How does the tail length and the separation between the tagged monomers influence the reconfiguration of a chain with internal friction for different solvent-quality?

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Abstract.
Recent experiments involving single proteins have shown the importance of internal friction in protein dynamics. In addition to internal friction, solvent-quality also plays an important role in elucidating the structure and dynamics of proteins. Using a single chain based model where internal friction is introduced via dashpots between the neighbouring monomers and the solvent-quality is taken care of by introducing a mean field Flory type parameter, we monitor the effect of separation of two tagged monomers along the chain and the tail length on the reconfiguration time. We show that irrespective of the degree of compactness, the reconfiguration time remains unchanged beyond a tail length. Our calculations can also reproduce different trends observed in experiments.

1. Introduction
In recent past single molecule based studies have shown not only the existence of internal friction in proteins but also its profound effect on protein dynamics [1, 2]. In particular, measurements of the reconfiguration dynamics of some unfolded proteins such as cold shock protein and spectrin domain R17 [1, 2] reconfirmed the importance of internal friction in proteins. The reconfiguration times shown to have a linear dependence on the solvent viscosity but with a non-zero intercept that attributes to the time scale for internal friction. However it was Khatri and McLeish who first showed that internal friction can be introduced starting with the celebrated Rouse model by placing a dashpot in parallel to the harmonic springs which connect the neighbouring monomers [3]. It is obvious that the amount of internal friction a polymer would experience should depend on its conformation, solvent-quality and the concentration of the denaturant added to the solvent. Keeping these in mind, very recently we have proposed a generalised polymer model which can take care of internal friction, solvent-quality and denaturant concentration [4]. This new model is named “solvent dependent compacted Rouse with internal friction (SDCRIF)” [4] and is an extension of existing models [5, 6, 7]. To take care of the solvent-quality the excluded volume effect is included at the mean field level following the work by Panja and Barkema [8] by introducing a parameter $\nu$ analogous to the Flory exponent in the expression for the correlation function of the normal modes of the polymer. In experiments denaturant are usually added to proteins for expanding them from a more compacted state to an unfolded state and as a
Figure 1. (a) Scheme showing how the relative separation between the monomers is changed along the chain. (b) Scheme showing how the tail is added to one end of the chain and then the tail length is increased.

Figure 2. $\tau_{nm}$ vs $|n - m|$ for different solvent-quality for $k_c = 0.5k_{c,0}$.

consequence internal friction also decreases with reduced non-bonded interactions [9, 10]. This has been also taken into account in SDCRIF model by introducing a harmonic potential in the system which can control the compactness of the polymer. Further the strength of this potential is considered to be proportional to the internal friction.

In this paper primarily two questions have been addressed. The first one is how the reconfiguration time changes in different solvent condition with the separation of monomers along the chain. This is important since in single molecule FRET based experiments [1], the donor and acceptor need not always be at the two ends of the protein but could also be placed in the interior of the chain (Fig. (1)). The next problem is to study the behaviour of the reconfiguration time by keeping the position of the monomers fixed and introducing additional
monomers (or tail) to one end of the chain chain as presented in the second scheme of the Fig. (1).

The paper is arranged as follows. The polymer model is discussed in Section 2 and the results are presented in Section 3. The conclusion is made in Section 4.

2. Polymer model

The simplest description of a polymer chain is given by the Rouse model [11, 12]. In this model the polymer is represented as a series of Brownian particles connected by harmonic springs without any hydrodynamics interactions and excluded volume effects. The equation of motion for the \( n^{th} \) monomer of a Rouse chain is given by

\[
\xi \frac{\partial R_n(t)}{\partial t} = k \frac{\partial^2 R_n(t)}{\partial n^2} + f(n, t)
\]  

(1)
Figure 5. $\tau_{nm}$ vs tail length for different solvent-quality for $k_c = 0.5k_{c,0}$. 

Figure 6. $\tau_{nm}$ vs tail length for different solvent-quality for $k_c = k_{c,0}$. 

Here, $n$ can take up any value from 0 to $N$ for a polymer having $(N + 1)$ monomers connected via springs having force constant $k = \frac{3k_B T}{D_p}$ and $\xi$ is the friction co-efficient. $f(n, t)$ is the random force acting on the $n^{th}$ with first and second moments

$$\langle f(n, t) \rangle = 0, \langle f_\alpha(n, t_1)f_\beta(m, t_2) \rangle = 2\xi k_B T \delta_{\alpha\beta}\delta(n - m)\delta(t_1 - t_2)$$

The novelty of our recently proposed model, “solvent dependent compacted Rouse with internal friction (SDCRIF)” lies in the fact that it takes care of the effects of solvent-quality, denaturant concentration in addition to the internal friction to the chain dynamics [4]. In normal mode description, this SDCRIF behaves very similarly to the simple Rouse chain and has the following equation of motion holds

$$\xi_p \frac{dX_p(t)}{dt} = -k_p X_p(t) + f_p(t)$$
Figure 7. $\tau_{nm}$ vs tail length for different solvent-quality for $k_c = 1.5k_{c,0}$.

Where, $R_n(t) = X_0 + 2 \sum_{p=1}^{\infty} X_p(t)cos\left(\frac{p\pi n}{N}\right)$, $\xi_p = 2N\xi + \frac{2\pi^2p^{2v+1}\xi_{int}}{N^{2v}}$ and $k_p = 2Nk_c + \frac{6\pi^2k_BTp^{2v+1}}{N^{2v+1}}$. The relaxation time for $p^{th}$ normal mode is given by $\tau_p = \frac{\xi_p}{k_p} = \frac{2N\xi}{k_p} + \tau_{int}$ where, $\tau_{int} = \frac{\xi_{int}}{k+kcN^{2v+1}/p^{2v+1}\pi^2}$. Here, $\nu$, $k_c$ and $\xi_{int}$ are the three parameters which take care of solvent-quality, denaturant concentration and internal friction respectively. $\nu$ is the the mean field Flory exponent that account for the solvent-quality. Value of $\nu$ speaks for the solvent-quality. Typically, $\nu = 3/5$ corresponds to the good solvent, $1/2$ for the $\theta$ solvent and $1/3$ for the poor solvent [13, 14]. On the other hand, the compactness of the polymer is controlled by introducing a harmonic potential to the system of strength $-\frac{\partial}{\partial R_n} \left(\frac{k}{2} (R_n - 0)^2\right)$. This is to replicate the denaturation of proteins from their native structures to completely unfolded state. It is obvious that $k_c$ and $\xi_{int}$ should be related to each other since internal friction is higher when the polymer is in more compacted state and vice-versa. As mentioned in our earlier work $k_c$ and $\xi_{int}$ can be connected using an ansatz $k_c = \tilde{k}_c + A\xi_{int,0} (c_0 + c_1n_b + c_2n_b^2 + ...)$ and $\xi_{int} = \xi_{int,0} (c_0 + c_1n_b + c_2n_b^2 + ...)$ [7], with $n_b$ being the number of non-neighbouring monomers interacting with the monomer and $k_{c,0} = \tilde{k}_c + A\xi_{int,0}$, which corresponds to a situation when only the two nearest neighbours of a monomer contribute to its internal friction and this corresponds to $c_0 = 1$. Even in the absence of internal friction $\tilde{k}_c$ can vary the compactness of the polymer which makes the ansatz applicable for the polymers with no internal friction.

The time-correlation function for the normal modes is

$$\langle X_{p\alpha}(0)X_{q\beta}(t) \rangle = \frac{k_pT}{k_p} \delta_{pq} \delta_{\alpha\beta} \exp\left(-t/\tau_p\right)$$  \hspace{1cm} (4)

The position correlation function of a vector connecting say $n^{th}$ and $m^{th}$ monomer can be determined from the correlation function of the normal modes

$$\phi_{nm}(t) = \langle R_{nm}(0), R_{nm}(t) \rangle = 12 \sum_{p=1}^{\infty} \frac{k_pT}{k_p} \exp\left(-t/\tau_p\right) \left[ \cos \left(\frac{p\pi n}{N}\right) - \cos \left(\frac{p\pi m}{N}\right) \right]^2$$  \hspace{1cm} (5)

The reconfiguration time is calculated as follows [15]
\[ \tau_{nm} = \int_0^\infty dt \tilde{\phi}_{nm}(t) \]  

(6)

Where, \( \tilde{\phi}_{nm}(t) = \frac{\phi_{nm}(t)}{\phi_{nm}(0)} \)

### 3. Results and Discussions

We make use of Eq. (6) to calculate the reconfiguration time (\( \tau_{nm} \)) between two interior monomers of the polymer and have plotted against the separation between the monomers in Fig. (2). For this we follow the scheme as depicted in Fig. (1), thus by keeping one of the end monomers fixed the other monomer is moved towards the interior of the chain starting at the other end. From the Fig. (2) it can be clearly seen that the reconfiguration time increases with increasing solvent-quality and this is obvious since the polymer goes to a more unfolded state from collapsed state as the solvent-quality changes from poor to good. Another interesting aspect of the figure is the trend of reconfiguration time with the increasing separation between the monomers \( n \) and \( m \). The plot shows an initial increase of \( \tau_{nm} \) with \( |n - m| \), but as the two monomers move towards the two opposite ends of the chain, \( \tau_{nm} \) starts decreasing. In other words \( \tau_{nm} \) passes through a maxima. This happens presumably because when the distance between two monomers is large, the contributions from the lower normal modes will be predominant. As a consequence the correlation decay of \( R_{nm} \) becomes slow which results in slow reconfiguration of the chain. However, with increasing distance the MSD also increases which results in faster correlation decay and consequently smaller \( \tau_{nm} \). Because of these two competing factors, reconfiguration time passes through a maxima \[6, 7\]. In Fig. (3) and Fig. (4) the same plots are shown at higher values of \( k_c \). Surprisingly the trend of reconfiguration time against \( |n - m| \) changes with increasing \( k_c \). It is observed that there exists two opposite trends. In one case, \( \tau_{nm} \) passes over a maxima and in other case it goes through a minima as \( |n - m| \) increases. It is observed that \( k_c \) and \( \nu \) both controls this trend. When the polymer is in more compact state, which means higher \( k_c \) and lower \( \nu \), the reconfiguration time decreases with increasing distance between the monomers, however with increasing solvent-quality the trend reverses. The decreasing nature of \( \tau_{nm} \) with the increasing distance between the monomers was observed by Nettels et al \[16\] while performing single molecule experiments with cold shock proteins.

Next we have looked into the effect of increasing tail length on reconfiguration time in Fig. (5). We follow the scheme depicted in Fig. (1) to add tail to one of the ends of the chain. In the beginning \( \tau_{N0} \) i.e. the end-to-end reconfiguration time for a polymer with length \( N = 66 \) is calculated, which is followed by addition of more monomers to one end of the polymer and calculation of end-to-interior reconfiguration time between the same two monomers i.e. \( n = 66 \) and \( m = 0 \). Similar calculations are done for different solvent-quality and shown in the same Fig. (5). It is observed that the reconfiguration time reaches a saturation value after increasing for a while with the increasing tail-length. This is in consistent with the fact that although chain reconfiguration becomes slower for the increment of the total chain-length, when the tail becomes too long it fails to affect the reconfiguration of the other end of the chain. Similar trends for looping times were observed by Doucet et al when they performed simulation for in polypeptide chains \[17\]. For two higher \( k_c \) values the reconfiguration time has been studied as a function of tail-length as shown in Fig. (6) and Fig. (7) and in every cases the \( \tau_{nm} \) for the polymer in poor solvent saturates early in comparison to the one in good solvent for a relatively shorter tail-length. This is expected given the more collapsed state of the polymer in poor solvent makes one end of the polymer less susceptible to the effects coming from the other end. Throughout the paper the value of parameters used are: \( \xi = 3.8 \times 10^{-12} \text{kg s}^{-1} \) and \( T = 300 \text{K} \).
4. Conclusions
Using a model of single chain with internal friction and a mean field description of the solvent-quality we show how these factors influence the reconfiguration dynamics of a chain. In particular we analyse the effect of adding a tail and increasing the separation between the monomers along the chain to the reconfiguration time. Our calculation shows that the parameters controlling the solvent-quality ($\nu$), denaturant concentration ($k_c$) and internal friction ($\xi_{int}$) can reproduce different trends observed in experiments [16].

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