A biologically inspired two-species exclusion model: effects of RNA polymerase motor traffic on simultaneous DNA replication

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Abstract. We introduce a two-species exclusion model to describe the key features of the conflict between the RNA polymerase (RNAP) motor traffic, engaged in the transcription of a segment of DNA, concomitant with the progress of two DNA replication forks on the same DNA segment. One of the species of particles (\(P\)) represents RNAP motors while the other (\(R\)) represents the replication forks. Motivated by the biological phenomena that this model is intended to capture, a maximum of two \(R\) particles only are allowed to enter the lattice from two opposite ends whereas the unrestricted number of \(P\) particles constitutes a totally asymmetric simple exclusion process (TASEP) in a segment in the middle of the lattice. The model captures three distinct pathways for resolving the co-directional as well as head-on collision between the \(P\) and \(R\) particles. Using Monte Carlo simulations and heuristic analytical arguments that combine exact results for the TASEP with mean-field approximations, we predict the possible outcomes of the conflict between the traffic of RNAP motors (\(P\) particles engaged in transcription) and the replication forks (\(R\) particles). In principle, the model can be adapted to experimental conditions to account for the data quantitatively.

Keywords: exclusion processes, driven diffusive systems, stochastic particle dynamics, traffic models
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1. Introduction

The totally asymmetric simple exclusion process (TASEP) [1–4] was originally introduced as a simplified model describing the kinetics of protein synthesis [5, 6]. Since then many more applications to biological systems have been found, especially in situations [7–27], where the kinetics are dominated by the traffic-like collective motion of molecular motors (for reviews, see [28–32]).

A genetic message encoded chemically in the sequence of the monomeric subunits on a specific segment of DNA is ‘transcribed’ into an RNA molecule by a molecular motor called RNA polymerase (RNAP). In each of its steps on the DNA track a RNAP motor elongates the nascent RNA molecule by a single subunit using the same DNA strand as the corresponding template [33]. In other words, synthesis of an RNA is essentially a template-directed polymerization carried out by an RNAP and the processes is called transcription. Only one particular segment of one of the two duplex DNA strands serves as the template for a specific RNA. The same DNA segment can be transcribed many times to synthesize multiple copies of the same RNA, one in each round of transcription. Single-species exclusion models have been developed also for the traffic-like collective movements of multiple RNAP motors on the same segment of DNA while each RNAP synthesizes a distinct copy of the same RNA [34–39].

A molecular machine called DNA polymerase (DNAP) is a key component of a replisome which is a multi-machine macromolecular complex that replicates DNA. DNA replication occurs once, and only once, during the lifetime of a cell before it divides into two daughter cells. Once replication is initiated, this process gets terminated only after the entire length of the DNA gets replicated. As a double-stranded DNA is unzipped locally and the two freshly exposed strands are replicated simultaneously (although not exactly in the same fashion) by replisomes, Y-shaped junctions called replication forks, are formed. The progress of replication can be described in terms of two replication

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forks that move in opposite directions; when two such replication forks, approaching each other from opposite ends of the segment, collide head-on, replication of that segment of DNA is completed \[33\]. Theoretical models for the ‘nucleation’ of replication competent replication forks and the growth of the replicated domains of the DNA have been reported in the past \[40–46\] (see also \[47, 48\] for reviews). Note that if each replication fork is represented by a particle, none of the DNA segments already traversed by a particle, irrespective of its direction, are allowed to be traversed by another particle of the same species because no segment of DNA can be replicated more than once.

Interestingly, even during DNA replication concomitant transcription of its various segments can take place. The possibility of head-on collision between an RNAP and a replication fork appears obvious. Moreover, since the rate of replication is 10–20 times faster than that of transcription, a replication fork can catch up with an RNAP from behind thereby causing co-directional collision. Thus, the RNAPs engaged in the transcription can suffer either co-directional or head-on encounter with replication fork(s) if simultaneously the same segment of the DNA is replicated by the replisomes. Both types of collisions can have disastrous consequences for the cell \[49\].

In principle, a cell could avoid transcription-replication conflict (TRC) completely if it could separate transcription and replication processes spatially and temporally \[51\]. Although by delaying replication some cells have been found to prevent potentially disastrous TRC with heavy RNAP traffic under some special circumstances \[50\] such a mechanism does not seem to be ubiquitous. Instead, there are strong indications that evolution might have tinkered the positions and orientations of the templates for RNA molecules on the DNA so as to reduce the possibility of such TRC \[51\]. Nevertheless, such conflicts are still unavoidable. Therefore, a cell has to either tolerate or resolve TRC sufficiently rapidly. Several mechanisms of TRC resolution have been discovered \[52–55\] since the pioneering experimental investigation by Alberts and co-workers (see \[56, 57\] for a review of the early works). However, to our knowledge, no quantitative theoretical model of TRC and their resolution has been reported so far.

It has been appreciated for a long time that, given a segment of DNA, the heavier the traffic of RNAP motors, the larger is the number of encounters suffered by a replication fork over the given segment of DNA. The larger number of such encounters are also a potential cause for more disastrous effects on the DNA replication. The different dynamical phases of the RNAP motors are characterized by different spatio-temporal organization of the RNAPs on the DNA track. Therefore, a systematic study of the effects of RNAP traffic on the DNA replication is desirable for a quantitative understanding of the consequences of the TRC. Such a quantitative study is the main aim of this paper.

In this paper we propose a TASEP-based minimal model that captures the essential aspects of RNAP traffic on a segment of DNA concomitant with the progress of DNA replication forks from the two ends of the same DNA segment. One of the two species of particles represents RNAP motors all of which move co-directionally, i.e. say, from left to right. In contrast, only two particles of the second species, each representing a DNA replication fork, approach each other from opposite ends of the same track, i.e. one from the left and the other from the right. The kinetics of the model incorporates all the known natural mechanisms of TRC resolution.
This formulation, as explained in the section 2, leads to a two-species exclusion process on a 3-segment lattice in one dimension which also includes ‘Langmuir kinetics’, i.e. attachment and detachment of particles in the bulk \([\text{58}]\). Once a replication fork enters the segment that is being transcribed by the RNAP motors, it begins to interfere with the ongoing transcription. Beyond this point, as the replication fork moves further forward, the spatial region of conflict between the two species of particles also keeps shrinking. Thus, the model of the two-species exclusion process developed here is highly non-trivial. By a combination of analytical arguments and computer simulations, we investigate the effect of the two processes, i.e. transcription and replication, on each other. More specifically, we indicate (a) the trends of variation of the mean time for completion of replication and (ii) the statistics of the successful and unsuccessful replication events, in the different phases of the RNAP traffic \([\text{2–4}]\).

2. Model

The schematic diagram of the model is shown in figure 1. For simplicity, motion of both species of particles are assumed to occur along a single common track represented by a one dimensional lattice of a total length \(L\), where, \(L\) is the total number of equispaced sites on the lattice. As stated in the introduction, once DNA replication begins, the process goes on and is, finally, terminated only when replication of both the strands of the entire double-stranded DNA is completed. In contrast, only a specific segment of a single strand of the double-stranded DNA, marked by a ‘start’ site and a ‘stop’ site at its two ends, serves as the template for the synthesis of a specific RNA \([\text{33}]\). Therefore, irrespective of the number of copies of a specific RNA synthesized, each RNAP motor driving this specific transcription process initiates its walk at the same start site. On the other hand, during replication not only this segment but also the sites upstream of the transcription start site and sites downstream of the transcription stop sites on the DNA have to be replicated \([\text{33}]\). Therefore, we divide the lattice into three segments: sites \(i = 1\) to \(i = L_1 - 1\) (segment 1), \(i = L_1\) to \(i = L_2\) (segment 2), and site \(i = L_2 + 1\) to \(i = L\) (segment 3).

One of the two species of particles, labelled by \(P\), represent the RNAP motors; all the \(P\) particles can move, by convention, only from left to right, i.e. from \(i\) to \(i + 1\). There is no restriction on the number of \(P\) particles that can populate the lattice, except the limits arising naturally from the rates of entry, exit and forward hopping that are described below. In contrast, not more than two particles of the second species, labelled \(R\) and representing the replication forks, can ever enter the lattice irrespective of the kinetic rates, i.e. probabilities per unit time of the various kinetic processes that are described below. One of the \(R\) particles, denoted by \(R_\ell\) moves from left to right (\(i\) to \(i + 1\)) whereas the other, denoted by \(R_r\) moves from right to left (\(i + 1\) to \(i\)) on the lattice.

The \(R_\ell\) particle can enter the lattice only at \(i = 1\) with the probability \(\gamma\) per unit time. Similarly, the particle \(R_r\) can enter the lattice only at \(i = L\) with the probability \(\delta\) per unit time. After entry, the particles \(R_\ell\) and \(R_r\) can hop to the next site in their respective pre-determined directions of motion with the rates \(B_1\) and \(B_2\), respectively.

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Figure 1. A schematic diagram of the model. The whole lattice is divided into three segments \{1, 2, \ldots, L_1 - 1\}, \{L_1, \ldots, L_2\} and \{L_2, \ldots, L\}. An \(R\) particle (green arrow) can enter, either from the first site of segment 1 (i.e. \(i = 1\)) with the probability \(\gamma\) per unit time or from the last site of segment 3 (i.e. \(i = L\)), with the probability \(\delta\) per unit time. An \(R\) particle that enters through \(i = 1\) is allowed to hop from left to right (i.e. \(i \to i + 1\)) with rate \(B_1\), if the target site is empty. But, if an \(R\) particle enters through \(i = L\) it is allowed to hop only from right to left (i.e. \(i \to i - 1\)), with rate \(B_2\). Both the \(R\) particles continue their motion until they meet each other, at a pair of nearest neighbour sites. However, inside segment 2, a new \(P\) particle (yellow circle) can attach only at \(i = L_1\), with rate \(\alpha_q\), only if this site is empty. Once attached, a \(P\) particle can hop forward only from left to right (i.e. \(i \to i + 1\)) by a single site in each step, with rate \(q\), provided the target site is empty. Normally, a \(P\) particle would continue its hopping till it reaches the the site \(L_2\) from where it detaches with rate \(\beta_q\). Thus, the lattice sites in the segments 1 and 3 can be occupied by only the \(R\) particles, whereas a mixed population of \(R\) and \(P\) particles can exist in the segment 2.

(see figure 1). Both these particles can continue hopping, obeying the exclusion principles and rules of resolution of encounters with \(P\) particles as described below, till they encounter each other head-on at the two nearest-neighbor sites on the lattice indicating completion of replication.

Unlike the \(R\) particles, all the \(P\) particles can enter the lattice only at the site \(i = L_1\) with the attachment rate (i.e. probability per unit time) \(\alpha_q\) provided that site is not already occupied by any other particle of either species. Once entered, a \(P\) particle can hop forward to the next site with the rate \(q\) if, and only if, the target site is not already occupied by any other \(P\) or \(R\) particle. A \(P\) particle can continue hopping forward, obeying the exclusion principle and the rules of resolution of the encounter with \(R\) particles, till it reaches the site \(i = L_2\) from where it can exit with the rate \(\beta_q\).

Thus, the division of lattice into three segments is based on the scenario where the lattice sites in the segments 1 and 3 can be occupied exclusively by only the \(R\) particles whereas the sites in middle region (i.e. segment 2) can be populated by both the \(P\) and \(R\) particles. However, in the segment 2 the \(P\) particles encounter the \(R_\ell\) particle co-directionally and \(R_r\) particle head-on. The final encounter between the two \(R\) particles, when they meet each other at two nearest-neighbour sites, is head-on.

Next we described the kinetics of both types of particles in the segment 2 which capture the mutual exclusion of the RNAP motors as well as the rules of resolution of the conflicts between transcription and replication. Mutual exclusion is captured by the simple rule that no site can be occupied simultaneously by more than one particle irrespective of the species to which it belongs. The three possible outcomes of the encounter between a \(P\) particle at the site \(i\) and an \(R_\ell\) particle at site \(i - 1\) or an \(R_r\) particle at the site \(i + 1\) are as follows (see Figure 2):
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Figure 2. Schematic representation of interference between the R particles and the P particles. In (a) and (b) R particle can pass the P particle, with rates $p_{co}$ and $p_{contra}$. In (c) and (d) the R particle can knock the P particle out of the track, with rate $D$. In (e) and (f) P particle can block the progress of the R particle thereby causing its eventual collapse, with rate $C$.

(a) The R particle can bypass the P particle with the rates $p_{co}$ and $p_{contra}$, in the cases of co-directional and contra-directional encounter respectively, without dislodging the latter from the lattice and, therefore, both the particles can continue hopping in their respective natural direction of movement after the encounter.

(b) The R particle can knock the P particle out of the track, with the rate $D$ irrespective of the direction (co- or contra-directional) encounter and it resumes its hopping after the P particle is swept out of its way thereby aborting the transcription by that P particle prematurely.

(c) Upon an encounter with P particles, an R particle does not necessarily always win. In such situations, occasionally, the R particle detaches from the lattice with a probability $C$ per unit time irrespective of the direction of encounter; this scenario captures the possible collapse of the replication fork that can cause genome instability. Once the replication fork collapses, the victorious P particle(s) can resume their onward journey on the lattice.

If the R particles, entering from the sites $i = 1$ and $i = L$, eventually meet each other on a pair of nearest-neighbour sites of the lattice, thereby indicating completion of the replication of the entire stretch of DNA from $i = 1$ to $i = L$, we identify it as a successful event of type 1 (from now onwards we refer to it as sr1). On the other hand, if one of the R particle stalls or collapses at any site inbetween $L_1$ and $L_2$ whilst the other continues hopping until it reaches a nearest neighbor of that particular site of stall or collapse, it also indicates successful completion of replication and, therefore, identified as a successful event of type 2 (from now onwards, referred to as sr2). But if both the R particles are stalled (i.e. replication fork has collapsed) before completely covering the entire lattice together by hopping between the sites 1 and $L$, then the process is identified as an unsuccessful event (usr). Dividing the sum total of the times
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taken by all the sr1 and sr2 events by the total number of all such events we obtain the
mean hopping time of an \( R \) particle (\( \tau \)), which is the mean time required for successful
completion of replication of the DNA of length \( L \) (in the units of ‘base pairs’).

3. Results

Although our model captures just a few key aspects of the biological processes involved
in the TRC, the proposed model is already too complex to allow a rigorous analytical
treatment. We therefore rely mainly on Monte Carlo (MC) simulations. However, in
certain limiting situations, the computer simulations are complemented by an approxi-
mate analytical theory, that draws heavily on the known exact results for TASEP with
single species of particles. The transparent arguments of the analytical derivations
provide some insight into the underlying physical processes. However, the analytical
derivation is based primarily on heuristic arguments some steps of which are essen-
tially equivalent to mean-field approximations. Therefore, the accuracy of our heuristic
analytical arguments have been checked in comparison with the corresponding data
obtained from the MC simulations.

In the MC simulations we adopted random sequential updating to investigate the
effects of traffic of \( P \) particles on the kinetics of \( R \) particles, i.e. the effects of ongoing
transcription on replication. The data collected during the simulations are averaged
over 10 000 realizations each starting from a fresh initial configuration. We convert
the rates into probabilities by using the conversion formula \( p_k = k \, dt \) where, \( k \) is an
arbitrary rate constant and \( dt \) is an infinitesimally small time interval; the typical
numerical value of \( dt \) used in our simulations is \( dt = 0.001 \) s. Unless stated explicitly
otherwise, the numerical values of the relevant parameters used in the simulations are
\( L = 2000, \, L_1 = 500, \, L_2 = 1500, \, B_1 = B_2 = 300 \, s^{-1}, \, \beta_q = 1000 \, s^{-1} \) and \( q = 30 \, s^{-1} \).

3.1. Effects of steady traffic of RNAPs on replication time

The time needed for a successful completion of replication (from now onwards, referred
to as ‘replication time’) is identified as the time taken by the two \( R \) particles to meet
head-on, starting from their simultaneous entry into the lattice through \( i = 1 \) and
\( i = L \). In order to measure the replication time in the steady traffic of \( P \) particles in
the MC simulations, we first switch on the entry of only the \( P \) particles (i.e. transcrip-
tion) through \( i = L_1 \). The two \( R \) particles are allowed to enter simultaneously, through
\( i = 1 \) and \( i = L \) only after the flux of the \( P \) attains its constant value in the non-equi-
librium steady-state of the TASEP. Once the \( R \) particles enter the segment 2 and start
encountering the \( P \) particles, the rate of replication begins to get adversely affected.

We first present the derivation of the analytical results before comparing with the
corresponding data obtained from MC simulation. Suppose \( n \) denotes the number of
particles in the segment 2 of the lattice. In the limit \( n \gg 1 \), the effects of a single \( R \) par-
ticle on the flow of the \( P \) particles is expected to be negligibly small so that the move-
ment of the \( P \) particles can be approximated well by a purely single-species TASEP
in the segment 2. Under this assumption, the flux \( J_P \) of the \( P \) particles corresponding
to the number density $\rho$ inside segment 2 is given by the standard formula (see, for example, [59])

$$J_P = q\rho(1 - \rho).$$

(1)

Since, because of the open boundaries, $n$ fluctuates with time even in the steady state, the number density $\rho = n/(L_2 - L_1)$, also fluctuates with time. The effective velocity of the $P$ particles corresponding to the flux (1) in segment 2 is given by

$$v_P = \frac{J_P}{\rho} = q(1 - \rho).$$

(2)

First we explore the parameter regime where $\beta$ is so large that at sufficiently low values of $\alpha$ the $P$ particles would be in the low-density (LD) phase of the TASEP (in the ‘initiation’-limited regime in the terminology of transcription). With the increase of $\alpha$ the system would make a transition to the maximal current (MC) phase of TASEP (‘elongation-limited’ regime of transcription). For the analytical derivation, we assume the following simplified situations:

(a) None of the $R$ particles collapse (i.e. $C = 0$) upon an encounter with $P$ particles,

(b) None of the $P$ particles can detach from the lattice prematurely (i.e. $D = 0$),

(c) In the absence of any hindrance, the rate of replication by both the forks is identical, i.e. the symmetric case: $B_1 = B_2 = B$.

Since the time intervals between the entry of the $P$ particles at $i = L_1$ are quite long, the number of $P$ particles encountered co-directionally by $R_\ell$ and that head-on by $R_r$ would be almost identical under the conditions (a)–(c) above, the most-probable location for the head-on meet of the two oppositely moving $R$ particles is expected to be the midpoint of the segment 2 (i.e. at $i, i + 1 \approx L/2, L/2 \pm 1$), and

(d) In order to simplify the analytical expressions, we also assume that the length of the segment 2 is $\approx L/2$.

Let us define

$$\frac{\alpha_q}{q} \rightarrow \alpha, \quad \frac{\beta_q}{q} \rightarrow \beta,$$

(3)

as the rescaled initiation and termination rates, respectively, of a $P$ particle. Using the well known results for the flux and density profile of TASEP under open boundary conditions [60, 61], we get expressions for $J_2$ and $v_2$, in all three possible phases: In the LD phase,

$$J_P = q\alpha(1 - \alpha), \quad v_P = q(1 - \alpha),$$

(4)

in the high density (HD) phase,

$$J_P = q\beta(1 - \beta), \quad v_P = q(1 - \beta),$$

(5)
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and in the MC phase,

\[ J_P = \frac{q}{4}, \quad v_P = \frac{q}{2}. \quad (6) \]

Next, we define the effective velocity of an \( R \) particle inside segment 2. For \( R_\ell \)

\[ v_{R_\ell} = \begin{cases} B_1(1 - \rho) & \text{if no } P \text{ particle in front} \\ p_{co} (1 - \rho) & \text{if } P \text{ particle is in front} \end{cases} \quad (7) \]

whereas for \( R_r \)

\[ v_{R_r} = \begin{cases} B_2(1 - \rho) & \text{if no } P \text{ particle in front} \\ p_{contra} (1 - \rho) & \text{if } P \text{ particle is in front} \end{cases} \quad (8) \]

Note that, by definition, \( p_{co} \) and \( p_{contra} \) are the probabilities of hopping to the next-nearest neighbour site. Therefore, the factor \((1 - \rho)\) in the lower lines of equations (7) and (8) accounts for the vacancy of the targeted next-nearest neighbour site. In contrast, \( B_1 \) and \( B_2 \) are defined as the nearest-neighbour hopping probabilities; the factor \((1 - \rho)\) multiplying \( B_1 \) and \( B_2 \) in the upper lines of the equations (7) and (8) accounts for the vacancy of the targeted nearest-neighbour site. In the mean-field approximation the probability of vacancy of the nearest-neighbour site and that of the next-nearest-neighbour sites are identical and each is equal to \( 1 - \rho \).

Therefore, the relative velocities \( v_r \) with which an \( R \) particle approaches a leading \( P \) particle, are \( v_{R_\ell} - v_P \) and \( v_{R_r} + v_P \) for co-directional and contra-directional encounter, respectively. The average separation \( d \) between the \( P \) particles, i.e. distance headway between the successive particles, in the segment 2 is

\[ d = \frac{1}{\rho}. \quad (9) \]

From expressions (2), (7) and (8), the average interaction times \( \tau_{co} \) and \( \tau_{contra} \), between an \( R \) particle and a \( P \) particle, during co-directional and contra-directional encounter, are given by,

\[ \tau_{co} = \frac{d}{v_{R_\ell} - v_P} = \frac{1}{2\rho} \left[ \frac{1}{B_1(1 - \rho) - q(1 - \rho)} + \frac{1}{p_{co}(1 - \rho) - q(1 - \rho)} \right], \quad (10) \]

and

\[ \tau_{contra} = \frac{d}{v_{R_r} + v_P} = \frac{1}{2\rho} \left[ \frac{1}{B_2(1 - \rho) + q(1 - \rho)} + \frac{1}{p_{contra}(1 - \rho) + q(1 - \rho)} \right], \quad (11) \]
where we have arrived at the expression for $\tau_{\text{co}}$ assuming it to be an average of the contributions from the two situations mentioned in (7). Similarly the expression for $\tau_{\text{contra}}$ is also the average of the two contributions from the alternative cases mentioned in (8).

Next, we define $N_{\text{co}}$ and $N_{\text{contra}}$, as the total number of encounters that an $R$ particle can suffer inside the segment 2. We derive approximate expressions for $N_{\text{co}}$ and $N_{\text{contra}}$. When the conditions (a)–(d) are satisfied, $N_{\text{co}}$ and $N_{\text{contra}}$ are given by the expressions

$$N_{\text{co}} = N_{\text{contra}} \approx \frac{\rho L}{4},$$

(12)

where the factor $L/4$ arises from the fact that each of the $R$ particles has to traverse a distance of $L/4$ to reach the middle of the segment 2. From expressions (10)–(12), we calculate the total hopping time of an $R$ particle inside segment 2, i.e. $\tau_{\text{int}}$, as a product of the total number of interactions and average encounter time. In a steady state, $\tau_{\text{int}}$ is given by

$$\tau_{\text{int}} = N_{\text{co}} \tau_{\text{co}} + N_{\text{contra}} \tau_{\text{contra}}$$

$$= \frac{\rho L}{4} (\tau_{\text{co}} + \tau_{\text{contra}}).$$

(13)

Further, we calculate the total replication time $\tau$ as a summation of replication times inside segment 1 and 3 and replication time $\tau_{\text{int}}$ inside segment 2,

$$\tau = \frac{\tau_{\text{int}}}{2} + \frac{L}{4B_1}$$

$$= \frac{\rho L}{8} (\tau_{\text{co}} + \tau_{\text{contra}}) + \frac{L}{4B_1},$$

(14)

where the extra factor of 1/2 in the first term on the right hand side is needed to average over the two directions of the encounter. Note that the dependence of $\tau$ on $\alpha_q$ arises in (14) from the use of the result $\rho(\alpha) = \alpha$ for the LD phase of $P$ particles where the relation between $\alpha$ and $\alpha_q$ is given by (3).

In figure 3, we show the variation of replication time $\tau$ with the rate of transcription initiation (i.e. entry rate $\alpha_q$ of the $P$ particles), for a constant transcription termination rate (exit rate of $P$ particles) $\beta_q$. With the increase of $\alpha_q$, $\tau$ increases, and eventually saturates, above a critical value of $\alpha_q$. This behavior is qualitatively reproduced by the heuristic analytical arguments. The latter, however, tends to slightly overestimate the mean replication time.

The steady state density profiles of the $P$ particle are plotted in the inset of figure 3 for a few different values of $\alpha_q$. The trend of variation of the profiles with $\alpha_q$ is consistent with the transition from the LD phase to MC phase of the TASEP of the $P$ particles. For all those values of $\alpha_q$, for which system is in the LD phase, particle density $\rho$ increases with the increase of $\alpha_q$. Therefore, the total number of encounters that an $R$ particle can have inside segment 2 also increases, which results the increase in $\tau$. Above a critical value of $\alpha_q$, the TASEP in the segment 2 makes a transition to the MC phase where the number density $\rho$ of the $P$ particles and, hence, $\tau$, becomes independent of $\alpha_q$.

In figure 3 we have plotted $\tau$ against $\alpha_q$ for two distinct cases. In the first case $p_{\text{co}} = p_{\text{contra}} = 30$ s$^{-1}$ (i.e. the rates of passing are the same irrespective of the direction of
encounter). But in the second case the rates of passing are asymmetric, i.e. $p_{\text{contra}} < p_{\text{co}}$, where $p_{\text{co}} = 30\, \text{s}^{-1}$ and $p_{\text{contra}} = 20\, \text{s}^{-1}$. The higher value of $\tau$ in the latter case shows that even if one of the passing rates decreases, it leads to an increase of the time needed for completing the replication because an $R$ particle has to pause for a longer duration.

Next, based on similar heuristic mean-field-type arguments, we derive analytical expressions for the average replication time in the opposite limit where $\alpha$ is sufficiently high. In this parameter regime, at sufficiently small values of $\beta$, the system is in the high density (HD) phase of TASEP ('termination'-limited regime of transcription), but makes a transition to the MC phase with the increase of $\beta$. For the analytical arguments, we assume the same special scenario (a)–(c) above, i.e. $C = D = 0\, \text{s}^{-1}$.

In this case, because of the high value of $\alpha$ the particle $R_r$ is expected to suffer a large number of encounters with $P$ particles all of which approach it head-on. Even if it succeeds, entering the segment 2 through $i = L_2$, and moves ahead at a slow pace by passing oncoming $P$ particles, new $P$ particles continue to make fresh entries into this segment through $i = L_1$. Thus, the number of particles to be bypassed by $R_r$ keep increasing as time passes till $R_r$ exits the segment 2 through $i = L_1$. In contrast, the particle $R_\ell$ encounters far fewer $P$ particles because, after it enters the segment 2, the new entrant $P$ particles would be falling behind it and even some of those in front would make their exit from $i = L_2$ before $R_\ell$ catches up co-directionally from behind.

Therefore, we make the simplifying assumption (perhaps, a slight oversimplification) that the particle $R_r$ remains stalled at $i = L_2 + 1$ and replication is completed only when $R_\ell$ reached $i = L_2$.

The average number of $P$ particles within the segment from $L_1$ to $L_2$ is $(L_2 - L_1)\rho$ where $\rho$ is the average number density of the $P$ particles in this segment. The average spatial gap between the $P$ particles, as given by equation (9), is $1/\rho$ and the number of
gaps to be covered by an $R$ particle is $(L_2 - L_1)\rho$. Therefore, the total time spent by the $R$ particle in exchanging its position with the co-directionally moving $P$ particles is

$$\tau_{\text{exch}} = (L_2 - L_1)\rho/p_{co}. \quad (15)$$

The effective velocity of an $R$ particle in the segment between $L_2$ and $L_1$ is $B - q$. The total time spent by the $R$ particle in covering all the gaps by forward hopping is

$$\tau_{\text{hop}} = (L_2 - L_1)\rho \frac{1}{\rho(B - q)} = (L_2 - L_1)/(B - q). \quad (16)$$

The time taken by the $R$ particle to reach $L_1$ from $i = 1$ is

$$\tau_{\text{arr}} = L_1/B. \quad (17)$$

Thus, finally, the total time taken to complete the replication is

$$\tau = \frac{(L_2 - L_1)\rho}{p_{co}} + \frac{(L_2 - L_1)}{(B - q)} + \frac{L_1}{B}. \quad (18)$$

In figure 4, we show the variation of replication time $\tau$ with the rate of transcription termination (i.e. exit rate $\beta_q$ of the $P$ particles), for a constant transcription initiation rate (entry rate of $P$ particles) $\alpha_q$. Note that the dependence of $\tau$ on $\beta_q$ arises in (18) from the use of the result $\rho(\beta) = 1 - \beta$ for the HD phase of $P$ particles where the relation between $\beta$ and $\beta_q$ is given by (3). With the increase of $\beta_q$, $\tau$ decreases, and eventually saturates, above a critical value of $\beta_q$. This behavior is qualitatively reproduced by the heuristic analytical arguments which slightly overestimate the mean replication time. The steady state density profiles of the $P$ particle are plotted in the inset of figure 4 for a few different values of $\beta_q$. The trend of variation of the profiles with $\beta_q$ is consistent with the transition from the HD phase to MC phase of the TASEP of the $P$ particles. For all those values of $\beta_q$, for which system is in HD phase, particle density $\rho$ decreases with increase of $\beta_q$. Therefore, the total number of encounters that an $R$ particle can have inside segment 2 also decreases, which results the decrease in $\tau$. Above a critical value of $\beta_q$, the TASEP in the segment 2 makes a transition to the MC phase where the number density $\rho$ of the $P$ particles and, hence, $\tau$, becomes independent of $\beta_q$.

In the absence of collapse of the replication fork ($C = 0$) and premature detachment of RNAP ($D = 0$), the replication time is essentially decided by the density of the RNAP motors (i.e. $R$ particles). Since one or two $R$ particles hardly make any noticeable perturbation of the density that is prescribed by the exact theory for a pure TASEP of $P$ particles, the expressions (14) and (18) for the replication time $\tau$ are in excellent agreement with the corresponding data obtained from MC simulation of the model.

### 3.2. Histograms of the number of successful and unsuccessful replication events

In this subsection we show the effects of transcription on replication. For this purpose, we calculate how the distributions of the three processes, namely, sr1, sr2 and usr are affected by the encounter of $R$ particles with the $P$ particles.

- **Special case of $C \neq 0$ and $D = 0$**

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Nonzero $C$ gives rise to two other alternative scenarios. If only one of the $R$ particles collapses and the other does not replication is completed via the alternative route that we defined as $s_{r2}$. Similarly, collapse of both the $R$ particles leads to nonzero probability of $s_{usr}$. Note that any increase in the probabilities of $s_{r2}$ or $s_{usr}$, or both, cause reduction in the probability of $s_{r1}$ because $P_{s_{r1}} + P_{s_{r2}} + P_{s_{usr}} = 1$.

Suppose, on the average, the total number of $P$ particles in the segment between $i = L_1$ and $i = L_2$ is $N$. If $N$ events of passing in the segment between $i = L_1$ and $i = L_2$ is required for completion of replication without suffering collapse of either of the two replication forks, then the probability of $s_{r1}$ is

$$P_{s_{r1}} = \left( \frac{p}{p + C} \right)^N$$

For $s_{r2}$, one of the forks ($R$ particles) has to collapse while the remaining stretch of the segment between $i = L_1$ to $i = L_2$ is covered by the surviving fork. One of the forks may collapse after passing $n$ number of $P$ particles; the probability of its occurrence is $[C/(p + C)][p/(p + C)]^n$; the probability that the surviving fork passes the other remaining $P$ particles is $[p/(p + C)]^{N-n}$. Thus, the probability of $s_{r2}$ is

$$P_{s_{r2}} = \sum_{n=0}^{N-1} \left[ \left( \frac{C}{p + C} \right) \left( \frac{p}{p + C} \right)^n \right] \left( \frac{p}{p + C} \right)^{N-n}$$

$$= N \left( \frac{C}{p + C} \right) \left( \frac{p}{p + C} \right)^N.$$  

Exploiting normalization, we get the probability for $s_{usr}$

$$P_{s_{usr}} = 1 - P_{s_{r1}} - P_{s_{r2}}.$$
Note that $N = \rho(L_2 - L_1)$ is the average number of $P$ particles in the interaction segment between $i = L_1$ and $i = L_2$. In the LD regime of $P$ particles $\rho = \alpha = \alpha_q/q$.

In figure 5, we plot the distributions of ‘sr1’, ‘sr2’ and ‘usr’ as histograms for (a) five distinct values of $\alpha_q$ and a constant value of $\beta_q$, and (b) five distinct values of $\beta_q$ and a constant value of $\alpha_q$. The analytic approximations (19)–(21) reproduce qualitatively the behavior observed in the MC simulations. For a given sufficiently high value of $\beta_q$, segment 2 is in the LD phase at small values of $\alpha_q$. In this regime the number of eventual collapse of an $R$ particle during its encounters with $P$ particles is negligibly small. Therefore, for these small values of $\alpha_q$, number of events of the type ‘sr2’ and ‘usr’ are low and, hence the probability of sr1 is very weakly affected (see figure 5(a)). As $\alpha_q$ increases further, the number of eventual collapse increases because of the increasing

**Figure 5.** Distribution of sr1, sr2 and usr in the special case $C \neq 0$, $D = 0$ is plotted for five different values of (a) $\alpha_q$, for fixed $\beta_q = 1000$ s$^{-1}$ and (b) $\beta_q$, for fixed $\alpha_q = 1000$ s$^{-1}$. The data used for the bar plots have been obtained by MC-simulations. Lines have been obtained from the analytical expressions (19)–(21). Dotted line corresponds to $P_{sr1}$, dashed line corresponds to $P_{sr2}$ and continuous line corresponds to $P_{usr}$. The other relevant parameters used in this figure are $L = 2000$, $q = 30$ s$^{-1}$, $C = 0.05$ s$^{-1}$, $D = 0$ and $p_{co} = p_{contra} = p = 20$ s$^{-1}$. 
number of encounters with \( P \) particles, which is reflected in the significant increase in ‘sr2’ and ‘usr’ in figure 5(a). Increase in the probabilities of sr2 and usr results in the corresponding decrease in the probability of sr1 because of the normalization of the probabilities mentioned above. Number of the events ‘sr1’, ‘sr2’ and ‘usr’ attain their respective saturation values as \( \alpha_q \) increases above the critical value where the transition from LD phase to MC phase takes place (see figure 5(a)). Similarly, for a sufficiently high value of \( \alpha_q \), with increasing \( \beta_q \) the \( P \) particles exhibit a transition from the HD phase to the MC phase. Consequently, the decrease in the frequency of encounter of the \( P \) particles with the \( R \) particles. The likelihood of collapse of both the \( R \) particles in any run decreases as indicated by the increase of

Figure 6. Distribution of sr1, sr2 and usr in the general case \( C \neq 0, D \neq 0 \) is plotted for five different values of (a) \( \alpha_q \), for fixed \( \beta_q = 1000 \) s\(^{-1} \) and (b) \( \beta_q \), for fixed \( \alpha_q = 1000 \) s\(^{-1} \). In inset we plot the variation in \( N \) (i.e. average number of \( P \) particle detached from the track during their encounter with \( R \) particles) with (a) \( \alpha_q \) and (b) \( \beta_q \). These data have been obtained only from MC-simulations. The other relevant parameters used in this figure are \( L = 2000 \), \( q = 30 \) s\(^{-1} \), \( \alpha_q = 1000 \) s\(^{-1} \), \( D = 10 \) s\(^{-1} \) and \( p_{co} = p_{contra} = p = 20 \) s\(^{-1} \).
the probability of sr2. The concomitant increase of the probability of sr is also shown in figure 5(b).

- **Special case of** $C \neq 0$ **and** $D \neq 0$

Now, we consider the general case of our model allowing for the possibilities that $C \neq 0$ and $D \neq 0$. As we have already done in the restricted case of $C \neq 0$, $D = 0$, we characterize the effect of nonzero $C$ and $D$ also in terms of the statistics of ‘sr1’, ‘sr2’ and ‘usr’.

In figures 6(a) and (b), we plot the distributions of the events ‘sr1’, ‘sr2’ and ‘usr’ as histograms for (a) five different values of $\alpha_q$ at a constant high value of $\beta_q$ and (b) five different values of $\beta_q$ at a constant high value of $\alpha_q$. The trends of variation of these three probabilities are explained by the transition to the MC phase from (a) LD phase and (b) HD phase.

In the inset of figure 6, we display the effects of replication on transcription. We show the variation in the number $N$ of $P$ particles that detach from the lattice when they encounter an $R$ particle, for (a) fixed $\beta_q$ and (b) fixed $\alpha_q$. The trend of variation and the physical reason for this trend is also well explained by the transition to the MC phase from (a) LD phase and (b) HD phase.

### 3.3. Distribution of detachments of $P$ particles

In MC simulations, we measure the time intervals between two consecutive $P$ detachment events as $\delta t_1$, $\delta t_2 \ldots \delta t_n$, if $n + 1$ detachments take place in a single MC simulation run. Since this is a stochastic process these time intervals $\delta t_1$, $\delta t_2 \ldots \delta t_n$ are, in general, different from each other. We compute the number of consecutive $P$ detachment events corresponding to a given interval $\delta t$, i.e. if two time intervals are identical ($\delta t_i = \delta t_j = \delta t$), then, number of consecutive $P$ detachment events with the time interval $\delta t$ is 2. We repeat the procedure over 10 000 MC simulation runs to calculate the total number of consecutive $P$ detachment events with given interval $\delta t$, and then we divide this number by the number of MC simulation runs, i.e. 10 000, to calculate

**Figure 7.** Distribution of $N_\alpha$ is plotted with $\delta t$ for a constant $\alpha_q = 100$ s$^{-1}$. In inset we plot $N_\alpha$ with $\delta t$ on a semi-log axis to show the exponential fall of $N_\alpha$ with $\delta t$. These data have been obtained by MC-simulations only. The other relevant parameters used in this figure are $C = 0.05 s^{-1}$, $D = 10 s^{-1}$, $p_{\text{co}} = 20$ s$^{-1}$ and $p_{\text{contra}} = 20$ s$^{-1}$.  

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the average number $N_\alpha$ of consecutive $P$ detachments within the time interval $\delta t$ for a fixed rate $\alpha_q$.

In figure 7 we show the variation in $N_\alpha$ with $\delta t$ and we find that $N_\alpha$ falls exponentially as the time interval between two consecutive $P$ detachment events increases. To confirm the exponential behavior, in the inset we show the variation in $N_\alpha$ on a semi-log axis with $\delta t$.

4. Summary and conclusion

In this paper we have developed the first minimal model that captures the key kinetic rules for the resolution of conflict between ongoing transcription and concomitant replication of the same stretch of DNA. This model has been formulated in terms of a two-species exclusion process where one species of the particles (denoted by $P$) represents the RNAP motors while the two members of the other species (denoted by $R$) represent the two replication forks.

In contrast to all the multi-species exclusion models reported so far, the allowed populations of the two species are quite different in our model. A maximum of only two $R$ particles are allowed to enter the lattice; imposition of this restriction on the number of $R$ particles is motivated by the fact that none of the segments of DNA should be replicated more than once during the life time of a cell. In sharp contrast, the number of $P$ particles is not restricted except for the control of their population by the rate constants for their entry, exit and hopping. This choice is consistent with the fact that the multiple rounds of transcription of the same segment of DNA is not only possible but resulting synthesis of multiple identical transcripts is also desirable for the proper biological function of the cell. Moreover, all the $P$ particles move co-directionally, from left to right whereas one of the $R$ particles (namely, $R_1$) moves from left to right while the other $R$ particle (namely $R_2$) approaches it head-on from the opposite end. Another distinct feature of this model is that the lattice consists of three segments; the encounters of RNAP motors ($P$ particles) with the replication fork ($R$ particles) are confined within the middle segment (segment 2) whereas only the $R$ particles can occupy the sites in the segments 1 and 3.

It is worth pointing out that a two-species exclusion process has been developed in the recent past [62] to model the interference of the transcription of two overlapping segments of DNA. One thing that is common in both the transcriptional interference (TI) model of [62] and the TRC model developed here is the tendency of each species of particles to suppress the movement of the other species. However, there are several crucial differences between the two models. Unlike the restriction on the population of the $R$ particles in the model developed in this paper, no restriction on the allowed population of the either species was imposed in the TI model [62]. Moreover, all the members of a given species move in the same direction in the TI model, whereas in this paper $R_1$ and $R_2$ move in opposite directions. Furthermore, the region of interference of the two transcriptional processes is independent of time whereas, that in the TRC model here shrinks with the passage of time.

By a combination of analytical treatment, based on heuristic arguments, and Monte Carlo simulations we have analyzed the effects of the RNAP motor traffic on the DNA
A biologically inspired two-species exclusion model: effects of RNA polymerase motor traffic replication and vice versa. More specifically, we have shown how the transition from the LD phase to the MC phase and that from the high-density phase to the MC phase of $P$ traffic affects not only the total time required for successful completion of replication, but also how the statistics of successful and unsuccessful replication events are affected.

Any attempt of direct comparison between the theoretical predictions of our model and the experimental data may be premature at this stage. There are some important features of DNA replication in eukaryotic cells that we hope to incorporate in future extensions of our model. For example, even after two replication forks begin approaching each other head-on, new pairs of replication forks can nucleate in the unreplicated segment of the DNA in between the two. However, the price to be paid for a more realistic and detailed model would be to sacrifice the possibility of analytical treatments even on the basis of heuristic arguments. Nevertheless, computer simulations would still provide some mechanistic insight into the causes and consequences of the TRC.

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