Monte Carlo Simulations of Protein Folding using Lattice Models

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Abstract

Understanding the so-called native state conformation of protein molecules is of great importance due to the direct relationship between their structure and biological function. However, this conformation is typically adopted at the global free energy minimum located among an enormous number of conformational minima on a complex energy landscape. As a result, locating the native state through computational optimization methods and simplifying models has attracted considerable attention. The Monte Carlo-based simulated annealing method developed by Kirkpatrick *et al* was used to provide a heuristic solution to the energy minimization problem. Additionally, the problem was simplified through the use of the HP model (Dil, 1985) on a two-dimensional lattice with periodic boundary conditions. Results from this study provided insight on protein folding and more realistic simulation models.

Introduction

Simulated annealing is based on the idea of cooling molten material to form a perfect crystal. This heuristic optimization technique typically utilizes the Metropolis Monte Carlo algorithm (MMC) within a temperature cooling schedule to accept or reject re-configuration moves. In general, moves are accepted if one of the following is true:

1) $\Delta E < 0$

2) $\text{Rand}[0,1] \leq \text{Exp}[-\Delta E / T]$

The use of a cooling schedule and MMC allows the lattice chain to escape local energy minima while searching for the global minimum.

Despite the success of optimization techniques, it is realized through Levinthal's paradox that an examination of all possible conformations is computationally impossible due to the enormous number of degrees of freedom in a protein and the complexity of the energy landscape. Thus, simplifying lattice models are often used to make such a problem feasibly approachable. One model that is commonly used is the Hydrophobic-Polar (HP) model. This model provides addition simplifications because each amino acid monomer on a lattice point is designated as being either hydrophobic (H) or polar (P). As a result, only three types of interaction energies are possible: E_{HH}, E_{PP}, and E_{HP}.

Method

HP-Model

•Energy function:

$$H = \sum_{i<j} E_{p_i p_j} \delta(r_i - r_j)$$

$\delta(r_i - r_j) = 1$ for non-bonded nearest neighbor interactions between monomers and 0 otherwise

E_{HH}=-3, E_{HP}=-1.2, and E_{PP}=0 (Bahar et al, 1997)

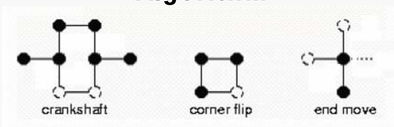
Simulation

•A self-avoiding random walk was used to grow each peptide chain to a length *n* on a 2D square lattice with periodic boundary conditions

•Cooling schedule (10,000 MC steps each T):

	T_{start}	T_{stop}	T_{step}
1	100	50	-5
2	49	25	-1
3	24.5	10	-0.5
4	9.75	7	-0.25
5	6.9	0.05	-0.05

Verdier-Stockmayer Algorithm



Used to reconfigure peptide conformation on 2-D lattice

Model Sequences (Rathore et al, 2002)

•**Sequence A:**

•(-Ala-Leu-Ser-Ser-Ala-Ala-Ser-)$_n$

(- H – H – P – P – H – H -- P-)$_n$

•Used for simulation of alpha helices

•**Sequence B:**

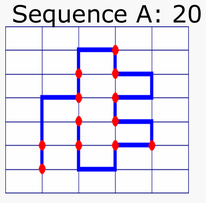
• (-Val-Ser-)$_n$ ⇔ (-- H — P --)$_n$

•Used for simulation of beta sheets

<E>$_T$,<E^2>$_T$, and $C(T) = \frac{\langle E \rangle_T - \langle E^2 \rangle_T}{T^2}$ calculated at each temperature

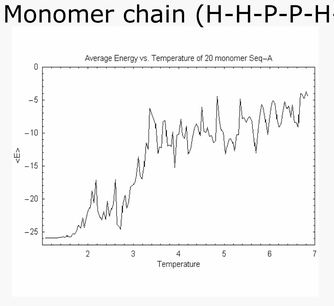
Results

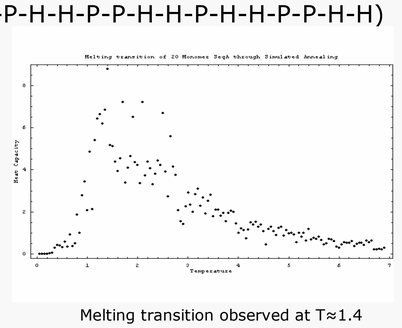
Sequence A: 20 Monomer chain (H-H-P-P-H-H-P-H-H-P-P-H-H-P-H-H-P-P-H-H)



Final conformation

E = -26.4



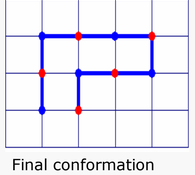


Melting transition observed at T≈1.4

•Observed to form possible 2D alpha helix

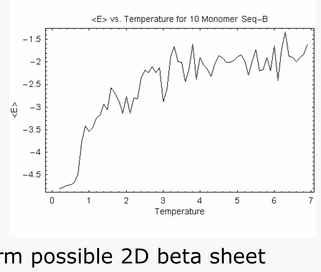
•Hydrophobic monomers arrange inwards due to favorable interactions

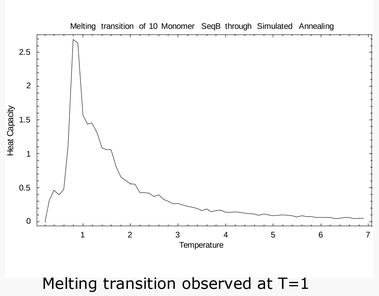
Sequence B: 10 Monomer chain (H-P-H-P-H-P-H-P-H-P)



Final conformation

E = -4.8





Melting transition observed at T=1

•Observed to form possible 2D beta sheet

Future Research

•Increased Metropolis run-time (increased iterations)

•Comparison of low energy configurations for small sequences with lowest energy structure(s) from deterministic algorithm

•Implementation of 3-dimensional lattice model and comparison with known native state structures

•Implementation of more effective reconfiguration moves

Acknowledgements

•The national BBSI program (http://bbsi.eeicom.com) is a joint initiative of the NIH-NIBIB and NSF-EEC, and the BBSI @ Pitt is supported by the National Science Foundation under Grant EEC-0234002.

•Mentor: Kenneth Jordan, PhD

•University of Pittsburgh

•Alpay Temiz

•Rajan Munshi, PhD

•Judy Wieber, PhD

•BBSI Staff and Participants

References

[1] Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller, A. H.; Teller, E. *Journal of Chemical Physics* (1953). 21: 1087-1092

[2] Kirkpatrick, S; Gelatt, C. D.; Vecchi, M. P. Science (1983), Volume 220: 671-679.

[3] Levinthal, C. University of Illinois Press (1968).

[4] Leach, A. Molecular Modeling: Principles and Applications, 2nd Edition. Prentice Hall (2001): 423-431.

[5] Dil, K. Biochemistry (1985), 24: 1501-1509.

[6] Klimov, D. K.; Thirumalai, D. Physical Review Letters (1996), Volume 76: 4070-4073.

[7] Bahar, I.; Atilgan, A. R.; Jernigan, R. L.; Erman, Burak. Proteins: Structure, Function, and Genetics (1997), 29: 172-185.

[8] Rathore, Nitin; de Pablo, Juan. *Journal of Chemical Physics* (2002), Volume 116: 7225-7230.