Limited Resources in a Driven Diffusion Process

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The advance of particles in many driven diffusion systems depends on the availability of resources in the surrounding environment. In the balance between supply and demand of such resources we are confronted with a regime in which, under limited resource availability, the flow is markedly reduced. In the context of mRNA translation this represents the finite availability of amino acid-tRNA molecules. In this limited resources regime a severe depletion of amino acid tRNAs is also observed. These dramatic effects are vital to our understanding of translation, and are likely to also be important for the many other applications of driven diffusion models.

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In many physical and biological processes the dynamics rely on the availability of specific resources; there is a balance between supply and demand. In this Letter we show, by recourse to an extension to a driven diffusion model (the totally asymmetric exclusion process, or TASEP), that there is a regime where the rate at which resources are replenished limits the dynamics. In the context of messenger RNA (mRNA) translation, which is the process of protein biosynthesis, this represents the finite availability and recharging of amino acid-transfer RNA (aa-tRNA) complexes. We identify a transition to a *limited resources* (LR) regime where the current is severely reduced; this further differs from the maximal current (MC) phase seen in earlier TASEPs in that it is accompanied by a depletion of aa-tRNAs. The fact that such a dramatic effect is seen has major implications for our understanding of translation and protein production, as well as the response of the cell to stress, e.g., resource starvation [1].

The TASEP is one of the paradigmatic models of nonequilibrium statistical physics. It has been used to describe a wide range of systems, including traffic flow [2], transport via molecular motors [3], interface growth [4], and, as examined here, mRNAs translation [5]. Under some conditions exact results for the stationary state of the system have been found [6], while more generally a mean field approach can accurately represent the system [6,7]. The TASEP consists of a 1D lattice of sites along which particles move. The dynamics unfold with particles hopping from one site to the next with a site dependent rate k_i (where i labels the site). Particles are excluding; i.e., a particle can only hop if the next site is vacant. Particles enter and leave the lattice only at the left and right ends with rates α and β, respectively. The system is characterized by the mean density of particles ρ and the current J.

In translation molecular machines called ribosomes move along an mRNA molecule, adding amino acids to a polypeptide chain as they go [8]. The mRNA is a string of nucleotides, every three of which forms a codon and gives a code for a specific amino acid. Amino acids are brought to the ribosome by mediator molecules called tRNAs, different types of which are specific to different amino acids. This process is crucial in understanding how different cells that contain the same genetic information select which proteins are produced (cell differentiation), and how the protein production mechanism might react to changes in the environment. In the TASEP the mRNA is represented by the lattice, with each site corresponding to one codon; the particles represent the ribosomes.

Much work has focused on the effect of particular codon usage [9]. It is thought that the rate at which a ribosome translates a single codon depends on the abundance of the relevant aa-tRNA complex. Some tRNAs are much more abundant than others, meaning that some codons are translated at much higher rates than others [9]. Also, since there are 20 common amino acids represented by 41 tRNAs, the code is redundant; i.e., the same sequence of amino acids can be encoded by more than one codon sequence. In fact, there are many mRNAs where a codon representing a very rare tRNA is used instead of a more common one; such a ''slow codon'' can act as a bottleneck, causing queues of ribosomes and delays to protein production. Several authors [7] have studied the effect of slow sites on ribosome density and protein production rate, addressing the question as to why such coding sequences might be of benefit.

Here we consider the additional complication that the number of available aa-tRNAs is dynamic: k_i is allowed to vary with the availability of resources. During translation an aa-tRNA binds to a ribosome; if it is of the correct type, the amino acid is added to the peptide chain and a bare tRNA is released. Whilst tRNAs are not used up in the process, it takes a finite time for them to be ''recharged'' with new amino acids. Since there are many mRNAs being translated by many ribosomes simultaneously, there is competition for aa-tRNA resources. We show that a finite tRNA charging rate leads to a new physically and bio-

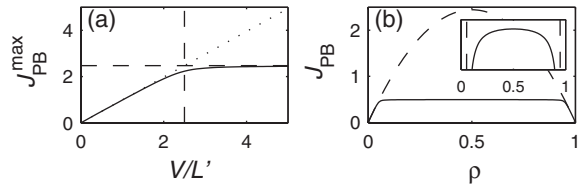

FIG. 1. (a) $J_{\mathrm{PB}}^{\max}$ as a function of V/L'. The dotted line shows $J = (\bar{T}/(\bar{T} + K_m))(V/L')$, and dashed lines are at $r\bar{T}/4$ (horizontal) and $r(\bar{T} + K_m)/4$ (vertical). (b) J_{PB} as a function of ρ. Dashed lines show case 1 ($V/L' = 5$), and solid lines case 2 ($V/L' = 0.55$). Other parameters as in text. Inset: zoom about the apparent plateau in J_{PB}.

logically significant regime. This is in contrast to other studies which consider the availability of ribosomes [10].

We derive below a mean field model for a TASEP which includes a finite rate of charging of tRNAs, before comparing with results from Monte Carlo simulations (MCS).

We model a system of N mRNAs, each represented by a TASEP of length L. We first consider a very simple model mRNA which uses only one type of codon (and therefore only one type of tRNA), i.e., $k_i = k$, for $i = 1, \ldots, L-1$. We write a mean field description of the model $\frac{d\rho_i}{dt} = k_{i-1}\rho_{i-1}(1-\rho_i) - k_i\rho_i(1-\rho_{i+1}), \quad i = 1, ..., L,$ where $k_0 = \alpha$ and $k_L = \beta$, and ρ_i gives the ensemble average occupancy at site i, with $\rho_0 = 1$ and $\rho_{L+1} = 0$ [6].

We derive an equation to describe the use and recharging of the aa-tRNA pool. Since the formation of the aa-tRNA complex is an enzymatic process we describe it using a Michaelis-Menten equation [11]. The charging rate is given by $V(\bar{T} - T)/(K_m + \bar{T} - T)$, where T is the number of aa-tRNAs and $\bar{T}$ is the total number of tRNAs. The constants V and K_m are the maximum recharging rate and the Michaelis constant, respectively. We assume that the availability of amino acids is not limiting, and that the hopping rate k depends linearly on the number of charged tRNAs, $k = rT$, where r is some intrinsic elongation rate. We expect that k will actually saturate at some maximum, though the linear approximation is justified since the cell is unlikely to overproduce tRNAs for energetic reasons. Every time a particle hops we reduce T by one; this leads to the equation

$$\frac{dT}{dt} = \frac{V(\bar{T} - T)}{K_m + \bar{T} - T} - \sum_{i=1}^{L'} k\rho_i(1-\rho_{i+1}), \qquad (1)$$

where the first term corresponds to recharging and the second to the use of aa-tRNAs. The quantity $L' = N(L-1)$ gives the total number of sites where aa-tRNAs can be used ($L-1$ since the Lth codon does not require a aa-tRNA, but instead a termination factor). In the steady state we identify the particle current $J = k\rho_i(1-\rho_{i+1})$, which is independent of i and corresponds biologically to the protein production rate. From Eq. (1) we can therefore write the hopping rate as a function of J

$$k = r\bar{T} - \frac{rK_mL'J}{V - L'J}. \qquad (2)$$

We proceed by considering first the equivalent system with periodic boundaries. As $\rho_i = \rho \ \forall \ i$, and from Eq. (2) we can write an implicit expression for the current $J_{\mathrm{PB}} = \rho(1-\rho)\left(r\bar{T} - \frac{rK_mL'J_{\mathrm{PB}}}{V - L'J_{\mathrm{PB}}}\right)$. Of the two solutions to this quadratic equation in J_{PB}, one can be disregarded as it is unphysical (nonzero current for zero density). From the remaining solution we find that the maximum value of J_{PB} occurs when $\rho = 1/2$, and we plot this a function of V/L' in Fig. 1(a). For small V/L', $J_{\mathrm{PB}}^{\max}$ increases almost linearly with V/L', but for values of $V/L' \geq r(\bar{T} + K_m)/4$, $J_{\mathrm{PB}}^{\max}$ saturates, reaching approximately $r\bar{T}/4$. Therefore, we distinguish between two regimes as case 1: $J_{\mathrm{PB}}^{\max} \approx \frac{r\bar{T}}{4}$ for $\frac{V}{L} > \frac{r(\bar{T}+K_m)}{4}$, and case 2: $J_{\mathrm{PB}}^{\max} \approx \frac{V}{L'}\frac{\bar{T}}{\bar{T}+K_m}$ for $\frac{V}{L} < \frac{r(\bar{T}+K_m)}{4}$. Figure 1(b) shows the current as a function of the density ρ for each case. In case 1 we observe behavior as in the original TASEP: the maximal current is determined by the steric interaction of the particles. In case 2 we observe a different type of behavior: J_{PB} *appears* to reach a plateau at some critical density, but actually there is a very shallow increase to a maximum at $\rho = 1/2$. We identify this as a "limited resources" (LR) regime; aa-tRNAs are being used up more quickly than they can be recharged, so the steady state value of k is reduced; the current cannot increase above $J \approx V/L'$ since V is the maximum possible recharging rate and JL' is the rate of aa-tRNA usage. The translation rate is governed by the recharging rate rather than steric interactions. Crucially, using biologically relevant parameters (see below), V/L' is 3 orders of magnitude smaller than $r(\bar{T} + K_m)/4$; i.e., we expect case 2 to be realized in biology. We note that these solutions retain the common features of previous TASEP models, such as one central maximum and symmetry about $\rho = 1/2$ (i.e., hole-particle symmetry).

Unless stated otherwise, throughout this Letter we use parameters which are realistic for the widely studied yeast, *S. cerevisiae*. A typical cell contains a total of 3.5×10^6 codons and 3×10^6 tRNAs, with a typical mRNA length of 500 codons. The total number of codons represents the system size. We study $N = 100$ individual TASEPs of $L = 500$ sites. Since we have scaled down the system size by a factor of 70, we also scale the other parameters accordingly. We use $\bar{T} = 4.3 \times 10^4$ and $r = 2.3 \times 10^{-4}$ s^{-1}, the latter being chosen to give a biologically realistic maximum hopping rate $r\bar{T} = 10$ s^{-1} [8]. We use $V = 1.95 \times 10^3$ s^{-1} and $K_m = 497$, which are based on recharging parameters for a typical tRNA synthetase (tyrosine-tRNA synthetase [12]). These biologically relevant parameters (which are typical for many enzymes) give $V/L' = 0.039$ s^{-1} and $r(\bar{T} + K_m)/4 = 2.5$ s^{-1}, so are well within case 2 as defined above. This implies that the balance between supply and demand of resources is an important

effect in translation, particularly for the cell's reaction to changes in its environment, e.g., resource starvation.

We now return to the open boundaries system. Using the "maximal current principle" [13] we can relate the periodic to the open system via

$$\mathcal{J} = \max J_{\mathrm{PB}}(\rho) \qquad \text{if } \rho_- > \rho > \rho_+, \tag{4}$$

where ρ_- (ρ_+) is an effective density associated with a reservoir of particles to the left (right) of site $i = 1$ ($i = L$) in the open system, and related to the rate α (β).

As in previous TASEP models, we find several regimes which we identify as low density (LD) and high density (HD) (corresponding to entry and exit limited) phases, and a maximal current (MC) phase. We find

$$\begin{aligned}
\mathcal{J}_{\mathrm{LD}} &= \frac{1}{2}\left[\alpha\left(1 - \frac{\alpha}{r(\bar{T}+K_m)}\right) + \frac{\bar{T}}{\bar{T}+K_m}\frac{V}{L'} - \sqrt{\left(\frac{\bar{T}}{\bar{T}+K_m}\frac{V}{L'} + \alpha\left(1 - \frac{\alpha}{r(\bar{T}+K_m)}\right)\right)^2 - \frac{4\alpha(r\bar{T}-\alpha)}{r(\bar{T}+K_m)}\frac{V}{L'}}\right], \\
\rho_{\mathrm{LD}} &= \frac{1}{2\alpha}\left[\alpha\left(1 + \frac{\alpha}{r(\bar{T}+K_m)}\right) - \frac{\bar{T}}{\bar{T}+K_m}\frac{V}{L'} + \sqrt{\left(\frac{\bar{T}}{\bar{T}+K_m}\frac{V}{L'} + \alpha\left(1 - \frac{\alpha}{r(\bar{T}+K_m)}\right)\right)^2 - \frac{4\alpha(r\bar{T}-\alpha)}{r(\bar{T}+K_m)}\frac{V}{L'}}\right],
\end{aligned} \tag{5}$$

for $\alpha < \beta$, $\alpha \leq \alpha^*$, and

$$\mathcal{J}_{\mathrm{MC}} = \tfrac{1}{2}\alpha^*, \qquad \rho_{\mathrm{MC}} = \tfrac{1}{2}, \qquad \text{for } \alpha, \beta \geq \alpha^*, \tag{6}$$

where

$$\alpha^* = \frac{r}{4}(\bar{T}+K_m) + \frac{V}{L'} - \sqrt{\left(\frac{r}{4}(\bar{T}+K_m) + \frac{V}{L'}\right)^2 - r\bar{T}\frac{V}{L'}}.$$

We do not include details of the HD phase ($\beta < \alpha$, $\beta < \beta^* = \alpha^*$), but due to particle-hole symmetry $\mathcal{J}_{\mathrm{HD}}$ can easily be obtained from the LD equation by replacing $\alpha \rightarrow \beta$. From now on we set β to a constant value $\beta \gg k$, since it is thought that translation is not limited by the termination step, so this is a reasonable approximation for a real cell. For clarity, we use the calligraphic $\mathcal{J}$ to refer to the exact equations above, and J with subscripts to refer to the approximations in the various regimes.

As for periodic boundaries we again see different behavior for the two cases as defined above; this is evident from the fact that from the maximal current principle, $\mathcal{J}_{\mathrm{MC}} \equiv J_{\mathrm{PB}}^{\max}$ [Fig. 1(a)]. For case 1 [Figs. 2(a)–2(c)] we see approximately the same behavior as in the original TASEP: as α is increased there is a second order phase transition at α^* from LD $\rightarrow$ MC. By taking the limit $V \rightarrow \infty$ in Eqs. (5) and (6) we find $J_{\mathrm{LD}} \approx \alpha(1 - \alpha/r\bar{T})$ and $J_{\mathrm{MC}} \approx r\bar{T}/4$.

For the biologically relevant case 2 we see behavior different from the original TASEP. In Figs. 2(d)–2(f) we plot J, ρ and k as functions of α. We show that at small α, the current follows the same equation for J_{LD} as in case 1, but at a critical value α^{LR} we see a dramatic change in the behavior to a regime where the current is approximately independent of α, and the density rapidly increases. We also note a severe decrease in the hopping rate k. Although in moving to the LR regime it appears that some quantities have a discontinuity in their derivatives, the change is actually smooth with the parameter K_m controlling the "sharpness." This is equivalent to the regime in the periodic system where there *appears* to be a plateau; actually there is a very small increase in the current (and we are still in the LD phase) until α^*, where we move to the MC phase where $J_{\mathrm{LR\text{-}MC}} \approx V\bar{T}/L'(\bar{T}+K_m)$ [see Fig. 1(b) inset]. Also, note that the maximal current in case 2 is dramatically decreased compared to that in case 1.

In Fig. 2 we also show stochastic MCS results. The simulations proceed in a similar manner to previous studies [6]. We pick with equal probability either a site on one of the lattices (we represent the reservoir of particles waiting to hop onto the lattice as site 0) or a tRNA. If we choose a site and it is occupied, the particle hops with probability $k\delta t$ ($\alpha\delta t$ or $\beta\delta t$ for initiation or termination) provided the next site is vacant. If we choose a tRNA and it is not already bound to an amino acid, we recharge it with probability $V\delta t/(K_m + \bar{T} - T)$. We repeat this $N(L+1) + \bar{T}$ times in each MCS step of length δt. Every time a particle hops or a tRNA is recharged we update the probabilities accordingly. Simulations are run for 10^5 s with the first 10^4 s disregarded to account for transient effects. Error bars represent the fluctuations in J, ρ and k [14].

The existence of the LR regime in case 2 is due to the fact that as we increase the rate α at which particles hop onto the lattice, we increase the rate at which aa-tRNAs are

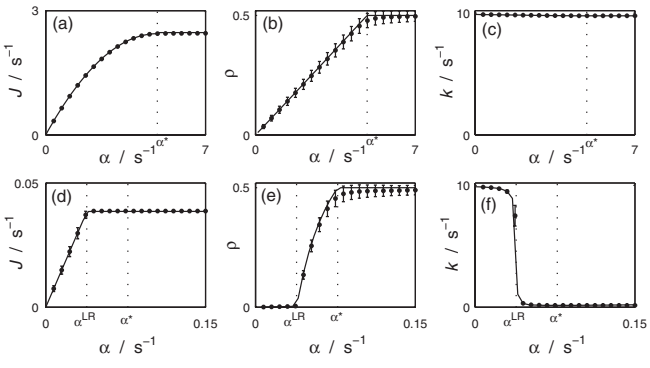

FIG. 2. J, ρ and k as functions of α. Points show MCS results, solid lines the mean field model, and dotted lines α^{LR} and α^*. (a)–(c) Show case 1 ($V/L' = 5$; other parameters as text) and (d)–(f) case 2 (parameters as text). Deviation of the points from the lines is due to spatial correlations in the density and fluctuations which are not accounted for by the mean field model. The fluctuations (shown in error bars) are small since the system contains many mRNAs and tRNAs, and these further reduce if we increase the size of the system.

used. If the aa-tRNAs are being used more quickly than they can be recharged we see a reduced value of the hopping rate k (an effect not considered in previous models). For small V we find $\alpha^{\mathrm{LR}} \approx V\bar{T}/L'(\bar{T} + K_m)$.

The biological interpretation of these results is that due to the fact that the enzymatic recharging is finite, the maximum protein production rate will depend on the balance between the supply of, and the demand for, aa-tRNAs. Moreover we note that since $K_m \ll \bar{T}$, $\alpha^{\mathrm{LR}} \approx V/L'$; i.e., the transition to the LR regime is robust to small changes in the total number of tRNAs. If the recharging rate were fast enough (case 1) such that the current was only limited by the steric repulsion between the ribosomes, then the maximum protein production rate would be proportional to the total number of tRNAs only, and competition for ribosomes would not be a dominant effect.

It should be noted that a real ribosome actually covers around 9 codons as it translates an mRNA. The inclusion of particles of length d is straightforward [15], and despite the breaking of hole-particle symmetry gives results qualitatively similar to those above (not shown).

We have shown that the production rate of proteins can be dramatically limited by the recharging process of tRNA molecules. Depending on the recharging parameters, we find two distinct cases. In case 1 the maximum current that can be achieved is solely limited by the steric interactions of the particles. In case 2, the current is severely limited by the finite recharging rate, and as α is increased we obtain a LD $\rightarrow$ LR-LD $\rightarrow$ LR-MC transition (where LR-LD and LR-MC denote the limited resources regime within in the LD and MC phases, respectively). At first glance case 2 gives a similar profile for $J(\alpha)$ as seen in a TASEP with a slow bottleneck site, where there is a first order transition to a queueing phase [7], however, here we have no bottlenecks, no queues form, and there is no phase transition at α^{LD}. It is particularly interesting that α^{LR} and $J_{\mathrm{LR\text{-}MC}}$ are independent of the intrinsic hopping rate r, and approximately independent of the total number of tRNAs; i.e., only the *recharging*, and not the abundance of tRNAs is important. This is a result of our choice of a linear dependence of k on T. We feel that this is a justified approximation, however, as we expect the value of $\bar{T}$ in a real cell to be below any saturation point, since it is thought that translation is limited by correct aa-tRNA selection and not the translocation process itself [9]. Biologically relevant parameters belong to case 2, so we would expect to be able to observe the LR regime experimentally. A hallmark of the LR regime is the sharp reduction in the ''charging level'' of aa-tRNAs [we note the stark difference between Figs. 2(c) and 2(f)]. This has not been present in previous models, and since such a large change in the ''charging levels'' of aa-tRNAs can easily be observed experimentally, is an ideal candidate for verification of the effect.

Finite tRNA recharging may also be important in understanding the response to cellular stress, e.g., a reduction of the availability of amino acids would have a similar effect as reducing V in this model.

Finally, we expect that a similar LR regime may arise in other TASEP models. For example in models of transportation via molecular motors [3] the motors ''walk'' along actin filaments using energy obtained by ATP hydrolysis. If the ATP molecules are supplied at a finite rate, one might expect to observe ''limited resources'' when the rate at which ATP molecules are hydrolyzed increases above some critical value. We have performed simulations using a different form for the recharging and we do indeed observe similar behavior.

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