Monte Carlo Simulations of Protein Folding using Lattice Models

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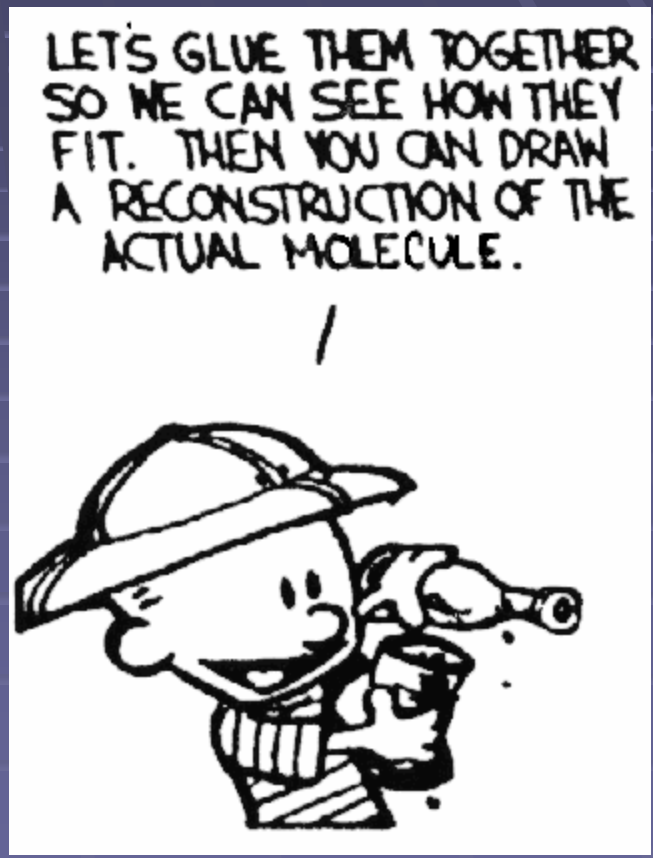
Goals

- Investigate folding of peptide sequences through simulation
- Gain insight on computational algorithms in protein folding
  - Random walk
  - MC-based Simulated Annealing

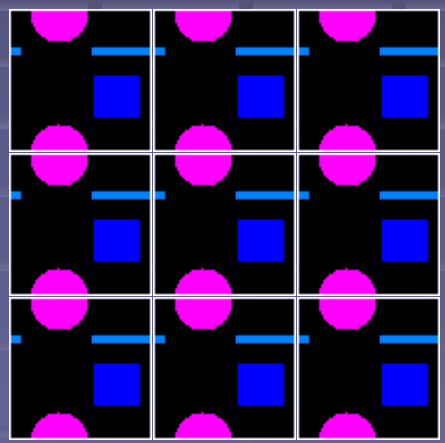


Introduction

- Protein native state
  - Direct relationship between conformation and biological function
  - Conformation located at global energy minimum on complex energy landscape
  - Methods of interest include computational techniques for optimization
  - “Levinthal’s Paradox”
  - Need for simplifying models (i.e., lattice models)

Lattice Model

- Two-dimensional square lattice
- Periodic boundary conditions—”Infinite lattice”



Lattice Model

- HP-lattice Model
  - Hydrophobic effect assumed to be driving force in protein folding
  - Amino acid monomers are modeled as being either hydrophobic (H) or polar (P)
    - Three possible interaction energies: E_{HH}, E_{HP}, and E_{PP}
  - Energy function:

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

    - $\delta(r_i - r_j)=1$ if monomers r_i and r_j are adjacent non-bonded nearest neighbors and 0 otherwise

Simulated Annealing

- Based on idea of cooling molten material to form a perfect crystal
- Performed from effectively high temperature and cooled to frozen state
- Utilizes Metropolis Monte Carlo to minimize energy function
  - Moves accepted if:

    1) $\Delta E < 0$

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

Methodology

- Artificial peptide sequences:
  - SeqA used for simulation of alpha helices

    $(\text{-Ala-Leu-Ser-Ser-Ala-Ala-Ser-})_n$

    $(\text{- H – H – P – P – H – H -- P-})_n$

    20 Monomer Seq-A analyzed

  - SeqB used for simulation of beta sheets

    $(\text{-Val-Ser-})_n$

    $(\text{-- H --- P --})_n$

    10 Monomer Seq-B analyzed

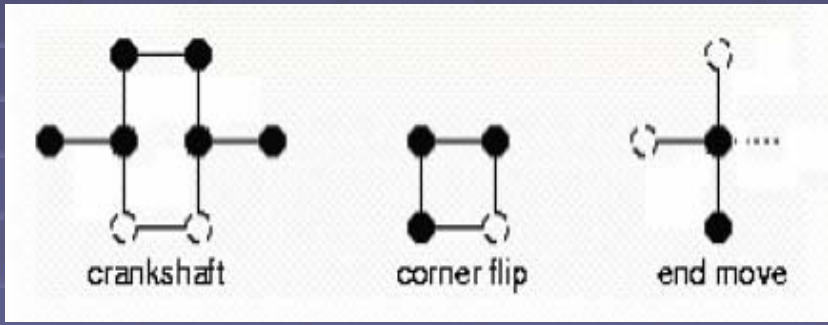
Methodology

- Self-avoiding random walk to generate peptide chain of length *n*
- Simulated annealing: 10,000 Metropolis iterations per temperature

Temperature Schedule			
	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

Methodology

- Metropolis reconfiguration based on Verdier-Stockmayer algorithm
  - End rotation, Kink jump, and crankshaft



- HP Interaction energies:
  - E_{HH} = -3 (most favorable)
  - E_{HP} = -1.2
  - E_{PP} = 0

Analysis

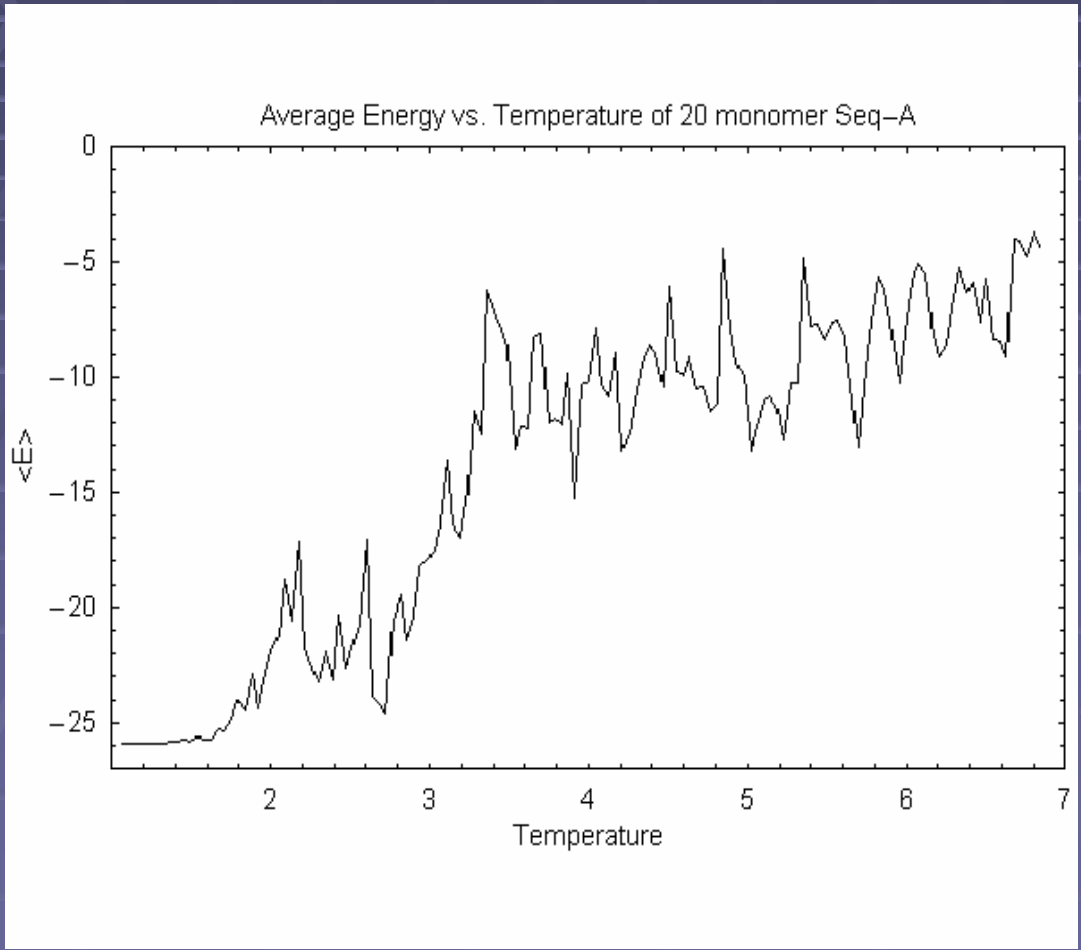
- $\langle E \rangle_T$ and $\langle E^2 \rangle_T$ calculated at each temperature
- Heat capacity calculated:

$$C(T) \propto \frac{\langle E^2 \rangle_T - \langle E \rangle_T^{\,2}}{T^2}$$

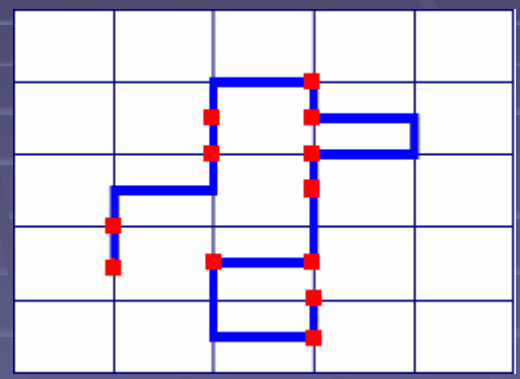
- Melting transition temperature observed
- Low energy conformation obtained

Results: 20 Monomer Seq-A

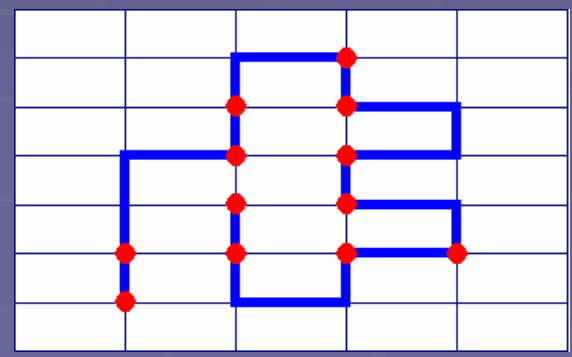
(H-H-P-P-H-H-P-H-H-P-P-H-H-P-H-H-P-P-H-H)



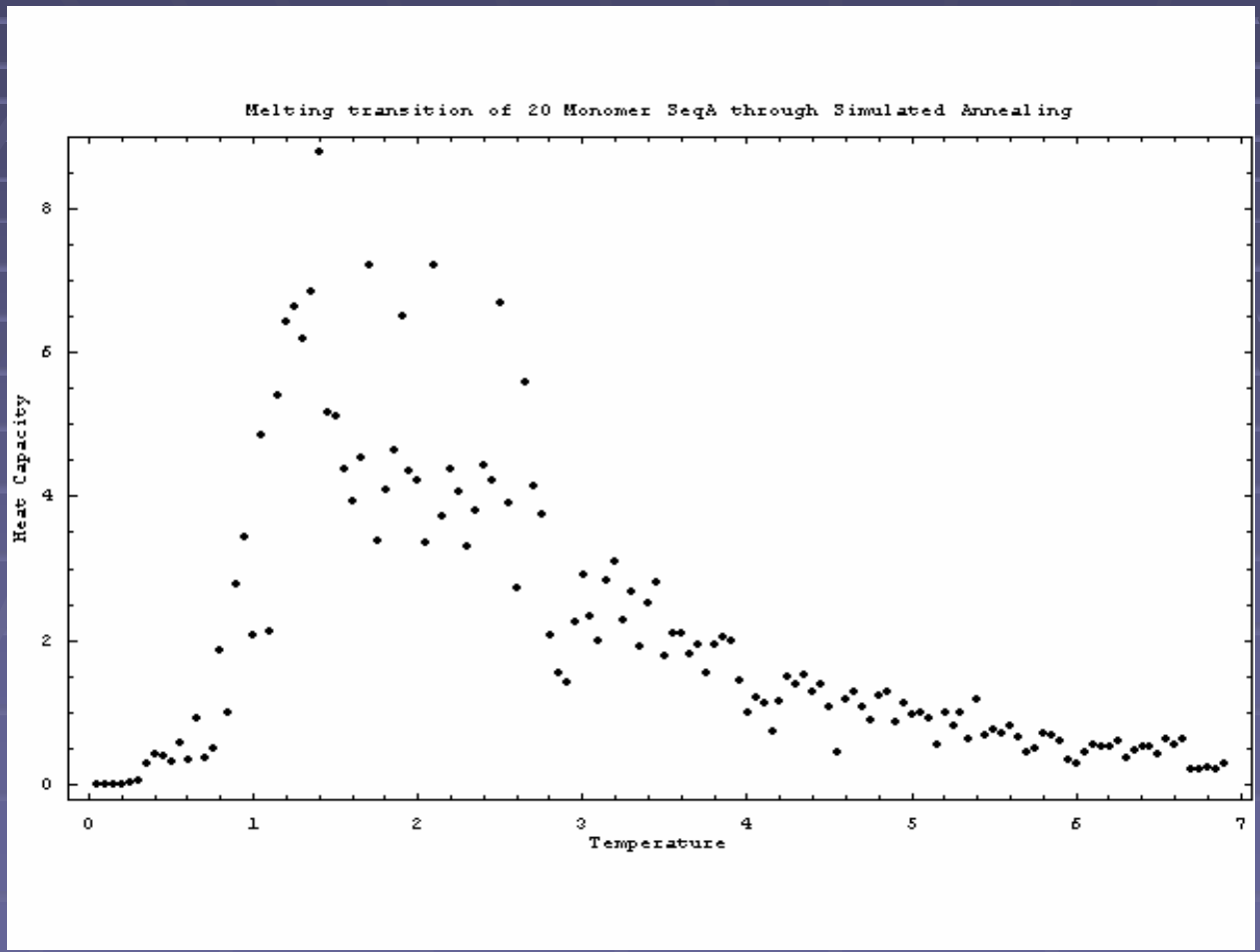
- Initial conformation (E=-17.4)



- Final conformation (E= -26.4)



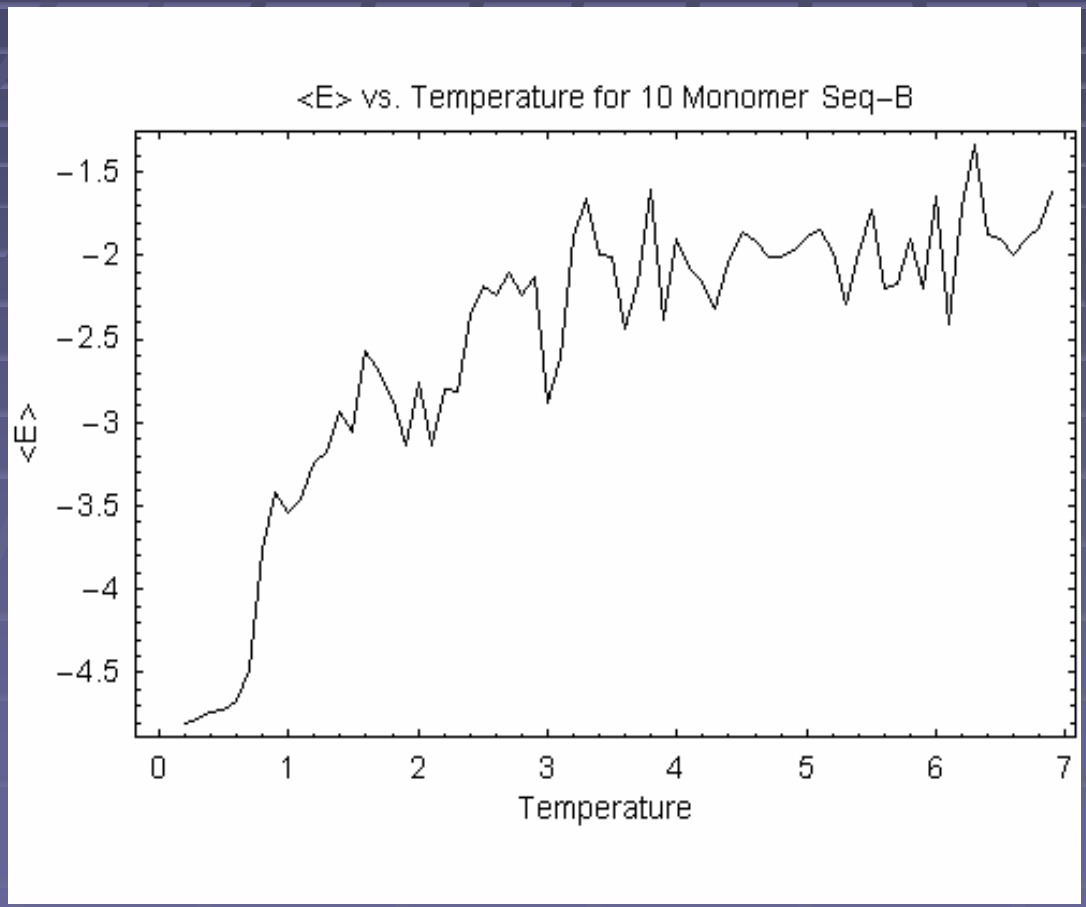
Results: 20 monomer Seq-A



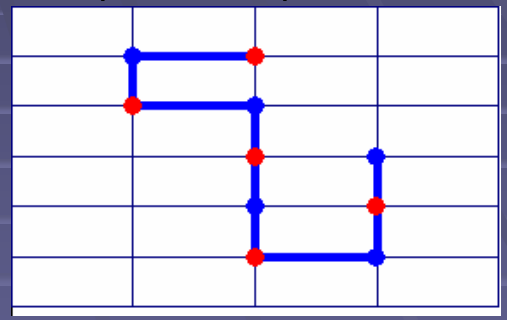
- Graph of C(T) vs. T shows phase transition
- $T_c \approx 1.4$

Results:10 Monomer Seq-B

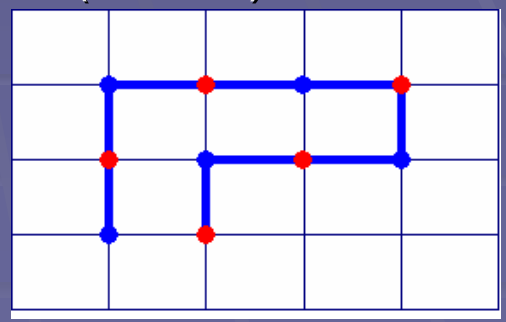
(H-P-H-P-H-P-H-P-H-P)



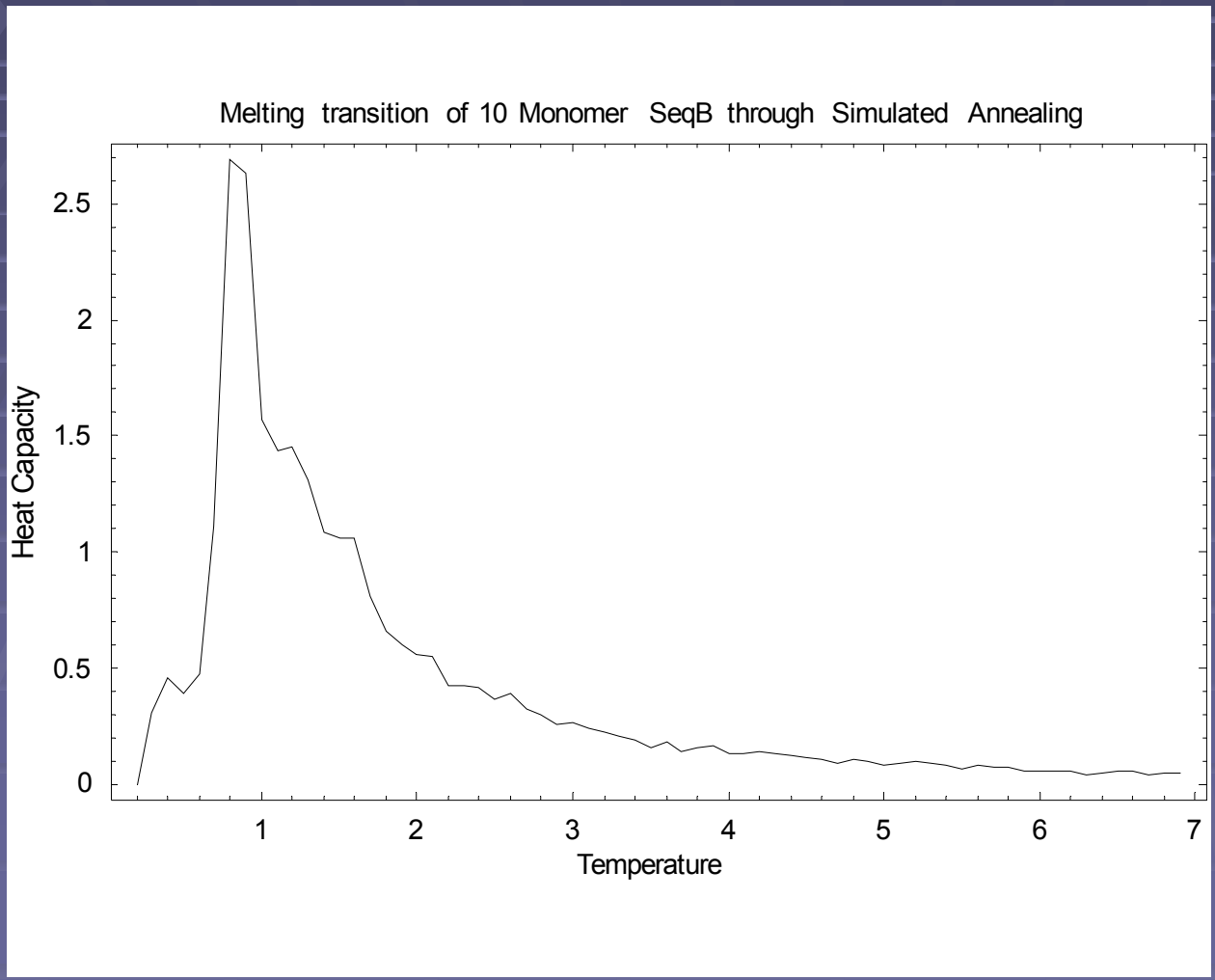
- Initial configuration (E= -3.6)



- Final configuration (E=-4.8)



Results: 10 Monomer Seq-B



- $T_c \approx 1$

Conclusions

- Melting transitions were observed on plots of heat capacity vs. T
- Low energy conformations obtained
- Seq-A
  - observed to form possible 2D alpha helix conformation
  - Hydrophobic monomers arranged inwards
- Seq-B
  - Observed to form possible 2D beta-sheet

Future Work

- Increased Metropolis run-time (increased iterations)
- Comparison of low energy configurations for small sequences (<14 monomers) with lowest energy structure(s) from deterministic algorithm
- Implementation of 3-dimensional lattice model
- Comparison of 3-D folding structure with known native state structures
- Implementation of more effective reconfiguration moves

References

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