

## Relaxation in a perfect funnel

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We have exactly solved the relaxational dynamics of a model protein that possesses a kinetically perfect funnel-like energy landscape. We find that the dependence of the relaxation time  $\tau$  on the density of states (DOS) and the energy level spacing distributions of the model displays several main types of behavior depending on the temperature  $T$ . This allows us to identify possible generic features of the relaxation. For some ranges of  $T$ ,  $\tau$  is insensitive to the density of states; for intermediate values of  $T$  it depends on the energy level spacing distribution rather than on the DOS directly, and it becomes gradually more dependent on DOS with increasing temperature; finally, the relaxation can also be determined exclusively by the presence of a deep gap in the energy spectrum rather than by the detailed features of the density of states. We found that the behavior of  $\tau$  crucially depends on the degeneracy of the energy spectrum. For the special case of exponentially increasing degeneracy, we were able to identify a characteristic temperature that roughly separates the relaxational regimes controlled by energetics and by entropy, respectively. Finally, the validity of our theory is discussed when roughness of energy landscape is added. [S1063-651X(97)04804-6]

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### I. INTRODUCTION

It is well known that natural proteins fold into their native structures remarkably quickly in times on the order of 1 s in spite of the enormous number of possible physical configurations [1]. On the other hand, it is also clear that heteropolymers with completely random monomer-monomer interactions usually do not fold on a reasonable time scale [2]. One explanation put forward to resolve this discrepancy is that protein sequences are “optimized” such that not only is there a stable unique structure for the ground state [3], but there is also a funnel-like energy landscape that leads to efficient folding kinetics [4–6]. A principle of minimal frustration was proposed [8] to enforce a selection of the interactions between monomers such that as few energetic conflicts occur as possible. Among other things, considerable theoretical effort has concentrated on finding proper models for protein folding and investigating various sequencings that lead to fast folding kinetics. Due to the immense complexity of the problem, much of our understanding and intuition has been obtained from a variety of computer simulations based on lattice models [9–11].

In this paper we concentrate on the folding scenario involving a funnel-like energy landscape [4–6] where the funnel “guides” the protein into the low energy native structure. Along the pathway, the protein is believed to go through several distinct states including the molten globule state, a folding transition region, and a glass transition region. Even though the funnel landscape possesses a certain amount of roughness, which slows the folding kinetics, the folding process is largely speaking guided by the global funnel structure and the protein can in this way rapidly find its native state. Although there is no clear experimental evidence of the existence of this folding scenario, it is nevertheless theoretically interesting and has attracted much attention in the literature. In general, the folding kinetics for funnel-like energy landscapes is very complicated and analytical studies have proved to be quite difficult. In this regard, an

interesting study is due to Zwanzig [7] where some of the general properties of the folding kinetics were examined using an extremely simple model.

Even though there are many folding models for specific proteins, we believe that it is intuitively useful to investigate the generic behavior of the folding kinetics. This, in some sense, is similar to finding universality classes in critical phenomena. The purpose of this paper is to report our studies in this direction. In particular we examine a simple statistical mechanical model that mimics all the basic properties of a perfect funnel-like landscape in the absence of roughness. We also discuss the validity of our results for the case of involving a small amount of roughness (see below). The landscape itself consists of a set of energy levels forming a quasicontinuous spectrum with a single level lying far below this spectrum. All the levels represent conformational energies of the protein with the lowest level representing the native state. This model is quite general and is not exclusive to proteins. It could, for example, represent certain classes of polymers.

There are many interesting questions concerning protein folding kinetics that we would like to answer from an analysis of our model. For instance, for a protein sequence that folds rapidly to its native state, what is the role played by the energy spectrum along the folding pathway? What is the role of energy level spacing statistics on the folding kinetics? How does the relaxation process of our system depend on parameters such as temperature? These are interesting and difficult general questions that are relevant to the folding kinetics, since the protein passes through the energy spectrum during the folding process. An analytical answer to these questions for a general protein problem has so far not been possible. However, as we show below for our model, which is a generalization of that studied in Ref. [7], analytical solutions can be found when the funnel structure has no roughness and reasonable approximations could be made to find an answer when small roughness is included. Our perspective is that exact solutions are valuable since they can be

used as a starting point for further more complicated models, similar to our experiences in critical phenomena and phase transitions.

To this purpose, we have derived analytical expressions for our model (see below) that show that the energy spectrum and the energy spacing statistics can play an important role in folding kinetics. In particular the dependence of the folding time  $\tau$  on the energy level distribution of the various models can be classified into three main types of behavior depending on the temperature  $T$ . For a considerable range of  $T$ ,  $\tau$  is insensitive to the level distribution; for intermediate values of  $T$  it depends directly on the distribution and becomes gradually more model dependent; finally, in the third case the folding kinetics is determined exclusively by the presence of the deep gap in the energy spectrum rather than by the details of the energy level distribution. We found that the behavior of  $\tau$  crucially depends on the degeneracy of the energy spectrum. For the special case of exponentially increasing degeneracy, we were able to identify a characteristic temperature that roughly separates the relaxational regimes controlled by energetics and by entropy, respectively. Our general formula for this simple model is consistent with existing literature in the appropriate limits and we present numerical solutions to confirm the physical picture indicated by our analytical results.

This paper is organized in the following manner. A general expression for the relaxation time is derived in Sec. II. Sections III and IV presents results for the applications of this expression. Finally a short summary is presented in Sec. V.

## II. RELAXATION KINETICS

By analogy with Ref. [7], we focus on a perfect funnel-like energy landscape defined by an abstract ‘‘reaction coordinate’’  $X$ . For example,  $X$  could represent a specific protein structure that has energy  $E(X)$ . We emphasize again that whether or not a real protein possesses funnel-like energy landscape is unclear, but we shall examine the consequences of this landscape. A perfect funnel with no roughness is schematically shown in Fig. 1. Clearly this is a considerable simplification of the problem, but it allows us to investigate the relaxational kinetics completely analytically. As discussed below, other features can be systematically added on later, such as a small amount of roughness.

Thus, as the system relaxes or the ‘‘protein’’ folds, it rolls down the funnel,  $E(X)$ , to the final native structure characterized by energy  $E_0$ . Now a particular model can be described in terms of its energy level distribution or its density of states. Here we consider the situation where there are  $N$  quasicontinuous energy levels with density of states  $D(E)$  and one distant level  $E_0$ , lying at a distance  $\Delta E_0$  below the quasicontinuous spectrum (see Fig. 1). During the folding process (relaxation process) we assume [7] that in any transition between configurations,  $X$  changes only by  $\pm 1$ , which means that the system performs a nearest neighbor random walk in one-dimensional reaction coordinate space. For the perfect funnel energy landscape considered here,  $X \rightarrow X \pm 1$  also implies that energy transitions only occur between nearest neighboring levels. In this work we use Metropolis transition rates, the same as used in Ref. [7], which is justified

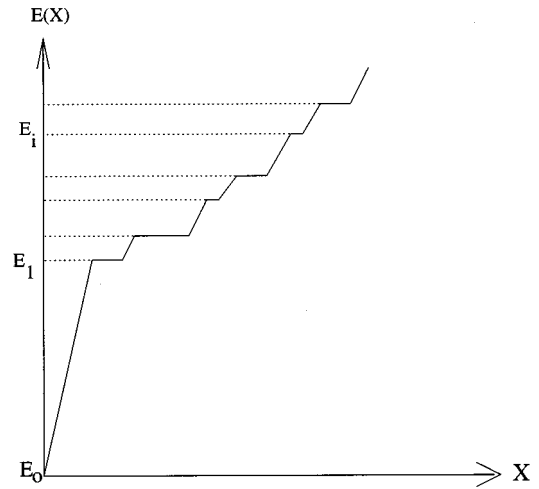


FIG. 1. Schematic plot of the perfect funnel-like energy landscape in reaction coordinate space. The energy spectrum has a low lying ground state with energy  $E_0$  and a quasicontinuum part that is specified by the levels  $E_i$  with  $i \in [1, N]$ .

since no roughness is included in the model. On the other hand, if the landscape is very rough indicating entanglement of the polymer or protein, Metropolis rates will not be adequate. The Metropolis rates satisfy the requirement of detailed balance,

$$W(X \rightarrow X+1)P_X(\text{eq}) = W(X+1 \rightarrow X)P_{X+1}(\text{eq}), \quad (1)$$

where  $P_X(\text{eq})$  is the equilibrium distribution given by a Boltzmann factor. Using  $g_X$  and  $g_{X+1}$  as the degeneracies of the  $X$  and  $X+1$  energy levels, one can then introduce the following transition rates:  $W(X \rightarrow X+1) = (g_{X+1}/g_X)\exp[-(E_{X+1}-E_X)/T]$  and  $W(X+1 \rightarrow X) = 1$ . The second condition, which is independent of temperature  $T$ , corresponds to the zero roughness on the  $E(X)$  landscape.

The folding or relaxation kinetics is studied using a master equation. We focus on the probability,  $P_i$  ( $i=0,1,2,\dots,N$ ), of being at energy level  $E_i$  during the relaxation. Introducing variables  $\alpha_i \equiv \exp[-\Delta F_i/T]$  where  $\Delta F_i = F_{i+1} - F_i$ ,  $i \in \{0, N-1\}$ , and  $F_i = E_i - T \ln g_i$  we can write down the following matrix equation for the evolution of the probabilities:

$$\frac{d\bar{P}}{dt} = A\bar{P}, \quad (2)$$

where the matrix coefficient is given by

$$A = \begin{pmatrix} -\alpha_0 & 1 & 0 & 0 & \cdot \\ \alpha_0 & -1-\alpha_1 & 1 & 0 & \cdot \\ 0 & \alpha_1 & -1-\alpha_2 & 1 & \cdot \\ 0 & 0 & \alpha_2 & -1-\alpha_3 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix}. \quad (3)$$

Because the total probability is a constant, the matrix  $A$  is thus degenerate and there are only  $N$  independent probabilities out of a total of  $N+1$ . We denote the average nearest

neighbor energy level spacing by  $\bar{U}$ . We then make the reasonable assumption that  $\bar{U} \ll \Delta E_0$ , which is basically a consequence of having a spectrum with a few low lying energy levels and a quasicontinuous part in the upper part of a spectrum. Several limits can be obtained directly from the form of the matrix  $A$ . For  $0 \leq T \ll \bar{U}$  and  $\bar{U} \ll T \ll \Delta E_0$ ,  $A$  essentially becomes a constant matrix largely independent of temperature except with only a few temperature dependent terms and thus the folding kinetics is independent of the energy spectrum  $D(E)$ . The same is true for very high temperatures where entropy is the dominant factor. At temperatures  $T \sim \Delta E_0 \gg \bar{U}$ , almost all matrix elements of  $A$  become constants except those few involving energy differences comparable to the  $\Delta E_0$ . This suggests that in this case the folding kinetics is exclusively determined by the presence of the gap in the energy spectrum while almost all quasicontinuous levels are already excited.

A nontrivial result was obtained for the temperature range  $T \sim \bar{U}$ . Here the kinetics can substantially depend on the energy distribution of the quasicontinuous part of the spectrum. We first find a relaxation time at temperatures small enough that one can disregard the rate of escape from the native state. In this range the master equation of (2) becomes  $dP_0/dt = P_1$  and

$$\frac{d\bar{P}'}{dt} = M\bar{P}', \quad (4)$$

where  $\bar{P}'$  is a vector  $(P_1, P_2, \dots, P_N)$ . The matrix  $M$  is a submatrix of  $A$  without its first row and first column. As the relaxation proceeds, i.e., when our system rolls down the perfect funnel  $E(X)$ , the total relaxation time from the highest energy level  $E_N$  to the lowest one  $E_0$ , gives a measure of the relaxation time. To determine this relaxation time  $t_{\text{rel}}$  we notice that the system has relaxed when all states with  $P_i$ ,  $i \in \{1, N\}$ , have been sequentially relaxed. Therefore  $t_{\text{rel}} \sim \sum_{i=1}^N t_i$ , where  $t_i$  are the relaxation times for the states with  $P_i$ .

It is worth pointing out that at low temperatures the relaxation time of a system coincides with its folding time into the ground (native) state because the native state at these temperatures is an equilibrium state of the system. As temperature increases, however, the equilibrium state of the system shifts to the quasicontinuous part of the spectrum. Hence  $t_{\text{rel}}$  will characterize the folding time to the appropriate equilibrium. Keeping this in mind, we now calculate  $t_{\text{rel}}$ . From Eq. (4) we have  $\sum_{i=1}^N t_i = -\sum_{i=1}^N 1/\lambda_i$  where  $\lambda_i$  are the eigenvalues of the matrix  $M$ . As  $\det(M) \neq 0$ ,  $1/\lambda_i$  are the eigenvalues of matrix  $M^{-1}$ . In this way we finally obtain  $t_{\text{rel}}$  in terms of the trace of  $M^{-1}$  since  $t_{\text{rel}} \sim -\text{Tr}(M^{-1})$ .

The calculation of  $\text{Tr}(M^{-1})$  is lengthy and is included in the Appendix. Here we outline the main steps. We notice that  $M = L + \delta L$ , where  $L$  is a constant matrix and  $\delta L$  contains the temperature dependent elements of  $M$ . We seek  $M^{-1}$  in a perturbative form given by  $M^{-1} = \sum_{i=0}^{+\infty} S^{(i)}$ . It turns out that this sum only has a finite number of nonvanishing terms and can thus be summed exactly. Essentially, from  $MM^{-1} = I$  one derives a set of equations for  $S^{(i)}$  that can be solved to give  $S^{(i)} = (-1)^i (S^0 \delta L)^i S^0$ , where  $S^0$  is a triangular matrix with all the upper right elements equal to

– 1. Because of the simplicity of  $\delta L$  and  $S^0$ ,  $(S^0 \delta L)^i = 0$  for all  $i \geq N$ . After lengthy but straightforward algebra we obtain

$$M^{-1} = \left\| \begin{array}{cccccc} 1 & 0 & 0 & 0 & \cdot \\ \alpha_1 & 1 & 0 & 0 & \cdot \\ \alpha_1 \alpha_2 & \alpha_2 & 1 & 0 & \cdot \\ \alpha_1 \alpha_2 \alpha_3 & \alpha_2 \alpha_3 & \alpha_3 & 1 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{array} \right\| S^0. \quad (5)$$

$$\begin{aligned} \tau = -\text{Tr}(M^{-1}) &= N + \alpha_1 + \alpha_2 + \dots + \alpha_1 \alpha_2 + \alpha_2 \alpha_3 + \dots \\ &+ \alpha_1 \alpha_2 \alpha_3 + \dots. \end{aligned} \quad (6)$$

We now solve the problem in general for all  $T$ . To find the relaxation time  $\tau$  of this perfect-funnel model, we use the fact that the total probability is conserved, i.e., that

$$P_0 = 1 - \sum_{i=1}^N P_i. \quad (7)$$

Then Eq. (2) is equivalent to

$$\frac{d\bar{P}'}{dt} = \alpha_0 \bar{\delta} + (M - \alpha_0 \delta M) \bar{P}', \quad (8)$$

where  $\bar{\delta} \equiv \{1, 0, 0, \dots\}$ . Thus the kinetics will be determined by the matrix  $(M - \alpha_0 \delta M)$ , where  $\delta M$  is a matrix with the first row consisting of 1 and the rest of the elements equal to zero. As discussed above, the relaxation time of the system can be found as the trace of  $(M - \alpha_0 \delta M)^{-1}$ . To compute this trace we use the perturbation expansion introduced above and seek an inverse matrix in the form

$$(M - \alpha_0 \delta M)^{-1} = H_{(0)} + H_{(1)} + H_{(2)} + \dots. \quad (9)$$

Using the identity

$$I \equiv (M - \alpha_0 \delta M)(H_{(0)} + H_{(1)} + H_{(2)} + \dots),$$

we find a set of equations for  $H^{(i)}$  that can be solved to give  $H^{(i)} = M^{-1}(\alpha_0 \delta M M^{-1})^i$ , where  $M^{-1}$  is found earlier and is given by Eq. (5). Hence,

$$\begin{aligned} (M - \alpha_0 \delta M)^{-1} &= M^{-1}(1 + \alpha_0(\delta M M^{-1}) + \alpha_0^2(\delta M M^{-1})^2 \\ &+ \dots). \end{aligned}$$

Introducing a new quality

$$R_i \equiv 1 + \alpha_i + \alpha_i \alpha_{i+1} + \alpha_i \alpha_{i+1} \alpha_{i+3} + \dots + \alpha_i \dots \alpha_{N-1} \quad (10)$$

one can easily show that the required inverse matrix can be written as

$$\begin{aligned} (M - \alpha_0 \delta M)^{-1} &= M^{-1} + \alpha_0 M^{-1} \delta M M^{-1} [1 - (\alpha_0 R_1) \\ &+ (\alpha_0 R_1)^2 - (\alpha_0 R_1)^3 + \dots]. \end{aligned} \quad (11)$$

This is an important result and the trace of this matrix gives the relaxation time of our model.

Formally the sum in the brackets of Eq. (11) is a geometric series, which we can rewrite in a more compact form:

$$(M - \alpha_0 \delta M)^{-1} = M^{-1} + \frac{\alpha_0}{1 + \alpha_0 R_1} M^{-1} \delta M M^{-1}. \quad (12)$$

Strictly speaking the summation of the series is allowed only when  $\alpha_0 R_1 < 1$ . Thus in principle we should use Eq. (11) when this condition is not satisfied. It turns out, by numerical comparisons, that Eq. (12) is correct even for  $\alpha_0 R_1 > 1$ . Even though this indicates that there is most probably a more direct way of deriving Eq. (12) rather than via the series expansion used here, we use Eq. (12) to proceed further and present numerical confirmation of this procedure later.

The relaxation time is then given by

$$\tau = -\text{Tr}(M^{-1}) - \frac{\alpha_0}{1 + \alpha_0 R_1} \text{Tr}(M^{-1} \delta M M^{-1}). \quad (13)$$

Using the explicit forms of the matrices as given by Eq. (5) and  $\delta M$ , after lengthy but straightforward algebra we obtain

$$\text{Tr}(M^{-1}) = N + \sum_{i=1}^{N-1} \sum_{j=1}^{N-i} \alpha_j \cdots \alpha_{j+i-1} \quad (14)$$

and

$$\begin{aligned} \text{Tr}(M^{-1} \delta M M^{-1}) &= R_1 + (R_1 + R_2) \alpha_1 + (R_1 + R_2 + R_3) \alpha_1 \alpha_2 \\ &+ \cdots + (R_1 + \cdots + R_N) \alpha_1 \cdots \alpha_{N-1}. \end{aligned} \quad (15)$$

If we define  $Z_i$  as  $Z_i \equiv \sum_{j=i}^N \exp(-F_j/T)$ ,  $Z_i$  is then the partition function for the  $N-i$  energy levels starting at  $i$  and  $R_i$  is given by  $R_i = Z_i \exp(F_i/T)$ . The above results can then be considerably simplified and the expression for  $\tau$  becomes

$$\tau = -\text{Tr}(M^{-1}) - \frac{\sum_{i=1}^N Z_i^2 \exp(F_i/T)}{Z_0}. \quad (16)$$

Using Eqs. (14)–(16) we arrive at the main result of this work,

$$\begin{aligned} \alpha_j \alpha_{j+1} \cdots \alpha_{j+i-1} &= \exp - \frac{E_{j+1} - E_j + E_{j+2} - E_{j+1} + \cdots + E_{j+i} - E_{j+i-1}}{T} \\ &= \exp - \frac{E_{j+i} - E_j}{T}. \end{aligned} \quad (20)$$

The relaxation time  $\tau$  can therefore be expressed as follows in terms of the level spacing probability:

$$p_{(i)}(S) \equiv \sum_{j=1}^{N-i} \delta(E_{j+i} - E_j - S),$$

$$\tau = \eta_1 + \eta_2, \quad (17)$$

where

$$\eta_1 = \left( N + \sum_{i=1}^{N-1} \sum_{j=1}^{N-i} \alpha_j \cdots \alpha_{j+i-1} \right), \quad (18)$$

$$\eta_2 = - \frac{\sum_{i=1}^N Z_i^2 \exp(F_i/T)}{Z_0}. \quad (19)$$

Because this result is quite complicated, we first apply it in the next section to various specific situations, and then present numerical results obtained using the general expression of Eqs. (17)–(19).

### III. THE ROLE OF LEVEL STATISTICS

As a first application of the result given by Eq. (17), we examined the case where the energy levels are nondegenerate, i.e.,  $g_X = 1$  for all  $X$ , then local free energy  $F_i$  coincides with the energy  $E_i$ . In this limit the expression for the relaxation time can be greatly simplified. Also, we shall focus on low temperatures. In this case we shall prove that the relaxation time  $\tau$  is determined by the energy level spacing distributions. These distributions can be computed from the density of states  $D(E)$ . Since very different models, i.e., different  $D(E)$ 's, can give quite similar spacing distributions, the relaxation in this temperature regime is quite generic. In the next section we shall show that even when  $g_X > 1$ , similar conclusions can be reached if the temperature is lower than some characteristic temperature.

#### A. The relaxation time

For temperatures much smaller than the energy gap between the ground state and the first excited state,  $\Delta E_0$ , and taking into account that there are no exponentially divergent pieces in the second term  $\eta_2$  of Eq. (17), we can safely neglect  $\eta_2$  since it is much smaller than the  $\eta_1$  term. Furthermore we notice that

which measures the probability that  $E_{j+i} - E_j$  equals  $S$  for all level indices  $j$ . Using this definition we find

$$\sum_{j=1}^{N-i} \alpha_j \cdots \alpha_{j+i-1} = \int_0^{+\infty} p_{(i)}(S) \exp\left(-\frac{S}{T}\right) dS.$$

From Eqs. (17) and (18) we obtain

$$\tau = t_{\text{rel}} \approx N + \sum_{i=1}^{N-1} \int_0^{+\infty} p_{(i)}(S) \exp\left(-\frac{S}{T}\right) dS. \quad (21)$$

It is clear that small values of the level spacing  $S$  give the largest contribution to the integrals in Eq. (21) and this is especially true for low temperatures. On the other hand, for higher order energy level spacing distributions,  $p_{(i)}(S)$  is small for small values of  $S$ . Hence, for low  $T$  the term containing the nearest neighbor spacing distribution,  $p_{(1)}(S)$ , is most important in determining the relaxation time  $\tau$ . As  $T$  increases  $\tau$  begins to depend on higher order energy level spacing distributions. Since more and more  $p_{(i)}(S)$  begin to play a role as  $T$  increases, we expect the model details to become increasingly important. However, it is easy to show that  $p_{(i)}(S)$  for large  $i$  must be universal: as the levels are far apart there is little level correlation and the spacing distribution therefore approaches a Gaussian. Hence we expect model independence to return when  $T$  reaches values  $\gtrsim \bar{U}$ . Finally, if  $p_{(i)}(S)$  is less sensitive to model peculiarities than the density of states,  $D(E)$ , we expect that the relaxation kinetics measured by the relaxation time  $\tau$  is approximately generic as it only depends on several low order spacing distributions in this low temperature range. We shall confirm this picture by computing  $p_{(i)}(S)$  and in particular  $p_{(1)}(S)$  in terms of  $D(E)$ .

### B. The spacing distribution

To relate  $P_{(i)}(S)$  to the density of states  $D(E)$ , which specifies our models, let us take any two energy levels and consider the probability that the first level lies in the interval  $[E, E+dE]$  while the second level lies in  $[E+S, E+S+dS]$ . To find  $p_{(i)}(S)$  we use an approximate approach [13–15] analogous to mean field theory in which the energy distribution  $D(E)$  is assumed to be locally random. This allows us to use a simple approach based on probability theory. First we note that there are  $i-1$  levels in the interval  $[E, E+S]$  and the remaining  $N-i$  levels are outside this interval. The probability for this to occur is proportional to [12]

$$D(E)D(E+S) \left[ 1 - \int_E^{E+S} D(t) dt \right]^{(N-i)} \times \left[ \int_E^{E+S} D(t) dt \right]^{(i-1)} dS dE. \quad (22)$$

Integrating over  $E$  and normalizing the resulting expression, we obtain

$$p_{(i)}(S) = C \int_{-\infty}^{+\infty} D(E)D(E+S) \left[ 1 - \int_E^{E+S} D(t) dt \right]^{(N-i)} \times \left[ \int_E^{E+S} D(t) dt \right]^{(i-1)} dE, \quad (23)$$

where  $C$  is the normalization factor. In spite of its involved appearance, this equation is easy to investigate. For example, consider  $p_{(1)}(S)$ , which is written as

$$p_{(1)}(S) = N(N+1) \int_{-\infty}^{+\infty} D(E)D(E+S) \times \left[ 1 - \int_E^{E+S} D(t) dt \right]^{(N-1)} dE. \quad (24)$$

It is easy to see that if  $D(E)$  is substantially larger than zero on an interval  $\xi$ , then due to the factor  $[1 - \int_E^{E+S} D(t) dt]^{(N-1)}$ ,  $p_{(1)}(S)$  will also be substantially larger than zero on a scale of  $\xi/N$ . If  $S \ll 1$ , in the  $N \rightarrow \infty$  limit we can expand the integrand to obtain

$$p_{(1)}(S) = N(N+1) \sum_{i=0}^{+\infty} (-1)^i \frac{(SN)^i}{i!} \int_{-\infty}^{+\infty} D^{i+2}(E) dE. \quad (25)$$

From Eq. (25) it can also be deduced that the scale on which  $p_{(i)}(S)$  is substantially greater than zero is  $O(1/N)$ . Furthermore, it is clear from Eqs. (23) and (25) that  $P_{(i)}(S)$  is determined by the values of a set of definite *integrals* of the density of states distribution,  $D(E)$ , and its powers rather than the specific details of the level distribution itself.

How sensitively does  $p_{(1)}(S)$  depend on  $D(E)$ ? Consider two completely different models specified by  $D_1(E) = \exp(-E)$  with  $E \in [0, +\infty]$ , and  $D_2(E) = [(d+1)/E_0^{d+1}]E^d$  with  $E \in [0, E_0]$  and  $d > 0$ . Using Eq. (25) we can explicitly compute the nearest neighbor spacing distribution  $p_{(1)}(S)$  for the two models. It is easy to show that both models give the same form of  $p_{(1)}(S)$  for large values of the parameter  $d$ . Furthermore, even for  $d \sim O(1)$  the difference is only  $\sim (d+1)/d$ . The fact that the two chosen forms of  $D(E)$  are considerably different from one another shows that different models described by different forms of  $D(E)$  can have similar nearest energy level spacing distributions. Hence they can have similar relaxation times as specified by Eq. (21) in the appropriate temperature range.

## IV. A MORE GENERAL CASE

In Sec. III we considered the case in the absence of level degeneracy. In that case the relaxation time can be expressed in terms of the level spacing distributions. However, when some of the energy levels are degenerate, we were in general not able to write Eq. (17) in a simple form like Eq. (21) in terms of the level spacing probability,  $p_{(i)}(S)$ . In addition if the degeneracy  $g_X$  of the energy levels rises exponentially as the number of the energy level increases we cannot neglect the  $\eta_2$  term even if the temperature is much smaller than  $\Delta E_0$ . In this more general case, the level degeneracies and the energetics will compete to control the relaxation. Thus we expect the relaxation time  $\tau$  to have a nonmonotonic behavior as the temperature is changed. In particular, a characteristic temperature  $T_f$  is found that roughly separates the relaxation regime, which is controlled by energetics and the regime controlled by entropy.

### A. The characteristic temperature

We now examine the special case of level degeneracy, which is approximately realized in protein spectra [7] where  $g_X \sim \gamma^X$  and  $\gamma$  is a constant greater than unity in this case

local free energy  $F_i$  equals  $F_i = E_i - i \ln \gamma$ . In this case it is easy to show, using Eq. (17), that

$$\tau = \eta_1 + \eta_2 = \left( N + \sum_{i=1}^{N-1} \int_0^{+\infty} p_{(i)}(S) \exp \left[ i \ln \gamma - \frac{S}{T} \right] dS \right) - \frac{\sum_{i=1}^N Z_i^2 \exp(F_i/T)}{Z_0}.$$

It is easy to show that the  $\eta_2$  term as a whole scales as  $\exp[N(\ln \gamma - \bar{U}/T - E_0/NT)]$  for temperatures  $T > \bar{U}/\ln \gamma$ , and the temperature at which this term becomes order unity is given by  $T_f \sim (\bar{U} + E_0/N)/\ln \gamma$ , which is comparable with the average level spacing and becomes independent of the ground state energy  $E_0$  as  $N$  approaches infinity. For  $T > T_f$ ,  $|\eta_2|$  is a rapidly increasing function of  $N$  and at  $T \sim T_f$  the two terms  $\eta_1$  and  $\eta_2$  become comparable.

Our results show that the relaxation time of the model involves competition between the two terms  $\eta_1$  and  $\eta_2$ . The fact that  $|\eta_1|$  becomes comparable with  $|\eta_2|$  at  $T_f$  implies a change of behavior as temperature  $T$  is swept across  $T_f$ . To gain further intuition concerning the behavior of the system at  $T = T_f$ , we examined the limit for which all the  $N$  levels in the quasicontinuous part of the spectrum are equidistant and  $U$  is the energy difference between any two adjacent levels. Again let  $\Delta E_0$  be the distance between the native state and the lowest energy of the quasicontinuous part of the spectrum. The equilibrium probabilities of each level will then become

$$P_0 = \frac{\exp(\Delta E_0/T)}{\exp(\Delta E_0/T) + (K^N - 1)/(K - 1)}$$

and

$$P_i = \frac{K^i}{\exp(\Delta E_0/T) + (K^N - 1)/(K - 1)},$$

where  $K = \exp(\ln \gamma - U/T) = \exp[\ln \gamma (1 - T_f/T)]$ . Here we have defined  $T_f = U/\ln \gamma$ . Because  $N$  is large, this expression for  $K$  together with the expressions for  $P_0$  and  $P_i$  above shows that for  $T < T_f$  the population of the energy levels will be given by  $P_0 \sim 1$  and  $P_i \ll P_0$  for all  $i \in \{1, N\}$ . The equilibrium state of the system is then the ground state of our spectrum. For  $T > T_f$ , on the other hand,  $P_i \ll P_{i+1}$  for all  $i \in \{0, N-1\}$ , so that the equilibrium state will be shifted to the upper part of the quasicontinuous spectrum. Hence for  $T < T_f$  or  $T > T_f$  the equilibrium state of the system is relatively well defined. In the case when  $T \sim T_f$  all the levels in the spectrum become almost equally probable and hence large fluctuations can be expected. From the kinetic point of view, this means that at  $T \sim T_f$  the fluctuations lead to slow relaxation and thus large values of  $\tau$ . In this sense this behavior is similar to the well-known ‘‘critical slowing down’’ found for critical phenomena. From this argument it follows that for  $T \sim T_f$  one should expect the occurrence of a maximum in the relaxation time of a system. Finally we note that

the characteristic temperature can also be obtained by the convergence criterion for the series of Eq. (11), namely,  $\alpha_0 R_1 = 1$ .

We may conclude from our discussions that as soon as our system has energy levels with increasing degeneracies, there exists a temperature scale  $T_f$  that is determined by the average level spacing of the spectrum and the degeneracy parameter  $\gamma$ . Close to  $T_f$  the tendency of increasing entropy overcomes the tendency of relaxing into a state with lowest energy, and this leads to a sharp increase in the relaxation time of our system (see below for numerical calculations). Thus we expect a change in the behavior of the relaxation as temperature is varied by crossing  $T_f$ . In this sense, the characteristic temperature  $T_f$  can be regarded as the ‘‘folding temperature.’’ This is indeed what is observed in Ref. [7] for situations similar to that discussed in the last paragraph. Numerical results for this case will be presented in the next subsection.

For  $T \ll T_f$ , we can again neglect the  $\eta_2$  term, and the relaxation time can be expressed as

$$\tau = t_{\text{rel}} \sim N + \sum_{i=1}^{N-1} \int_0^{+\infty} p_{(i)}(S) \exp \left[ i \ln \gamma - \frac{S}{T} \right] dS. \quad (26)$$

Similar to the discussion in the last section, it is clear that as the temperature increases from zero to  $T_f$ ,  $\tau$  becomes increasingly dependent on the higher order energy level spacing distributions. However, when  $T \sim 0$ ,  $\tau$  is only determined by the nearest neighbor spacing distribution  $p_{(1)}(S)$ . Thus the relaxation at very low temperatures is still generic in the sense of the discussion in the last section, namely,  $\tau$  is insensitive to the density of states  $D(E)$ .

For proteins in general, it is reasonable to assume that the number of levels is large, i.e., that  $N \rightarrow \infty$ . Then the characteristic temperature  $T_f$  is of the order of  $\bar{U}/\ln \gamma$ . In order to examine higher temperatures, we first consider  $T > T_f$  and the  $\eta_1$  term as given by Eq. (26). In this case the exponential in the integrand of Eq. (26) is larger for larger values of the summation index  $i$ . Therefore for  $T > T_f$ , only higher order energy level spacing distributions  $p_{(i)}(S)$  play a substantial role. However, as mentioned above,  $p_{(i)}(S)$  approaches a Gaussian for large  $i$  and hence the  $\eta_1$  part of the relaxation time again becomes generic for  $T > T_f$ . In addition, it is easy to see that the leading contribution in the  $\eta_2$  term is due to the difference in energies between the highest and the lowest energy levels for  $T > T_f$  and is of the order of  $\exp(N\langle S \rangle/T)$ . Since this also defines quite general properties of a given model, we expect weak model dependence for the  $\eta_2$  term as well. Hence we conclude that above the characteristic temperature, the relaxation time is only weakly dependent on the detailed features of a given model.

The major model dependence is expected in the range  $0 \ll T \leq T_f$ , while  $T_f$  itself is determined by the degeneracy parameter  $\gamma$  and average level spacing. The striking feature of the current case is that as  $T$  reaches  $T_f$  there is an increase in the dependence of  $\tau$  on the higher order energy level spacing distribution: at very low  $T$  it is  $p_{(1)}(S)$  that determines  $\tau$ , while above  $T_f$  it is the higher  $p_{(i)}(S)$  that is responsible. The important conclusion is that it is possible for different models that correspond to different density of states

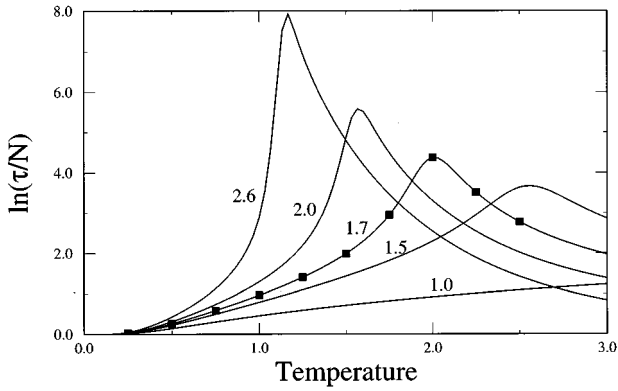


FIG. 2. Logarithm of the relaxation time  $\tau$  as a function of temperature  $T$  for various degeneracy parameters  $\gamma$  as indicated by the numbers near the curves. The unit of  $T$  is the level spacing  $U$ , and an arbitrary unit is set for  $\tau$ . The solid squares were computed from a direct numerical inversion of the matrix  $(M - \alpha_0 \delta M)$  of Eq. (9) followed by a calculation of the trace of  $(M - \alpha_0 \delta M)^{-1}$ . The solid lines were calculated using the analytical form of Eq. (17). Clearly these two methods give exactly the same answers throughout the whole temperature range.

$D(E)$  to have similar spacing distributions  $p_{(1)}(S)$ . If this is the case the folding time is weakly sensitive to the details of a given model in the lower temperature range  $T \ll \bar{U}$  for the nondegenerate models and  $T \ll T_f$  for the degenerate models.

### B. Numerical results

Although we have obtained all our results analytically, it is useful to obtain some numerical data as this gives considerable intuition about the relaxation kinetics of the model studied here. For this purpose, we employ the model of Ref. [7]. In particular we assume that it has  $N$  energy levels with equal nearest neighbor spacings  $U$  in its quasicontinuous part and  $\Delta E_0$  below is the ground state. We assume  $\Delta E_0 \gg U$ . The degeneracy of the quasicontinuous part is given by  $\gamma^{i-1}$ , where  $i$  is the index of energy level. In the calculations we used  $N=100$ ,  $U=1$ , and the energy gap between the ground state and the bottom of the quasicontinuous part of the spectrum  $\Delta E_0=12$ .

Then from our general result given by Eq. (17), the relaxation time can be easily calculated and we obtain, for the whole temperature range,

$$\tau = N \frac{K^N - 1}{K - 1} - K \left( \frac{K^N - 1}{K - 1} \right)' - \sum_{i=1}^N \left( \frac{K^{N-i+1} - 1}{K - 1} \right)^2 K^{i-1} \frac{\alpha_0}{1 + \alpha_0 (K^N - 1)/(K - 1)}. \quad (27)$$

Here  $K \equiv \gamma \exp(-U/T)$  and the prime means differentiation with respect to  $K$ . A simpler expression can be obtained when the limit  $N \rightarrow \infty$  is taken.

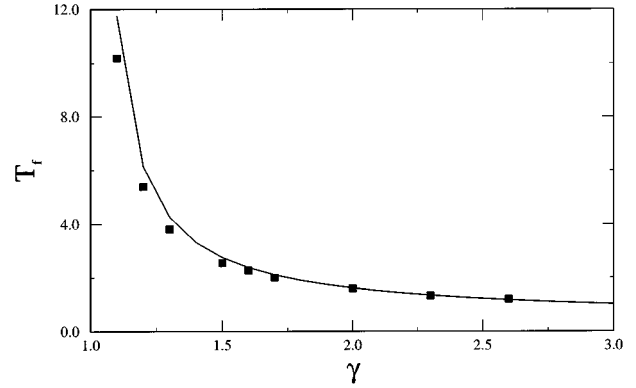


FIG. 3. Characteristic temperature  $T_f$  as a function of the level degeneracy parameter  $\gamma$ . The unit of  $T_f$  is the level spacing  $U$ . The solid line is obtained from  $T_f \approx U / \ln \gamma + \Delta E_0 / N \ln \gamma$ . The solid squares in this figure correspond to the temperatures at which the relaxation time achieves its maximum, i.e., the peak positions of Fig. 2. These two prescriptions give nearly the same values for  $T_f$ .

The relaxation time  $\tau$  as a function of temperature for various degeneracy parameters  $\gamma$  is shown in Fig. 2. We computed  $\tau$  in two ways: either from a direct numerical inversion of the matrix  $(M - \alpha_0 \delta M)$  of Eq. (9) and then finding its trace, or by using the analytical form of Eq. (17). Figure 2 shows that these two methods give exactly the same results throughout the whole temperature range, justifying the mathematical procedure that led to Eq. (17). Several observations are in order. First, when the energy levels are nondegenerate, i.e., when  $\gamma=1$ , there are no entropic effects in the model and the system simply rolls down the perfect funnel landscape in the relaxation process. In this case there is no characteristic temperature  $T_f$  and  $\tau$  is completely determined by the energy level spacing distribution, as discussed before. Secondly, for cases with increasing level degeneracies, i.e., for  $\gamma > 1$ , the relaxation time shows the expected maximum. Also the position of the maximum is exactly at the characteristic temperature  $T_f$  (see below). The behavior is consistent with that reported in Ref. [7]. Finally, the “transition” at  $T_f$  becomes sharper as  $\gamma$  is increased. This is expected, as it is similar to the situation that occurs in a finite system where a thermal phase “transition” becomes sharper when the degree of freedom is increased.

In Fig. 3 the characteristic temperature as obtained from  $T_f \approx U / \ln \gamma + \Delta E_0 / N \ln \gamma$  is shown as a function of the degeneracy parameter  $\gamma$ . From this expression  $T_f$  decreases monotonically as  $\gamma$  is increased, which must be true because higher degeneracies of the energy spectrum lead to higher entropies involved. The data points in this figure were taken from the peak positions of Fig. 2 and are in good agreement with the theoretical definition. Hence we conclude that  $\tau$  takes maximum values at the characteristic temperature  $T_f$ .

### C. A discussion on the effect of roughness

So far our analysis is rigorous when the energy landscape is a perfect funnel in the absence of roughness. Including

arbitrary roughness will make the problem essentially unsolvable analytically. However, under the assumption that the roughness is small, our analysis can be extended to estimate the effects of it. In this section we will not attempt a rigorous treatment of the influence of roughness on the polymer dynamics. Rather, we will specify in what way the results of our theory will be modified if roughness is included. Our analysis follows the work of Leite and Onuchic [17].

The energy landscape roughness can be modeled [17] by a distribution of states at a given value of the reaction coordinate  $X$ . The roughness is considered small if the width of the distribution is smaller than the average energy level spacing in the spectrum. Then, each energy level  $E(X)$  considered so far can be thought of as being “smeared” out by an energy probability distribution  $g(X, E) = 1/[2\pi\delta E(X)^2]^{1/2}\exp\{-[E-\bar{E}(X)]^2/2\delta E(X)^2\}$ . Here  $\delta E(X)$  characterizes the “strength” of the roughness or the width of the energy band corresponding to a particular value of  $X$ . For this roughness model, following Ref. [17], a useful concept that arises is a coordinate-dependent phase transition [17]. After the introduction of small roughness, the narrow band of states within  $\delta E(X)$  can be considered to be a subsystem with its own dynamics. This consideration predicts [17] that for an energy band with coordinate  $X$  there is a critical temperature  $T_c(X) = \delta E(X)/[2\ln\Omega(X)]^{1/2}$  where  $\Omega(X)$  is a number of conformations corresponding to the level at  $X$ . If  $T \leq T_c(X)$  for a particular  $X$ , the band at  $\bar{E}(X)$  will behave in such a way that the dynamics inside this band is glasslike. This means that the system will tend to be frozen in a few low lying states of this band while relaxing inside it. This effect will have an important influence on the relaxational dynamics. In the case of protein folding we model  $\Omega(X) \sim \gamma^X$ , and therefore  $T_c(X) = \delta E(X)/[2X \ln\gamma]^{1/2}$ , where  $X = 0, 1, 2, \dots$

Although  $\delta E$  may depend explicitly on  $X$ , let us first consider the limiting case when  $\delta E$  is a constant over the spectrum. In this case for system temperature  $T \leq \delta E/(2X \ln\gamma)^{1/2}$  there are  $I_f = (\delta E/T)^2 1/2 \ln\gamma$  low lying energy bands with “glasslike” dynamics. The lower the temperature, the more “frozen” bands would be in the system. As the global dynamics involves a total number of energy states that is proportional to  $\sum_i^N \gamma^i = \gamma^{N+1}/(\gamma-1)$ , a “global” phase transition temperature can be estimated, following Ref. [17], as  $T_c^g \sim \delta E/(2N \ln\gamma)^{1/2}$  where  $N$  is the number of energy bands ( $N = \max\{X\}$ ). It is important to compare this temperature scale with the folding temperature discussed previously,  $T_f \sim \bar{U}/\ln\gamma$ . The number of “frozen” levels at the folding temperature is  $I_f \sim (\delta E/\bar{U})^2 \ln\gamma/2 = T_c^g N^{1/2}/T_f$ . This number can serve as a criterion for the definition of roughness “strength.” One can easily see that if the roughness  $\delta E \leq \bar{U}$ , then  $I_f \sim 1$ . We thus conclude that only a few low lying energy bands with  $X \sim 1$  are frozen at  $T_f$ . In this case the results derived from a perfect funnel should be applicable for temperatures  $T \sim T_f$ , and the relaxation kinetics can be slowed down in the lower part of a spectrum near the ground state.

The above discussion is for a constant  $\delta E$  and more realistically there is  $X$  dependence of this quantity. For protein

models it is natural to use the measure of compactness, such as the total number of nearest contacts, to specify the energy states. If  $C_L$  is the maximum number of contacts for a polymer with  $L$  monomers, then we may define  $C_L - X$  to give the total number of contacts at energy  $E(X)$ . It is reasonable to assume that for a structure with a larger number of contacts, more interaction parameters are involved in computing the energy. In general for a given distribution of these parameters, the energy bandwidth  $\delta E$  is thus larger. For this reason we expect a decreasing  $\delta E(X)$  as  $X$  is increased (although the level degeneracy  $\gamma^X$  is increasing). Hence the validity of the perfect funnel results can be assessed by using the largest  $\delta E(X)$  appropriate to the lower part of the spectrum and the discussion of the last paragraph.

## V. SUMMARY

This work was motivated by a particular protein folding scenario based on a funnel-like energy landscape. We studied the relaxational behavior when a system possesses a perfectly smooth energy funnel. Our model is specified by a density of states  $D(E)$  for the quasicontinuous part, and a very low ground state level  $E_0$ . The levels of the quasicontinuous part may have exponentially increasing degeneracies characterized by a degeneracy parameter  $\gamma$ . Because the funnel is smooth, the relaxation is very simple and can be obtained by using Metropolis rates. Indeed, the problem has been solved in closed form for the whole temperature range in the absence of roughness.

We found that the dependence of the relaxation time  $\tau$  on the energy level and the level spacing distributions of the models displays three main types of behavior depending on the temperature  $T$ . In the case where the energy levels are nondegenerate, a general formula can be obtained relating  $\tau$  to the level spacing distribution. Because  $\tau$  is largely speaking determined by the nearest level spacing distribution, which we have shown to be only weakly dependent on  $D(E)$ , we conclude that the relaxation behavior can be said to exhibit “universal” features. In the degenerate case, which is more realistic for protein models, a characteristic temperature  $T_f$  is found that separates the relaxation regimes dominated by energetics or by entropic effects. Hence in this sense  $T_f$  can be thought of as a “folding temperature” for the model studied here. We found that  $\tau$  is weakly dependent on the specific density of states of a given model if  $T \leq T_f$  while becoming more and more model sensitive as  $T$  approaches  $T_f$ . Again, at  $T > T_f$  the system becomes almost insensitive to the detailed features of  $D(E)$ . Across  $T_f$  the relaxation time shows a maximum, indicating the “folding transition,” in agreement with the earlier model of Zwanzig [7]. A possible experimental study of the relationship between the energy level distribution and folding kinetics as examined by our model would involve a systematic study of several proteins using a combination of thermodynamic techniques such as calorimetry [16] and folding assays.

The discussion presented here is only valid for a perfect funnel-like energy landscape, i.e., that of a “good” protein sequence. The connection to a particular model is through



the density of states  $D(E)$ , which can always be obtained numerically. If small amount of roughness is added via a finite width of the energy state distribution for a particular reaction coordinate  $X$ , the validity of the perfect funnel results can be examined following the approach of the recently published work of Ref. [17]. In general, our theory correctly describes the kinetics of the model system including roughness in a temperature range  $T > N^{1/2} T_c^g$ : below this temperature kinetics slows down by the roughness and approach glassylike dynamics at  $T \sim T_c^g$ . As discussed in the last section,  $T_c^g$  is small for small amount of roughness (small  $\delta E$ ).

Finally we comment that while our work was motivated by the protein folding problem, the model is, however, only specified by the density of states and relaxation in a perfect funnel with a low lying ground state. Thus the formulas derived here are applicable to any other situations where a similar arrangement applies. On the other hand, as far as protein folding is concerned, the model studied here possesses many features of more realistic models.

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#### APPENDIX

In this Appendix we derive Eq. (5). From matrix  $A$  of Eq. (3), we obtain matrix  $M$  by deleting the first row and first column. Hence  $M \equiv L + \delta L$  can be written as

$$M \equiv \begin{pmatrix} -1 & 1 & 0 & 0 & \cdot \\ 0 & -1 & 1 & 0 & \cdot \\ 0 & 0 & -1 & 1 & \cdot \\ 0 & 0 & 0 & -1 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix} + \begin{pmatrix} -\alpha_1 & 0 & 0 & 0 & \cdot \\ \alpha_1 & -\alpha_2 & 0 & 0 & \cdot \\ 0 & \alpha_2 & -\alpha_3 & 0 & \cdot \\ 0 & 0 & \alpha_3 & -\alpha_4 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix}. \quad (\text{A1})$$

It can be verified that matrix  $L^{-1}$  takes a triangular form with all the upper right elements equal to  $-1$ . To find  $M^{-1}$ , we seek for a series form  $M^{-1} = \sum_{i=0}^{+\infty} S^i$ . The proper expressions of matrices  $S^i$  are obtained by using the equality  $M^{-1}M = I$  where  $I$  is the unit matrix. Expansion of this equality gives  $(\sum_{i=0}^{+\infty} S^i)(L + \delta L) = I$ . Gathering terms in equal powers of  $\delta L$  we obtain the solution  $S^0 = L^{-1}$  and  $S^i = (-1)^i (S^0 \delta L)^i S^0$ .

The quantity  $S^0 \delta L$  is obtained by a direct multiplication,

$$S^0 \delta L = \begin{pmatrix} 0 & 0 & 0 & 0 & \cdot \\ \alpha_1 & 0 & 0 & 0 & \cdot \\ 0 & \alpha_2 & 0 & 0 & \cdot \\ 0 & 0 & \alpha_3 & 0 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix}. \quad (\text{A2})$$

This is a triangular matrix with an empty diagonal. It is well known that for any  $N \times N$  triangular matrix with an empty diagonal, the  $i$ th power of this matrix gives a zero matrix if  $i \geq N$ . Hence we conclude that our series expansion of  $M^{-1}$  is, in fact, a finite series. Summing the  $N - 1$  nonzero terms we obtain the result

$$M^{-1} = \begin{pmatrix} 1 & 0 & 0 & 0 & \cdot \\ \alpha_1 & 1 & 0 & 0 & \cdot \\ \alpha_1 \alpha_2 & \alpha_2 & 1 & 0 & \cdot \\ \alpha_1 \alpha_2 \alpha_3 & \alpha_2 \alpha_3 & \alpha_3 & 1 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix} L^{-1} = - \begin{pmatrix} 1 & 1 & 1 & 1 & \cdot \\ \alpha_1 & 1 + \alpha_1 & 1 + \alpha_1 & 1 + \alpha_1 & \cdot \\ \alpha_1 \alpha_2 & \alpha_2 + \alpha_1 \alpha_2 & 1 + \alpha_2 + \alpha_1 \alpha_2 & 1 + \alpha_2 + \alpha_1 \alpha_2 & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix}. \quad (\text{A3})$$

This gives the result of Eq. (5). One can easily verify this result by direct multiplication to confirm  $MM^{-1} = I$ .

- [1] See, for example, articles in *Protein Folding*, edited by T.E. Creighton (Freeman, New York, 1992).  
 [2] J.D. Bryngelson and P. Wolynes, *J. Phys. Chem.* **93**, 6902 (1989).  
 [3] N. Go and H. Abe, *Biopolymers* **20**, 991 (1981).  
 [4] Peter E. Leopold, Mauricio Montal, and José Nelson Onuchic,

- Proc. Natl. Acad. Sci. USA* **89**, 8721 (1992).  
 [5] P.G. Wolynes, J.N. Onuchic, and D. Thirumalai, *Science* **267**, 1619 (1995).  
 [6] J.N. Onuchic, P.G. Wolynes, Z. Luthey-Schulten, and N.D. Socci, *Proc. Natl. Acad. Sci. USA* **92**, 3626 (1995).  
 [7] R. Zwanzig, *Proc. Natl. Acad. Sci. USA* **92**, 9801 (1995).

- [8] J.D. Bryngelson and P.G. Wolynes, Proc. Natl. Acad. Sci. USA **84**, 7524 (1987).
- [9] J.D. Honeycutt and D. Thirumalai, Proc. Natl. Acad. Sci. USA **87**, 3526 (1990); Biopolymers **32**, 695 (1992); Z. Guo, D. Thirumalai, and J.D. Honeycutt, J. Chem. Phys. **97**, 525 (1992).
- [10] E.I. Shakhnovich and A.M. Gutin, Nature **346**, 773 (1990).
- [11] A. Sali, E.I. Shakhnovich, and M. Karplus, Nature **359**, 248 (1994).
- [12] The details of the calculation will be presented elsewhere.
- Maxim Skorobogatyy (unpublished).
- [13] M.L. Mehta, *Random Matrices and the Statistical Theory of Energy Levels* (Academic, New York, 1967).
- [14] V.I. Abkevich, A.M. Gutin, and E.I. Shakhnovich, J. Chem. Phys. **101**, 6052 (1994).
- [15] A. Pandey, Ann. Phys. (N.Y.) **119**, 170 (1979).
- [16] Y. V. Griko, E. Freire, G. Privalov, H. van Dael, and P.L. Privalov, J. Mol. Biol. **252**, 447 (1995).
- [17] Vitor B. P. Leite and José N. Onuchic, J. Phys. Chem. **100**, 7680 (1996).