Periodic force induced stabilization or destabilization of the denatured state of a protein

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We have studied the effects of an external sinusoidal force in protein folding kinetics. The externally applied force field acts on the each amino acid residues of polypeptide chains. Our simulation results show that mean protein folding time first increases with driving frequency and then decreases passing through a maximum. With further increase of the driving frequency the mean folding time starts increasing as the noise-induced hoping event (from the denatured state to the native state) begins to experience many oscillations over the mean barrier crossing time period. Thus unlike one-dimensional barrier crossing problems, the external oscillating force field induces both *stabilization or destabilization of the denatured state* of a protein. We have also studied the parametric dependence of the folding dynamics on temperature, viscosity, non-Markovian character of bath in presence of the external field. © *2011 American Institute of Physics*. [doi:10.1063/1.3635774]

I. INTRODUCTION

Enhancement of reaction kinetics due to interplay between barrier fluctuation rate and thermal noise-assisted barrier crossing events known as resonant activation,[1] is an interesting observation in early 1990s. This phenomenon provides a better understanding of the mechanisms of various chemical and biological processes. Examples include: dissociation kinetics of large molecules in coupled chemical systems,[2] oxygen binding mechanisms to hemoglobin,[3] modelling the dynamics of dye laser, ratchet models for the directional movements of molecular motors, transport through artificial nanopores[4] etc. The interesting mechanism for enhancing rate via resonant activation has triggered a numerous theoretical investigations for Markovian and non-Markovian nature of the bath and external deriving forces.[5–10] This phenomenon has been experimentally realized[11] in a tunnel diode biased in a strongly asymmetric bistable state in the presence of two independent sources of electronic noise. The interference effects of resonant activation and stochastic resonance have also been studied to the aim for stochastic localization of particles confined in a bistable potential as well as in a multi-well system.[12,13]

The overwhelm majority of the previous studies on barrier crossing dynamics over a fluctuating energy barrier are based on the dynamics of a molecule having a single degree of freedom. It is modeled by a Brownian particle in a bistable or metastable potential with fluctuating barrier. But dynamics of the molecules having large number of degrees of freedom offers a significantly different situation, due to its structural rigidity and several interaction energies. Here, in addition to the energetic barrier and fluctuation statistics, the dynamics of the molecules is largely controlled by entropic factors.

The folding dynamics of macromolecules like proteins is an example of thermally activated barrier crossing dynamics in a multidimensional space. Here, all the degrees of freedom are coupled to each other through various interactions, such as nearest-neighbor interactions, dihedral potentials, hydrogen bonds, ion pairs, van der Waals interactions etc. Over the years a considerable attention has been focused on better understanding of folding mechanisms and potential energy landscapes. The studies of protein folding dynamics under different external conditions such as salt concentration, temperature, confinement, *p*H, and viscosity of the medium etc.[14–24] provide important information about its structure and functionality. Again, the single molecule pulling experiments by highly sensitive force probes such as atomic force microscopy[25–27] and optical and magnetic tweezers[28–30] make it possible to realize various interactions due to internal degrees of freedom of a macromolecule. Motivated by the recent studies[25,26,28,30] in this context we have investigated the effect of an applied external periodic field of non-thermal origin on the protein folding dynamics. We have assumed that the external electric field interacts with charge or dipole moment of the amino acid residues.

To accomplish our goal we have considered the well-known coarse-grained off-lattice models[24,31] for polypeptide chain (where each amino acid residue is considered as a single bead centered at their C^{α} position). The interaction energies which play roles in the folding dynamics are taken into account by a Go-like Hamiltonian.[38] By setting the Langevin equations for each bead we have followed the dynamics of protein chains in presence of external fluctuations (field).

A number of experimental studies[32,33] imply that Markovian dynamics cannot accurately account the effect of

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viscosity on the barrier crossing phenomenon in a solution phase and the theory based on the non-Markovian dynamics shows a better agreement between theoretical and experimental results. Therefore, to capture the important effects of non-Markovian dynamics and also for a sake of generality we have considered exponentially decaying memory of the thermal fluctuations. Moreover, the present study is an extension of earlier studies[34–37] on barrier crossing dynamics in low dimensional systems in presence of periodic force. To compare the features of folding kinetics of macromolecules with one-dimensional barrier crossing problems, we also simulate a non-Markovian Langevin dynamics in a bistable potential in presence of barrier fluctuations.

Specifically our objective here is twofold. First, we intend to explore the effects of an applied external oscillating field on protein folding to the goal of extracting generic features of multidimensional barrier crossing dynamics in contrast to the one dimensional cases. The second objective is to investigate the effects of the oscillating time periodic force field on the following three important features of protein folding kinetics: (i) turnover behavior of mean folding time with solvent viscosity, (ii) U-shaped mean folding time vs. temperature profiles, and (iii) double minimum in mean folding time as a function of the correction of thermal fluctuations.

To address the above challenging issues we simulate folding dynamics of the 16-residue peptide β-hairpin (C-terminal from protein G, PDB ID:2gb1) and 76-residue protein ubiquitin (PDB ID:1ubq). The PDB structures of these proteins are shown in Fig. 1.

II. THE MODEL

To study protein folding dynamics we consider coarse-grained off-lattice models[24] for polypeptide chains in which each amino acid residue is represented as a single bead centered at its C^α position. Moreover, we follow the dynamics of polypeptide chains by Go-like Hamiltonian,[38] in which the interactions between residues forming native contacts are assumed to be attractive and non-native interactions are repulsive. The energy of a configuration of a protein is specified by the coordinates r_i of the C^α atoms and is given by[24]

$$E = \sum_{bonds} K_r(r_{i,i+1} - r_{0i,i+1})^2 + \sum_{angles} K_\theta(\theta_i - \theta_{0i})^2 + \sum_{dihedral} K_\phi^{(1)}[1 - \cos(\phi_i - \phi_{0i})] + \sum_{dihedral} K_\phi^{(3)} \times [1 - \cos(3(\phi_i - \phi_{0i}))] + \sum_{i<j-3}^{NC} \epsilon_H \left[5R_{ij}^{12} - 6R_{ij}^{10}\right] + \sum_{i<j-3}^{NNC} \epsilon_H \left(\frac{C}{r_{ij}}\right)^{12}. \quad (1)$$

Here $r_{i,i+1}$ is the distance between ith and $(i+1)$th beads. θ_i is the bond angle formed by three subsequent beads: $(i-1)$th, ith, and $(i+1)$th. ϕ_i denotes the dihedral angle around the ith bond and r_{ij} is the distance between the ith and jth residues. The subscripts 0, NC, and NNC refer to the native configuration, the native contact, and the non-native contact, respectively. r_{0ij} is the distance between the ith and the jth residues in the native conformation and $R_{ij} = \frac{r_{0ij}}{r_{ij}}$. Amino acid residues are assumed to be in the native contact if r_{0ij} is less than a given cutoff distance(d_c). Here, we have assumed the cutoff distance $d_c = 6$ Å.

The first term of Eq. (1) presents harmonic potential due to chain connectivity between two adjust beads. The second term is also harmonic potential arising due to bond angle between three subsequent beads. The third term presents dihedral potential for every four adjacent C^α atoms. Dihedral potential is a sum of two periodic components with periods: $\tau_\phi = 2\pi/(\phi_i - \phi_{0i})$ and $\tau_\phi = 2\pi/3(\phi_i - \phi_{0i})$. The last two terms in Eq. (1) are due to the non-local native interactions and the short-range repulsive force for non-native pairs, respectively. Parameters K_r, K_θ, K_ϕ, ϵ_H denote the relative strength of each kind of interaction; we choose $K_r = 100\epsilon_H/\text{Å}^2$, $K_\theta = 20\epsilon_H/\text{rad}^2$, $K_\phi^{(1)} = \epsilon_H$, $K_\phi^{(3)} = 0.5\epsilon_H$, where ϵ_H is the characteristic hydrogen bond energy and $C = 4$ Å.

The dynamics of the protein chain in a thermal bath can be described by setting a Langevin equation for each bead (C^α-atoms of each amino acid residue) of the protein chain,

$$m\ddot{\vec{r}} = \vec{F}_c - \int_0^t \gamma(t-t')\dot{\vec{r}}dt' + \vec{\eta}(t), \quad (2)$$

where m denotes the mass of a bead and $\vec{F}_c = \nabla E$ corresponds to force derived from the potential energy associated with the protein molecule (Eq. (1)). The potential force $\vec{F}_c$ depends on the positions of the all beads. Therefore, N coupled Langevin equations are needed to follow the time evolution of a protein having N amino acid residues (beads). The thermal fluctuations due to environment are modelled by colored Gaussian noise. The frictional kernel $\gamma(t)$ is related to thermal fluctuation $\xi(t)$ by the well-known fluctuation-dissipation relation,

$$\langle \eta_k(t)\eta_l(t')\rangle = k_B T \delta_{kl}\gamma(t-t'), \quad (3)$$

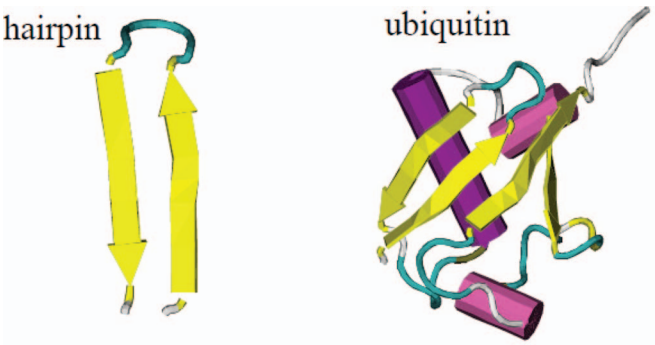

FIG. 1. The PDB structures of two proteins studied in this work. For the cutoff distance $d_c = 6.5$ Å, the total number of native contact is equal $Q_{max} = 13$ and 99 for hairpin and ubiquitin, respectively.

where, k_B and T are the Boltzmann constant and temperature of the system, respectively. η_k is the kth components of $\vec{\eta}(t)$, where $k, l = x,\ y,\ z$; the three orthogonal components. To capture essential features of the non-Markovian dynamics we consider exponentially decaying frictional memory kernel[39–41] with the following form:

$$\gamma(t-t') = \frac{\gamma_0}{\tau}\exp\left(-\frac{|t-t'|}{\tau}\right), \tag{4}$$

where γ_0 is the frictional coefficient in the Markovian limit and τ bears the memory effect of the non-Markovian dynamics. Then $\vec{\eta(t)}$ is a solution of the following differential equation:

$$\dot{\vec{\eta}} = -\vec{\eta}/\tau + \frac{\sqrt{\gamma_0 k_B T}}{\tau}\zeta(t),$$

where $\zeta(t)$ is a Gaussian white noise having variance two. It should be noted that for the frictional memory kernel (4) the integro-differential (2) can be simplified as $m\ddot{\vec{r}} = \vec{F}_c + \vec{\eta}(t)$ and $\dot{\vec{\eta}} = -\vec{\eta}/\tau - \gamma_0\dot{\vec{r}}/\tau + \frac{\sqrt{\gamma_0 k_B T}}{\tau}\zeta(t)$.

We have considered the situation where the dynamics polypeptide chains is affected by an external sinusoidal force. It implies that free energy of the system periodically oscillates in an asymmetric way. Under such situation the dynamics of the protein chain is governed by the following equations:

$$m\ddot{\vec{r}} = \vec{F}_c - \int_0^t \gamma(t-t')\dot{\vec{r}}dt' + \vec{\eta}(t) + \vec{A}_0\sin\omega t. \tag{5}$$

Unlike the standard pulling experiments (where the external force is applied to termini of bio-molecules), here the external oscillatory force filed acts on all amino acid residues. However, the last term in the above equation accounts effective interaction between the charge or dipole on the amino acid and electric field. The resultant force vector corresponding to this interaction is parallel to the $\ddot{\vec{r}}$. Thus $\vec{A}_0$ in the above equation is parallel to the acceleration vector. We have implemented this in the simulation scheme.

A. Simulation

In order to analyze the effects of an external field on the protein folding dynamics we have calculated the folding time for different parameter sets (frequency of the external field, dissipation constant of the medium, temperature, noise correlation time etc.) by numerically solving the Langevin equation (5). The relevant equations (3) and (5) were integrated using the velocity form of Verlet algorithm with the time step $\Delta t = 0.001\tau_L$, τ_L is the characteristic time scale of the system which are defined by $\tau_L = (ma^2/\epsilon_H)^{1/2} \approx 3$ ps, where a is the characteristic bond length between two successive beads $a = 4$ Å. The mean folding time is the averaged first passage time from a random configuration (thermodynamically unstable) to the native state (thermodynamically stable state). Our calculated mean folding time is the averaged over 250–1000 trajectories depending on the values of different parameters to have good statistics. To this end we would like mention that in the present paper we have exploited the numerical scheme of our earlier study.[42]

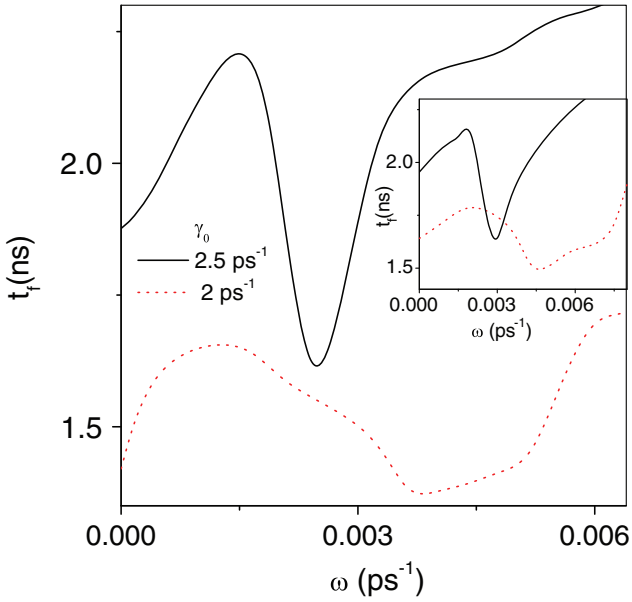

FIG. 2. Plot of mean folding time t_f of $\beta-$hairpin vs the frequency of the external driving force. We chose $T = 298$ K, $A_0 = 0.3$ pN, $\tau = 1.0$ ps. The inset presents the results of Markovian limit, $\tau \to 0$.

B. Results and discussions

We have calculated the mean folding time(t_f) of $\beta-$hairpin as a function of frequency of the external field at temperature $T = 0.53\epsilon_H/k_B = 298$ K, where $\epsilon_H = 0.98$ K cal/mol is the hydrogen bond energy. This is depicted in Fig. 2. The folding time of $\beta-$hairpin first increases with increasing frequency of the external force followed by its decrease after passing through a maximum. With further increase of frequency the folding time starts increasing. Thus, the mean folding time versus driving frequency profiles possess both a maximum and a minimum. A similar feature has been observed (not shown here) at the Markovian limit, $\tau \to 0$. It should be noted that the maximum is not observed in the one-dimensional barrier crossing problem. To demonstrate this issue and for a qualitative comparison with a one-dimensional case, we have considered barrier crossing dynamics of a Brownian particle, modelled by the following generalized Langevin equation:[43]

$$m\dot{v} = q - q^3 - \int_0^t \gamma(t-t')\dot{v}(t')dt' + \zeta(t), \tag{6}$$

where q and v are the position and velocity of a Brownian particle. Here, the folding time is defined as a mean barrier crossing time, is obtained by solving the above equation and plotted in Fig. 3. The results for the corresponding Markovian limit have been depicted in the inset of Fig. 3. Figure 3 reveals that, for a one-dimensional case, the mean escape time versus driving frequency plots possess no maximum. This aspect has also been reported earlier by several groups using numerical experiment[36] and analytical calculation.[37] Also, there are experimental and theoretical studies modelling catalytic reactions[35,44] which show that mean escape time vs. driving frequency plots exhibit only a minimum but no maximum. Thus, appearance of the maximum at low frequency regime is a generic signature of barrier crossing dynamics in many

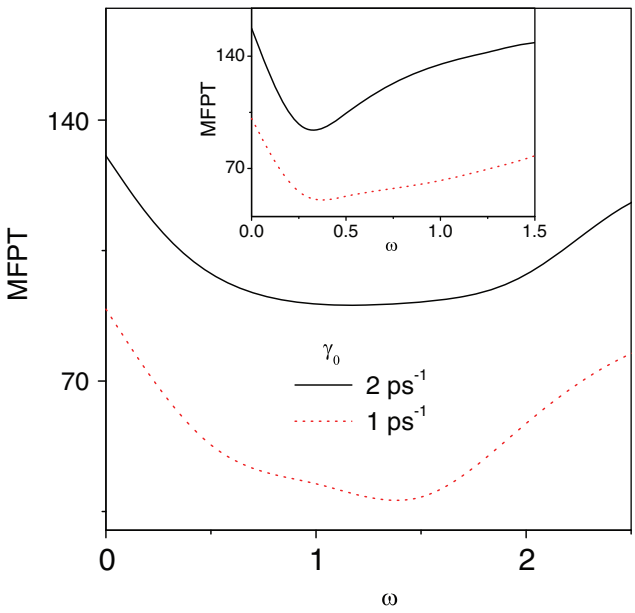

FIG. 3. Plot of mean first passage time, MFPT vs ω the frequency of the external driving force. We chose the double well potential as $V(q) = 1/4q^4 - 1/2q^2$. We use $T = 0.1$, $A_0 = 0.25$, $\tau = 1.0$. In the inset same plot is drawn in the limit $\tau \to 0$. (units are arbitrary)

dimensional systems. In protein folding kinetics, in addition to energetic barrier, entropy of activation plays a significant role. The appearance of the maximum (in the t_f vs. ω) at low frequency regime may be attributed to increase of the fluctuations in configurational entropy during the barrier crossing rather than activated transport towards the transition state by the periodic force. For further increase of frequency, the energy transfer to activate towards the transition state dominates over the increase of fluctuations in configurational entropy and the mean folding time decreases until the energy transfer rate becomes small. Thus the maximum and the minimum in t_f vs ω plots is a result of interplay between two important quantities, entropy and activation energy. Similar features of

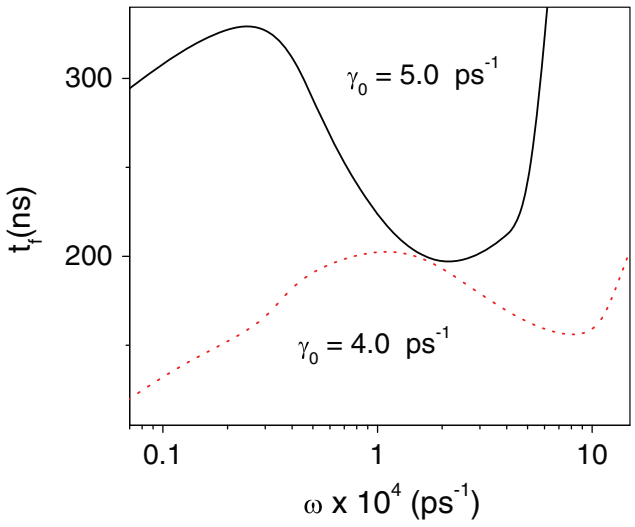

FIG. 5. Plot of mean folding time t_f of ubiquitin vs the frequency of the external driving force. We chose $T = 298$ K, $A_0 = 0.1$ pN, $\tau = 1.0$ ps.

folding time as a function of driving frequency has been observed for the higher driving amplitude and damping. It has been presented in Fig. 4.

Figures 2 and 4 reveal that the position of the minimum in the mean folding time vs. frequency plots is very sensitive to viscosity (damping) of the medium. Positions of the minima are shifted to the lower frequency with increasing damping. The pleasurable explanation of this behavior is as follows: At low viscosity, because of the strong spatial diffusion the acceleration of folding kinetics starts to work over the entropy effect slowly compared to high damping case. Therefore, the minimum at the higher driving frequency for lower damping constant is observed.

Our another interesting observation from the Figs. 2 and 4, the minimum is shallow and flat for low damping cases compared to the high damping situation. Because of strong spatial diffusion in the former case, the effect of the periodic

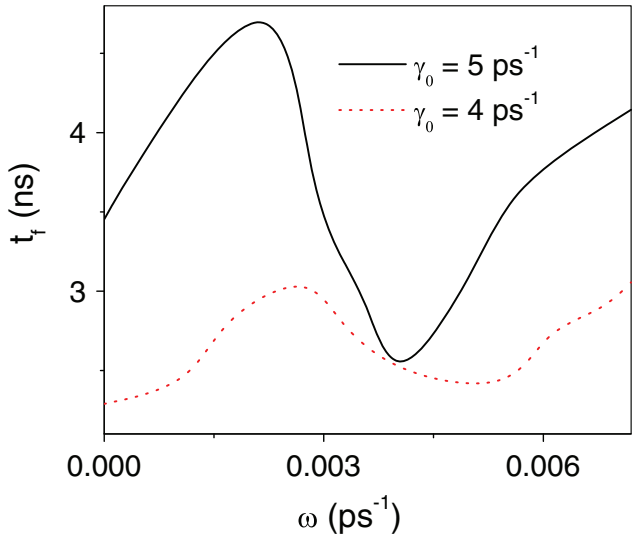

FIG. 4. This plot shows the dependence of mean folding time of $\beta-$hairpin on the frequency of the external derive in the heavy damping situation. The chosen parameters are $T = 298$ K, $\tau = 1.0$ ps, $A_0 = 1$ pN.

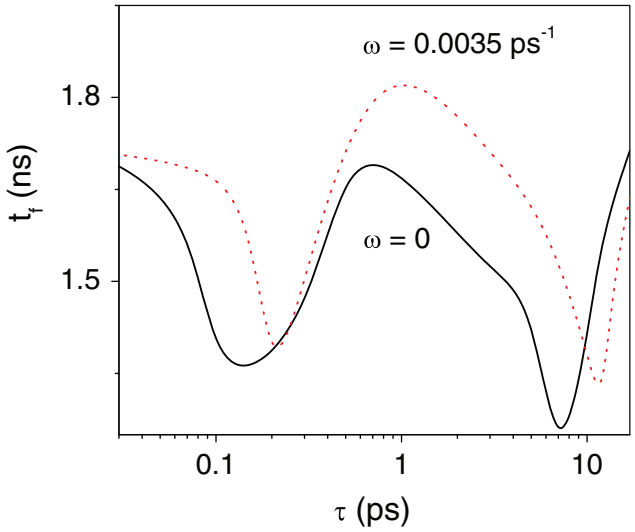

FIG. 6. This plot shows the dependence of mean folding time of $\beta-$hairpin on the correlation time of the non-Markovian noise. The chosen parameters are $T = 298$ K, $\gamma = 1.0$ ps^{-1}, $A_0 = 1.0$ pN.

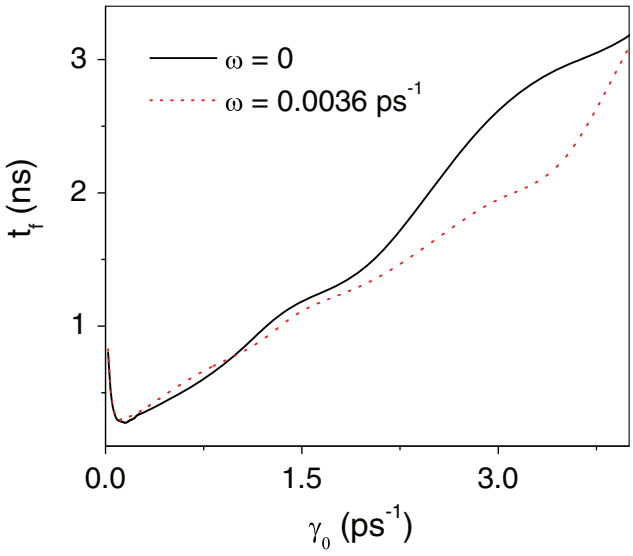

FIG. 7. This plot shows the dependence of mean folding time of $\beta-$hairpin on the viscosity of the medium. The chosen parameters are $T = 298$ K, $\tau = 1.0$ ps, $A_0 = 1$ pN.

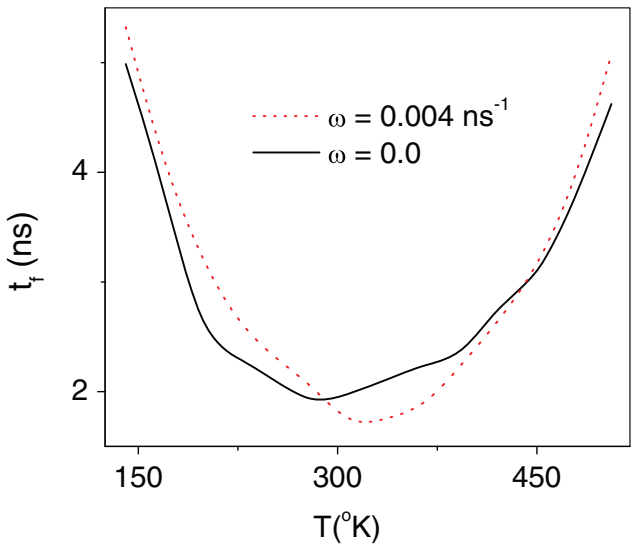

FIG. 8. This plot shows the dependence of mean folding time of $\beta-$hairpin on the temperature of the system. The chosen parameters are $\gamma = 2$ ps^{-1}, $\tau = 1.0$ ps, $A_0 = 1$ pN.

force (by virtue of doing mechanical work on the particle in the dynamics) is weaken and it suppresses activation as well as slow down the variation of folding time with increase of the driving frequency. Thus, the increase of the damping constant enhances activation at the cost of decreasing its robustness.

To generalize our conclusions we have also studied folding kinetics of a long protein, ubiquitin. Figure 5 presents mean folding time of ubiquitin versus driving frequency for different values of the damping constant. Here also the mean folding time passes through a maximum and a minimum. Other behaviors are also very similar to $\beta-$hairpin.

Next, we have explored effects of the non-Markovian bath in the folding dynamics in presence of external field. The folding time of $\beta-$hairpin shows two minima with noise correlation time (shown in Fig. 6). The reason for appearance of unusual two minima has discussed in detail in our recent study.[42] However, the second minimum appears at higher correlation time in presence of the periodic force. To explain this we recall the fluctuation dissipation relation (3). It implies that the variance of noise decreases with increase of noise correlation time. Increase of noise correlation time leads to decrease of fluctuations in entropy. Because of higher entropy in presence of the driving force, the noise correlation starts playing role in the dynamics at its larger value. Thus, the shifting of positions of the minima are attributed to the excess entropy due to the external field.

Figure 7 depicts the variation of folding time of $\beta-$hairpin as a function of viscosity of the medium in presence of external periodic force. We observe that the folding time differs significantly around only the region where the folding kinetics is accelerated due to the applied periodic field.

To elucidate the effect of external forcing on the U-shaped mean folding time versus temperature profile, we calculate the folding time both in presence and absence of the external force. This is depicted in Fig. 8. It shows that the folding time is greater than the corresponding unperturbed case in the regime where increase of entropy dominates over the energy transfer to activate towards the transition state and is lower when the latter dominates over the former. Acceleration of folding kinetics due to the external field causes a shift of the minimum (see Fig. 8) towards the higher temperature and also lowers the width of U-shaped temperature profiles.

III. CONCLUSION

Based on the coarse-grained off-lattice models for a polypeptide chain and setting Go-like Hamiltonian for the system we have followed the dynamics of the protein chain by solving $N-$coupled Langevin equations in presence of an external field. In order to make the model more realistic we have assumed the non-Markovian heat bath. Our main conclusions of this study are as follows:

(A) Under influence of an oscillating electric filed the mean folding time of $\beta-$hairpin shows a maximum and a minimum in mean folding time vs driving frequency plots. This feature is in a sharp contrast to the one-dimensional barrier crossing problem where only a minimum is observed in the same profile. Thus, periodic force can induce stabilization or destabilization of the denatured state of a protein. The folding kinetics of a longer protein, ubiquitin also exhibits a similar feature. Therefore, the above observation is true for both long and small proteins.

(B) Even in presence of an oscillating force field of amplitude 0.1–1 pN the following three important features of protein folding kinetics remain intact: (i) turnover behavior of mean folding time with solvent viscosity, (ii) U-shaped mean folding time vs. temperature profiles, and (iii) double minimum in mean folding time as a function of the correction of thermal fluctuations. It implies that the above properties are very robust to external perturbations. But the following new features are noticed for the presence of the external force field.

(a) In the presence of the periodic force the second minimum appears at relatively higher noise correlation time of

the thermal noise in the plot t_f it vs. τ. This is due to excess entropy of the system, which is produced by external fluctuations.

(b) Increase in the damping strength enhances acceleration of folding kinetics by the periodic force at the cost of decreasing its robustness.

(c) Finally, we observe acceleration of the folding kinetic due to presence of the external field in the variation of mean folding time with viscosity of the medium and temperature.

We hope our theoretical findings could be verified experimentally measuring protein folding time in the presence of a monochromatic isotropic electromagnetic radiation. For a given intensity of the radiation amino acid residues experience a resultant amplitude vector $\vec{A}_0$. In presence of an isotropic electric field the magnitude of $\vec{A}_0$ would be independent on the orientation of the protein chain and time. We have considered this aspect in our present study.

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