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Probing structural and dynamical transitions in polymer globules by force

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The dynamics of proteins and biopolymers play a crucial role in their function. By using Brownian dynamics we show that polymer globules, which serve as a model system for proteins, undergo a size-dependent dynamical transition from a liquid-like state at high T to a frozen state at low T with a relaxation time that diverges at the transition point. Furthermore, a stretch-induced melting transition is shown to be readily controlled by external forces that exploit the polymer connectivity to modify the size of the globule. This pathway could be a general route to enhance the rate of conformational changes in naturally occurring biopolymers.

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The dynamical properties of globular biopolymers, such as proteins, DNA, and their aggregates, have important consequences in the regulation of many biological functions. For example, transitions between two distinct conformations of a protein will be dictated by the internal barriers within the reaction pathway [1]. On larger length scales the ability of transcription enzymes to access a certain gene will be regulated by the “breathing modes” of the confined DNA in a chromosome [2,3]. If the conformational dynamics of these globular biopolymers are somewhat altered, so will the intrinsic time scales in which their functions occur. Understanding the features that control the dynamics of such processes is thus of much importance. In this Rapid Communication we consider a homopolymer globule which has previously served as a model system upon which more refined models of static and conformational properties of proteins are based, and investigate its dynamic behavior with Brownian dynamics simulations [4,5]. Specifically, we study the role of force and size on the characteristic reorganization time scales of globular polymers, and elucidate principles that govern the dynamics of collapsed biopolymers such as chromatin, molten globule proteins, and the von Willebrand factor [1–4,6].

The static properties of homopolymer globules have been widely studied using computer simulations, revealing the existence of two phases separated by a solid-liquid phase transition [7–11]. This supplements classical theory results and serves as the foundation for more complicated protein models of static properties [4,5]. The ordering (or solidification) transition has been characterized by the presence of a sharp peak in the heat capacity, and is well described by considering the balance between the surface energy of the globule and the change in the bulk energy [7–9]. Rampf *et al.* introduced the appropriate scaling [7]:

$$T_M^\infty - T_M = BN^{-1/3}, \quad (1)$$

where the T_M^∞ is the melting phase transition temperature for a infinitely large (bulk) system and T_M is the liquid-solid transition temperature of the finite globule. B is a

proportionality constant and N is the number of monomers in the chain.

The aforementioned investigations focus entirely on the equilibrium properties of these globules [7–11] and find that the differences in static properties such as the globule radius or monomer density above and below T_M are rather minor. Here however we demonstrate that minute changes in the static globular properties near T_M are accompanied by enormous changes in the dynamical properties of the system, such as the internal relaxation time scales. In fact, by probing the dynamical properties we locate in a direct and very sensitive fashion the underlying equilibrium phase transitions. Particularly, we find that the characteristic relaxation time of the monomers in the globule increases dramatically at the liquid-solid transition, and undergoes a drastic jump which is dependent on the length of the polymer and the attraction strength between monomers. Furthermore, there are important ramifications in the overall behavior of these globules in the context of chain pulling since small variations in size can lead to dramatic modifications of the dynamics or function of globular polymers. Our results thus indicate that by probing the stretching response of single proteins or aggregates, one can identify the force-dependent regimes or phases. Also, the ideas presented here should be useful as a way to study the dynamical and conformational transitions in larger aggregates such as chromosomes, which are known to require both long large-scale relaxation times to maintain the overall structure while undergoing fast local rearrangement to facilitate function [3].

To start, we model our system as a homopolymer globule and study it using Brownian dynamics simulations [12,13]. Our polymer is based on a bead-spring model and is composed of N beads held together by harmonic potentials. The beads further interact with the other monomers by Lennard-Jones potentials. The position \mathbf{r}_i of bead i is determined by integrating the discretized Langevin equation

$$\dot{\mathbf{r}}_i(\tilde{t} + \Delta\tilde{t}) = \mathbf{r}_i(\tilde{t}) - \Delta\tilde{t}(\tilde{\mu}_0 \nabla_{\mathbf{r}_i} \tilde{U}[\{\mathbf{r}_N\}]) + \sqrt{2\Delta\tilde{t}\tilde{\mu}_0} \xi_i, \quad (2)$$

where a is the bead radius, $\mu_0 = 1/(6\pi\eta_0 a)$ is the Stokes mobility, η_0 is the solvent viscosity, ξ_i is the random force which satisfies the relationship $\langle \xi_i(t)\xi_j(t') \rangle = 2kT\mathbf{I}\delta_{ij}\delta(t-t')$, and \mathbf{I} is the identity matrix. Values designated with

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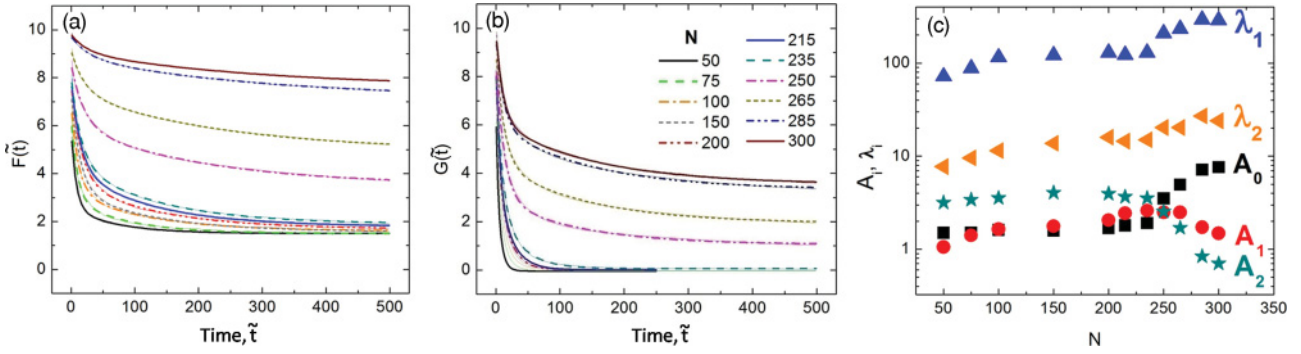


FIG. 1. (Color online) Plots of time-correlation functions $F(\tilde{t})$ (a) and $G(\tilde{t})$ (b) for a variety of N values at $\tilde{\epsilon} = 2.08$ are shown. There is a distinct change in the correlation dynamics as N is increased above $N = 250$. Both graphs are fit to double-exponential fits and the fit parameters for (a) are shown in (c). This plot demonstrates that there is a substantial change in A_i values at $N^* \approx 250$, which is due to the appearance of prominent relaxation modes that operate on time scales well beyond accessible simulation times.

a tilde are dimensionless, with distances normalized by a , energies normalized by kT , and times normalized by the characteristic diffusion time $\tau = a^2/(\mu_0 kT)$. The potential on the overall chain $\tilde{U} = \tilde{U}_e + \tilde{U}_{LJ}$ is given by two contributions, the elastic springs connecting consecutive beads along the chain $\tilde{U}_e = \tilde{\kappa}/2 \sum_{i=1}^{N-1} (r_{i,i+1} - 2a)^2$ and the Lennard-Jones potential $\tilde{U}_{LJ} = \tilde{\epsilon} \sum_{i,j} [(2a/r_{ij})^{12} - 2(2a/r_{ij})^6]$ operating between all beads. Values of $\tilde{\epsilon} > 0.41$ drive the polymer chain to undergo a coil-globule collapse transition, a process which has been previously studied in great detail [14,15].

This simulation protocol is used over time scales of more than 5×10^8 time steps with $\Delta\tilde{t} = 5 \times 10^{-4}$, which allows us to characterize the globule under a number of different conditions. N is varied between 50 and 300, $\tilde{\epsilon}$ is varied between 0.8 and 4.0, and a number of different initial conformational relaxation routes are considered. All globules, except where noted otherwise, are prepared by relaxing the globule from an extended chain at the $\tilde{\epsilon}$ where the test will be run, and the simulation will be analyzed from the point that the chain forms a coherent globule.

The dynamics of the globules are characterized using two different time-correlation functions, denoted as $F(\tilde{t})$ and $G(\tilde{t})$. These functions are constructed from a neighbor matrix \mathbf{M}_{ij} defined as

$$\mathbf{M}_{ij} = \begin{cases} 1, & r_{ij} < 3a \quad \text{and} \quad i \neq (j, j+1, j-1), \\ 0, & \text{otherwise.} \end{cases} \quad (3)$$

Using this matrix the time-correlation functions are given by

$$F(\tilde{t}) = \frac{1}{N} \sum_i^N \sum_j^N \mathbf{M}_{ij}(\tilde{t}_0) \mathbf{M}_{ij}(\tilde{t}_0 + \tilde{t}) \quad (4)$$

and

$$G(\tilde{t}) = \frac{1}{N} \sum_i^N \sum_j^N \mathbf{M}_{ij}(\tilde{t}_0) \prod_{k=1}^{n_t} \mathbf{M}_{ij} \left(\tilde{t}_0 + \frac{k\tilde{t}}{n_t} \right). \quad (5)$$

These correlation functions conceptually demonstrate the relaxation of the globule by tagging the monomers immediately neighboring a bead of interest and tracking how they diffuse away over time. The two functions differ in how they treat the return of previously tagged monomers to the neighborhood

of the bead of interest, with $F(\tilde{t})$ allowing the monomers to return and $G(\tilde{t})$ only considering monomers that have remained neighbors for the entire time \tilde{t} . Examples of both functions are shown in Fig. 1, with both Figs. 1(a) and 1(b) representing the same interaction energy $\tilde{\epsilon}$ for a variety of chain lengths N . Both functions can be well fit to a double exponential that represents the existence of two observable time scales, $F(\tilde{t}), G(\tilde{t}) = A_0 + A_1 e^{-\tilde{t}/\lambda_1} + A_2 e^{-\tilde{t}/\lambda_2}$. We will more often use $F(\tilde{t})$ since it decays to a value that provides underlying clues as to the long-time behavior of the polymer chain through the finite value of A_0 . A_0 reflects the volume that the initially tagged beads can explore V_{av} , by the relation $A_0 = F(0)^2 [4\pi a^3 / (3V_{av})]$, where $F(0)$ is the initial number of nearest neighbors and $F(0) [4\pi a^3 / (3V_{av})]$ is the fraction of their volume to the overall V_{av} . At infinitely long times all of the beads are interchangeable so $V_{av} = 4N\pi a^3 / (3f)$, where f is a geometric packing factor that represents the bead density.

Figures 1(a) and 1(b) demonstrate the distinct feature that at a critical value of N the time correlation between beads increases drastically. This can be seen by noting that $G(\tilde{t} = 500) > 0$ at large N . This is quantitatively represented in Fig. 1(c), which plots the parameters of the double-exponential fit. At a certain critical value of $N = N^*$ there is a drastic increase in the value of A_0 between $N = 235$ and $N = 260$ for this particular $\tilde{\epsilon} = 2.08$. This represents a transition in the dynamic behavior of the globule, since according to the relation for A_0 the available volume for a bead to explore V_{av} decreases significantly above N^* . This reflects the solid-liquid transition seen in previous literature, only now it has manifested in the dynamic behavior of the globule [7,8]. The verification that this is indeed a transition from a low- to high-ordered state is given in [16] through the use of radial distribution functions.

We seek to characterize this solid-liquid transition as a function of the globule parameters. We take the value of $F(500\tau)$ to be roughly analogous to A_0 , which is plotted as a function of the interaction energy $\tilde{\epsilon}$ for a variety of N values. The results are plotted in Fig. 2 and demonstrate a marked increase in the $F(500\tau)$ at some critical interaction energy $\tilde{\epsilon}^*$. As a verification of the strong N dependence seen in Fig. 1, it is clear that the value of $\tilde{\epsilon}^*$ is a function of N . The data in

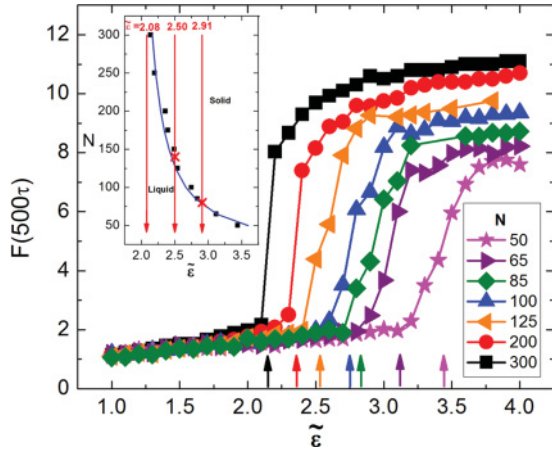


FIG. 2. (Color online) Plot of the $\tilde{\epsilon}$ dependence of $F(500\tau)$ for a variety of N values. The value of $F(500\tau)$ approximates A_0 and displays the same drastic increase in value at a critical value of $\tilde{\epsilon}^*$. We indicate the location of $\tilde{\epsilon}^*$ for each N with arrows corresponding to the point $F(500\tau) \approx 5$. $\tilde{\epsilon}^*$ is clearly a function of N , and the inset maps the transition on the $\tilde{\epsilon}$ - N plane. Gratifyingly the resulting globule solid-liquid transition curve corresponds well to the scaling introduced by Rampf shown in Eq. (1) [7]. Red traces represent the trajectory of the globule as it shrinks due to the pulling that is demonstrated in Fig. 3. The red “x”s represent the apparent solid-liquid transition seen in these simulations, which directly corresponds to the transition seen in quiescent globules.

Figs. 1(c) and 2 can be combined to produce a phase diagram that maps out the structure of the polymer globule as a function of N and $\tilde{\epsilon}$ (which is shown in the inset of Fig. 2). We can fit this plot to Eq. (1) using the relationship $T \sim \tilde{\epsilon}^{-1}$ and the parameters $\tilde{\epsilon}_{M,\infty}^{-1} = 0.82$ and $B = 1.65$ [7]. This fit is shown in the inset of Figure 2 as a blue line that is in excellent agreement with the simulation data (black points).

The transition also manifests itself in the nonequilibrium dynamics of the globule, which has important ramifications in the response of the globules to external stimuli. Here we use the example of pulling the ends of a stable globule to demonstrate this effect. In these simulations, we use a pulling protocol very similar to Alexander-Katz *et al.* [12]. We begin with a fully extended chain with the ends connected to springs that strongly fix the ends to the desired extension. This adds another potential $\tilde{U}_f = \tilde{\kappa}/2[(\mathbf{r}_0 + \mathbf{r}^*)^2 + (\mathbf{r}_N - \mathbf{r}^*)^2]$ that supplements the previously indicated potential through which the simulation is run. The extension L of the chain is controlled by fixing the value of $\mathbf{r}^* = \hat{x}L/2$ such that the tethers are located on the x axis. The tethers at the ends of the chain are allowed to relax from $L = Na$ to $L = 0.2Na$ with a velocity $\tilde{v} = \nu\tau/a$, and the chain is then pulled from this conformation at the same \tilde{v} .

We measure the force \tilde{f} required to extend the chain at velocity $\tilde{v} = 0.001$ as the chain is extended from the relaxed $\tilde{L} = L/(2Na) = 0.1$ to the fully extended $\tilde{L} = 1$ conformation. Typical traces are averaged over 20 runs and are shown in Fig. 3 for the case of $N = 300$ at $\tilde{\epsilon} = 2.08, 2.50$, and 2.91 . We considered a relaxation protocol where the chain was allowed to relax from an extended state to an extension length of $\tilde{L} = 0.1$, and then the interaction energy of the globule was lowered to $\tilde{\epsilon} = 0.8$ to allow rapid reorganization of the

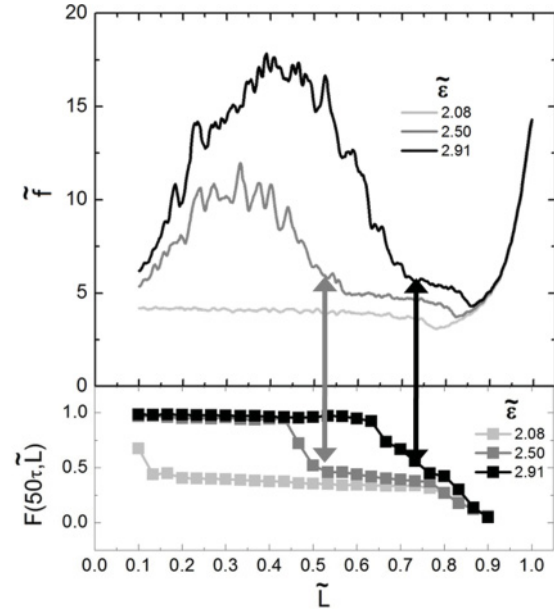


FIG. 3. (Top panel) Force \tilde{f} vs extension \tilde{L} plots for an annealed globule of $N = 300$, with $\tilde{\epsilon} = 2.08, 2.50, 2.91$ (solid, dashed, dotted lines, respectively) and $\tilde{v} = 0.001$. The curve at $\tilde{\epsilon} = 2.08$ demonstrates only the features of a liquid globule, while the curves at $\tilde{\epsilon} = 2.50$ and 2.91 initially demonstrate the response characteristic of a solid globule. Upon passing the transition points shown in the Fig. 2 inset (indicated in this figure by the arrows), the pulling response reverts to liquid-like behavior. This transition is also seen in direct measurements of the globule reorganization dynamics by plotting $F(50\tau, \tilde{L})$ vs \tilde{L} , which demonstrates a similar transition that is also indicated by arrows.

structure for 500τ . The desired $\tilde{\epsilon}$ was reapplied, and the chain was pulled from this structure.

In the averaged force extension traces given in Fig. 3 there are three distinct regimes. The regime close to full extension is universal and represents the rapid increase in force as the polymer approaches full extension ($\tilde{L} \approx 1$). Before the onset of this behavior, there is a low-force regime that represents the unwinding of a liquid globule. This regime encompasses the entirety of the subfull extension regime for polymers that are collapsed at low values of $\tilde{\epsilon}$, such as the trace for $\tilde{\epsilon} = 2.08$ in the top panel of Fig. 3. At higher values of $\tilde{\epsilon}$ a third regime appears at low extension. Extension in this regime requires much higher forces, and corresponds to the presence of the solid-globule phase. Larger forces are necessary due to the slow dynamics of rearrangement, which in the liquid globule allow the globule to respond to the application of force. These regimes are general characteristics that do not greatly depend on pulling protocol [17]. The transition from the high-force to low-force regimes correspond to the solid-liquid transition characterized in quiescent globules, and is indicated by arrows in Fig. 3. The inset of Fig. 2 demonstrates, via the red arrows, the traces shown in Fig. 3 in N - $\tilde{\epsilon}$ space. The point at which the transition from the high-force to low-force regime occurs is indicated with a red “x”. To further reinforce the connection between the dynamical changes in a quiescent globule and a pulled globule we consider a local $F(\tilde{f}, \tilde{L})$ that describes the relaxation of the globule at a given extension \tilde{L}

during the pulling process. We show curves of $F(\tilde{t}, \tilde{L})$ in [16], and can compare the function $F(\tilde{t} = 50\tau, \tilde{L})$ to the pulling traces as indicated in the lower panel of Fig. 3. The transition to much lower values of $F(\tilde{t} = 50\tau, \tilde{L})$ at low \tilde{L} indicates a change in globule relaxation dynamics that corresponds well with the transition in force-extension behavior (as indicated by the arrows in Fig. 3). Clearly the dynamics of the quiescent globule describe well the response of the globule to external forces.

This investigation has demonstrated that there is a pronounced change in the relaxation dynamics of a homopolymer globule due to the appearance of a liquid-solid transition, which depends on the interaction energy $\tilde{\epsilon}$ and the size N of the polymer globule. These dynamical regimes can be readily accessed upon the application of pulling forces, which utilize chain connectivity to drive this dynamic transition. We expect that our predictions of globule pulling behavior, which is based on simulation data, could be experimentally verified using laser traps or Atomic Force Microscopy experiments such as those already widely used in the study of single biological

molecules [18,19]. The manipulation of polymer globules is a key motif in the regulation of biological molecules, and thus these dynamical transitions might play a crucial role in regulating biological function. For example, similar models have been successful in predicting force-based conformational changes in the von Willebrand factor, with this transition providing a possible explanation for sudden changes in scaling behavior [6,13]. Also, chromatin is known for the coexistence of multiple relaxation time scales, and it is believed that this broad spectrum is due to the activity of remodeling proteins that pull on different parts of the fiber similar to our pulling protocols [3]. The model and conceptual framework developed here can qualitatively explain the appearance of such disparate time scales, which to our knowledge was not previously understood.

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