A Biologically Motivated Asymmetric Exclusion Process: interplay of congestion in RNA polymerase traffic and slippage of nascent transcript *

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We develop a theoretical framework, based on exclusion process, that is motivated by a biological phenomenon called transcript slippage (TS). In this model a discrete lattice represents a DNA strands while each of the particles that hop on it unidirectionally, from site to site, represents a RNA polymerase (RNAP). While walking like a molecular motor along a DNA track in a step-by-step manner, a RNAP simultaneously synthesizes a RNA chain; in each forward step it elongates the nascent RNA molecule by one unit, using the DNA track also as the template. At some special "slippery" position on the DNA, which we represent as a defect on the lattice, a RNAP can lose its grip on the nascent RNA and the latter’s consequent slippage results in a final product that is either longer or shorter than the corresponding DNA template. We develop an exclusion model for RNAP traffic where the kinetics of the system at the defect site captures key features of TS events. We demonstrate the interplay of the crowding of RNAPs and TS. A RNAP has to wait at the defect site for longer period in a more congested RNAP traffic, thereby increasing the likelihood of its suffering a larger number of TS events. The qualitative trends of some of our results for a simple special case of our model are consistent with experimental observations. The general theoretical framework presented here will be useful for guiding future experimental queries and for analysis of the experimental data with more detailed versions of the same model.

I. INTRODUCTION

The totally asymmetric simple exclusion process (TASEP) [1–4] is one of the simplest models of interacting self-propelled particles on a discrete lattice. Such driven systems can never be in thermodynamic equilibrium, but can attain non-equilibrium steady states (NESS) [5, 6]. One of the key properties of the NESS is the non-vanishing particle flux which is defined as the number of particles passing through a site per unit time. The effects of different types of defects and inhomogeneities on the flux and the density profile of the particles have been investigated extensively over the last three decades [7–20].

Wide varieties of collective traffic-like phenomena in non-living as well as in living systems have been modelled by various appropriate extensions of TASEP [3, 21–24]. Spatially localized bottlenecks, that arise naturally in many of those systems, have also been modelled as defects of the lattice [25]. In this paper we focus on some unusual effects of a unique ‘defect’ located on a long-chain molecule, called DNA, that serves as the track for RNA polymerase (RNAP) [26], a class of nano-motors [27–29] in living cells. The collective movement of multiple RNAPs simultaneously on a DNA track resembles, at least superficially, vehicular traffic on highways [3, 21].

Our main aim is to develop a general theoretical framework to address some general questions on the interplay of this specific ‘defect’ and RNAP traffic.

Genetic message is encoded chemically in the sequence of the monomeric subunits of DNA in a language that is based on a 4-letter alphabet. Transcription of this message is carried out by a molecular machine called RNA polymerase (RNAP) [26]; it synthesizes a RNA molecule (the transcript) whose sequence of monomeric subunits is complementary to that of a specific segment of its DNA that encodes the corresponding genetic message. Each RNAP can also be regarded as a molecular motor [27–29] for which the DNA template also serves as the track for its unidirectional, albeit noisy, movement during transcription [26].

Experiments revealed the existence of specific stretches of DNA sequence where the nascent RNA may slip, backward or forward, with respect to the RNAP although the RNAP motor itself does not slip simultaneously on its DNA track [30]. In fact, at any given slippage-prone site, multiple successive events of backward and/or forward slippage may occur before the correct transcription can resume. It is the ‘slippage prone site’, where the nascent RNA slips from the grip of the RNAP motor, that we treat here as ‘defect’ on the DNA track.

Thus, transcript slippage (TS) results in the heterogeneity of the length of the final products of transcription because of the incorporation of more or fewer nucleotides, respectively, as compared to the length of transcript encoded in the DNA. While this phenomenon has received much attention over the past few decades [30, 31], the detailed mechanism of TS, its causes and consequences are

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still unclear. In this paper we focus on the consequences, rather than the causes, of TS.

Often the same segment of DNA (here loosely defined as the ‘gene’) is simultaneously transcribed by several RNAPs, each synthesizing a distinct copy of the same RNA. A RNAP is expected to dwell longer at the slippery site in congested traffic because of the hindrance caused by the leading vehicle. The longer a RNAP dwells at the slippery site, the larger is the number of TS events it is likely to suffer. Thus, traffic congestion can influence the extent of TS. In the past, RNAP traffic has been modelled theoretically by extending the TASEP [32–33]. Here we develop a TASEP-based model to investigate the interplay of TS and RNAP traffic.

In traffic engineering it is essential to first characterize the driving behaviors of individual drivers before embarking on a study of vehicular traffic on highways. In the same spirit, here we study the statistical characteristic of a single RNAP that undergoes TS at a specific location on the DNA track, before studying of RNAP traffic on the same track. Thus, in this paper, we consider two different situations. In the first, a single RNAP is assumed to be moving alone on the DNA track whereas, in the second, many RNAPs move simultaneously in the same direction on a single DNA track. More specifically, we study three aspects of TS: (a) how is the rate of transcription by a single RNAP affected by TS?, (b) how the error due to TS is affected by the traffic-congestion during the collective movement of RNAPs? and (c) how, in turn, the collective traffic-like movement of RNAP is affected by TS statistics?

To study the effect of a transcript slippage on the movement of each individual RNAP on the DNA track and, equivalently, the rate of transcription, we use the technique of calculating First Passage Time (FPT) [39–41]. With this objective, we first construct a stochastic kinetic theoretical framework that incorporates the effect of arbitrary numbers of backward and forward slippage. Then, as a concrete example, we consider a special case of the model that can be treated analytically without much of mathematical difficulty. For this concrete case, we compute the time taken by the RNAP motor to traverse a slippery site for the first time. This time is intrinsically stochastic and is termed here as the first-passage time. We interpret the results physically to explain how the movement of a RNAP on the DNA template (track) is affected by TS.

To study the interplay of RNAP traffic and TS, we use the conceptual framework of TASEP [11]. First, using Mean Field Approximation (MFA), we again compute the mean time needed to traverse a slippage site in a traffic of RNAPs on the same DNA track. We also carry out Monte Carlo (MC) simulations of the model and compare the MC data with the corresponding mean-field theoretic predictions to test the level of accuracy of the MFA. Finally, we also compare the theoretically predicted probability distribution of the longer and shorter transcripts with the experimental data [12] [15] obtained through advanced sequencing technologies [41].

The paper is organized in the following manner. In sec. II, we begin by sketching a brief introduction to the phenomenon of TS, followed by the description of our stochastic kinetic model of TS. In sec. III, we study the effect of TS on a single RNAP. In sec. IV, we investigate the effect of RNAP traffic congestion on TS. In sec. V, we analyze the effect of TS on RNAP traffic flow. Finally, in sec. VI, we present a summary of the results and draw conclusions.

II. MODEL AND BIOLOGICAL MOTIVATION

We begin this section with a brief overview of the TS process, as depicted schematically in Fig. I in the subsection II A. Then, motivated by this biological phenomenon, in the subsection II B we develop our theoretical model. The distinct kinetic states are displayed, and the inter-state transitions are indicated, in Fig. 2.

A. TS phenomenon

During normal transcription (see Fig. 1(a)), incorporation of every nucleotide, as directed by the template DNA, is followed by the motor-like forward movement of the RNAP by one nucleotide along the DNA that also serves as its track. Thus, in normal transcription, each event of elongation of the nascent RNA transcript by one nucleotide is tightly coupled to the translocation of RNAP by one nucleotide on the template DNA.

The slippery sequence on the DNA is represented by an array of A’s [30]. Fig. I(b) describes a transcription process wherein a single backward slippage of the nascent RNA transcript occurs. Due to the backward slippage, the active site of the RNAP turns empty for the second time during its sojourn at the slipper site, and it transcribes the same nucleotide for a second time, resulting in the insertion of an extra nucleotide on the transcript. Fig. 1(c) describes a single forward slippage of the nascent RNA transcript without forward movement of RNAP; this forward slippage of the nascent transcript results in the active site of the RNAP getting occupied with the previously added nucleotide in the transcript thereby preventing incorporation of a fresh nucleotide even though the RNAP moves forward by one nucleotide on the DNA template. In both Fig. 1(b) and (c), the transcript slips without the concomitant movement of RNAP and that the polymerization of the transcript is not coupled with the translocation of RNAP. Typically, either of these mechanisms can be repeated thereby causing multiple rounds backward or forward slippage of the transcript at these slippery sites.
FIG. 1: A pictorial depiction of (a) normal transcription, without slippage, by an RNAP, (b) transcription with backward slippage of nascent RNA, (c) transcription with forward slippage of nascent RNA. The white circle represents active site of an RNAP and blue color letter ‘U’ depicts the incorporation of a nucleotide in the active site. Array of nucleotides ‘A’ represents slippery sequence in the DNA strand and the slanted black solid line represents nascent RNA. Backward and forward slippages of the nascent RNA transcript are indicated by red and green arrows, respectively. In Fig (a), after incorporation of a nucleotide ‘U’, RNAP can move one step forward with respect to DNA template. In Fig (b), after incorporation of a nucleotide ‘U’, nascent RNA slips backward with respect to RNA as well as DNA template, by keeping RNAP fixed in its position. This results in addition of an extra nucleotide ‘U’ to the transcript. In Fig (c), before the incorporation of a ‘U’, nascent RNA can slip forward with respect to RNA as well as DNA template, by keeping RNAP fixed in its position, resulting in a shortening of the transcript by one nucleotide.

B. Kinetic model motivated by TS

In our model, we represent the DNA template as a one-dimensional lattice of length \( L \). We label the sites of the lattice by the integer index \( j \) (\( 1 \leq j \leq L \)). Each lattice site corresponds to a nucleotide on the DNA template. The instantaneous position of a RNAP is denoted by the integer index \( j \); in each round of successful error-free elongation of the nascent RNA by one unit, the RNAP takes a forward step from \( j \) to \( j+1 \). The special site where TS can take place has been labelled by the integer \( J \) (i.e., \( j = J \)). Since our study is primarily on TS, and since TS is known to occur at a special slippery site, we focus in this section exclusively on the triplet of sites \( J-1, J \) and \( J+1 \).

For a completely normal error-free transcription of the full length template DNA, the RNAP takes \( L \) steps on the track synthesizing a RNA transcript of length \( L \) i.e., exactly equal to the length of the DNA template. However, in case of transcription with \( n \) successive rounds of backward slippage at a specially designated slippery site, insertion of \( n \) number of nucleotides leads to the synthesis of a longer transcript of total length \( L+n \). Similarly, for \( n \) successive rounds of forward slippage at the slippery site, missing the transcription of \( n \) nucleotides on the template (i.e., effectively, deletion of \( n \) nucleotides) produces a shorter transcript of total length \( L-n \). The extra length of the nascent RNA caused by the slippage is labelled by an integer index \( \mu \) that can, in principle, be positive, negative or zero. According to our convention \( \mu \) is positive (negative) in case backward (forward) slippage; in contrast, \( \mu = 0 \) if the nascent transcript suffers no slippage or it suffers equal numbers of forward and backward slippages at the slippery site \( J \). Throughout this paper we use the term “slippage state” to denote the magnitude of \( \mu \).

The theoretical framework that we have formulated is very general and can treat any arbitrary number \( N_b \) of backward or \( N_f \) number of forward slippage of the transcript while the RNAP is occupying the specific lattice site \( J \). However, for the purpose of presentation of concrete results here through an explicit analytical calculation, we have allowed a maximum of two backward slippage events (\( N_b = 2 \), corresponding to \( \mu = +1,+2 \)), and a maximum of a single forward slippage (\( N_f = 1 \) that would correspond to \( \mu = -1 \)). Since backward slippages have been found to occur more often than the reverse process, in the example shown in Fig. possibilities of two successive backward slippage are shown against the possibility of a single forward slippage. The allowed transitions are indicated by the arrows and the corresponding rates are also shown next to the respective arrows in Fig. The special case shown in Fig. is, indeed, simple enough to be treated analytically. However, analytical calculations become more and more difficult with the increasing number of backward (or forward) slippage events (i.e., with the increase in the allowed values of \( N_b \) and \( N_f \)). Nevertheless, in principle, the strategy of modelling followed here can be implemented numerically also for any arbitrary values of \( N_b \) and \( N_f \) if calculations becomes too difficult to carry out analytically.

Thus, for the special case of the model shown in Fig. the state of the RNAP motor at a particular instant is indicated by the pair \( (j, \mu) \), where \( j \) is its position on the DNA template i.e \( j = 1 \) to \( L \) and \( \mu (\mu = 0, +1, +2, -1) \) is the ‘extra length’ of the associated nascent transcript. Fig. clearly shows that, in this special case, a RNAP can follow four different pathways when it encounters a slippery site: (1) the transitions \( (J-1,0) \) to \( (J,0) \) to
II. PASSAGE OF RNAP ACROSS SLIPPERY SITE SUFFERING TRANSCRIPT SLIPPAGE

A. First Passage Times across slippery site and transient behaviour

We define the time \( \tau \) taken by the RNAP motor to reach, for the first time, the position \( J + 1 \), starting from the position \( J - 1 \) as the first-passage time. Since the kinetics of transcription, including TS, is probabilistic, \( \tau \) varies from one RNAP to another. In this section we calculate the probability distribution (more precisely, the probability density function) \( f(\tau) \) of \( \tau \).

\[ \langle \tau \rangle = \int_0^\infty \tau f(\tau) \, d\tau \quad (1) \]

if \( f(\tau) \) is known.

We define \( P_\mu(J,t) \) as the probability of finding the RNAP in the “slippage state” \( \mu \) at site \( J \) on the DNA track at time \( t \). The master equations governing the time evolution of \( P_\mu(J,t) \) corresponding to the \( N \)-state kinetic model, written using the matrix notation, is

\[ \frac{d\mathbf{P}(t)}{dt} = \mathbf{A} \mathbf{P}(t). \quad (2) \]

where \( \mathbf{P}(t) \) is a \( N \)-component column vector. Sometimes the computation of the distribution of FPT turn out to be easier in terms of Laplace transforms. Carrying out Laplace transform of both sides of

\[ \mathcal{L} \left[ \frac{d\mathbf{P}(t)}{dt} \right] = \mathcal{A} \mathcal{L} \mathbf{P}(t) \quad (3) \]

we get

\[ s \mathbf{\tilde{P}}(s) - \mathbf{P}(0) = \mathbf{A} \mathbf{\tilde{P}}(s) \quad (4) \]

and hence

\[ \mathbf{\tilde{P}}(s) = (s \mathbf{I} - \mathbf{A})^{-1} \mathbf{P}(0) \quad (5) \]

where \( \mathbf{I} \) is the identity matrix, \( \mathcal{L} \) indicates the Laplace transform operator and \( \mathbf{\tilde{P}}(s) \) is the Laplace transform of \( \mathbf{P}(t) \). In principle, after taking inverse Laplace transform of \( \mathbf{\tilde{P}}(s) \), one would get the distribution of FPT

\[ \mathbf{P}(t) = \mathcal{L}^{-1} \left[ \mathbf{\tilde{P}}(s) \right] \quad (6) \]

Often the set of kinetic equations are so complicated that the operation of inverse Laplace transform (6) cannot be completed analytically to get closed-form analytical expression for \( P_\mu(J,t) \). In such situations, the mean first passage time can still be obtained by taking appropriate derivatives of \( \mathbf{\tilde{P}}(s) \) if the latter can be calculated in the s-space (Laplace space):

\[ \int_0^\infty t \, P_\mu(J,t) \, dt = - \frac{d}{ds} \tilde{P}_\mu(J,s) \bigg|_{s=0} \quad (7) \]

In the special case of the 6-state kinetic model shown in Fig. 2 defining

\[
\begin{pmatrix}
P_b(J-1,t) \\
P_b(J,t) \\
P_b(J+1,t) \\
P_{+1}(J,t) \\
P_{-1}(J,t) \\
P_{+2}(J,t)
\end{pmatrix}
\]
Along with the normalization condition
\[ P_0(J - 1, t) + \sum_{\mu} P_{\mu}(J, t) + P_0(J + 1, t) = 1, \quad (9) \]
we have
\[
A = \begin{pmatrix}
- q & 0 & 0 & 0 & 0 & 0 \\
q & -(q_0 + b_1 + f_1) & 0 & 0 & 0 & 0 \\
0 & q_0 & 0 & q_1 & q_2 & q_3 \\
0 & b_1 & 0 & -(q_1 + b_2) & 0 & 0 \\
0 & f_1 & 0 & 0 & -q_1 & 0 \\
0 & 0 & 0 & b_2 & 0 & -q_2
\end{pmatrix} \quad (10)
\]

For the calculation of the first-passage time, we impose the initial conditions:
\[
P(0) = \begin{pmatrix}
1 \\
0 \\
0 \\
0 \\
0 \\
0
\end{pmatrix} \quad (11)
\]

Probability density of first-passage times to reach the target site \( J + 1 \) between time \( t \) and \( t + dt \) is,
\[
f(t) = q_0 P_0(J, t) + q_1 P_{+1}(J, t) + q_{-1} P_{-1}(J, t) + q_{+2} P_{+2}(J, t)
\quad (12)
\]
The transition matrix \( A \) can be simply diagonalized as follows:
\[
A|\lambda_n\rangle = \lambda_n|\lambda_n\rangle \quad (13)
\]
where the eigenvalues \( \lambda_n \) are given by
\[
\lambda_1 = 0, \quad \lambda_2 = -q, \quad \lambda_3 = -b_1 - f_1 - q_0,
\lambda_4 = -q_{-1}, \quad \lambda_5 = -b_2 - q_1, \quad \lambda_6 = -q_{+2}. \quad (14)
\]
The time-dependence of the eigenvectors are simply written as
\[
|\lambda_n(t)\rangle = e^{\lambda_n t}|\lambda_n\rangle. \quad (15)
\]
Now we expand the initial state \( |P(0)\rangle \), given by (11), in terms of the eigenvectors of \( A \) as
\[
|P(0)\rangle = \sum_{n=1}^{6} c_n |\lambda_n\rangle, \quad (16)
\]
where
\[
c_1 = 1, \quad c_2 = \frac{b_1 b_2 q}{x_1 x_2 x_3}, \quad c_3 = \frac{b_1 b_2 q}{x_1 x_2 x_3 x_4},
\]
\[
c_4 = \frac{f_1 q}{x_1 x_2}, \quad c_5 = \frac{b_1 b_2 q}{x_1 x_2 x_3 x_4},
\]
\[
c_6 = \frac{b_1 b_2 q}{x_1 x_2 x_3 x_4 x_5} \quad (17)
\]
and
\[
x_1 = b_1 + f_1 + q_0 - q, \quad x_2 = b_2 + q_{+1} - q,
\]
\[
x_3 = q_{+2} - q, \quad x_4 = q_{-1} - q,
\]
\[
x_{jk} = x_j - x_k. \quad (18)
\]
From which we have
\[
|P(t)\rangle = \sum_{n=1}^{6} c_n e^{\lambda_n t}|\lambda_n\rangle. \quad (19)
\]
Explicitly each component can be written as
\[
P_0(J - 1, t) = e^{-qt},
\]
\[
P_0(J, t) = q e^{-qt} \left(1 - e^{-x_1 t}\right),
\]
\[
P_{+1}(J, t) = \frac{b_1 b_2 q e^{-qt}}{x_1 x_2} \left(1 - e^{-x_2 t}\right), \quad \frac{1 - e^{-x_1 t}}{x_1},
\]
\[
P_{-1}(J, t) = \frac{f_1 q e^{-qt}}{x_1 x_2} \left(1 - e^{-x_1 t}\right) \left(1 - e^{-x_2 t}\right)
\]
\[
P_{+2}(J, t) = \frac{b_1 b_2 q e^{-qt}}{x_1 x_2 x_3 x_4 x_5} \times \left(x_1 x_2 - e^{-x_3 t} + x_3 x_4 - e^{-x_1 t} e^{-x_2 t} + x_3 x_4 - e^{-x_1 t} e^{-x_2 t} \right), \quad (20)
\]
Finally, the expression for the remaining probability $P_0(J+1,t)$ can be obtained simply using the normalization condition \( \sum_{j=0}^{\infty} P_j(J+1,t) = 1 \), i.e.,

$$P_0(J+1,t) = 1 - \left\{ P_0(J-1,t) + P_0(J,t) + P_{+1}(J,t) + P_{-1}(J,t) + P_{+2}(J,t) \right\}. \quad (21)$$

The exact expressions \cite{20,21} for the six probability densities $P_0(J-1,t), P_0(J,t), P_0(J+1,t), P_{+1}(J,t), P_{-1}(J,t)$ and $P_{+2}(J,t)$ are drawn graphically for two sets of the rate constants in Fig.3 (a) and (b). On the same graph we also plot the corresponding numerical data obtained from our MC simulations of the model with the same set of values of the rate constants. The excellent agreement between the theory and simulation establishes the high accuracy of the simulation data because the analytical expressions \cite{20} are exact. The variation of the probabilities with time are consistent with the intuitive expectation based on the initial conditions. The only difference between the Fig.3 (a) and Fig.3 (b) is that $P_{+2}(J,t)$ saturates to a constant value in the latter whereas it decays to zero in the former. This qualitative difference arises from the choice of parameter value $q+2 = 0$ in Fig.3 (b) because of which probability $P_{+2}(J,t)$ cannot decay to zero with the passage of time.

The exact expression of the distribution of first-passage times can now be obtained by substituting \cite{20,21} into the relation \cite{12}. Fig.4 shows the distribution of the first passage time $\langle \tau \rangle$ for four different values of $b_1$, keeping all the other parameter values fixed.

The variation of the mean first-passage time $\langle \tau \rangle$ with $b_1$ is shown for four different values of $b_2$ in Fig.5 (a) and for four different values of $f_1$ in Fig.5 (b). The higher is the rate of slippage the longer it takes for the RNAP to pass the defect site.

**B. Steady state: fractions of slipped transcripts**

Since no TS is assumed to occur at the $L - 1$ sites labelled by $j \neq J$, the lengths of the transcripts synthesized by the RNAPs in the 6-state model can have only the lengths $L, L-1, L+1$ and $L+2$. For the steady state of the system, we can define the corresponding probabilities by the relations

$$P_L = \frac{P_0(J+1)}{P(J+1)} = \frac{q_0}{b_1 + f_1 + q_0},$$

$$P_{L+1} = \frac{P_{+1}(J+1)}{P(J+1)} = \frac{b_1 q_{+1}}{(b_1 + f_1 + q_0)(b_2 + q_{+1})},$$

$$P_{L-1} = \frac{P_{-1}(J+1)}{P(J+1)} = \frac{f_1}{b_1 + f_1 + q_0},$$

$$P_{L+2} = \frac{P_{+2}(J+1)}{P(J+1)} = \frac{b_1 b_2}{(b_1 + f_1 + q_0)(b_2 + q_{+1})} \quad (22)$$

where

$$P(J+1) = P_0(J+1) + P_{+1}(J+1) + P_{+2}(J+1) + P_{-1}(J+1). \quad (23)$$
Thus, $P_L, P_{L+1}, P_{L-1}, P_{L+2}$ can be interpreted as the fractions of the respective species of the transcripts synthesized.

Fig. 6 shows the histogram for probability of types of nascent mRNA are plotted with different values of first backward slippage rate $b_1$. Parameter values are $b_2 = 1$ s$^{-1}$ and $f_1 = 2$ s$^{-1}$. All other parameters are kept fixed at values: $q = q_0 = 30$ s$^{-1}$, $q_{-1} = q_{-2} = 20$ s$^{-1}$ and $q_{+2} = 10$ s$^{-1}$. Lines correspond to exact expressions (22), where green, blue, red and orange continuous lines correspond to $P_L, P_{L+1}, P_{L+2}$ and $P_{L-1}$, respectively. Bar plots are obtained from simulation data.

Fig. 7 shows a schematic diagram of RNAP traffic on the DNA track of length $L$ in presence of slippage at site $J$. RNAPs can enter the DNA track only at site $i = 1$ with rate $\alpha$ if the entry site is empty and RNAPs can leave the DNA track after it reaches the termination site $i = L$ with rate $\beta$. In between, RNAPs can hop forward, iff the target site is empty, with the normal transcription rate $\mu$ except at site $J$, where it can hop with rates $\mu_{\mu}$ ($\mu = 0, \pm 1, \pm 2$), depending on the slippage state (refer to Fig. 2).

A RNAP can enter the DNA track, with rate $\alpha$, if the entry site $i = 1$ is empty. If the RNAP is located at any other position $i \neq J$, it can move forward, with rate $\mu$ if, and only if, the target site is empty. On the other hand while located at the special site $J$ a RNAP can hop forward with rates $\mu_{\mu}$ ($\mu = 0, \pm 1, \pm 2$), depending on the slippage state (refer to Fig. 2). A RNAP can detach from the track at the exit site $i = L$ with rate $\beta$. At the slippery site $J$, the nascent RNA can slip backward with rates $b_1, b_2$, etc. and forward with the rate $f_1$.

Let $P_{\mu}(i, t)$ denote the probability of finding RNAP in slippage state $\mu$ at site $i$ on the DNA track at time $t$. So, the probability that the site $i$ is occupied by
a RNAP at time \( t \), irrespective of its slippage state, is 
\( P(i, t) = \sum_j P_{ij}(t) \), where \( \mu = 0, +1, +2, -1 \). We can refer to this model as a biologically motivated extension of TASEP with a special kind of defect located at the specific site \( i = J = L/2 \). Under mean field approximation, the master equation for the probabilities \( P_\mu(i, t) \) are given by

\[
\begin{align*}
\frac{dP_0(1, t)}{dt} &= \alpha(1 - P(1, t)) - qP_0(1, t)(1 - P(2, t)) \\
\frac{dP_0(i, t)}{dt} &= qP_0(i - 1, t)(1 - P(i, t)) - qP_0(i, t)(1 - P(i + 1, t)) \quad \text{for } 1 < i < L/2 \\
\frac{dP_0(L/2, t)}{dt} &= qP_0(L/2 - 1, t)(1 - P(L/2, t)) - qP_0(L/2, t)(1 - P(L/2 + 1, t)) - b_1P_0(L/2, t) - f_1P_0(L/2, t) \\
\frac{dP_0(L/2 + 1, t)}{dt} &= qP_0(L/2, t)(1 - P(L/2 + 1, t)) - qP_0(L/2 + 1, t)(1 - P(L/2 + 2, t)) \\
\frac{dP_0(i, t)}{dt} &= qP_0(i - 1, t)(1 - P(i, t)) - qP_0(i, t)(1 - P(i + 1, t)) \quad \text{for } L/2 + 1 < i < L \\
\frac{dP_0(L, t)}{dt} &= qP_0(L - 1, t)(1 - P(L, t)) - \beta P_0(L, t) \\
\frac{dP_{+1}(L/2, t)}{dt} &= b_1P_0(L/2, t) - q_{+1}P_{+1}(L/2, t)(1 - P(L/2 + 1, t)) - b_2P_{+1}(L/2, t) \\
\frac{dP_{+1}(L/2 + 1, t)}{dt} &= q_{+1}P_{+1}(L/2, t)(1 - P(L/2 + 1, t)) - qP_{+1}(1/2 + 1, t)(1 - P(L/2 + 2, t)) \\
\frac{dP_{+1}(i, t)}{dt} &= qP_{+1}(i - 1, t)(1 - P(i, t)) - qP_{+1}(i, t)(1 - P(i + 1, t)) \quad \text{for } L/2 + 1 < i < L \\
\frac{dP_{+1}(L, t)}{dt} &= qP_{+1}(L - 1, t)(1 - P(L, t)) - \beta P_{+1}(L, t) \\
\frac{dP_{-1}(L/2, t)}{dt} &= f_1P_0(L/2, t) - q_{-1}P_{-1}(L/2, t)(1 - P(L/2 + 1, t)) \\
\frac{dP_{-1}(L/2 + 1, t)}{dt} &= q_{-1}P_{-1}(L/2, t)(1 - P(L/2 + 1, t)) - qP_{-1}(1/2 + 1, t)(1 - P(L/2 + 2, t)) \\
\frac{dP_{-1}(i, t)}{dt} &= qP_{-1}(i - 1, t)(1 - P(i, t)) - qP_{-1}(i, t)(1 - P(i + 1, t)) \quad \text{for } L/2 + 1 < i < L \\
\frac{dP_{-1}(L, t)}{dt} &= qP_{-1}(L - 1, t)(1 - P(L, t)) - \beta P_{-1}(L, t) \\
\frac{dP_{+2}(L/2, t)}{dt} &= b_2P_{+1}(L/2, t) - q_{+2}P_{+2}(L/2, t)(1 - P(L/2 + 1, t)) \\
\frac{dP_{+2}(L/2 + 1, t)}{dt} &= q_{+2}P_{+2}(L/2, t)(1 - P(L/2 + 1, t)) - qP_{+2}(L/2 + 1, t)(1 - P(L/2 + 2, t)) \\
\frac{dP_{+2}(i, t)}{dt} &= qP_{+2}(i - 1, t)(1 - P(i, t)) - qP_{+2}(i, t)(1 - P(i + 1, t)) \quad \text{for } L/2 + 1 < i < L \\
\frac{dP_{+2}(L, t)}{dt} &= qP_{+2}(L - 1, t)(1 - P(L, t)) - \beta P_{+2}(L, t)
\end{align*}
\]

In the steady state the right hand sides of all these equations vanish and the corresponding solutions of the equations are obtained iteratively by checking whether the difference of the numerical values of two successive iterations is less than \( \epsilon \) where \( \epsilon \approx 10^{-8} \) is a preassigned small number.
In our MC simulation of the model, starting from an initial condition, the flux was monitored in each run to ensure that the system reaches a steady state where the flux becomes independent of time. Then, starting from an even longer instant of time \( t_{steady} \) the numerical data from the simulation were recorded for the computation of the steady-state properties; the collection of the data were continued till a time \( t_{max} \) where the simulation run was terminated. Each step of MC update was assumed to correspond to an infinitesimal time interval \( dt = 5 \times 10^{-4} \) s.

In our notation, we have \( \alpha \to \alpha/q \) and \( \beta \to \beta/q \). In low density (LD) phase, density is determined by \( \alpha (\rho = \alpha) \) and hence \( \alpha < 1/2 < \beta \). In high density (HD) phase, density is determined by \( \beta (\rho = 1 - \beta) \) and hence \( \alpha > 1/2 > \beta \). In maximal current (MC) phase, \( \rho = 1/2 \) and hence \( \alpha = \beta > 1/2 \).

### A. Effects of traffic congestion on extent of TS

![Figure 8](image-url)

**FIG. 8:** Distributions of probability of first backward slippage state, \( P_{11}(J, t) \) with time \( t \), for different values of \( \rho \). Parameter values for slippage rates: \( b_1 = 4 \) s\(^{-1} \), \( b_2 = 1 \) s\(^{-1} \) and \( f_1 = 2 \) s\(^{-1} \). All other parameters were kept fixed at values: \( q = q_0 = 30 \) s\(^{-1} \), \( q_{1+} = q_{-1} = 20 \) s\(^{-1} \) and \( q_{+2} = 10 \) s\(^{-1} \). Lines correspond to analytical result and discrete data points were obtained from simulation.

In this subsection, we compute the mean-time taken by each RNAP to transcribe a DNA template of length \( L \), on which the defect (i.e., the slippery site) is located at \( J \), in the steady state of the RNAP traffic. The simplest way to account for the traffic congestion is to replace the hopping rates of RNAPs, from one site to the next, by effective rates obtained by multiplying the actual rate with the factor \((1 - \rho)\), where \( \rho \) is the number density of the RNAPs.

Fig. [8] shows the variation in probability distributions of first backward slippage state plotted against time for different values of \( \rho \). The trend observed in the graph is due to crowding i.e. the RNAPs have to face hindrance to move forward.

The denser is the traffic congestion, the longer is the dwell time of an arbitrary RNAP at the slippery site and the larger is the expected number of TS events that can occur during the duration of that dwell. This intuitive expectation is, indeed, supported by the data shown in Fig.9 where \( P_{+2}(J) \) and \( P_{+2}(J + 1) \) have been plotted as functions of the number density \( \rho \).

![Figure 9](image-url)

**FIG. 9:** The steady state probabilities \( P_{+2}(J) \) and \( P_{+2}(J + 1) \) are plotted in the main figure and inset, respectively, as functions of the number density \( \rho \). The parameter values chosen for this figure are \( b_1 = f_1 = q_{+2} = 0.3 \) s\(^{-1} \) and \( q = q_0 = q_{1+} = q_{-1} = b_2 = 30 \) s\(^{-1} \).

For plotting this figure we have chosen \( b_1 = f_1 = q_{+2} = 0.3 \) s\(^{-1} \) and \( q = q_0 = q_1 = q_{-1} = b_2 = 30 \) s\(^{-1} \). Because of the small values of \( b_1 \) and \( f_1 \), the likelihood of the first TS event, irrespective of forward or backward, is normally quite low. However, as the value of \( \rho \) increases, the dwell times of the RNAPs increase at all sites, including that located at the slippery site. Consequently, during that longer period of stay at the slippery site, the RNAP suffers multiple rounds of TS; this is reflected in the increase in the magnitude of \( P_{+2}(J) \) in Fig.9.

The probability \( P_{+2}(J) \) and \( P_{+2}(J + 1) \) are plotted as functions of \( \alpha \) (for fixed \( \beta \)) in Fig.10a and as as a function of \( \beta \) (for fixed \( \alpha \)) in Fig.10b. As \( \alpha \) increases both \( P_{+2}(J) \) and \( P_{+2}(J + 1) \) increase but the rate of increase decreases gradually and, eventually saturates because the RNAP traffic makes a transition from the LD phase to the MC phase where the flux of RNAPs saturates. Similarly, for a fixed \( \alpha \), as \( \beta \) increases the transition from the HD phase to MC reduces the effective dwell time of each RNAP at the defect site which, in turn, reduces the probabilities of multiple TS events at that site. Moreover, the transition to the MC phase also leads to the saturations of the values of \( P_{+2}(J) \) and \( P_{+2}(J + 1) \) with increasing \( \beta \).

Fig. 11 shows the histogram for slippage statistics plotted against \( \rho \). In MC phase (\( \rho = 0.5 \)) and even in the LD phase (\( \rho < 0.5 \)), \( P_{L+1} \) and \( P_{L-1} \) have significantly low values and remain unaffected by the change in \( \rho \). In
PL-1
 PL
 PL+1
 PL+2
 Ptranscript length
 0
 0.2
 0.4
 0.6
 0.8
 1
 0
 0.02
 0.04
 5
 9
 15
 20
 24
 27
 P+2(J)
 α (s⁻¹)
 0
 0.001
 0.002
 0.003
 5
 9
 15
 20
 24
 27
 P+2(J+1)
 β (s⁻¹)
 0
 0.02
 0.04
 5
 9
 15
 20
 24
 27
 P+2(J)
 β (s⁻¹)
 0
 0.02
 0.04
 5
 9
 15
 20
 24
 27
 P+2(J+1)
 α (s⁻¹)

FIG. 10: The steady state probabilities $P_{+2}(J)$ and $P_{+2}(J + 1)$ are plotted in the main figure and inset, respectively, as functions of $\alpha$ (in (a)) and $\beta$ (in (b)). For both the figures the parameter values chosen are $b_1 = f_1 = q_{+2} = 0.3s^{-1}$ and $q = q_0 = q_{+1} = q_{-1} = b_2 = 30s^{-1}$; $\beta = 30s^{-1}$ in (a) and $\alpha = 30s^{-1}$ in (b).

HD phase ($\rho > 0.5$), $P_L$ decreases and $P_{L+1}$, $P_{L+2}$ and $P_{L-1}$ increases due to the crowding effect. Because of hindrance, RNAPs have to wait longer time at slippage site and it enhances the chance of slippages.

V. EFFECT OF TRANSCRIPT SLIPPAGE ON RNAP TRAFFIC FLOW

The time taken by a RNAP, on the average, in the steady state of the RNAP traffic to transcribe can be written as

$$T_{ss} = \frac{1}{\beta P(L)} = \frac{1}{\beta(P_0(L) + P_{+1}(L) + P_{+2}(L) + P_{-1}(L))} \quad (28)$$

We obtained the mean-field theoretic estimate of $T_{ss}$ by substituting the mean-field values of the probabilities in the denominator of (28).

For the computation of $T_{ss}$ in our MC simulation, we use the formula

$$T_{ss} = \frac{(t_{max} - t_{steady})dt}{N}$$

where, $N$ is the total number of departing RNAPs counted at $i = L$ over the duration $t_{max} - t_{steady}$ and $dt$ is the duration of each time step of the simulation. We have taken $\alpha = \beta = 30s^{-1}$ (Maximal current phase) and $dt = 5 \times 10^{-4} \text{ s} =$ time step for MC simulation and MF approximation. We have taken the length of the DNA track (L) to be of 1000 lattice sites.

In Fig.12 we have plotted steady state mean time ($T_{ss}$) as a function of $b_1$, for several different values of $b_2$, the trend of variations of the curves are very similar to those in Fig.5(a) except for the magnitude which is much longer because of the traffic congestion.

Steady state density profiles of the RNAP traffic in different phases have been shown in Fig.13. We have taken the slippage site to be located at the mid-point of the track ($i = L/2$). This site can be regarded as a defect site on the homogeneous lattice. From the density profile plots, it is clear that the system behaves like a combination of two lattices (or two TASEPs). For TASEP without slippage site, LD phase exists between $\alpha < q/2 < \beta$. With slippage site, TASEP 1 reaches LD I phase for $\alpha < q/2 > \beta_{eff}$ and TASEP 2 reaches in LD II phase for $\alpha_{eff} < q/2 < \beta$ (see in Fig.13(a)). Similarly for TASEP without slippage site, HD phase exists between $\alpha > q/2 > \beta$. With slippage site, TASEP 1 reaches HD II phase for $\alpha > q/2 > \beta_{eff}$ and TASEP 2 reaches...
FIG. 12: Variation of $T_{ss}$ with $b_1$ keeping all the other parameters fixed at values $q = q_0 = 30 \text{ s}^{-1}$, $q_{-1} = q_{-2} = 20 \text{ s}^{-1}$, $q_{+1} = 10 \text{ s}^{-1}$ and $f_1 = 1 \text{ s}^{-1}$. Lines correspond to MF theory and points have been obtained from MC simulations. Only exception is that the results shown in magenta colour corresponds to parameter values $q = q_0 = q_{+1} = q_{-1} = q_{+2} = 30 \text{ s}^{-1}$.

in HD I phase for $\alpha_{eff} < q/2 > \beta$ (see in Fig.13(b)). Similarly, for TASEP without slippage site, MC phase exists between $\alpha > q/2 < \beta$. With slippage site, the MC phase disappears and TASEP 1 reaches HD II phase for $\alpha > q/2 > \beta_{eff}$ and TASEP 2 reaches LD II phase for $\alpha_{eff} < q/2 < \beta$ (see in Fig.13(c)).

VI. SUMMARY AND CONCLUSION

Motivated by the biological phenomenon of TS in RNAP traffic, we have developed a stochastic kinetic model based on TASEP where a special lattice site is treated as an unusual `defect`. The state of each particle, which represents a RNAP, is denoted by two integer indices. The first index denotes its position on the lattice while the second expresses the extra length of the associated RNA transcript because of TS.

In the first part of this paper, we have derived exact analytical expression for the mean time taken by a single RNAP to traverse the defect site, in the absence of steric hindrance from any other RNAP. This mean time is extracted from the corresponding probability density distribution that we have derived here using the formalisms of first-passage time. The exact analytical expressions that we report are important statistical properties that characterize the passage of a single RNAP across the defect site while motoring along its DNA track.

In the second part of this paper, we have investigated the interplay of TS at the defect site and RNAP traffic on the lattice where the RNAP traffic has been modelled as a TASEP. We have presented multiple evidences to establish increase in the number of TS events suffered by a RNAP while dwelling at the defect site for longer duration because of the traffic congestion. We have also indicated how the TS process affects the flux of the RNAP traffic. We have found good agreement between our theoretical predictions, based on an approximate analysis of the TASEP model and the corresponding data obtained by carrying out Monte Carlo simulations of the same model.
In spite of the simplicity of the special case of the model and the approximations made in its analytical treatment, the theoretically predicted probability distribution of the longer and shorter transcripts qualitatively matches the experimental data [22, 23] obtained through advanced sequencing technologies [24]. We hope that our theoretical predictions will encourage more experimental studies. Understanding of this phenomena may also expose the causes of various diseases, like Alzheimer’s disease and Down’s syndrome [20, 21], and may also help in finding a cure for them.

A single RNAP can be interpreted as a physical realization of a Turing machine [15] which is an idealized device conceptualized for abstract ‘computation’ [16]. In the simplest formulation, a finite set of discrete states are assigned to a Turing machine. It can move forward and backward on a tape in discrete steps; the step size being the size of the boxes marked on the tape. Each box on the tape stores a digit. The head of the Turing machine can read the digit stored in the box at its current location. The Turing machine reads this ‘input’ and the result of its ‘computation’ is an ‘output’ digit and a concomitant transition of state of the machine according to the fixed set of rules (algorithm) prescribed in the beginning.

In the process of transcription, the template DNA strand can be interpreted as the tape and the sequence of nucleotides are the analogues of sequence of digits stored on the tape. The RNAP can be regarded as a physical realization of a Turing machine; its biochemical and conformational states being the counterparts of the internal states of a Turing machine. But, in contrast to the digits that are the output of a Turing machine, the output of the ‘computation’ (which biologists refer to as transcription) by the RNAP is a RNA which is, essentially, another tape. Thus, a RNAP is a ‘tape-copying Turing machine’ (TCTM) [17–19]. Therefore, the general theoretical framework developed here may be of interest also in the theory of computation.

Thus, the work reported here is of interdisciplinary nature. It has been motivated by a biological phenomenon. The models and their analysis are based of theoretical techniques of nonequilibrium statistical physics. The results provide insight into the spatio-temporal organization in a complex physical system with point defect. Borrowing some of the ideas from the perspective of theory of TCTM may also enrich other research field like theory of computation.

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