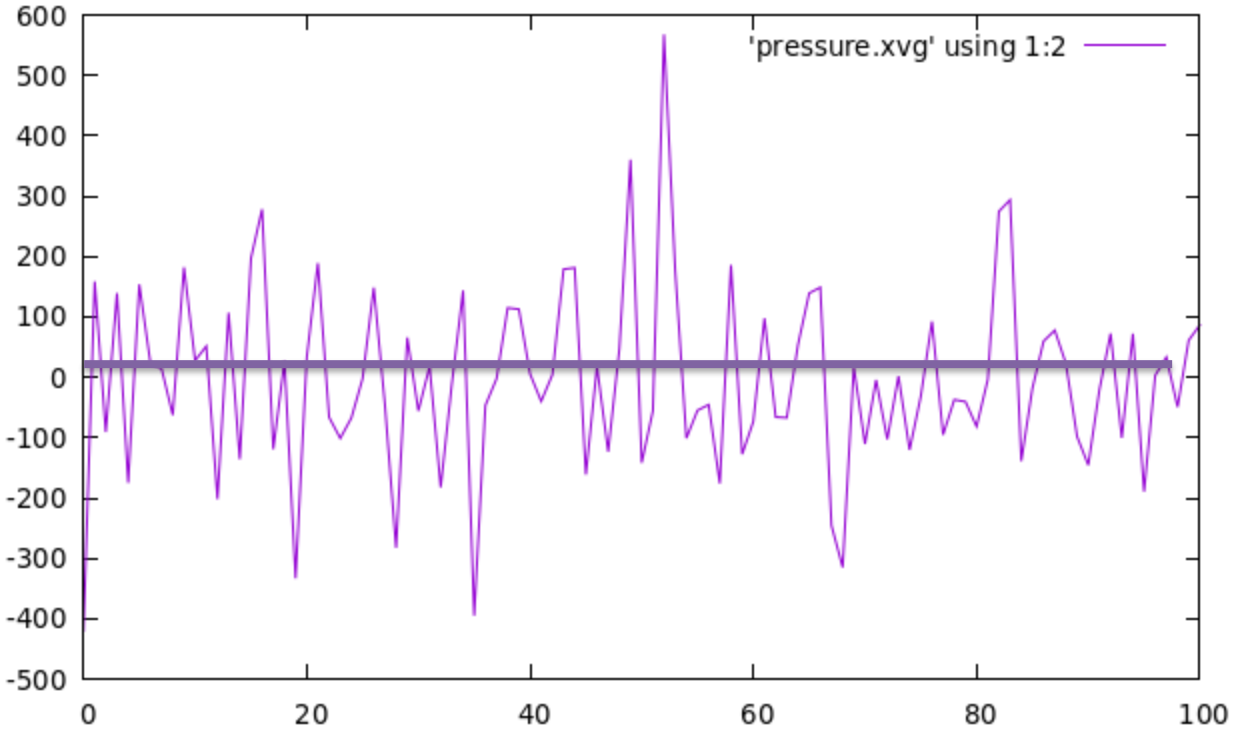
Equilibration of the System - NPT

- In the second stage of equilibration , the system is considered in the *NPT* ensemble.

  N – no. of particles, **P – Pressure**, T – Temperature are constant

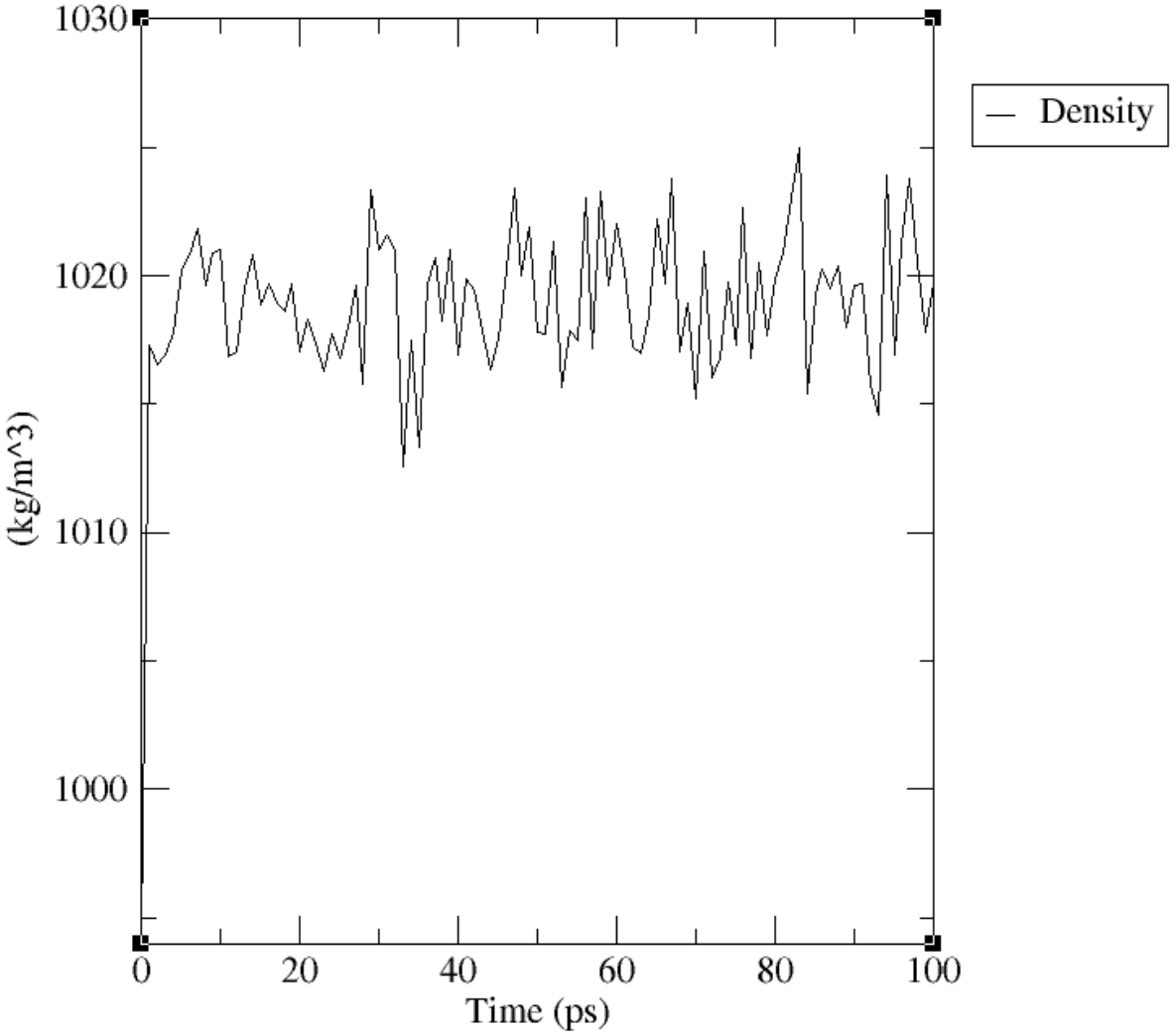
- Also known as isothermal-isobaric ensemble

- The pressure reaches the plateau at 4 atm



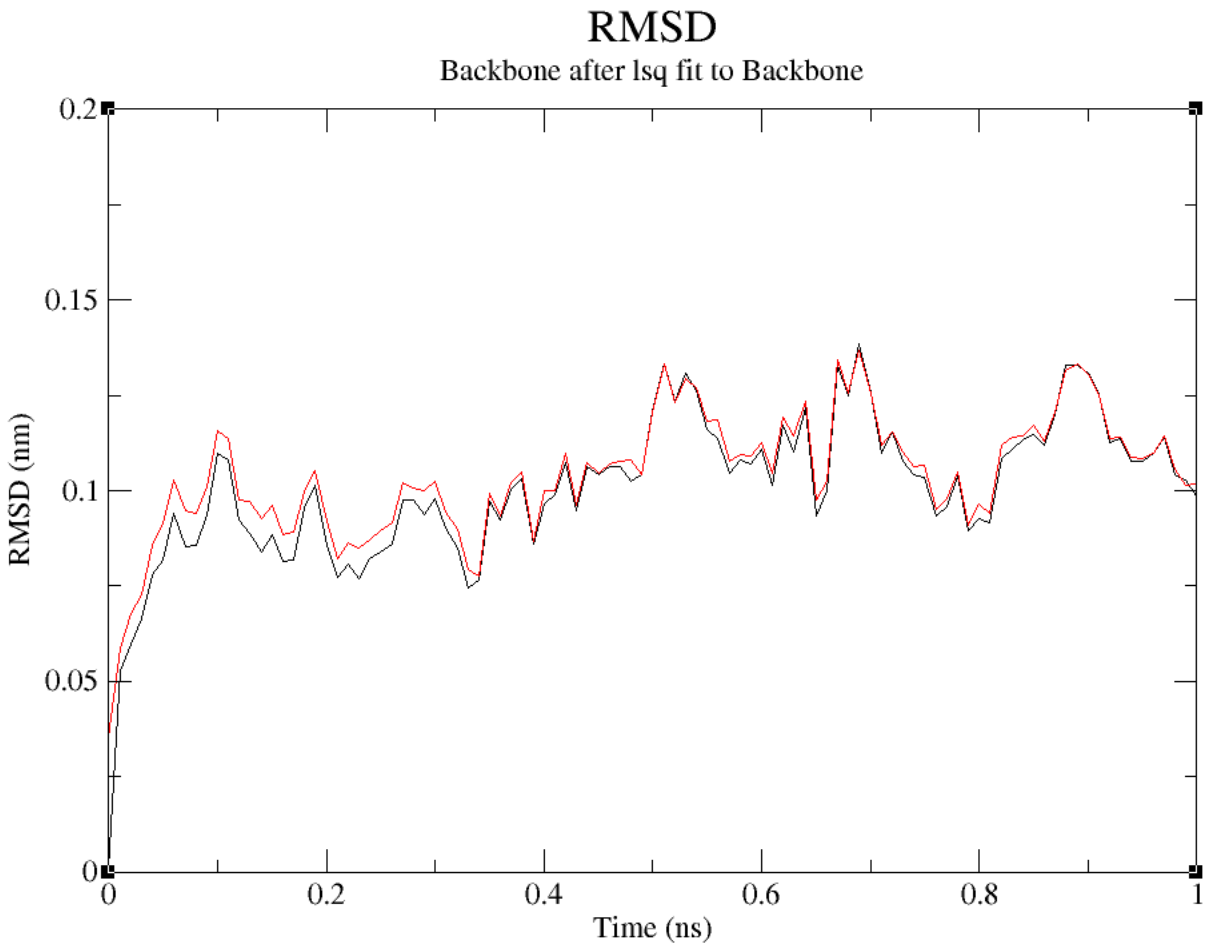
Equilibration of the System - NPT

- The density settles at 1018.94 (kg/m^3)



Molecular Dynamics

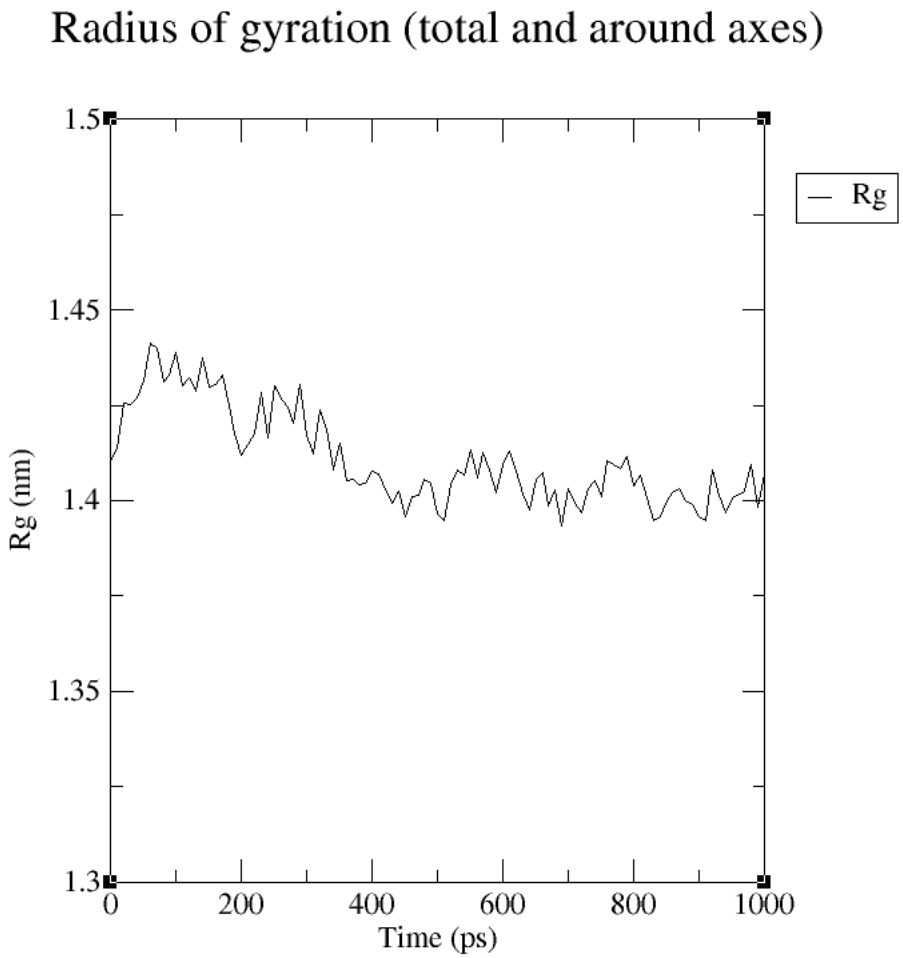
- The system is now equilibrated and ready for molecular dynamics simulation.



Molecular Dynamics

- The radius of gyration (R_g) gives the measure of compactness of the system.

- Large change in R_g means protein is unfolding otherwise the protein is stably folded.



Thank you