Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 7524–7528, November 1987
Biophysics

Spin glasses and the statistical mechanics of protein folding

(disordered systems/irreversible denaturation/molten-globule state/biomolecular self-assembly)

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Communicated by Hans Frauenfelder, June 15, 1987 (received for review March 13, 1987)

ABSTRACT **The theory of spin glasses was used to study a simple model of protein folding. The phase diagram of the model was calculated, and the results of dynamics calculations are briefly reported. The relation of these results to folding experiments, the relation of these hypotheses to previous protein folding theories, and the implication of these hypotheses for protein folding prediction schemes are discussed.**

The mechanism of globular-protein folding remains a central problem of molecular biology (1). Folding is the final stage in the translation of genetic information to a working protein and is one of the simplest examples of biological self-organization. A complete understanding of protein folding should lead to a scheme for predicting three-dimensional protein structure from one-dimensional sequence information, which would have important applications in biotechnology. Even falling short of a complete theory, there are many puzzling features of the kinetics and thermodynamics of protein folding that require qualitative explanation. In this paper we hope to highlight these features and to explain how some hypotheses drawn from the theory of spin glasses can illuminate some features of protein folding in a very simplified model.

Physicochemical studies of protein folding have a long history (1–5). Despite these studies, a unified account of the dynamics of the process has failed to arise. Thermodynamically near physiological conditions the smaller proteins often exhibit all-or-none behavior, going discontinuously from the unfolded phase to the folded phase. This is reminiscent of a phase transition in a finite system (5). In larger proteins, deviations from this behavior have been ascribed to the domain structure of proteins. Farther away from physiological conditions more complex behavior has been observed, suggesting that a third "misfolded" or "collapsed" phase for protein molecules exists.

The kinetic behavior of protein folding is more complicated than the thermodynamic behavior. Generally multiexponential kinetics is observed and in some cases discrete intermediates inferred (6). The range of time scale is puzzling. Refolding of denatured protein into a biologically active form takes 1 msec to 100 sec or longer. This period of time may be viewed in two different ways. On one hand the time is much too short for an exhaustive random search for the minimum free-energy structure; on the other hand it is clearly much longer than a simple "downhill run" to the minimum free-energy structure. Nucleation models suggested by the all-or-none character of the thermodynamics also do not fit the kinetics.

In the absence of microscopic models the solution of the time-scale problem has been attributed to the existence of "folding pathways." The relative slowness of folding is ascribed to the existence of many local minima of the free energy (7).

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We should also bear in mind that the *in vivo* studies of folding may give a biased view of the biological process. Robust, easily foldable proteins are the easiest to study. *In vivo*, some proteins may fold sequentially following their synthesis on the ribosome, so that the search for a thermodynamic equilibrium may be too slow to be relevant. Occasionally irreversible denaturation that is not ascribable to aggregation is observed (2). In addition the speculative concept of "protein drift" has been introduced to explain aging of proteins (8–11) and to explain unusual cooperativity observed in some cases of oligomer association (12). Time dependent free energies of folding were postulated by Xu and Weber (12) to analyze this cooperativity.

Many of the issues raised in the preceding paragraphs are similar to issues in the statistical mechanics of glasses and glass transitions. For example we often think of crystalline, liquid, and glassy states of simple material. Clearly in the glassy state many different free-energy minima can coexist and interconvert. The properties of glasses can be dependent on the history of their preparation, and in the glassy state very slow aging processes occur.

The relevance of the application of theories from glass physics to the dynamics of completely folded proteins has already been discussed (13, 14). These dynamics involve the motion of residues over small distances on the order of 0.1 to 1.0 Å. Folding dynamics occur on a larger length scale from a few to tens of angstroms. Thus a rather "coarse-grained" Hamiltonian should suffice to describe the overall features of folding. Some coarse-grained descriptions are familiar in the Ising model descriptions of the various secondary structure transitions such as the helix–coil transition in polymers (15). We use a similar description here. In folding, however, the establishment of tertiary structure requires interaction of residues that are distantly separated along the sequence. In addition, the heterogeneity of the amino acid sequence implies a complicated form for the coarse-grained Hamiltonian. Despite this complexity a low-energy structure in which secondary and tertiary structural features are all in harmony exists. We will argue here that these features of the interactions can be captured by a many-state spin glass model with random and ferromagnetic interactions, and we will use a random-energy approximation to calculate the equilibrium properties of our model.

We will also briefly comment on folding dynamics, particularly on the existence of intermediates. To conclude we discuss our results in relation to the experimental results and to other theories of protein folding, such as the nucleation and diffusion–collision models. We also comment on the relationship of our model and of spin glass theories in general to protein-folding prediction schemes.

THE MODEL AND ITS PROPERTIES

Protein folds may be represented by specifying the three-dimensional conformation of the polypeptide backbone (16–18), and the backbone is usually described by listing two dihedral angles per amino acid residue. Some careful exper-

imental work by Brandts (19) has shown that the entropy loss of the chain from folding is about 5.1 cal/mol·K residue* (1 cal = 4.184 J); so, if we consider the folded structure to be a single state, then the unfolded protein has ≈10 states available to each residue. These results suggest a coarse-grained model where the gross protein conformation is described by listing the discrete conformational state of every amino acid in the chain with every amino acid having one native conformation and ν other conformations (ν is on the order of 10).

The examination of successfully folded proteins leads to an important general feature of a model Hamiltonian to describe folding. The folded structure is very compact, and the secondary and tertiary structures are not in conflict. Super secondary structures accommodate both local hydrogen bonding and packing requirements. If it were not for this relative lack of frustration in final, folded structures, secondary-structure prediction schemes would fail spectacularly. This feature was used extensively by Gō in his models of folding (5), and we make use of it also. We call it the principle of minimal frustration. There are several kinds of interactions in protein folding. First, there is an energy associated with the state of each amino acid residue that we call $-\varepsilon_i(\alpha_i)$, where i refers to the amino acid under consideration and α_i refers to the state of the ith amino acid. Second, there are interactions along the chain, e.g., hydrogen bonding in α-helices. We will use the standard approximation of taking this interaction to be between nearest-neighbor residues (15), so we may write the energy of each bond of this type as $-J_{i,i+1}(\alpha_i, \alpha_{i+1})$. Finally, there are the long-range interactions, i.e., interaction between residues that are far apart along the chain. These occur when bends in the chain bring two amino acids close together, e.g., by hydrophobic forces. We will write their energies $-K_{i,j}(\alpha_i, \alpha_j, r_i, r_j)$, where r_i is the position of the ith residue.

We may write the energy of the protein as

$$E = -\sum_i \varepsilon_i(\alpha_i) - \sum_i J_{i,i+1}(\alpha_i, \alpha_{i+1}) - \sum_{i,j} K_{i,j}(\alpha_i, \alpha_j, r_i, r_j). \quad [1]$$

Naively, we may view the $\varepsilon_i(\alpha_i)$ as being related to the primary structure, the $J_{i,i+1}(\alpha_i, \alpha_{i+1})$ as being responsible for the secondary structure, and the $K_{i,j}(\alpha_i, \alpha_j, r_i, r_j)$ as being responsible for the tertiary structure. We will label the (ν + 1) discrete states of each residue with the integers 0 through ν. We will always label the properly folded, native state of a residue with zero. We call the interaction between two native-state residues a native interaction. All other two-residue interactions are called nonnative.

Suppose that we are given a molecule of a particular protein with N amino acids that is in a specific conformation with N_0 amino acids in their native state. The energy of this molecule is given by Eq. 1, an exceedingly complex function of $\{\alpha_i\}$ and $\{r_i\}$. The traditional application of statistical mechanics to an ensemble of these conformations results in a relatively intractable problem. We will make progress with an indirect method. Our strategy is to replace a complex Hamiltonian with a stochastic one that has the same statistical characteristics, i.e., we study the distribution of energies associated with different microstates. This idea is reminiscent of Wigner's use of random matrices to describe the highly excited states of heavy nuclei (20). We will take the energy of the protein molecule to be a random variable assigned from a distribution $P(E, N_0)$, whose statistical properties have some of the same characteristics as the distribution of energy levels that arises from the Hamiltonian in Eq. 1. Random energy levels have been used by Derrida (21, 22) to study spin glasses, and our work uses many of his results. A spin glass is a magnetic system where ferromagnetic and antiferromagnetic bonds are randomly distributed (23–25). The connection between Derrida's work and more traditional methods of statistical mechanics has been discussed in the context of spin glasses by Gross and Mézard (26). Our model differs from conventional solid-state spin glasses where disorder is fixed on a lattice, because in our case the complex sequence is free to move in space. We will assume that the energies of different protein conformations are uncorrelated. Mathematically this means that the joint probability distribution for n configurations with N_0 native residues and energies $E_1, E_2, \ldots, E_n$ is given by $P(E_1, E_2, \ldots, E_n, N_0) = \Pi_{i=1}^{n} P(E_i, N_0)$. This assumption is an approximation, and Derrida has shown (21, 22) that it reproduces the phase diagram of an infinite-range spin glass with qualitative accuracy. We call this approximation the random-energy approximation. The random-energy approximation is clearly reasonable for protein folding because changing a single amino acid state will bring very different parts of the chain together. This approximation may be systematically improved by taking account of pair correlations, triplet correlations, etc., among the energies. Derrida and Gardner (27, 28) have already shown how the approximation may be extended to include pair correlations. Now we return to our protein molecule and use Eq. 1 to estimate the probability that it has energy E. First, we consider the tertiary structure terms, i.e., the $\{K_{i,j}\}$. The forces responsible for these interactions are fairly short ranged, so we will assume that they are significant only for residues that adjoin each other in space. Typically each residue will be neighbored by z other residues that are distant from it along the sequence. The parameter z will vary slightly with the degree of folding, and we will take z to be on the order of 2 or 3, which is between the value of z we expect in the completely unfolded and the completely folded states. The nonnative interactions of these adjoining residues will have a distribution of energies with mean $-\bar{K}$ and standard deviation ΔK. The native interactions must satisfy the principle of minimal frustration, and the simplest way to ensure this is to set all native tertiary interaction energies equal to $-K$ where $K > \bar{K}$. Similarly we take the nonnative secondary-structure interaction energies to be distributed with the mean $-\bar{J}$ and the standard deviation ΔJ, all native secondary-structure interaction energies to equal $-J$, nonnative primary-structure energies to be distributed with the mean $-\bar{\varepsilon}$ and the standard deviation $\Delta\varepsilon$, and all native primary-structure energies to equal $-\bar{\varepsilon}_0$, where $J > \bar{J}$ and $\varepsilon_0 > \bar{\varepsilon}$. Finally we will assume that the native and nonnative residues are distributed randomly throughout the protein. This is equivalent to the mean-field approximation that has been successfully used to describe the behavior of numerous many-particle systems (29, 30), e.g., the Flory theory of polymer solutions (31). Now the stochastic incarnation of the Hamiltonian of Eq. 1 is a sum of random variables with known probability distributions so $P(E,N_0)$ is a Gaussian with the mean

$$\bar{E}(N_0) = -N_0\varepsilon_0 - \left(\frac{N_0^2}{N}\right)L - (N - N_0)\bar{\varepsilon} - \left(N - \frac{N_0^2}{N}\right)\bar{L}, \quad [2]$$

where $L = J + zK$, $\bar{L} = \bar{J} + z\bar{K}$, and the standard deviation

$$\Delta E(N_0) = \left[(N - N_0)\Delta\varepsilon^2 + \left(N - \frac{N_0^2}{N}\right)\Delta L^2\right]^{1/2}, \quad [3]$$

where $\Delta L^2 = \Delta J^2 + z\Delta K^2$.

*The quoted entropy takes into account only the entropy loss of the degrees of freedom of the chain and applies only to residues that go from an unfolded to a folded state.

Now we study $n(E)$, the density of energy levels. Each specific protein has its own $n(E)$ function. Summing over all values of N_0, we obtain the average $\langle n(E)\rangle$.

$$\langle n(E)\rangle = \sum_{N_0=0}^{N} C(N_0)[2\pi\Delta E(N_0)^2]^{-1/2} \times \exp\left\{-\frac{[E-\bar{E}(N_0)]^2}{2\Delta E(N_0)^2}\right\}, \quad [4]$$

where

$$C(N_0) \equiv \frac{N!}{N_0!(N-N_0)!}\,\nu^{N-N_0} \quad [5]$$

is the number of protein states with N_0 residues in their native state. In the thermodynamic limit ($N \to \infty$) the behavior of this sum may be obtained by looking at the largest term. We find

$$\log\langle n(E)\rangle = N \max_{0<\rho<1}\left\{-\rho\log\rho - (1-\rho)\log(1-\rho)\log\left(\frac{1-\rho}{\nu}\right) - \frac{[\varepsilon+\bar{\varepsilon}+\bar{L}+(\varepsilon_0-\bar{\varepsilon})\rho+(L-\bar{L})\rho^2]^2}{2[\Delta\varepsilon^2+\Delta L^2-\Delta\varepsilon^2\rho-\Delta L^2\rho^2]}\right\} \equiv \max_{0<\rho<1} S(E,\rho), \quad [6]$$

where ε is the energy per residue, $\rho = N_0/N$, S is given a physical interpretation below, and we are ignoring terms of order $\log N$. The statistical independence of energy levels implies that the fluctuations of $n(E)$ about $\langle n(E)\rangle$ are of order $\langle n(E)\rangle^{1/2}$, so if $\langle n(E)\rangle$ is large, then

$$\log n(E) \approx \log\langle n(E)\rangle. \quad [7]$$

Our system has two critical energies, a very low energy, E_1, and a very high energy, E_2. If $E_1 < E < E_2$, then $(1/N)\log\langle n(E)\rangle$ is positive, so the average number of microstates with energy E is very large, and Eq. 7 is valid. If $E < E_1$ or $E > E_2$ then $(1/N)\log\langle n(E)\rangle$ is negative so the average number of microstates with energy E is $<<1$. Eq. 7 is not valid in this regime. In the thermodynamic limit the equilibrium entropy of the chain as a function of its energy is the maximum value of $S(E,\rho)$ for $E_1 < E < E_2$, and there are simply no microstates for $E < E_1$ and $E > E_2$. For a system with fixed energy, the equilibrium state of the system is the state that maximizes the entropy (32), so we may interpret $S(E,\rho)$ in the entropy of the chain for general E and ρ. [As long as $(1/N)\log\langle n(E)\rangle$ is positive.] However, for most purposes it is much easier to work with fixed temperature. Therefore, we will calculate the Helmholtz free energy as a function of temperature (T) and ρ, and then minimizing the free energy for fixed T will have the same physical content as maximizing $S(E,\rho)$. First, we use the well-known relation $1/T = \partial S/\partial E$ with Eq. 6 to obtain the energy per residue as a function of temperature,

$$\varepsilon = -(\bar{\varepsilon}+\bar{L}) - \frac{(\Delta\varepsilon^2+\Delta L^2)}{T} - \left(\varepsilon_0 - \bar{\varepsilon} - \frac{\Delta\varepsilon^2}{T}\right)\rho - \left(L - \bar{L} - \frac{\Delta L^2}{T}\right)\rho^2. \quad [8]$$

Next, by substituting Eq. 8 into Eq. 6, we obtain the entropy per residue s as a function of temperature,

$$s = -\rho\log\rho - (1-\rho)\log\left(\frac{1-\rho}{\nu}\right) - \frac{\Delta\varepsilon^2+\Delta L^2-\Delta\varepsilon^2\rho-\Delta L^2\rho^2}{2T^2}. \quad [9]$$

Finally, the free energy per residue f is

$$f = -\bar{\varepsilon} - \bar{L} - \frac{\Delta\varepsilon^2+\Delta L^2}{2T} - \left(\varepsilon - \bar{\varepsilon} - \frac{\Delta\varepsilon^2}{2T}\right)\rho - \left(L - \bar{L} - \frac{\Delta L^2}{2T}\right)\rho^2 + T\rho\log\rho + T(1-\rho)\log\left(\frac{1-\rho}{\nu}\right). \quad [10]$$

For high temperatures the entropy per residue is approximately $\log(1+\nu)$. As the temperature is lowered the entropy decreases until a critical temperature given by

$$T_0 = \left\{\frac{\Delta\varepsilon^2+\Delta L^2-\Delta\varepsilon^2\rho-\Delta L^2\rho^2}{2\left[-\rho\log\rho-(1-\rho)\log\left(\frac{1-\rho}{\nu}\right)\right]}\right\}^{1/2} \quad [11]$$

is reached. Below this temperature the entropy of the chain is zero, because it is trapped in one of its low-energy states (21, 22, 26). We will call this low-temperature phase the "frozen phase." Further lowering of the temperature does not change the properties of the chain, because it remains frozen in one microstate. This sudden freezing is a property of the random-energy approximation. Taking pair correlations of the energy levels into account leads to a more gradual freezing (27, 28). The physical nature of the frozen phase has been made clear by Gross and Mézard (26), who studied a spin system that could be solved exactly with the random-energy approximation. The main conclusions of their study are known to be valid for many disordered systems. They found that for $T < T_0$ the system freezes into one of its many free-energy valleys so that the frozen phase is a kind of glass. In the context of our paper this means that if we consider a solution of many identical protein chains, then in the frozen state each chain has a definite (nonnative) conformation, but not all of these conformations are the same.

Our model has three kinds of phases. There is a disordered phase where any conformation may be found in a solution of many protein molecules. There is an ordered phase where all protein molecules tend to be in the native, folded state. Finally there are glassy phases where the protein molecules tend to be in a few nonnative states. We show a typical slice of the phase diagram in Fig. 1.

The energies responsible for protein folding are on the order of T per residue, so we expect the energy parameters in Eq. 10 to be about the same order of magnitude. A free energy function with reasonable characteristics is obtained with these values, e.g., $(\varepsilon_0 - \bar{\varepsilon} - \Delta\varepsilon^2/2T) = -0.2T$, and $(L - \bar{L} - \Delta L^2/2T) = 2.6T$. The folded phase is favored by $\approx 0.07T$ per residue and $\approx 75\%$ of the residues participate in folding. This is in harmony with experimental work (19).

We briefly report the results of some simple calculations on the dynamics of our model. We will present the details elsewhere. We used an activated dynamics, where the protein changes state by changing one amino acid at a time. We did not restrict the state-to-state changes in energy because changing a single amino acid changes the energy of a protein molecule by a large amount. We found that the number of metastable states of a protein molecule goes as

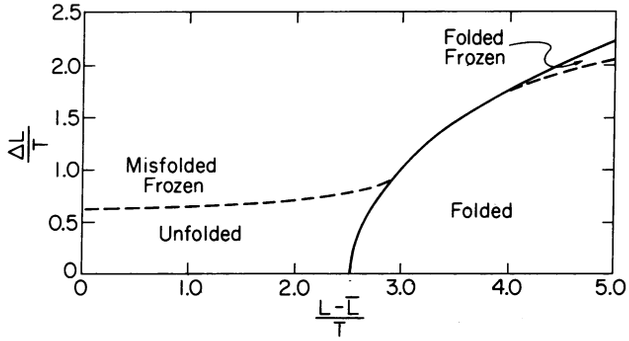

FIG. 1. The calculated phase diagram of our model for $\varepsilon_0 - \bar{\varepsilon} = \Delta\varepsilon = 2.18T$. There are four phases: unfolded; correctly folded; folded frozen, a frozen phase in which the native structure is favored; and misfolded frozen, a frozen phase in which the native structure is not favored. First-order phase boundaries are indicated by solid lines, and second-order phase boundaries are indicated by dashed lines.

$\exp(\alpha N)/N$ where α is on the order of 1. The deeper of these minima would appear as kinetic intermediates in protein folding experiments. We also found that the distribution of rates for escaping the metastable states is approximately log-normal for high temperatures and becomes very flat and broad for temperatures $<T_0$.

DISCUSSION

The spin-glass paradigm offers a picture for reconciling cooperativity and diversity in protein folding. In this section we discuss the current simplified form of the model, the connection of this picture with some of the previous work on folding and discuss prospects for the future.

The principle of minimal frustration used in the model leads to a first-order-like transition from native to random-coil states. In a finite-size protein, this type of transition is rounded out into an all-or-none chemical equilibrium (5). The innovative feature resulting from the model is the frozen phase. This phase has slow dynamics and is characterized by a multitude of misfolded states. The frozen phase may play a role in the irreversible denaturation of some proteins, e.g., elastase (2). There is also some evidence for a similar phase when proteins are put in very unnatural conditions of pH, temperature, etc. Dolgikh *et al.* (33) have observed a compact, "molten-globule" state in α-lactalbumin at acid pH, as have Ohgushi and Wada (34) in cytochrome *c*.

Although the globule state is not completely frozen (as in the simplest random-energy model), in some cases long-lived secondary structural features are found, and proton-exchange kinetics is slower than in the random coil. The microcalorimetry studies of Dolgikh *et al.* (33) indicate a more continuous transition than from native structure to random coil. This is in harmony with the present identification with the spin glass where the transition should have no latent heat. Of course it will be interesting to compare this picture with the hypothesis that the phase is like polymer collapse of a homopolymer.

More broadly the model can say something about the connection between nucleation (35, 36) and diffusion–collision models (37, 38) of folding. The free-energy surface in terms of the fraction of native residues has a double-well structure, since the random coil is entropically favored and the native structure is energetically favored through the minimal frustration aspect of the model. Nucleation kinetics follows if we consider only diffusion on this one-dimensional surface. The spin-glass aspect of the model suggests, however, that the distribution of life times involving nonnative structures can be quite broad thus leading to a picture more like diffusion–collision models.

Finally the spin-glass perspective may have relevance to protein-folding prediction. Even when such schemes do not try to imitate the physical process of folding, they often involve the optimization of a fitness function combining rules for both secondary and tertiary structure (39). If the appropriate weighting of these rules or if the minimal-frustration aspect is neglected, the fitness function will have a structure much like the energy function of spin glasses. Thus locally guided search for extrema would exhibit the range of slow dynamics possible in the spin-glass model (40). Exploitation of the phase diagram of the spin-glass model may lead to ways around the bottlenecks of such schemes.

We enjoyed helpful discussions with Hans Frauenfelder, Yaotain Fu, John Morgan, Gregorio Weber, and Jonathan Widom. We thank Pierre-Gilles de Gennes for an enlightening comment on an early version of this paper. This work was supported by Grant 83-16981 from the National Science Foundation Department of Materials Research.

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