J. At. Mol. Sci.
doi: 10.4208/jams.060210.062410a

Vol. **1**, No. 4, pp. 280-291
November 2010

Statistical properties of single molecule under stochastic gating

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Received 2 June 2010; Accepted (in revised version) 24 June 2010;
Published online 2 August 2010

Abstract. We discuss the blinking statistical behaviors of dynamics of single molecule system, using the recently developed generating function method. We make a thorough study for the fluorescence blinking behaviors and get the statistical properties of the jumping events respectively onto ON state or OFF state, including the waiting time and waiting time distribution for every directional jumping event, the cumulants of jumping events, the cross correlation, the joint probabilities between two directional jumping events and the probabilities.

PACS: 33.50.Dq

Key words: single molecule, stochastic gating, statistical properties

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1 Introduction

The observation of blinking phenomenon is ubiquitous for all single molecule studies, such as various quantum dots [1–3], single polymer segment [4],fluorescent proteins [5–8], single dye molecules [9] and so on. About the distribution of sojourn time on ON state (fluorescence) or OFF state (nonfluorescence), there are some descriptions, such as the single exponential distribution for the three-level system, the nonexponential distribution for the condensed phase system with continuum manifold states and power law distribution for the single semiconductor quantum dots. The studies of physical mechanism behind the fluorescence intermittency in quantum dots have been proposed, including different pictures [10].

Due to the effect of conformational (environment) fluctuation, the conversion rate between the ON state and OFF state can be considered as the stochastic variable. In a widely discussed example, i.e., the reaction of ligand binding to the protein, the rate of

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ligand binding to proteins is more slower than that while reaction were completely diffusion controlled. The entrance of ligand to the protein is blocked by a number of side chains and thus ligand could not bind if these side chains were fixed at their equilibrium positions [8]. The blocking behaviors of the side chains act as a gate and the gate would fluctuate between open and closed positions. The opening and closing of the gate is a stochastic process. Further, Zwanzig [7] considered that the conversion process is assumed to be passage through a bottleneck, which is geometrical. The decay rate of passage through the bottleneck is proportional to the area of the bottleneck and the external fluctuations influence the cross-sectional area.

In this study, we assume that the reactivity fluctuates stochastically and the ligand has a finite size. When the radius of bottleneck is smaller than the size of ligand, the decay rate of single molecule is zero, while lager than the size of ligand, the rate of passage through the bottleneck is proportional to the cross-sectional area of this bottleneck. The influence of environment changes the cross-sectional area of bottleneck.

Similarity, the blinking behaviors of an enzyme single molecule can be considered using this stochastic gating model. The reductive and oxidative reactions are respectively corresponding to the activity (ON state) and nonactivity (OFF state) of fluorescence [9].

We use the generating function method to consider the statistics of jumping events, the different directions jumping statistics can be got respectively. The paper is organized as follows. In Section 2 of this paper, we present the theoretical derivation of the generating function for single molecule fluorescence blinking and the statistical quantities, that can be extracted. In Section 3, we give the numerical results of statistical properties for single system fluorescence blinking. The conclusions are given in Section 4.

2 Theoretical framework

The dynamics of fluorescence intermittency is corresponding to the transformation between the ON state and the OFF state in blinking statistics. Due to the influences of environment fluctuations, the transformation rate can be considered as the stochastic variable. The time-dependent dynamics equation about the single biological system can be shown

$$ON \underset{k_{ON}(t)}{\overset{k_{OFF}(t)}{\rightleftharpoons}} OFF \,. \tag{1}$$

The generating function approach has been formed to calculate SMS fluorescence blinking statistics behaviors. We have used the generating function to study the statistical properties of single molecule system [11–17]. This approach is amenable to both analytical and numerical calculations for many of statistical properties inherent to SMS measurement. In comparison with previous works [18], we introduce two “auxiliary” variables s_1 and s_2, respectively accounting the OFF state jumping times and ON state jumping times within a time interval. The generating function form about Eq. (1) was defined [11,12,19]

$$\mathcal{P}(s_1,s_2,t)=\sum_{n_1,n_2=0}^{\infty} p_{n_1n_2}(t)s_1^{n_1}s_2^{n_2}, \tag{2}$$

where $p_{n_1n_2}(t)$ is the probabilities of the single molecule from ON to OFF n_1 times and form OFF to ON n_2 times. s_1 and s_2 are the counting variables. According to the definitions [11], we write the coupled equations for the evolution of P and Q

$$\begin{aligned}\dot{P}(s_1,s_2,t)&=-k_{ON}(t)P(s_1,s_2,t)+s_1k_{OFF}(t)Q(s_1,s_2,t),\\ \dot{Q}(s_1,s_2,t)&=s_2k_{ON}(t)P(s_1,s_2,t)-k_{OFF}(t)Q(s_1,s_2,t),\end{aligned} \tag{3}$$

and the generating function

$$\mathcal{P}(s_1,s_2,t)\equiv P(s_1,s_2,t)+Q(s_1,s_2,t). \tag{4}$$

We can formally let the transformation rate $k_{ON}(t)=K_{eq}k_{OFF}(t)$ and $k_{OFF}(t)=k_{OFF}(r(t))$ and $r(t)$ is a random function of time t. Here, we respectively consider the calculations of blinking statistical variables for the ON state and the OFF state. The average values of the generating function $\mathcal{P}(s_1,s_2,t)$ can be divided into two separate stages following Zwanzic [20]. First, we can calculate a partial average $\overline{P}(r,s_1,s_2,t)$ and $\overline{Q}(r,s_1,s_2,t)$ by employing the following equations

$$\begin{aligned}\dot{\overline{P}}(r,s_1,s_2,t)=&-k_{ON}(r)\overline{P}(r,s_1,s_2,t)\\ &+s_1k_{OFF}(r)\overline{Q}(r,s_1,s_2,t)+\hat{\mathcal{Z}}\overline{P}(r,s_1,s_2,t),\\ \dot{\overline{Q}}(r,s_1,s_2,t)=&s_2k_{ON}(r)\overline{P}(r,s_1,s_2,t)\\ &-k_{OFF}\overline{Q}(r,s_1,s_2,t)+\hat{\mathcal{Z}}\overline{Q}(r,s_1,s_2,t),\end{aligned} \tag{5}$$

where $\hat{\mathcal{Z}}$ is the so-called "master" operator (for the discrete disorder process) or "Smoluchowski" operator (for the continuous disorder process).

The complete noise average of the generating function can be obtained by

$$\langle\mathcal{P}(s_1,s_2,t)\rangle=\int dr(\overline{P}(r,s_1,s_2,t)+\overline{Q}(r,s_1,s_2,t)). \tag{6}$$

For the continuous disorder process, the "Smoluchowski" operator is $\hat{\mathcal{Z}}=\lambda\theta\frac{\partial}{\partial r}(\frac{\partial}{\partial r}+\frac{r}{\theta})$. For this type process, the time-dependent of $r(t)$ is determined by the Langevin equation [20,21]

$$\frac{\mathrm{d}r(t)}{\mathrm{d}t}=-\lambda r(t)+F(t), \tag{7}$$

where λ is the decay rate and $F(t)$ is the Gaussian white noise. As is customary one requires the thermal equilibrium information about the first and second moments of $r(t)$ and $F(t)$,

$$\begin{aligned}&\langle r(t)\rangle_{eq}=0, \quad \langle r^2(t)\rangle_{eq}=\theta,\\ &\langle F(t)\rangle_{eq}=0, \quad \langle F(t)\cdot F(t')\rangle_{eq}=2\lambda\theta\delta(t-t').\end{aligned} \tag{8}$$

Base on the preceding discussion, the full set of 12 equations about generating function to be solved is then

$$\dot{\mathbb{Y}}(s_1,s_2,t)=\begin{pmatrix} \mathbb{M} & 0 & 0 & 0 & 0 & 0 \\ \frac{\partial}{\partial s_1}\mathbb{M} & \mathbb{M} & 0 & 0 & 0 & 0 \\ \frac{\partial}{\partial s_2}\mathbb{M} & 0 & \mathbb{M} & 0 & 0 & 0 \\ 0 & 2\frac{\partial}{\partial s_1}\mathbb{M} & 0 & \mathbb{M} & 0 & 0 \\ 0 & 0 & 2\frac{\partial}{\partial s_2}\mathbb{M} & 0 & \mathbb{M} & 0 \\ 0 & \frac{\partial}{\partial s_2}\mathbb{M} & \frac{\partial}{\partial s_1}\mathbb{M} & 0 & 0 & \mathbb{M} \end{pmatrix} \times \mathbb{Y}(s_1,s_2,t)+\hat{\mathcal{Z}}\mathbb{Y}(s_1,s_2,t), \tag{9}$$

where $\mathbb{M}$ is a function of s_1 and s_2, which is of the form

$$\mathbb{M}(s_1,s_2)=\begin{pmatrix} -k_{ON} & s_1 k_{OFF} \\ s_2 k_{ON} & -k_{OFF} \end{pmatrix}, \tag{10}$$

and $\mathbb{Y}(s_1,s_2,t)=\left(\mathcal{P},\, \partial\mathcal{P}/\partial s_1,\, \partial\mathcal{P}/\partial s_2, \partial^2\mathcal{P}/\partial s_1^2, \partial^2\mathcal{P}/\partial s_2^2,\, \partial^2\mathcal{P}/\partial s_1\partial s_2\right)^{\dagger}$. Here $\mathcal{P}$ is a function of s_1, s_2 and t given by (4).

Once the generating function is gotten, we can extract some statistical quantities of blinking jumping behaviors, for example, the waiting time respectively for OFF state jumping and ON state jumping

$$\langle\tau\rangle_{OFF}=\int_0^\infty \langle\mathcal{P}(s_1,s_2,t)\rangle|_{s_1=0,s_2=1}dt, \tag{11a}$$

$$\langle\tau\rangle_{ON}=\int_0^\infty \langle\mathcal{P}(s_1,s_2,t)\rangle|_{s_1=1,s_2=0}dt, \tag{11b}$$

waiting time distributions D for no blinking jumping, D_{OFF} for OFF state jumping and D_{ON} for ON state jumping

$$D_0=-\frac{dP_{00}}{dt}, \tag{12a}$$

$$D_{OFF}=-\frac{dP_0(OFF)}{dt}, \tag{12b}$$

$$D_{ON}=-\frac{dP_0(ON)}{dt}, \tag{12c}$$

the moments of the jumping times onto the OFF state or the ON state

$$\langle N^{(n)}\rangle_{OFF}=\frac{\partial^n}{\partial^n_{s_1}}\langle\mathcal{P}(s_1,s_2,t)\rangle|_{s_1=s_2=1}, \tag{13}$$

$$\langle N^{(n)}\rangle_{ON}=\frac{\partial^n}{\partial^n_{s_2}}\langle\mathcal{P}(s_1,s_2,t)\rangle|_{s_1=s_2=1}, \tag{14}$$

and the cross correlation of the blinking jumping times for the OFF state and the ON state

$$\langle N_{s_1} N_{s_2} \rangle = \frac{\partial^2}{\partial s_1 \partial s_2} \langle \mathcal{P}(s_1, s_2, t) \rangle |_{s_1=s_2=1}. \tag{15}$$

The joint probability of the times for OFF and ON states jumping is shown by

$$P_{n_1 n_2} = \frac{1}{n_1! n_2!} \frac{\partial^{(n_1+n_2)}}{\partial s_1^{n_1} \partial s_2^{n_2}} \langle \mathcal{P}(s_1, s_2, t) \rangle |_{s_1=s_2=0}, \tag{16}$$

and the probability of the n times only for OFF state jumping or ON state jumping within the time interval $[0,t]$ are respectively defined by

$$\begin{aligned} P_n(OFF) &= \frac{1}{n!} \frac{\partial^n}{\partial s_1^n} \langle \mathcal{P}(s_1, s_2, t) \rangle |_{s_1=0, s_2=1}, \\ P_n(ON) &= \frac{1}{n!} \frac{\partial^n}{\partial s_2^n} \langle \mathcal{P}(s_1, s_2, t) \rangle |_{s_1=1, s_2=0}. \end{aligned} \tag{17}$$

Some statistical quantities about the stochastic gating of fluorescence blinking are considered using the geometrical fluctuating bottleneck model. Similar to be the Zwanzig's fluctuating bottleneck model, we consider the dependence of the passage rate on relaxation rate of the gate radius: the *open-or-closed stochastic gating*. With regard to the rate of transformation between the ON state and the OFF state, the blinking jumping can not happen and the transformation rate is zero, when the radius of the bottleneck is smaller than r_0. r_0 indicate the radius of the ligand. The rate of escape through the bottleneck, $k_{OFF}(t)$ is given by

$$k_{OFF}(r(t)) = \begin{cases} 0, & 0 \leqslant \mathrm{r} \leqslant r_0, \\ k(r(t) - r_0)^2, & \mathrm{r} \geqslant r_0. \end{cases} \tag{18}$$

A reflecting boundary condition is used at $r=0$, avoiding negative values of the radius of the gate. The initial condition is chosen a Gaussian equilibrium distribution function. It is obviously seen that when $r_0 = 0$ the Zwanzig's model can be got.

3 Numerical results

Relative to the timescale of blinking rate modulation, we consider the fast and slow rate blinking conditions. The bottleneck radiuses r_0 can be respectively taken from 0 to 8 for the fast case and from 0 to 2 for the slow case, which have achieved the extremity of the considering question.

Waiting time and waiting time distribution. The open gate is corresponding to the ON state in blinking dynamics. While the gate is open, the ligand will have the probability to bind onto the protein. After the binding, the protein becomes inert. This is similar to the reductive reaction in the single molecule enzymatic dynamics. The survival probability of protein without a bound ligand or the enzyme with the oxidative form is an interest quantity to the kinetics. Initially, the researchers disclaimed the exponential distribution of the waiting time for ON state jumping or OFF state jumping. Then, some found that the distribution for the sojourn time on ON state or OFF state followed the power law form [1]. Here, using the generating function, we get the waiting time for each directional jumping and the waiting time distributions for ON state jumping, OFF state jumping and no jumping.

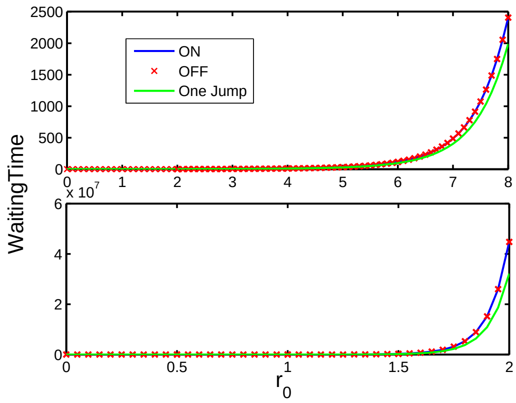

Figure 1: (Color online) The waiting time of the OFF state jumping and ON state jumping as the function of r_0, while the blinking rates are fast or slow. The parameters used are from Ref. [18]: $K_{eq}=2.0$, $\lambda=1.0$, $\kappa=5.0$ and $\theta=5.0$ (for fast case); $K_{eq}=2.0$, $\lambda=1.0$, $\kappa=0.2$ and $\theta=0.2$ (for slow case).

Fig. 1 shows the waiting time as a function of ligand radius r_0, respectively for the fast (top row) and slow (bottom row) blinking rates. The blue solid and red cross lines are waiting time for ON and OFF state jumping, and green lines for any jumping without regard to the direction. For the fast or slow rate blinking, the waiting time is initially increasing slowly, then becomes fast as the increase of radius r_0 at any jumping case. The waiting time for ON state jumping and OFF state jumping are identical, and greater than jumping without direction. Because the jumping without direction is only for one jump process, but the waiting time for ON or OFF state jumping is according to waiting time for double jumping (one ON state jumping and one OFF state jumping). The distribution as the r_0 and the relation between the OFF state and the ON state are consistent with the reaction-diffusion process.

For the relatively small radius r_0, the binding of ligand to the protein can easily happen and don't wait for long time, corresponding to the smaller waiting time for ON state jumping and OFF state jumping. With the increase of ligand radius, the waiting time for the passage through the bottleneck drastically gets long. This variation tendency of waiting time as the ligand radius r_0 is according to our common understanding.

Following, the top two lines of Fig. 2 show the distributions D of waiting time for no jumping, the OFF state jumping and the ON state jumping, respectively for the fast (the first line) and slow (the right line) rate blinking. For any blinking rate process and

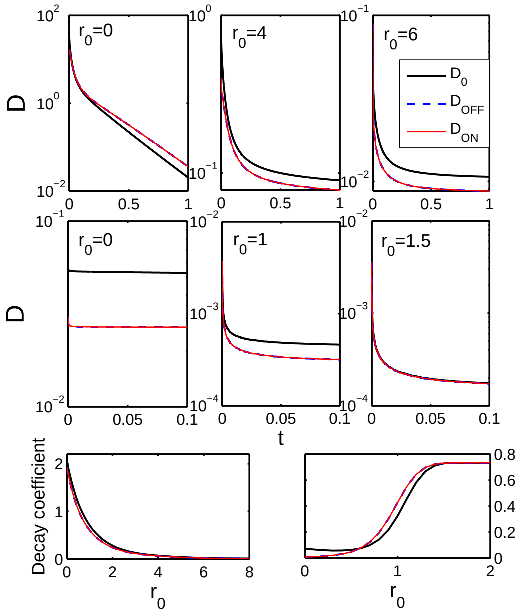

Figure 2: (Color online) The distributions of waiting time as the function of time t and the decay coefficient of these distributions (in the bottom line) as function of radius r_0 for no jumping, the OFF state jumping and the ON state jumping, while the blinking rates are fast (left column) and slow (right column). The parameters for fast and slow cases are the same as those in Fig. 1.

the any radius, the decay behaviors of waiting time distribution as the time all show an exponential decay ultimately, in spite of the nonexponential behavior originally. And the decay behaviors have the very same tendency for the OFF state jumping and the ON state jumping, but different from no jumping process showing by the black lines.

For the fast rate blinking, we respectively consider the three kinds of waiting time distributions for $r_0 = 0$, 4 and 6. As the increasing of the radius r_0, the originally non-exponential decay and ultimately exponential decay also exist, but the coefficients of exponential decays become small and become equal. For $r_0 = 4$ and $r_0 = 6$, the same decay behaviors appear and the three processes have the same decay coefficient. Moreover, the exponential decay behaviors have divergency and the divergency becomes broad as the radius from 4 to 6. On the whole, the values of waiting time distribution for three jumping processes all reduce as the increasing of radius for the same time, corresponding to the lengthening of waiting time, which is in accordance with the change behavior of waiting time in Fig. 1. In the bottom of left column, the ultimately exponential decay coefficient of distribution for the fast rate blinking is given as the function of radius r_0. We can clearly see that the decay coefficients of the OFF state and ON state jumping events are the same, and the coefficients for the three processes tend to be identical when the r_0 is relatively big.

For the slow rate blinking showing in the second line of Fig. 2, we also consider the three kinds of $r_0 = 0$, 1 and 1.5 for the three jumping processes. The originally nonexponential decay and ultimately exponential decay also appear for the considered three radius. But when $r_0 = 0$, there is obvious divergence between the waiting time distributions for no jumping process and the OFF (or ON) state jumping process. And as the increasing of r_0, the divergence gradually decrease and tends to uniformity while $r_0 = 1.5$. Also with the increasing of r_0, the waiting time for the three jumping processes becomes longer and longer. In the bottom of right column, the exponential decay coefficient for the slow rate blinking is shown as the increasing of radius r_0. Differently from the fast case, the decay coefficient is relatively small initially, then quickly increase and finally tends to be stable, as the increase of r_0. And the decay coefficients of the no jumping and the OFF (or ON) state jumping process are different for $r_0 = 0-5$ and then tend to be identical.

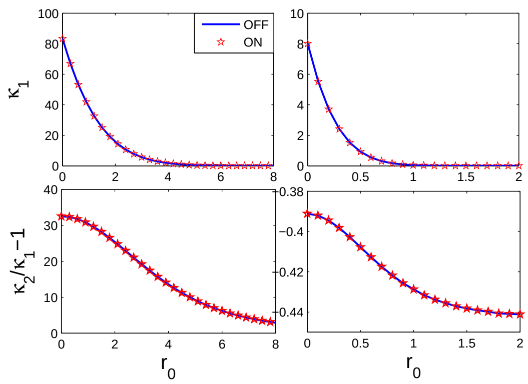

Figure 3: (Color online) The first cumulant κ_1 and second cumulant $\kappa_2/\kappa_1 - 1$ of blinking and as a function of r_0 for fast (left) and slow (right) rate blinking, considering respectively for the ON state jumping (star lines) and OFF jumping state (blue solid lines). The parameters for fast and slow cases are the same as those in Fig. 1.

The first and second cumulants of jumping times. Fig. 3 shows the first ($\kappa_1 = \langle N^{(1)} \rangle$) and second $\kappa_2/\kappa_1 - 1$ ($\kappa_2 = \langle N^2 \rangle - \langle N \rangle^2$) cumulants as a function of r_0 for the ON state jumping events and the OFF state jumping events, when the rate of blinking jumping events is fast (left) or slow(right). The first and second cumulants for the ON state jumping and the OFF state jumping show the same decay behaviors. The first cumulants is continuously increasing for the long time, so we take different calculation time for specific cases. For the fast and slow blinking rate, we respectively calculate the first cumulant at $t = 5$ and $t = 300$, showing in the top of Fig. 3. As the increasing of r_0, the first cumulants all reduce, no matter for the fast or slow blinking rate. These are identical with the fact, that the blinking frequency is becoming small with the increasing of r_0.

But the second cumulant will saturate to be a certain value with the increasing time at the any radius r_0, no matter for the ON state jumping or the OFF state jumping. In the bottom of Fig. 3, we give the stable value change of the second cumulant with the increasing of r_0. For the fast blinking rate case, the second cumulant is bigger than 0, but is less than 0 for the slow blinking rate case, for any r_0. Those are in accordance with the diversity of blinking rate.

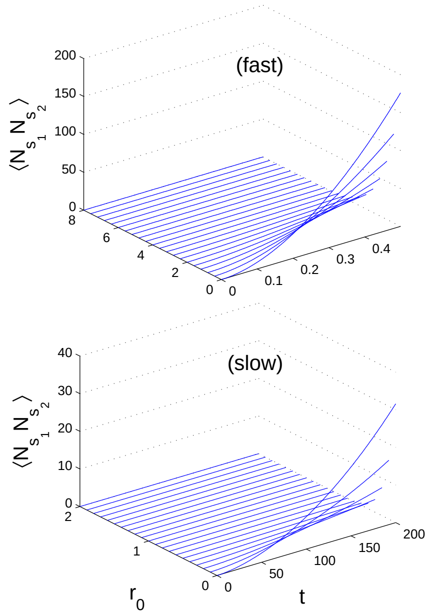

Figure 4: The cross correlation as functions of r_0, while the rate blinking is fast (top) or slow (bottom). The parameters for slow and fast cases are the same as those in Fig. 1.

The cross correlation of blinking jumping times for the OFF state and the ON state. The cross correlation $\langle N_{s_1} N_{s_2} \rangle$ of the blinking jumping times for different directions is calculated by using Eq. (15). The cross correlations for the fast and slow rate blinking are respectively shown in the top and bottom of Fig. 4. Due to the continuous increase of cross correlation with time t, we respectively take the calculation time $t = 0.5$ and $t = 200$ for fast and slow cases. We can see that the change behaviors display the similar decay nature as the increasing of r_0 and time t. But the cross correlation for the fast rate blinking is much bigger than the slow condition for every value of r_0, which is due to the bigger conversion rate for the fast rate blinking case. Relatively small r_0 can induces the strong correlation between the ON state jumping and the OFF state jumping. As the increasing of r_0, the cross correlations all gradually tend to be less correlation, no matter for fast rate or slow rate blinking. This is because the effect of bottleneck (or environment) is very strong for small radius r_0. But there is hardly jumping event for the relatively big r_0 of every rate blinking case.

The joint probability of the jumping times for the OFF state and ON state. The joint probability $P_{n_1 n_2}$ of the blinking jumping times can be got by using Eq. (16). In the Fig. 5, the different joint probabilities P_{10} and P_{11} are shown as the function of r_0 and time t, for the fast (left column) and slow (right column) rate blinking. As the increasing of r_0, the probability maximum of P_{10} and P_{11} appears more and more late in time, no matter for the fast or the slow rate blinking case.

For the fast rate blinking in the left part, the maximums of probabilities P_{10} and P_{11}

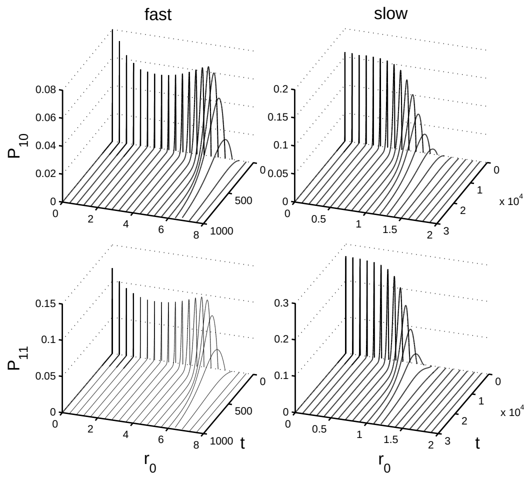

Figure 5: (Color online) The joint probabilities for the jumping times as the function of r_0 and time t (in top two lines), and the probability maximum as the function of r_0 (in the bottom line), while the blinking rates are fast (left column) or slow (right column). The parameters for slow and fast cases are the same as those in Fig. 1.

have a fluctuation, firstly reach a peak, and then rapidly drop to zero at big value of r_0. Obviously, the middle radius also can induce the big P_{11} or P_{10}, similar to the very small radius r_0. For the slow rate blinking, the changes show a stable behavior at first, then rapidly drop to zero at relatively big r_0. The larger radius makes against the passage through the bottleneck and there is hardly jumping event, no matter for the fast or for the slow rate blinking.

The probability of the jumping n times only for ON state or only for OFF state. These probabilities can be calculated from Eq. (17). For the slow rate blinking, we show the probability P_1 and P_2 as the function of time t and radius r_0 in Fig. 6, while the ON state jumping probability is shown in the left column and the OFF state jumping in the right column. As the increasing of r_0, the maximum of probability appears more and more late in time, no matter for P_1 or P_2. For the fast rate blinking case, the probability changes as the time t and r_0 present the same tendency and here we don't repeatedly give the picture.

Then in Fig. 7, we only give the maximums of P_1 and P_2 for the ON state and OFF state jumping in the fast or the slow rate blinking case. For any blinking rate, the change behaviors of maximum of P_1 or P_2 are the same for the OFF state jumping and the ON state jumping, showing by the solid and the star lines. Obviously, for the slow rate case, the maximum change of probability as the function of r_0 is according to the evolution of probability in Fig. 6, showing by the same color lines in the two figures. For the fast rate blinking case, the probability maximums as the function of radius have a peak and then rapidly drop to zero at the big r_0. For the slow rate blinking, the changes show a stable behavior at first, then rapidly drop to zero for big r_0.

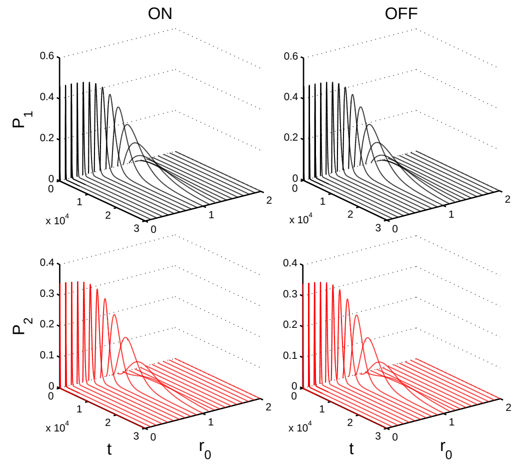

Figure 6: (Color online) The probability P_1, P_2 of one jumping and two jumpings only for the ON state (left column) or the OFF state (right column) as functions of time t and r_0, while the rate blinking is slow. The parameters used are: $K_{eq}=2.0$, $\lambda=1.0$, $\kappa=0.2$ and $\theta=0.2$.

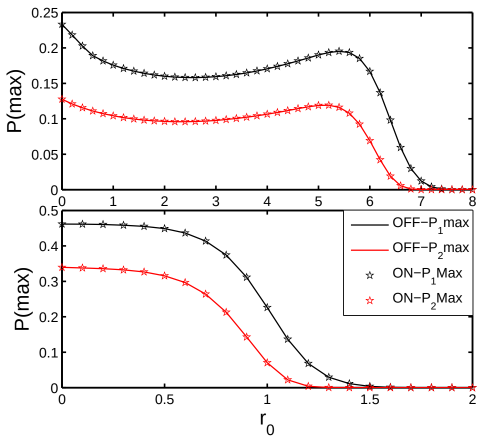

Figure 7: (Color online) The probability maximums only for the ON state jumping and the OFF state jumping as a function of r_0 for fast (top part) and slow (bottom part) rate blinking. The parameters for fast and slow cases are the same as those in Fig. 1.

4 Discussion and conclusion

In this study, we have studied the statistical properties of ubiquitous blinking phenomenon under stochastic gating and got the generating function framework with two "auxiliary" variables, counting the times of the OFF state jumping and the ON state jumping. Using the modified model, we considered the properties behaviors for the blinking jumping events comprehensively, from the waiting time distribution to the cumulants of jumping times. Also we gave the joint probability and cross correlation of blinking events, indicating the correlation degree between the times for ON state jumping and OFF state jumping. For the fast and slow rate blinking behaviors, there are different change behaviors at some ligand radius.

Acknowledgments. This work was supported by the National Science Foundation of China under Grant No.10874102, and National Basic Research Program of China under Grant No.2009CB929404. Partial financial supports from the Research Fund for the Doctoral Program of Higher Education under Grant No.200804220004 is acknowledged.

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