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On the stochastic dynamics of molecular conformation*

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Abstract: An important functioning mechanism of biological macromolecules is the transition between different conformed states due to thermal fluctuation. In the present paper, a biological macromolecule is modeled as two strands with side chains facing each other, and its stochastic dynamics including the statistics of stationary motion and the statistics of conformational transition is studied by using the stochastic averaging method for quasi Hamiltonian systems. The theoretical results are confirmed with the results from Monte Carlo simulation.

Key words: Biological macromolecule, Thermal fluctuation, Stationary statistics, Transition time, Stochastic averaging method
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INTRODUCTION

A biological macromolecule is a complex nonlinear dynamical system with many thousands degrees of freedom (DOF) and often affected by thermal fluctuation. Studying the dynamics of a biological macromolecule, including the transition between different conformed states, is necessary for understanding of its functions (Frauenfelder and Wolynes, 1985; McCammon and Harvey, 1987). The dynamics of molecular conformation without thermal fluctuation has been studied by Mezić (2006a; 2006b). However, the most important aspect in the dynamical behavior of biological macromolecules is the role of stochastic effects. For example, any theory for the chemical reaction of biological macromolecules has to be stochastic because these transformations are determined by diffusion processes and thermal fluctuations (Ebeling *et al.*, 2002).

In the last decade, the theory for the nonlinear stochastic dynamics in Hamiltonian formulation has been well developed in the field of mechanics (Zhu, 2003; 2006). A multi-degree-of-freedom (MDOF) strongly nonlinear dynamical system with light damping and weak external and/or parametric excitations of Gaussian white noises can be well studied by using the stochastic averaging method for quasi Hamiltonian systems (Zhu and Yang, 1997; Zhu *et al.*, 1997; 2002).

In the present paper, the biological macromolecular model previously used by Mezić (2006a; 2006b) and others, and the stochastic averaging method for quasi Hamiltonian systems are used to study the stochastic dynamics (including the statistics of stationary motion and the statistics of conformational transition) of biological macromolecules under thermal fluctuation. The analytical results are verified through comparing with the results from Monte Carlo simulation.

MODEL AND ITS MOTION EQUATION

Although a biological macromolecule is a complex dynamical system with many thousands DOF, only very simple models of it are allowed to make theoretical investigation. Here a simple model for a

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class of biological macromolecules shown in Fig.1 is considered. This model consists of two circular strands with many side chains attached to them. A side chain is represented by a single mass on a pendulum. These side chains are able to interact with other molecules or other side chains of the same molecule by forming hydrogen bonds. The lower strand with its side chains is held immobilized. The upper strand is also immobilized but its side chains are allowed to move in the plane orthogonal to the strand, i.e., to rotate around the strand. Such a model has been used, for example, for studying the coarse-grained dynamics of the DNA molecule (Peyrard, 2004; Yakushevich, 2004) and as a minimalist model of protein folding (Honeycutt and Thirumalai, 1992; Brown *et al.*, 2003).

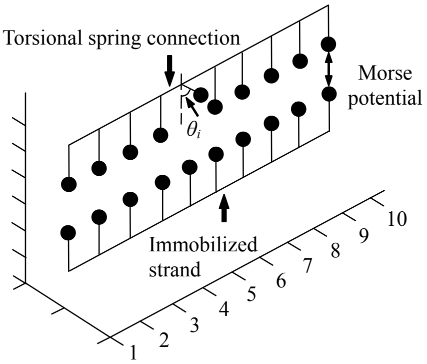

Fig.1 This figure is from (Mezić, 2006a; 2006b) showing a schematic representation of the model system Eq.(1). It consists of two strands with side chains. The lower strand with its side chains is held immobilized. The neighboring side chains interact with a torsional potential and interact with the immobilized side chains through Morse potential. The ends of the strands are connected

The attractive/repulsive force between a side chain on upper strand and its paired side chain on the lower strand is derived from the Morse potential. The side chains are also coupled to nearest neighbor side chains by torsional spring forces. The torsional motion of the side chains on the upper strand (Fig.1) is thus governed by Eq.(1):

$$\begin{aligned} mh^2\ddot{\theta}_i &= D_\mathrm{b}\{\exp[-a_\mathrm{d}(h(1-\cos\theta_i)-x_0)]-1\} \\ &\quad \cdot\exp[-a_\mathrm{d}(h(1-\cos\theta_i)-x_0)]\sin\theta_i \\ &\quad +k(\theta_{i+1}-2\theta_i+\theta_{i-1}), \end{aligned} \tag{1}$$

where i=1,2,…,N and N is the number of side chains on the upper strand; θ_i is the dihedral angle of the ith side chain and $\theta_{N+1}=\theta_1$, since the strands are assumed to be circular; m is the mass of the side chain; h is the pendulum length of the side chain; x_0 is the equilibrium distance for hydrogen bonds; a_d is the decay coefficient for the hydrogen bond force; D_b is the Morse potential amplitude; k is the torsional stiffness.

Except the forces considered, it is assumed that the model is also subjected to random forces and damping forces due to environmental molecule impacts or thermal fluctuation. Here only simple external random excitations and linear damping forces are used to represent these actions. For convenience, the mass m is assumed to be unit, i.e. $m\equiv1$, and new variables L and S are introduced as follows:

$$L=h/\sqrt{D_\mathrm{b}},\quad S=k/h^2, \tag{2}$$

then Eq.(1) becomes

$$\ddot{\theta}_i+\gamma\dot{\theta}_i+\partial U(\boldsymbol{\theta})/\partial\theta_i=\xi_i(t),\quad i=1,2,\ldots,N, \tag{3}$$

where $\boldsymbol{\theta}=[\theta_1,\theta_2,\ldots,\theta_N]^\mathrm{T}$; γ represents constant linear damping coefficient; potential $U(\boldsymbol{\theta})$ in Eq.(3) consists of Morse potential $M(\theta_i)$ and torsional potential $V(\boldsymbol{\theta})$, which read

$$\begin{gathered} M(\theta_i)=\frac{1}{2L^2a_\mathrm{d}h}\{\exp[-a_\mathrm{d}(h(1-\cos\theta_i)-x_0)]-1\}^2, \\ V(\boldsymbol{\theta})=\sum_{i=1}^{N}[S(\theta_{i-1}-\theta_i)^2/2],\ U(\boldsymbol{\theta})=V(\boldsymbol{\theta})+\sum_{i=1}^{N}M(\theta_i). \end{gathered} \tag{4}$$

$\xi_i(t)$ in Eq.(3) are Gaussian white noises in the sense of Stratonovich with correlation functions:

$$E[\xi_i(t)\xi_j(t+t')]=\begin{cases}2D\delta(t'), & i=j;\\ 0, & i\neq j,\end{cases} \tag{5}$$

where $\delta(t')$ is the Dirac delta function. It is seen from Eq.(5) that the random excitations in Eq.(3) are mutually independent and have the same intensity 2D. All the theoretical calculations and digital simulations in this paper are performed with the following same parameters: L=1, h=4, a_d=0.5 and x_0=3.

STATISTICS OF STATIONARY MOTION

The system governed by Eq.(3) can be regarded as an N-DOF stochastically excited and dissipated Hamiltonian system and Eq.(3) can be converted into the following Itô stochastic differential equations:

$$\begin{cases} \mathrm{d}\theta_i = v_i \mathrm{d}t, \\ \mathrm{d}v_i = -(\partial U(\boldsymbol{\theta})/\partial\theta_i + \gamma v_i)\mathrm{d}t + \sqrt{2D}\mathrm{d}B_i(t), \end{cases} \tag{6}$$

where $B_i(t)$ are the standard Weiner processes. The Hamiltonian H associated with system Eq.(6) reads

$$H = \sum_{i=1}^{N}(v_i^2/2) + U(\boldsymbol{\theta}). \tag{7}$$

It is well known that a Hamiltonian system can be integrable or nonintegrable (Tabor, 1989). An N-DOF 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 non-integrable Hamiltonian system, there is only one independent integral of motion, i.e., the Hamiltonian H. Here the Hamiltonian system with Hamiltonian H in Eq.(7) is nonintegrable since the Hamiltonian is non-separable.

Since H is a function of $\boldsymbol{\theta}$ and $\boldsymbol{v}=[v_1,v_2,\ldots,v_N]^{\mathrm{T}}$, and the Itô stochastic differential equation for H can be derived from Eq.(6) by using Itô differential rule (Itô, 1951) as follows:

$$\mathrm{d}H = \left(ND - \gamma\sum_{i=1}^{N} v_i^2\right)\mathrm{d}t + v_i\sqrt{2D}\mathrm{d}B_i(t). \tag{8}$$

Among $2N+1$ variables H, $\boldsymbol{\theta}$ and $\boldsymbol{v}$ in Eq.(8), only $2N$ variables are independent. Thus v_1 in Eq.(8) can be replaced by the other $2N$ variables as follows:

$$v_1 = \pm\sqrt{2[H - U(\boldsymbol{\theta})] - \sum_{i=2}^{N} v_i^2}. \tag{9}$$

Note that γ and $2D$ are small. It is seen from Eqs.(6) and (8) that Hamiltonian H is a slowly varying process while the generalized displacement $\boldsymbol{\theta}$ and generalized momenta $v_2,\ldots,v_n$ are rapidly varying processes. According to a theorem due to Khasminskii (1968), the H process converges in probability to a one-dimensional diffusion process in a time interval $0\le t\le T$, where $T\sim 0(\varepsilon^{-1})$. 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.(8). Using the first equation in Eq.(6), i.e., $\mathrm{d}\theta_1=v_1\mathrm{d}t$, the time averaging can be replaced by a space averaging with respect to θ_1 under the condition that H is kept constant. To eliminate $x_2,\ldots,x_n,v_2,\ldots,v_n$ in the averaged Itô equation, the resulting equation is further averaged with respect to $x_2,\ldots,x_n,v_2,\ldots,v_n$. The last step involves an ergodic hypothesis which may be stated as follows: The evolution of a completely non-integrable Hamiltonian system takes, with equal probability, through all states which are accessible from the starting point subject to the constraint of energy conservation (Binney *et al.*, 1992). As a result, the averaged Itô equation governing this diffusion process is thus given by

$$\mathrm{d}H = m(H)\mathrm{d}t + \sigma^2(H)\mathrm{d}B(t), \tag{10}$$

where coefficients $m(H)$ and $\sigma^2(H)$ are given by the following expressions:

$$\begin{cases} m(H) = \dfrac{1}{T(H)}\displaystyle\int_{\Omega}\left(ND - \gamma\sum_{i=1}^{N} v_i^2\right)\mathrm{d}\theta_1\mathrm{d}\theta_2\cdots\mathrm{d}\theta_N\mathrm{d}v_2\cdots\mathrm{d}v_N, \\ \sigma^2(H) = \dfrac{1}{T(H)}\displaystyle\int_{\Omega}\left(2D\sum_{i=1}^{N} v_i^2\right)\mathrm{d}\theta_1\mathrm{d}\theta_2\cdots\mathrm{d}\theta_N\mathrm{d}v_2\cdots\mathrm{d}v_N, \\ T(H) = \displaystyle\int_{\Omega}\left(\dfrac{1}{v_1}\right)\mathrm{d}\theta_1\mathrm{d}\theta_2\cdots\mathrm{d}\theta_N\mathrm{d}v_2\cdots\mathrm{d}v_N. \end{cases} \tag{11}$$

The domain Ω of the $(2N-1)$-fold integrals in Eq.(11) is defined as

$$\Omega = \left\{(\boldsymbol{\theta}, v_2, \cdots, v_N) \middle| \frac{1}{2}\sum_{i=2}^{N} v_i^2 + U(\boldsymbol{\theta}) \le H\right\}. \tag{12}$$

Replacing v_1 by Eq.(9) and finishing those integrations in Eq.(11), the following most compact expressions for averaged draft and diffusion coefficients can be obtained:

$$\begin{cases} m(H) = ND - 2\gamma A(H)/B(H), \\ \sigma^2(H) = 4DA(H)/B(H), \\ T(H) = \pi^{N/2} 2^{3N/2-2} B(H)/\Gamma(N/2), \\ A(H) = \int\limits_{\Sigma} \left(H - U(\boldsymbol{\theta})\right)^{N/2} \mathrm{d}\theta_1 \mathrm{d}\theta_2 \cdots \mathrm{d}\theta_N, \\ B(H) = \int\limits_{\Sigma} \left(H - U(\boldsymbol{\theta})\right)^{N/2-1} \mathrm{d}\theta_1 \mathrm{d}\theta_2 \cdots \mathrm{d}\theta_N, \end{cases} \quad (13)$$

where $\Gamma(\cdot)$ is the Gamma function and the domain Σ of the N-fold integrals in Eq.(13) is defined as

$$\Sigma = \{\boldsymbol{\theta} \mid U(\boldsymbol{\theta}) \le H\}. \quad (14)$$

The Fokker-Planck-Kolmogorov (FPK) equation associated with averaged Itô Eq.(10) is:

$$\frac{\partial p}{\partial t} = -\frac{\partial}{\partial H}[m(H)p] + \frac{1}{2}\frac{\partial^2}{\partial H^2}[\sigma^2(H)p], \quad (15)$$

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

$$p(H,0|H_0) = \delta(H - H_0), \quad (16)$$

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

$$p(H,0) = p(H_0). \quad (17)$$

FPK Eq.(15) is usually subjected to the following boundary conditions:

$$p, \partial p/\partial H \to 0, \quad \text{when } H \to \infty. \quad (18)$$

Usually, the one-dimensional FPK Eq.(15) usually can only be solved numerically. However, the stationary solution, i.e., the solution of reduced FPK equation without a time derivative term, can always be obtained analytically. The exact stationary solution of Eq.(15) is (Zhu and Yang, 1997):

$$p(H) = \frac{C}{\sigma^2(H)} \exp\left[2\int_a^H \frac{m(x)}{\sigma^2(x)} \mathrm{d}x\right], \quad (19)$$

where a is an arbitrary positive constant, C is a normalization constant.

The stationary solution Eq.(19) is the first approximation solution of original system Eq.(6). The corresponding joint stationary probability density $p(\boldsymbol{\theta},\boldsymbol{v})$ of the generalized displacements $\boldsymbol{\theta}$ and generalized momenta $\boldsymbol{v}$ can be obtained as follows (Zhu and Yang, 1997):

$$p(\boldsymbol{\theta},\boldsymbol{v}) = [p(H)/T(H)]\big|_{H=H(\boldsymbol{\theta},\boldsymbol{v})}. \quad (20)$$

The other stationary statistic of system Eq.(6) can be obtained from Eq.(20).

To check the accuracy of the results so obtained, Monte Carlo simulation of system Eq.(3) was performed. The sample functions for 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 a time step 0.05. The solution after 50000 steps was regarded as the stationary ergodic response and used to perform statistical analysis.

Some numerical results for the stationary probability densities $p(\theta_1)$ and $p(v_1)$ are shown in Figs.2~4. It is seen that the analytical solutions Eqs.(19) and (20) are well verified by the results from Monte Carlo simulation.

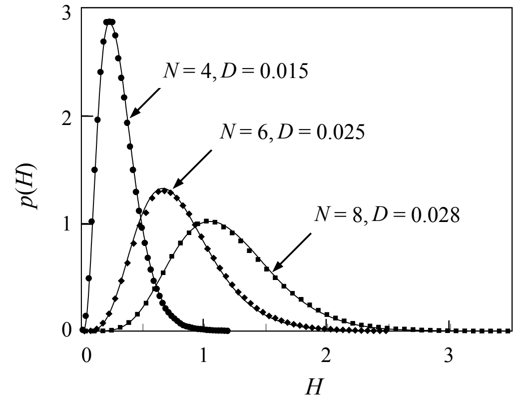

Fig.2 Stationary probability density $p(H)$ of the system energy H of model system Eq.(3) with different numbers of DOF. S=1, γ=0.2. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols ●, ♦, ■, respectively. The theoretical results are obtained from Eq.(19)

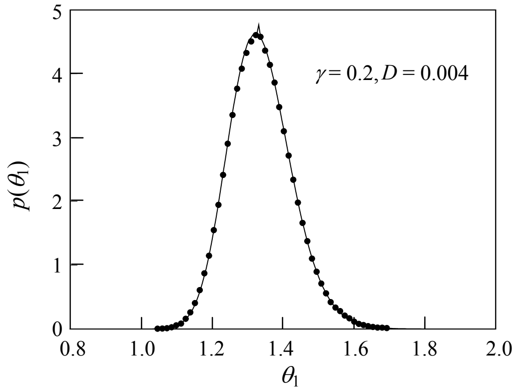

Fig.3 Stationary probability density $p(\theta_1)$ of dihedral angle (generalized displacement) θ_1 of model system Eq.(3). S=1, N=2. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols •, respectively. The theoretical result is obtained from Eq.(20) by integrating $p(\theta_1,\theta_2,v_1,v_2)$ with respect to θ_2, v_1 and v_2

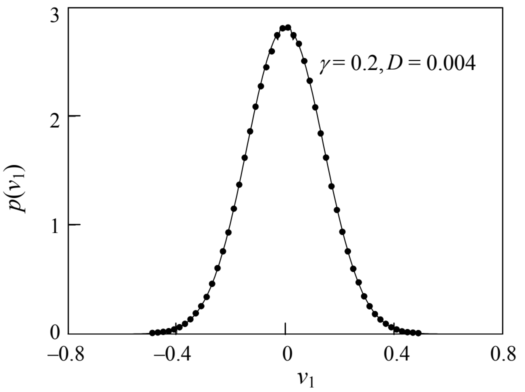

Fig.4 Stationary probability density $p(v_1)$ of velocity (generalized momentum) v_1 of model system Eq.(3). S=1, N=2. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols •, respectively. The theoretical result shown using solid line is obtained from Eq.(20) by integrating $p(\theta_1,\theta_2,v_1,v_2)$ with respect to θ_1,θ_2 and v_2

CONFORMATIONAL TRANSITION AS FIRST-PASSAGE OF ENERGY

The Hamiltonian system with Hamiltonian in Eq.(7) has two stable equilibrium states, which are called "exact conformed states" (Mezić, 2006a). They occur when all of the side chains reside in the left equilibrium state (Fig.5a) or in the right equilibrium state (Fig.5c). The two conformed states are associated with the two minima of the mores potential (Fig.6). Between the two stable equilibrium states there is an unstable state associated with the maxima of Morse potential and all side chains are up (Fig.5b). Under stochastic excitation, the state of system Eq.(3), starting from one conformed state, may pass through unstable equilibrium state and go to another conformed state. This is called the transition of conformed state. It is also called flip since all the side chains rotate from the left equilibrium position to right equilibrium position, or vice versa. The transition is a random event and happens occasionally when the stochastic forces and damping forces are small. In this section we study the conformational transition as a first-passage problem of energy.

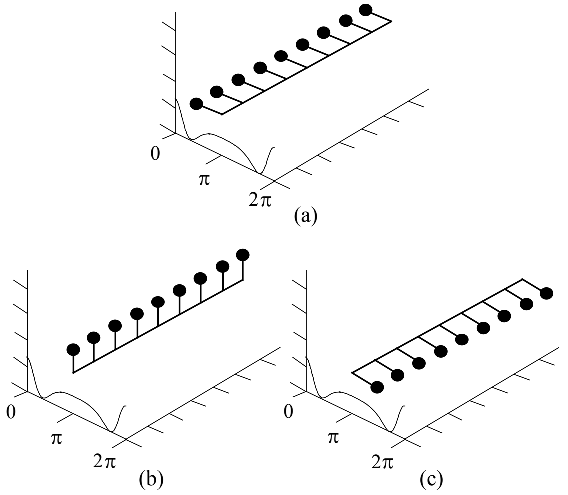

Fig.5 A schematic representation of the two stable conformation states and an unstable conformation state of the model system Eq.(3). (a) The initial stable conformation state; (b) The transient unstable conformation state; (c) The final stable conformation state

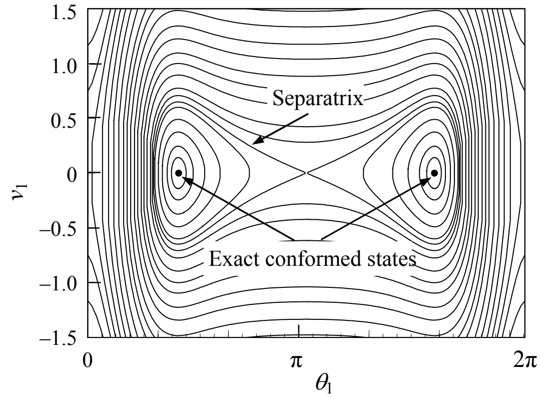

Fig.6 The phase plane of 1-DOF model system Eq.(3) with Morse potential in Eq.(4) only. Two stable equilibrium states (exact conformational states) are symmetric with respect to θ_1=π

To do so, let us introduce waiting time distribution $W(t|H_0)$ which is defined as the probability that the energy process $H(t)$, with initial value H_0 less than maximum energy H_p, never exceeds H_p up to time t, i.e.,

$$W(t|H_0)=\text{Prob}\left\{H(t')<H_p,t'\in(0,t]\,\middle|\,0\le H_0<H_p\right\}, \tag{21}$$

where H_p is also called energy threshold. The following backward Kolmogorov equation can be derived from the backward Kolmogorov equation governing the conditional transition probability density associated with FPK Eq.(15):

$$\frac{\partial W}{\partial t}=m(H_0)\frac{\partial W}{\partial H_0}+\frac{1}{2}\sigma^2(H_0)\frac{\partial^2 W}{\partial H_0^2}. \tag{22}$$

The boundary conditions associated with Eq.(22) are

$$W(t|H_0=0)=\text{finite},\quad W(t|H_0=H_p)=0. \tag{23}$$

The initial condition is

$$W(t=0|H_0<H_p)=1. \tag{24}$$

Eq.(22) with boundary conditions Eq.(23) and initial condition Eq.(24) can be solved numerically by using the 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 can be obtained as the negative derivative of $W(t|H_0)$ with respect to time, i.e.,

$$\rho(t|H_0)=-\partial W(t|H_0)/\partial t. \tag{25}$$

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

$$\tau(H_0)=\int_0^\infty t\rho(t|H_0)\mathrm{d}t=\int_0^\infty W(t|H_0)\mathrm{d}t. \tag{26}$$

On the other hand, $\tau(H_0)$ can also be obtained from solving the following Pontryagin equation:

$$m(H_0)\frac{\partial\tau}{\partial H_0}+\frac{1}{2}\sigma^2(H_0)\frac{\partial^2\tau}{\partial H_0^2}=-1, \tag{27}$$

The two boundary conditions associated with Eq.(27) are $\tau(H_0=0)$=finite and $\tau(H_0=H_p)=0$. Solving Eq.(27) together with the boundary conditions yields the following exact expression for $\tau(H_0)$:

$$\tau(H_0)=2\int_{H_0}^{H_p}\mathrm{d}u\int_0^u\frac{1}{\sigma^2(v)}\exp\left[-2\int_v^u\frac{m(w)}{\sigma^2(w)}\mathrm{d}w\right]\mathrm{d}v. \tag{28}$$

In the simulations and theoretical calculations, initial energy H_0 is set to be minimum, i.e., $H_0=0$, which is associated with one conformed state. The waiting time distribution $W(t|H_0)$, the probability density $\rho(t|H_0)$ and the mean first-passage time $\tau(H_0)$ are then simply denoted by $W(t)$, $\rho(t)$, τ, respectively. The numerical results are shown in Figs.7~9. It is seen that the results from the theoretical analysis and those from the simulation agree well. Only for the mean first-passage time τ, the analytical result is slightly lower than the simulation result (Fig.9).

CONCLUSION

In the present paper, the stationary motion and conformation transition of biological macromolecules under thermal fluctuation were investigated by using

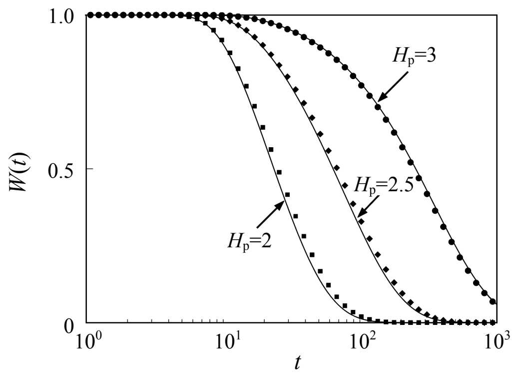

Fig.7 The waiting time distribution $W(t)$ of system energy for three passage thresholds H_p. S=1, D=0.032, γ=0.2, N=8. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols ●, ♦, ■, respectively. The theoretical results are obtained from Eq.(22)

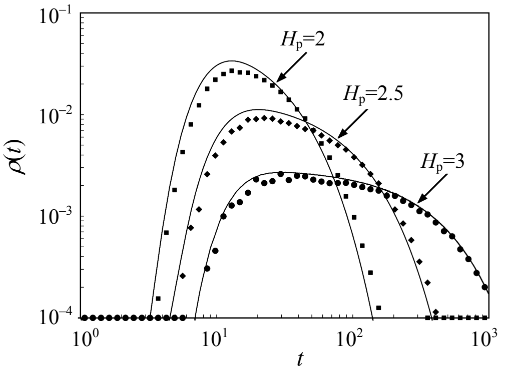

Fig.8 The probability density $\rho(t)$ of first-passage time of system energy for three passage thresholds H_p. S=1, D=0.032, γ=0.2, N=8. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols ●, ♦, ■, respectively. The theoretical results are obtained from Eq.(25)

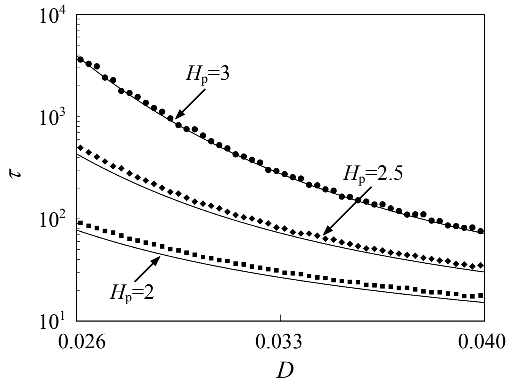

Fig.9 Mean first-passage time τ of energy for three passage thresholds H_p. S=1, γ=0.2, N=8. The results from theoretical calculation and Monte Carlo simulation are denoted by solid line and the symbols ●, ♦, ■, respectively. The theoretical results are obtained from Eq.(28)

the model previously used by Mezić and the stochastic averaging method for quasi non-integrable Hamiltonian systems. The conformational transition was treated as the first passage problem of system energy. The theoretical results were confirmed by the results from Monte Carlo simulation. Thus, the stochastic averaging method is very promising for studying the stochastic dynamics of biological macromolecules.

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