Glassy Dynamics of Protein Folding

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A coarse grained model of a random polypeptide chain, with only discrete torsional degrees of freedom and Hookean springs connecting pairs of hydrophobic residues is shown to display stretched exponential relaxation under Metropolis dynamics at low temperatures with the exponent $\beta \simeq 1/4$, in agreement with the best experimental results. The time dependent correlation functions for fluctuations about the native state, computed in the Gaussian approximation for real proteins, have also been found to have the same functional form. Our results indicate that the energy landscape exhibits universal features over a very large range of energies and is relatively independent of the specific dynamics.

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A huge amount of effort has recently been invested in modeling the interactions responsible for yielding the native states of proteins as their thermodynamic equilibrium state \([1,2]\). It has recently begun to be appreciated that such features of real proteins as the density of vibrational energy states \([3]\) may be reproduced by coarse-grained model hamiltonians which capture the essential mechanism driving the folding process, namely hydrophobic interactions \([3,4]\). In this paper we introduce and study a model of \(N\) coupled, over–damped torsional degrees of freedom with discrete allowed states. Under Metropolis Monte Carlo dynamics, with random initial conditions, we find that at low temperatures the model exhibits power law relaxation for the initial stages of decay, and at the later stages the relaxation obeys a stretched exponential with the exponent $\beta \simeq 1/4$. This type of relaxation behaviour is of the Kohlrausch-Williams-Watts type as observed experimentally for real proteins \([1,4,5]\). We find that at zero temperature the probability distribution function of the energy steps encountered along a relaxation path in phase space also obeys a stretched exponential form, with another exponent $\alpha \simeq 0.39$. We show that $\beta = \alpha/(\alpha + 1)$, yielding a value for $\beta$ which is in very good agreement with our simulation results.

We take as our point of departure the model proposed by Haliöglu, Bahar, Erman \([6]\). The central idea of this model is that all interactions in the protein are governed by confining square-law potentials, so all attractions may be treated as if the residues interact with each other through Hookean forces \([6,8]\).

To keep our model very simple, we consider covalent bonds as fixed rods of equal length. The residues located at the vertices may be polar \(P\) or hydrophobic \(H\). All the hydrophobic vertices are to be connected to each other with springs of equal stiffness. This feature mimicks the effective pressure that is exerted on the hydrophobic residues by the ambient water molecules, and results in their being driven to the relatively less exposed center of the molecule in the low lying energy states, whereas the polar residues are closer to the surface (see Fig. 1), a feature that is common to the native configurations. The constraints placed on the conformations due to the rigid chemical bond lengths and restriction of the chemical and dihedral angles to discrete values prevent the molecule from collapsing to a point.

![FIG. 1. A chain of \(N = 48\) residues, half of which are randomly chosen to be hydrophobic, (darker beads) shown a) in a random initial configuration and b) in a folded state reached under Metropolis dynamics. The chain has folded in such a way as to leave the polar residues on the outside. (Generated using RasMol V2.6)\(]
a highly degenerate ground state. Nevertheless, in our Monte Carlo study we considered a generic H-P sequence obtained by choosing fifty percent of the residues to be hydrophobic and distributing them randomly along the chain. In the absence of detailed knowledge regarding the rules singling out the realistic H-P sequences we believed this to be in keeping with our statistical approach. It might be speculated that the choice of equal probabilities for encountering H and P groups along the chain, and distributing them randomly, maximizes the configurational entropy of the chain [13] and enhances the “designability” giving rise to rather realistic results.

Our model for the protein chain consists of \( N \) “residues” which are treated as point vertices, connected to each other by rigid rods. The “bond angle” \( \alpha_i \) at the \( i \)’th vertex, \( i = 1, \ldots, N - 1 \), is fixed to be \((-1)^i\alpha\), with \( \alpha = 60^\circ \). The dihedral angles \( \phi_i \) can take on the values of 0 and \( \pm2\pi/3 \). The state (conformation) of the system is uniquely specified once the numbers \( \{\phi_i\} \) are given. Thus, the residues effectively reside on the vertices of a tetrahedral lattice.

The energy of the molecule is

\[
E = \frac{K}{2} \sum_{i,j} c_{i,j} |\mathbf{r}_i - \mathbf{r}_j|^2 = K \sum_{i,j} r_{ij}^2 V_{ij} r_{ij}
\]

If we define \( Q_i = 1 \) for the \( i \)’th vertex being occupied by a hydrophobic residue, and \( Q_i = 0 \) otherwise, we may write \( c_{i,j} = Q_i Q_j \) and

\[
V_{ij} = [(N - 1)c_{i+1} - c_{i,j-1} - c_{i,j+1}]\delta_{i,j} - (1 - \delta_{i,j})(1 - \delta_{i,j-1} - \delta_{i,j+1})\delta_{i,j}.
\]

The position vectors \( \mathbf{r}_i \) of each of the vertices in the chain can be expressed in terms of a sum over the directors \( \mathbf{R}_i \) of unit length representing the chemical bonds, which may be obtained from \( \mathbf{R}_i \) by successive rotations \( \mathbf{M}_k(\alpha_k) \) and \( \mathbf{T}_k(\phi_k) \) through the bond and the dihedral angles [14],

\[
\mathbf{r}_i = \sum_{j=1}^{i-1} \prod_{k=j}^{i-2} \mathbf{T}_k(\phi_k) \mathbf{M}_k(\alpha_k) \mathbf{R}_i,
\]

where we may choose \( \mathbf{R}_1 \) along any Cartesian direction in our laboratory frame without loss of generality.

In order to investigate the relaxation properties of the present model, we have employed Metropolis Monte Carlo dynamics. This consisted of \( a \) choosing a pair \((i,i')\) of dihedral angles randomly on the chain, and updating the \((\phi_i, \phi_{i'})\) in a way that preserves angular momentum, incrementing them in opposite directions by \( \Delta \phi = \pm 2\pi/3, b \) accepting the move with unit probability if \( \Delta E \leq 0 \) and with probability \( p = \exp(-\gamma \Delta E) \) for \( \Delta E > 0, c \) repeating the second step once before discarding the pair altogether and going to the first step. Here \( \gamma \) serves as an effective inverse temperature. We monitor the relaxation of the total energy as a function of “time” measured in the number of MC steps, (i.e., the number of pairs \((i,i')\) sampled) until a steady state is reached, typically in about 10,000 steps. The results for chains of \( N = 100 \) averaged over 20 randomly chosen initial configurations at zero temperature (\( \gamma = \infty \)) are shown in Fig. 2. Defining \( \epsilon \equiv (E - E_0)/E_I \), where \( E_0 \) is the (time-averaged) equilibrium energy and \( E_I \), the initial value, we find that it obeys a power law, \( \epsilon(t) \sim t^{-\sigma} \) with \( \sigma = 0.49 \pm 0.01 \) for the initial stages of the decay, while later stages can be fitted by a stretched exponential \( \epsilon(t) \sim e^{-\theta t^\beta} \) with \( \beta = 0.234 \pm 0.003 \). We also performed simulations for different values of \( \gamma \), for chains.
of \( N = 48 \), averaging over 100 runs with random initial configurations. For \( \gamma \to \infty \), \( \gamma = 0.5 \) and \( \gamma = 0.3 \), the above relaxation behaviour continues to hold and the exponents do not seem to depend on \( \gamma \), with \( \beta \simeq 1/4 \) and \( \sigma \simeq 1/2 \) as given in Table I.

Table I The exponent \( \sigma \) and \( \beta \) found for the power law and stretched exponential decay of the total energy with time, for different chain lengths \( N \) and inverse temperatures \( \beta \). The fits were obtained from a weighted least-squares computation.

| \( N \) | \( \gamma \) | \( \sigma \) | \( \Delta \sigma \) | \( \beta \) | \( \Delta \beta \) |
|---|---|---|---|---|---|
| 48 | \( \infty \) | 0.57 | 0.01 | 0.281 | 0.004 |
| 48 | 0.5 | 0.56 | 0.01 | 0.30 | 0.04 |
| 48 | 0.3 | 0.57 | 0.01 | 0.25 | 0.03 |
| 100 | \( \infty \) | 0.49 | 0.01 | 0.234 | 0.003 |

The variation of the total energy in time is sketched in Fig. 4 over a short sequence of relaxation events. Clearly one may write \( E(t) \), averaged over many independent runs, as \( \langle E(t) \rangle = \langle E(0) - \sum_{i=1}^{M} \Delta E_i \Theta(t - t_i) \rangle \) where \( \Theta \) is the Heavyside step function and \( t_i = \sum_{k=0}^{i-1} \tau_k \). Taking the time derivative one gets,

\[
\langle \dot{E}(t) \rangle = -\sum_{i=1}^{M} \Delta E_i \delta(t - \sum_{k=0}^{i-1} \tau_k) \quad . \tag{4}
\]

At zero temperature, the expectation value of \( \dot{E}(t) \) can be calculated by carrying out an integration over the distribution of waiting times \( \{ \tau_k \} \), and the distribution of energy steps encountered along the relaxation path. The expectation value, \( \langle \dot{E}(t) \rangle \) is then,

\[
\langle \dot{E}(t) \rangle = -t \sum_{j=1}^{M} \Delta E_j \delta(t - \sum_{k=0}^{j-1} \tau_k) \Delta E_j \tau_j \quad . \tag{5}
\]

**FIG. 4.** A schematic plot of the variation of the total energy with time.

The distribution of waiting times \( \tau_k \) is dependent only on the configuration of the chain at the \( k \)’th step and independent of the previous waiting times. Since the dynamics is just changing a pair of dihedral angles in opposite directions, for each conformation \( \{ \phi_i \} \) one may define an associated chain of \( N(N - 1)/2 \) sites, with each site corresponding to a pair \( (i, i') \) on the original chain. On the associated chain, a site will be assigned the value 1 if the corresponding pair has at least one “allowed” move, and the value 0 if both moves are “blocked.” Now the probabilities of encountering allowed or blocked moves as one implements the Metropolis dynamics outlined above are simply given by the density of 1’ s or 0’ s on the associated chain at a given relaxation step, namely, \( p_k \) and \( q_k = 1 - p_k \). Therefore, in the \( k \)’th conformation, the probability of making a transition after \( \tau_k \) blocked moves simply obeys the first passage time distribution \( \Pi \).

\[
P_k(\tau_k) = \mu_k e^{-\mu_k \tau_k} \quad , \quad \mu_k \equiv \| \ln q_k \| \quad . \tag{6}
\]

Writing the \( \delta \) function in equation (3) in the Fourier representation and performing the \( \tau \)-integrals we get

\[
\langle \dot{E}(t) \rangle = \frac{1}{2\pi} \sum_{j=1}^{M} \left( \Delta E_j \sum_{\ell=1}^{j-1} \left( \prod_{k=1}^{\ell} \frac{\mu_k}{\mu_k - \mu_\ell} \right) e^{-\mu_\ell t} \right) \Delta E_k \quad . \tag{7}
\]

We may argue that the larger the energy loss in a relaxation event, the longer it will take for the phase point to make a transition out of this state. Since \( \mu_k \) is roughly the expectation for \( \tau_k \), we assume that \( \mu_k \sim 1/\Delta E_k \). With the assumption that the energy steps encountered along a relaxation path are independently distributed, i.e., \( P(\Delta E_1 \ldots \Delta E_M) = \prod_{k=1}^{M} P(\Delta E_k) \) for a process of \( M \) steps, one finds,

\[
\langle \dot{E}(t) \rangle = -\frac{1}{2\pi} \sum_{j=1}^{M} (\Delta E_j \sum_{\ell=1}^{j-1} I_{j,\ell}(t)) \quad , \tag{8}
\]

where \( I_{j,\ell}(t) \) is

\[
I_{j,\ell}(t) \equiv \int_{0}^{\infty} d(\Delta E_k) \ e^{-\frac{\Delta E_k t}{\mu_k}} P(\Delta E_k) \times \left[ \prod_{k=0}^{\ell-1} \left( \frac{\Delta E_k}{\Delta E_k - \Delta E_k} \right) \Delta E_k \right] \quad . \tag{9}
\]

We have determined from our simulations that the distribution \( P(\Delta E_k) \) (see Fig. 5) also has the stretched exponential form \( P(\Delta E_k) = P_0 e^{-(\Delta E_k)^\alpha} \). The angular brackets then take the form

\[
\Delta E_k \int_{0}^{\infty} (\Delta E_k - \Delta E_k)^{-1} \exp(-(\Delta E_k)^\alpha) d\Delta E_k \quad \tag{10}
\]

which we approximate by \( \Delta E_k \exp(-(\Delta E_k)^\alpha) \). The integration in equation (8) is then straightforward, leading, upon substitution in (9), to

\[
E(t) \sim t \sum_{j=1}^{M} \left( \frac{j-1}{j} \right) \exp(-a_j t^3) \quad . \tag{11}
\]
where \( a_j = j(1 - \alpha)(\alpha j)^{-\beta}(1 + \beta)^{-1} \) and

\[
\beta = \frac{\alpha}{\alpha + 1}.
\]

Substituting the value of \( \alpha \) we find from our simulations, namely \( \alpha = 0.39 \pm 0.02 \), we get \( \beta = 0.28 \pm 0.01 \) which is the result we obtained from the fits to the MC simulations within our error bounds.

A study of the correlations between fluctuations about the native state [16] for the Beads-and-Springs model, with the H-P sequence and the contact map for the native states for seven real proteins (6lyz, 1cd8, 1bet, 1fil, 1bab, 1csq and 1hiv) was performed by Erman [17]. Using the Gaussian approximation [18] to the coherent scattering function and a normal mode analysis [5,6,19,20], he also finds a stretched exponential relaxation with \( \beta = 1/4 \). Experiments on real proteins and polymers [1,10–12] yield \( 0.2 \leq \beta \leq 0.4 \). Our results seem to be closer to 1/4 and smaller than the values most commonly found for spin-glasses [21], namely 1/3. It should also be noted that glassy behaviour is obtained here in the absence of quenched randomness, or of frustration arising from steric hindrances, which we do not take into account.

Comparing the relaxation behaviour near the native state with the behaviour we observe at relatively high energies for random heteropolymers, we conclude that the relaxation behaviour, and therefore the dynamics and the structure of the energy landscape are universal over a very large range of energies, and are relatively independent of the specific sequence or the details of the dynamics.

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