DNA biopolymer confinement and escape (molecular confinements)

BIOE 230

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What is the project?

- Simulate DNA escape from the cell nucleus using LAMMPS with a simplified bead-spring model, mimicking aging and disease-induced leakage.
  - Set up a DNA double helix with N beads connected by springs in a slightly thicker rectangular space, with attractive walls containing a slit for polymer escape.
  - Run molecular dynamics (MD) simulation with the initial setup and analyze output trajectory files to determine the fraction of the DNA polymer that escapes confinement.
  - Enhance simulations by adding solvent to mimic the aqueous environment, allowing exploration of hydrodynamic effects on DNA fluctuations.

Scientific background: what is DNA and RNA

- **DNA:**
  - A molecule carrying genetic instructions for growth, development, and reproduction in all known organisms.
  - Double-stranded helical molecule made of nucleotides with deoxyribose sugar, phosphate group, and nitrogenous bases (A, T, C, G).
  - Serves as the blueprint for the synthesis of proteins and plays a fundamental role in transmitting genetic information from one generation to the next.
- **RNA:**
  - Essential molecule for protein synthesis, gene regulation, and genetic information transmission.
  - Single-stranded molecule with ribose sugar, phosphate group, and nitrogenous bases (A, U, C, G).
  - RNA is vital for transmitting genetic information, regulating gene expression, and aiding protein synthesis by acting as a messenger between DNA and ribosomes.

Research Questions

- By simulating DNA polymer, can we change the parameters to simulate RNA assuming that both of these polymers behave similarly.
- What are the underlying mechanisms that govern DNA confinement within the cell nucleus and its potential escape through ruptures in the nuclear membrane?
- How do environmental factors such as solvent conditions, temperature, and pressure influence the structural and dynamical properties of DNA biopolymers under confinement?
- How do variations in DNA sequence and structure affect the dynamics of DNA confinement within the nucleus and its propensity for escape?
- What are the biological consequences of DNA leakage from the nucleus, and how does it contribute to genomic instability, cellular dysfunction, and disease development?

Introduction

- MD simulations track atomic positions and velocities to study molecular dynamics.
- Reveal structural, dynamical, and thermodynamic properties across scientific fields.
- Based on Newton's equations, numerically solved with integration methods like Verlet.
- Requires initial configuration and force field to describe interactions.
- Investigates phenomena like protein folding, ligand binding, and material properties.
- Runs across time scales from femtoseconds to milliseconds

Key Concepts

- **Newton's Equation of Motion:** Describe how atoms and molecules move and interact in response to forces.
  - F = ma
- **Force Fields:** Mathematical functions determining interactions between atoms and molecules, including bond stretching, angle bending, and non-bonded interactions.
  - $F_i = - \nabla U(r_i)$
- **Time Integration:** Numerically integrate Newton's equations to evolve the system's state over time, updating positions and velocities iteratively.
- **Ensemble Methods:** Simulate under different thermodynamic conditions to mimic experimental settings.
- **Boundary Conditions:** Use periodic boundary conditions to simulate an infinite system, preventing edge effects and allowing the simulation of bulk properties.

Applications of MD Simulations

- **Biomolecular Dynamics:** Study protein folding, ligand binding, enzyme catalysis, and membrane dynamics.
- **Materials Science:** Investigate material properties like mechanical strength, thermal conductivity, and diffusion behavior.
- **Drug Discovery:** Predict ligand binding, optimize drug candidates, and understand drug resistance mechanisms.
- **Chemical Reactions:** Study reaction kinetics, transition states, and reaction pathways.

Specific Aims

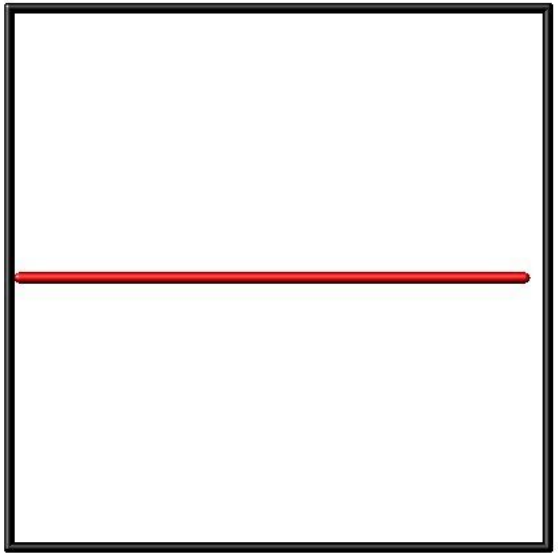
- Understand MD simulations of DNA.
- Understand the parameters that affect the mechanisms of how our MD simulations will behave, such as ligand binding. As well as how certain parameters may shift when protein folding occurs.
- To understand how parameters shift when protein folding occurs we want to observe how our simulated DNA/RNA affects parameters when DNA/RNA escapes a confinement, whether there are any changes in length or bond.

Backup Plan

- Simplify the parameters we want to control in DNA MD simulations.
  - Identify the most challenging parameter to control.
  - Learn how these parameters affect DNA MD simulations.
- If we encounter obstacles with the chosen parameters, consider changing them.
  - Analyze how different parameters impact the simulation results.
  - Adapt the parameters to optimize the simulation setup and achieve the desired outcomes.

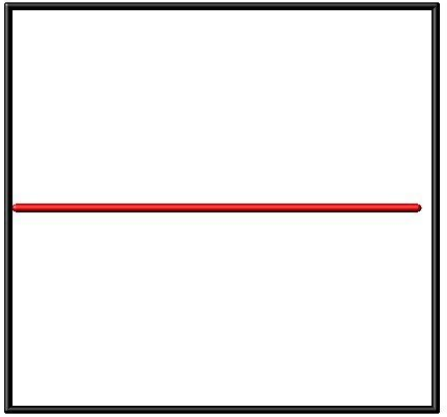
Our Results

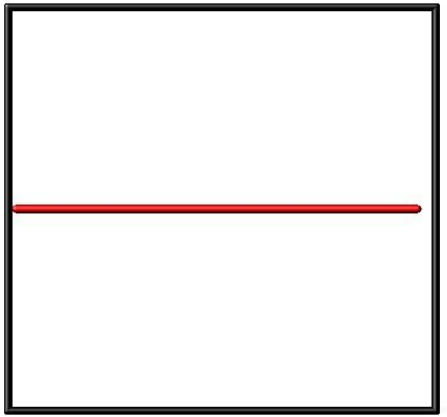
- In-class MD simulation
- Account for mass of nucleotides.
- Specific boundary conditions
- # of atoms
- Atom bond style
- Apply forces (such as Newton's 2nd law)
- Ensemble methods



Our results continued

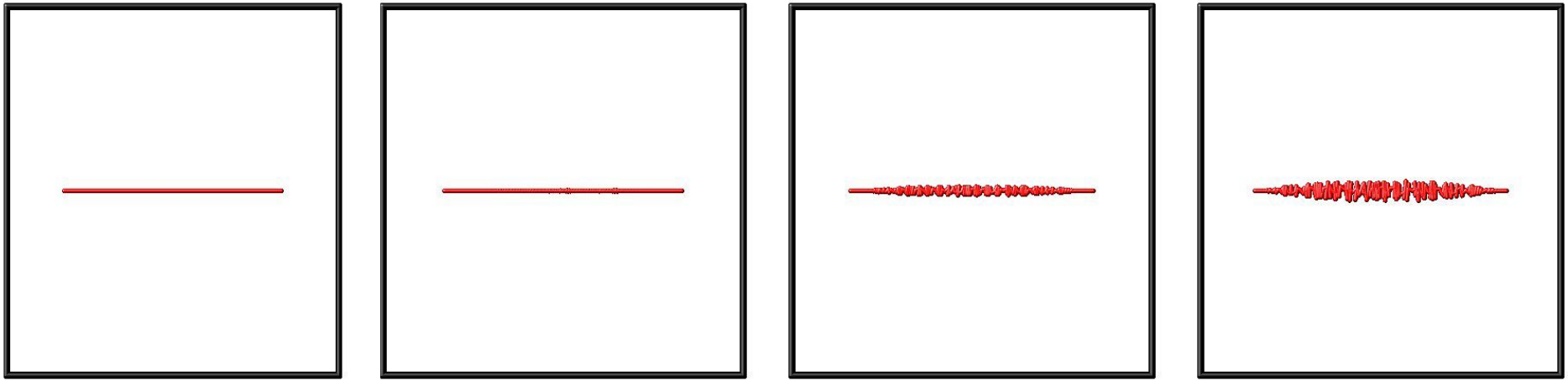
- Simulation accounting for weight of nucleotides.
- 4 atoms with individual weight
- Time step: 0.001
- Runs: 10000
- No solvent





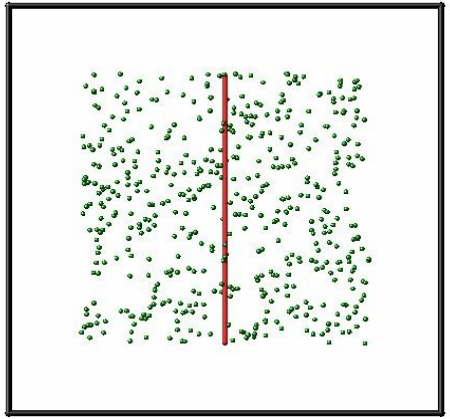
Parameters we controlled

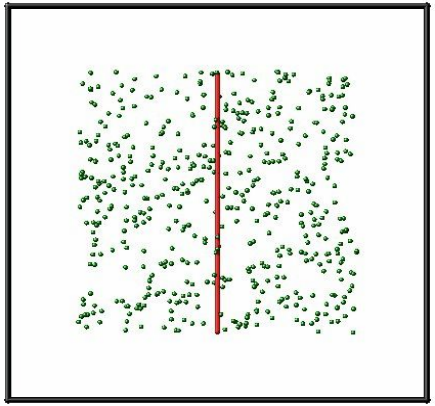
- Adding a region where the polymer will be enclosed in a rectangular box with one open end, however...



Parameters we controlled - Solvent

- Why are my solvent molecules not moving?
- Polymer was also not moving
- Lennards-Jones interactions were included, meaning polymer-polymer interaction, polymer to solvent and solvent to solvent.



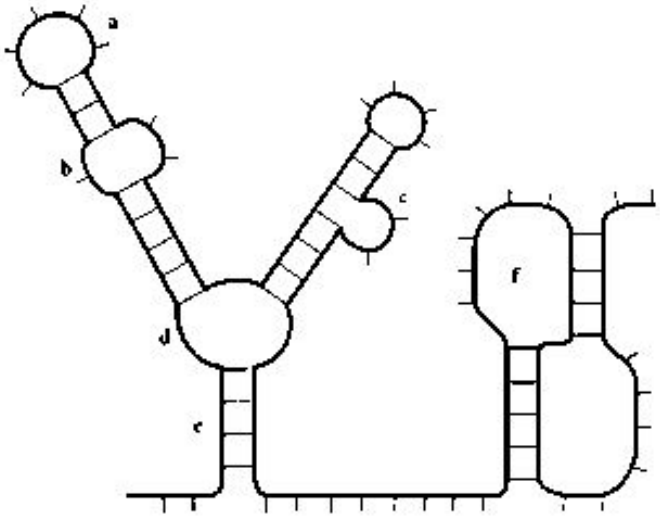


Did we achieve our goals

- Not quite, adding a solvent caused our polymer to not move.
- Did not simulate RNA within reasons
- Too ambitious

What we did not get to

- RNA simulation
  - Polymer was not properly confined in a small space to replicate DNA leaking or leaving the box, acting as a membrane.
- Failed to simulate the polymer to move inside a confined space.
- Solvent molecules were not moving nor were they affecting our polymer.

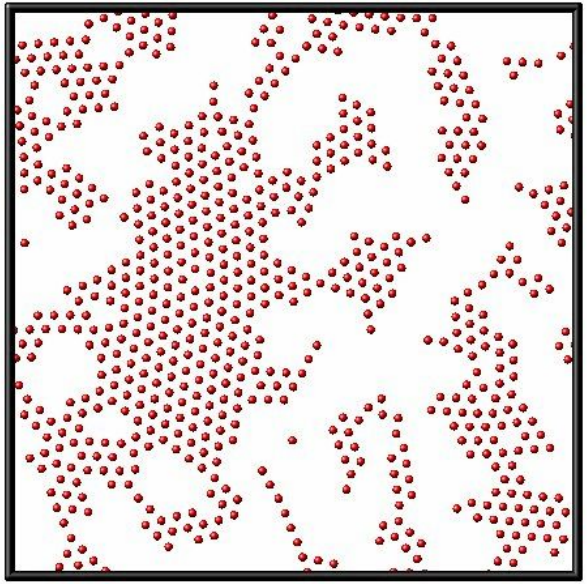


Next steps

- Implement a physical box that allows the polymer to move.
- Run a 3D simulation and account for mistakes that may happen.
- Apply changes in bonds, such as angle, torsion, stretch, etc.
- Ensure that our solvent actually affects our simulation.

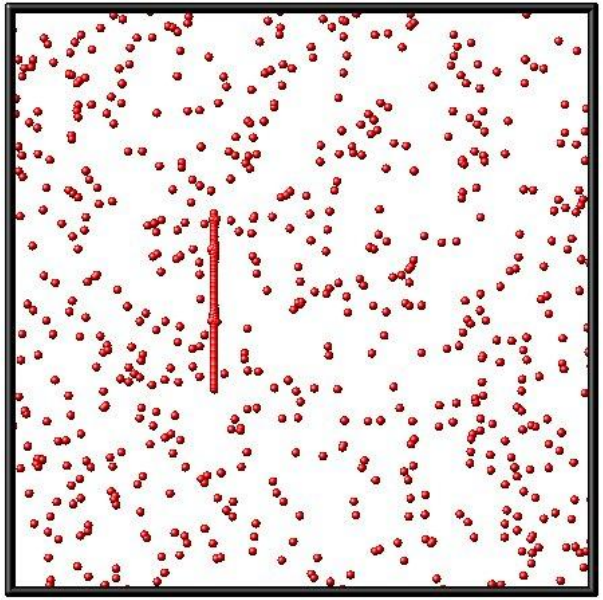
Modifications

- Implemented Cryst.lam and poly.lam into 1 file
  - Accounted for already existing commands
  - Some of the particles that were being created would overlap with others and give me errors, thus, we added ‘dump 1 all atom 100 dumn.initial.lammpstrj’ to observe these overlapping particles
  - Minimized energy to avoid overlapping, however, it kept overlapping and would only work whenever it was not overlapping.



Modifications continued

- Implemented Cryst.lam and poly.lam into 1 file
  - While we tried to implement a polymer with similar mass it would only show us the initial polymer but would not run afterwards.
  - Changed size of box, crystals, as well as polymer and attempted to reduce the number of atoms.



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