Cold Denaturation in Proteins.

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Plan

1. Introduction.

2. The Problem.

3. Model.

4. Results 1. : Two-states phase diagram.

5. Results 2 : Four-states phase diagram.

6. Conclusion.
Amino-acids and Bond between amino acids.
Proteins are large and linear chains made of amino acids
Put into water proteins fold in a unique compact structure.

Main folding force is the **Temperature Dependent** Hydrophobic Effect\(^a\).

\(^a\)Kauzmann 1959, Balwin 1987, Pratt-Pohorille 2002
Warm and Cold Denaturations\(^1\). 

\[ T(C) \]

\[ \text{pH} \]

Denat

\(^1\) Privalov, 1989
Statistical Physics approach.

\[ \mathcal{H}_{\text{mic}} = E_{\text{intr}}^{(m)} + E_{\text{solv}}^{(mm')} \]

\[ \Rightarrow Z(T) = \sum_{m=1}^{\Omega} \sum_{m' = 1}^{\Omega'} \exp \left( -\frac{E_{\text{intr}}^{(m)} + E_{\text{solv}}^{(mm')}}{T} \right) \]

\[ \sum_{m' = 1}^{\Omega'} \exp \left( -\frac{E_{\text{solv}}^{(mm')}}{T} \right) = z_{\text{solv}}^{(m)}(T) = \exp \left( -\frac{F_{\text{solv}}^{(m)}(T)}{T} \right) \]

\[ \Rightarrow Z(T) = \sum_{m=1}^{\Omega} \exp \left( -\frac{\mathcal{H}_{\text{eff}}^{(m)}(T)}{T} \right) \]

with \[ \mathcal{H}_{\text{eff}}^{(m)}(T) = E_{\text{intr}}^{(m)} + F_{\text{solv}}^{(m)}(T) \]
Effective hamiltonian.

\[ \Delta_{ij}^{(m)} = 1 \text{ if } i \text{ and } j \text{ are first neighbors.} \]

\[ B_{ij} : \text{coupling between } i \text{ and } j \]

\[ n_i^{(m)} : \text{number of cells around } i \]

\[ f_i(T) : \text{free energy of this solvent cell.} \]

\[ n_s^{(m)} : \text{total number of solvent cells} \]

\[ f_s(B_s, T) : \text{free energy of neat solvent} \]

\[ \mathcal{H}_{\text{eff}}^{(m)} = \sum_{i > j + 1} B_{ij} \Delta_{ij}^{(m)} + \sum_i n_i^{(m)} f_i(T) + 2n_s^{(m)} f_s(B_s, T) \]

More complicated form than the usual: \( \mathcal{H}_{\text{eff}}^{(m)} = \sum_{i > j + 1} B_{ij} \Delta_{ij}^{(m)} \)

Constant of the model.

Total lattice links: \( \sum_i \sum_j \Delta_{ij}^{(m)} + \sum_i n_i^{(m)} + n_s^{(m)} = K_1 \)

Links of monomer \( i \): \( \sum \Delta_{ij}^{(m)} + n_i^{(m)} = 4 \)
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\begin{cases}
  n_i^{(m)} = 4 - \sum_j \Delta_{ij}^{(m)} \\
n_s^{(m)} = \frac{1}{2} \sum_i \sum_j \Delta_{ij}^{(m)} + K_1 - 4N
\end{cases}
\]

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Effective Couplings.

\[
\mathcal{H}_{\text{eff}}^{(m)}(B_s, T) = \sum_i \sum_{j>i} B_{ij}^{\text{eff}}(B_s, T) \Delta_{ij}^{(m)}
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with \( B_{ij}^{\text{eff}}(B_s, T) = B_{ij} - f_i(T) - f_j(T) + 2f_s(B_s, T) \)

- takes a simple form
- which forms for \( f_i(T) \) and \( f_s(B_s, T) \) ?
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- which forms for \( f_i(T) \) and \( f_s(B_s, T) \)?
Solvation Model

\[ f_s(B_s, T) = B_s - \alpha T \ln N_s \]

Small \( B_s \) ⇒ bad solvent
Large \( B_s \) ⇒ good solvent

\[ n(B_i) = \frac{2N_s \exp \left( -\frac{B_i^2}{2\sigma^2} \right)}{\sigma \sqrt{2\pi} \text{ erfc} \left( \frac{B_{i \min}}{\sigma \sqrt{2}} \right)} \]

\[ z_i(T) = \int_{B_{i \min}}^{\infty} n(B_i) \exp \left( -\frac{B_i}{T} \right) dB_i \]

\[ f_i(T) = -\frac{\sigma^2}{2T} - T \ln \left( N_s \frac{\text{erfc} \left( \frac{B_{i \min}}{\sigma \sqrt{2}} - \frac{\sigma \sqrt{2}}{2T} \right)}{\text{erfc} \left( \frac{B_{i \min}}{\sigma \sqrt{2}} \right)} \right) \]
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The Chain and the Statistical averages.

The chain.

16-mers in 2D lattice
802 075 conformations
116 579 extended conformations
69 more maximally compact conf

Statistical average $\langle X(T) \rangle = \sum_{m=1}^{\Omega} X^{(m)}(T) P_{eq}^{(m)}(T)$ with

$P_{eq}^{(m)}(T) = \frac{1}{Z(T)} \exp \left( - \frac{H_{eff}^{(m)}}{T} \right)$.

Compactness: $\langle N_c(B_s, T) \rangle$
Order parameter: $\langle Q(B_s, T) \rangle$
Chain entropy, $S_{ch}$: $-\langle \ln P_{eq}^{(m)}(B_s, T) \rangle$

where

$N_c^{(m)} = \frac{1}{9} \sum_{i>j}^{N} \Delta_{ij}^{(m)}$
$Q^{(m)} = \frac{1}{9} \sum_{i>j}^{N} \Delta_{ij}^{(m)} \Delta_{ij}^{Nat}$

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where
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\[ -\langle \ln P_{eq}^{(m)}(B_s, T) \rangle \]
Results 1. Two-states phase diagram

- Graph (c) shows a three-dimensional phase diagram with axes labeled C, Bs, and T.
- Graph (d) illustrates another phase diagram with axes labeled <Q>, Bs, and T.
- Graph (e) depicts a line graph with points labeled Nat and Denat, illustrating a transition between states.
Results 1. Two-states phase diagram

![Diagram showing two-states phase diagram with pH on the x-axis and T(C) on the y-axis. The diagram illustrates the transition between native (Nat) and denatured (Denat) states at different pH values.]

![Diagram showing a different aspect of the phase diagram with Bs on the x-axis and the transition phase on the y-axis. The diagram highlights the denatured state (Denat) at varying Bs values.]
$\alpha = 0.5 \rightarrow 0.9$
Results 2: Four-states phase diagram.

\[ \langle N_c \rangle \]

\[ S_{ch} \]

\[ \tau dS_{ch} / dT \]

\( T_s = 0 \)
\( T_s = 2 \)
\( T_s = 4 \)
\( T_s = 6 \)
Result 2: Four-states phase diagram.
Conclusions.

Calculation of $H_{\text{eff}}^{(m)}(T)$ also simple than $E_{\text{intr}}^{(m)}$
Cold Denaturation due to hydrophobic effect

Realistic couplings must take into account of the temperature dependence of the hydrophobic effect.
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take into account of the temperature dependence of the hydrophobic effect.
Effective Couplings as function of $T$.

Figure: Curves of the different contributions to the effective coupling between the monomers 1 and 4 as function of the temperature for several values of the solvent quality. The two temperatures for which the coupling vanishes are shown for $B_s = -6.0$.

$$B_{ij}^{\text{eff}}(B_s, T) = B_{ij} - f_i(T) - f_j(T) + 2f_s(B_s, T)$$ may be:

- positive at low $T$
- negative at medium $T$
- positive at high $T$
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