Model of gene transcription including the return of a RNA polymerase to the beginning of a transcriptional cycle

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(Received 30 May 2009; revised manuscript received 10 October 2009; published 30 November 2009)

The gene transcription occurs via the RNA polymerase (RNAP) recruitment on the DNA promoter sequence, formation of a locally open DNA chain, promoter escape, steps of the RNA synthesis, and RNA and RNAP release after reading the final DNA base. Just after the end of the RNA synthesis, RNAP surrounds the closed DNA chain and may diffuse along DNA, desorb, or reach the promoter and start the RNA-synthesis cycle again. We present a generic kinetic model taking the latter steps into account and show analytically and by Monte Carlo simulations that it predicts transcriptional bursts even in the absence of explicit regulation of the transcription by master proteins.

DOI: 10.1103/PhysRevE.80.051925 PACS number(s): 87.16.A−, 05.10.−a

I. INTRODUCTION

The expression of the information encoded in genes occurs via a templated polymerization called transcription, in which the genes are used as templates to guide the synthesis of shorter molecules of RNA. Later on, many of RNAs, or, more specifically, messenger RNAs (mRNAs) serve to direct the synthesis of proteins by ribosomes. The whole process of gene expression can be regulated at all the steps. Specifically, the gene transcription, performed by RNAP during its association with DNA, is often controlled by the master regulatory proteins. Such proteins associate with DNA and either facilitate or suppress the RNA synthesis.

The paragraph above outlines the so-called *central dogma of molecular biology* [1]. Detailed description of all the species and processes mentioned there can be found in the corresponding textbooks (see, e.g., [2]). The original experimental studies scrutinizing and/or extending this dogma are countless. Among the most important novel results obtained in this field during the past decade, one can mention, e.g., the discovery of a large class of noncoding RNAs (ncRNAs) [3]. The functions of these RNAs are based on their abilities to bind to and modulate the activity of mRNAs and/or proteins.

Kinetic models of various aspects of gene expression are abundant. The most numerous models deal with the regulation of the mRNA synthesis by the master proteins and the mRNA-protein interplay. In the corresponding equations, the rate of the gene transcription is represented as a product of the transcription rate constant and a factor depending on protein concentration; i.e., the function of RNAP is not described in detail. During the past two decades, such models were widely used to explain stochastic bursts, bistability [4], and oscillations [5] in simple genetic networks and also complex genetic networks [6] (for the models treating ncRNAs, see [7] and references therein). The models of the elementary steps of gene expression, e.g., of the gene transcription [8,9] or mRNA translation to proteins [10], are less abundant, and many details of these steps are still open for debate.

Our present work is focused on the kinetics of gene transcription. The available models [8,9] (Sec. II) of this process imply that the transcription rate is determined by the first steps of transcription and do not scrutinize what happens in the end of the transcriptional cycle. In our model, we analyze the whole transcription cycle including the possibility of the return of RNAP to the beginning of a cycle. This problem is treated (Sec. III) by using the mean-field kinetic equations allowing us to understand the conditions of realization of the likely transcription scenarios including those exhibiting transcriptional bursts. To show bursts explicitly, we use Monte Carlo simulations (Sec. IV). Our key finding articulated in the conclusion (Sec. V) is that the transcriptional bursts are possible even in the absence of regulation of the transcription by the master proteins.

II. CONVENTIONAL SCHEME OF GENE TRANSCRIPTION

Basically, the gene transcription has long been established to occur via five phases including (i) the RNAP recruitment on the DNA promoter sequence, (ii) RNAP and DNA isomerization resulting in the formation of a locally open DNA chain (in other words, this is isomerization from a closed to an open complex), (iii) promoter escape, (iv) steps of the RNA synthesis by RNAP (elongation process), and (v) RNA and RNAP release after reading the final base of DNA [11,12]. With proper specification, this scheme is applicable both to prokaryotes and eukaryotes [12]. For example, bacteria contain only one form of RNAP including a core enzyme consisting of five subunits associated with a σ factor which is used to recognize promoter DNA sequences (the promoter escape is typically accompanied by loss of this factor). In contrast, eukaryotic cells contain three nuclear RNAPs, with RNAP II (Pol II) responsible for transcribing all mRNAs and numerous ncRNAs. Pol II, a 12-subunit enzyme, does not recognize promoter DNA by itself, but rather as part of the basal Pol II machinery including general transcription factors (proteins). Like σ factors, these general transcription factors usually dissociate from Pol II during the transition between initiation and elongation. Plants have dis-

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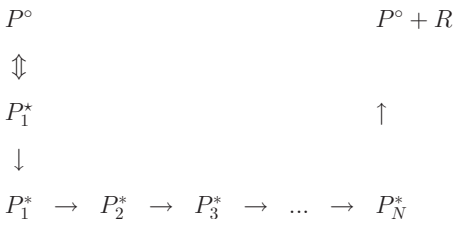

FIG. 1. Conventional scheme showing the RNAP pathway during transcription of a single gene. P° represents an unbound RNAP. $P_1^\star$ is RNAP associated with the DNA promoter site in the case when the DNA chain is closed. P_1^* corresponds to the RNAP-promoter state with a locally open DNA chain. $P_2^*, \ldots, P_N^*$ represent the RNAP states during the RNA (R) synthesis (the DNA chain is locally open).

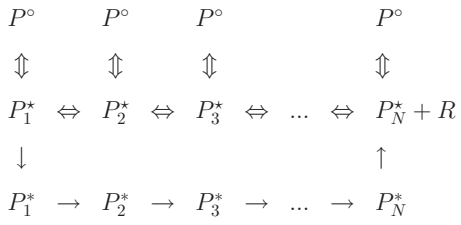

FIG. 2. Scheme of transcription of a single gene including the RNAP diffusion along DNA. $P_2^\star, \ldots, P_N^\star$ represent the states when RNAP is associated with the closed DNA chain (the other designations are as in Fig. 1). Note that the R formation and release occurs only via the step $P_N^* \rightarrow P_N^\star + R$.

tinct RNAP complexes, Pol IV and Pol V [13].

Schematically, the transcription mechanism described above is customarily [8] represented as shown in Fig. 1. Note that the initial RNAP association with DNA is reversible, $P^\circ \Leftrightarrow P_1^\star$ ($P_1^\star$ surrounds the closed promoter), while the open-complex formation, $P_1^\star \rightarrow P_1^*$, and the following steps of the RNA formation are irreversible, because these steps operate much like motor vehicles (for the corresponding models, see Ref. [9]). In reality, as already noted, every step on the pathway to gene expression and especially the transcription initiation can be regulated. In the conventional regulation schemes, activator or repressor proteins bind to specific DNA sequences near or overlapping with the RNAP binding sites [14]. Unconventional regulators found more recently bind directly to RNAP without binding to DNA [15].

In our treatment, we focus on the transcription steps and, to make equations compact, do not describe explicitly the regulation of these steps. Following this line, we also consider that the RNAP association step, $P^\circ \rightarrow P_1^\star$, is relatively slow so that the saturation effects are negligible. In this case, according to the conventional scheme [8] (Fig. 1), the probability that the gene is in the $P_1^\star$ state is described as

$$dp_1^\star/dt = k_a c - k_d p_1^\star - k_0 p_1^\star, \tag{1}$$

where c is the RNAP concentration, k_a and k_d are the association and dissociation rate constants, and k_0 is the rate constant of the transition from a closed to open complex (here and below we use a capital P for the RNAP states and a small p for the corresponding probabilities). Under steady-state conditions, one has

$$p_1^\star = \frac{k_a c}{k_d + k_0}, \tag{2}$$

and the transcription rate, W, can be identified with the rate of the first irreversible step, i.e.,

$$W = k_0 p_1^\star = \frac{k_0 k_a c}{k_d + k_0}. \tag{3}$$

To articulate the physics behind expression (3), we note that in the case under consideration the formation of each RNA is an independent process. For this reason, the transcription rate can be represented as $W = 1/\tau$, where τ is the average time between independent transcription acts. The latter time is given by the ratio of the average time between association acts, $1/(k_a c)$, and the probability of transcription after association, $k_0/(k_d + k_0)$, i.e., $\tau = (k_d + k_0)/(k_0 k_a c)$. With this expression for τ, we obtain expression (3) for W.

III. RETURN OF RNAP TO THE BEGINNING OF A CYCLE

Just after the end of the RNA synthesis, RNAP surrounds the closed DNA chain and then, like other proteins, may diffuse along DNA. During diffusion, RNAP may desorb from DNA (we use "desorb" and "dissociate" interchangeably) or alternatively reach the promoter and start the RNA-synthesis cycle again (Fig. 2). In the current literature, one can find many articles on protein diffusion along DNA [16]. Basically, RNAP is a protein (or, more specifically, enzyme) and can diffuse along the closed DNA chain [17]. In the kinetic models of gene transcription [8,9], this process is, however, ignored. Using the scheme shown in Fig. 2, one can write out a general set of kinetic equations describing transcription of a single gene with RNAP diffusion along the closed DNA chain. This scheme implies that RNAP diffuses along a gene but does not diffuse to adjacent genes, e.g., due to spatial constraints formed by master proteins. In general, the latter diffusion seems to be likely as well. Our present treatment is focused on the role of the former diffusion.

With increasing N, the number of equations and model parameters corresponding to the scheme in Fig. 2 rapidly increases, the treatment becomes cumbersome, and the results are far from generic. To keep the treatment generic, we analyze the minimal model with $N=2$ (Fig. 3). In this case, the bound RNAP can be in four states, $P_1^\star$, P_1^*, P_2^*, and $P_2^\star$, and if the saturation is negligible the corresponding probabilities are described as

$$dp_1^\star/dt = k_a c - k_d p_1^\star - k_0 p_1^\star - \kappa p_1^\star + \kappa p_2^\star, \tag{4}$$

$$dp_1^*/dt = k_0 p_1^\star - k_1 p_1^*, \tag{5}$$

$$dp_2^*/dt = k_1 p_1^* - k_2 p_2^*, \tag{6}$$

$$dp_2^\star/dt = k_a c - k_d p_2^\star + k_2 p_2^* + \kappa p_1^\star - \kappa p_2^\star, \tag{7}$$

where k_1 and k_2 are the rate constants of the transitions $P_1^* \rightarrow P_2^*$ and $P_2^* \rightarrow P_1^\star$, and κ is the rate constant of the diffusion jumps between the states $P_1^\star$ and $P_2^\star$.

$$\begin{array}{ccc} P^{\circ} & & P^{\circ} \\ \Updownarrow & & \Updownarrow \\ P_1^{\star} & \Leftrightarrow & P_2^{\star} + R \\ \downarrow & & \uparrow \\ P_1^{*} & \rightarrow & P_2^{*} \end{array}$$

FIG. 3. Minimal version of the scheme shown in Fig. 2.

The absence of saturation implies that $p_1^{\star}+p_1^{*}+p_2^{\star}+p_2^{*} \ll 1$. We analyze this case in order to keep our equations compact. All the equations corresponding to this limit can easily be generalized to the case with saturation. In particular, the most important expressions for the transcription rate are presented below in both cases [see Eqs. (12) and (13)].

In general, the rate constants of the transitions $P_1^{\star} \rightarrow P_2^{\star}$ and $P_2^{\star} \rightarrow P_1^{\star}$ are different, and the association and dissociation rate constants for the states $P_1^{\star}$ and $P_1^{\star}$ are different as well. We keep these rate constants equal in order to reduce the number of model parameters. In addition, we note that in order to open the DNA chain after the transition $P_2^{*} \rightarrow P_1^{\star}$, the core DNA enzyme should associate with a factor (e.g., σ factor) which helps to recognize promoter DNA sequences. In our analysis, this process is assumed to be rapid and not described explicitly.

Under steady-state conditions, Eqs. (4)–(7) yield

$$p_1^{\star} = \frac{k_a c(k_d + 2\kappa)}{k_d(k_d + k_0 + 2\kappa)}, \tag{8}$$

$$p_2^{\star} = \frac{k_a c(k_d + 2k_0 + 2\kappa)}{k_d(k_d + k_0 + 2\kappa)}, \tag{9}$$

$$p_1^{*} = \frac{k_0 k_a c(k_d + 2\kappa)}{k_1 k_d(k_d + k_0 + 2\kappa)}, \tag{10}$$

$$p_2^{*} = \frac{k_0 k_a c(k_d + 2\kappa)}{k_2 k_d(k_d + k_0 + 2\kappa)}, \tag{11}$$

$$W = k_0 p_1^{\star} = \frac{k_0 k_a c(k_d + 2\kappa)}{k_d(k_d + k_0 + 2\kappa)}. \tag{12}$$

Equations (4)–(12) have been obtained assuming the saturation to be negligible. With saturation, one can easily prove that the transcription rate is expressed via probabilities (8)–(11) as

$$W = \frac{k_0 p_1^{\star}}{1 + p_1^{\star} + p_2^{\star} + p_1^{*} + p_2^{*}}. \tag{13}$$

Substituting probabilities (8)–(12) into Eq. (13), one can express W explicitly via c and the reaction rate constants. The corresponding expression is, however, cumbersome and we do not present it here.

Equation (12) indicates that, depending on the rate of the RNAP jumps between the states $P_1^{\star}$ and $P_2^{\star}$, there are two qualitatively different regimes of the gene transcription. If the jumps are slow ($2\kappa \ll k_d$), the role of the jumps is negligible, and one can drop κ in Eq. (12). In this limit, as expected, Eq. (12) is reduced to Eq. (3). Physically, this means that after association with DNA, RNAP either desorbs or performs one transcription cycle and then desorbs. The physics behind expression (3) has already been discussed in Sec. II.

If the diffusion jumps are rapid ($2\kappa \gg k_d + k_0$), Eq. (12) is reduced to

$$W = k_0 k_a c / k_d. \tag{14}$$

In this case, the transcription rate is higher than that given by Eq. (3). This means that after association with DNA, RNAP either desorbs or performs one or a few transcription cycles and then desorbs. The outcome with one cycle is likely if $k_d \gg k_0$. In this limit, Eqs. (3) and (14) are equivalent. The regime with a few sequential transcription cycles, performed by RNAP between the association and dissociation events, occurs if $k_d \ll k_0$. In the latter limit, transcription rate (14) is much higher than that predicted by Eq. (3).

Figuratively, relatively rare active transcription periods with a few transcription cycles occurring during each period represent transcriptional bursts. Such bursts were observed in experiments [18]. The numerous corresponding models are based on the assumptions that this phenomenon is related to regulation of the transcription by master proteins (without [19] or with [20] feedbacks between the mRNA and protein formation; see also references therein and reviews [4]). Our analysis indicates that bursts can be observed even if there is no driving force related to master proteins.

To clarify the physics behind the bursts predicted by expression (14), we note that each burst is an independent process (the distribution of times between bursts is Poissonian). For this reason, the mean transcription rate can be represented as

$$W = \langle n \rangle / \tau, \tag{15}$$

where $\langle n \rangle$ is the average number of RNA formed per burst, and τ is the average time between bursts. To scrutinize Eq. (15), we consider that the diffusion jumps and transcription are rapid, i.e., $\min(\kappa, k_1, k_2) \gg k_d + k_0$ [note that expression (14) has been derived in this limit]. In this case, after association with DNA, RNAP is nearly uniformly distributed in states $P_2^{\star}, \ldots, P_N^{\star}$ (Fig. 2), and the analysis is fairly straightforward for arbitrary N. In particular, τ is given by the ratio of the average time between association acts, $1/(Nk_a c)$ (N is here because there are N sites for association), and the probability of at least one transcription after association, $k_0/(k_0 + Nk_d)$ (N is here because the start of the transcription is possible only on one site while the RNAP desorption occurs on N sites), i.e.,

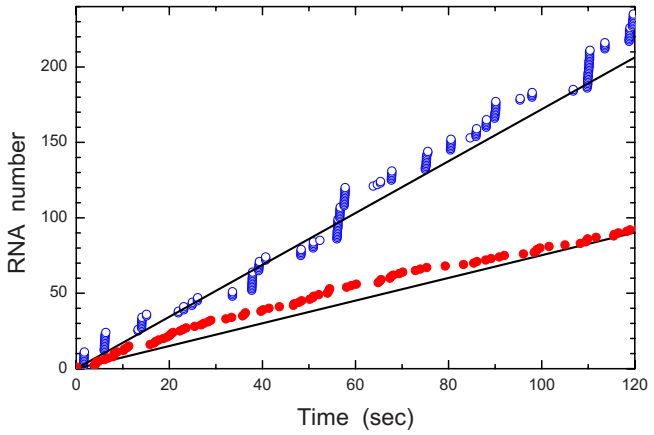

FIG. 4. (Color online) Number of RNA produced during gene transcription. The Monte Carlo kinetics without and with RNAP diffusion along the closed DNA chain are shown by filled and open circles, respectively, for $\kappa=0$ and $k_a c=1\ \mathrm{s}^{-1}$, and $\kappa=500\ \mathrm{s}^{-1}$ and $k_a c=0.2\ \mathrm{s}^{-1}$ (for the other parameters, see the text). Each data point corresponds to the formation of a new RNA. The solid lines show the mean-field kinetics calculated by using expression (13) for the transcription rate.

$$\tau=\frac{k_0+Nk_d}{Nk_0k_ac}. \tag{16}$$

The probability that RNAP produces n RNA after association is given by

$$\mathcal{P}_n=\frac{k_0^n}{(k_0+Nk_d)^n}\frac{Nk_d}{k_0+Nk_d}, \tag{17}$$

where $k_0^n/(k_0+Nk_d)^n$ is the probability of N sequential transcriptions after association, and $Nk_d/(k_0+Nk_d)$ is the probability of desorption after an arbitrary successful transcription act. Using expression (17), we have

$$\langle n\rangle=\frac{\sum_{n=1}^{\infty}n\mathcal{P}_n}{\sum_{n=1}^{\infty}\mathcal{P}_n}=\frac{k_0+Nk_d}{Nk_d}. \tag{18}$$

Substituting Eqs. (16) and (18) into expression (15), we obtain expression (14).

In addition, it is appropriate to note that for rapid transcription and RNAP diffusion jumps [this situation is described by Eqs. (14)–(18) and illustrated in Sec. IV below] RNAP rapidly returns to states $P_1^\star$ and $P_2^\star$ after each start of transcription. In this limit, the average duration of a burst is obviously determined by the rate of desorption, i.e., equals $1/k_d$.

IV. EXAMPLES OF STOCHASTIC KINETICS

To show explicitly the bursts predicted by our model, we should validate the choice of the parameter values. In general, all the steps occurring with the participation of RNAP include its reconfigurations, which are expected to run on the time scale of protein folding. This time scale is very wide (from 10^{-6} to 10^3 s [21]). In fact, the gene transcription is considered to be fast if its rate is $1-10\ \mathrm{s}^{-1}$ and accordingly the time scale of the rate-limiting step can hardly be shorter than 0.1–1 s (often, it is much longer especially in eukaryotic cells where many genes are silent). The other steps may occur much faster. The rate-limiting step has widely been assumed to be recruitment of RNAP [12,22]. However, recent studies indicate that, for many promoters in both prokaryotes

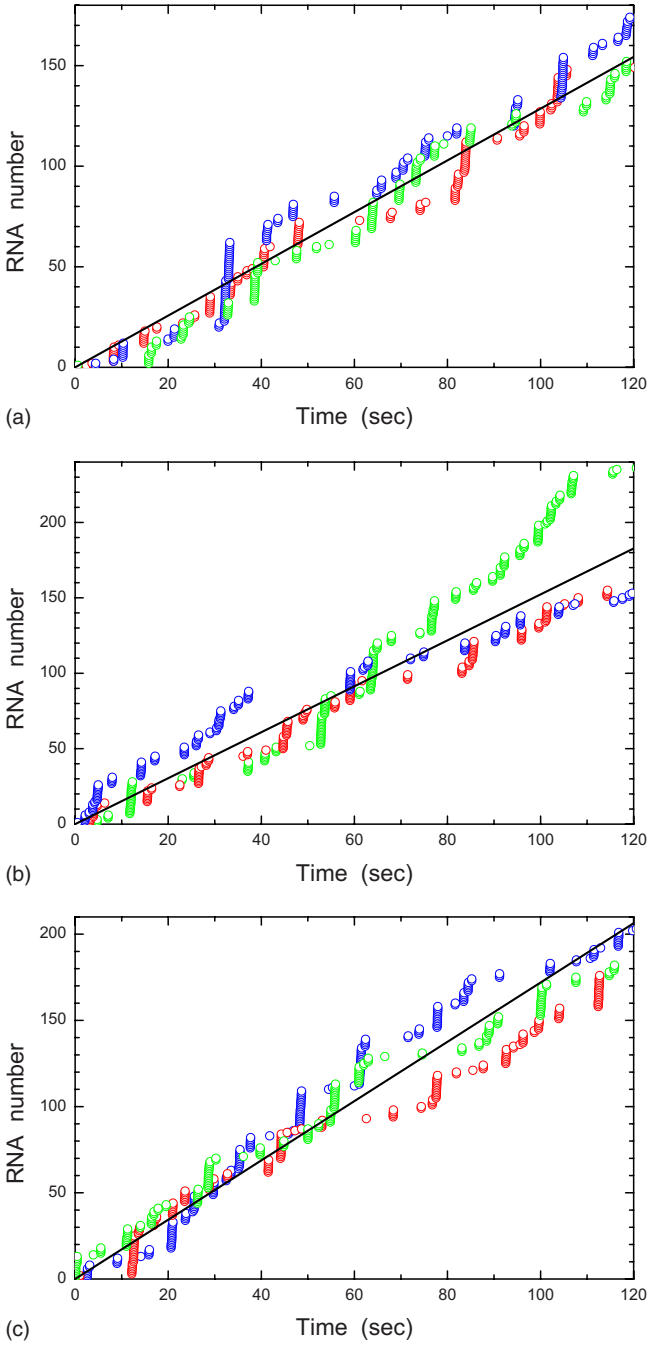

FIG. 5. (Color online) Monte Carlo kinetics with RNAP diffusion along the closed DNA chain with $k_a c=0.2\ \mathrm{s}^{-1}$ and $\kappa=100$ (a), 200 (b) and 500 s^{-1} (c) (for the other parameters, see the text). Each panel exhibits three runs. The solid lines show the mean-field kinetics calculated by using expression (13).

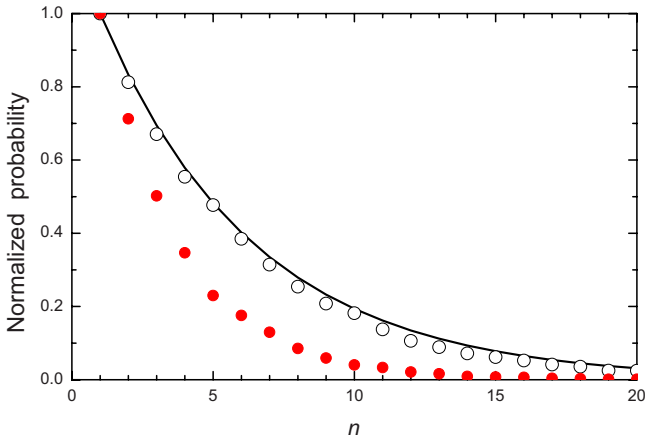

FIG. 6. (Color online) Normalized probability, $\mathcal{P}_n/\mathcal{P}_1$, that a burst contains n mRNA. Open and filled circles correspond to $\kappa=500$ and 50 s^{-1}, respectively (for the other parameters, see the text). The solid line is constructed by using Eq. (17).

and eukaryotes, the rate-limiting step in transcription initiation may occur after recruitment of RNAP [12,23]. Thus, various situations are possible.

Our Monte Carlo simulations of the gene transcription kinetics, taking into account saturation, were executed by employing the standard Gillespie algorithm [24]. Our key findings are illustrated in Fig. 4 showing the number of RNA produced during transcription. First, we use $k_a c=1$ s^{-1}, $k_d=10$ s^{-1}, $k_0=100$ s^{-1}, and $k_1=k_2=200$ s^{-1}, and neglect RNAP diffusion along the closed DNA chain, i.e., put $\kappa=0$. The corresponding kinetics is seen to not exhibit bursts. Then, we decrease $k_a c$ down to 0.2 s^{-1} and use $\kappa=500$ s^{-1} (the other parameters are the same). With decreasing $k_a c$, the transcription rate might be lower, but this effect is fully compensated by additional transcription cycles related to RNAP diffusion along the closed DNA chain, and one can observe transcriptional bursts (Fig. 4). According to the mean-field approximation, the number of produced RNA is equal to Wt, and the corresponding results obtained by using expression (13) are shown in Fig. 4 as well [for the parameters under consideration, the slope predicted by Eq. (12) is higher but only slightly]. As expected, the mean-field kinetics accurately describes the average transcription rate but does not reproduce bursts.

To illustrate the role of fluctuations in the kinetics in more detail, we show Fig. 5 for $k_a c=0.2$ s^{-1} and $\kappa=100$, 200, and 500 s^{-1} (the other parameters are as above). The normalized probability, $\mathcal{P}_n/\mathcal{P}_1$, that a burst contains n mRNA is presented in Fig. 6 for $k_a c=0.2$ s^{-1} and $\kappa=500$ s^{-1} and 50 s^{-1} (the other parameters are as above). The circles exhibit the Monte Carlo data, while the solid line is constructed by using the mean-field approximation [Eq. (17)]. As expected, the Monte Carlo data (open circles) obtained for rapid RNAP diffusion jumps ($\kappa=500$ s^{-1}) are close to the solid line.

V. CONCLUSION

We have presented a generic kinetic model of gene transcription, taking into account that just after the end of the RNA synthesis, RNAP may diffuse along DNA, desorb, or reach the promoter and start the RNA-synthesis cycle again. This model is useful from the viewpoint of describing the likely mechanisms of the DNA function. In this context, it can be considered as an extension of the earlier models described in Ref. [8]. On the other hand, the model is of interest from the point of view of simulations of stochastic kinetics, because it predicts transcriptional bursts even in the absence of explicit regulation of the transcription by master proteins. In the latter context, we may repeat that the available models [19,20] of such bursts imply regulation of the transcription by proteins.

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