Non-Arrhenius modes in the relaxation of model proteins

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(February 1, 2008)

Abstract

We have investigated the relaxational dynamics for a protein model at various temperatures. Theoretical analysis of this model in conjunction with numerical simulations suggests several relaxation regimes, including a single exponential, a power law and a logarithmic time dependence. Even though a stretched exponential form gives a good fit to the simulation results in the crossover regime between a single exponential and a power law decay, we have not been able to directly deduce this form from the theoretical analysis.
I. INTRODUCTION

The manner in which proteins relax to their equilibrium or folded configurations is an important subject of current research [1]. In particular the folding kinetics, namely the asymptotics of the relaxation of a physical quantity such as the total energy, provides useful clues to the general folding problem. In this work we shall provide both numerical and theoretical results concerning the asymptotic behavior of relaxation of a model protein following a rapid temperature quench from high to low. We emphasize and attempt to answer the very relevant question: what is the true (possible) asymptotics of such a relaxation of a protein? Due to the complex nature of this question, we shall use a simplified protein model for our numerical simulations which is based on the monomer-monomer interaction matrix of Ref. [2]; and our analytical work is based on the hierarchically constrained dynamics for glassy relaxation [3].

There existed studies of the relaxational dynamics or related equilibrium properties of protein-like heteropolymers where part or the whole of the monomer-monomer interaction is modeled by a stochastic term [1,4–9]. This random interaction clearly gives rise to a complicated free energy landscape with a large number of highly degenerate energy levels. These heteropolymers are believed to simulate certain protein behavior: interesting and important results for our intuitive understanding of the folding kinetics have been obtained through these studies. Using a lattice copolymer model with Metropolis Monte Carlo dynamics, Ref. [8] examined the folding kinetics as a function of the simulation time $t$ for various temperature $T$, starting from an unfolded initial copolymer configuration. Importantly, the folding of the copolymer was found to take place in a two-stage process: a rapid collapse followed by a slower adjustment toward the ground state, for a broad range of temperatures. A kinetically defined glass transition temperature $T_g$ and a thermodynamically defined folding temperature $T_{fold}$ were naturally found from the copolymer simulation data [8]. These temperature scales were used to characterize the foldability of the polymers [8]. Refs. [14] directly measured the relaxation of the total system energy $E$ for a random heteropolymer after a temperature quench where the interaction parameters between the monomers were drawn from a Gaussian distribution. The Monte Carlo [5] and molecular dynamics [9] data were well fit to a stretched exponential form as a function of the simulation time $t$. One additional interesting finding of these simulations was that for longer heteropolymers the collapse followed a two-stage process [9] characterized by different sketching exponents, while for short chains only one stage was found [4].

Along another line of development, fruitful results have been obtained from analyzing even simpler discrete models such as the random energy model [10]. The application of this model to protein folding was carried out in Ref. [11] where the folding time was analyzed. Interestingly, the random energy model gives different relaxation asymptotics depending on the details of the transition matrix between different microstates [12] even though the detailed balance condition has been enforced. Indeed, power-law [12] decay or logarithmic [14] decay were both obtained. This is to be compared with the possible stretched exponential...
Previous investigations indicated clearly that a detailed analysis of the energy level distribution is one requirement for understanding the related relaxation modes. However, this is not sufficient to determine the relaxation behavior completely. It is also important to know how the random heteropolymer or protein can make transitions between different energy levels corresponding to different polymer configurations. If such transitions are possible, one says that the levels are connected and the numerical values of the transition rates will determine the ease of transition. However, due to the microscopic origin of the connectedness and the transition rules, it becomes difficult to account for these parameters correctly. It is therefore a difficulty problem to predict the true asymptotics of a relaxation in these systems.

From the Master Equation approach point of view, there are difficulties for the investigation of dynamical systems involving random interactions, and in particular to predict the precise form of the relaxation process for folding. Let’s consider the relaxation to equilibrium in the unbiased random energy model \cite{14}. Here it was believed that the relaxation to equilibrium due to a temperature quench from above to below the freezing temperature follows a two stage kinetics \cite{14}. The first stage is characterized by a logarithmic relaxation of the extensive part of the energy, while in the second stage, when the system has already reached its frozen state, the relaxation follows a power law decay. However it has also been suggested that the relaxation dynamics can be described by a stretched exponential time dependence \cite{13}, or a single power law decay \cite{12}. In all these references a master equation was used to investigate the kinetics of relaxation in the context of the random energy model.

Why are there several different predictions for the asymptotics of the relaxational dynamics for the same model? The answer is related to the fact that different transition rates used in the Master Equation can lead to different asymptotics \cite{12}. If we define $W_{ij}$ to be a transition rate from the $i$-th energy level to the $j$-th one, and define $P_i^{eq}, P_j^{eq}$ to be the equilibrium probabilities for the two states, then according to detailed balance $W_{ij} P_i^{eq} = W_{ji} P_j^{eq}$. In terms of the energies of the $i$-th and $j$-th levels, the detailed balance condition takes the form $W_{ij} \exp \left( -\frac{E_i}{T} \right) = W_{ji} \exp \left( -\frac{E_j}{T} \right)$. Koper and Hilhorst suggested \cite{12} a general form of the transition rates: $W_{ij} = W_0 \exp \left( -(1-q)\frac{E_i}{T} \right) + q \frac{E_j}{T}$ where $0 \leq q \leq 1$. Adjusting the value of $q$ may lead to different asymptotics from the Master Equation. Indeed, one finds a stretched exponential decay \cite{13} by choosing $q = 0$, while a power law decay \cite{14,12} for $q = 1$ (choosing $q = 1$ means that all energy levels have the same activation energy).

While the relaxational dynamics by quenching to low temperatures is clearly complicated, one would in the case of high temperatures intuitively expect a single exponential relaxation as can be shown by investigating the high temperature limit using a highly connected random master equation. At $T \to \infty$, detailed balance gives $W_{ij} = W_{ji}$. Assuming that only a fraction $\gamma$ of states is connected, a possible choice of the transition rate is $W_{ij} = 1$ with probability $\gamma$ and $W_{ij} = 0$ with probability $1 - \gamma$. A study of the related random master equation leads to the conclusion that its eigenvalue distribution is sharply peaked at $N\gamma$ with a width of the order of $\sqrt{N}$ where $N$ is the number of states. This means that there
is a dominant time scale which is approximately given by $\frac{1}{\gamma}$, leading to single exponential decay at the high temperature region [15].

Since the random energy model and a highly connected random master equation are related to the problem of protein folding (both approaches are combined in the work of Ref. [11]), we arrive at the following picture for the behavior of the relaxational dynamics of proteins. At high temperatures, relaxation is described by a single exponential decay. Upon quenching from an unfolded state to equilibrium with a final temperature of the order of the freezing temperature, one might expect a power law, or a stretched exponential decay, while quenching to a temperature below the freezing point may well lead to an extremely slow logarithmic decay.

In the following sections we examine the above physical picture carefully by means of both numerical and analytical methods. Our analysis also provides insight into the crossover in the relaxation from a single exponential form at high temperatures to a non-Arrhenius relaxation near the freezing temperature. Our numerical simulations are based on Monte Carlo dynamics [8] for a protein model and we fit the data to various possible decay modes. In the theoretical model we note the analogy between random heteropolymer relaxation and spin glass dynamics, this allows us to construct an analytical model for the protein relaxation. The key idea is that the constraints to the relaxation of the degree of freedom at each energy level along the relaxation pathway must be taken account [3], and the constraint at a lower energy level depends on what happens on the higher one. The asymptotics of our analytical model together with the simulation data allows a physically reasonable picture to emerge for the relaxational dynamics of proteins.

The paper is organized as follows. Section II gives the results of numerical simulations for the distinct asymptotic relaxation behavior of the folding process at various temperatures using random sequences with protein-like energetics [17]. Section III contains our theoretical analysis where we derive the asymptotics of the relaxation. Finally Section IV is reserved for a short summary. The detailed algebra for the analysis is organized into two Appendices.

**II. NUMERICAL SIMULATION**

We simulated the relaxational dynamics of a model protein by focusing on the energy relaxation as a function of the simulation time. The simulation was carried out using the Monte-Carlo (MC) method on a 3D cubic lattice for a model protein with 27 amino acid residues. The contact interaction between the residues is described by the model of Li, Tang and Wingreen [2]. In this model, an analysis of the correlations between the elements of the Miyazawa-Jernigan (MJ) contact energy matrix [16], gave the contact energy of the protein in the following form [2,17],

$$E = \vec{n} \vec{q}.$$  

(1)

Here $\vec{n}$ and $\vec{q}$ are $L$ dimensional vectors. $L$ is the number of residues: $L = 27$ throughout all our numerical simulations. The vector $\vec{n}$ describes the geometric shape of the protein.
and its element $n_i$ is equal to the number of nearest neighbor contacts made by the $i$-th residue with other residues, as discussed in Ref. [17]. The vector $\vec{q}$ describes the interaction strength of the residues: the $i$-th element of $\vec{q}$ corresponds to the strength of the $i$-th monomer on the chain. The values of $q_i$ were found from a fit to the MJ matrix in Ref. [2].

Since there are twenty different amino acid residues, there will be twenty different values of $q_i$ as documented in Ref. [2]. As the MJ matrix was obtained from experimental data, the elements of $\vec{q}$ can be viewed as empirical parameters to our model. To use Eq. (1), we call two residues nearest neighbors if they are not connected along the chain but are separated by one lattice constant. In our simulation we fixed the value of $q_i$ in the range of $-2.5 < q_i < 0.0$, where a more hydrophobic amino acid residue has a more negative value of $q_i$. For example, for the 2D model protein depicted in Fig. (1), the first integer above each monomer corresponds to the number of nearest neighbors for that monomer, while the value $q_i$ of that monomer is written in parentheses. Then from Eq. (1), the total energy of this 2D protein is $E = 3q_1 + 2q_2 + q_3 + q_4 + q_6 + q_8 + q_9 + q_{11} + q_{12}$. We emphasize again that $\vec{n}$ specifies the geometry of the conformation while $\vec{q}$ specifies its protein sequence. Finally, we comment that in writing down Eq. (1) we have neglected a quadratic term [2,17] which gives a small correction to the linear term of Eq. (1). However, the relaxational dynamics of the model protein is not substantially affected by this quadratic term.

Our simulation considered nine randomly generated protein sequences, i.e. nine different $\vec{q}$ vectors. For each sequence we generated a set of relaxation curves corresponding to different quenches to different final temperatures and we studied the decay modes by averaging over the data for all nine sequences. The allowed moves for a monomer in the Monte Carlo simulation were chosen to be the end move, the corner move, and the crankshaft move [8]. For a given protein sequence, the initial state of the model protein was chosen to be completely unfolded so that the initial temperature $T_i = 16$ was about four times higher than that of the folding temperature of our model. After the equilibration of the protein at the high temperature $T_i$, it was quenched to a set of different final temperatures $T_f$ and the energy relaxation curves were recorded. Every quench $T_i \to T_f$ consisted of the following operations: a short equilibration of the system at high temperature $T_i$ using 50,000 MC steps followed by a quench to the final temperature $T_f$. The relaxation data was then stored over 200,000 MC steps. After a relaxation curve was recorded the same procedure was repeated many times for thermal averages starting from the same initial condition: 200 to 1500 quenches were averaged depending on the value of $T_f$ so as to obtain a smooth relaxation curve. Finally, we averaged over a set of different initial equilibrium configurations each with the same value of $T_i$.

Typical relaxation curves for a particular sequence and a set of different $T_f$ are presented in Fig. (2). All curves show a fast decay immediately after the temperature quench followed by a slow relaxation to the asymptotic regime. As we were interested in the non-Arrhenius relaxation modes, we fitted these relaxation curves by a stretched exponential, a power law and a logarithmic form respectively. The stretched exponential decay was taken to have the form
\[ R(t) = a_0 + a_1 e^{(-\frac{t}{a_2})^\gamma}. \]  

(2)

The power law decay was chosen to be

\[ R(t) = a_0 + \left(\frac{a_2}{t}\right)^\beta. \]  

(3)

Finally, the logarithmic decay mode was fitted by

\[ R(t) = a_0 - a_1 \ln t. \]  

(4)

In equations (2,3,4), \( a_0, a_1, a_2, \gamma, \) and \( \beta \) are fitting parameters. In the following we analyze these fittings.

The fitted value of the stretched exponent \( \gamma \) is shown in Fig. (3) as a function of the final temperature \( T_f \). This plot is obtained from a particular sequence \( \vec{q} \). In the fit we used the entire range of the relaxation data where \( t \in (2.0, 10.0) \) (see Fig. (2)). Although there are substantial error bars for \( \gamma \), its temperature dependence appears to have three different regions. At high \( T_f \), the data is consistent with \( \gamma \approx 1 \). This is reasonable since the relaxational dynamics at a high \( T_f \) should, as discussed above, be a single exponential decay. For an intermediate range of \( T_f \) as shown in Fig. (3), \( \gamma = \gamma(T_f) \) reduces steadily with \( T_f \). Finally at very low temperatures, \( T_f \in (0.0, 2.0) \), \( \gamma \) has a value close to 0.3. However, such a small value of \( \gamma \) usually indicates that the decay is actually not in a stretched exponential form but has instead a different relaxational behavior such as a power law.

The result of fitting the relaxation curves to a power law is summarized in Fig. (4), where the fitted power \( \beta \) is shown as a function of \( T_f \). The difficulty in fitting to a power law is that a divergence occurs at the quenching time \( t = 2 \) (see Fig. (3)). Since we expect the power law decay to be a possible asymptotic of the relaxation, we used the simulation data for the time period of \( t \in (2.1, 10.0) \) to avoid the divergence. Also, as the final temperature \( T_f \) increases, the characteristic relaxation time (parameter \( a_2 \)) decreases substantially and it becomes quite difficult to fit the data to a power law accurately. This is the reason why the dependence of \( \beta \) on \( T_f \) shown on Fig. (4) is only shown below \( T_f = 3.0 \). Nevertheless, it is clear that this dependence in the range \( T_f \in (2.0, 3.0) \) is given by roughly a straight line, namely \( \beta \sim T_f - T_f^\beta \). Extrapolating this line backwards gives \( T_f^\beta \sim 1.5 \). An important feature of Fig. (4) is that as \( T_f \) is in the range \( \in (0.0, 2.0) \), the relaxation become extremely slow and the power \( \beta \) levels off at a small value \( \beta \sim 0.3 \). The fact that both the stretched exponent \( \gamma \) and the power law \( \beta \) change their behavior at nearly the same value of \( T_f(\sim 2.0) \) signals that a transition to a frozen state occurs near this temperature.

We attempted to fit the relaxation data for the low temperature range \( T_f \in (0.0, 2.0) \) with a logarithmic decay. An almost perfect fit was found for all the sequences at \( T_f^{\log} \sim 1.5 \), as shown in Fig. (5). Note that \( T_f^{\log} \sim T_f^\beta \). We believe that the logarithmic decay mode sets in near the freezing temperature as demonstrated by the random energy model [14]. We thus denote this special temperature scale to be \( T_G \): \( T_G \sim T_f^{\log} \sim T_f^\beta \). We shall use the notation \( T_G \) in the rest of this paper as it is reminiscent of a glass transition temperature. Note
that the nature of glass transition temperature for copolymer systems has been thoroughly examined in Ref. \[8\] and we refer interested readers to that article for details concerning the related physics.

Our numerical prediction of the occurrence of a low temperature logarithmic decay mode at temperature \(T_\text{G}\) agrees with the prediction for the random energy model of Ref. \[14\]. In addition, from the theoretical analysis of the random energy model in Ref. \[12\], it follows that the relaxation near \(T_\text{G}\) should follow a power law decay with a power \(\beta \sim (T - T_\text{G})\). Our simulation data presented in Fig. 4 is consistent with this linear dependence. On the other hand, we found that fitting the data near the freezing point \(T_\text{G}\) with a stretched exponential does not produce an exponent \(\gamma\) lying along the line which would be expected from Ref. \[13\]. Finally, from our numerical data it still remains unclear whether the asymptotics above the freezing temperature follows a stretched exponential decay, although it is apparent that the data can be reasonably well fitted by such a stretched exponential.

### III. THEORETICAL ANALYSIS

To understand the simulation data presented in the last section, in the following we make a theoretical analysis of the relaxation based on the model of hierarchically constrained dynamics for glassy system relaxation \[3\].

The conventional Arrhenius relaxation is described by a single exponential decay with a time scale \(\tau\)

\[
R(t) = R_0 \exp\left(-\frac{t}{\tau}\right)
\]

where \(R(t)\) is the physical quantity of interest. We obtain a more complicated relaxation behavior by assuming a distribution of time scales. Suppose that \(P(\tau)\) is a continuous distribution of possible time scales in our system, then, using the notion of parallel relaxation we write for the total relaxation process \[3\]

\[
R(t) = R_0 \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} P(\tau) \exp\left(-\frac{t}{\tau}\right) d\tau
\]

This approach is especially attractive in the case where dynamics is modeled by the Master Equation. As the Master Equation is a first order differential equation, the general solution will be a sum of exponential decays with time scales inversely proportion to the eigenvalues \(\lambda\) of the transition matrix. A distribution of time scales \(P(\tau)\) thus corresponds to the distribution of inverse eigenvalues \(P\left(\frac{1}{\lambda}\right)\).

As pointed out by Palmer et. al. \[3\], though a description of relaxation by \(6\) is certainly appealing, the nature of \(P(\tau)\) is not \textit{a priori} clear. In the dynamics of such complex systems as random polymers or proteins, it is intuitively plausible that \(P(\tau)\) should take into account the dynamic constraints: \textit{e.g.} monomer A cannot move until monomer B moves out of the way. \(P(\tau)\) may also depend on such factors as ergodicity breaking in a frozen state of the
system. The theory should also involve a hierarchy of degrees of freedom from fast to slow. For the protein problem, the fastest degrees of freedom could involve single-atom motion, while slower degrees of freedom could involve a diffusion of domains of secondary structure.

The original theory of Ref. [3] considered a discrete set of levels \( n = 1, 2, 3, \ldots, N \) with the degrees of freedom in level \( n \) represented by \( N_n \) pseudospins \( S_i \). Each spin in the \((n-1)\)th level is only free to change its state if a condition on some spins at level \( n \) is satisfied, thus providing a hierarchy of constraints. This is the key idea of the model as shown schematically in Fig. (6). We take the constraint to be that \( \tilde{\mu}_n \) spins in level \( n \) (\( \tilde{\mu}_n < N_n \)) attain one particular state out of their \( 2^{\tilde{\mu}_n} \) possible states. Then the average relaxation times \( \tau_{n-1} \) will be related to \( \tau_n \) as \( \tau_{n-1} = 2^{\tilde{\mu}_n} \tau_n \). Hence,

\[
\tau_n = \tau_N \exp \left( \sum_{i=n}^{N} \mu_i \right) \tag{7}
\]

where \( \mu_i = \tilde{\mu}_i \ln 2 \), and \( \tau_N \) sets the time scale of the relaxation. The average relaxation can now be written as follows

\[
R(t) = R_0 \sum_{n=1}^{N} N_n \exp \left( -\frac{t}{\tau_n} \right) \tag{8}
\]

\[
\tau_n = \tau_N \exp \left( \sum_{i=n}^{N} \mu_i \right) . \tag{9}
\]

To apply this theory to protein folding dynamics, we notice that the summation is taken over \((N - n)\) higher energy levels in Eq. (7) since the states corresponding to the higher energy levels (the unfolded states) relax very fast because of minimal dynamical constraints. Clearly, as the folding proceeds and the level index \( n \) decreases, there will be an increased number of dynamical constraints on folding as the protein becomes geometrically more compact. Hence the relaxation times for the more folded states should increase in comparison to those of the less folded states. The meaning of the “pseudospins” of Ref. [3] in our protein problem can be elucidated by noticing the similarity of a spin flip and a local monomer move. For instance, a crankshaft move, a corner move or an end move in our Monte Carlo simulation could be compared with a pseudospin flip, while a configuration of spins could represent a protein conformation. Two energetically close protein conformations may differ from each other by a local move of a monomer, similar to the flip of a spin. It is much easier to make a local move (a spin flip) in an unfolded state than in a folded state because of the energetics consideration and the importance of volume exclusion interactions in compact protein conformations. Clearly, the analogy of pseudospin flips to local monomer moves can be extended to more realistic off-lattice protein models.

From the above discussion, we now make some assumptions about the form of \( \mu_i \) and \( N_n \) for the protein problem. First, from the form of Eq. (7) one can immediately deduce that \( \mu_i \) should depend upon temperature. When \( T \to \infty \), the relaxation should be a single exponential, from Eq. (8) we conclude \( \tau_n (T \to \infty) = const \) and it should not depend
on $n$. The simplest form for $\mu_i$ satisfying these conditions is $\mu_i = \frac{T_f}{T}$. As far as $N_n$ is concerned, it should be proportional to the total number of states on each level. When $T \to \infty$, all the pseudospins are excited so that $N_n$ in this limit equals to the number of pseudospins on the $n$th level. As temperature decreases and the system finally goes into the frozen state, the number of pseudospins on each level should decrease to the order of unity signifying ergodicity breaking in the relaxational dynamics. For our protein problem, in the low temperature limit the decrease in the number of pseudospins corresponds to the restriction of the dynamical space to a set of specific pathways for protein relaxation. In our model we choose $N_n$ to depend on temperature in the form

$$N_n = \lambda^{n(1-\mu_g)}$$

where $\mu_g = \frac{T_g}{T}$ and $T_g$ corresponds to the “level freezing” temperature of Ref. [18]. Summarizing all these considerations, our complete model for protein relaxational dynamics is given by

$$R(t) = R_0 \sum_{n=1}^{N} \lambda^n \exp\left(-\frac{t}{\tau_n}\right)$$

(11)

$$\tau_n = \tau_N \exp\left(\sum_{i=n}^{N} \frac{T_f}{T}\right).$$

(12)

It is convenient to write our model in an integral form, so that

$$R(t) = R_0 \int_{\tau_{\min}}^{\tau_{\max}} P(\tau) \exp\left(-\frac{t}{\tau}\right) d\tau$$

(13)

Here the function $N(n)$ is the continuous version of (10).

To make further analysis tractable and considering the fact that $N$ is large, we make a reasonable assumption that $T_g^n$ and $T_f^n$ to be roughly constants for all energy levels, so that $\mu_g = \frac{T_g}{T}$ and $\mu_f = \frac{T_f}{T}$. The above expressions can be written in terms of the distribution of time scales $\tau$:

$$R(t) = R_0 \int_{\tau_{\min}}^{\tau_{\max}} (N(n) \frac{dn}{d\tau})|_{\tau=\tau_n} \exp\left(-\frac{t}{\tau}\right) d\tau$$

(14)

where $\tau_{\min} = \tau_N$ and $\tau_{\max} = \tau_N \exp\left(\sum_{i=n}^{N} \mu_i\right)$. Comparing the above equation with (3), we notice that the distribution of time scales is just

$$P(\tau) = N(n) \frac{dn}{d\tau}|_{\tau=\tau_n},$$

(15)

where the right hand side is understood as replacing all $n$ dependence by $\tau$ through the transformation $\tau = \tau_n$ using Eq. (12). It is then straightforward to obtain,

$$R(t) = R_0 \int_{\tau_{\min}}^{\tau_{\max}} P(\tau) \exp\left(-\frac{t}{\tau}\right) d\tau$$

(16)
with an unnormalized distribution of time scales
\[ P(\tau) \sim \left( \frac{\tau^N}{\tau} \right)^{(1-\mu g)\ln \lambda} \tau^{1+\eta} . \]  

(17)

Denoting
\[ \beta \equiv \frac{1 - \mu g \ln \lambda}{\mu f \ln \lambda} = \frac{T - T^g}{T_f \ln \lambda} \]  

(18)

we obtain a main result of this analysis,
\[ R(t) = R_0 \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} \left( \frac{\tau^N}{\tau} \right)^{\beta+1} \exp \left( -\frac{t}{\tau} \right) d\tau . \]  

(19)

One of the important outcomes of our model is that the distribution of time scales is a power law. We now discuss several possible cases for different temperatures.

**A. The case of \( T < T^g \)**

For low temperatures \( T < T^g \), from Eq. (18) \( \beta < 0 \). We define \( \eta \equiv -\beta \) so that \( \eta > 0 \). Then the normalized time scale distribution (17) becomes
\[ P(\tau) = \frac{\eta}{\tau_{\text{min}}} \left( \frac{\tau_{\text{max}}}{\tau_{\text{min}}} \right)^{\eta - 1} \left( \frac{\tau_{\text{min}}}{\tau} \right)^{1-\eta} . \]  

(20)

The relaxation, obtained from Eq. (19), is
\[ R(t) = R_0 \eta^\eta \frac{\tau_{\text{max}}^\eta - \tau_{\text{min}}^\eta}{\tau_{\text{max}}^\eta - \tau_{\text{min}}^\eta} \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} \chi^{-1-\eta} \exp(-\chi) d\chi \]  

(21)

where \( \tau_{\text{min}} = \tau_N \) and \( \tau_{\text{max}} = \tau_N \exp(N T_f / T^g) \). \( R(t) \) is normalized so that \( R(t)|_{t=0} = 1.0 \). Notice that we cannot simply extend the integration from \( (\tau_{\text{min}}, \tau_{\text{max}}) \) to \( (0, \infty) \) because the integral would then diverge. Still, it is not difficult to obtain an asymptotic form of this expression as \( \eta \to 0 \) and \( t \gg \tau_{\text{min}} \). From the detailed analysis presented in Appendix I, the final asymptotic of the relaxation for this temperature range is given by,
\[ R(t) \approx c_1 - c_2 \ln t \]  

(22)

where \( c_1 \) and \( c_2 \) are constants.

Fitting the low temperature simulation data of the last section to this logarithmic decay, as shown in Fig. (5), a very good fit is obtained in the interval \( 1.5 \geq T \geq 1.25 \). Since \( T^g \) is the level freezing temperature, and when all the individual energy levels freeze, the whole system freezes. Thus we must have \( T^g \sim T_G \) which is the freezing transition temperature discussed in section II. This allows us to conclude that the hierarchically constrained dynamics model presented in this section has a logarithmic decay mode for low temperatures \( T < T_G \) as the true asymptotic.
B. The case of $T > T^g$

When at higher temperatures $T > T^g$, from Eq. (18) we have $\beta > 0$. In this case, a normalized time scale distribution, (17), will be

$$P(\tau) = \frac{\beta}{\tau_{\text{min}} \left[ 1 - \left( \frac{\tau_{\text{max}}}{\tau_{\text{max}}} \right)^{\beta} \right]} \left( \frac{\tau_{\text{min}}}{\tau} \right)^{1+\beta}.$$  \hspace{1cm} (23)

The relaxation is thus

$$R(t) = \beta \left( \frac{1}{\tau_{\text{min}}} \right)^{1+\beta} \frac{1}{(\tau_{\text{min}})^{\beta} - (\tau_{\text{max}})^{\beta} t^\beta} \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} \chi^{\beta-1} \exp(-\chi) d\chi.$$  \hspace{1cm} (24)

As $\tau_{\text{max}} \gg t \gg \tau_{\text{min}}$, the integral in $R(t)$ can be extended from $(\tau_{\text{min}}, \tau_{\text{max}})$ to $(0, \infty)$ without introducing too much error (the integral is also convergent in the whole interval). Hence,

$$R(t) \approx \text{const}(\beta) \left( \frac{\tau_{\text{min}}}{t} \right)^{\beta}.$$  \hspace{1cm} (25)

We thus obtain a power law decay for the relaxation when $T > T^g$. Moreover, since the exponent $\beta = \frac{T - T^g}{T_f \ln\lambda}$, we can expect a linear dependence of $\beta$ as a function of temperature near the freezing transition point. Our simulation data of Fig. (4) agrees with this result and gives $T^g = 1.5, \frac{T_f}{T^g \ln\lambda} = 1.2$.

C. The case of $T \gg T^g$

We note that formally, the case of $\beta > 0$ should be divided into two regimes: $1 > \beta > 0$ and $\beta \geq 1$. The latter has a special point $\beta = 1$ because of the integrand of Eq. (24) which can be written as follows

$$\Theta(\beta, t) \equiv \int_{0}^{t} \chi^{\beta-1} \exp(-\chi) d\chi.$$  \hspace{1cm} (26)

Taking into account the continuous behavior of $\Theta(\beta, t)$ for $\beta > 1$, let us calculate the relaxation

$$R(t) = \frac{\beta}{(\tau_{\text{min}})^{\beta} - (\tau_{\text{max}})^{\beta} t^\beta} \Theta(\beta, t)$$  \hspace{1cm} (27)

as $\beta = p$ where $p$ is any positive integer. In this case $\Theta(\beta, t)$ can be calculated analytically and the details are given in Appendix II. The relaxation function is found to be

$$R(t) = \exp\left(-\frac{t}{\tau_{\text{min}}}\right) \left(1 + \frac{\left(\frac{t}{\tau_{\text{min}}}\right)}{(p+1)} + \frac{\left(\frac{t}{\tau_{\text{min}}}\right)^2}{(p+1)(p+2)} + \frac{\left(\frac{t}{\tau_{\text{min}}}\right)^3}{(p+1)(p+2)(p+3)} + \ldots\right)$$  \hspace{1cm} (28)

Hence, as temperature increases, non-Arrhenius decay modes would be observed as asymptotics at $t \gg (p+1)\tau_{\text{min}}$, while an initial stage of relaxation $t \lesssim (p+1)\tau_{\text{min}}$ will be an
Arrhenius-like single exponential decay. As temperature increases, the overall relaxation time to equilibrium becomes shorter and, finally, it becomes impossible to distinguish non-Arrhenius asymptotics at the tail of the relaxation function. Notice that the onset of the single exponential decay occurs at temperatures corresponding to $\beta > \sim 1$ or $T > T_g + \frac{T_f}{\ln \lambda}$.

From the simulation data of Fig. (4), we can calculate that this occurs as $T > \sim 2.7$ which corresponds approximately to the midpoint of the crossover regime from $\gamma = 1.0$ to $\gamma \sim 0.3$ on Fig. (3). This result indicates that although one can fit the simulation data as a stretched exponential, it is quite possible that this fit does not in fact give the correct asymptotic nature of the crossover from a single exponential to a power law decay as temperature changes.

Finally, we comment that we were not able to obtain a stretched exponential asymptotic decay from our analytical theory. In general, a transition from single exponential decay at high temperatures to power law decay at lower temperatures could proceed via a set of more intricate functions reminiscent of stretched exponentials. However, whether these functions have stretched exponentials as their true asymptotics can not as yet be resolved from the theory presented in this section.

IV. SUMMARY

In this work we addressed the problem of the relaxational dynamics of a model protein for temperature quenches from an unfolded state at high temperature to a range of low temperatures. The results of our Monte Carlo simulations and our theoretical analysis of a hierarchical model proposed for the protein relaxation dynamics clearly indicate three different decay modes: first a logarithmic decay at $T \lesssim T^g$, next an asymptotic power law decay at $T \gtrsim T^g$ with the power $\beta \sim (T - T^g)$ and finally, as the temperature increases to $T \gtrsim T^g + \frac{T_f}{\ln \lambda}$, a single exponential decay. Here the temperature scale $T^g$ describes a freezing transition where the decay mode changes. Our numerical and analytical results suggest that a crossover from a power law relaxation to a single exponential decay occurs via an intricate interplay between the time intervals for which these decay modes are valid, although this crossover can be reasonably fitted numerically to a stretched exponential form.

ACKNOWLEDGMENTS

The authors wish to thank Christine Villeneuve for helpful discussions and assistance concerning the Monte Carlo simulations. We gratefully acknowledge support by the Natural Sciences and Engineering Research Council of Canada and le Fonds FCAR du Québec. One of the authors (MJZ) is an Associate of the Canadian Institute for Advanced Research.
In the appendix we derive the logarithmic decay form for low temperatures \( T < T_g \). As stated in section III, the relaxation function at \( \beta < 0 \), \( \eta = -\beta \) is

\[
R(t) = \frac{\eta^t}{\tau_{\text{max}}^\eta - \tau_{\text{min}}^\eta} \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} \chi^{-1-\eta} \exp(-\chi) d\chi.
\]  

(29)

We can rewrite this expression in a form

\[
R(t) = \frac{\eta^t}{\tau_{\text{max}}^\eta - \tau_{\text{min}}^\eta} \int_{\tau_{\text{min}}}^{\tau_{\text{max}}} \chi^{-1-\eta} \left( \sum_{i=0}^{\infty} \frac{(-1)^i}{i!} \chi^i \right) d\chi.
\]  

(30)

After integration of the \( \chi \) variable, we have

\[
R(t) = 1 + \frac{\eta}{\tau_{\text{max}}^\eta - \tau_{\text{min}}^\eta} \left[ \sum_{i=1}^{\infty} \frac{(-1)^i}{i!} \left( \frac{t}{\tau_{\text{min}}^\eta - \tau_{\text{min}}^\eta} \right)^i \right] + O(\eta).
\]  

(31)

As \( \eta \to 0 \) and noticing \( \tau_{\text{max}} \gg \tau_{\text{min}} \), \( R(t) \) becomes

\[
R(t) = 1 + \frac{1}{\ln(\tau_{\text{min}}/\tau_{\text{max}})} \left[ \sum_{i=1}^{\infty} \frac{(-1)^i}{i!} \left( \frac{t}{\tau_{\text{min}}^\eta} \right)^i \right] + O(\eta).
\]  

(32)

To sum up the series, we differentiate \( R(t) \) to obtain

\[
R(t)' = \frac{1}{\ln(\tau_{\text{min}}/\tau_{\text{max}})} \left[ \sum_{i=1}^{\infty} \frac{(-1)^i}{i!} \left( \frac{t}{\tau_{\text{min}}^\eta} \right)^{i-1} \right] + O(\eta).
\]  

(33)

We can now perform the summation to obtain

\[
R(t)' = \frac{1}{\ln(\tau_{\text{min}}/\tau_{\text{max}})} \left[ e^{-\frac{t}{\tau_{\text{min}}^\eta}} - 1 \right] + O(\eta). 
\]  

(34)

As \( t \gg \tau_{\text{min}} \), \( R(t)' \) becomes even simpler

\[
R(t)' = -\frac{1}{\ln(\tau_{\text{min}}/\tau_{\text{max}})} t + O(\eta). 
\]  

(35)

Final integration yields

\[
R(t) = \text{const} - \frac{1}{\ln(\tau_{\text{min}}/\tau_{\text{max}})} \ln(t) + O(\eta)
\]  

(36)

which is the logarithmic decay.
APPENDIX II

For $\beta > 0$,

$$\Theta(\beta, t) = \int_0^{\tau_{\min}} \chi^{\beta - 1} \exp(-\chi) d\chi$$  \hspace{1cm} (37)

The relaxation function is then given by

$$R(t) = 3D \frac{1}{(\tau_{\min})^{\beta}} - \frac{1}{(\tau_{\max})^{\beta}} \frac{t^\beta}{t^\beta} \Theta(\beta, t) .$$  \hspace{1cm} (38)

Choosing $\beta = p$, where $p$ is a positive integer, and assuming that $\tau_{\max} \gg \tau_{\min}$, we obtain

$$\Theta(\beta, t) = \int_0^{\tau_{\min}} \chi^{p-1} \exp(-\chi) d\chi$$  \hspace{1cm} (39)

and

$$R(t) = p(\tau_{\min})^p \Theta(p, t) .$$  \hspace{1cm} (40)

$\Theta(\beta, t)$ is a standard integral and can be evaluated to give

$$\Theta(\beta, t) = 3D(p - 1)! (1 - \exp(-\frac{t}{\tau_{\min}})(1 + \frac{(t/\tau_{\min})}{1!} + \frac{(t/\tau_{\min})^2}{2!} + \ldots + \frac{(t/\tau_{\min})^{p-1}}{(p - 1)!})) .$$  \hspace{1cm} (41)

Noticing that

$$1 + \frac{(t/\tau_{\min})}{1!} + \frac{(t/\tau_{\min})^2}{2!} + \ldots + \frac{(t/\tau_{\min})^{p-1}}{(p - 1)!} = \exp\left(\frac{t}{\tau_{\min}}\right) - \sum_{p} \frac{(t/\tau_{\min})^i}{i!}$$  \hspace{1cm} (42)

after substitution to (41) and (40) we find

$$R(t) = \exp\left(-\frac{t}{\tau_{\min}}\right)(1 + \frac{(t/\tau_{\min})}{(p + 1)} + \frac{(t/\tau_{\min})^2}{(p + 1)(p + 2)} + \frac{(t/\tau_{\min})^3}{(p + 1)(p + 2)(p + 3)} + \ldots)$$  \hspace{1cm} (43)

which is the desired result.
REFERENCES

[1] For a recent review of the protein folding subject, see, for example, the article of Ken A. Dill et al., in Protein Science, 4, 561 (1995) and Joseph D. Bryngelson, Jose Nelson Onuchic, Nicholas D. Socci, and Peter G. Wolynes in Proteins: Structure, Function, and Genetics 21, 167 (1995).

[2] Hao Li, Chao Tang and Ned Wingreen, Phys. Rev. Lett. 79, 765 (1997).

[3] R.G. Palmer et al., Physical Review Letters 53, 958 (1984).

[4] E.I. Shakhnovich and A.M. Gutin, Biophys. Chem. 34, 187 (1989).

[5] E.I. Shakhnovich and A.M. Gutin, Europhys. Lett., 8, 327 (1989).

[6] G. Iori, E. Marinari and G. Parisi, J. Phys. A 24 5349 (1991); G. Iori, E. Marinari, G. Parisi and M.V. Struglia, Physica, 185A, 98 (1992).

[7] Hue Sun Chan et al., J. Chem. Phys.,96 (1992).

[8] Nicholas D. Socci and Jose Nelson Onuchic, J. Chem. Phys. 101, 1519 (1994).

[9] C. Villeneuve, Hong Guo and M.J. Zuckermann, Macromolecules, 30, 3066, 1997.

[10] B. Derrida, Phys. Rev. Lett., 45, 79(1980); Phys. Rev. B 24, 2613 (1981).

[11] J.D. Brungelson and P.G. Wolynes, J. Phys. Chem. 93, 6902 (1989).

[12] G.J.M. Koper and H.J. Hilhorst, Europhysics Letters 3, 1213 (1987).

[13] C. De Dominicis, H. Orland and F. Laine, Le Journal De Physique-Letters 46, L-463 (1985).

[14] E.I. Shakhnovich and A.M. Gutin, Europhysics Letters 9, 569 (1989).

[15] Robert Zwanzig, J. Chem. Phys. 103, 9397 (1995).

[16] S. Miyazawa and R.L. Jernigan, Macromolecules 18, 534 (1985).

[17] M. Skorobogatiy, H. Guo, M. Zuckermann, Macromolecules, 30,3403 (1997).

[18] Vitor B. P. Leite and José N. Onuchic, J. Phys. Chem. 100, 7680 (1996).
FIGURES

FIG. 1. A 2D lattice model of a protein. The figure over each monomer indicates the number of its nearest neighbors. The parameter in parentheses indicates the strength of amino-acid situated on a particular site.

FIG. 2. A typical set of relaxation curves for a temperature quench $T_1 \rightarrow T_f$, for a given sequence and different final temperatures. The unit of time is 25,000 Monte Carlo steps.

FIG. 3. Fit to a stretched exponential decay. All nine $\gamma - T_f$ curves for different sequences were averaged to obtain the averaged behavior of the stretched exponential relaxation as a function of the final temperature of the quench. An individual $\gamma - T_f$ curve for a particular sequence was obtained by fitting the relaxation curves to a stretched exponential form.

FIG. 4. Fit to a power law decay. All nine $\beta - T_f$ curves for different sequences were averaged to obtain the average behavior of the power law relaxation as a function of the final temperature of the quench. An individual $\beta - T_f$ curve for a particular sequence was obtained by fitting the relaxation curves to a power law decay form.

FIG. 5. Fit to a logarithmic decay mode for a specific sequence. Similar fits for other sequences show that the best fit is found for $T_f \sim 1.5$.

FIG. 6. Model of hierarchically constrained dynamics for relaxation. The probability of the pseudospin flip on the $(n - 1)th$ level is coupled to the probability of occurrence of a specific configuration of pseudospins on level $n$. 
