PHY 411-506 Computational Physics II

Chapter 12: Interdisciplinary Topics

Lecture 2

Wednesday April 9, 2008

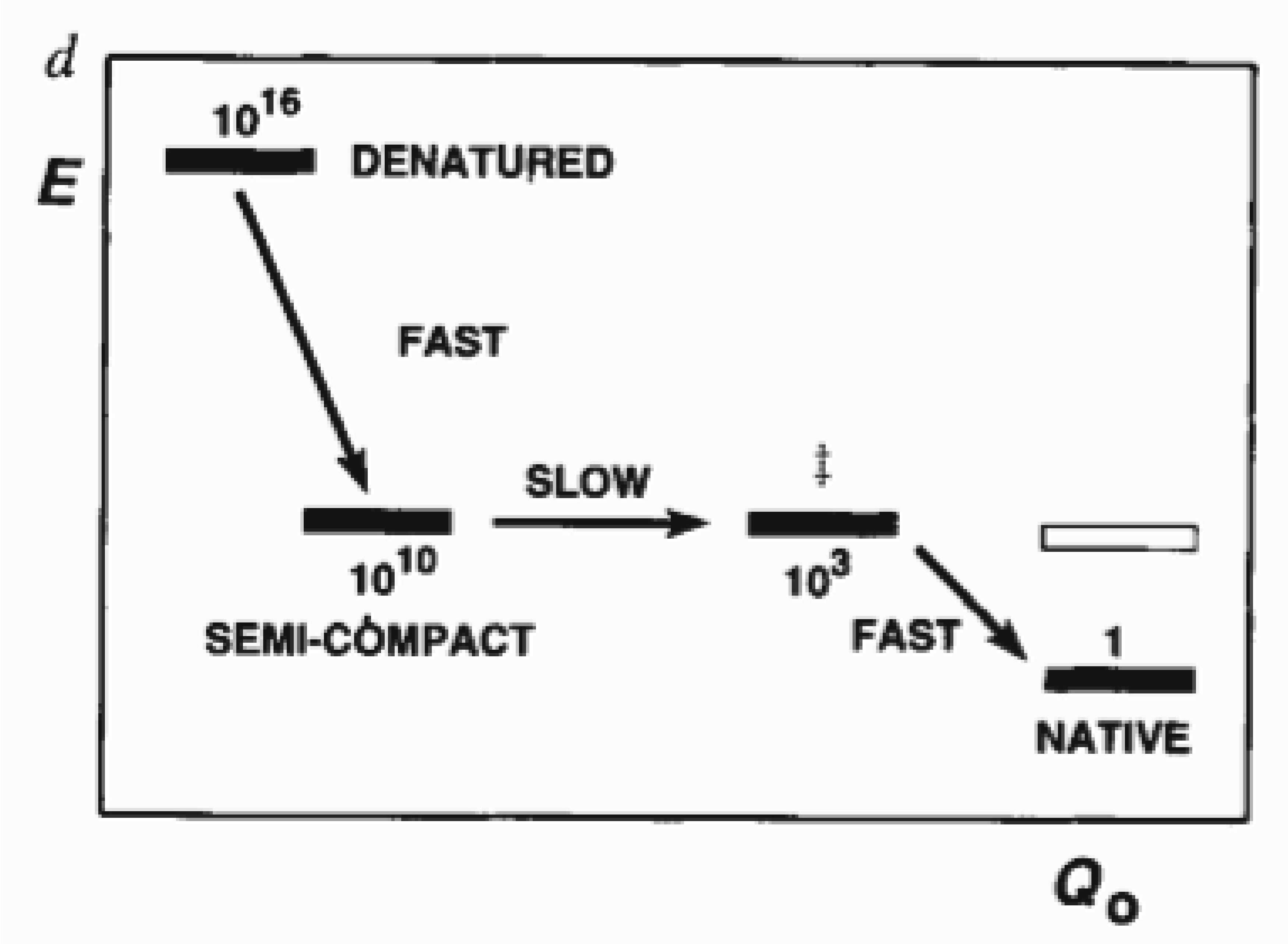
Lecture Outline

Mechanism of Protein Folding

- The textbook lists important papers by Martin Karplus and co-workers
  - Shakhnovich, Farztdinov, Gutin and Karplus, Phys. Rev. Lett. **67**, 1665 (1991) describe a Monte Carlo study of a 27 monomer chain on a simple cubic lattice
  - Šali, Shakhnovich and Karplus, Nature **369**, 248 (1994) describe a folding sequence that resolves the Levinthal paradox
  - The Nature article is based on Šali, Shakhnovich and Karplus J. Mol. Biol. **235**, 1614 (1994)
  - See also How Does a Protein Fold
  - Random coil state of a polymer
  - Molten globule state
  - Native state of a biomolecule

THE number of all possible conformations of a polypeptide chain is too large to be sampled exhaustively. Nevertheless, protein sequences do fold into unique native states in seconds (the Levinthal paradox). To determine how the Levinthal paradox is resolved, we use a lattice Monte Carlo model in which the global minimum (native state) is known. The necessary and sufficient condition for folding in this model is that the native state be a pronounced global minimum on the potential surface. This guarantees thermodynamic stability of the native state at a temperature where the chain does not get trapped in local minima. Folding starts by a rapid collapse from a random-coil state to a random semi-compact globule. It then proceeds by a slow, rate-determining search through the semi-compact states to find a transition state from which the chain folds rapidly to the native state. The elements of the folding mechanism that lead to the resolution of the Levinthal paradox are the reduced number of conformations that need to be searched in the semi-compact globule ($\sim 10^{10}$ versus $\sim 10^{16}$ for the random coil) and the existence of many ($\sim 10^{3}$) transition states. The results have evolutionary implications and suggest principles for the folding of real proteins.

(Abstract of Nature article)



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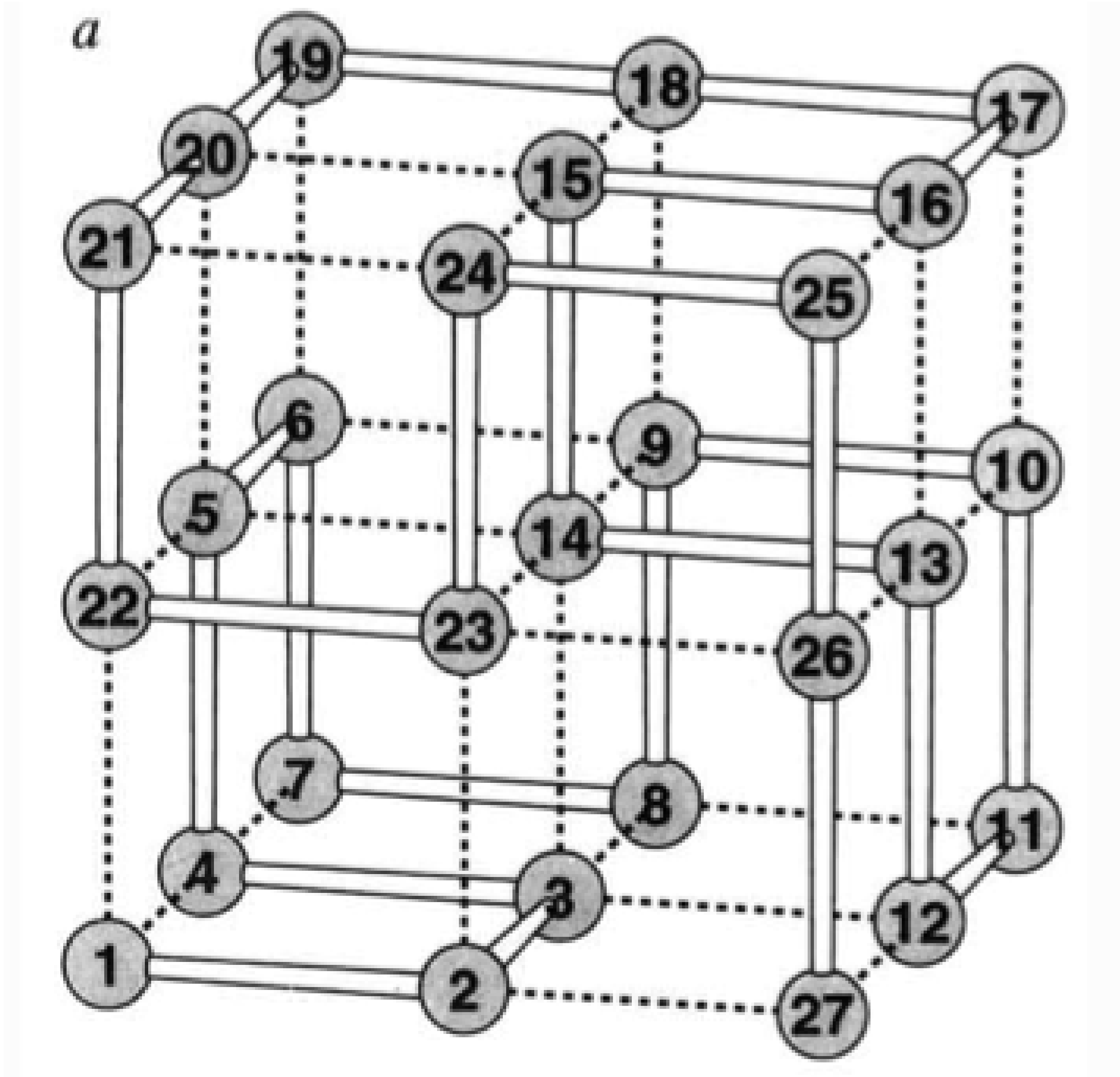


(A native state)

Lattice Monte Carlo Model

- Use chains with $N = 27$ monomers on a cubic lattice
  - ◇ Unbreakable covalent bonds have unit length
  - ◇ Contacts (weaker bonds) between non-bonded monomers separated by unit distance
    - ◦ Terminal monomers have 5 possible contact
    - ◦ Non-terminal monomers have 4
  - ◇ Fully compact self-avoiding chain is a $3 \times 3 \times 3$ cube with 28 contacts
    - ◦ 103,346 such globules unrelated by symmetry, total 4,960,608
- Energy of chain

$$E = \sum_{i<j} B_{ij} \Delta(r_i - r_j)$$

  - ◇ Contact delta function

$$\Delta(r_i - r_j) = \begin{cases} 1 & \text{if } i, j \text{ in contact} \\ 0 & \text{otherwise} \end{cases}$$

- $\diamond$ B_{ij} chosen randomly from a Gaussian distribution

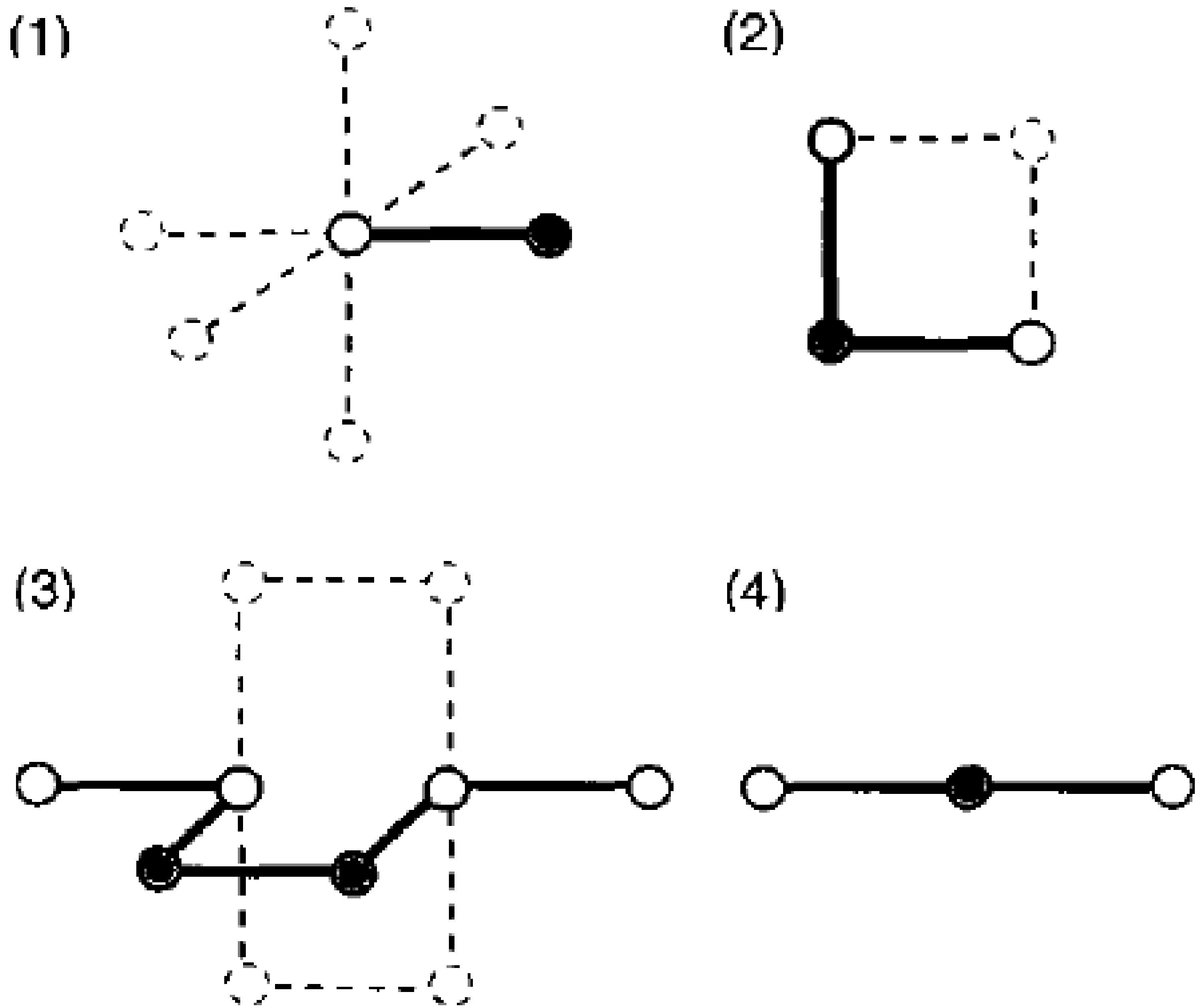
$$P(B_{ij}) = \frac{e^{-(B_{ij}-B_0)^2/(2\sigma_B^2)}}{\sqrt{2\pi\sigma_B^2}}$$

  - $\circ$ $B_0 > 0$ simulates hydrophobicity, causes chain to collapse in solution
  - $\circ$ σ_B simulates heterogeneity (different amino acids)

- Metropolis Monte Carlo algorithm
  - $\diamond$ Start with random self-avoiding congiguration
  - $\diamond$ Make an allowed (self-avoiding, don't break covalent bond) trial move
    - $\circ$ Choose a single monomer at random with 20% probability, or
    - $\circ$ Two covalently bonded monomers with 80% probability
    - $\circ$ See figure for allowed moves
  - $\diamond$ Accept the move if

$$e^{-(E_{\rm trial}-E)/(k_{\rm B}T)} > \rho$$

where $0 < \rho < 1$ is a uniform random deviate ($k_{\rm B}T \approx 1$)



(Allowed moves (1,2) single monomer (3) double "crankshaft")

Folding and non-folding sequences