Dynamics of Forster Energy Migration Across Polymer Chains in Solution

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Abstract

Long distance excitation energy transfer between a donor and an acceptor embedded in a polymer chain is usually assumed to occur via the Forster mechanism which predicts a $R^{-6}$ distance dependence of the transfer rate, where $R$ is the distance between the donor and the acceptor. In solution $R$ fluctuates with time. In this work, a Brownian dynamics simulation of a polymer chain with Forster energy transfer between the two ends is carried out and the time dependence of the survival probability $S_P(t)$ is obtained. The latter can be measured by fluorescence resonance energy transfer (FRET) technique which is now widely used to study conformations of biopolymers via single molecule spectroscopy. It is found that the survival probability is exponential-like when the Forster radius ($R_F$) is comparable to the root mean square radius ($L$) of the polymer chain. The decay is strongly non-exponential both for small and large $R_F$, and also for large $k_F$. Large deviations from the Wilemski-Fixman theory is obtained when $R_F$ is significantly different from $L$.

1 Introduction

Fluorescence resonance energy transfer (FRET) is a powerful technique to study many aspects of structure and dynamics of polymers and biopolymers.$^{1-8}$ In this technique, the polymer is doped with a donor and an acceptor at suitable positions along the chain. The donor is initially excited optically by a laser light which subsequently transfers its energy to the acceptor which is located at a distance $R$ from the donor. In many applications, the distance between the donor and the acceptor is fixed, as in the case of

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rigid biopolymers.\textsuperscript{4,5,7,8} However, in many cases of interest, this distance is a fluctuating quantity.\textsuperscript{1−3,6} For example, the distance between the two ends of a polymer in solution executes a Brownian motion. If the polymer is assumed to be an ideal Gaussian chain, then the mean square distance between the two ends is $Nb^2$, where $N$ is the number of the monomer units and $b$ is monomer (or the Kuhn) length. Thus, as the number of monomers in the chain increases, the average distance between the two ends also increases. The probability distribution of $R$, $P(R)$, however, remains peaked at $R = 0$ for ideal chain, although its height decreases as $1/\sqrt{N}$. All these properties play important parts in determining the observed dynamics of excitation energy transfer.

The usually assumed mechanism for excitation energy transfer between a donor and an acceptor is the Forster mechanism\textsuperscript{6} which gives the following expression for the singlet-singlet resonance energy transfer rate, $k(R)$,

$$k(R) = k_F \frac{1}{1 + (R/R_F)^6}$$

(1)

where $R_F$ is the Forster radius and $k_F$ is the rate of excitation transfer when the separation between the donor and the acceptor is very small, that is $R/R_F \to 0$. The Forster radius is usually obtained from the overlap of the donor fluorescence with the acceptor absorption and several other available parameters\textsuperscript{5}.

The dynamics of Forster energy migration has been traditionally investigated by performing time domain measurements of the decay of the fluorescence (due to excitation transfer) from the donor.\textsuperscript{1,4−6} More recently, this technique has been used in single molecule spectroscopy of biopolymers\textsuperscript{7,8}. In the latter, distance dependence of FRET provides relevant information about the conformation and dynamics of single biopolymers. Recently, FRET from single protein molecules has also been used to study protein folding\textsuperscript{9}. At any given time after the initial excitation, the fluorescence intensity is a measure of the "unreacted" donor concentration. As both $k_F$ and $R_F$ are determined by the donor-acceptor pair, the rate of decay of the fluorescence intensity provides a direct probe of the conformational dynamics of the polymer.

When the polymer is in solution, each monomer (or polymer bead) executes Brownian motion. Because of the connectivity of the polymer chain, this Brownian motion
of the monomers are strongly correlated. This many body nature of polymer dynamics can be described by a joint, time dependent probability distribution $P(r^N, t)$ where $r^N$ denotes the positions of all the $N$ polymer beads. The time dependence of the probability distribution $P(r^N, t)$ can be described by the following reaction-diffusion equation\textsuperscript{10,11}

$$\frac{\partial}{\partial t} P(r^N, t) = \mathcal{L}_B(r^N, t) P(r^N, t) - k(R) P(r^N, t)$$

(2)

where $\mathcal{L}_B$ is the full $3N$ dimensional diffusion operator given by,

$$\mathcal{L}_B(r, t) = D \sum_{j=1}^{N} \frac{\partial}{\partial r_j} P_{eq}(r, t) \frac{\partial}{\partial r_j} \frac{P(r, t)}{P_{eq}(r, t)}$$

(3)

$R$ is the scalar distance between the two ends of the polymer chain and $D$ is the center of mass diffusion coefficient.

The solution of Eq.2 with the sink term given by the Forster expression is highly non-trivial. In two seminal papers, Wilemski and Fixman presented a nearly analytic solution of the problem for any arbitrary sink.\textsuperscript{10,11} The WF theory has been tested (only for the average rate) by computer simulations when the sink is a Heaviside function.\textsuperscript{11–13} We are not aware of any such simulation study with the Forster rate. Such a study is clearly important.

The objective of this paper is mainly two fold. First, to present results of detailed Brownian dynamics (BD) simulations of Eq.2, with $k(R)$ given by the Forster rate (Eq.1). Detailed investigation into the time dependence of the survival probability at a time $t$ after the initial excitation ($S_P(t)$) is presented. We believe that this is the first such calculation of $S_P(t)$ for this kind of a problem. We find that the time dependence of $S_P(t)$ can be non-exponential for a large range of the relevant parameter space ($N, k_F, R_F$). Second, we present a detailed comparison of the simulated rate with the WF theory. This comparison has been carried out at the level of time dependent survival probability, again, we believe, for the first time.

The organization of the rest of the paper is as follows. In next section, we present the details of the BD simulation. In section III, we discuss the WF theory. In section IV we present the simulation results and the comparison with the WF theory. Section V
concluded with a discussion.

2 Simulation Details

Brownian Dynamics (BD) simulations of polymer motion have been carried out with an idealized Rouse chain, in which the set of beads are connected by the harmonic potential,

$$\beta U = \frac{3}{2b^2} \sum_{j=1}^{N-1} (r_j - r_{j+1})^2$$  \hspace{1cm} (4)

where the position vector of a bead $j$ is denoted by $r_j$, and $N$ is the number of beads constituting the polymer chain. The mean squared bond length is $b^2$. Equilibrium end-to-end distance of the polymer chain is,

$$\langle (r_N - r_0)^2 \rangle = L^2 = N b^2$$ \hspace{1cm} (5)

In Rouse model, there exists no excluded volume forces and the hydrodynamic interactions between the monomer beads are ignored\textsuperscript{13}. More details on this model can be found elsewhere\textsuperscript{13}. In our present study the polymer chain is additionally characterized by the presence of two reactive end groups. This essentially implies that within the time interval $\Delta t$, the two end groups react with a probability $k(R)\Delta t$.

The initial configuration for each trajectory has been selected from a Monte Carlo generated random distribution. The following equation of motion has been used in the simulations,

$$r_j(t + \Delta t) = r_j(t) + F_j(t)\Delta t + \Delta X^G(t)$$ \hspace{1cm} (6)

where the positions of the j-th bead at time $t$ and $t+\Delta t$ are denoted by $r_j(t)$ and $r_j(t+\Delta t)$, respectively. $F_j(t)$ is the total force acting on bead $j$ and $\Delta X^G(t)$ is a random Brownian displacement, taken from a Gaussian distribution with zero mean and the variance $\langle (X^G)^2 \rangle = 2\Delta t$. In writing Eq.1, we have set both $D_0$ and $K_B T$ equal to unity; the latter is Boltzmann constant times the temperature. Here we adopted a time step, $\Delta t = 0.001$. However, smaller time steps as low as 0.0001 has been employed in the limit of both large $k_F$ and large $R_F$ values, to account for the faster dynamics. During the simulation both the mass $m$ and the root mean-square bond length $b^2$ of the bead have been set to unity for computational convenience.
The trajectory generated by using the above procedure needs to be terminated when the two end groups react. This has been done in simulations in the following way. Each time the trajectory is updated, the existing end to end distance $R$ is used in Eq.1 to calculate the distance dependent rate constant, $k(R)$. We then call a random number generator to get a value between zero and unity. If this value is less than $k(R)\Delta t$, then the trajectory is terminated. Otherwise, the trajectory is continued. One forms a histogram over many such trajectories. This procedure generates an irreversible FRET.

For each polymer chain constructed randomly, we have equilibrated it for 10,000 time steps before switching on the reaction. Subsequently, 50,000 to 1 Lakh trajectories with different initial configurations were generated and the survival probability $S_p(t)$ was obtained by averaging over all the trajectories. This procedure was systematically applied for the polymer chains containing the beads, $N = 20, 50$ and $100$.

Before proceeding with the simulations of the Forster transfer, we reproduced the results of Pastor, Zwanzig and Szabo (PZS)$^{12}$ on the mean first passage time with Heaviside sink function of infinite strength. Our simulation results agreed with those of PZS within the uncertainty given by PZS.

3 Wilemski-Fixman Theory$^{10,11}$

Several decades ago Wilemski and Fixman (WF) developed a non-trivial theory for the diffusion limited intrachain reaction of a flexible polymer.$^{10,11}$ To account for the chemical reaction they have added a sink term $S$ to the manybody diffusion equation, just as in Eq.2. The WF equation of motion is well-known and we present it below for the sake of completion

$$\frac{\partial}{\partial t} P(\mathbf{r}_N, t) + \mathcal{L}_B P(\mathbf{r}_N, t) = -k_0 S(R) P(\mathbf{r}_N, t).$$

(7)

In the notation of the present work

$$k_0 = k_F; S(R) = \frac{1}{1 + (R/R_F)^6}. \quad (8)$$

The operator $\mathcal{L}_B(\mathbf{r}_N, t)$ is given by Eq.3. As already mentioned, the treatment of WF is general and can be applied to a reaction with arbitrary sink.
Let us define a survival probability $S_p(t)$ as the probability that the chain has not reacted after time $t$. $S_p(t)$ is then given by,

$$S_p(t) = \int P(r^N, t) dr_1 dr_2 ... dr_N$$  \hspace{1cm} (9)

In order to obtain the survival probability WF made a closer approximation, according to which the Laplace transform of $S_p(t)$ can be written as,

$$\hat{S}_p(s) = \frac{1}{s} - \frac{k\upsilon_{eq}}{s^2(1 + k\hat{D}(s)/\upsilon_{eq})}$$  \hspace{1cm} (10)

where $\hat{D}(s)$ is defined as,

$$\hat{D}(s) = \int_0^\infty e^{-st} D(t) dt$$  \hspace{1cm} (11)

which is the Laplace transform of sink-sink time correlation function $D(t)$ defined as,

$$D(t) = \int d^3R_1 \int d^3R_2 S(R_1)S(R_2)G(R_1, R_2, t)$$  \hspace{1cm} (12)

The Green function appearing in the above equation is given by,

$$G(R_1, R_2, t) = \left(\frac{3}{2\pi L}\right)^{3/2} \left(\frac{1}{(1 - \rho^2)^{3/2}}\right) exp\left(-\frac{R^2 - 2\rho(t)R_2 + R_2^2}{2L^2(1 - \rho^2)}\right)$$  \hspace{1cm} (13)

where $\rho(t)$ is the normalized time correlation function of end-to-end vector $\langle R(0) R(t)\rangle/\langle R^2 \rangle$ which can be obtained analytically and is given by the following equation,

$$\rho(t) = \frac{8}{\pi^2} \sum_{l;\text{odd}} \frac{4}{l^2} exp(-\lambda_l t)$$  \hspace{1cm} (14)

If we neglect excluded volume and hydrodynamic interactions, $\lambda_l$ is given by the following expression\textsuperscript{10,11}.

$$\lambda_l = 3D_0(l\pi/Nb)^2,$$  \hspace{1cm} (15)

Finally $\upsilon_{eq}$ is given as,

$$\lim_{t \to \infty} D(t) = (\upsilon_{eq})^2$$  \hspace{1cm} (16)

Note that $\upsilon_{eq}$ is the rate when the distribution of the polymer ends is at equilibrium. Thus, $\upsilon_{eq}$ gives the initial rate of decay of $S_p(t)$ which will show up as the transient behavior. In most cases, the rate of decay should become progressively slower, as the population from the sink region decreases as the reaction proceeds.
Once the choice of sink function specified, it is straightforward to calculate the survival probability by utilizing the above set of equations. WF choice was the heaviside sink function. Later, Doi showed that WF method is easy to apply if the heaviside sink function is replaced with a Gaussian sink function. Bettizetti and Perico studied the dependence of the rate on the choice of sink function with in the framework WF theory and supported the WF closure approximation. Surprisingly, no analysis of the time dependence of the survival probability, $S_P(t)$ has ever been reported. In this study we follow the original scheme proposed by WF to obtain $S_P(t)$ analytically. In doing so we use the Stefanest algorithm to obtain $S_P(t)$ through the Laplace inversion of Eq. 10.

4 Results and Discussion

Before discussing the results let us describe the scaling that has been used to compare the results obtained by simulation with the theory. In the reduced unit notation adopted in simulation, the rate constant has been scaled as $\tilde{k}_F = k_F b^2 / D_0$ and the real time has been scaled by $b^2 / D_0$. However, in the original WF theory, time is scaled by $6D/L^2$ where $D$ is the center of mass diffusion. In the free draining limit, so $D = D_0 / N$ and $L^2 = Nb^2$. Thus, the numbers obtained from WF theory is to be converted to the simulation scaling for a comparison of results. The Forster radius is scaled by the bead diameter, $b$. Another important parameter in this problem is the root mean square radius of the polymer as this determines the end to end distribution. Although we have carried out simulations for $N=20$, 50 and 100, in this report we shall concentrate mostly on $N=50$.

Figures 1 and 2 depict the time dependence of the survival probability $S_P(t)$ for two different values of $R_F$, $R_F = 1$ and $R_F = 5$, respectively, for a fixed $N = 50$. In figure 1, $k_F$ has been varied from 50 to 0.1, that is, over two orders of magnitude. The decay remains non-exponential over the whole range. In figure 2, $k_F$ has been varied from 10 to 0.1. Here the decay is exponential-like. These two figures demonstrate the strong dependence of the decay profile of $S_P(t)$ on $R_F$. Note that the earlier experiments which fitted the quantum yield to the Forster expression obtained values which are rather large, comparable to the ones shown in figure 2. This could have been due to the use of an equilibrium end-to-end
distribution in the fitting, instead of a time dependent probability distribution. In model calculations, one usually assumes a small value of $R_F$ (often in the form of a Heaviside sink function). This strong dependence of decay profile on $R_F$ could be potentially useful in unravelling mechanism and dynamics of energy transfer.

It is not difficult to understand the above results qualitatively. For an ideal Gaussian chain, the maximum in the probability distribution that the two ends are separated by a distance $R$ is located at $\sqrt{(2N/3)b}$. For $N=50$, this value is 5.773b. Therefore, when $R_F$ is equal to 5, the decay is facilitated by the presence of a large fraction of the distribution at a distance of separation where the transfer rate is large. This can explain the exponential-like decay for $R_F = 5$ (figure 2). However, the situation is completely different for $R_F = 1$. Here the probability of finding a polymer with end-to-end distance so small is negligible and the transfer rate where the bulk of the population is located is very small because of the strong $R$ dependence of the Forster transfer rate. Therefore, the decay of the survival probability starts slowly (Fig.1) and is determined by the interplay between the diffusion and the rate. This explains the shape of figure 1.

The above discussion also suggests that the shape of the survival probability can depend rather strongly on the length of the polymer chain. This is because the Forster distance for a given donor-acceptor pair is likely to be independent of the length of the polymer chain. But the distribution and also the diffusion rate will be determined by $N$. However, this dependence is not trivial and will be discussed elsewhere.

In figures 3 and 4, we have compared predictions of the WF theory with the simulations. In figure 3, $S_P(t)$ is plotted for two very different values of $k_F$ ($K_F = 1$ and 10) at $R_F = 5$ for $N = 50$. It is seen that while the agreement is satisfactory at short times for both the cases, the same is not true at long times, particularly for the smaller $k_F$. In the latter case the simulation also finds a larger non-exponentiality, as discussed later. In figure 4, $S_P(t)$ is plotted for $R_F = 1$, $k_F = 1.0$ (and $N = 50$). It is seen that the WF theory breaks down in this limit. This is one of the main results of the present study. The agreement improves for smaller $K_F$ but becomes worse in the opposite limit.

We have also simulated both larger and smaller chains. Since the size of the polymer
scales with N, it is not possible to compare results for different sizes. In figure 5, we show the comparison between the simulation results and the WF theory for $N = 100$ at $R_F = 8$ and $k_F = 0.1$. This is the most favorable parameter space for the WF theory. Although the simulated $S_P(t)$ decays somewhat faster, the WF theory prediction is not totally off. We have not yet searched for any scaling laws (in N, $R_F$ and L) dependence – work is under progress in this direction.

In figures 6 and 7, we present logarithmic plots of $S_P(t)$ to show the extent of non-exponentiality, for different values of $R_F$ and $k_F$. It can be seen that while the decay is nearly exponential for small $K_F$ (which is expected), it is strongly non-exponential when the value of $k_F$ becomes comparable to or larger than the bead diffusion rate, $D_0/b^2$.

The inability of the Wilemski-Fixman theory to explain the time dependence of the survival probability is surprising. We note that earlier theoretical studies have considered only the mean first passage time. In figure 8 we have compared the simulated end-to-end vector time correlation function ($\rho(t)$) with the slightly approximate expression used by WF. The agreement is good, as expected. This agreement improves further for larger N. Thus, the failure of WF (as shown in Fig.4) must be due to the closure approximation.

5 Conclusions

Use of FRET in single molecule spectroscopy of polymers and biopolymers requires accurate knowledge of the mechanism of energy transfer, more importantly, the distance dependence of the transfer rate. The fluorescence quantum yield can provide only an average estimate of the distance between the donor and the acceptor if the mechanism is well-understood. This could be sufficient for rigid systems. For many systems of interest, for example for understanding the dynamics of protein folding or in the collapse of polymers, one requires the time dependence of the excitation migration. This will be measured in terms of the time dependent survival probability.

In this work we have presented results of detailed Brownian dynamics simulations of Forster energy transfer between the two ends of an ideal Gaussian chain. As noted by previous workers\textsuperscript{12}, this apparently simple problem is actually highly non-trivial because
this is a manybody problem. We have calculated survival probability for a large number of values of the transfer rate $k_F$ and the Forster radius, $R_F$. It is found that while the survival probability is exponential-like for small values of $k_F$ (compared to the monomer diffusion rate, $D_0/b^2$) and intermediate $R_F$, it is strongly non-exponential for small (compared to $L$) $R_F$.

We have compared the results of the simulation with the well-known theory of Wilemski and Fixman. It is found that the theory is reliable when the Forster radius $R_F$ is comparable to the root mean square radius $L$ of the polymer chain and the transfer rate $k_F$ is comparable to or smaller than the monomer diffusion rate $D_0/b^2$. However, the agreement is not at all satisfactory in the limit when $R_F$ is much smaller or larger than $L$.

What is the reason for the failure of the WF theory when $R_F$ is substantially different from the root mean square radius of the polymer? While it is obvious that the WF closure approximation is inadequate in many situations, the exact reason for the failure is not clear. In fact, for the nature of the decay curve for large or small $R_F$ can possibly be understood even from a one dimensional theory, provided the end to end distance correlation function $\rho(t)$ is given. This problem will be discussed elsewhere.[16]

Note that the distance dependent rate appears in several other chemical processes, like in electron transfer reactions where the rate of transfer is known to show an exponential distance dependence. It will be interesting to study this problem with the method employed here. Another important, long standing problem is the study of reactions in realistic polymer chains with excluded volume and hydrodynamic interactions. Work in this direction is under progress.

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Figure captions:

**Figure 1.** The survival probability obtained from Brownian dynamics (BD) simulations of Eq.2 is plotted against the scaled time for several values of $k_F$ at $R_F = 1$. The curves from top to bottom represent the cases with $k_F = 0.1, 1, 10$ and 50, respectively.

**Figure 2.** The survival probability $S_p(t)$, obtained from BD simulations is plotted for $k_F = 0.1, 1$ and 10 at $R_F = 5$. Curves from top to bottom show $S_p(t)$ at $k_F = 0.1, 1$ and 10, respectively.

**Figure 3.** BD simulation results have been compared with WF theory at a Forster radius, $R_F = 5$. The upper set shows the case with $k_F = 1$ and the lower set is for $k_F = 10$. In both the cases, symbols shows the simulation results while the WF theory predictions are represented by the full lines.

**Figure 4.** WF theory has been compared with the simulation results at a lower value of $R_F$, namely $R_F = 1$ and for $k_F=1$. WF theory prediction has been shown by the full line while the symbols represent the simulation results. As seen from the figure, WF theory seems to break down in this limit.

**Figure 5.** The comparison between WF theory and simulation results has been shown for a larger polymer chain, $N = 100$, for $R_F = 8$ and $k_F = 0.1$. Symbols and the full line represents the results of simulation and WF theory, respectively.

**Figure 6.** The semilog plot of the survival probability $S_p(t)$ which has been obtained from simulations, is plotted against the scaled time at $k_F = 0.1$ and $R_F = 5$. This figure shows that the decay is nearly exponential for $R_F = 5$ and small $k_F$.

**Figure 7.** The semilog plot of the survival probability, obtained from simulations is plotted against the scaled time at $k_F = 1.0$ and $R_F = 1$. Highly non-exponential behavior of $S_p(t)$, is very clear in this limit.

**Figure 8.** The end-to-end vector time correlation function $\rho(t)$ is plotted against the scaled time for a polymer of mean square length $L^2 = 50b^2$. Symbols shows the simulated $\rho(t)$ while the $\rho(t)$ obtained from WF expression is shown by full line.
\( S_p(t) \) vs. time

- \( \text{time} \) ranges from 0 to 300
- \( S_p(t) \) ranges from 0 to 1

The graph shows the decay of \( S_p(t) \) over time.
$S_p(t)$

time

$F_F = 0.1$

$R_F = 5$
