PH 509 | Computational Physics,
under **Prof. Anand Sengupta**

PROTEIN FOLDING

Exploring Dynamics, Energetics, and Metastability in Protein Folding Simulations

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Objective

- Proteins can be viewed as chains in which the links are the amino acids.
- The structure of a protein when it is in its biologically active state is known as the tertiary structure (folded state).
- The biological functions of a protein are a result of its tertiary structure.
- If we want to understand how a protein works, we must understand its tertiary structure.

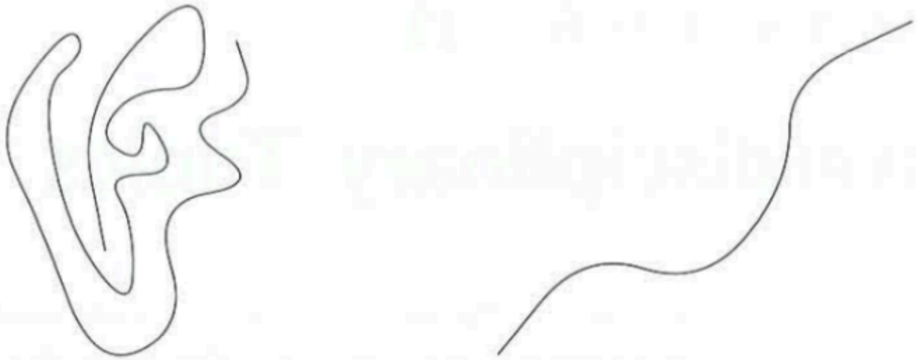

Fig 1. Schematic protein in a folded state (left and unfolded stat (right)

Simulating Fold Transition in 2D

Process:

- **Initialization**: Generates random amino acid sequence (`A`) and interaction energies matrix (`J`).
- **Protein Folding Simulation**: Iteratively moves amino acids, checking energy changes and avoiding steric clashes.
- **Energy Calculation**: Computes energy change based on interactions and position changes.
- **Neighbor Check**: Ensures new positions don't overlap with neighboring amino acids.
- **Plotting**: Visualizes final folded protein structure.
- **Performance Optimization**: Utilizes `numba` for JIT compilation, enhancing simulation speed.

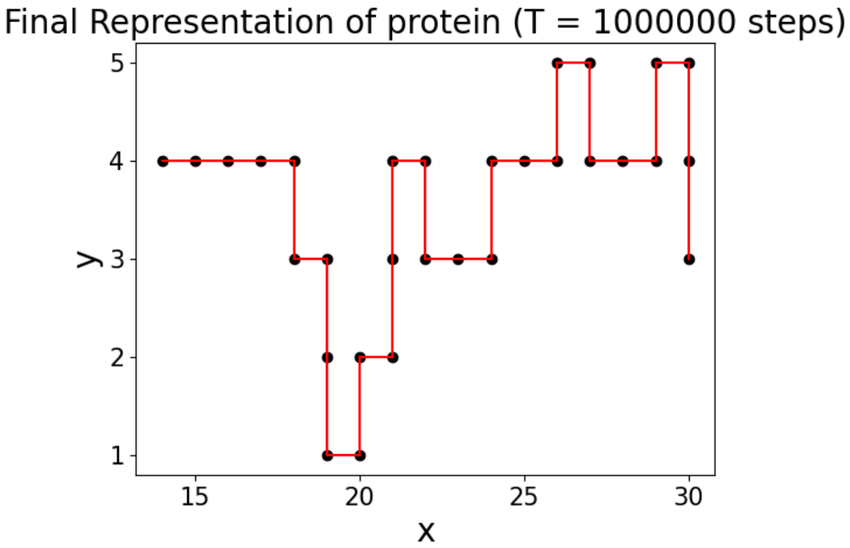

Fig 2. Lattice Model for a protein that underwent fold transition simulation

Simulating Fold Transition in 2D

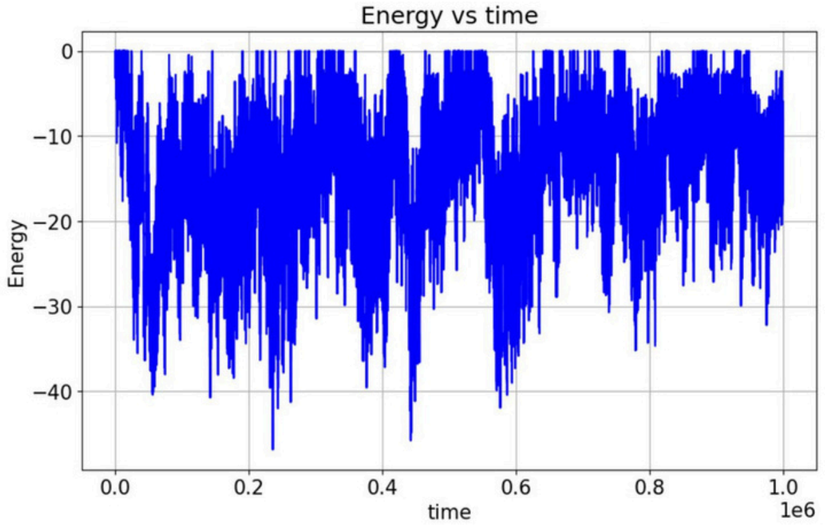

Fig 3. Energy vs Monte Carlo Step for a protein undergoing fold transition

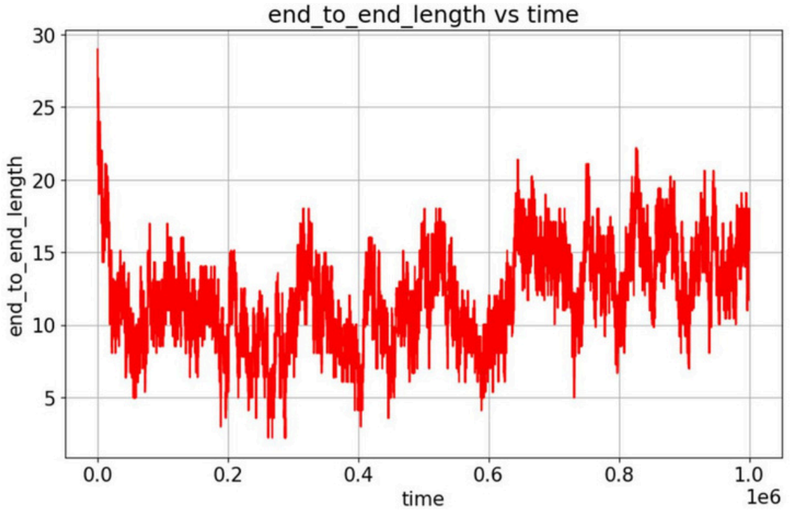

Fig 4. End to End Length vs Monte Carlo Step for a protein undergoing fold transition

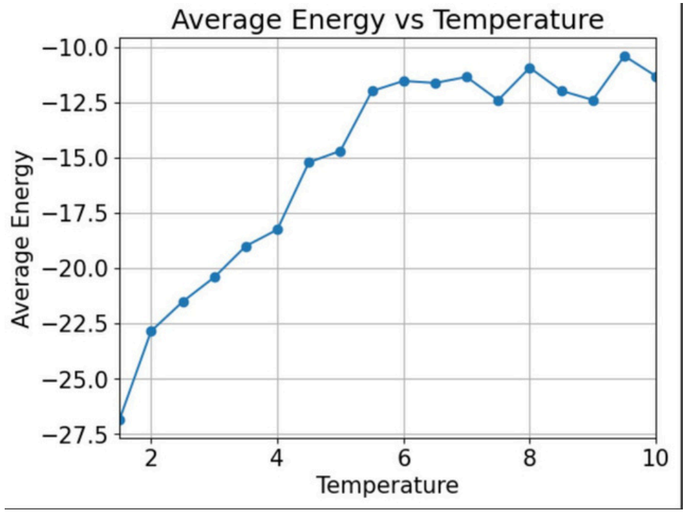

Fig 5. Average Energy vs Temperature for a protein undergoing fold transition

Simulating Fold Transition in 3D

Changes were made to the 2D fold transition simulation code for 3D fold transition simulation.

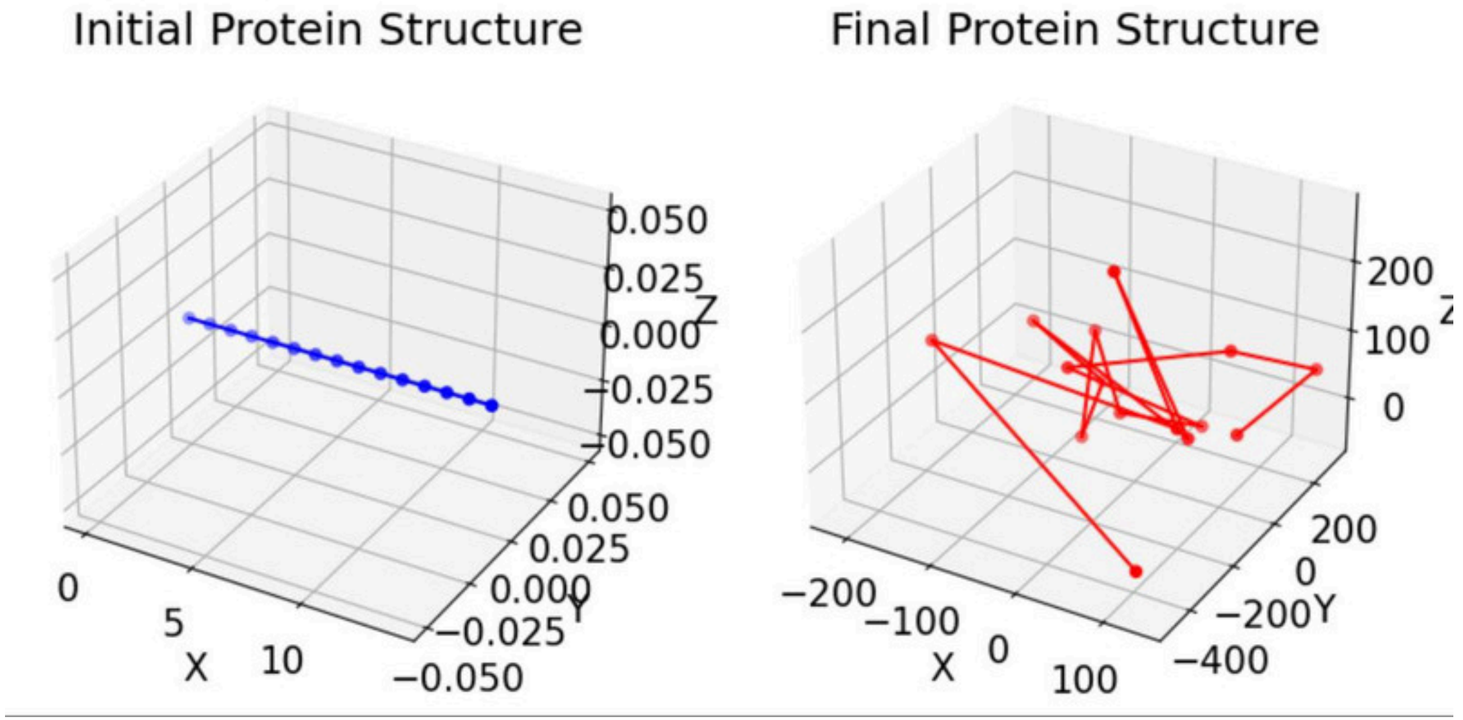

Fig 6. 3D Lattice Model for unfolded protein (left) and folded protein (right)

Width of Psuedotransition

According to the Fig 5, we can clearly observe that the protein was in the unfolded state at T=10 and its energy extensively falls at around T=2 where the protein is in the folded state.

Thus, Width of Psuedo Transition = 10 - 2 = 8

Width of Psuedo Transition for 2D fold transition = 8

Study of distribution of J

Process and Motivation:

- **Uniform vs. Random Interactions**: Compares uniform interaction strengths to randomly varying signs, reflecting diverse amino acid interactions.
- M**imics Biological Conditions:** Mimics water attraction and repulsion by amino acids, affecting folding.
- **Folding Dynamics Insights**: Offers insights into folding kinetics, stability, and intermediates under varied interactions.

Uniform Interaction

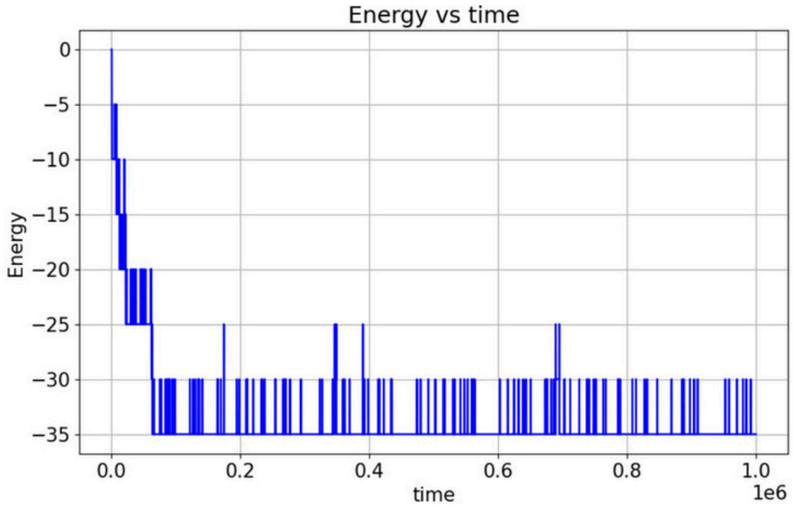

Fig 8. Energy vs Monte Carlo Step for a protein undergoing fold transition for Uniform J

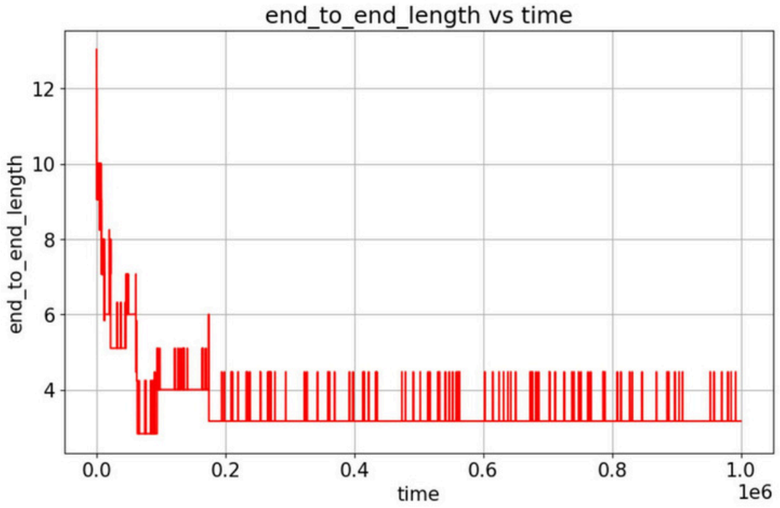

Fig 9. End to End Length vs Monte Carlo Step for a protein undergoing fold transition for Uniform J

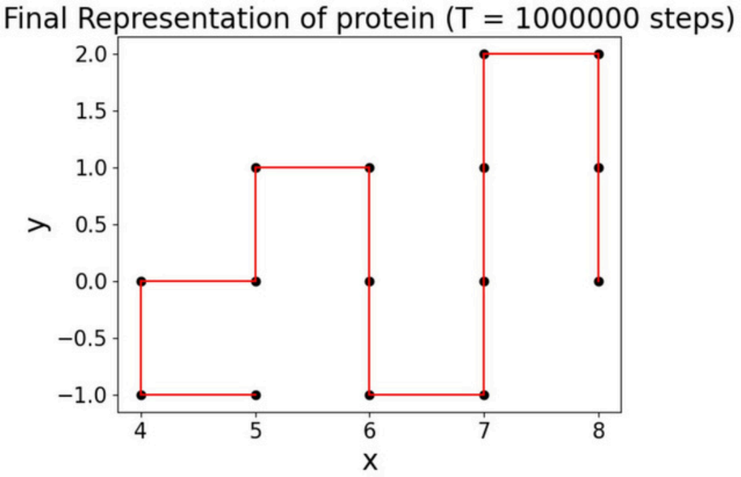

Fig 10. Lattice Model of a folded protein for Uniform J

Random Interaction

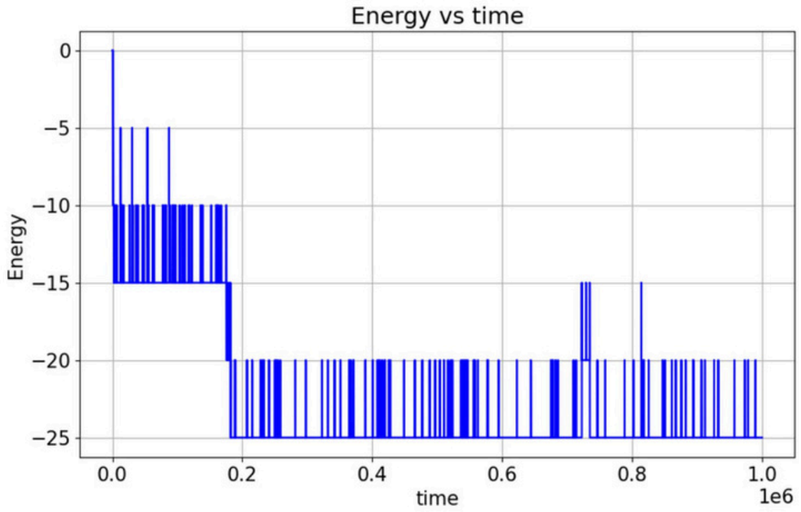

Fig 11. Energy vs Monte Carlo Step for a protein undergoing fold transition for Random J

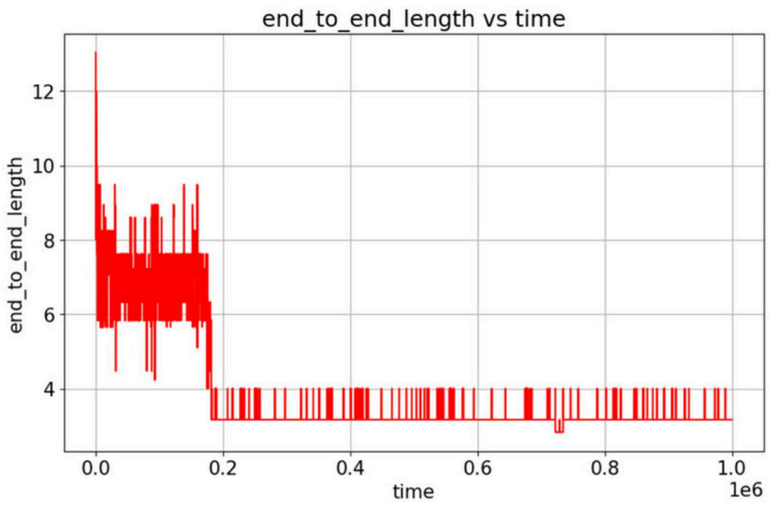

Fig 12. End to End Length vs Monte Carlo Step for a protein undergoing fold transition for Random J

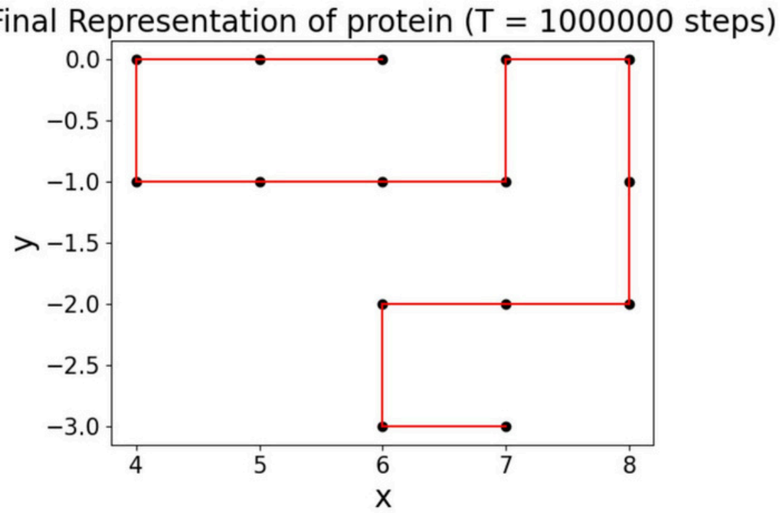

Fig 13. Lattice Model of a folded protein for Random J

Mean-Square Size (Δ)

Process:

- **Mean-Square Size (Δ):** Defines a measure of the size of a protein chain by calculating the average squared distance of each amino acid from the center of mass.
- **Investigation Objective:** Aims to investigate how Δ varies with temperature and its comparison to the behavior of the end-to-end distance.
- **Calculation Method:** Involves computing Δ by averaging the squared distances of all amino acids from the center of mass.
- **Temperature Dependency:** Explores how Δ changes with temperature, indicating alterations in the overall size and compactness of the protein structure.
- **Comparison with End-to-End Distance:** Contrasts the behavior of Δ with the traditional end-to-end distance measurement to assess if Δ provides additional insights into protein folding and structure.
- **Insight into Protein Conformation:** Offers insights into the relationship between temperature, protein size, and conformational changes, providing a more comprehensive understanding of protein behavior.

Mean-Square Size (Δ)

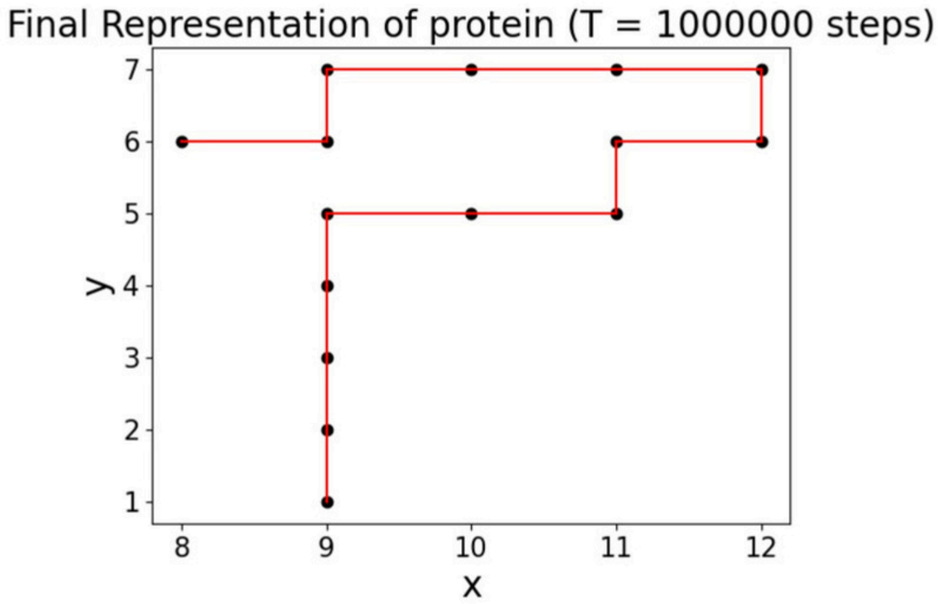

Fig 14. Lattice Model for a protein that underwent fold transition simulation

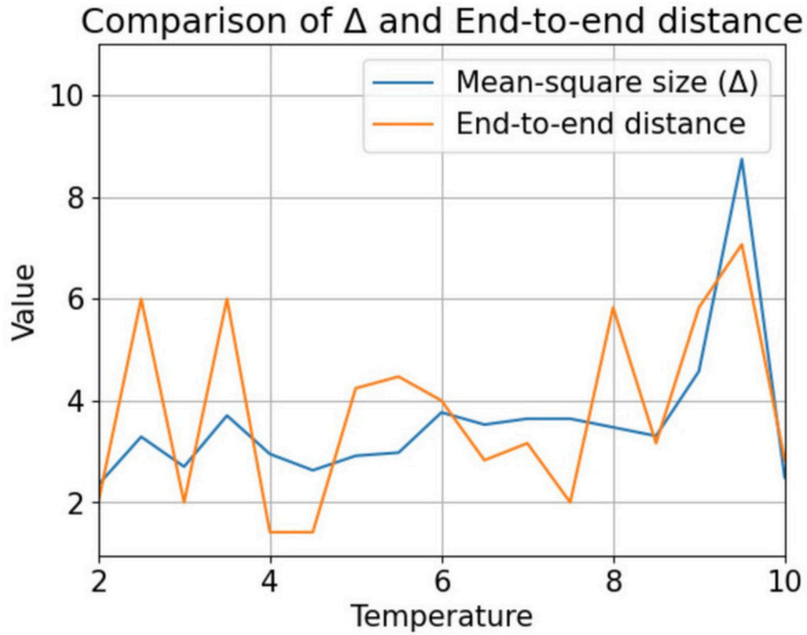

Fig 15. Mean-Square Size and End-to-End Distance vs Temperature

Energy Landscape

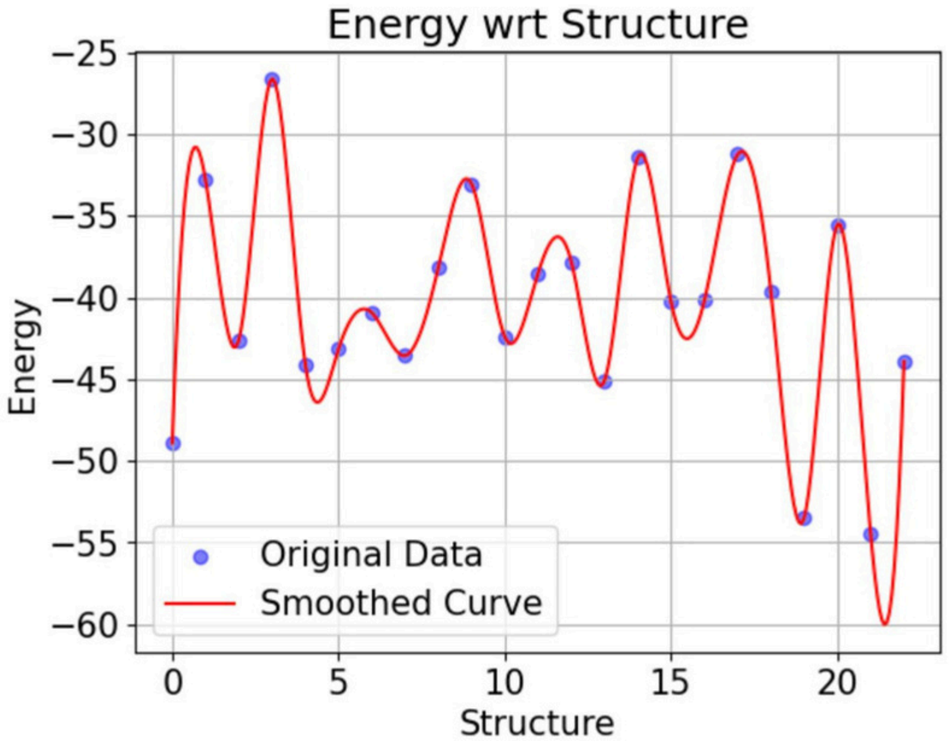

Fig 14. Schematic Energy Landscape for N=30

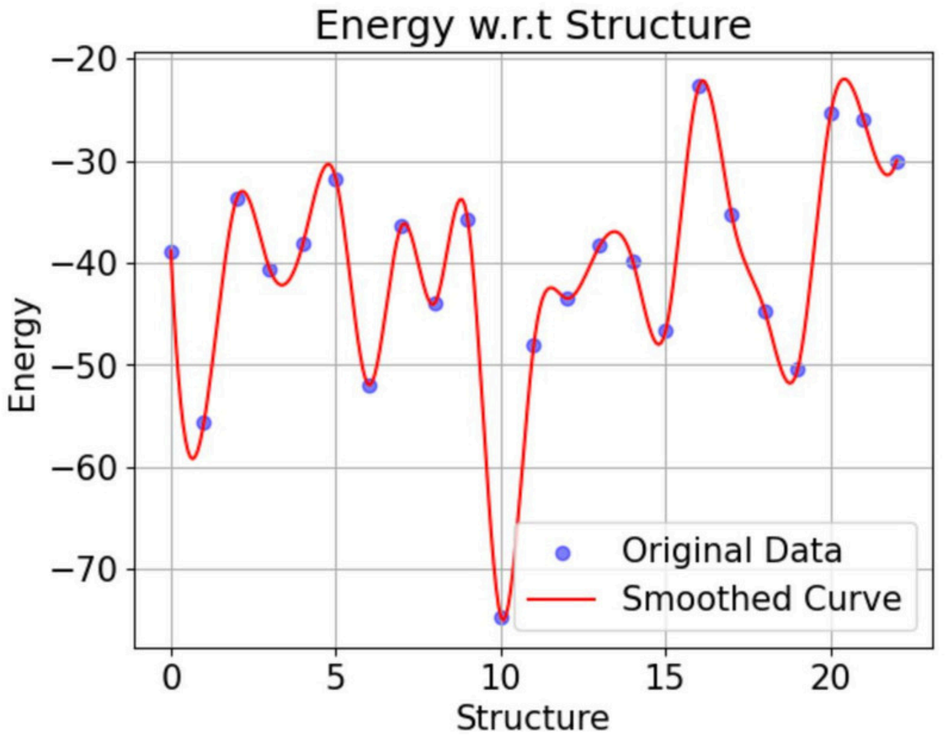

Fig 15. Schematic Energy Landscape for N=50

Problem of Metastability

- **Multiple Simulations:** Conduct multiple simulations of protein folding for the same model protein with 30 amino acids.
- **Metastable States:** Allow the protein chain to fold at a temperature of T=1 to enable it to reach metastable states, where it settles into energetically favorable configurations.
- **Comparative Analysis:** Compare the actual structures obtained from different simulations to assess the similarity or dissimilarity between the folded states.
- **Structural Comparison:** Evaluate whether the structures of the metastable states are similar or markedly different, indicating the presence of distinct folding pathways or conformations.
- **Energy Barrier Estimation:** Estimate the size of energy barriers separating the different metastable states based on the differences in energy levels between these states.

Problem of Metastability

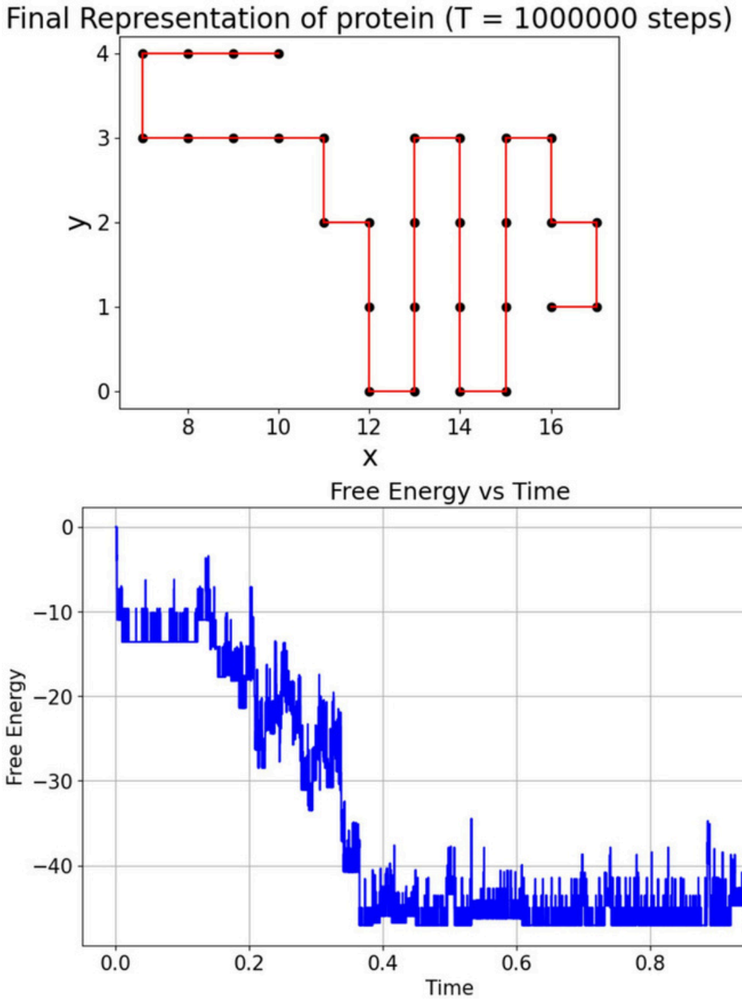

Fig 16. For N=30 and T=1 (Metastate-1)

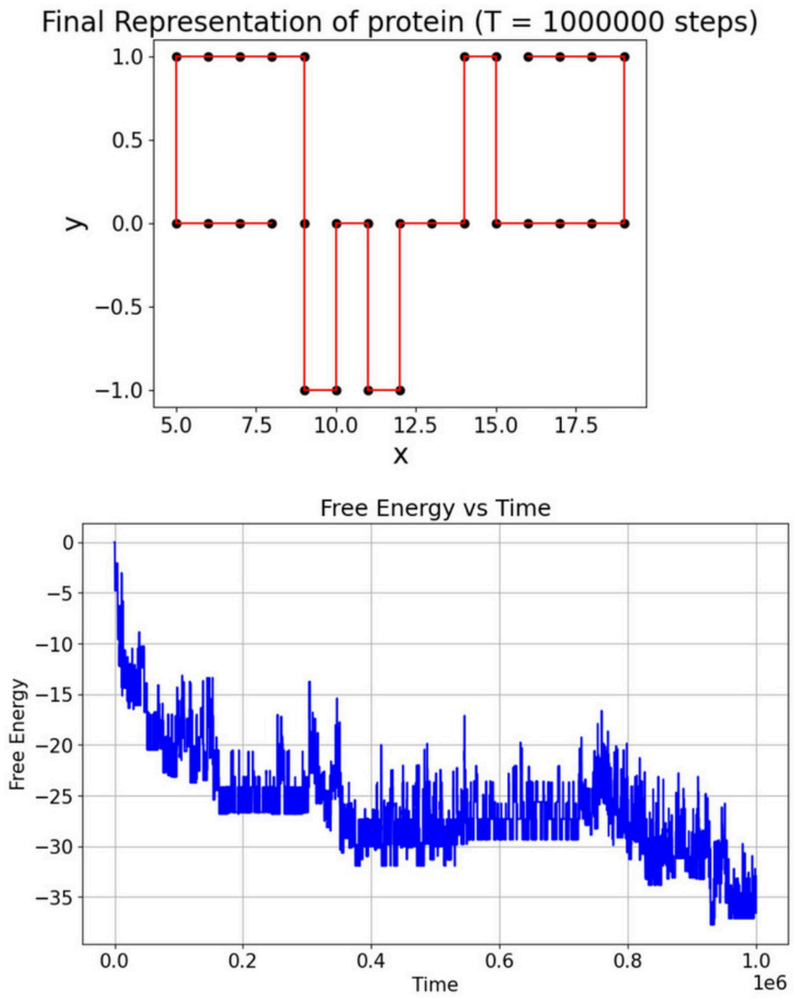

Fig 17. For N=30 and T=1 (Metastate-2)

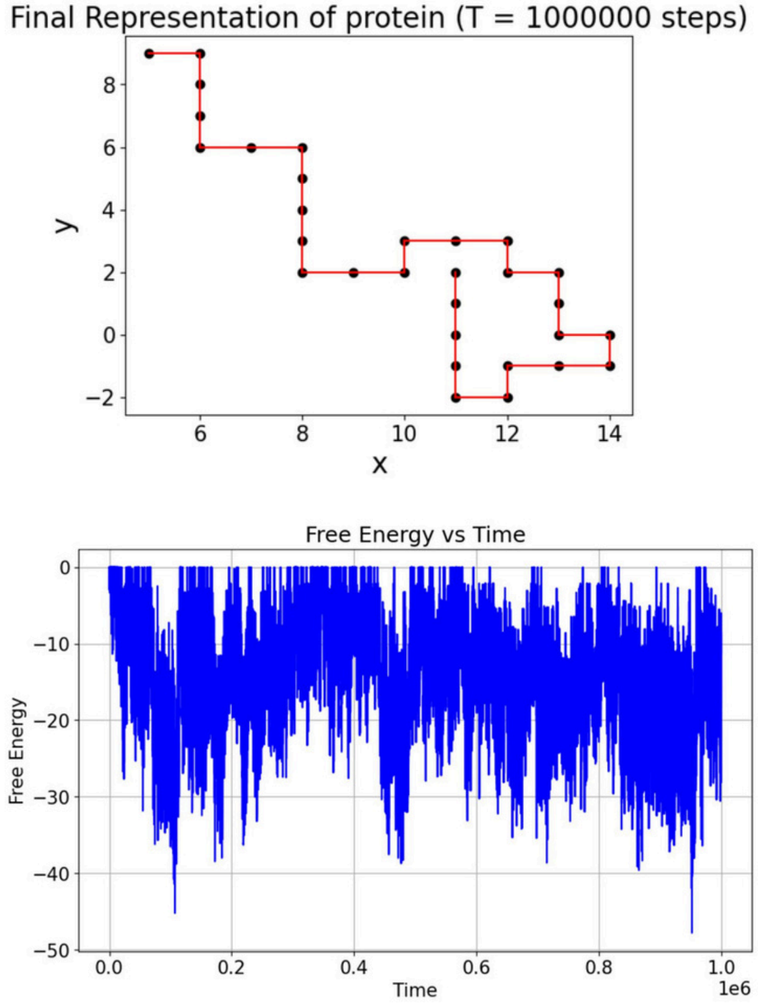

Fig 18. For N=30 and T=10

Thank you