Stochastic dynamics and denaturation of thermalized DNA

Mao Lin Deng[1] and Wei Qiu Zhu[1,2,*]

[1]*Department of Mechanics, State Key Laboratory of Fluid Power Transmission and Control, Zhejiang University, Hangzhou 310027, China*

[2]*Division of Mechanics, Research Center of Applied Sciences, Academia Sinica, Taipei 115, Taiwan, China*

(Received 5 June 2007; published 28 February 2008)

In the first part of the paper, the stochastic dynamics of the Peyrard-Bishop-Dauxois (PBD) DNA model is studied. A one-dimensional averaged Itô stochastic differential equation governing the total energy of the system and the associated Fokker-Planck equation governing the transition probability density function of the total energy are derived from the Langevin equations for the base-pair (bp) separation of the PBD DNA model by using the stochastic averaging method for quasinonintegrable Hamiltonian systems. The stationary probability density function of the average energy and the mean square of the bp separation are obtained by solving the reduced Fokker-Planck equation. In the second part of the paper, the local denaturation of the thermalized PBD DNA model is studied as a first-passage-time problem in the energy. A backward Kolmogorov equation and a Pontryagin equation are derived from the averaged Itô equation and solved to yield the waiting-time distribution and the mean bp opening time. All the analytical results are confirmed with those from Monte Carlo simulation. It is pointed out that the proposed method may yield a reasonable mean bp opening time if the friction coefficient is fixed using experimental results.

I. INTRODUCTION

More than fifty years after the discovery of its double-helix structure, DNA is still of increasing interest to scientists who try to unveil its remarkable properties and functions. Although the detailed structure of DNA is known, the static structure of the DNA molecule is not sufficient to explain its functions. In fact, DNA breathing (local denaturation and reclosing of the double-stranded structure) is ceaseless. From the biological point of view, this breathing is a necessary step for DNA replication, transcription, denaturation, and protein binding. Owing to the relatively weak hydrogen bonds in base pairs (bps) (energy less than $2k_B T$ per bp [1]), the denaturation can be activated by thermal fluctuation. Usually, larger bubbles (local denatured regions) occurred in AT-rich regions [2]. At the melting temperature T_m, the size and number of the denaturation bubbles increase, and eventually the two strands separate; this is called the denaturation transition or melting. Recently, the dynamics of DNA bubbles has been monitored by using fluorescence correlation spectroscopy [3]. It was found that the characteristic relaxation time is 20–100 μs, which is 3–4 orders of magnitude higher than the open bp lifetime estimated by NMR (nuclear magnetic resonance of imino-proton exchange) [4].

So far, most theoretical studies and molecular dynamical simulations on DNA bubble dynamics have used the Poland-Scherage model [5] or the Peyrard-Bishop-Dauxois (PBD) model [6,7]. The Poland-Scherage free energy was introduced into the Langevin equation governing the stochastic bubble dynamics, and the corresponding one-dimensional Fokker-Planck equation governing the probability density of open bps was established. The expressions for the bubble survival distribution and characteristic time for bubble clos-

ing and opening were obtained [8–11]. On the other hand, the PBD model has been used for estimating the DNA melting temperature, thermodynamical instability of DNA, and identification of the starting site for DNA transcription [12–15]. Each of these two models has its merits and shortcomings, and these two groups of theoretical studies yield results for the mean bp opening time that are different by several orders of magnitude. Even for the same parameters, e.g., the friction coefficient, values differing by several orders of magnitude have been obtained in these two groups of studies [14,15]. To be consistent with experimental results, some parameters in theoretical studies have to be fixed or rescaled [3,13].

Since the study of bubble dynamics of heteropolymeric DNA is more difficult than that of homopolymeric DNA [16,17], as a first step, only homopolymeric DNA is considered in the present paper. Here, the PBD DNA model is regarded as a multiple-degree-of-freedom nonlinear dynamical system, and the thermal fluctuation is taken into account by adding random excitations and friction terms to the model equations based on the fluctuation dissipation theorem and Einstein relation. In the last decade, the nonlinear stochastic dynamics in Hamiltonian formulation has been well developed in mechanics by the present second author and his coworkers [18,19]. In the present paper, the stationary behavior and local denaturation of the thermalized PBD DNA model will be studied by using the stochastic averaging method for a quasi-Hamiltonian system [20–22], and the results will be confirmed by using Monte Carlo simulation. Finally, it will be pointed out that the theoretical result for the mean bp open time may be matched with the experimental data by properly adjusting the friction coefficient.

II. EQUATIONS FOR THERMALIZED PBD DNA MODEL

The PBD model, a popular model for DNA, is illustrated in Fig. 1. It comprises two backbones representing the sugar-

---

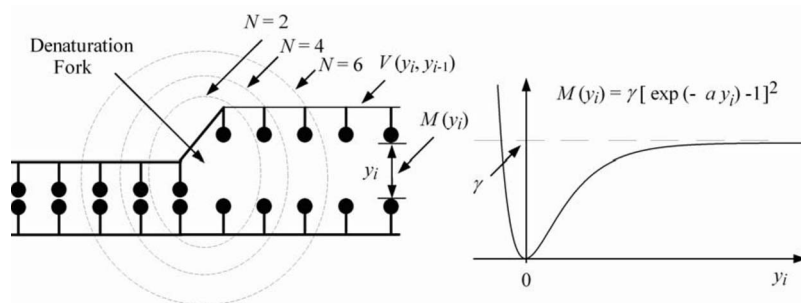*Corresponding author: wqzhu@yahoo.com

FIG. 1. A schematic representation of the PBD DNA model. It consists of two backbones with side chains facing each other. The neighboring bps interact with each other with a PBD potential and each base interacts with its complementary base with a Morse potential.

phosphate strands and some side chains attached to the backbones representing the bases. These side chains or bases in one strand are able to interact with their complementary side chains attached to the other strand. The following Morse potential $M(y_i)$ describes the interaction between the two bases in each pair:

$$M(y_i) = \gamma(e^{-ay_i} - 1)^2, \tag{1}$$

where y_i denotes the displacement from the equilibrium position of the relative distance between the two bases within the ith bp [6,7]; γ is the dissociation energy of the bp ($\gamma \approx 0.03$ eV at room temperature 25 °C); a is a parameter that sets the spatial scale of the potential; $a \approx 4.5$ Å^{-1} is determined according to a measurement that stretching a bp by 0.1 Å gives a variation of energy of 0.04 eV [23]. The Morse potential has been chosen to model the hydrogen bond in bps since it has the following excellent properties (see Fig. 1). (i) It gives a strong repulsive force in the bp when $y_i < 0$; (ii) it has a minimum and the attractive or repulsive force is zero at the equilibrium position $y_i = 0$; (iii) it becomes flat and the interaction of the bps vanishes gradually for very large y_i.

Only the bending motion of backbones is taken into account. The following approximate potential $V(y_i, y_{i-1})$ describes the stacking interaction between adjacent bases:

$$V(y_i, y_{i-1}) = \frac{1}{2} K\{1 + \rho \exp[-\alpha(y_i + y_{i-1})]\}(y_i - y_{i-1})^2, \tag{2}$$

where the nonlinear intersite coupling, given by the exponential term which effectively modifies a harmonic spring constant, is essential for representing local constraints in nucleotide motions, which result in long-range cooperative effects. Physically, the constraint describes the change of the next-neighbor stacking interaction due to the distortion of the hydrogen bonds connecting a bp, mediated by the redistribution of the electrons on the corresponding bases. Potential (2) has proved to be successful in giving not only a qualitative but also a quantitative description of DNA denaturation. The value chosen for K is $K \approx 0.06$ eV Å^{-2}, which is obtained from the experimental results showing that proton-deuterium exchange can occur on one bp without affecting the neighbors [23]. $\rho = 2$ and $\alpha = 0.35$ Å^{-1} are usually chosen for molecular dynamical simulation [13,15]. The stacking energies

are also highly dependent on the base sequence [24].

To model the thermal denaturation process of DNA, it is assumed that the main contribution to local opening of bps is made by the separation of the two backbones. As a second hierarchy of models, the helical structure of DNA is neglected in PBD model to simplify the theoretical analysis. The mass of all bases is assumed to be the same. As a result, the motion for the model in Fig. 1 is governed by the following Langevin equations:

$$m_b \frac{d^2 y_i}{dt^2} = -\frac{\partial U(\mathbf{y})}{\partial y_i}, \quad U(\mathbf{y}) = \sum_{i=1}^{N} M(y_i) + \sum_{i=2}^{N} V(y_i, y_{i-1}),$$

$$i = 1, 2, \ldots, N. \tag{3}$$

The Hamiltonian or total energy of the system is of the form

$$H = \frac{1}{2} m_b \sum_{i=1}^{N} \left(\frac{dy_i}{dt}\right)^2 + U(\mathbf{y}), \tag{4}$$

where $\mathbf{y} = (y_1, y_2, \ldots, y_N)$ and N is the number of bps. m_b is the mass of base, the average value of which is about $m_b \approx 327$ daltons. The parameter values are hereafter rescaled as follows: lengths in units of Å; energies in units of $k_B T_r$ (k_B is the Boltzmann constant and $T_r = 37$ °C is the reference temperature); mass in units of one base mass m_b. Thus, the time unit t_0 is defined through $k_B T_r = m_b \text{Å}^2 t_0^{-2} \approx 0.0267$ eV, which yields $t_0 = 1.13$ ps. Using these new units, the dimensionless values of γ and K in Eqs. (1) and (2) are $\gamma \approx 1$ at 25 °C and $K \approx 2$.

To study the dynamical behavior of DNA under thermal fluctuation, a thermal bath is added to the PBD. A prevalent and simple way to simulate a thermal bath is by adding a fluctuating force $\sqrt{2D_\xi}\xi_i(t)$ and a friction force $\varepsilon \, dy_i/dt$ to each degree of freedom of the system Eq. (3) [25], where ε is a constant linear friction coefficient and $\xi_i(t)$ are Gaussian white noises in the sense of Stratonovich with correlation functions

$$E[\xi_i(t)\xi_j(t + t')] = \begin{cases} \delta(t'), & i = j, \\ 0, & i \neq j. \end{cases} \tag{5}$$

Here $\delta(t')$ is the Dirac delta function and the fluctuation dissipation theorem or the Einstein relation $D_\xi = \varepsilon k_B T$ (T is the temperature) is applied. After this, Eq. (3) becomes
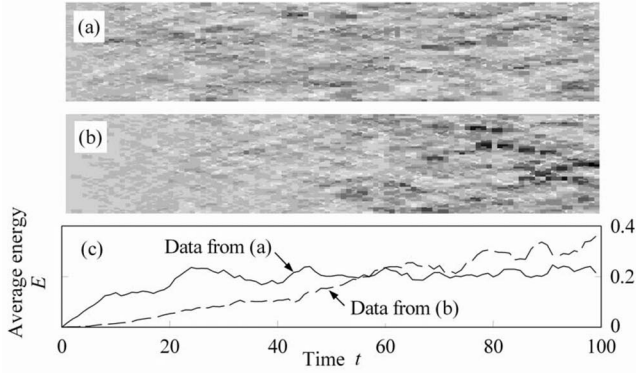
FIG. 2. Results obtained from Monte Carlo simulation of the thermalized PBD DNA model with 50 bps. $\gamma=1$ for 25 °C. The separation distance of the bps is shown by the gray scale. (a) In the case of constant excitation intensity $D_\xi=0.02$. The horizontal coordinate is time t (in units of t_0). (b) In the case of a linear intensity D_ξ ramp ranging from 0 to 0.04. The horizontal coordinate is time or temperature. (c) Average energy E (in units of $k_B T_r$). The data for the two curves are taken from Figs. 3(a) and 3(b).

$$\frac{d^2 y_i}{dt^2} + \varepsilon \frac{dy_i}{dt} + \frac{\partial U(\mathbf{y})}{\partial y_i} = \sqrt{2D_\xi}\xi_i(t), \quad i = 1, 2, \ldots, N. \quad (6)$$

Note that all variables in Eq. (6) are dimensionless after rescaling.

III. STATIONARY STATISTICS OF THERMALIZED PBD DNA MODEL

The observation of DNA molecules under thermal denaturation using cryomicroscopy showed that the denaturation starts as local openings, called "denaturation bubbles," that grow with temperature and invade the whole molecule at the denaturation temperature, causing the separation of the two strands. Some numerical results obtained from a simulation that mimics the thermal denaturation of the PBD model with 50 bps are shown in Fig. 2. Figure 2(a) is for the case of constant temperature 25 °C and constant excitation intensity $D_\xi=0.02$. Occasionally, the bp separation distance is large in some regions, corresponding to the denaturation bubbles. After some time, those bubbles disappear and other bubbles occur. In Fig. 2(b), the excitation intensity D_ξ increases in a linear manner from 0 to 0.04. It is seen that the denaturation is preceded by formation and growth of denaturation bubbles. As a quantitative measure of the denaturation process, the average energy E (obtained from the total energy H divided by number N of bps) of the PBD DNA model is shown in Fig. 2(c), where the data of the two curves are taken from Figs. 2(a) and 2(b), respectively. It is seen clearly that the average energy fluctuates around a constant for constant temperature and increases with increasing temperature. Thus, the average energy of the PBD DNA model will be used for measuring the thermal denaturation in the following theoretical analysis.

Equation (6) can be regarded as an N-degree-of-freedom stochastically excited and dissipated Hamiltonian system [18,19]. It can be converted into the following Itô stochastic differential equations:

$$dy_i = v_i dt, \quad dv_i = -\left[\partial U(\mathbf{y})/\partial y_i + \varepsilon v_i\right]dt + \sqrt{2D_\xi}dB_i(t), \quad (7)$$

where $B_i(t)$ are the standard Weiner processes. The Hamiltonian H or total energy of system (7) now reads

$$H = \sum_{i=1}^{N} \frac{1}{2}v_i^2 + U(\mathbf{y}). \quad (8)$$

It is seen from Eq. (8) that the necessary energy barrier γ_0 for initiating a bubble has not been included in the Hamiltonian H.

A Hamiltonian system may be integrable or nonintegrable. An N-degree-of-freedom Hamiltonian system is said to be integrable or completely integrable if there exist N independent integrals of motion which are in involution (the Poisson bracket of any two of these integrals vanishes). For a nonintegrable Hamiltonian system, there is only one independent integral of motion, i.e., Hamiltonian H. The Hamiltonian system with Hamiltonian H in Eq. (8) is nonintegrable since $U(\mathbf{y})$ is nonseparable. Thus, Eq. (7) governs a stochastically excited and dissipated nonintegrable Hamiltonian system. The stochastic averaging method for quasinonintegrable Hamiltonian systems [20] can be applied to obtain the statistics of the system.

Since H is a function of $\mathbf{y}$ and $\mathbf{v}$, the Itô stochastic differential equation for H can be derived from Eq. (7) by using the Itô differential rule as follows:

$$dH = (ND_\xi - \varepsilon \sum_{i=1}^{N} v_i^2)dt + v_i dB_i(t). \quad (9)$$

Among the $2N+1$ variables H, $\mathbf{y}$, and $\mathbf{v}$ in Eq. (9), only $2N$ variables are independent. In fact, v_1 can be replaced by the other $2N$ variables using the following expression:

$$v_1 = \pm \sqrt{2[H - U(\mathbf{y})] - \sum_{i=2}^{N} v_i^2}. \quad (10)$$

Note that the friction coefficient ε and excitation intensity $2D_\xi$ are usually small. The Hamiltonian H in Eq. (9) is thus a slowly varying process while the generalized displacement $\mathbf{y}$ and generalized momenta $v_2, \ldots, v_N$ are rapidly varying processes. According to a theorem due to Khasminskii [26], the H process converges weakly to a one-dimensional diffusion process in a time interval of order ε^{-1}. In other words, the H process may be replaced in the first approximation by a diffusion process.

The Itô equation for this diffusion process can be obtained by applying time averaging to Eq. (9). Making use of the first equation in Eq. (7), i.e., $dy_1 = v_1 dt$, the time averaging can be replaced by a space averaging with respect to y_1 under the condition that H is kept constant. To eliminate $y_2, \ldots, y_N$ and $v_2, \ldots, v_N$ in the averaged Itô equation, the resulting equation is further averaged with respect to $y_2, \ldots, y_N$ and $v_2, \ldots, v_N$. The last step involves an ergodic hypothesis which may be stated as follows: the evolution of a completely nonintegrable Hamiltonian system takes it, with equal probability, through all states that are accessible from the starting point

subject to the constraint of energy conservation. As a result, the averaged Itô equation for the Hamiltonian H is given by

$$dH = m(H)dt + \sigma^2(H)dB(t), \qquad (11)$$

where the coefficients $m(H)$ and $\sigma^2(H)$ are obtained as follows [20]:

$$m(H) = \frac{1}{T(H)} \int_\Omega \left(ND_\xi - \varepsilon \sum_{i=1}^{N} v_i^2 \right) dy_1 dy_2 \cdots dy_N dv_2 \cdots dv_N,$$

$$\sigma^2(H) = \frac{1}{T(H)} \int_\Omega \left(2D_\xi \sum_{i=1}^{N} v_i^2 \right) dy_1 dy_2 \cdots dy_N dv_2 \cdots dv_N,$$

$$T(H) = \int_\Omega \left(\frac{1}{v_1} \right) dy_1 dy_2 \cdots dy_N dv_2 \cdots dv_N. \qquad (12)$$

The integral domain Ω of the $(2N-1)$-fold integrals in Eq. (12) is defined as

$$\Omega = \left\{ (y, v_2, \ldots, v_N) \Big| \frac{1}{2} \sum_{i=2}^{N} v_i^2 + U(y) \le H \right\}. \qquad (13)$$

Replacing v_1 with Eq. (10) and evaluating those integrals in Eq. (12), the following compact expressions for the coefficients in Eq. (12) can be obtained:

$$m(H) = ND_\xi - 2\varepsilon A(H)/B(H),$$

$$\sigma^2(H) = 4D_\xi A(H)/B(H), \quad T(H) = \frac{\pi^{N/2} 2^{3N/2 - 2}}{\Gamma(N/2)} B(H),$$

$$A(H) = \int_\Sigma [H - U(y)]^{N/2} dy_1 dy_2 \cdots dy_N,$$

$$B(H) = \int_\Sigma [H - U(y)]^{n/2 - 1} dy_1 dy_2 \cdots dy_N, \qquad (14)$$

where $\Gamma(\cdot)$ is the Gamma function and the integral domain Σ of the N-fold integrals in Eq. (14) is defined as

$$\Sigma = \{ y | U(y) \le H \}. \qquad (15)$$

The Fokker-Planck equation associated with the averaged Itô equation (11) is

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial H}[m(H)p] + \frac{1}{2}\frac{\partial^2}{\partial H^2}[\sigma^2(H)p], \qquad (16)$$

where $p = p(H, t | H_0)$ is the transition probability density function of Hamiltonian H with initial condition

$$p(H, 0 | H_0) = \delta(H - H_0), \qquad (17)$$

or $p = p(H, t)$ is the probability density of H with initial condition

$$p(H, 0) = p(H_0). \qquad (18)$$

The Fokker-Planck equation (16) is usually subjected to the following boundary condition:

$$p, \partial p/\partial H \to 0 \quad \text{when } H \to \infty. \qquad (19)$$

The one-dimensional Fokker-Planck equation (16) usually can only be solved numerically. However, the exact stationary solution, i.e., the solution of the Fokker-Planck equation (16) without a time-derivative term, can always be obtained analytically. It is [20]

$$p(H) = \frac{C}{\sigma^2(H)} \exp\left(2 \int_e^H \frac{m(x)}{\sigma^2(x)} dx \right), \qquad (20)$$

where e is an arbitrary positive constant; C is the normalization constant, which can be obtained by letting the integral of the probability density $p(H)$ in the domain $(0, \infty)$ be equal to 1.

The stationary solution in Eq. (20) is the first approximation for the stationary probability density of Hamiltonian in the original system (6). The corresponding joint probability density $p(y, v)$ can be obtained as follows [20]:

$$p(y, v) = [p(H)T(H)]|_{H=H(y,v)}. \qquad (21)$$

The other stationary statistics such as the stationary probability density $p(E)$ of the average energy $E = H/N$ and the mean square $E[y_i^2]$ can then easily be obtained from Eq. (21) as follows:

$$p(E) = Np(H)|_{H=NE},$$

$$E[y_i^2] = \int_{-\infty}^{\infty} y_i^2 p(y, v) dy_1 \cdots dy_N dv_1 \cdots dv_N. \qquad (22)$$

To check the accuracy of the theoretical solution (22), a Monte Carlo simulation of system (6) was performed. The sample functions for the independent Gaussian white noises $\xi_i(t)$ were generated by using the Box-Muller method. Then the response was solved numerically by using the fourth-order Runge-Kutta method with time step 0.02. The long-time solution after 20 000 steps was regarded as the stationary ergodic response and taken to perform the statistical analysis. Hereafter, the results obtained from simulation and theoretical analysis are denoted by symbols ● ♦ and lines, respectively.

The results for the stationary probability density of the average energy, $p(E)$, are shown in Fig. 3. The N-fold integrals in Eq. (14) require huge computations when the number of bps, N, is large. Here the theoretical results up to $N = 6$ are obtained. It is seen that the theoretical results and those from simulation are in very good agreement. The theoretical result and that from simulation for the mean square separation distance $E[y_i^2]$ are shown in Fig. 4. It is seen from Fig. 4 that the two results are also in good agreement. Thus, we believe that Eqs. (20)–(22) provide very good theoretical formulas for the stationary statistics of the thermalized PBD DNA model.

IV. LOCAL DENATURATION OF PBD DNA MODEL

As shown in Fig. 1, at any time during the denaturation process, there exists a forklike structure consisting of closed
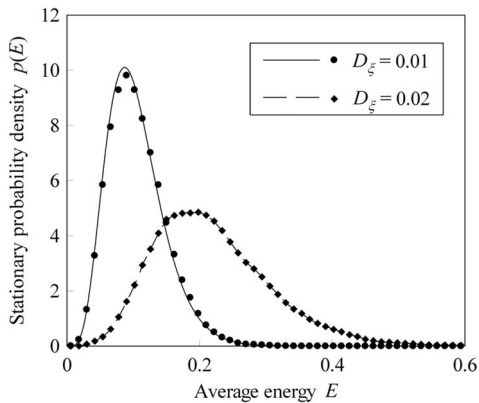
FIG. 3. Stationary probability density $p(E)$ of the average energy E (in units of $k_B T_r$) for PBD DNA model with different numbers of bps. The theoretical results from Eq. (22) are shown using a solid line and the corresponding results from simulation are shown by using symbols ● ♦. $\gamma=0.6$ for 37 °C, $\varepsilon=0.1$, $N=6$.

and open bps. Obviously, the dynamical behavior of the bps near the fork plays a key role in the denaturation process. Thus, it is reasonable to investigate the local denaturation using the forked part of the PBD DNA model. This supposition is verified by the simulation results shown in Fig. 5. In the simulation, a bp is considered as open when its relative displacement is larger than a threshold, which was chosen as 1 Å [15]. It is seen from Fig. 5 that the mean time for opening a bp approaches a constant after the number of bps in the fork reaches $N=10$. In view of the huge computations for a large number of bps in a fork, a fork consisting of $N=6$ bps is taken in the following theoretical calculation. The mean time for opening a bp in the fork is estimated by treating it as the mean first-passage time of energy in the fork.

For studying this problem, we introduce the waiting-time distribution $W(t|H_0)$, which is defined as the probability that the energy process $H(t)$ with initial value H_0 ($<H_p$) is always less than a critical value H_p until time t, i.e.,

$$W(t|H_0) = \text{Prob}\{ H(t') < H_p, t' \in (0,t] | 0 \le H_0 < H_p\},$$
(23)

where H_p is called the energy threshold. Since $W(t|H_0)$ is the integral of the conditional transition probability density
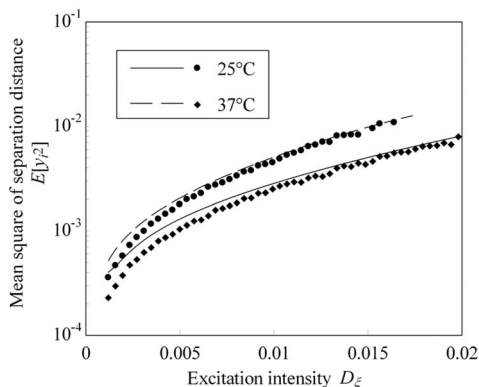

FIG. 4. Mean square $E[y_i^2]$ of bp separation distance y_i as a function of excitation intensity D_ξ; $\varepsilon=0.1$, $N=3$.
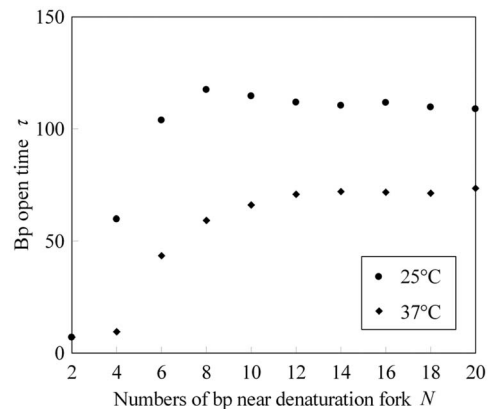

FIG. 5. Mean time τ (in units of t_0) for opening one bp as function of the bp numbers N in the fork.

$p(H,t|H_0)$, the following backward Kolmogorov equation for $W(t|H_0)$ can be derived from the backward Kolmogorov equation governing the conditional transition probability density $p(H,t|H_0)$ associated with the Fokker-Planck equation (16):

$$\frac{\partial W}{\partial t} = m(H_0)\frac{\partial W}{\partial H_0} + \frac{1}{2}\sigma^2(H_0)\frac{\partial^2 W}{\partial H_0^2}.$$
(24)

The boundary conditions are

$$W(t|H_0=0) = \text{finite}, \quad W(t|H_0=H_p) = 0.$$
(25)

The initial condition is

$$W(t=0|H_0<H_p) = 1.$$
(26)

Equation (24) with boundary condition (25) and initial condition (26) can be solved numerically by using a finite-difference method of Crank-Nicolson type.

Once the waiting-time distribution $W(t|H_0)$ is known, the probability density $\rho(T|H_0)$ of the first-passage time T can be obtained as follows:

$$\rho(T|H_0) = -\partial W(t|H_0)/\partial t|_{t=T},$$
(27)

while the mean first-passage time $\tau(H_0)$ can be obtained from $\rho(T|H_0)$ or $W(t|H_0)$ as follows:

$$\tau(H_0) = \int_0^\infty T\rho(T|H_0)dT = \int_0^\infty W(t|H_0)dt.$$
(28)

$\tau(H_0)$ can also be obtained by solving the following Pontryagin equation:

$$m(H_0)\frac{\partial \tau}{\partial H_0} + \frac{1}{2}\sigma^2(H_0)\frac{\partial^2 \tau}{\partial H_0^2} = -1.$$
(29)

The two boundary conditions for Eq. (29) are $\tau(H_0=0)$ =finite and $\tau(H_0=H_p)=0$. Solving Eq. (29) together with the
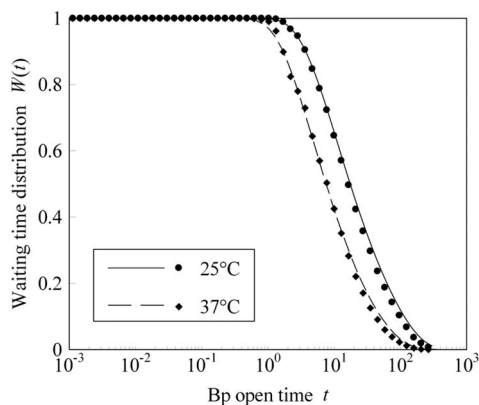
FIG. 6. Waiting-time distribution $W(t)$ for a fork with six pb's, $\varepsilon=0.01$, $D_\xi=\varepsilon k_B T_r$.

two boundary conditions yields the following exact expression for $\tau(H_0)$:

$$\tau(H_0) = 2\int_{H_0}^{H_p} du \int_0^u \frac{1}{\sigma^2(v)} \exp\left(-2\int_v^u \frac{m(w)}{\sigma^2(w)} dw\right) dv. \quad (30)$$

The denaturation rate is then equal to $1/\tau$.

In numerical calculation, the following parameter values are taken: $\gamma=1$ for $T=25$ °C and $\gamma=0.6$ for $T=37$ °C in standard salt conditions [10,23]. The initial energy $H_0 =4.19$ is determined according to the potential $U(y)$ of the fork in the initial state ($y_1=y_2=y_3=0$ Å, $y_4=y_5=y_6=1$ Å); and the energy threshold $H_p=4.78$ is determined as the potential $U(y)$ of the fork in the passage state ($y_1=y_2=0$ Å, $y_3=y_4=y_5=y_6=1$ Å). Some results for the waiting-time distribution $W(t)$, probability density $\rho(T)$ of the first-passage time, and mean first-passage time τ as a function of friction coefficient ε are shown in Figs. 6–8 using solid and dashed lines. The results from Monte Carlo simulation are also shown in these figures using symbols ● and ◆ for comparison. It is seen that the two results are in good agreement. However, the mean time for opening a bp shown in Fig. 8 is
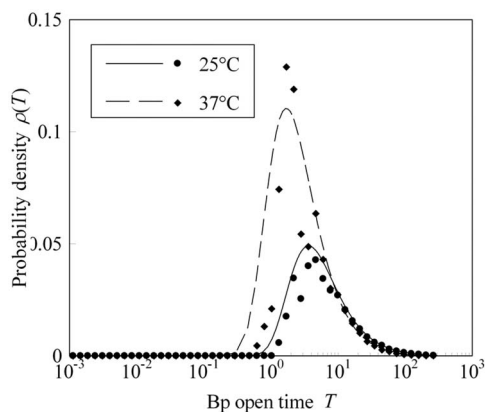

FIG. 7. Probability density $\rho(T)$ of first-passage time T (in units of t_0) for a fork with six pb's, $\varepsilon=0.01$, $D_\xi=\varepsilon k_B T_r$.
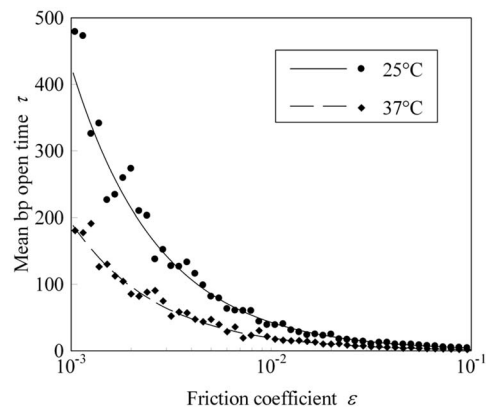

FIG. 8. Mean time τ (in units of t_0) for opening one bp in a fork with six pb's as a function of friction coefficient ε (in units of $m_b t_0^{-1}$). $D_\xi=\varepsilon k_B T_r$.

about 10–400 ps, which is 2–3 orders of magnitude lower than the open bp lifetime estimated by using NMR [4] and 5–6 orders of magnitude lower than the characteristic relaxation time 20–100 μs reported by Ref. [3]. Nevertheless, the mean time for opening a bp shown in Fig. 8 can be adjusted to the order of microseconds by choosing the friction coefficient ε of the order of $10^{-6} m_b t_0^{-1}$. This adjustment may be reasonable since, on one hand, to yield a result consistent with experiment, the parameters in theoretical analysis often need to be fixed or rescaled [3,13], and, on the other hand, so far, the parameters such as the friction coefficient have no known definite value [14,15].

V. CONCLUSIONS

In the present paper, the stochastic dynamics and local denaturation of the thermalized PBD DNA model have been studied by using the stochastic averaging method for quasi-Hamiltonian systems. According to the fluctuation dissipation theorem and the Einstein relation, the thermal fluctuation was taken into account by adding random excitations and friction terms into the governing equations of the PBD DNA model. The system was treated as a stochastically excited and dissipated nonintegrable Hamiltonian system. Stationary statistics, such as the stationary probability density $p(E)$ of the average energy and the mean square separation distance $E[y_i^2]$ of bps have been obtained. By treating the bp opening as a first passage of energy, the statistics for local denaturation, such as the waiting-time distribution $W(t)$, the probability density $\rho(T)$, and the mean time τ of first passage of energy, have been obtained theoretically. All the analytical results have been well confirmed by using the results from Monte Carlo simulations. Thus, we believe that the proposed method is very promising and the analytical results provide a good description of the dynamical behavior and local denaturation of the thermalized PBD DNA model. However,

compared with experimental results using NMR and fluorescence correlation spectroscopy, the mean bp opening time found was several orders of magnitude in error. Nevertheless, it was pointed out that parameters such as the friction coefficient may be adjusted to yield a result consistent with experimental data.

ACKNOWLEDGMENTS

[1] J. Santalucia, Jr., Proc. Natl. Acad. Sci. U.S.A. **95**, 1460 (1998).

[2] T. Hwa, E. Marinari, K. Sneppen, and L.-H. Tang, Proc. Natl. Acad. Sci. U.S.A. **100**, 4411 (2003).

[3] G. Altan-Bonnet, A. Libchaber, and O. Krichevsky, Phys. Rev. Lett. **90**, 138101 (2003).

[4] M. Guéron and J. L. Leroy, Methods Enzymol. **261**, 383 (1995).

[5] D. Poland and H. A. Scheraga, J. Chem. Phys. **45**, 1456 (1966).

[6] M. Peyrard and A. R. Bishop, Phys. Rev. Lett. **62**, 2755 (1989).

[7] T. Dauxois, M. Peyrard, and A. R. Bishop, Phys. Rev. E **47**, R44 (1993).

[8] D. J. Bicout and E. Kats, Phys. Rev. E **70**, 010902(R) (2004).

[9] A. Bar, Y. Kafri, and D. Mukamel, Phys. Rev. Lett. **98**, 038103 (2007).

[10] A. Hanke and R. Metzler, J. Phys. A **36**, L473 (2003).

[11] H. C. Fogedby and R. Metzler, Phys. Rev. Lett. **98**, 070601 (2007).

[12] N. Theodorakopoulos, M. Peyrard, and R. S. MacKay, Phys. Rev. Lett. **93**, 258101 (2004).

[13] A. Campa and A. Giansanti, Phys. Rev. E **58**, 3585 (1998).

[14] T. S. van Erp, S. Cuesta-Lopez, J. G. Hagmann, and M. Peyrard, Phys. Rev. Lett. **95**, 218104 (2005).

[15] G. Kalosakas, K. Ø. Rasmussen, A. R. Bishop, C. H. Choi, and A. Usheva, Europhys. Lett. **68**, 127 (2004).

[16] T. Novotný, J. N. Pedersen, T. Ambjörnsson, M. S. Hansen, and R. Metzler, Europhys. Lett. **77**, 48001 (2007).

[17] T. Ambjörnsson, S. K. Banik, O. Krichevsky, and R. Metzler, Phys. Rev. Lett. **97**, 128105 (2006).

[18] W. Q. Zhu, Appl. Mech. Rev. **59**, 230 (2006).

[19] W. Q. Zhu, *Nonlinear Stochastic Dynamics and Control—Hamiltonian Theoretical Framework* (Science Press, Beijing, 2003) (in Chinese).

[20] W. Q. Zhu and Y. Q. Yang, J. Appl. Mech. **64**, 157 (1997).

[21] W. Q. Zhu, Z. L. Huang, and Y. Q. Yang, J. Appl. Mech. **64**, 975 (1997).

[22] W. Q. Zhu, Z. L. Huang, and Y. Suzuki, Int. J. Non-Linear Mech. **37**, 419 (2002).

[23] M. Peyrard, Nonlinearity **17**, R1 (2004).

[24] W. Saenger, *Principles of Nucleic Acid Structure* (Springer, Berlin, 1984).

[25] W. Ebeling, L. Schimansky-Geier, and Y. M. Romanovsky, *Stochastic Dynamics of Reacting Biomolecules* (World Scientific, Singapore, 2002).

[26] R. Z. Khasminskii, Kibernetika **4**, 260 (1968) (in Russian).