DNA Breathing Dynamics Under Periodic Forcing: Study of First Passage Time

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Abstract. We study the DNA breathing dynamics under a periodic forcing by examining the first passage time distribution associated with the bubble lifetime. We consider an overdamped random walk on the Poland-Scheraga free energy landscape in the number of broken base pairs to describe the breathing dynamics. Using backward Fokker-Planck method, we derive analytical closed form expression of the distribution P$(\boldsymbol{t_f}|\boldsymbol{x_0})$ of the first passage time $\boldsymbol{t_f}$ which characterizes bubble lifetime for a bubble of an initial size $\boldsymbol{x_0}$. This distribution is examined in details in the limit of small and large bubble sizes. We confirm our analytical predictions by numerically simulating the corresponding Langevin equation which governs the breathing dynamics. We obtain a very good agreements between our analytical predictions with simulated resulted in the appropriate limits. Further, we analyze the effect of forcing on the bubble lifetime and obtain nontrivial scaling behavior of the first passage time distribution which can be verified experimentally.

INTRODUCTION

Using the method of mechanical response by applying an external force on biomolecules one can study the energy landscape of biomolecules. This type of studies enable us to study different cellular process like transcription , replication or protein bindings involving DNA which is under the action of different mechanical type stresses mimicking the effect of different enzymes . The experiments which studies these mechanical unzipping of DNA [1–2] are based on moving apart of the DNA molecule double helix by pulling apart one strand fromthe other one by using an atomic force microscope, optical or magnetic tweezers. This kind of experiment will give us informationof base pair (bp) content of a sequence [1–2] or one can be able to estimate interaction energies of bps through the chain [3].For the last few years people are studying the dynamic response of DNA by applying alternating periodic force on DNA [4-5]. One aspect of such study is to analyze the possible effects of THz fields on DNA biomolecules [4-5]. Since, the hydrogen bonds between nucleotides of a bp weak are in theTHz frequency range and thus one can expect resonant effects. The other aspects of ac mechanical forces acting on single molecule experiments are discussed in [6,7]. In Ref. [6] the authors proposed a periodic driving protocol to enable folding and unfolding of a protein and one may get a better resolution to reconstruct the free energy landscape of the molecule. In Ref. [7], the stochastic resonance and resonant activation are discussed in details for the folding-unfolding of short DNA hairpins.

Thus, one can understand that the application of external force [4-7],can lead to unzipping of the double-stranded DNA. This phenomenon is referred to as DNA denaturation. The process starts by separating the double strand locally into single strands to form loops, or, “bubbles.” These bubbles vary in size through stepwise zipping andunzipping of the base pairs at the two zipper forks, where the bubble connects to the double strand. The dynamics of fluctuating bubble is known as breathing dynamics and the effect of THz field on such process is an intense research area in recent years [4-7].

Our theoretical analysis is based on Poland Scheragafree energy function [8] and we develop our theory on the basis of recently developed backward Fokker-Planck method to derive first passage Brownian functional [9-10].

In this work, following the picture of random walk in the Poland-Scheraga free energy landscape , we complementprevious single-bubble studies by suggesting and analyzing new measures for exploring the DNA breathing process. We study first-passage time distribution based on "Brownian" functional method [10] of the fluctuating bubble, We separately study the small and large bubble limits, which exhibit different behaviours. The functionals of interest characterize the lifetime of the bubble. Another objective of this work is to advocate the use of the recently studied backward Fokker-Planck (BFP) method to study DNA breathing dynamics under periodic forcing. Thus, we will also be able to analyze the effect of external force on bubble lifetime.

MODEL, METHOD AND MEASURE

Following the approach of Poland-Scheraga we interpret bubbles are occurring due to free-energy changes to thedouble-helical ground state [8]. The size of a bubble is measured by the number of broken base pairs, and we denote this number by the continuous variable $x \geq 0$, the Poland-Scheraga free energy can be written as $F(x) = \gamma_0 + \gamma x + ck_B T ln x$,where γ_0 is the free-energy barrier to form the initial bubble, and the term γx is required inbreaking x base pairs. The third term stand for entropy loss in forming a closed polymer loop with $k_b$is the Boltzmann constant, T is the temperature, while c is a universal constant determined by the loopconfigurations. At finite temperature the stochastic dynamics will be governed by the following overdamped dimensionless Langevin equation :

$$\frac{dx}{dt} = C_2 - \frac{C_1}{x} + F\cos(\omega t) + \xi(t) \ , \quad (1)$$

with $C_1 = \frac{c}{2}, C_2 = \frac{\gamma}{2k_B T} = \frac{\gamma_1(T-T_m)}{2k_B T T_m}$, $\gamma_1 = 4k_B T_r$ $<\xi(t)>= 0$ and $<\xi(t)\xi(t')>= \delta(t-t')$, T_m is the melting temperature and T_r =310 K . One can define a characteristic bubble size$x_{ch} = \frac{C_1}{|C_2|}$, so that for small bubbles$x < x_{ch}$, the Langevin dynamics is essentially governed by the $-C_1/x$ term . On the other hand, for large bubbles with x $> x_{ch}$ the dynamics is dictated by the C_2 term. We will basically explore one measurable quantity, i.e. the probability distribution function (PDF) $P(t_f|x_0)$of first passage time t_f for initial bubble size x_0. This quantity gives us the information of the time of closure for bubbles of initial sizex_0, and provides us information about bubble lifetime. A related quantity is the survival probability $C(x_0, t) = 1 - \int_0^t dt_f\, P(t_f|x_0)$ which can be inferred from experiments by measuring fluorescence correlations of a tagged DNA[11].

RESULTS

For large bubbles the dynamics is governed by $\frac{dx}{dt} = C_2 + F\cos(\omega t) + \xi(t)$. (2)

Now transforming from (x,t) to (z,τ) space by using the following transformation equation

$$\tau = \frac{1}{2}\int dt + A \text{ and } z = x + \int (C_2 + F\cos(\omega t))\, dt + B, \quad (3)$$

One can write down the corresponding Fokker-Planck equation in (z,τ) space for the Eq. (2) as follows $\frac{\partial P(z,\tau)}{\partial \tau} = \frac{\partial^2 P(z,\tau)}{\partial z^2}$. Then the corresponding backward Fokker-Planck equation becomes

$$\frac{d^2 Q}{d{z_0}^2} - pU(z_0)Q(z_0) = 0 \quad (4)$$

To calculate PDF of first-passage time $P(t_f|x_0)$, we can substitute $U(z_0) = 1$ in Eq. (4) and using proper boundary conditions $Q(z_0 = 0) = 1$ and $Q(z_0 \to \infty) = 0$ we obtain

$$Q(z_0, p) = e^{-\sqrt{p} z_0^{(1)}} - \exp(-\eta) e^{-\sqrt{p} z_0^{(2)}} \quad (5)$$

This is in Laplace transformed space, so we need to do an inverse Laplace transform of Eq. (5) to obtain PDF in the (z,τ) space as follows : $P(\tau_f|z_0) = \frac{1}{\sqrt{4\pi}}\frac{z_0^{(1)}}{\tau_f^{3/2}}\exp\left(-\frac{{z_0^{(1)}}^2}{4\tau_f}\right) - \exp(-\eta)\frac{1}{\sqrt{4\pi}}\frac{z_0^{(2)}}{\tau_f^{\frac{3}{2}}}\exp\left(-\frac{{z_0^{(2)}}^2}{4\tau_f}\right)$, (6)

where, $z_0^{(1)} = \int_0^{t_f}(C_2 + F\cos(\omega t))dt + x_0$, $z_0^{(2)} = \int_0^{t_f}(C_2 + F\cos(\omega t))dt - x_0$ and $\eta = x_0\frac{M(t)}{S(t)}$ $M(t) = \int_0^{t_f}(C_2 + F\cos(\omega t))dt = C_2 t_f + \frac{F}{\omega}\sin(\omega t_f)andS(t) = \frac{1}{2}\int_0^{t_f} ds = t_f/2$. Hence $\eta = \frac{2x_0(C_2 t_f + \frac{F}{\omega}\sin(\omega t_f))}{t_f}$. Therefore first passage time in (x,t) space is given by :$P(t_f|x_0) = \frac{x_0}{\sqrt{2\pi}t_f^{3/2}}\exp -\left(\frac{[\omega(x_0 + C_2 t_f) + F sin(\omega t_f)]^2}{2\omega^2 t_f}\right)$ (7)

For small bubble dynamics Langevin equation is

$$\frac{dx}{dt} = -\frac{C_1}{x} + F\cos(\omega t) + \xi(t) \tag{8}$$

And the corresponding backward Fokker-Planck equation is

$$\frac{d^2Q(x_0)}{dx_0{}^2} + \left(F\cos(\omega t) - \frac{C_1}{x_0}\right)\frac{dQ(x_0)}{dx_0} - pU(x_0)Q(x_0) = 0 \tag{9}$$

To compute the probability distribution function for first-passage time we substitute $U(x_0) = 1$ and solving Eq.(9) with boundary condition $Q(x_0 = 0) = 1$ and $Q(x_0 \to \infty) = 0$we obtain

$$Q(x_0, p) = x_0{}^{2C_1+1} e^{-\left(F\cos(\omega t)+\sqrt{(F\cos(\omega t))^2+2p}\right)x_0}\left[AU\left(a, b; 2\sqrt{(F\cos(\omega t))^2 + 2p}x_0 + B£_a^b\left(2\sqrt{(F\cos(\omega t))^2 + 2p}x_0\right)\right],\right.$$

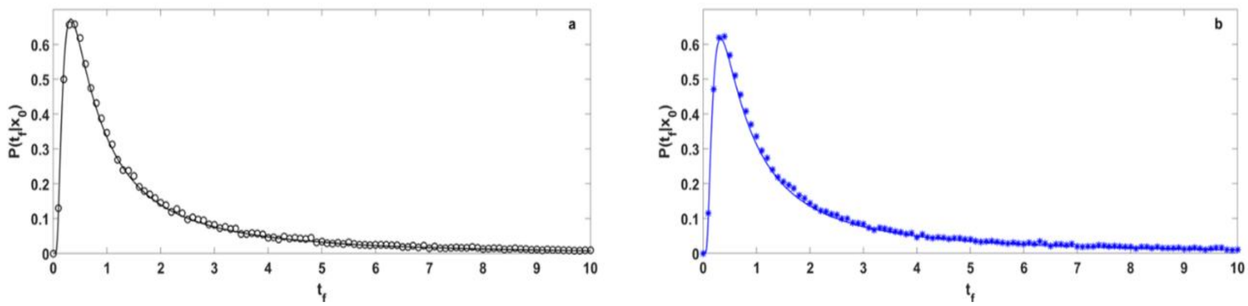

Figure 1: Plot of probability distribution function of first passage time $P(t_f|x_0)$ for the case of large bubble dynamics (a) for F=0.1 (black circle: simulated result and black continuous line: analytical result) (b) for F=0.2 (blue asterisk: simulated result and blue continuous line: analytical result). Rest we have used $x_0 = 1, \omega = 0.1$ and $C_2 = -0.5$.

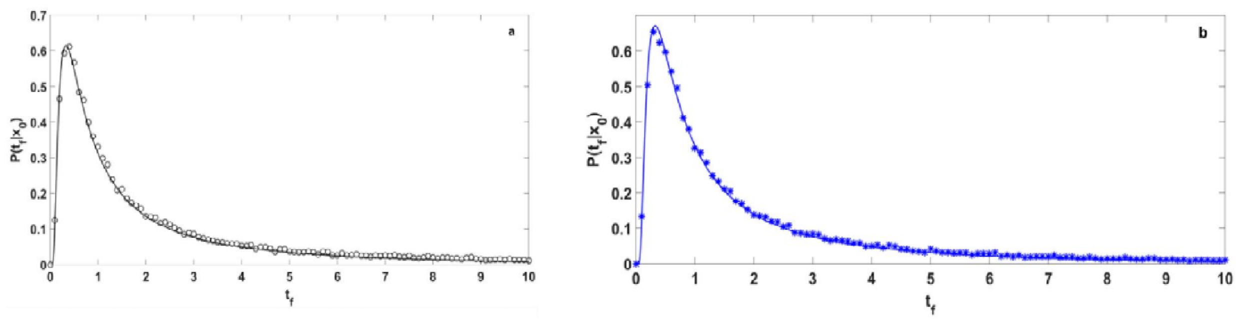

Figure 2 : Plot of probability distribution function of first passage time $P(t_f|x_0)$for the case of large bubble dynamics (a) for C_2=-0.9 (black circle: simulated result and black continuous line: analytical result) (b) for C_2=-1.0 (blue asterisk: simulated result and blue continuous line: analytical result). Rest we have used $x_0 = 1, \omega = 0.1$ and $F = 0.6$.

Where $U(a, b; x)$ is a confluent hypergeometric function and $£_a^b(x)$ is the generalized Laguerre polynomial. $a = \frac{C_1 F\cos(\omega t)\sqrt{(F\cos(\omega t))^2+2p} - C_1\sqrt{(F\cos(\omega t))^2+2p}}{\sqrt{(F\cos(\omega t))^2+2p}}$and $b = 2C_1 + 1$, A and B are constants which are determined from boundary conditions. As $x_0 \to 0$, $U(a, b; x)$ doesn't converge. Therefore, we set A=0. And from the first boundary condition we get $B = \frac{a^b}{\gamma(b)}$. Therefore

$$Q(x_0, p) = \frac{a^b}{\gamma(b)x_0^{2C_1+1}} e^{-\left(F\cos(\omega t_f)+\sqrt{\left(F\cos(\omega t_f)\right)^2+2p}\right)x_0} £_a^b\left(2x_0\sqrt{\left(F\cos(\omega t_f)\right)^2 + 2p}\right) \tag{10}$$

To get the probability distribution function for the first passage time, we need to take the Laplace transform of $Q(x_0, p)$in Eq. (10) which is given by

$$P(t_f|x_0) = \frac{x_0{}^{2C_1+1}}{2^{2C_1+1}} e^{-F\cos(\omega t_f)x_0} t_f^{-\frac{3}{2}-C_1} exp\left[-\frac{\left(F\cos(\omega t_f)\right)^2 t_f}{2} - \frac{x_0^2}{2t_f}\right] £_{2F\cos(\omega t_f)}^{C_1-1/2}\left(F\cos(\omega t_f)t_f\right) \tag{11}$$

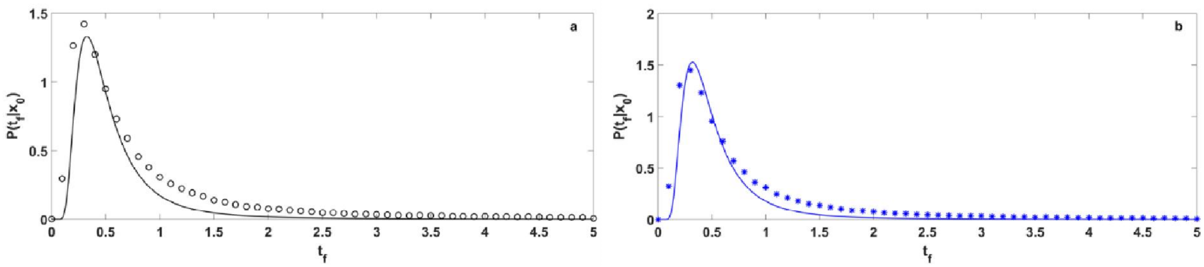

Figure 3: Plot of probability distribution function of first passage time $P(t_f|x_0)$ for the case of small bubble dynamics (a) for C_1=2.8 (black circle: simulated result and black continuous line: analytical result) (b) for C_1=2.9 (blue asterisk: simulated result and blue continuous line: analytical result). Rest we have used $x_0 = 1.7, \omega = 0.5$ and $F = 0.5$.

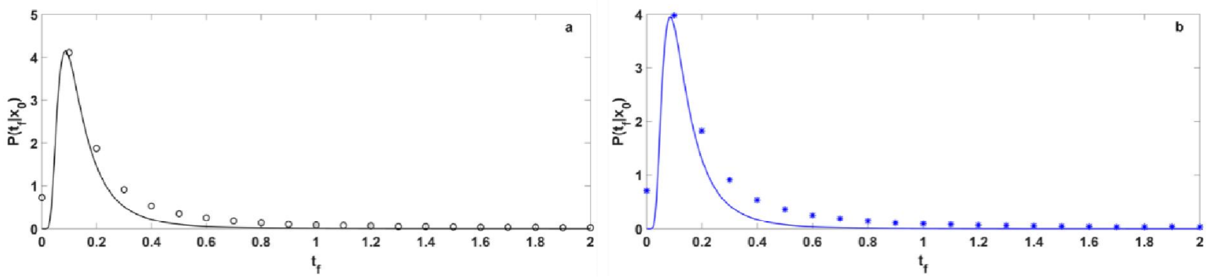

Figure 4: Plot of probability distribution function of first passage time $P(t_f|x_0)$ for the case of small bubble dynamics (a) for F=0.8 (black circle: simulated result and black continuous line: analytical result) (b) for F=1.0 (blue asterisk: simulated result and blue continuous line: analytical result). Rest we have used $x_0 = 0.8, \omega = 0.6$ and $C_1 = 2.1$.

Numerical simulation: The statistical properties of Brownianfunctionals studied here can be numerically obtained by integrating the overdampedLangevin equation (1). Using a second-order stochastic Runge-Kutta algorithm [12], we update the trajectory by following the rule,

$x(\Delta t) = x_0 + \frac{1}{2}[F(x_0) + F(x_0 + F(x_0)\Delta t + \Gamma_0)] + \Gamma_0$, with$F(x_0) = C_2 - \frac{C_1}{x_0} + F\cos(\omega t)$, Here, $\Gamma_0$is a random number sampled from a Gaussian distribution with zero mean and width given by $<\Gamma_0^2> = \Delta t$. For all simulations presented inthis work, we take $\Delta t = 10^{-3}$. We generate a one lakh set of paths, all starting at a particular $x_0$and ending close to the origin (within a preassigned numerical tolerance value). Averaging over an ensemble, we generate pdf of first passage time that we compare with our analytical results.

CONCLUSIONS

In this work, we studied probability distribution function for first passage time for the periodically driven DNA breathing dynamics at temperature below and above the denaturation temperature, which gives the lifetime of the bubble. For large asymptote, for the case of large bubble dynamics we found that PDF of first passage time behaves like $t_f^{-3/2}\exp\left(-\frac{(FSin(\omega t_f))^2}{2t_f}\right)$ and for the case of small bubble it behaves as $t_f^{-C_1-3/2}\exp\left(-\frac{(Fcos(\omega t_f))^2}{2t_f}\right)$ i.e. in both the cases we found power-law behaviours modified by exponential dependent forcing.Hence, the bubble lifetime is highly dependent on the entropicparameterC_1, the base pair dissociation parameter $C_2$and the periodic forcing. Our backward Fokker-Planck method elegantly incorporates the time dependent drift and constant diffusion. Also, we found good agreement between the analytical result and numerically simulated result using the stochastic Runge-Kutta algorithm.

REFERENCES

1. A.G. Markelz, IEEE J. Selected Topics Quantum Electron. **14** (2008) 180.
2. L. Ho, M. Pepper, P. Taday, Nature Photonics **2** (2008) 541; A.P. George, et al., Opt. Express **16** (2008) 1578.
3. H. Frohlich, Proc. Natl. Acad. Sci. USA **72** (1975) 4211.

4. L. Verschaeve, Mutation Res. **681** (2009) 259.
5. A. Korenstein-Ilan, et al., Rad. Res. **170** (2008) 224.
6. J.S. Olshevskaya, et al., Proc. IEEE Sibircon **210** (2008);J.S. Olshevskaya, et al., Zhurn. Vyssh. Nervn. Deyat. Im. I.P. Pavlova **59** (3) (2009) 353.
7. N.P. Bondar, et al., Bull. Exp. Biol. Med. **145** (2008) 4.
8. D. Poland and H. A. Scheraga, Theory of Helix-Coil Transitions in Bio-Polymers (Academic Press, New York, (1970).
9. S. N. Majumdar, Current Science **89**, 2076 (2005).
10. J. Randon-Furling and S. N. Majumdar, J. Stat. Mech.: Theory Exp. P10008 (2007).
11. G. Altan-Bonnet, A. Libchaber, and O. Krichevsky, Phys. Rev. Lett. **90**, 138101 (2003).
12. A. C. Bra´nka and D. M. Heyes, Phys. Rev. E **58**, 2611 (1998).