Using Simulations to explore the folding properties of the 2CI2 Protein

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Background

Significance

As practical experiments become more expensive and time consuming, coupled with the fact that direct measurement of transition states and intermediates in physical experiments are prohibitively difficult.
A new methodology that has risen to study these difficult structures is the use of simulations to understand experimental research more fully.

Big Picture Question: How can we observe the transition states of 2CI2 protein using computer simulation?

Objective:

1.Make protein model of the 2CI2 protein (C_α model).
2.Fold it and unfold it with simulations.
3.Compare the results with experimental data.

This process will then be compared with experimental data to determine the degree of error in the folded states and thus that degree can be used as our confidence in the accuracy of the simulation's intermediate data.

Hypothesis – Identifying the Folding States

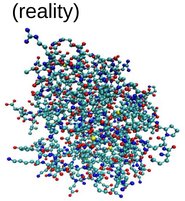
Within the research we also explored how the kinetic energy can alter Q (the fraction of folded state contact pairs found in the crystal structure). We will need to identify the difference in the folding states as folded, unfolded, or a transition state based on their Q values to determine the simulation's validity.

Problem: Transition states are not able to be monitored or created in a stable form in the laboratory setting.

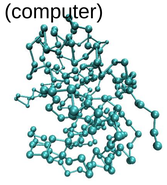
Hypothesis: Simulation will show an acceptable folding error when compared to experimental data, and thus can be used in further experimentation

Simplifying the Simulations

All-atom structure (reality)



Simple C_α model (computer)



All-atom structure is stripped down to only the C_α atom "skeleton".

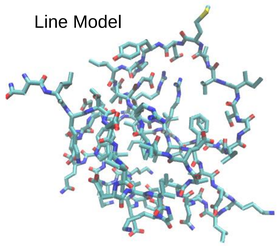
Methods

Bonding Properties of 2CI2

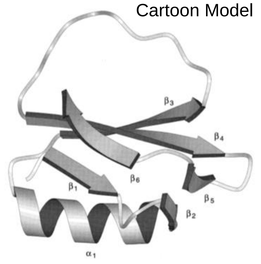
The Chymotrypsin inhibitor 2 Protein contains a couple of unique secondary structures, including a single alpha helix and 6 beta sheets that make up its structure.

The Chymotrypsin inhibitor 2 Protein bonding angles are also important, understanding that secondary structures prevent some contacts from forming gives us valuable data when preparing the simulation.

Line Model

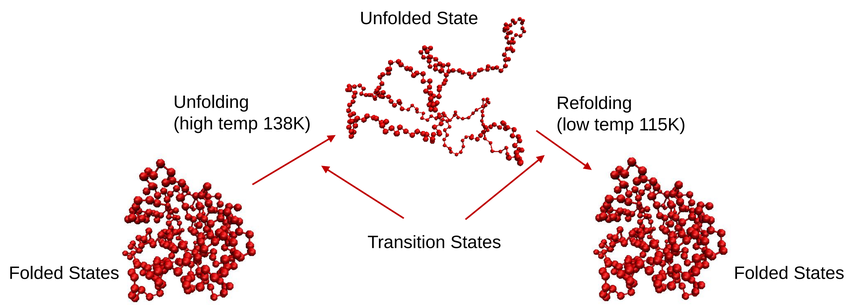


Cartoon Model



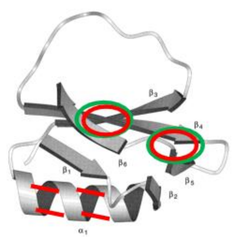
Chymotrypsin inhibitor 2 Protein

How Kinetic Energy Affects Protein Structures

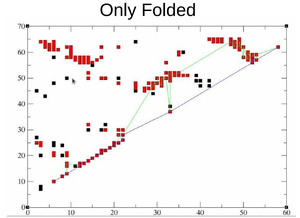


Simulation data on Q Contacts

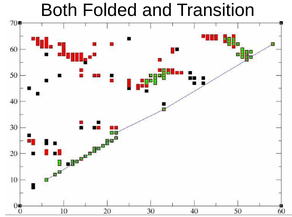
The Graphs below show the different steps in determining the Q contacts that happen at the folded, unfolded, and transitions states. The color squares show Red-Folded contacts, Green-Transition Contacts, Blue-Unfolded Contacts, Black-Total Contacts. When a color overlaps that means that contact will most likely remain present in any state that coincides with the color. This means that the Q value is high when there is many contacts happening (Folded State) and the Q value is low when there is not as many contacts (Unfolded State). In the graph to the right shows the major contact regions, the red circle and lines show secondary structures that have contacts whether the 2CI2 protein is folded or non folded and the green has contacts that will be lost when it is unfolded.



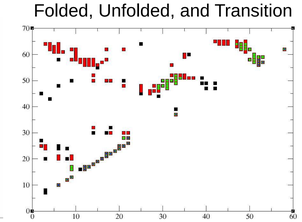
Only Folded



Both Folded and Transition

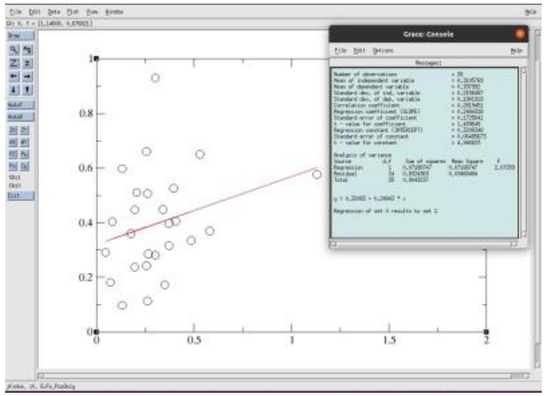


Folded, Unfolded, and Transition

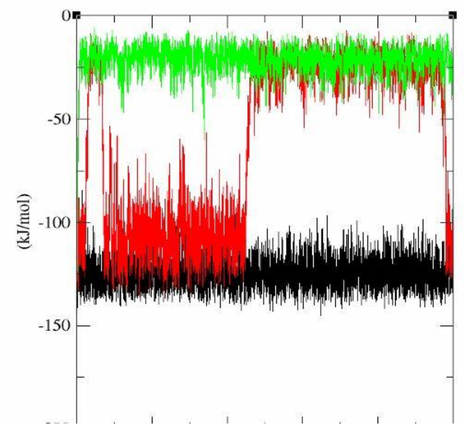


Best Graph

Results



The graph shows the experimental and simulation data being compared with a linear regression line.



The graph shows the folding and unfolding process of the 2CI2 protein, which also shows the kinetic energy which was used as a comparison between experimental and simulation values.

Conclusion

The hypothesis is supported as the simulation is accurate to the experimental data because the treatment of EvTS_PosOnly shows a comparison between the simulation and experimental data with a similar fit. The results showed that when the protein was folded, the 4-contact energy was near -300 kJ/mol; and when the temperature was increased the protein flipped and unfolded having contact energy of -40 kJ/mol showing that the occurrence of misfolded proteins directly relates to the protein's energy state. This shows that the simulation was able to replicate experimental data, while also being accurate enough to allow further examination of transition states available in the simulation that couldn't be practically accessed in an experimental setting.

References:
1.Finke J.M., (2021) 495 Capstone Tasks, *University of Washington Tacoma. Canvas*