

Transcriptional bursts: a unified model of machines and mechanisms

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Transcription is the process whereby RNA molecules are polymerized by molecular machines, called RNA polymerase (RNAP), using the corresponding DNA as the template. Recent *in-vivo* experiments with single cells have established that transcription takes place in “bursts” or “pulses”. In this letter we present a model that captures not only the mechano-chemistry of individual RNAPs and their steric interactions but also the switching of the gene between the ON and OFF states. This model accounts for the statistical properties of the transcriptional bursts. It also shows how the quantitative features of the distributions of these bursts can be tuned by controlling the appropriate steps of operation of the RNAP machines.

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Genetic messages are encoded chemically in DNA. During gene expression this message is first *transcribed* into mRNA and then, from it, *translated* into proteins by well coordinated operation of intracellular machineries [1]. The two machines, which play key roles in transcription and translation are the RNA polymerase (RNAP) [2] and the ribosome [3, 4], respectively. Each of these machines is like a mobile workshop that synthesizes a bio-polymer according to a template which also serves as the track for the movement of the workshop. Because of the probabilistic nature of the steps of gene expression, the number of mRNA and protein molecules corresponding to a single gene fluctuate randomly (see ref.[5, 6, 7, 8, 9] for reviews). It has been observed experimentally [10, 11, 12, 13] that relatively long periods T_{off} of transcriptional inactivity are interspersed with brief periods T_{on} of transcriptional “bursts”. Several statistical properties of these random “bursts” (or, “pulses”) have been used to characterize the temporal pattern in transcriptional events [10, 11, 12].

Qualitatively similar bursts of transcriptional activities have been observed in both prokaryotes and eukaryotes. Some possible mechanisms of transcriptional burst have been suggested. Transcription, i.e., the process of synthesis of RNA from the corresponding DNA template, can be broadly divided into three stages, namely, *initiation*, *elongation* and *termination*. When the gene is switched “ON”, initiation of transcription by RNAPs can take place till the gene switches back to the “OFF” state [14]. Unbinding and binding of transcription repressor molecules can give rise to such switching “ON” and “OFF” of a bacterial gene. In eukaryotic cells, chromatin remodelling enzymes can act as activators of transcription. Even if the gene does not switch OFF, burst-like transcriptional activities are possible if several RNAPs queue up behind a stalled RNAP and then, suddenly, the stalled RNAP gets reactivated [15, 16]. The latter becomes very pronounced [17] when pausing is caused by backtracking of the RNAP [18].

To our knowledge, the switching of the gene between the active (ON) and inactive (OFF) states is a common feature of almost all the models of transcriptional noise [19, 20]. But, these models capture the en-

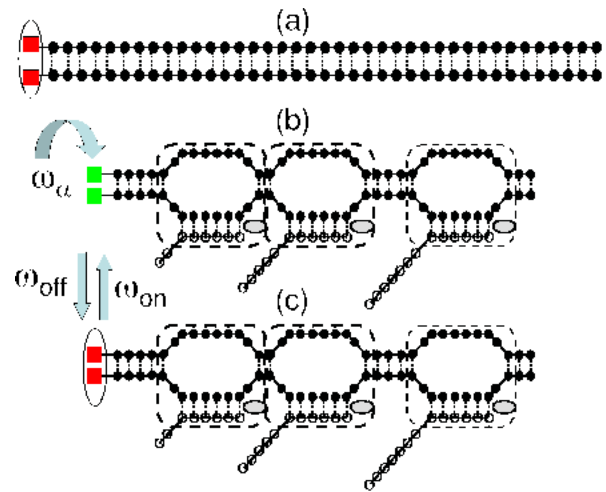


FIG. 1: (Color online) A pictorial depiction of the model. The three dashed squares represent three TECs. The solid lines connecting filled circles represent the single strands of DNA while the string of open circles denotes the elongating RNA molecule. The dashed lines connecting the circles denote the unbroken non-covalent bonds between the complementary subunits on the DNA and RNA strands. Each of the grey ovals represents the catalytic site on the corresponding RNAP. The green and red squares indicate the ON and OFF states of the gene. The rates of the transitions between the ON and the OFF states as well as the rate of transcription initiation in the ON state of the gene are also shown explicitly.

tire processes of RNA production by a single effective rate constant. In contrast, models developed to understand the operational mechanisms of RNAP motors [17, 21, 22, 23, 24, 25, 26, 27, 28] explicitly describe the different stages of transcription, namely, initiation, elongation and termination, but (except for ref.[28]) do not address the question of temporal fluctuations in transcription. The main aim of this letter is to combine the key features of these two types of models within a single unified theoretical framework.

More specifically, we extend our recent model of RNAP traffic [28] by allowing the gene to switch between the

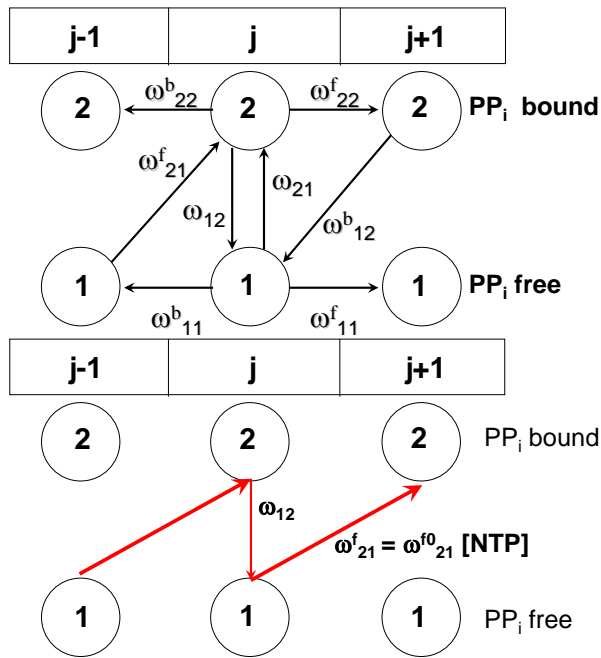


FIG. 2: (Color online) Allowed mechano-chemical transitions of individual RNAPs during the elongation stage in our model. The indices $j - 1, j, j + 1$ denote an arbitrary sequence of three nucleotides on the template DNA. The encircled symbols 1 and 2 denote the two possible chemical states; no pyrophosphate (PP_i) is bound to the RNAP in the state 1 whereas PP_i -bound state is labelled by the index 2. The directions of the arrows and the associated symbols indicate the possible transitions and the corresponding rate constants, respectively. Elongation of the nascent RNA transcript is accompanied by forward movement of the RNAP whereas backward movements of the RNAP correspond to depolymerization of the RNA. The full model, shown in (a), allows mechano-chemical transitions which branch off the dominant pathway of an individual RNAP shown in (b).

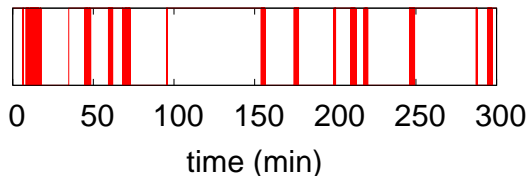


FIG. 3: (Color online) A typical time series of the transcriptional events in the model; each vertical bar corresponds to the completion of polymerization of a RNA molecule.

“ON” and “OFF” states. In other words, this extended model explicitly describes the following processes: (i) switching “ON” and “OFF” of the gene, (ii) initiation, elongation and termination of transcription, (iii) mechano-chemical cycles of the individual RNAP motors in the elongation stage, and (iv) congestion of traffic of RNAPs caused by their steric interaction. Consequently,

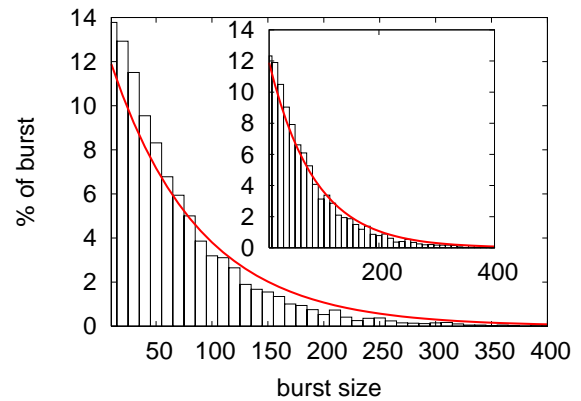


FIG. 4: (Color online) The distribution of the sizes of the transcriptional bursts in our model plotted using $\Delta t = 0.5$ min ($\Delta t = 2.5$ min in the inset). The continuous line (red) is obtained from the theoretically predicted form (6). The data points, plotted as bars, were obtained from computer simulations of the model.

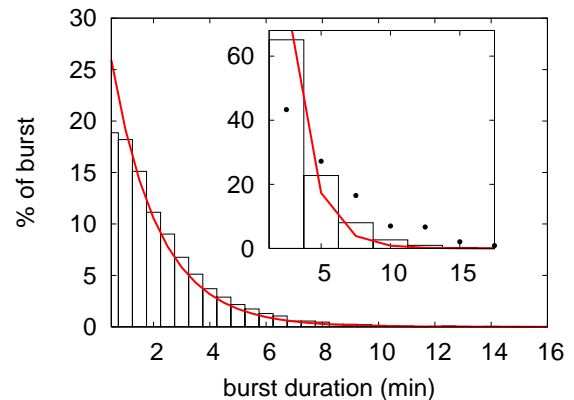


FIG. 5: (Color online) Distribution of the durations of transcriptional bursts in our model plotted using $\Delta t = 0.5$ min ($\Delta t = 2.5$ min in the inset). The continuous lines (red) are obtained from the theoretically predicted form (7). The data points, plotted as bars, were obtained from computer simulations of the model. The black dots in the inset represent the experimental data reported by Chubb et al. in ref.[11].

this model can predict the contributions of the processes (i)-(iv) on transcriptional noise; estimation of the contributions made by the processes (ii)-(iv) was beyond the scope of all the earlier models of transcriptional noise.

Carrying out computer simulations of this model we obtain the time series of the transcriptional events. We sort the transcriptional events of each time series obtained from our simulations into “bursts” by using well-defined criteria (which we describe below). We compare various statistical properties of these theoretically predicted transcriptional bursts with the corresponding experimental results. We then suggest an alternative statis-

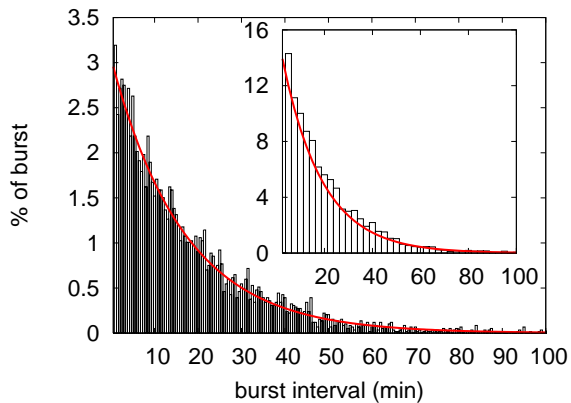


FIG. 6: (Color online) Distribution of the intervals between successive bursts of transcriptional activities in our model plotted using $\Delta t = 0.5$ min ($\Delta t = 2.5$ min in the inset). The continuous lines (red) are obtained from the theoretically predicted form (8). The data points, plotted as bars, were obtained from computer simulations of the model.

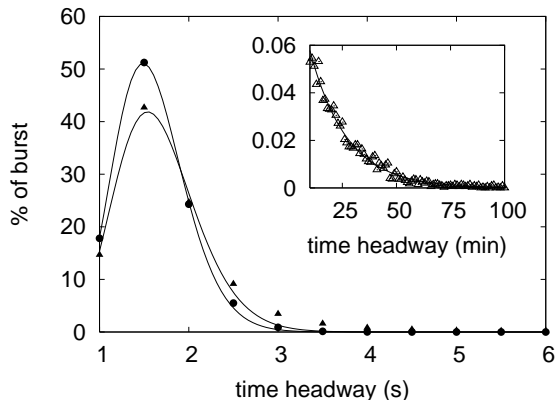


FIG. 7: Distribution of the time headways between the successive RNAPs in our model (triangles). The filled circles show the time headway distribution in the hypothetical scenario (which was assumed in ref.[28]) where the gene remains in the ON state throughout the period of computation. The inset shows the long tail of the time headway distribution which corresponds to the time gaps between the successive bursts.

tical analysis of the transcriptional noise in terms of some new distributions which are motivated by superficial similarities between RNAP traffic and vehicular traffic. We also derive an approximate analytical expression for this statistical analysis in a simplified special case and demonstrate its use by comparing with the corresponding data obtained from computer simulations.

Before presenting our quantitative model, we summarize a few essential steps in transcription. The RNAP locally unzips the two DNA strands creating a “bubble” whereby a single stranded DNA (ssDNA) template is exposed to it. Together with the DNA bubble and the grow-

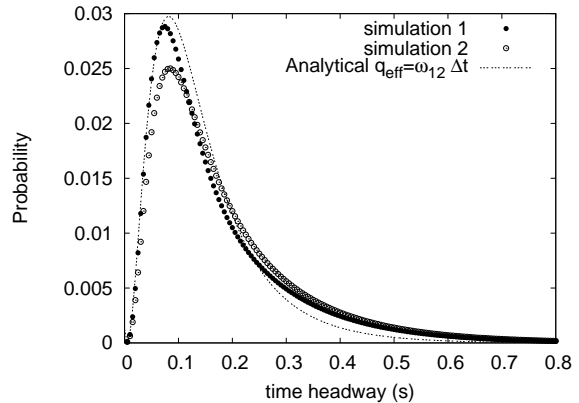


FIG. 8: Comparison between the approximate analytical expression (10) for the TH distribution (denoted by the line) and the corresponding simulation data (denoted by the discrete data points) in the special case where $r = 1$; periodic boundary conditions are imposed and the gene remains “ON” during the entire duration of observation. For the two sets of simulation data labelled as “simulation 1” and “simulation 2” the mechano-chemical transitions shown in figs.2(b) and 2(a), respectively, have been used.

ing RNA transcript, the RNAP forms a macromolecular complex called the “transcription elongation complex” (TEC). The size of a single TEC is such that each incorporates r successive nucleotides of the DNA template. During elongation, each mechano-chemical cycle of the RNAP consists of several steps. The major steps of this cycle involve the selection of the appropriate subunit for mRNA, as dictated by the DNA template and, then, its attachment to the growing mRNA transcript by a reaction that is catalyzed by the RNAP. Release of pyrophosphate (PP_i), one of the products of this reaction is the rate-limiting step in each cycle. Thus, in each cycle, an RNAP steps forward by one nucleotide. The elongation process ends when the TEC encounters the corresponding “termination sequence” and the nascent mRNA is released by the RNAP.

Our model of transcription is shown schematically in fig.1 where the essential components of each of the TECs are shown explicitly. The green and red squares at the start regions of the gene indicate the “ON” and ‘OFF” states of the gene, respectively. The rate constant (i.e., probability per unit time) of transition from the “OFF” state to the “ON” state is denoted by the symbol ω_{on} whereas that of the reverse transition is denoted by ω_{off} . Initiation and termination of transcription are captured by the same prescription which have been used in our earlier work reported in ref.[28]; the corresponding rate constants being ω_α and ω_β , respectively.

In our model, the mechano-chemical cycle of individual RNAPs in the elongation stage and the nature of their steric interactions are identical to those used in ref.[28]. For the sake of completeness, all the possible mechano-chemical transitions of an individual RNAP during the

elongation stage are shown in fig.2(a). Since pyrophosphate release is the rate limiting step, we assume that, at any given instant of time, a RNAP can exist in one of the two possible “chemical” states; no pyrophosphate (PP_i) is bound to the RNAP in the state 1 whereas the PP_i -bound state of the RNAP is labelled by the index 2. The rate of PP_i release is denoted by ω_{12} while the reverse reaction takes place at the rate ω_{21} . The rate constants ω_{21}^f , ω_{11}^f and ω_{22}^f correspond to polymerization of RNA whereas the rate constants ω_{12}^b , ω_{11}^b and ω_{22}^b correspond to depolymerization of the RNA.

For our numerical calculations, we have used the same set of rate constants which we used in ref.[28]; these are as follows:

$$\begin{aligned}
\omega_{21}^f &= \omega_{21}^{f0} \cdot [NTP], \text{ with } \omega_{21}^{f0} = 10^6 \text{ M}^{-1} \cdot \text{s}^{-1} \\
\omega_{11}^f &= \omega_{11}^{f0} \cdot [NMP], \text{ with } \omega_{11}^{f0} = 46.6 \text{ M}^{-1} \cdot \text{s}^{-1} \\
\omega_{22}^f &= \omega_{22}^{f0} \cdot [NMP], \text{ with } \omega_{22}^{f0} = 0.31 \text{ M}^{-1} \cdot \text{s}^{-1} \\
\omega_{21} &= \omega_{21}^0 \cdot [PP_i], \text{ with } \omega_{21}^0 = 10^6 \text{ M}^{-1} \cdot \text{s}^{-1} \\
\omega_{12} &= 31.4 \text{ s}^{-1} \\
\omega_{12}^b &= 0.21 \text{ s}^{-1} \\
\omega_{11}^b &= 9.4 \text{ s}^{-1} \\
\omega_{22}^b &= 0.063 \text{ s}^{-1}
\end{aligned} \tag{1}$$

where $[NTP]$, $[NMP]$ and $[PP_i]$ denote the concentrations of nucleoside triphosphate (NTP), nucleoside monophosphate (NMP) and pyrophosphate (PP_i), respectively. Moreover, for the figures in this letter, we have used $\omega_\alpha = 5.0\text{s}^{-1}$, $\omega_\beta = 50\text{s}^{-1}$, $\omega_{off} = 0.01\text{s}^{-1}$, $\omega_{on} = 0.001\text{s}^{-1}$, and the concentrations $[NTP] = 10^{-4}\text{M}$, $[PP_i] = 10^{-6}\text{M}$, $[NMP] = 10^{-6}\text{M}$.

Note that, in spite of all the possible transitions shown in fig.2(a), the dominant pathway is the one shown in fig.2(b), where ω_{21}^f is proportional to the concentration of the available NTP subunits. All the quantitative predictions of our theory would remain equally valid if RNAP remains immobilized while the template DNA passes through it in steps of one base pair, a scenario based on the concept of “transcriptional factory” *in-vivo* [29]. This alternative scenario would be mathematically related to the one used in this paper by just a coordinate transformation [30]- from the rest frame of the template DNA to that of the RNAP.

Mere visual examination of the time series of the transcriptional events (see Fig.3 for a typical one) establishes the occurrence of random bursts of transcriptional activities in our model [14]. In order to sort these events into separate bursts, let us use a resolution Δt . Members of the same “burst” are separated from the immediate preceding and succeeding transcriptional events by time gaps smaller than Δt while the time gap between any pair of successive bursts is at least Δt (or, longer). Our choice of $\Delta t = 2.5$ min. is motivated by the corresponding choice in typical laboratory experiments. We have

also analyzed the same data using $\Delta t = 0.5$ min to test whether the conclusions drawn from our sorting procedure are, indeed, robust.

The number of transcriptional events in a burst is a measure of its *size*. The probability of the occurrence of a burst of size n is given by

$$P(n) = P_{on} p_{tr}^n P_{off}, \tag{2}$$

where P_{on} and P_{off} are the probabilities of the gene switching ON and OFF, respectively, while p_{tr} is the probability that a transcriptional event is completed by a RNAP. We can recast equation (2) into the exponential form

$$P(n) = P_{on} P_{off} \exp(-n/b), \tag{3}$$

where $(1/b) = -\ln p_{tr}$. Obviously, b is the average size of a transcriptional burst; the higher is the magnitude of p_{tr} the larger is the average size of the bursts.

Our model goes beyond most of the earlier models of noise in transcription of a single gene because our model can predict the explicit dependence of P_{on} , P_{off} and p_{tr} on the rates of the steps of the mechano-chemical cycles of individual RNAPs as well as on their interactions. Suppose, ω_{eff} is the effective rate constant associated with the process of forward movement of the RNAP by one site (i.e., one nucleotide). Obviously, considering only the dominant pathway shown in fig.(2(b)) $\frac{1}{\omega_{eff}} = \frac{1}{\omega_{12}} + \frac{1}{\omega_{21}^f}$

and, hence, $\omega_{eff} = \frac{\omega_{12} \omega_{21}^f}{\omega_{12} + \omega_{21}^f}$. An RNAP can attach to DNA strand only after the preceding RNAP vacates the initial r sites on the lattice. The rate at which a RNAP moves by r sites is $k_{eff} = \frac{\omega_{eff}}{r}$. Since $k_{eff} \ll \omega_\alpha$, the rate limiting step in the process of transcription will be the initiation which will be determined essentially by k_{eff} . Hence, $P_{tr} \propto \exp\left(\frac{-1}{k_{eff} \langle T_{on} \rangle}\right)$ where $\langle T_{on} \rangle = \frac{1}{\omega_{off}}$. Thus,

$$P_{tr} \propto \exp\left(\frac{-\omega_{off}}{k_{eff}}\right) \tag{4}$$

Moreover,

$$P_{on} = \frac{\omega_{on}}{\omega_{on} + \omega_{off}} \text{ and } P_{off} = \frac{\omega_{off}}{\omega_{on} + \omega_{off}} \tag{5}$$

Finally, after normalization, the discrete distribution of the burst sizes is given by

$$P(n) = \left(1 - \exp\left(\frac{-\omega_{off}}{k_{eff}}\right)\right) \exp\left(\frac{-n \omega_{off}}{k_{eff}}\right). \tag{6}$$

A typical distribution of the sizes of the bursts, obtained from computer simulations of our model, is plotted in Fig.4 using two different values of Δt . These data are in excellent agreement with the theoretically predicted distribution (6); this exponential distribution is also consistent with the corresponding experimental observations [10, 11]. Moreover, the data plotted in the inset of Fig.4

also fit an exponential distribution thereby establishing that our conclusion is robust and independent of the actual magnitude of Δt as long it remains within a reasonable range.

The duration of a burst is measured by the time interval between the first and the last transcriptional events which are members of the same burst. It is straightforward to see that the normalized distribution $P(t_{dur})$ of the burst durations t_{dur} is given by

$$P(t_{dur}) = \omega_{on} \exp(-\omega_{on} t_{dur}) \quad (7)$$

The theoretically predicted exponential distribution (7) is in excellent quantitative agreement with the corresponding numerical data obtained by direct computer simulations (see Fig.5). The experimental data reported by Chubb et al.[11] are also plotted in the inset of Fig.5. The nature of the distribution (namely, the exponential form) established by our theory and simulation is consistent with that observed in the experiments. The quantitative difference between the results predicted by our model and those obtained from experiments arises from the fact that the rate constants for the system used in the experiments are not necessarily identical to those used in plotting the results of our theory and simulation.

The time interval between a two successive bursts is the time gap between the last event of the earlier burst and the first event of the later burst. The normalized distribution $P(t_{int})$ of the intervals t_{int} between successive bursts is given by

$$P(t_{int}) = \omega_{off} \exp(-\omega_{off} t_{int}) \quad (8)$$

The quantitative agreement between this theoretical prediction and the corresponding simulation data (see Fig. 6) is also consistent with the form of the distribution indicated by the experimental data reported by Chubb et al. [11]. However, because of the large scatters in the experimental data, no quantitative comparison between our theoretical predictions and experimental observations could be made.

Drawing an analogy to vehicular traffic [31], we define the *time headway* to be the time gap between the departures of the successive RNAPs from the termination site. Thus, according to this definition, the time-headway is the time gap between the completion of the synthesis of successive RNA molecules. A typical distribution of the time headways is plotted in fig.7. In the same figure we have also plotted the time headway distribution for a hypothetical scenario (which was considered in ref.[28]) where the gene always remains ON. The best fit to both these curves are gamma functions (with slightly different parameters). A comparison between these two curves shows that the switching ON and OFF of the genes leads to a weak broadening of the distribution; the longer tail caused by the gap between the successive bursts is shown separately in the inset of fig.7.

We have been able to obtain an analytical estimate of the TH distribution only in a special limiting case exploiting the formal analogy with the models of vehicular

traffic [31]. Approximating the mechano-chemical cycle of each RNAP during the elongation stage by the pathway shown in fig.2(b), we can represent each RNAP (or, more precisely, each TEC) by a rigid rod, of length r , which can hop from one nucleotide to the next on the template DNA with an *effective* hopping probability q per time step. Thus,

$$q \simeq \omega_{12} dt, \quad (9)$$

where dt is the duration of each discretized time step. In this limit our original model reduces to the totally asymmetric simple exclusion process (TASEP) for hard rods of length r [32], provided the gene always remains in the ON state. In the special case $r = 1$ the rods reduce to particles and the corresponding exact TH distribution for TASEP (with parallel updating) is given by [33, 34]

$$\begin{aligned} \mathcal{P}_\tau = & \left[\frac{qy}{\rho - y} \right] \{1 - (qy/\rho)\}^{t-1} \\ & + \left[\frac{qy}{(1-\rho) - y} \right] \{1 - (qy/(1-\rho))\}^{t-1} \\ & - \left[\frac{qy}{\rho - y} + \frac{qy}{(1-\rho) - y} \right] p^{t-1} - q^2(t-1)p^{t-2}, \end{aligned} \quad (10)$$

where

$$y = \frac{1}{2q} \left(1 - \sqrt{1 - 4q\rho(1-\rho)} \right). \quad (11)$$

and ρ is the number density of the particles.

In order to test the range of validity of the expression (10) in the context of RNAP traffic, we have carried out computer simulations of our model for $r = 1$ under periodic boundary conditions keeping the gene always ON. In the first set of simulations, we have used the simplified mechano-chemical cycle shown in fig.2(b) whereas in the second set we retained all the mechano-chemical transitions allowed in fig.2(a). The expression (10) is in excellent agreement with the simulation data for the unbranched mechano-chemical cycle shown in fig.2(b). Moreover, even when the branched pathways of fig.2(a) exist, the simulation data are in reasonably good agreement with (10).

In this letter we have reported a model that is ideally suited to study the effects of the steps of the mechano-chemical cycle of individual RNAPs and their steric interactions on the transcriptional bursts which are caused primarily by the switching of the gene between ‘‘ON’’ and ‘‘OFF’’ states. For the sake of simplicity, we have illustrated our approach with a minimal model of RNAP mechano-chemistry which assigns only two possible distinct chemical states to an RNAP at any given location. For a more (biologically) realistic description, this mechano-chemistry of the RNAPs can be easily replaced by a more appropriate one without changing the overall framework of our model.

Suppose T_{obs} is the total time interval of observation and data collection in each single-cell experiment on transcriptional noise. In ref.[28], our theoretical analysis was restricted to a temporal regime such that (I) $T_{obs} < T_{on}$, where T_{on} is the average duration for which the gene remains ON, and (II) $T_{obs} \ll T_{cell}$, where T_{cell} is the mean life time of the cell before its division into the two daughter cells. Under these restrictions, our model of transcription [28] did not exhibit transcriptional bursts. In this letter we have shown that the same model can account for transcriptional bursts when we relax the constraint (I). We show that the statistical properties of

noisy transcription in our model in the temporal regime $T_{on} \ll T_{obs} < T_{cell}$ are in excellent agreement with the corresponding experimental data. Moreover, drawing an analogy to vehicular traffic, we have reanalyzed the time series of the transcriptional events from a totally different perspective which does not require any sorting of the raw data into separate bursts.

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