

Force-induced conformational transition in a system of interacting stiff polymers: Application to unfolding

Sanjay Kumar*

*Department of Physics, Banaras Hindu University, Varanasi 221 005, India
and Max-Planck-Institute for the Physics of Complex Systems, Noethnitzer, Strabe 38, D-01187, Dresden, Germany*

Debaprasad Giri†

Physics Section, MMV, Banaras Hindu University, Varanasi 221 005, India

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We consider a stiff polymer chain in poor solvent and apply a force at one end of the chain. We find that by varying the stiffness parameter, the polymer undergoes a transition from the globule state to the foldedlike state. The conformation of the folded state mimics the β sheet as seen in the titin molecule. Using the exact enumeration technique, we study the extension-force and force-temperature diagrams of such a system. The force-temperature diagram shows the re-entrance behavior for a flexible chain. However, for a stiff chain this re-entrance behavior is absent and there is an enhancement in θ temperature with the rise of stiffness. We further propose that the internal information about the frozen structure of a polymer can be read from the distribution of end-to-end distance which shows a sawtoothlike behavior.

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Conformational and structural properties of biopolymers play an important role in the biological phenomena. Protein folding is a phenomenon which is associated with the primary structure of the chain. Their stability or resistance to unfolding are investigated either by varying the pH of the solution or by varying the temperature [1]. Many proteins unfold due to the force instead of change in the chemical environment or temperature. For example, the effect of stress on the titin molecule is a force induced transition from the native state to the unfolded state [2]. The presence of strong hysteresis together with sudden jump seen in the force vs extension curve suggests that the unfolding is a first order transition [3]. Theoretically, this type of transition has been studied in the framework of statistical mechanics considering a flexible polymer chain in a poor solvent under the influence of external force [4], and for DNA type polymers under an unzipping force [5]. However, stiffness plays an important role as is seen in a wormlike chain (WLC) model [2,3], which has not been incorporated in the lattice model so far to explain the phase diagram of such molecules under the influence of the external force.

Recently the phase diagram of homo-semiflexible polymer chain with zero force has been studied by mean field theory [6] and Monte Carlo simulation [7] which shows three distinct phases, namely (i) an open coil phase at high temperature, (ii) a molten globule collapse at low temperature and low stiffness, and (iii) a “frozen” or “folded” state at low temperature and large stiffness. Our aim in this paper is to describe the effect of external force applied at one end of the stiff polymer chain in a poor solvent. We consider self-attracting self-avoiding walks (SAWs) on a square lattice [8]. One end of the chain is subjected to an external force while

the other end is kept fixed. The stretching energy E_s arising due to the applied force F is taken as

$$E_s = -F \cdot x, \quad (1)$$

where x is the x component of end-to-end distance ($|x_1 - x_N|$). Stiffness in the chain is introduced by associating an energy barrier ϵ_b with every “turn” (or bend) of the walk [9]. We associate a negative energy ϵ_u for each nonbonded occupied nearest neighbor pairs. The partition function of such a system may be written as

$$Z_N = \sum_{(N_b, N_u, |x|)} C_N(N_b, N_u, |x|) b^{N_b} u^{N_u} \omega^{|x|}. \quad (2)$$

$C_N(N_b, N_u, |x|)$ is the total number of SAWs [10] of N steps having N_b turns (bends) and N_u nearest neighbor pairs, respectively. ω is the Boltzmann weight for the force which is defined as $\exp[\beta(F \cdot \hat{x})]$, where \hat{x} is the unit vector along the x axis. β is defined as $1/kT$ where k is the Boltzmann constant and T is the temperature. $b = \exp(-\beta\epsilon_b)$ and $u = \exp(-\beta\epsilon_u)$ are Boltzmann weights of bending and nearest neighbor interaction, respectively.

Since the polymer is on the lattice where continuous overall rotations are not possible, we assume that under the applied force there is an alignment of protein along the force direction with zero torque. This is equivalent to the assumption that the relaxation for the overall rotational degrees of freedom is much shorter than that of the structural relaxation that is responsible for the unfolding or folding process. Apart from logarithmic factors, the low temperature limit of the rotationally averaged contribution to the free energy due to tension obtained in the context of rubber elasticity [11] coincides with Eq. (1).

In all the single-molecule experiments, a finite size of the chain is used and no true phase transition can occur in a single macromolecule, therefore we calculate the “state dia-

*Electronic address: yashankit@yahoo.com

†Electronic address: dgiri@bhu.ac.in

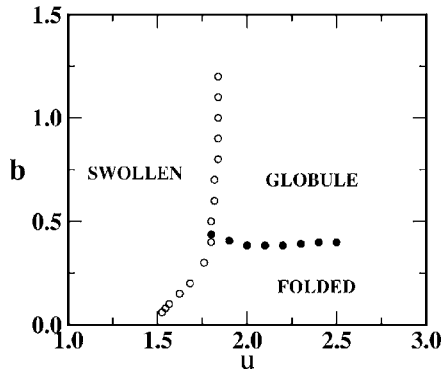


FIG. 1. State diagram shows the variation of b (Boltzmann weight of bending) with u (Boltzmann weight of nearest neighbor interaction) of a linear semiflexible polymer chain in two-dimensional space. The collapsed state includes both the globule and folded states. The open circle represents transition from swollen state to the collapsed state and the filled circle represents transition from the folded state to the globule state.

gram” instead of the “phase diagram” [12]. We obtained $C_N(N_b, N_u, |x|)$ up to $N \leq 30$ steps walk on a square lattice by the exact enumeration method and use it to calculate $Z_N(b, u, \omega)$. The boundaries in the state diagram may be found for $F=0$ from the maxima of fluctuation of $N_u (= \partial \langle N_u \rangle / \partial \epsilon_u)$ or fluctuation of $N_b (= \partial \langle N_b \rangle / \partial \epsilon_b)$. The sudden change in the nonbonded nearest neighbors N_u indicates a phase transition; hence maxima in the derivative of N_u with respect to ϵ_u indicates the location of a phase transition. The swollen to collapsed transition line (which is also called the θ line) is obtained from the peak value of $\partial \langle N_u \rangle / \partial \epsilon_u$ for fixed value of b (shown in Fig. 1 by open circle). The folded to globule transition line (shown in Fig. 1 by filled circle) has been obtained from the peak value of $\partial \langle N_b \rangle / \partial \epsilon_b$ at fixed u .

There are three states marked by swollen, frozen (or folded), and globule as shown in Fig. 1. For $b=1$, we restore the value of $u_c=1.93$ using the extrapolation scheme [13] for a flexible polymer chain, that is in good agreement with the value found by Foster [14] and the Monte Carlo simulation result (1.94 ± 0.005) [15]. However, we shall confine ourselves here to the constant force ensemble to get the exact boundaries for finite N .

From Fig. 1, we find that the θ line bends to left as stiffness increases (b decreases) indicating the enhancement of θ temperature. Intuitively one might think that stiffness favors the extended state but the fact is that stiffness favors a folded state in a poor solvent at low temperature. It is obvious that on a square lattice hairpinlike structures [Fig. 2(a)] minimize

the number of folds and maximize the number of nearest neighbors. Due to this increase in nearest neighbors, there is a decrease in u (i.e., rise in θ temperature). Such a trend in the θ line has also been observed by extensive Monte Carlo simulation by Bastolla and Grassberger [7]. For large N , resulting configurations will give rise frozen or foldedlike state and the partition function will be then dominated by configurations similar to Fig. 2(b). Since the number of such configurations is very small, entropy associated with the folded state will be quite low. The length of the fold will be of the order of $N^{1/2}$ and depends on $(\beta \epsilon_b)$.

To study the order of transition from the frozen state to the globule state at zero force, we calculated the entropy (S) using the following relation of free energy (G):

$$G = -kT \ln Z_N(T), \quad (3)$$

$$S = - \left(\frac{\partial G}{\partial T} \right). \quad (4)$$

We use two different sets of ϵ_b at fixed $u=4.0$ and plotted the entropy with temperature in Fig. 3. In the first set [Fig. 3(a)], we choose $\epsilon_b = -0.08$ eV and -0.16 eV, implying $b = \exp(+\beta \epsilon_b)$ is greater than 1, and this corresponds to a flexible chain. For the second set [shown in Fig. 3(b)] ϵ_b is positive ($b < 1$), and this corresponds to the stiff chain. It can be seen that for the stiff chain there is a sudden jump in entropy [shown in Fig. 3(b)] corresponding to a transition from the folded state to the globule state while it is absent in the case of a flexible polymer chain.

Although in principle the frozen structures [Fig. 2(b)] can be seen everywhere in the “folded” state, numerically it is easier to observe this for smaller $b (< 0.2)$ and larger $u (> 1.93)$. In this regime we have numerically computed the Boltzmann contribution of the individual conformation of the polymer chain in the partition function and verified that the maximal contribution comes from the structure similar to Fig. 2(b) (like the β sheet seen in titin molecules). Hence in this region, it will be possible to study the effect of force on the unfolding transition by applying force at one end of the chain. To do so we set $\epsilon_u = -1$ and the Boltzmann constant $k=1$ and study the force-temperature and extension-force curve. It can be shown that in this scale $F = (\ln \omega / \ln u)$, $T = 1 / \ln(u)$, and $\epsilon_b = -(\ln b / \ln u)$.

The variation of critical force with temperature for unfolding transition where the polymer goes from the collapsed state to the unfolded state (or extended state) is shown in Fig. 4. Note that the collapsed state consists of both the globule and the folded state. The transition line separates the

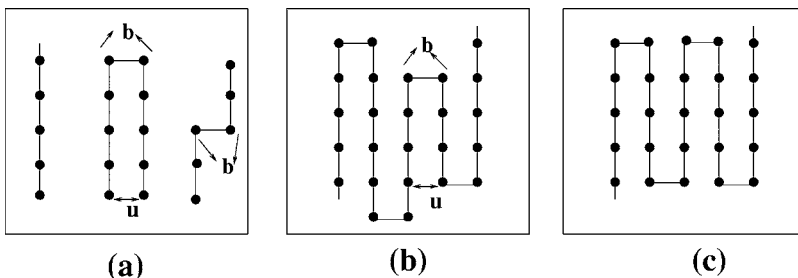


FIG. 2. Typical conformations of polymer chain at higher value of u and lower value of b in two-dimensional space. (a) This represents a situation where hairpin structure will be preferred rather than the other conformations. (b) The resulting conformation at large N . (c) The conformation at $T=0$. This can be mapped by Hamiltonian walk.

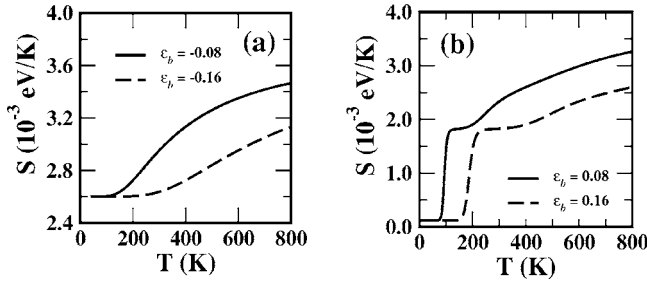


FIG. 3. Plot of entropy (S) vs temperature (T) for different values of stiffness parameter (ϵ_b).

collapsed state from the unfolded state. It is not possible to see the transition from the folded to the globule state because it is not induced by the force. It is interesting to note that for a stiff polymer chain, critical force increases monotonically with temperature and becomes almost constant at very low temperature. However, in the case of a flexible polymer chain, we observe a phenomenon of “re-entrance” i.e., the critical force goes through maximum as the temperature is lowered. For example, one can see that the polymer chain at fixed force (say $F=0.9$) is in the extended state at low temperature. With the increase in temperature, the chain is found in the collapsed state. With the further rise of temperature, it acquires again the conformations of the extended (swollen) state. Similar re-entrance behavior is also found in the transfer matrix calculation of the directed walk models of flexible polymer chain [16]. However, if we introduce stiffness in the chain, the re-entrance behavior is found to be suppressed. This is because in the globule state, the entropy associated with the flexible chain is very high, while the stretched chain has almost zero entropy (i.e., the polymer forms a rodlike shape). This indicates that the polymer goes from a high entropy state to the low entropy state under the application of force for the flexible polymer chain. However, in the case of the stiff polymer chain, the collapsed state has frozen structures with almost zero entropy, therefore no re-entrance is observed in going from the frozen state to the extended state. This can be seen using a phenomenological argument near $T=0$ where the conformation of the polymer chain in the collapsed state looks like Fig. 2(c) similar to the conformations formed by the Hamiltonian walks. Thus, from the principle of balance of energy, the free energy of the folded state and the free energy of the stretched state due to the force (using Eq. (1)) can be equated as [13]

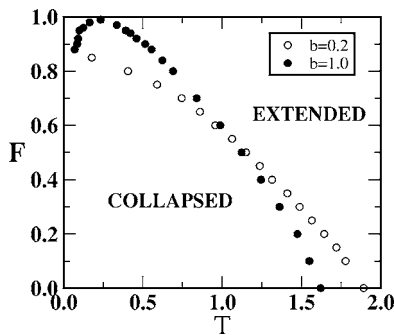


FIG. 4. Force-temperature diagram for fixed b . Here collapsed state consists of both the globule and the folded state.

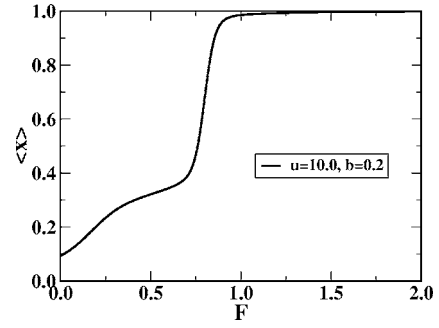


FIG. 5. Plot of $\langle x \rangle$ vs F for fixed u and b . Here $u=10.0$ and $b=0.2$.

$$-FN = N\epsilon_u + 2\sqrt{N}(\epsilon_b - \epsilon_u) - NTS_c. \quad (5)$$

The second term of the right hand side in Eq. (5) is a surface correction term which also includes the bending energy. The third term is due to the entropy associated with the collapsed state (S_c per monomer). Minimization of energy with respect to N and substituting $\epsilon_u=-1$, Eq. (5) gives

$$F_c(T) = 1 - \frac{(1 + \epsilon_b)}{\sqrt{N}} + TS_c. \quad (6)$$

For large N , the second term goes to zero. For finite $N=30$ (as we have taken in our study), the correction term is important which gives $F_c=0.8174$. This is in good agreement with the value found from Fig. 4 near $T=0$. It is to be noted that for a flexible polymer, the entropy associated with the globule is finite and hence there is a positive slope (dF_c/dT), while for the stiff chain the entropy associated with the frozen structure is almost zero and hence there is no slope, therefore we do not find any re-entrance behavior in this case.

The extension vs force ($\langle x \rangle$ vs F) curve is shown in Fig. 5. From the figure, it is evident that for small forces, a polymer chain is in the compact folded state and slightly oriented along the force direction. At larger forces, the polymer chain has the conformations similar to the extended (swollen) structure. Completely stretched states can be obtained only by applying very high forces. A similar behavior is also seen in the case of flexible polymer chain under the influence of external forces [17]. Molecular dynamics simulation of protein under the stress of an external denaturing force acting on a terminal end or on the entire chain [18] shows the intermediate stages during the unfolding and the extension-force curves are similar to Fig. 5 found by us.

We also study the probability distribution curves $P(x)$ with x for flexible and stiff chains defined by

$$P(|x|) = \frac{1}{Z_N(b, u, \omega)} \sum_{(|x|)} C_N(N_b, N_u, |x|) b^{N_b} u^{N_u} \omega^{|x|}. \quad (7)$$

In Fig. 6, we have shown $P(x)$ for different values of ω and at fixed $u=3.0$ corresponding to the collapsed state.

The probability distribution curves have many interesting features. For flexible chains i.e., $b=1$, the maxima of $P(x)$ corresponds to the collapsed state at $F=0$ ($\omega=1.0$). For

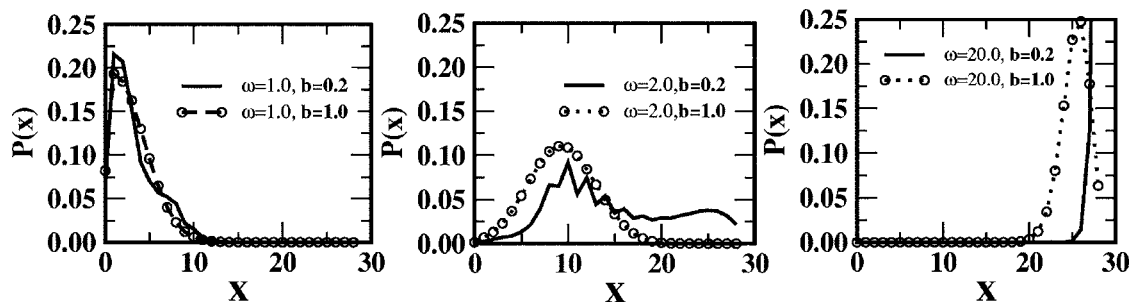


FIG. 6. Plot of $P(x)$ vs x for flexible ($b=1.0$) and stiff ($b=0.2$) polymer chain at different ω (Boltzmann weight of the force). At intermediate force the sawtooth behavior in the probability distribution gives the signature of unfolding events in the frozen structure.

higher force, $\omega=20$ both flexible and semiflexible polymers are found to be in the “rodlike” state. However, at intermediate force, the probability distribution curve has a “sawtooth” -type of behavior for the stiff chain while it is continuous for the flexible chain. The x component of the end-to-end distribution function gives information about the internal structure of the folded state by applying the suitable force. For small forces, the thermal fluctuations are too weak to unfold the polymer chain, and it stays in the folded state most of the time. This fact is more or less reflected in the structureless distribution function with a well defined peak at the most likely value of the end-to-end distance. In contrast, when we apply a force close to the critical force, the small thermal fluctuations are sufficient to open up the loops in the β sheet [as shown in Fig. 2(b)]. Here, one sees the statistical unfolding events in the structure of the distribution functions in the form of the “sawtooth” kind of behavior for the stiff chain while it is continuous for the flexible chain. The presence of intermediate stages seen during the unfolding in the molecular dynamic simulation [18] and the one found by us

in the probability distribution curve suggests to the experimentalist to “tease” the folded polymer (proteins) by some external force and then measure the distribution function. This may reveal some interesting information about the folded state.

In this paper we have studied the complete state diagram of stiff polymer chain under the influence of external force. We showed the existence of the foldedlike state in a stiff homopolymer. We have also found that there is an enhancement of θ temperature (decrease in u) with the rise of stiffness parameter ϵ_b . The absence of re-entrance in the stiff chain has been explained by using the phenomenological argument. We have also tried to explain the unfolding event as seen in the titin molecule on the basis of the probability distribution curve.

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