Molecular Theory of Associative Memory Hamiltonian Models of Protein Folding

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A molecular-level theory of the phase diagram of folding proteins is developed and applied to associative memory Hamiltonian models. Equilibrium collapse, folding, and glass transitions are described with a unified variational treatment, and quantitative estimates of the capacity of recall are found.

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There are two difficulties in determining protein structure from sequence by computer simulation. Correct free-energy functions are riddled with local minima, unrelated structurally to the folded protein. There is also the problem of finding the correct free-energy function. It is reasonable to try to infer an energy function from known examples. Both the local-minima problem and the problem of pattern recognition can be studied using spin-glass theory.[1-5] A concrete realization of these ideas is provided by associative memory Hamiltonians which have been introduced by Friedrichs and Wolynes.[4] These models use the spatial statistics of a database of known structures to determine an energy function. Computer simulation of these models readily shows their qualitative behavior. Deeper analytical understanding can come from mean-field theories. Detailed theories of random heteropolymer collapse and of models with unique folded structures[5] have introduced many important techniques. These studies rely largely on the continuous description of the chain, traditional in polymer physics. Transition temperatures and the mechanism of folding, however, depend on physics at the continuum cutoff, thus making necessary a theory at a molecular level. We discuss here a unified mean-field theory for associative memory Hamiltonians that treats the competing transitions. This theory can be used both for the present models and for other atomistic models of proteins incorporating distance-constraint information.

The simplest associative memory Hamiltonians describe protein tertiary structure by the coordinates of the backbone α carbons $\{\mathbf{r}_i\}$. Sequence information is encoded by charges $\{q_i^T\}$ which are usually related to hydrophobicity, but may encode other properties. The connectivity of the backbone is assured by harmonic-bond-potential terms with spring constants adjusted to give the properties of the unfolded chain correctly. Exactly analogously to the spin-spin interactions introduced in Hopfield neural networks,[6] the interactions between different residues are given by the charge-density correlation function over a database of proteins, giving

$$H=k_BTA\sum_{i=1}^{N-1}(\mathbf{r}_i-\mathbf{r}_{i+1})^2-\sum_{\mu=1}^{M}\sum_{i,j=1}^{N}q_i^\mu q_j^\mu q_i^T q_j^T V(\mathbf{r}_{ij}-\mathbf{r}_{ij}^\mu)\,. \tag{1}$$

The sum is over M database structures, $\{\mathbf{r}_i^\mu\}$ with charges $\{q_i^\mu\}$. We can divide the interaction into the coherent part $\bar{V}$, arising from distance pairs in database proteins matching those of the folded target, and an incoherent part V', from nonmatching distances which we treat as noise. For simplicity now, we take the pairs contributing to the noise as being independent random variables, in distance and in charge. We write

$$\bar{V}(r_{ij},r_{ij}^T)=V(r_{ij}-r_{ij}^T)\left(1+\sum_\mu{}'\,q_i^\mu q_j^\mu q_i^T q_j^T V(r_{ij}-r_{ij}^\mu)\right), \tag{2a}$$

and

$$V'(r_{ij})=\sum_\mu{}'\,q_i^\mu q_j^\mu q_i^T q_j^T V(r_{ij}-r_{ij}^\mu)[1-V(r_{ij}-r_{ij}^T)]\,, \tag{2b}$$

the prime indicating a sum on all memories other than the target. The coordinates of the folded target are $\{\mathbf{r}_i^T\}$.

The noise can be treated statistically and introduces spin-glass transitions. Using replicas,[7] the thermodynamic properties can be inferred from the average of $\ln Z$ over possible databases:

$$[\ln Z]_{\rm av}=\lim_{n\to 0}\frac{1}{n}([Z^n]_{\rm av}-1),\quad [Z^n]_{\rm av}=\int\prod_\alpha^n\prod_i d\mathbf{r}_i^\alpha\left[\prod_\alpha\delta\left(\sum_i\mathbf{r}_i^\alpha\right)\right]\left[\exp\left(-\sum_\alpha^n\frac{H(\mathbf{r}_i^\alpha)}{k_BT}\right)\right]_{\rm av}. \tag{3}$$

For a large number of incoherent memories the noise statistics will be approximately Gaussian. A cumulant expansion of Z^n leads to an effective Hamiltonian coupling different replicas:

$$H_{\rm eff}=k_BT\sum_\alpha^n\sum_i A(\mathbf{r}_i^\alpha-\mathbf{r}_{i+1}^\alpha)^2-\sum_\alpha^n\sum_{i,j}[\bar{V}(r_{ij}^\alpha,r_{ij}^T)]_{\rm av}=\frac{1}{2k_BT}\sum_{\alpha,\beta}^n\sum_{i,j}[V'(r_{ij}^\alpha)V'(r_{ij}^\beta)]_{\rm av}\,. \tag{4}$$

The interaction terms are given by the mean and variance of the interaction potentials.

This effective Hamiltonian has a rich phase structure. There will be an expanded random coil state, a folded state in which the residues are localized near the folded structure, and a liquidlike globule state compact compared to the coil but having little organized three-dimensional structure. Within the collapsed states, there are glass transitions. Just as in crystallization from a melt, the proximity to the glass transition affects the rate of folding.[3]

The mean-field theory, therefore, must contain several order parameters, taken as the radius of gyration of the polymer, the mean-square deviation from the correct folded structure, and an overlap order parameter for the different glassy minima. A reference Hamiltonian is introduced in which the energy terms reflect these order parameters:

$$\frac{H_{\rm ref}}{k_BT}=A\sum_{\alpha}^{n}\sum_{i}(\mathbf{r}_i^{\alpha}-\mathbf{r}_{i+1}^{\alpha})^2+B\sum_{\alpha}^{n}\sum_{i}(\mathbf{r}_i^{\alpha})^2 +C\sum_{\alpha}^{n}\sum_{i}(\mathbf{r}_i^{\alpha}-\mathbf{r}_i^{T})^2+\sum_{\alpha,\beta}^{n}D_{\alpha\beta}\sum_{i}(\mathbf{r}_i^{\alpha}-\mathbf{r}_i^{\beta})^2. \quad (5)$$

The term proportional to C measures the deviation from the folded target and is related to the Debye-Waller factor. B reflects the overall radius of gyration. The replica coupling term determines the overlap of the glassy states. The replica-symmetry breaking of this model resembles the Potts glass;[8,9] thus the matrix $D_{\alpha\beta}$ exhibits one stage of replica-symmetry breaking, having zeros on the diagonal and D for the off-diagonal related replicas. The reference Hamiltonian is equivalent to a set of n/m polymers in which the subunits are m-dimensional hypertetrahedra coupled to the target structure harmonically as in Fig. 1. Mean-field values of C, B, and $D_{\alpha\beta}$ are obtained, using the Peierls variation principle $\delta F=0$, where

$$F=\langle H_{\rm eff}\rangle-\langle H_{\rm ref}\rangle-k_BT\ln Z_{\rm ref}. \quad (6)$$

$\langle\cdots\rangle$ denotes the thermal average with the reference Hamiltonian. Because $H_{\rm ref}$ is harmonic, $Z_{\rm ref}$ and the various expectation values can be calculated and, for any specific choice of potential parameters and database statistics, the variational equations solved numerically. The explicit analytical expression of Eq. (6) will be presented in a subsequent publication. For the sake of simple formulas, we analyze a concrete model of the potential and the database statistics. We choose the pair interactions as Gaussians, $V=(v/N)\exp[-\varepsilon(r_{ij}^{\alpha}-r_{ij}^{T})^2]$, and assume the database contains the target while the pair distribution of residues for nontarget proteins in the database can be approximated as a Gaussian, $g(r_{ij}^{\mu})=2\sqrt{\zeta/\pi}\exp[-\zeta(r_{ij}^{\mu})^2]$. Nontarget proteins have charges equally likely to be positive or negative relative to the target. With these assumptions the majority of the folding energy comes from pairs distant in sequence.

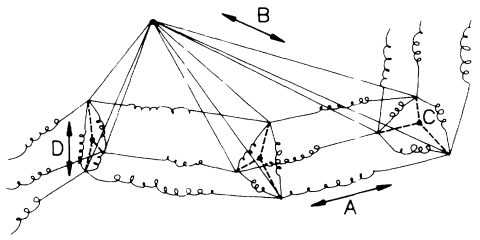

FIG. 1. The interactions in the reference Hamiltonian are those of n/m polymers of m-dimensional hypertetrahedra.

Different limits can be used in the different phases. In the coil and nonglassy globule phases, the parameter B alone determines the radius of the globule. Since $A\gg B\gg C\approx D$ in these phases, we can write the energy in terms of the globule radius R which depends on B/A. The resulting free energy yields a first-order collapse transition from the random coil state with $R=N^{1/2}$ to the molten globule state with $R=\zeta^{-1}$ at a temperature $k_BT_{CG}\approx M^{1/2}N^{-1/3}v$.

First-order folding transitions can occur directly from the coil state or from the molten globule. In the folded phase, C will generally be larger than A. Retaining only the lowest-order terms in A/C, the variational equation for C is

$$\frac{\delta}{\delta C}\left[\frac{3}{2}nk_BTN\ln\left(\frac{C}{A}\right)-\frac{n}{2}Nv\left(\frac{C}{2\varepsilon+C}\right)^{1/2}-\frac{n(n-1)}{4\sqrt{2k_BT}}MN^{-1/3}v^2\left(\frac{C}{2\varepsilon+C}\right)^{1/2}\right]=0. \quad (7)$$

The limit of stability of the folded phase is given by $C\geq(\varepsilon/A)A$. This is like the Lindemann criterion for melting. The equilibrium transition temperature from the globule is found, however, by equating the free energies of the molten globule and the folded phase with nonzero C. This results in a reentrant phase transition with an upper and a lower folding temperature which depend on the number of memories:

$$k_BT_F^{+}\cong\frac{v}{\ln(C/A)}-MN^{-4/3}v,\quad k_BT_F^{-}\cong MN^{-4/3}v. \quad (8)$$

Notice that if the number of memories M exceeds roughly $N^{4/3}/\ln(C/A)$, the folding transition disappears. This indicates one limit on the capacity of the associative memory models for uncorrelated memories. This capacity is larger than that found in simulations. It is interesting that these models exhibit cold denaturation, which has been observed in real proteins.[10] There it is thought to be an effect coming from the temperature dependence of hydrophobic interactions. The lower transition can be preempted by a glass transition. When the number of memories is small, the folding proceeds directly from the

coil with a transition temperature depending on Hamiltonian parameters much as T_F^+.

Both the globule state and the folded state have ideal glass transitions at low temperature. The difficulty of the search problem in folding is maximal at the globule glass transition. In the random-energy approximation,[3] essentially all configurations must be searched at T_G. One expects slowing down to occur as T_G is approached for these models too. To find T_G the limit $n \to 0$ must be taken with m taking the noninteger value x; $0 \le x \le 1$. Because there is only one level of replica-symmetry breaking, the glass state is characterized by two parameters: xD, measuring the Debye-Waller factor of related glassy states, and x itself, describing the size of the clusters of related states. x measures the configurational complexity below the phase transition.[8,9] The variational equation for xD is similar to that for C,

$$\frac{\delta}{\delta xD}\left\{\frac{3}{2}nk_BTN\frac{x-1}{x}\left[\ln\left(\frac{2xD}{A}\right)-\left(\frac{xD}{2A+xD}\right)^{1/2}\right]-\frac{n(x-1)}{4k_BT}MN^{-1/3}v^2\left(\frac{xD}{\varepsilon+xD}\right)^{1/2}\right\}=0, \tag{9}$$

given a Lindemann stability criterion for xD, $xD \ge (\varepsilon/A)A$.

The variational equation for x describes when obligate thermodynamic freezing must occur. The ideal thermodynamic glass transition occurs at

$$k_BT_G \cong \frac{M^{1/2}N^{-2/3}v}{\sqrt{\ln(xD/A)}}. \tag{10}$$

We see that the glass transition temperature increases with the number of memories and, indeed, since xD is roughly the same as C, the glass transition temperature is of the order of the folding temperature when M reaches a value close to the capacity that we had already determined from the reentrant phase transition.

In addition to the thermodynamic glass transition, Potts glasses exhibit a dynamical transition in the mean-field limit, wherein individual glassy states acquire thermodynamically large barriers between them. In the viscous liquids, this corresponds to the onset of activated motions, agreeing with the approximate mode-coupling theories.[9] Following the Potts-glass analogy, one evaluates the temperature at which this occurs, k_BT_A, by requiring the variational equation for xD to be satisfied, extracting only the terms in the free energy proportional to $x-1$. This gives $k_BT_A \cong M^{1/2}N^{-1/3}v$. For these long-range models, activation barriers to rearrangement arise soon after a globule is formed. Although the barriers in this regime grow with the size of the protein, they do so slowly.[11] For a protein of size 100, these barriers may only be of order $10k_BT$ and can be overcome by reasonably long annealing runs. Dynamics in the globular regime might be treated more effectively with global Monte Carlo moves rather than local ones.

In summary, a rough phase diagram for the associative memory models can be obtained as in Fig. 2. More precise phase diagrams are needed to carry out the optimization of parameters in associative memory Hamiltonians. The engineering goal of the computational protein folder is to obtain energy functions that easily reach the global minimum. As in crystal nucleation from a melt, the rate of nucleation reaches a maximum between T_F^+ and T_G. The accurate variational expressions for T_F^+ and T_G for different encodings of the protein sequence (choice of charges) will allow a route to an optimal folding code. The further consideration of correlated databases, requiring only a rather straightforward modification of the energy expression Eq. (6), will be necessary, however.

The ideas used here to describe protein glass and folding transitions in associative memory models can be extended. The accuracy of structures determined from experimental distance constraints can be assessed with the present formalism. More elaborate molecular Hamiltonians, including excluded volume, can be studied using effective harmonic reference systems.[12] The replica techniques and treatment of the statistics of misfolded minima may be used in concert with computer simulations to see what features of the sequence are used by nature to avoid glass transitions and lead to efficient folding mechanisms.

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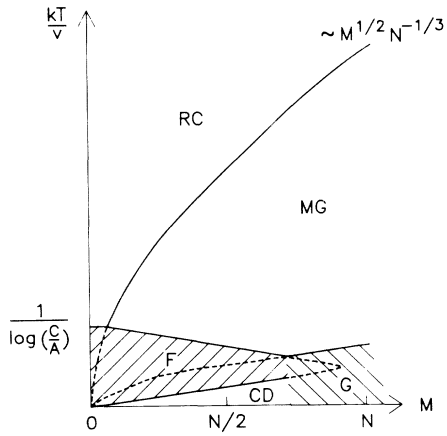

FIG. 2. The phase diagram as a function of temperature and number of uncorrelated memories. The phase RC is random coil, MG the molten globule, F the folded state, G the ideal glass state, and CD the cold denatured phase. The diagram assumes $N=100$, $\varepsilon/A=4$, and $C/2A=D/A=2$. The transition lines occur at $k_BT_{RC\text{-}F}=0.12v$, $k_BT^+_{MG\text{-}F}=0.12v-0.00065Mv$, $k_BT^-_{MG\text{-}F}=0.00065Mv$, and $k_BT_G=0.009\times M^{1/2}v$.

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