Driven transport on a flexible polymer with particle recycling: a model inspired by transcription and translation

Lucas D. Fernandes
Departamento de Entomologia e Acarologia, Escola Superior de Agricultura Luiz de Queiroz - Universidade de São Paulo (USP), 13418-900, Piracicaba/SP, Brazil and
Department of Life Sciences, Imperial College London, Silwood Park, Ascot, Berkshire, SL5 7PY, UK

Luca Ciandrini
Laboratoire Charles Coulomb (L2C), Université de Montpellier and CNRS, Montpellier, France
CBS, Université de Montpellier, CNRS and INSERM, Montpellier, France and
DIMNP, Université de Montpellier and CNRS, Montpellier, France
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Many theoretical works have attempted to coarse grain gene expression at the level of transcription and translation via frameworks based on exclusion processes. Usually in these models the three-dimensional conformation of the substrates (DNA and mRNA) is neglected, and particles move on a static unidimensional lattice in contact to an infinite reservoir. In this work we generalise the paradigmatic exclusion process and study the transport of particles along a unidimensional polymer-like flexible lattice immersed in a three-dimensional particle reservoir. We study the recycling of particles in the reservoir, how the transport is influenced by the global conformation of the lattice and, in turn, how particle density dictates the structure of the polymer.

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Introduction. Since their first formulation at the end of the 60’s [1], driven lattice models drew the attention of the scientific community for both their relevance in non-equilibrium statistical mechanics, the novelty of their theoretical approaches, and their powerful applications in transport processes [2].

Historically, the prototypical model of unidimensional traffic, the totally asymmetric simple exclusion process (TASEP), has been developed and then extended to describe the collective movement of biological “active particles” such as ribosomes, RNA polymerases or motor proteins, on their respective unidimensional substrates (mRNA, DNA, microtubules or actin filaments). Most of state-of-the-art models describing the gene expression stages of transcription and translation exploit implicitly or explicitly this class of models [3-6]; despite their coarse-grained nature, these frameworks are able to capture the main features of the biological processes.

Although it is incontestable that strands of mRNA or DNA molecules are dynamical objects with complex three-dimensional conformations, common models approximate those tracks with unidimensional unstructured lattices and neglect their polymer-like nature. The interdependence between the lattice conformation and the transport process, however, should be considered when focusing on quantitative modelling aimed to compare experimental data and extract information on the molecular mechanisms. For instance, spatial clustering of genes in transcription factories [7] suggests an interplay between structural conformation of the DNA, gene expression and local recycling of polymerases. Similar effects, including the importance of local ribosome concentrations, can also be expected in translation since the ribosomes are not uniformly distributed in the cytoplasm [8]. Furthermore, different conformations assumed by the transcript can explain the gene length-dependence of mRNA translation, as we have recently addressed [9]. Although there are a few models considering the effects of the transport on the substrate dynamics [10] or on local structures [11], its impact on the overall three-dimensional conformation of the lattice has not been explored.

In this paper we propose a non-equilibrium model of transport on a polymer-like substrate, which is immersed in a three-dimensional reservoir of diffusing particles. In our derivation we implicitly consider that the timescales of transport and polymer dynamics are well separated [12]. We gathered in [13] the assumptions of the model.

We investigate (i) how the three-dimensional structure of the lattice affects the particle recruitment and the transport process, as well as (ii) how the driven lattice gas impacts, via the particle density, global features of the polymer. We start with a short review of the well known TASEP results, then we couple the system to a three-dimensional diffusive reservoir of particles, and eventually study the interplay between the local concentration of particles, the lattice conformation and the transport process.

Reminder of TASEP results. In its simplest formulation the TASEP consists of a discrete lattice of $L$ sites where particles are injected from one end with rate $\alpha$, move from one site to the following one -if empty- with rate $p$, and are eventually removed from the last site with rate $\beta$, as illustrated in Fig. 1(a). The
The system is usually studied by varying the dimensionless parameters $\bar{\alpha} := \alpha/p$ and $\bar{\beta} := \beta/p$, and the phase diagram of the system is known exactly \cite{14}. This is a rich model showing three different regimes (LD, low density; HD, high density; MC, maximal current), as well as first and second-order phase transitions. The LD-HD transition line shows a coexistence between the two phases, and it is often named SP (shock phase). The phase diagram is sketched in Fig. 1(b), and each phase is characterised by a density of particles $\rho$ (average number of particles per site) and current $J$ (particles passing through a site per unit time). Mean-field approaches give the steady-state correct results, which we report in Table I in the thermodynamic $L \to \infty$ limit.

### Table I. Summary of the TASEP mean-field results.

| Phase | Limits | Density | Current |
|-------|--------|---------|---------|
| LD    | $\bar{\alpha} < \bar{\beta}$, $\bar{\alpha} < 1/2$ | $\rho = \bar{\alpha}$ | $J = p\bar{\alpha}(1 - \bar{\alpha})$ |
| HD    | $\bar{\alpha} > \bar{\beta}$, $\bar{\beta} < 1/2$ | $\rho = 1 - \bar{\beta}$ | $J = p\bar{\beta}(1 - \bar{\beta})$ |
| MC    | $\bar{\alpha}, \bar{\beta} \geq 1/2$ | $\rho = 1/2$ | $J = p/4$ |

**Coupling TASEP on a polymer and a diffusive reservoir.**

In the standard TASEP, the lattice is immersed in an infinite reservoir of particles for which the density determines the entry rate $\alpha$; the system can also be coupled to a finite reservoir of particles, and the effects of competition and depletion of a homogenous reservoir without spatial extension has been tackled previously \cite{15}. Here instead we assume that the entry rate depends on the local concentration of particles $c$ in a reaction volume $V_a$ of radius $a$ around the first site, see Fig. 1(c):

$$\bar{\alpha} = \frac{\alpha_0}{p} \int_{V_a} c(r) d^3r,$$

where $c(r)$ is the concentration of particles in the reservoir at the position $r$, and $\alpha_0$ plays the role of the reaction rate constant. As a lattice, we consider a worm-like chain polymer with persistence length $l_p$, the relation between its length $L$ and the end-to-end distance $R$ is given by \cite{16}

$$R = \left[ \frac{2l_p^2}{l_p - 1 + e^{-\frac{L}{l_p}}} \right]^\frac{1}{2} \sim \sqrt{2pL},$$

where we have approximated Eq. (2) since $L \gg l_p$ in many practical cases. For instance, a typical mRNA of length $L = 300$ codons has a persistence length of $\sim 1$ codon $\sim 1$ nm \cite{17}. For practical reasons we consider that the origin of the coordinate reference system coincides with the centre of the reaction volume surrounding the entry site.

In order to couple the transport process and the reservoir of particles we need to compute $c(r)$ inside $V_a$, which can be done by solving the diffusion equation with a sink at position $0$ ($S_-$) and a source at position $R$ ($S_+$):

$$D \nabla^2 c(r) = S_+(r) - S_-(r),$$

where $D$ is the diffusion coefficient of the particles in the reservoir. The sink and the source respectively describe the depletion, where particles are injected in the first site of the lattice, and their appearance around the last site where they abandon the unidimensional track. We exploit the steady-state condition, and considering for the sake of simplicity that the reaction volumes of sink and source are the same, we have $S_+(r) := \pm J/V_a$. This connects the diffusion Eq. (3) to the TASEP currents in the three different phases (see Table I). We notice that the source $S_+$ term in Eq. (3) introduces a spatial feedback, which we also refer to as particle recycling, as particles leave the end site and, via diffusion, contribute to the local concentration inside the sink $S_-$. The Poisson equation (3) is the same holding in electrostatics to compute the potential $V(r)$ in a system with two spherical and homogeneous distributions of charges \cite{18, 19}. For an individual $S_\pm$, the concentration $c(x)$ at a distance $x$ from the centre of each sphere can then be written as

$$c(x) = \begin{cases} 
\pm \frac{J}{4\pi D x^2} & \text{outside } S_\pm \\
\pm \frac{J}{8\pi D a^2} (3a^2 - x^2) & \text{inside } S_\pm 
\end{cases}$$

By exploiting the linearity of the diffusion equation and fixing the density far away from the lattice to be $c_\infty$, we construct the expression of $c(r)$ used to compute the entry rate. Solving the integral in Eq. (4), we obtain the expression for the injection $\bar{\alpha}$ as a function of the current $J$ and the distance $R$ between the entry and exit sites:

$$\bar{\alpha} = \bar{\alpha}_\infty + \frac{J}{p} \Gamma,$$

where
where $\tilde{\alpha}_\infty := \alpha_0 c_\infty / p$ corresponds to the injection parameter usually considered in standard TASEP-based models (i.e. without particle recycling and reservoir depletion), and

$$\Gamma := \begin{cases} \frac{\alpha_0}{4\pi Da} \left( \frac{1}{2d} - \frac{6}{5} \right) & \text{for } d \geq 1 \\ \frac{\alpha_0}{4\pi Da} d^2 \left[ \frac{3}{2} d^2 - \frac{1}{5} d^3 - 2 \right] & \text{for } d < 1 \end{cases}$$

for $d := R/2a$ \[13\]. We recover the standard TASEP when $\Gamma = 0$, i.e. when $D \to \infty$ and we can neglect the spatial inhomogeneities in the reservoir.

Coupling Eq. [5] to the particle current in the LD, HD and MC phases shows how these different regimes affect the spatial feedback and thus the injection $\tilde{\alpha}$. Equation [5] will therefore take different forms according to the phase of the TASEP (see Table I):

$$\tilde{\alpha} = \begin{cases} \tilde{\alpha}_\infty + \tilde{\alpha}(1 - \tilde{\alpha}) \Gamma & \text{(LD)} \\ \tilde{\alpha}_\infty + \beta(1 - \tilde{\beta}) \Gamma & \text{(HD)} \\ \tilde{\alpha}_\infty + \Gamma / 4 & \text{(MC)} \end{cases}$$

Only in the LD phase we need to solve a second order equation to find $\tilde{\alpha}$ and obtain

$$\tilde{\alpha}_{LD} = \frac{(1 - \Gamma)^2 + 4 \tilde{\alpha}_\infty \Gamma}{2 \Gamma}.$$  

We recall that the solution $\tilde{\alpha}_{LD}$ is relevant only if $\tilde{\alpha} < \tilde{\beta}$ and $\tilde{\alpha} < 1/2$ (otherwise the system is in HD or MC); we always find only one physical solution $\tilde{\alpha}_{LD}$.

The phase boundaries given in Table I can be rewritten in terms of the new parameters and in Fig. 2(a) we show the phase diagram of the system in the $\{\tilde{\alpha}_\infty, \tilde{\beta}\}$ plane for different values of $\Gamma$ (color online). As expected from Eq. (5), only one physical solution $\tilde{\alpha}_{LD}$.

We compute an effective persistence length $l_{\text{eff}}$ by considering the portion of the lattice occupied by particles ($\rho l$), which has a persistence length $\ell/2$ equal to half the particle length $\ell$, and the portion of the lattice that is empty $(1 - \rho l)$, with a persistence length $l_p$. $l_{\text{eff}} = \rho l^2 + (1 - \rho l) l_p$. This relation is valid only when $\ell/2 \geq l_p$, and otherwise $l_{\text{eff}} = l_p$. We can then redefine

$$R := \sqrt{2 l_{\text{eff}}} L = R_0 F_\rho,$$

where

$$R_0 := \sqrt{2l_p L},$$

$$F_\rho := \left[ 1 + \rho \ell \left( \frac{\ell}{2 l_p} - 1 \right) \right]^{1/2}, \quad \ell/2 \geq l_p.$$  

Here $R_0$ is the mean end-to-end distance of an empty polymer and $F_\rho = R/R_0 \geq 1$ is a measure of how much the polymer is flattened by the particle occupancy. We use either $R$ or $F_\rho$ as proxies for the polymer conformation. The parameter $\Gamma$ then reads

$$\Gamma = \begin{cases} \Gamma_0 + \frac{\alpha_0}{4\pi Da} \frac{1}{R_0} \left( 1 - \frac{F_\rho}{F_\rho} \right) & d \geq 1 \\ \left[ \Gamma_0 + \frac{\alpha_0 d_0^2}{4\pi Da} \left[ \frac{3}{2} (F_\rho - 1) - \frac{1}{5} d_0^2 (F_\rho^3 - 1) \right] \right] F_\rho^2 & d < 1 \end{cases}$$

where $\Gamma_0$ is obtained by calculating the parameter $\Gamma$ from Eqs. [4] by setting $R = R_0$ and $d_0 := R_0 / 2a$. We emphasise that we recover the results of the previous section when $\ell/2 \leq l_p$ and therefore the transport process
phases, although, this time, $\Gamma$ is a function of Eqs. (7) to compute the entry parameter in the different and polymer properties are decoupled. We can still use extended coexistence region of the phase diagram - Fig. 2(b).

By solving those equations it is possible to determine the respective values of density and current, see Table I). The density of particles $\rho$ and polymer conformation as a proxy for transport regimes. The density of particles $\rho$ thus impacts the typical polymer conformation as given in Eq. 9. As shown in Fig. 3(a), obtained by numerically solving Eq. (11), with increasing $\alpha_\infty$, we observe that the polymer conformation undergoes a transition from a compact to a more flattened shape ($F_\rho > 1$) driven by the accumulation of particles on it. We emphasise that $\alpha_\infty$ is proportional to the particle concentration, meaning that features of the polymer conformation will vary by changing the particle concentration $c_\infty$.

In Fig. 4(b) we show how regimes of the polymer conformation coincide to the different phases of the exclusion process. We can appreciate that $R$ follows the different dynamical TASEP phases: when the system is in LD, the polymer is in its compactest shape, while the ends get separated in the MC and the polymer becomes more and more stretched deep in the HD phase, as sketched in Fig. 4(b).

Discussion. We have developed a novel approach to study the interdependence between transport on a uni-dimensional substrate (the exclusion process) and the three-dimensional conformation of the lattice on which the particles move. We propose a coupling between driven transport and polymer dynamics that influences the three-dimensional conformation of the polymer, and thus particle recycling. Our model then couples active transport in 1D and passive transport in 3D, expanding previous investigations on purely 1D systems 21.

In our approach the physical properties of the uni-dimensional lattice thus play a fundamental role. We show that, in this perspective, features of the lattice such as its length or persistence length cannot be overlooked –as usually done in coarse grained modelling– to provide a complete description of the transport process. The conformation of the lattice on which the particles move. We propose a coupling between driven transport and polymer dynamics that influences the three-dimensional conformation of the polymer, and thus particle recycling. Our model then couples active transport in 1D and passive transport in 3D, expanding previous investigations on purely 1D systems 21.

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The role of mRNA circularisation in determining gene expression is still largely unknown. The full circularisation of eukaryotic transcripts is assisted by molecular partners promoting the interaction between their ends; when this interaction is disrupted the translation efficiency strongly decreases [24]. This is consistent with our model, which predicts optimal ribosome recycling with full circularisation ($\Gamma = 0$). The formation of the circularised state, however, competes with the stiffening of the polymer induced by high density translation, which reinforces the importance of considering the process on a flexible substrate.

Dynamical effects that could be present in the LD-HD coexistence region may be addressed by Molecular Dynamics simulations. Future works might also explore extensions to inhomogeneous TASEP [26], finite resources [15], TASEP with extended particles [27] or particles that modify local curvature differently from the flatting that we considered.

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* [luca.ciandrini@umontpellier.fr]