Transcription rate of RNA polymerase under rotary torque

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We investigated the transcription rates of RNA polymerases that were subjected to rotational drag. By combining chemical kinetics with mechanical equations, we derived formulas for the transcription rate in the case where the torque was caused by the hydrodynamic drag to DNA rotation.

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I. INTRODUCTION

During transcription, RNA polymerases (RNAPs) rotate hundreds of times around DNA, trailing the helical structure of the strands. Any mechanical obstruction to this rotary motion subjects the DNA to a torsional stress, and the RNAPs synthesize RNA transcripts against the rotary torque.

The transcription elongation on torsionally stressed DNA fragments can be realized *in vitro* by fixing RNAPs on beads or glass plates and enabling DNA fragments to be freely transcribed. In this case, the torsional stress is caused by the hydrodynamic drag to DNA rotation.

The torsional stress of DNA also occurs *in vivo* due to the viscous drag or interactions with surrounding proteins. However, in normal cells, DNA supercoiling is relaxed by enzymes such as topoisomerases and gyrases, which have catalytic activities to sever and unwind DNA strands. Therefore, the global DNA supercoiling due to the transcription occurs only in cells whose topoisomerase or gyrase activities are sufficiently low. Such cells are of medical interest, since many of the anticancer drugs are topoisomerase inhibitors.

In this paper, we study the effects of torsional stress on the transcription rates. First, we investigate the general properties of our model, which is a generalization of the models studied by Jülicher and Bruinsma [1]. Then, we compare the model with the existing experiments, and finally, we propose a more stringent experimental test for our model.

II. THE MODEL

In Ref. [1], Jülicher and Bruinsma studied a couple of mechanochemical models that describe the transcription elongation of RNA polymerases against the external force pulling the downstream end of DNA strands. They assumed the flexible internal structures of RNAPs as the essential ingredient of the transcription process. This has been supported by recent evidences, which suggest that the bridge helix of RNAP is strongly bent during transcription [2]. Based on this, they expressed the transcription process as a series of polymerization and translocation steps. In the polymerization steps, RNAPs are considered to convert the chemical energy of RNA polymerization reaction into the mechanical deformation energy, and in the translocation steps to release their deformation energy. They combined these reaction steps with a kind of stationary state condition and derived expressions for the mean transcription rates. Their models successfully explained the force-rate curves of Ref. [3], which were similar to the Fermi distribution function. Below we follow the basic construction of the models of Ref. [1], but neither do we assume any specific form of energy function for the RNAP deformation nor any special relation among the coupling constants, in order to derive the general features of our model.

As in Ref. [1], we introduce a pair of reaction coordinates (n,m), where n is a non-negative integer that measures the distance between the position of RNAP from the transcription start site in units of base pairs, and m is an integer that measures the deformation of RNAPs. With these reaction coordinates, we express the transcription processes as a sequence of RNA polymerization and translocation steps.

The RNA polymerization steps occur within the RNAPs and no work is done against external forces. In each of these steps, a ribonucleoside triphosphate (NTP) bonds with RNA covalently, releasing a pyrophosphate (PPi),

$$\mathrm{RNA}_n + \mathrm{NTP} \rightleftharpoons \mathrm{RNA}_{n+1} + \mathrm{PPi}. \tag{1}$$

At the same time, the RNAPs are assumed to store internal deformation energy. The corresponding reaction equation is given by

$$(P) \quad (n,m) \underset{\overline{k'_{\mathrm{P}}}(m)}{\overset{k'_{\mathrm{P}}(m)}{\rightleftharpoons}} (n,m+1), \tag{2}$$

where $k'_{\mathrm{P}}(m)$ and $\overline{k'_{\mathrm{P}}}(m)$ are the forward and backward reaction rates, respectively.

In the RNAP translocation steps, RNAPs slide along DNA and relax their internal stress. The RNAPs do work against external forces in these steps. The reaction equation can be written as

$$(T) \quad (n,m+1) \underset{\overline{k_{\mathrm{T}}}(m)}{\overset{k_{\mathrm{T}}(m)}{\rightleftharpoons}} (n+1,m). \tag{3}$$

When m decreases by 1, an RNAP moves by one base pair.

The detailed balance relations at the equilibrium are given by

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$$\frac{k'_{\mathrm{P}}(m)}{\overline{k'_{\mathrm{P}}(m)}} = \exp\left(\frac{\Delta G_{\mathrm{P}}(m)}{k_B T}\right),$$

$$\frac{k_{\mathrm{T}}(m)}{\overline{k_{\mathrm{T}}(m)}} = \exp\left(\frac{\Delta G_{\mathrm{T}}(m)}{k_B T}\right).$$

Here, $\Delta G_{\mathrm{P,T}}$ are the free energy gains of forward reactions, and k_B and T are the Boltzmann constant and temperature, respectively. Hereafter, the subscripts P and T indicate the polymerization reaction in Eq. (2) and the translocation reaction in Eq. (3), respectively.

The rates of forward reactions $k'_{\mathrm{P}}(m)$, $k_{\mathrm{T}}(m)$ are given by the Arrhenius formula [4],

$$k'_{\mathrm{P}}(m) = [\mathrm{NTP}]k_{\mathrm{P}}(m) = k_{\mathrm{P},0}[\mathrm{NTP}]\exp(-\Delta U_{\mathrm{P}}/k_B T),$$

$$k_{\mathrm{T}}(m) = k_{\mathrm{T},0}\exp(-\Delta U_{\mathrm{T}}/k_B T),$$

where [NTP] is the NTP concentration, $\Delta U_{\mathrm{P,T}}$ are the activation energies, and $k_{\mathrm{P},0}$, $k_{\mathrm{T},0}$ are the reaction constants independent of the NTP, PPi concentration, and temperature.

With these equations, the mean transcription rate ν is given by

$$\begin{aligned}\nu &= [k'_{\mathrm{P}}(\overline{m}) - \overline{k'_{\mathrm{P}}}(\overline{m}+1)](\mathrm{bp/sec}) \\ &= [\mathrm{NTP}]k_{\mathrm{P}}(\overline{m})[1 - e^{\Delta G_{\mathrm{P}}(\overline{m})/k_B T}] \\ &= [k_{\mathrm{T}}(\overline{m}) - \overline{k_{\mathrm{T}}}(\overline{m})](\mathrm{bp/sec}) = k_{\mathrm{T}}(\overline{m})[1 - e^{\Delta G_{\mathrm{P}}(\overline{m})/k_B T}],\end{aligned} \tag{4}$$

where bp denotes "base pairs." The mean elastic deformation of RNAPs is $\overline{m}$, which is obtained by equating the rate of increasing m with the rate of decreasing m,

$$k'_{\mathrm{P}}(\overline{m}) + \overline{k_{\mathrm{T}}}(\overline{m}) = \overline{k'_{\mathrm{P}}}(\overline{m}) + k_{\mathrm{T}}(\overline{m}).$$

This equation can be written as

$$1 = \frac{k_{\mathrm{T}}(\overline{m})}{[\mathrm{NTP}]k_{\mathrm{P}}(\overline{m})}\left(\frac{1 - e^{-\Delta G_{\mathrm{T}}(\overline{m})/k_B T}}{1 - e^{-\Delta G_{\mathrm{P}}(\overline{m})/k_B T}}\right). \tag{5}$$

Equations (4) and (5) describe the mean behaviors of a large number of RNAPs.

III. WITHOUT EXTERNAL LOAD

We first consider the case in which no external forces are applied. In this case, the free energy gains of reactions are given by

$$\Delta G_{\mathrm{P}}(m) = \mu + [\mathcal{E}(m) - \mathcal{E}(m+1)] = \Delta\mu - W_{\mathrm{deform}}(m),$$

$$\Delta G_{\mathrm{T}}(m) = \mathcal{E}(m+1) - \mathcal{E}(m) = W_{\mathrm{deform}}(m).$$

Here, $\Delta\mu$ is the chemical energy of RNA polymerization reaction (1), which is given by

$$\Delta\mu = \Delta G_0 + k_B T \ln\left(\frac{[\mathrm{NTP}]}{[\mathrm{PPi}]}\right),$$

where ΔG_0 is the standard free energy of the reaction. The term $W_{\mathrm{deform}}(m) = \mathcal{E}(m+1) - \mathcal{E}(m)$ expresses the increase in internal stress energy of RNAPs. We replace the variable $\overline{m}$ with the Boltzmann factor of deformation energy $x = \exp(-W_{\mathrm{deform}}/k_B T)$. Then Eqs. (5) and (4) become

$$1 = \frac{k_{\mathrm{T}}(x)}{[\mathrm{NTP}]k_{\mathrm{P}}(x)}\left(\frac{1-x}{1-x^{-1}g}\right),$$

$$\nu = [\mathrm{NTP}]k_{\mathrm{P}}(x)(1 - x^{-1}g) = k_{\mathrm{T}}(x)(1-x),$$

where $g = \exp(-\Delta\mu/k_B T)$. We note that the positivity of the rate ν implies $g < x < 1$.

In the limit of $[\mathrm{NTP}] \to \infty$ with fixed [PPi]/[NTP], both the forward and backward rate of RNA polymerization reactions are much larger than those of translocation reactions. Since the RNAP motion in response to its internal stress is infrequent, the Boltzmann factor of deformation energy x becomes comparable to that of chemical energy g. The transcription rate in this limit is given by

$$\nu = k_{\mathrm{T}}(g)(1-g)\left[1 - \frac{c_1}{[\mathrm{NTP}]} + O\left(\frac{1}{[\mathrm{NTP}]^2}\right)\right]. \tag{6}$$

This shows that the transcription rate is determined by the translocation step sown in (3). The coefficient c_1 of the leading correction is given by

$$c_1 = \frac{k_{\mathrm{T}}(g)(1-g)}{k_{\mathrm{P}}(g)}\left(\gamma_{\mathrm{T}}(g) - \frac{g}{1-g}\right),$$

where $\gamma_{\mathrm{T}} = \partial \ln k_{\mathrm{T}}(x)/\partial \ln(x)|_{x=g}$. Since the rate ν approaches its maximum in the limit of $[\mathrm{NTP}] \to \infty$, $\gamma_{\mathrm{T}}(g) - g/(1-g)$ is negative for any $0 < g < 1$.

Equation (6) is a series expansion over the dimensionless parameter $(1-g)k_{\mathrm{T}}(g)/k_{\mathrm{P}}(g)[\mathrm{NTP}]$, and higher-order terms are important when $[\mathrm{NTP}] \lesssim N_c(g) = (1-g)k_{\mathrm{T}}(g)/k_{\mathrm{P}}(g)$.

For $[\mathrm{NTP}] \ll N_c(g)$, RNAPs frequently seek for a comfortable position in the DNA strands. Accordingly, the internal stresses of RNAPs are almost zero ($x \sim 1$). In this case, the transcription rate is given by

$$\nu = k_{\mathrm{P}}(1)[\mathrm{NTP}](1-g)\{1 - c_2[\mathrm{NTP}] + O([\mathrm{NTP}]^2)\}, \tag{7}$$

where c_2 is given by

$$c_2 = \frac{k_{\mathrm{P}}(1)(1-g)}{k_{\mathrm{T}}(1)}\left(\gamma_{\mathrm{P}} + \frac{g}{1-g}\right)$$

with $\gamma_{\mathrm{P}} = \partial \ln k_{\mathrm{P}}(x)/\partial \ln(x)|_{x=1}$. The leading term of (7) is the same form as derived from the simple chemical equation (1). The correction terms should reduce the rate ν for any g, since the rate ν is an upper-bounded function of [NTP]; hence, γ_{P} is a non-negative number.

These limiting behaviors of the transcription rates are the same as those obtained from the Michaelis-Menten formula for enzyme reactions [4],

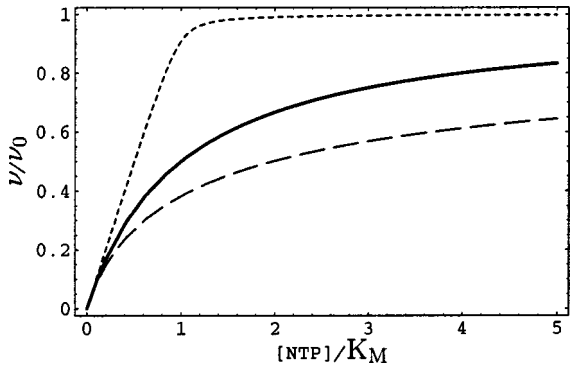

FIG. 1. Transcription rates ν as a function of NTP concentration [NTP]. Both ν and [NTP] are made dimensionless using ν_0 and K_M of Eq. (8), respectively. Solid line: $\gamma_{1P}=1$; $\gamma_{1,T}=0$; g, arbitrary. Dotted line: $\gamma_{1P}=0$, $\gamma_{1T}=0$, $g=0.01$. Broken line: $\gamma_{1P}=2$, $\gamma_{1T}=0$, $g=0.01$.

$$\nu = \nu_0 \frac{[\mathrm{NTP}]}{[\mathrm{NTP}] + K_M}$$

with

$$\begin{aligned} \nu_0 &= k_T(g)(1-g), \\ K_M &= k_T(g)/k_P(1). \end{aligned} \tag{8}$$

However, the characteristic value $N_c(g)$ of the NTP concentration is different from $K_M=K_M(g)$ of the Michaelis-Menten formula. If the ratio $N_c(g)/K_M(g)$ is very small, then the rate ν rapidly reaches its maximum with [NTP]. On the other hand, if $N_c(g)/K_M(g)$ is very large, the approach of the rate ν to its maximum is much slower than the corresponding Michaelis-Menten curve.

These behaviors are illustrated in Fig. 1 where [NTP] dependence of the rate ν for fixed [NTP]/[PPi] are shown in three typical cases. In Fig. 1, we have chosen a specific form of activation energies for concreteness,

$$\begin{aligned} \Delta U_P &= \Lambda_P + \gamma_{1P} W_{\mathrm{deform}}, \\ \Delta U_T &= \Lambda_T + \gamma_{1T} W_{\mathrm{deform}}, \end{aligned}$$

where $\Lambda_{P,T}$ are constants with dimension of energy and $\gamma_{1P,T}$ are dimensionless constants. The solid line ($\gamma_{1P}=1$; $\gamma_{1,T}=0$; g, arbitrary) corresponds to the Michaelis-Menten curve. The dotted line ($\gamma_{1P}=0$, $\gamma_{1T}=0$, $g=0.01$) reaches the maximal rate more rapidly than the Michaelis-Menten curve, while the broken line ($\gamma_{1P}=2$, $\gamma_{1T}=0$, $g=0.01$) shows a slower rise than the other curves.

IV. WITH EXTERNAL LOAD

We next consider the case in which an external load is applied. In this case, there is an additional term $\Delta G_{\mathrm{ext,T}} = -W_{\mathrm{ext}}$ for the free energy gain of the translocation step, while the free energy gain ΔG_P of the polymerization step is unchanged from the no force case. W_{ext} is the work done by the RNAP against the external force at each translocation step. In the following, we assume that the activation energies are linearly dependent on the work W_{ext}.

$$\begin{aligned} \Delta U_{\mathrm{ext,P}} &= \gamma_{\mathrm{ext,P}} W_{\mathrm{ext}}, \\ \Delta U_{\mathrm{ext,T}} &= \gamma_{\mathrm{ext,T}} W_{\mathrm{ext}}, \end{aligned} \tag{9}$$

where $\gamma_{\mathrm{ext,P}}$ and $\gamma_{\mathrm{ext,T}}$ are dimensionless coefficients which are arbitrary, but tame functions of the reaction coordinate m; therefore, tame functions of x. The linear dependence on the work W_{ext} should be valid unless W_{ext} is too large. We only consider the case where the work W_{ext} is smaller than the chemical energy $\Delta\mu$. Then Eqs. (5) and (4) become

$$1 = \frac{k_T(x,y)}{[\mathrm{NTP}]k_P(x,y)} \left(\frac{1 - xy^{-1}}{1 - gx^{-1}} \right), \tag{10}$$

$$\nu = [\mathrm{NTP}]k_P(x,y)(1 - gx^{-1}) \tag{11}$$

$$= k_T(x,y)(1 - xy^{-1}), \tag{12}$$

where $y=\exp(-W_{\mathrm{ext}}/k_BT)$. The positivity of the rate $\nu>0$ implies $g<x<y$, which means that the deformation energy should be larger than the work against the external force and smaller than the chemical energy.

The limiting behaviors of transcription rate ν at large and small [NTP] are given by

$$\begin{aligned} \nu &= \begin{cases} k_T(g,y)(1 - gy^{-1}) & \text{for } [\mathrm{NTP}] \gg N_c(g,y) \\ [\mathrm{NTP}]k_P(y,y)(1 - gy^{-1}) & \text{for } [\mathrm{NTP}] \ll N_c(g,y) \end{cases} \\ &\sim \begin{cases} k_T(g) y^{\gamma_{\mathrm{ext,T}}(g)} & \text{for } [\mathrm{NTP}] \gg N_c(g,y) \\ k_P(y) y^{\gamma_{\mathrm{ext,P}}(y)} & \text{for } [\mathrm{NTP}] \ll N_c(g,y), \end{cases} \end{aligned}$$

where

$$N_c(g,y) = \frac{(1 - gy^{-1})k_T(g,y)}{k_P(g,y)} \sim N_c(g) y^{\gamma_{\mathrm{ext,T}}(g) - \gamma_{\mathrm{ext,P}}(g)}$$

and $k_T(g)$, $k_P(g)$, and $N_c(g)$ are given by the corresponding functions in the case of no external load. Since we are only interested in the case where the external forces reduce the rate ν, the coefficient functions $\gamma_{\mathrm{ext,T}}(x)$, $\gamma_{\mathrm{ext,P}}(x)$ of Eqs. (9) are non-negative functions. If the coefficient of the activation energy of the translocation step is positive $\gamma_{\mathrm{ext,T}}(x)>0$, then the maximal rate ν at sufficiently large [NTP] decreases exponentially with the external force. If the coefficient is negligible [$\gamma_{\mathrm{ext,T}}(x)\sim 0$], the maximal rate remains unchanged from the no force case. In this case, if the activation energy of the polymerization step is independent of the external work W_{ext}[$\gamma_{\mathrm{ext,P}}(x)\sim 0$], then the rate is unaffected by the external force. On the other hand, if the coefficient of the polymerization step is positive [$\gamma_{\mathrm{ext,P}}(x)>0$], the characteristic NTP concentration $N_c(g,y)$ increases with the external force. If the system has these particular coupling constants ($\gamma_{\mathrm{ext,T}}\sim 0, \gamma_{\mathrm{ext,P}}>0$), the force-rate curve at a fixed and large [NTP] takes a form similar to the Fermi distribution function where the rate is constant until the force reaches a critical force and

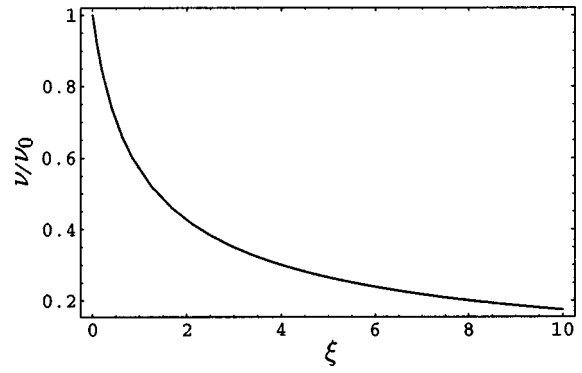

FIG. 2. The reduction of maximal transcription rate ν/ν_0 as a function of the dimensionless viscous coefficient ξ. ν and ν_0 are the maximal transcription rate with and without the viscous drag, respectively. ξ is defined in Eq. (16).

decreases rapidly ($\propto y^{\gamma_{\mathrm{ext,P}}(y)}$) when the force exceeds the critical value.

V. COMPARISON WITH EXPERIMENTS

We now compare our model with the existing experimental works [3,5]. In Ref. [5], Harada *et al.* studied the transcription rates of RNAPs under the rotary torque. They fixed RNAPs on a glass surface and measured the rotation rates of DNA by observing a bead attached to the downstream end of each DNA fragment. They found the saturation of rotation rates for large [NTP], at the value significantly smaller than that of freely transcribing RNAPs.

This reduction of the maximal rate can be naturally understood as a result of the increased potential barrier of the translocation step due to the viscous drag to the DNA rotation. Therefore, the energy barrier of the translocation step depends on the external load by the rotary torque with a positive coupling constant ($\gamma_{\mathrm{ext,T}}>0$). Since the rotary torque τ by the viscous drag is expressed as $\zeta\theta_0\nu$ with a viscous coefficient ζ and the winding angle of DNA per base pair $\theta_0=2\pi/10.4$ rad/bp, the maximal rate is obtained by solving

$$\nu = \nu_0(g) y^{\gamma_{\tau,T}(g)} \tag{13}$$

$$= \nu_0(g)\exp\left(-\frac{\gamma_{\tau,T}(g)\zeta\theta_0^2\nu}{k_BT}\right) \tag{14}$$

with respect to ν. Here, ν_0 is the maximal rate in the case of no load. The above equation is solved with the so called Lambert function $W(\xi)$,

$$\nu = \nu_0(g)\frac{W(\xi)}{\xi}. \tag{15}$$

Here, ξ is defined by

$$\xi = \gamma_{\tau,\mathrm{T}}(g)\theta_0^2\zeta\nu_0(g)/k_BT \tag{16}$$

and can be considered as the dimensionless version of the viscous coefficient ζ. Figure 2 shows the reduction of the rate ν with increasing ξ. The normalized rate ν/ν_0 decreases like $\sim\ln(\xi)/\xi$ for a large dimensionless viscous coefficient $\xi\gg1$.

Unfortunately, there are experimental uncertainties in the estimation of viscous coefficient ζ due to the hydrodynamic interactions of beads with the glass surface [5]. These uncertainties may be avoided by pulling the bead with sufficient strength to keep it away from the glass surface instead of the very weak force ($\sim$0.1 pN) applied in Ref. [5]. However, this introduces another external load f to the transcription elongation.

In Refs. [3,6], Wang *et al.* measured the pulling force dependence of the transcription rate $\nu=\nu(f)$ in the experimental system similar to Ref. [5]. They observed that the f-ν curves were similar to the Fermi distribution function, that is, the rate ν stays constant until the pulling force f reaches a critical force f_c and rapidly drops when $f>f_c$. They found that the measured critical forces f_c were more than 10 pN. In contrast to the rotary torque, these results imply that the potential barrier of the translocation step is independent of the pulling force f and that the pulling force f is only coupled with the potential barrier ΔU_{P} of the polymerization process.

Since the transcription of bead-attached DNA fragments necessarily introduces the rotary torque, one needs to consider both the rotary torque and the pulling force simultaneously. We assume that these two external loads independently contribute to the system, and express the effect of the loads on the potential barriers as the sum of each contribution.

$$\Delta U_{\mathrm{ext,P}} = \gamma_{f,\mathrm{P}}W_f + \gamma_{\tau,\mathrm{P}}W_\tau,$$

$$\Delta U_{\mathrm{ext,T}} = \gamma_{f,\mathrm{T}}W_f + \gamma_{\tau,\mathrm{T}}W_\tau,$$

where the works to the external forces W_τ and W_f are given by $W_\tau=\tau\theta_0$ and $\mathcal{W}_f=fa$, with the distance between neighboring base pairs $a=0.34$ nm. Since the potential barrier ΔU_{T} of the translocation step is independent of the pulling force f, the coefficient $\gamma_{f,\mathrm{T}}$ is zero.

The experiments of Ref. [3] were conducted under two conditions, namely, [NTP]=1000 μM, [PPi]=1 μm and [NTP]=1000 μM, [PPi]=1000 μM. In the first case, the transcription rate ν_0 of freely transcribing RNAPs was 30 bp/sec and the maximal rate ν of RNAPs subject to the rotary torque was 16 bp/sec, while $\nu_0=15$ bp/sec and $\nu=7$ bp/sec in the second case [3,7].

Since a few piconewton of pulling force is sufficient to keep the DNA fragments straight and to keep the beads away from any obstruction such as the glass plate, the viscous coefficient ζ equals the viscous coefficient of the bead, given by the well-known formula [8]

$$\zeta = \pi\eta D^3, \tag{17}$$

where $\eta=10^{-9}$ pN nm^{-2} sec is the viscosity of water and D is the diameter of beads and equals 500 nm [3].

Then, the coupling constant $\gamma_{\tau,\mathrm{T}}$ is estimated by the equation

$$\gamma_{\tau,\mathrm{T}} = \frac{k_B T}{\theta_0^2 \zeta \nu} \ln\left(\frac{\nu_0}{\nu}\right). \tag{18}$$

It gives the coupling coefficients $\gamma_{\tau,\mathrm{T}}=1.1$ and $\gamma_{\tau,\mathrm{T}}=3.1$ in cases [NTP]/[PPi]=1000 and [NTP]/[PPi]=1, which indicates that the rotary toque couples with the system strongly at small free energy $\Delta\mu$.

With these couplings, we estimate the viscous coefficient ζ in the experiments of Ref. [5], assuming that the RNAPs of Refs. [3,5] have the same activities. ζ is calculated by the formula

$$\zeta = \frac{k_B T}{\gamma_{\tau,\mathrm{T}} \theta_0^2 \nu} \ln\left(\frac{\nu_0}{\nu}\right)$$

with the rates $\nu_0=22$ bp/sec and $\nu=2.1$ bp/sec [5]. The viscous coefficients $\zeta=11.2$ pN nm sec and $\zeta=4.0$ pN nm sec are obtained in cases [NTP]/[PPi]=1000 and [NTP]/[PPi]=1, respectively. Since the viscous coefficient of the bead of Ref. [5] calculated by Eq. (17) is 1.9 pN nm sec, our model is consistent with Ref. [5] provided that Harada's experiments are conducted around [NTP]/[PPi]$\sim$1 and the increase of viscous coefficient ζ (130–300 %) due to the hydrodynamic interaction of beads with the glass plate is taken into account [5].

VI. SUMMARY

In summary, we investigated the effect of rotary torque on the transcription rates. We showed that the rotary torque and pulling force are differently coupled with the system and that the maximal transcription rates at [NTP]$\to\infty$ with fixed [NTP]/[PPi] are significantly reduced under the rotational load. These results suggest that the cancer cells whose topoisomerase activities are inhibited by anticancer drugs terminate the transcription rapidly due to the rotational friction, although ordinary explanations for the deaths of these cells are centered on the DNA replication phases. Our results may also be useful in studying the detailed molecular mechanism of the transcription elongation.

It is obvious that the available experimental results are not sufficient to verify our model. Since our model predicts that the coupling coefficient $\gamma_{\tau,\mathrm{T}}$ of the toque to the activation energy in (18) is independent of the magnitude of viscosity for fixed [NTP]/[PPi], we suggest an experiment to measure the maximal rates ν for different bead sizes under the same NTP and PPi concentrations. As we have shown, the pulling forces do not affect the maximal rates unless they approach the critical force $f_c>10$ pN; therefore, a few piconewton of pulling force may be applied to simplify the estimation of viscous coefficients.

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