Protein Simulation and Visualization Using Programming

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Background

Significance

The use of programming to run simulations and visualize structures can aid in understanding the molecular functions of biomolecules. This method can be used to any organism's structure. This knowledge could lead to breakthroughs in medicine, healthcare, and bioengineering.

Objective:

1. Model proteins so that the folded state has the lowest energy (native topology model).
2. Find temperature for transition state.
3. Compare the outcomes of transition state evaluations with those of experimental assessments.

Project Background

Because of its simplicity, Chymotrypsin Inhibitor 2 (CI2) is a unique model of protein folding. Folded states, Unfolded states, and transition states between Folded and Unfolded states are the only three essential conformation states. Transition states are the least well-understood and most complex to investigate.

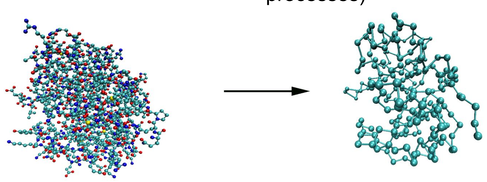
Questions:
What is the structure of a native topology model's transition state simulations?

How does the experimental results compare to the simulated structure?

The Approach

All-atom structure (closer to reality)

Simple C_α model (easier to simulate biological processes)

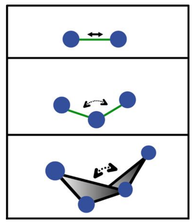


All-atom structure is stripped down to a C_α atom “skeleton model” enabling simulation of biologically-relevant processes such as protein folding .

Methods

Defining energy Terms “Force Field” or “Rules of the Unverse”

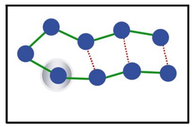
$$E_{total} = E_{bond} + E_{angle} + E_{dihedral} + E_{LJ} + E_{rep}$$



$$E_{bonds} = \sum_{bonds} \frac{1}{2} \varepsilon_r (r - r_0)^2$$

$$E_{angle} = \sum_{angles} \frac{1}{2} \varepsilon_\theta (\theta - \theta_0)^2$$

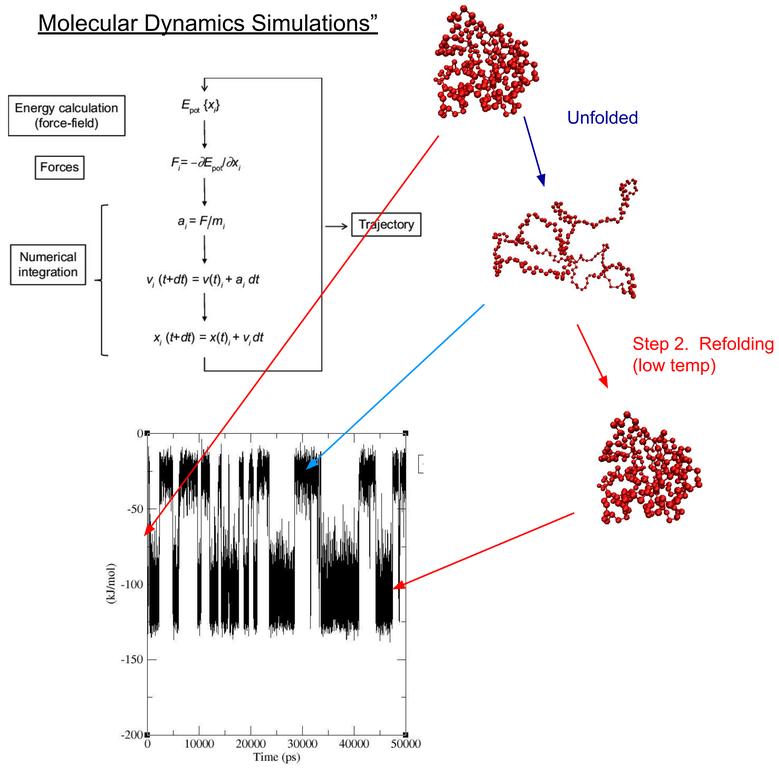
$$E_{dihedral} = \sum_{dihedrals} \left[\varepsilon_\phi^1 \left[1 - \cos(\phi - \phi_0) \right] + \varepsilon_\phi^2 \left[1 - \cos(3(\phi - \phi_0)) \right] \right]$$



$$E_{LJ} = \sum_{|i-j|>3} \varepsilon_{LJ} \left[5 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - 6 \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{10} \right]$$

$$E_{rep} = \sum_{i,j} \varepsilon_{rep} \left(\frac{\sigma_{12}}{r_{12}} \right)^{12}$$

Molecular Dynamics Simulations”



Results

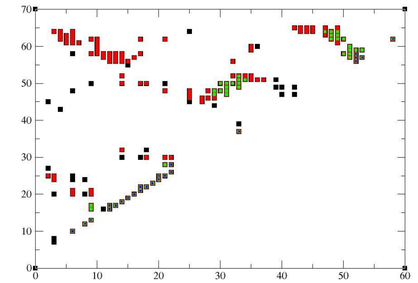


Figure 1.

The interactions between residues in the crystal structure of CI2 are represented by black squares. The contacts of CI2 for the folded structure are represented by red squares. The connections of CI2 in the transition state are represented by green squares. The unfurled contacts are represented in blue. It's worth noting that the squares depicted are for contacts that are present more than 50% of the time. Overlapping squares are contacts shared by all structures.

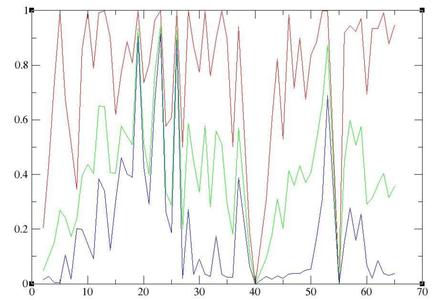


Figure 2.
The graph colors are represented in the same way as in Figure 1. The depicted points are averages of contact locations within the protein. Between conformation states, it's easy to see what residues in CI2 have in common.

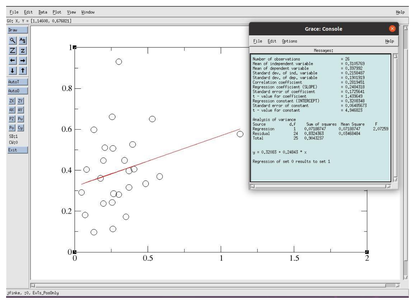


Figure 3.

Figure 2 (green lines) shows the correlation of simulated data with experimental assessments of transition state organization (phi-value analysis). 2

There is some convergence (slope = 0.25; r2 = 0.28). However, there is always potential for improvement.

Conclusion

Partially supported hypothesis (experimental transition state structure is partially captured). To achieve better results, there is still room for development.

References:

1. Rao, M.K., Chapman, T.R. Finke J.M., (2008) Crystallographic B-factors highlight energetic frustration in aldolase folding. J. Phys. Chem. B., Vol. 112, pp. 10417-10431.
2. Itzhaki and Fersht (1995) The structure of the transition state for folding of chymotrypsin inhibitor 2 analyzed by protein engineering methods: evidence for a nucleation-condensation mechanism for protein folding. J. Mol. Biol., Vol. 254, pp. 260-288.