Entropic droplets and activated events near the glass transition of a random heteropolymer

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Abstract

The barriers between metastable states near the glass transition of a random heteropolymer are studied using replicas by describing inhomogeneous states. The instanton solution for a replica space free energy functional is found numerically to estimate the size of activation barriers and of the critical nuclei themselves between the dynamic and the static glass transition temperatures.
Quantifying escape from configurational traps on a rugged free energy landscape is important for understanding the dynamics of spin glasses \cite{1}, structural glasses \cite{2}, and folded proteins \cite{3}, and for protein folding \cite{4}. A first step towards understanding barriers is to appreciate the organization of the stable minima \cite{5}. This has only been carried out completely for infinite range spin glasses. That organizational structure inspires many of the dynamical theories \cite{4,6–9}. Barriers in mean field spin glasses scale with the system size, but the finite range of interactions allows escape from traps through localized reconfigurations with finite barriers in the thermodynamic limit. The Vogel-Fulcher law for viscosity of structural glasses has been explained through such a mechanism \cite{10}. Various mean field theories of structural glasses resemble those for spin glasses lacking reflection symmetry. In strict mean field theory these models undergo a dynamical transition at a temperature $T_A$, where a macroscopic number of frozen free energy minima appear, and a static transition at $T_K$, the Kauzmann temperature, where the configurational entropy of the minima disappears. Kirkpatrick and Wolynes (KW) pointed out that that individual free energy minima between $T_A$ and $T_K$ will be inherently unstable for short range interaction models because of entropic droplets. The extensive configurational entropy provides a driving force for a localized region in a local minimum to reconfigure and escape the trap. Their analysis gave a modified Vogel-Fulcher law while a later scaling picture incorporating entropic droplets gave precisely the usual form used empirically \cite{11}. Parisi has presented a novel instanton argument in replica space yielding the original KW form \cite{12}. Here, we use replica instanton calculations to quantify reconfiguration barriers for the random heteropolymer.

Reconfiguration barriers determine the configurational diffusion coefficients that enter the theory of protein folding times \cite{4,13}. At low $T$, trap escape is rate limiting. Whether the escape barrier is extensive can be tested experimentally in a crude fashion since proteins are mesoscopic with finite chain length $N$. The size scaling is presently controversial \cite{13–15}. The barriers computed in the strict mean field limit of uniform transitions are of order $\sim 0.1 N k_B T_K$ at the static transition $T_K$ using parameters fit to the lattice model thermodynamics \cite{1}. This seems to be consistent with recent simulation results at low tem-
perature \cite{14}. Our calculations suggest entropic droplets are often large in the random heteropolymer so that the mean field arguments are a good starting point for mesoscopic systems of the size of the smaller proteins. One caveat is that polymers have additional entanglement constraints not present in structural or spin glasses. These are neglected here.

We focus on the temperature range near the glass-like transition of a finite-size heteropolymer in a poor solvent so that it is collapsed. The droplet we deal with is a small globular region of the polymer that may take on many configurations, local in space but not necessarily in sequence, buried in a remaining frozen glassy portion. We utilize replica formalism and derive a Landau-like free energy functional in terms of the Debye-Waller factor for a residue which plays the role of an Edwards-Anderson order parameter which is taken as spatially varying.

We introduce the standard bead contact Hamiltonian for a random heteropolymer which includes finite range random interactions between monomers;

\[ H = k_B T \sum_i \frac{(r_{i+1} - r_i)^2}{2a^2} + \frac{1}{2} \sum_{i \neq j} b_{ij} e^{-(r_i-r_j)^2/\sigma^2} + \frac{c}{6} \sum_{i \neq j \neq k} e^{-[(r_i-r_j)^2+(r_j-r_k)^2]/\sigma^2}, \]

(1)

where \( r_i \) represents positions of Kuhn segments \( (i = 1 \sim N) \), \( a \) is the Kuhn length, \( b_{ij} \) and \( c \) are the second and third virial coefficients, respectively, and \( \sigma \) is the characteristic length of interactions. \( b_{ij} \) are Gaussian random variables with distribution, \( P(b_{ij}) = (2\pi b^2)^{-1/2} \exp \left[-(b_{ij} - b_0)^2/2b^2\right] \).

The free energy \( F_{av} \) is first averaged over this random interaction using standard replica formalism \cite{14}, to obtain an effective Hamiltonian, \( H_{eff} = H_0 + H_1 + H_2 \) where \( H_0 = k_B T \sum_{i,\alpha} (r_{i+1} - r_i)\alpha^2/2a^2 \) represents the elasticity, \( H_1 = 1/2(b_0 - \beta b^2/2) \sum_{i \neq j,\alpha} \exp[-(r_i\alpha - r_j\alpha)^2/\sigma^2] + c/6 \sum_{i \neq j \neq k,\alpha} e^{-[(r_i\alpha - r_j\alpha)^2+(r_j\alpha - r_k\alpha)^2]/\sigma^2} \) are effective homopolymeric interactions and \( n \) is the number of replicas. The inter-replica interaction part \( H_2 \), responsible for breaking ergodicity, can be written in terms of an overlap order parameter function \( Q_{\alpha\beta} \) defined by \( Q_{\alpha\beta}(r_1, r_2) = \sum_i \delta(r_1 - r_i\alpha)\delta(r_2 - r_i\beta) \) \cite{14}, where \( \alpha \) and \( \beta \) are replica indices;
\[ H_2 = -\frac{\beta b^2}{4} \int dr_1 dr_2 dr_3 dr_4 \left[ \sum_{\alpha \neq \beta} Q_{\alpha\beta}(r_1, r_2)Q_{\alpha\beta}(r_3, r_4) \right] e^{-\frac{(r_1 - r_3)^2 + (r_2 - r_4)^2}{\sigma^2}}. \]  

(2)

Exact integration over the bead variables is difficult, but a variational approach extended into replica space [16,8,9] can be used with a reference Hamiltonian \( H_{\text{ref}} \) to calculate a variational free energy \( F_{\text{var}} \) by finding extrema of \( F_{\text{var}} \equiv -k_B T \ln Z_{\text{ref}} + \langle H_{\text{eff}} - H_{\text{ref}} \rangle \). \( Z_{\text{ref}} \) is the partition function for \( H_{\text{ref}} \) and \( \langle \cdots \rangle \) means the average with \( H_{\text{ref}} \). The physical free energy \( F_{\text{av}} \) is \( \lim_{n \to 0} F_{\text{var}}^*/n \), where * means its extreme value. We use the same reference Hamiltonian as ref.I (with \( C = 0 \) in ref.I),

\[ \beta H_{\text{ref}} = \sum_{\alpha,i} \left( r_{i+1}^\alpha - r_i^\alpha \right)^2/(2a^2) + B \sum_{\alpha,i} (r_i^\alpha)^2 + D \sum_{\alpha \neq \beta,i} d_{\alpha\beta} (r_i^\alpha - r_i^\beta)^2, \]  

(3)

where \( B \) measures the confinement to a globule and \( D \), and \( d_{\alpha\beta} \) are variational parameters specifying the vibrational freedom in a minimum and the replica symmetry breaking related to the configurational entropy, respectively. We assume \( d_{\alpha\beta} \) has the same structure as mean field Potts spin glasses; \( n \) replicas are divided into \( n/m \) groups, each of which has size \( m \) and the matrix element \( d_{\alpha\beta} \) is 1 if \( \alpha \) and \( \beta \) (\( \alpha \neq \beta \)) belong to the same group and 0 otherwise. It is straightforward, though cumbersome, to obtain \( F_{\text{var}} \) as a function of these parameters. As in Ref.I the homogeneous glassy state characterized by a large constant \( D \) (i.e. \( D \gg A \gg B \)) in the reference Hamiltonian yields an asymptotic high \( D \) expression for the free energy of the homogeneous glassy phase. A globally appropriate homogeneous expression can be obtained by interpolating to the \( D = 0 \) limit yielding the non-gradient terms in eq.(5) (see below).

An entropic droplet is described by an inhomogeneous situation where part of the polymer is trapped in a particular metastable state while another part can be in any minimum. The exterior of the droplet has large \( D \) describing the part trapped in a particular metastable region while the interior with small \( D \) represents a region which can exist in multiple states. For explicitness, we shall assume the interaction range \( \sigma \) is small compared to the scale on which \( D \) varies. Expanding the quadratic order parameter interaction in eq.(2) around the
midpoint of the two coordinates yields a $(\nabla D)^2$ term describing the surface tension between
mean field minima [17]. Defining a dimensionless Debye-Waller factor $y \equiv 2mD\sigma^2/2$, the
free energy functional becomes in this approximation $F[y(r)] = F_{\text{Globule}} + \int d\mathbf{r} f(y(\mathbf{r}))$, where
$F_{\text{Globule}}$ is the constant free energy for the globule and
\begin{equation}
    f(y(r)) = \frac{m-1}{m} \frac{3}{2} \rho k_B T \ln \left( \frac{2a}{\sigma} \right)^2 \left( y + 1 \right) - \left( m-1 \right) \frac{\beta b^2}{4} \nu \rho \left[ \left( \frac{y}{y+1} \right)^{3/2} - \frac{45}{128} \sigma^2 \frac{\nabla y^2}{(y+1)^{7/2}} \right].
\end{equation}

is the inhomogeneous free energy density. $\rho(\mathbf{r})$ is the density of beads and $\nu = (\pi \sigma^2/2)^{3/2}$.
The surface tension is proportional to $b^2$ and originates from the randomness of the inter-
actions. Although not strictly true for the Gaussian confinement model, we have ignored
derivatives of $\rho$, which are expected to small in a well collapsed state with excluded volume.
In the functional, $m y$ and $\rho$ are functions of $\mathbf{r}$. The former two play the main roles in glassy
behavior.

The uniform solutions are essentially the same as in ref. I for a contact interaction model.
Since $\rho$ does not exhibit any peculiar behavior, we use the so-called volume approximation
where the monomer density $\rho_{\alpha}(\mathbf{r}) = \rho$ is taken inside polymer and zero otherwise. Putting
$y(\mathbf{r}) = \bar{y}$, we first maximize with respect to $m$ for each $\bar{y}$ (denoting it as $m^*(\bar{y})$). Fig. II shows
$f(m^*(\bar{y}), \bar{y})$ for several temperatures. In the high temperature limit, there is no saddle
solution and only the globule state $\bar{y} = 0$ is stable. The dynamic glass transition takes place
at the temperature $T_A$ where a non-zero saddle solution $\bar{y} > 0$ appears. This describes a
glassy trapped state. At temperatures below $T_A$, there are two minima in $f(\bar{y})$, one for the
globule ($\bar{y} = 0$), which is thermodynamically equivalent to the sum over metastable minima,
and the other for a particular metastable glassy minimum, $(\bar{y} = y_G > 0)$. As temperature
decreases, the free energies for the two solutions approach each other and become degenerate
at the Kauzmann temperature $T_K$ where the static transition occurs. As in spin glasses [18],
the uniform solution yields an estimate of a lower bound for the barriers between two lowest
minima as the local maximum of $f(m^*(\bar{y}), \bar{y})$, which we denote as occurring at $y^\dagger$. Starting
from zero at $T_A$ the uniform solution barrier height is extensive and grows as temperature
decreases and saturates around $T_K$ [9]. $T_A/T_K$ evaluated with typical parameters for flexible polymers ($(2a/\sigma)^2 = 4, \rho v = 1$) is about 1.4.

The globule state between $T_A$ and $T_K$ obtained by the ordinary replica theory represents a weighted sum of multiple local minima. Thus, the difference between the most probable free energy of a minimum and the globule free energy corresponds to the logarithm of the degeneracy of local minima, i.e., an extensive basin configurational entropy. For the short range infinite system between $T_A$ and $T_K$ local minima are not separated by a thermodynamically large barrier but a finite one. KW argue the free energy of an entropic droplet with a radius $R$ is $F \sim \Sigma R^2 - T s_c R^3$, where $\Sigma$ is the surface tension and $s_c$ is the configurational entropy density. Since $s_c$ disappears at $T_K$, the critical size of the droplet diverges at $T_K$ where the static glass transition occurs.

Inhomogeneous saddle point solutions of the free energy functional in the replica formulation give a microscopic theory of the barrier analogous to the KW result for $T_A > T > T_K$. The random interactions are integrated out and so the interface of the replicated droplet will be spherical, minimizing the surface energy. In spherical coordinates, the stationary phase condition for $y(r)$ leads to an Euler-Lagrange equation [19], that corresponds to the Newton equation of a dissipative system, where time is $r$ and a coordinate is $y$. For an infinite polymer, the appropriate solution has the boundary conditions $dy/dr|_{r=0} = 0$ and $y(\infty) = y_G$. Since the dissipation diverges at $r = 0$, the solution stays at $y = 0$ at the beginning of trajectory ($r \sim 0$), falls after a while with an infinitesimal initial velocity, and stops at $y = y_G$. Since the dissipation monotonically decreases with $r$, there is one such trajectory for each temperature. The critical radius $r_c$ defined by the value of $r$ where $y(r_c) = y^\dagger$ is shown as a function of temperature in Fig.2. Fig.3 shows the critical free energy of the droplet in an infinite system as well as that for a uniform transition for a finite but large $N$. In these figures, we indicate by dashed lines the results obtained by the so-called thin wall approximation [19], which assumes a plane domain wall giving a free energy of the KW form.

For protein-like parameters, just below $T_A$, the free energy barrier for a droplet in an infi-
nite system is higher than the barrier for a uniform transition of a polymer with a moderate size (e.g. 1000-mer). The interface for the droplet of small radius costs a considerable surface energy reflecting the difficulty of healing the interface. A polymer of this size escapes from traps through a nearly uniform reconfiguration. Decreasing temperature, a localized escape mechanism begins to dominate (Fig.3) for a sufficiently large polymer, but the critical radius then increases upon further cooling until it again reaches the whole size of the polymer, because the entropic driving force for transition finally disappears at $T_K$. Thus, very close to $T_K$, the spatially uniform transition again dominates. The width of the spherical domain wall is $\sim 3\sigma$. This is not much smaller than the radius of the smaller lattice models for proteins. The thin wall approximation is accurate for larger droplets (lower temperature), but it drastically underestimates the free energy for small droplets. The numerical accuracy of these results, of course, depends on how well the real system is approximated by the contact model but the trends should be robust.

We have described droplets that are local in space. There is an alternative escape route; an entropic droplet local in sequence. This can be treated using a similar reference Hamiltonian to eq.(3), but with $D_i$ depending on sequence number $i$. Straightforward calculation shows that the activation barrier for the sequentially localized droplet is proportional to the size of system $N$ between $T_A$ and $T_K$, while for droplets local in space the activation energy is independent of $N$ except very close to $T_K$. Entropic droplets local in sequence therefore do not change the story much. Droplets local both in sequence and space correspond for glassy traps with the *foldons* of a minimally frustrated system and may be relevant when topological constraints are considered [20].

The explicit droplet solutions discussed here are oversimplified. For structural glass and Potts glasses the interface has a more complex structure [11]. Wetting due to multiple states in the interface reduces the effective surface tension significantly. This leads to the Vogel-Fulcher dependence $\Delta F \sim (T - T_K)^{-1}$. We have not yet succeeded in quantifying this wetting phenomenon in the replica instanton formalism. Inhomogeneous states of a polymer (and short range Potts-type models, in general) may not, rigorously speaking, be
described by the simple one level RSB scheme but require a $P(q)$ with finite width peaks. A treatment of the interface like that for the short range SK model [12] may incorporate the wetting effect.

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FIGURES

FIG. 1. Free energy density for the uniform solution as a function of $y = 2mD\sigma^2/2$ for several temperatures. The value of $m$ is maximized for each $y$. Parameters used are $(2a/\sigma)^2 = 4$ and $\rho\nu = 1$ and Temperatures are $T = 0.32b$, $0.292b \sim T_A$, $0.24b$ and $0.2039b \sim T_K$.

FIG. 2. Critical radii of droplet plotted with respect to $T$. The solid (dashed) curve represents the spherical droplet (that by the thin approximation). Parameters used are the same as Fig.[1].

FIG. 3. Free energy barriers for droplets and uniform transitions with respect to $T$. Each curve is for 1)the droplet, 2)the droplet by the thin approximation, 3)the 100-mer uniform transition and 4)that of 1000-mer. Parameters used are the same as Fig.[1].