Ribosome Flow Model on a Ring
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Abstract—The asymmetric simple exclusion process (ASEP) is an important model from statistical physics describing particles that hop randomly from one site to the next along an ordered lattice of sites, but only if the next site is empty. ASEP has been used to model and analyze numerous multiagent systems with local interactions including the flow of ribosomes along the mRNA strand.

In ASEP with periodic boundary conditions a particle that hops from the last site returns to the first one. The mean field approximation of this model is referred to as the ribosome flow model on a ring (RFMR). The RFMR may be used to model both synthetic and endogenous gene expression regimes.

We analyze the RFMR using the theory of monotone dynamical systems. We show that it admits a continuum of equilibrium points and that every trajectory converges to an equilibrium point. Furthermore, we show that it entrains to periodic transition rates between the sites. We describe the implications of the analysis results to understanding and engineering cyclic mRNA translation in-vitro and in-vivo.

Index Terms—Monotone dynamical systems, first integral, asymptotic stability, ribosome flow model, entrainment, asymmetric simple exclusion process, mean field approximation, mRNA translation, cyclic mRNA.

I. INTRODUCTION

The asymmetric simple exclusion process (ASEP) is an important model in statistical mechanics [39]. ASEP describes particles that hop along an ordered lattice of sites. The dynamics is stochastic: at each time step the particles are scanned, and every particle hops to the next site with some probability if the next site is empty. This simple exclusion principle allows modeling of the interaction between the particles. Note that in particular this prohibits overtaking between particles.

The term “asymmetric” refers to the fact that there is a preferred direction of movement. When the movement is unidirectional, some authors use the term totally asymmetric simple exclusion process (TASEP). ASEP was first proposed in 1968 [23] as a model for the movement of ribosomes along the mRNA strand during gene translation. In this context, the lattice models the mRNA strand, and the particles are the ribosomes. Simple exclusion corresponds to the fact that a ribosome cannot move forward if there is another ribosome right in front of it. ASEP has become a paradigmatic model for non-equilibrium statistical mechanics [8], [3]. It is used as the standard model for gene translation [52], and has also been applied to model numerous multiagent systems with local interactions including traffic flow, kinesin traffic, the movement of ants along a trail, pedestrian dynamics and ad-hoc communication networks [39], [43].

In ASEP with open boundary conditions, the lattice boundaries are open and the first and last sites are connected to two external particle reservoirs that drive the asymmetric flow of the particles along the lattice. In ASEP with periodic boundary conditions the lattice is closed, so that a particle that hops from the last site returns to the first one. In particular, the number of particles on the lattice is conserved.

Recently, the mean field approximation of ASEP with open boundary conditions, called the ribosome flow model (RFM), has been analyzed using tools from systems and control theory [28], [27], [29], [51], [26], [35]. In this paper, we consider the mean field approximation of ASEP with periodic boundary conditions. This is a set of $n$ deterministic nonlinear first-order ordinary differential equations, where $n$ is the number of sites, and each state-variable describes the occupancy level in one of the sites. We refer to this system as the ribosome flow model on a ring (RFMR). To the best of our knowledge, this is the first study of the RFMR using tools from systems and control theory.

In the physics literature, many properties have been proven for the ASEP with periodic boundary conditions and homogeneous transition rates (see, e.g. [11]). Another case that is amenable to analysis is where the transition rates vary but depending on the particles rather than on the sites (see e.g. [2] and the references therein). However, an analytical understanding of ASEP with site-dependent inhomogeneous transition rates is still pending. In contrast, most of the results in this paper hold for the general case of an inhomogeneous RFMR.

The RFMR may model, for example, the translation of a circular mRNA or DNA molecule. Circular RNA forms have been described in all domains of life (see for example, [10], [2], [7], [6], [14], [4], [5]). Specifically, it was shown that in prokaryotes it is possible to regulate translation from circular DNA [4], [5]. In the case of eukaryotes, the canonical scanning model requires free ends of the mRNA [21]; however, it is well-known that in these organisms mRNA is often (temporarily) circularized by translation initiation factors [50].

We show that the RFMR admits a continuum of equilibrium points, and that every trajectory converges to an equilibrium point. Furthermore, if the transition rates between the sites vary in a periodic manner, with a common period $T$, then every trajectory converges to a periodic solution with period $T$. In other words, the RFMR entrains (or phase-locks) to the periodic excitation. In the particular case where all the transition rates are equal all the state variables converge to the same
that site initial conditions represent normalized occupancy levels, we always consider becomes fuller. This is a relaxed version of simple exclusion.

\[
\dot{x}_1 = \lambda_0 x_n (1 - x_1) - \lambda_1 x_1 (1 - x_2), \\
\dot{x}_2 = \lambda_1 x_1 (1 - x_2) - \lambda_2 x_2 (1 - x_3), \\
\dot{x}_3 = \lambda_2 x_2 (1 - x_3) - \lambda_3 x_3 (1 - x_4), \\
\vdots \\
\dot{x}_{n-1} = \lambda_{n-2} x_{n-2} (1 - x_{n-1}) - \lambda_{n-1} x_{n-1} (1 - x_n), \\
\dot{x}_n = \lambda_{n-1} x_{n-1} (1 - x_n) - \lambda_n x_n (1 - x_1). 
\]

Here \( x_i(t) \in [0, 1] \) is the normalized occupancy level at site \( i \) at time \( t \), so that \( x_i(t) = 0 \) [\( x_i(t) = 1 \)] means that site \( i \) is completely empty [full] at time \( t \). The transition rates \( \lambda_1, \ldots, \lambda_n \) are all strictly positive numbers. To explain this model, consider the equation \( \dot{x}_2 = \lambda_1 x_1 (1 - x_2) - \lambda_2 x_2 (1 - x_3) \). The term \( r_{12} := \lambda_1 x_1 (1 - x_2) \) represents the flow of particles from site 1 to site 2. This is proportional to the occupancy \( x_1 \) at site 1 and also to \( 1 - x_2 \), i.e., the flow decreases as site 2 becomes fuller. This is a relaxed version of simple exclusion. The term \( r_{23} := \lambda_2 x_2 (1 - x_3) \) represents the flow of particles from site 2 to site 3. The other equations are similar, with the term \( r_{n1} := \lambda_n x_n (1 - x_1) \) appearing both in the equations for \( \dot{x}_1 \) and for \( \dot{x}_n \) due to the circular structure of the model (see Fig. \ref{fig:1}).

The RFMR encapsulates simple exclusion, unidirectional movement along the ring, and the periodic boundary condition of ASEP. This is not surprising, as the RFMR is the mean field approximation of ASEP with periodic boundary conditions (see, e.g., \cite{3} p. R345 and \cite{40} p. 1919).

Note that we can write \ref{eq:1} succinctly as

\[
\dot{x}_i = \lambda_{i-1} x_{i-1} (1 - x_i) - \lambda_i x_i (1 - x_{i+1}), \quad i = 1, \ldots, n,
\]

where here and below every index is interpreted modulo \( n \). Note also that \( 0_n \) [\( 1_n \)] is an equilibrium point of \ref{eq:1}. Indeed, when all the sites are completely free [completely full] there is no movement of particles between the sites.

Let \( C^n := \{ y \in \mathbb{R}^n : y_i \in [0, 1], \ i = 1, \ldots, n \} \), i.e., the closed unit cube in \( \mathbb{R}^n \). Since the state-variables represent normalized occupancy levels, we always consider initial conditions \( x(0) \in C^n \). It is straightforward to verify that \( C^n \) is an invariant set of \ref{eq:1}, i.e. \( x(0) \in C^n \) implies that \( x(t) \in C^n \) for all \( t \geq 0 \).

Note that \ref{eq:1} implies that

\[
\sum_{i=0}^{n} \dot{x}_i(t) \equiv 0, \quad \text{for all } t \geq 0,
\]

so the total occupancy \( H(x) := 1_n'x \) is conserved:

\[
H(x(t)) = H(x(0)), \quad \text{for all } t \geq 0.
\]

The dynamics thus redistributes the particles between the sites, but without changing the total occupancy level. In the context of translation, this means that the total number of ribosomes on the mRNA is conserved.

Eq. \ref{eq:2} means that we can reduce the \( n \)-dimensional RFMR to an \( (n - 1) \)-dimensional model. In particular, the RFMR with \( n = 2 \) can be explicitly solved. In this case we can obtain explicit expressions for important quantities, e.g., the rate of convergence to equilibrium. This solution is detailed...
in Appendix B.

If we change the first [last] equation in (1) to \( \dot{x}_1 = \lambda_0 (1-x_1) - \lambda_1 x_1 (1-x_2) [\dot{x}_n = \lambda_{n-1} x_{n-1} (1-x_n) - \lambda_n x_n] \)
we obtain the RFM. This may seem like a minor change, but in fact the dynamical properties of the RFM and the RFMR are very different. For example, in the RFM there is no first integral. Also, in the RFM there is a single equilibrium point in \( C_n \), whereas as we shall see below the RFMR has a continuum of equilibrium points in \( C_n \).

The next section describes several theoretical results on the RFMR. Since the case \( n = 2 \) is solved in Appendix B, we assume from here on that \( n \geq 3 \). Applications of the analysis to gene translation are discussed in Section IV.

III. MAIN RESULTS

A. Strong Monotonicity

A cone \( K \subset \mathbb{R}^n \) defines a partial ordering in \( \mathbb{R}^n \) as follows. For two vectors \( a, b \in \mathbb{R}^n \), we write \( a \leq b \) if \( (b-a) \in K \); \( a < b \) if \( a \leq b \) and \( a \neq b \); and \( a \ll b \) if \( (b-a) \in \text{int}(K) \). The system \( \dot{y} = f(y) \) is called monotone if \( a \leq b \) implies that \( y(t,a) \leq y(t,b) \) for all \( t \geq 0 \). In other words, the flow preserves the partial ordering \( \leq \). It is called strongly monotone if \( a < b \) implies that \( y(t,a) < y(t,b) \) for all \( t > 0 \).

From here on we consider the particular case where the cone is \( K = \mathbb{R}^n_+ \). Then \( a \leq b \) if \( a_i \leq b_i \) for all \( i \), and \( a \ll b \) if \( a_i < b_i \) for all \( i \). A system that is monotone with respect to this partial ordering is called cooperative.

**Proposition 1** Let \( x(t,a) \) denote the solution of the RFMR at time \( t \) for the initial condition \( x(0) = a \). For any \( a, b \in C^n \) with \( a \leq b \) we have
\[
x(t,a) \leq x(t,b), \quad \text{for all } t \geq 0.
\]
Furthermore, if \( a < b \) then
\[
x(t,a) \ll x(t,b), \quad \text{for all } t > 0.
\]
In the context of translation, this means the following. Consider two possible initial ribosome densities on the same cyclic mRNA strand, \( a \) and \( b \) with \( a_i < b_i \) for all \( i \), that is, \( b \) corresponds to a higher ribosome density at each site. Then the trajectories \( x(t,a) \) and \( x(t,b) \) emanating from these initial conditions continue to satisfy the same relationship between the densities for all time \( t \geq 0 \).

B. Stability

Denote the \( s \) level set of \( H \) by
\[
L_s := \{ y \in C^n : 1_n^t y = s \}.
\]
The next result shows that every level set contains a unique equilibrium point, and that any trajectory of the RFMR emanating from any point in \( L_s \) converges to this equilibrium point. In the context of translation on a cyclic mRNA strand, this means that a perturbation in the distribution of ribosomes along the strand (that does not change the total number of ribosomes) will not change the asymptotic behavior of the dynamics. It will still converge to the same unique steady state

![Fig. 2. Trajectories of (1) with \( n = 3 \) for three different initial conditions in \( L_2' : [1 0 1]' \), \([1 1 0]' \), and \([0 1 1]' \). The equilibrium point \( e_{L_2} \) is marked with a circle.](image)

**Theorem 1** Pick \( s \in [0,n] \). Then \( L_s \) contains a unique equilibrium point \( e_{L_s} \) of the RFMR, and for any \( a \in L_s \),
\[
\lim_{t \to \infty} x(t,a) = e_{L_s}.
\]
Furthermore, for any \( 0 \leq s < p \leq n \), we have
\[
e_{L_s} \ll e_{L_p}.
\]
Thm. [1] implies that the RFMR has a continuum of linearly ordered equilibrium points, namely, \( \{ e_{L_s} : s \in [0,n] \} \), and also that every solution of the RFMR converges to an equilibrium point.

**Example 1** Consider the RFMR with \( n = 3 \), \( \lambda_1 = 2 \), \( \lambda_2 = 3 \), and \( \lambda_3 = 1 \). Fig. [2] depicts trajectories of this RFMR for three initial conditions in \( L_2' : [1 1 0]' \), \([1 0 1]' \), and \([0 1 1]' \). It may be observed that all the trajectories converge to the same equilibrium point \( e_{L_2} \approx [0.5380 \ 0.6528 \ 0.8091]' \). Fig. [3] depicts all the equilibrium points of this RFMR. Since \( \lambda_2 > \lambda_1 \) and \( \lambda_2 > \lambda_3 \), the transition rate into site 3 is relatively large. As may be observed from the figure this leads to \( e_3 \geq e_1 \) and \( e_4 \geq e_2 \) for every equilibrium point \( e \).

Fix an arbitrary \( s \in [0,n] \). To simplify the notation, we just write \( e \) instead of \( e_{L_s} \) from here on. Then
\[
1_n^t e = s,
\]
and since for $x = e$ the left-hand side of all the equations in (1) is zero,

$$
\lambda_n e_n (1 - e_1) = \lambda_1 e_1 (1 - e_2) = \lambda_2 e_2(1 - e_3)
$$

$$
\vdots
$$

$$
= \lambda_{n-1} e_{n-1}(1 - e_n).
$$

(7)

Thus, the flow along the chain always converges to a steady-state value

$$
R := \lambda_i e_i(1 - e_{i+1}), \quad \text{for all } i.
$$

Using (7) and the equation $1' e = s$ it is possible to derive a polynomial equation for $e_1$. For example, when $n = 2$

$$
(\lambda_2 - \lambda_1) e_1^2 + (\lambda_1(s - 1) - \lambda_2(s + 1)) e_1 + \lambda_2 s = 0,
$$

whereas for $n = 3$ we get

$$
\lambda_1 \lambda_3 (\lambda_1 + \lambda_2 + \lambda_3) e_1^4 \\
+ (\lambda_2 \lambda_3^2 - \lambda_1^2 (\lambda_2 + \lambda_3 s) - \lambda_3 \lambda_1 (\lambda_2 (2s - 1) + \lambda_3 (s + 1))) e_1^3 \\
+ (\lambda_3 \lambda_1 (\lambda_2 (s^2 - 3) + \lambda_3 (2s - 1))) e_1^2 \\
+ \lambda_2 (\lambda_2 (2s - 2) + \lambda_3 (s - 1)) - \lambda_2 \lambda_3^2 (s + 2) e_1^2 \\
+ \lambda_3 (\lambda_2 \lambda_3 (2s + 1) + \lambda_1 (\lambda_2 (1 - (s - 2)s) - \lambda_3 (s - 1))) e_1 \\
- \lambda_2 \lambda_3^2 s = 0.
$$

These equations can be solved numerically, but their analysis seems non-trivial.

C. Differential Analysis

Differential analysis is a powerful tool for analyzing non-linear dynamical systems (see, e.g., [24], [33], [1]). The basic idea is to study the difference between trajectories that emanate from different initial conditions. The next result shows that the RFMR is non-expanding with respect to the $L_1$ norm.

Proposition 2 For any $a, b \in C^n$,

$$
|x(t, a) - x(t, b)|_1 \leq |a - b|_1, \quad \text{for all } t \geq 0.
$$

(8)

In other words, the $L_1$ distance between trajectories can never increase. From the biophysical point of view, this means that the $L_1$ difference between two profiles of ribosome densities, related to two different initial conditions, in the same cyclic mRNA/DNA is a non-increasing function of time.

Example 2 Pick $a, b \in C^n$ such that $b \leq a$. By monotonicity, $x(t, b) \leq x(t, a)$ for all $t \geq 0$, so $d(t) := |x(t, a) - x(t, b)|_1 = 1' e (x(t, a) - x(t, b))$. Thus,

$$
\dot{d}(t) = 1' e \dot{x}(t, a) - 1' e \dot{x}(t, b) = 0 - 0,
$$

so clearly in this case (8) holds with an equality. □

Pick $a \in C^n$, and let $s := 1'a$. Substituting $b = e_{L_s}$ in (8) yields

$$
|x(t, a) - e_{L_s}|_1 \leq |a - e_{L_s}|_1, \quad \text{for all } t \geq 0.
$$

(9)

This means that the convergence to $e_{L_s}$ is monotone in the sense that the $L_1$ distance to $e_{L_s}$ can never increase. Combining (9) with Theorem 1 implies that every equilibrium point of the RFMR is semistable [16].

D. Entrainment

Suppose now that the transition rates along the cyclic mRNA (or DNA) molecule are periodically time-varying functions of time with a common (minimal) period $T > 0$. This may correspond for example to periodically varying abundances of tRNA due to the cell-division cycle that is a periodic program for cell replication. A natural question is will the mRNA densities along the mRNA strand (and thus the translation rate) converge to a periodically-varying pattern?

We can study this question using the RFMR as follows. We say that a function $f$ is $T$-periodic if $f(t + T) = f(t)$ for all $t$. Assume that the $\lambda_i$s are time-varying functions satisfying:

- there exist $0 < \delta_1 < \delta_2$ such that $\lambda_i(t) \in [\delta_1, \delta_2]$ for all $t \geq 0$ and all $i \in \{1, \ldots, n\}$
- there exists a (minimal) $T > 0$ such that all the $\lambda_i$s are $T$-periodic.

We refer to the model in this case as the periodic ribosome flow model on a ring (PRFMR).

Theorem 2 Consider the PRFMR. Fix an arbitrary $s \in [0, n]$. There exists a unique function $\phi_s : \mathbb{R}_+ \to C^n$, that is $T$-periodic, and

$$
\lim_{t \to \infty} |x(t, a) - \phi_s(t)| = 0, \quad \text{for all } a \in L_s.
$$

In other words, every level set $L_s$ of $H$ contains a unique periodic solution, and every solution of the PRFMR emanating from $L_s$ converges to this solution. Thus, the PRFMR entrains (or phase locks) to the periodic excitation in the $\lambda_i$s.

Note that since a constant function is a periodic function for any $T$, Thm. 2 implies entrainment to a periodic trajectory.
We refer to this as the **homogeneous ribosome flow model on a ring** (HRFMR). Also, (7) becomes
\[
e_n(1 - e_1) = e_1(1 - e_2) = e_2(1 - e_3) = \cdots = e_{n-1}(1 - e_n),
\]
and it is straightforward to verify that \(e = c_1 \lambda_n, c \in \mathbb{R}, \) satisfies (11).

Define the **averaging operator** \(\operatorname{Ave}(\cdot) : \mathbb{R}^n \rightarrow \mathbb{R} \)
by \(\operatorname{Ave}(z) := \frac{1}{n} \sum_{i=1}^{n} z_i.\)

**Corollary 1** For any \(a \in \mathbb{C}^n\) the solution of the HRFMR satisfies
\[
\lim_{t \to \infty} x(t, a) = \operatorname{Ave}(a) 1_n.
\]

From the biophysical point of view, this means that equal transition rates along the circular mRNA lead to convergence to a uniform distribution of the ribosome densities.

Note that (12) implies that the steady-state flow is \(R = \lambda c \operatorname{Ave}(a)(1 - \operatorname{Ave}(a)).\) Thus, \(R\) is maximized when \(\operatorname{Ave}(a) = 1/2\) and the maximal value is \(R^* = \lambda c/4.\)

**Remark 1** It is possible also to give a simple and self-contained proof of Corollary 1 using standard tools from the literature on consensus networks [30]. Indeed, pick \(\tau > 0\) and let \(i\) be an index such that \(x_i(\tau) \geq x_j(\tau)\) for all \(j \neq i.\) Then
\[
\dot{x}_i(\tau) = x_{i-1}(\tau)(1 - x_i(\tau)) - x_i(\tau)(1 - x_{i+1}(\tau)) \\
\leq x_i(\tau)(1 - x_i(\tau)) - x_i(\tau)(1 - x_i(\tau)) = 0.
\]
Furthermore, if \(x_i(\tau) > x_j(\tau)\) for all \(j \neq i\) then \(\dot{x}_i(\tau) < 0.\) A similar argument shows that if \(x_i(\tau) \leq x_j(\tau)\) \([x_i(\tau) < x_j(\tau)\] for all \(j \neq i\) then \(\dot{x}_i(\tau) \geq 0\) \([x_i(\tau) > 0.\) Thus, the maximal density never increases, and the minimal density never decreases. Define \(V(\cdot) : \mathbb{R}^n \rightarrow \mathbb{R}_+ \) by \(V(y) := \max_i y_i - \min_i y_i.\) Then \(V(x(t))\) strictly decreases along trajectories of the HRFMR unless \(x(t) = c 1_n\) for some \(c \in \mathbb{R},\) and a standard argument (see, e.g., [23]) implies that the system converges to consensus. Combining this with (2) completes the proof of Corollary 1.

We note in passing that Corollary 1 implies that the HRFMR may be interpreted as a nonlinear average consensus network. Indeed, every state-variable replaces information with its two nearest neighbors on the ring only, yet the dynamics guarantee that every state-variable converges to \(\operatorname{Ave}(a).\) Consensus networks are recently attracting considerable interest [30], [33], [34], and have many applications in distributed and multi-agent systems.

The physical nature of the underlying model provides a simple explanation for convergence to average consensus. Indeed, the HRFMR may be interpreted as a system of \(n\) water tanks connected in a circular topology through identical pipes. The flow in the system is driven by the imbalance in the water levels, and the state always converges to a homogeneous...
distribution of water in the tanks. Since the system is closed, this corresponds to average consensus.

We next analyze the linearized model of the HRFMR near an equilibrium point to obtain information on the convergence rate and the amplitude of the oscillations.

1) Local analysis: Every trajectory of the HRFMR converges to \( c_1 n \), where \( c \) depends on the initial condition. Let \( y := x - c_1 n \). Then a calculation shows that the linearized dynamics of \( y \) is given by

\[
\dot{y} = Qy,
\]

where

\[
Q := \begin{bmatrix}
-1 & c & 0 & 0 & \ldots & 0 & 1 - c \\
1 - c & -1 & c & 0 & \ldots & 0 & 0 \\
0 & 1 - c & -1 & c & \ldots & 0 & -1 \\
\vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\
c & 0 & 0 & 0 & \ldots & 1 - c & -1
\end{bmatrix},
\]

(14)

By known results on circulant matrices (see, e.g., [15]), the eigenvalues of \( Q \) are

\[
\gamma_\ell = -1 + cw^{\ell-1} + (1 - c)w^{(\ell-1)(n-1)}, \quad \ell = 1, \ldots, n,
\]

where \( w := \exp(2\pi\sqrt{-1}/n) \), and the corresponding eigenvectors are

\[
v^\ell := [1 \quad \omega^{(\ell-1)} \ldots \omega^{(\ell-1)(n-1)}]^T, \quad \ell = 1, \ldots, n.
\]

(16)

In particular, \( \gamma_1 = 0 \), with corresponding eigenvector \( v^1 = 1_n \). This is a consequence of the continuum of equilibria in the HRFMR.

Note that

\[
\text{Re}(\gamma_\ell) = -1 + \cos(2\pi(\ell - 1)(n-1)/n),
\]

\[
= -1 + \cos(2\pi(\ell - 1)/n),
\]

and this implies that

\[
\text{Re}(\gamma_\ell) \leq \text{Re}(\gamma_2) = \cos(2\pi/n) - 1, \quad \ell = 2, \ldots, n.
\]

Thus, for \( x(0) \) in the vicinity of the equilibrium

\[
|x(t) - c_1 n| \leq \exp((\cos(2\pi/n) - 1)t)|x(0) - c_1 n|.
\]

(18)

The exponential convergence rate decreases with \( n \). For example, for \( n = 2 \), \( \cos(2\pi/n) - 1 = -2 \), whereas for \( n = 10 \), \( \cos(2\pi/n) - 1 \approx -0.191 \). In other words, as the length of the chain increases the convergence rate decreases. This is the price paid for the fact that each site “communicates” directly with its two neighboring sites only.

Our simulations suggest that (13) actually provides a reasonable approximation for the real convergence rate (i.e., not only in the vicinity of the equilibrium point) in the HRFMR. The next example demonstrates this.

Example 4 Consider the HRFMR with \( n = 4 \). Fig. 5 depicts \( \log(|x(t) - (1/4)1_4|) \) for the initial condition \( x(0) = [1 \ 0 \ 0 \ 0] \). Note that here \( \log(|x(0) - (1/4)1_4|) = \log(\sqrt{3}/4) \). In this case, \( \text{Re}(\gamma_2) = -1 \), so (13) becomes \( \log(|x(t) - c_1 n|) \approx -t + \log(|x(0) - c_1 n|) \). Also shown is the graph of \(-t + \log(\sqrt{3}/4)\). It may be seen that the real convergence rate is slightly faster than the estimate [15].

Eq. (17) implies that \( c \) does not affect the convergence rate in the linearized system. It does however affect the oscillatory behavior until convergence. To see this, note that the solution of (13) is

\[
y(t) = \sum_{i=1}^{n} s_i \exp(\gamma_i t) v^i,
\]

(19)

where the \( s_i \)s satisfy

\[
y(0) = \sum_{i=1}^{n} s_i v^i.
\]

Since \( \gamma_1 = 0 \) and \( \text{Re}(\gamma_i) < 0 \) for all \( i > 1 \), (19) implies that \( \lim_{t \to \infty} y(t) = s_1 v^1 \), so \( s_1 = 0 \). The three eigenvalues with the largest real part are \( \gamma_1, \gamma_2, \) and \( \gamma_n \), so for large \( t \),

\[
y(t) \approx s_2 \exp(\gamma_2 t) v^2 + s_n \exp(\gamma_n t) v^n.
\]

It follows from (15) that

\[
\alpha := \text{Re}(\gamma_2) = \text{Re}(\gamma_n) = \cos(2\pi/n) - 1,
\]

\[
\beta := \text{Im}(\gamma_2) = -\text{Im}(\gamma_n) = (2c - 1) \sin(2\pi/n),
\]

so \( v^n = v^2, s_n = s_2 \) and this yields

\[
y(t) \approx 2|p| \exp(\alpha t) \cos(\beta t + \angle p),
\]

where \( p := s_2 v^2 \). The oscillatory behavior thus depends on \( c \). For \( c = 1/2 \) the solution has no oscillations at all, and as \( c \) moves away from 1/2 the oscillations become larger. The reason for this is that for \( c = 1/2 \) the linear equation (13) corresponds to the case where each agent weights the contribution from its two neighbors equally. As \( c \) moves away from 1/2 the weights become different and this imbalance leads to oscillations until the state-variables converge to the correct values.
Example 5 Let \( z(c) := \begin{bmatrix} c + 0.1 & c - 0.1 \end{bmatrix} \). We simulated the trajectories of the HRFMR with \( n = 3 \) for four initial conditions: \( x_0 = z(c) \), with \( c = 0.1, 0.3, 0.5, \) and \( 0.9 \). Note that \( \frac{1}{3}Y^2z(c) = c \), so \( \lim_{t \to \infty} x(t, z(c)) = c13. \) Fig. 6 depicts
\[
d(t, c) := (x_1(t, z(c)) - c) - (x_1(t, z(1/2)) - 1/2)
\]
as a function of \( t \). It may be seen that as \( |c - 1/2| \) increases the oscillations increase. This agrees with the analysis above.

F. The Case of a Single Slow Rate

It is interesting to consider the case where all the transition rates are equal to \( \lambda_s \), except for \( \lambda_1 \) that has value \( \lambda_q \), with \( \lambda_q < \lambda_s \). For TASEP with periodic boundary conditions this case has been studied in \[15, 18\]. It corresponds to a translation regime with the elongation rates basically uniform (with rate \( \lambda_s \)), yet the re-initiation, and possibly termination, rate (modeled by \( \lambda_q \)) is slower. In this case, Eq. (7) of the RFMR becomes
\[
e_n(1 - e_1) = \frac{\lambda_q}{\lambda_s} e_1(1 - e_2) = e_2(1 - e_3) = \cdots = e_{n-1}(1 - e_n), \tag{20}
\]
so we assume from here on, without loss of generality, that \( \lambda_s = 1 \).

When \( \frac{1}{3} - \frac{1}{2} \) is small, i.e., the normalized total occupancy is close to \( 1/2 \) the steady-state \( e \) has the form depicted in Fig. 7. The slow rate yields an increase [decrease] in the steady-state particle density to the immediate left [right]. In other words, the slow rate induces a “traffic jam” segregating the steady-states into high- and low-density regions. Near the slow site the densities become more or less uniform with a low density \( e_1 \) and a high density \( e_h \). Substituting this in (20) gives
\[
e_h(1 - e_h) \approx \lambda_q e_h(1 - e_l) \approx e_l(1 - e_l),
\]
so \( e_l \approx \frac{\lambda_q}{1 + \lambda_q} \), and \( e_h \approx 1 - \frac{1}{1 + \lambda_q} \). Note that this implies that \( e_l + e_h \approx 1 \). For example, for \( \lambda_q = 0.05 \) this gives \( e_l \approx 0.047619, e_h \approx 0.952381 \), and this agrees well with the case depicted in Fig. 7.

The steady-state flow is thus
\[
R = e_h(1 - e_h) \approx \frac{\lambda_q}{(1 + \lambda_q)^2}.
\]
Let \( m_l, m_h \) denote the number of \( e_i \)s satisfying \( e_i \approx e_l \), so that \( m_h := n - m_l \) approximates the number of \( e_i \)s satisfying \( e_i \approx e_h \). Then the equation \( s \approx m_le_l + m_he_h \) yields
\[
m_l \approx \frac{n - s(1 + \lambda_q)}{1 - \lambda_q}.
\]
For example, for the case \( n = 40, s = 20.3, \lambda_q = 0.05 \) this gives \( m_l \approx 19.6684 \), and this agrees well with the case depicted in Fig. 7.

From the biophysical point of view, these results suggest that a slower re-initiation step (that may interact and delay the termination step) will lead to a ribosomal “traffic jam” before the STOP codon.

IV. DISCUSSION

The ribosome flow model on a ring (RFMR) is the mean field approximation of ASEP with periodic boundary conditions. We analyzed the RFMR using tools from monotone dynamical systems theory. Our results show that the RFMR has several nice properties. It is an irreducible cooperative dynamical system admitting a continuum of linearly ordered
equilibrium, points and every trajectory converges to an equilibrium point. The RFMR is on the “verge of contraction”, and it entrains to periodic transition rates.

Topics for further research include the following. ASEP with periodic boundary conditions has been studied extensively in the physics literature and many explicit results are known. For example, the time scale until the system relaxes to the (stochastic) steady state is known [3]. A natural research direction is based on extending such results to the RFMR.

For the RFM, that is, the mean-field approximation of ASEP with open boundary conditions, it has been shown that the steady-state translation rate $R$ satisfies the equation

$$0 = f(R),$$

where $f$ is a continued fraction [28]. Using the well-known relationship between continued fractions and tridiagonal matrices (see, e.g., [49]) yields that $R^{-1/2}$ is the Perron root of a certain non-negative symmetric tridiagonal matrix with entries that depend on the $A$s [35]. This has many applications. For example it implies that $R = R(\lambda_0, \ldots, \lambda_n)$ in the RFM is a strictly concave function on $\mathbb{R}_{+}^{n+1}$ [35]. It also implies that sensitivity analysis in the RFM is an eigenvalue sensitivity problem [30]. An interesting research question is whether $R$ in the RFMR can also be described using such equations.

Another interesting topic for further research is studying a network of several connected RFMs. The output of each RFM is divided between the inputs of all the RFMs. This models competition for the ribosomes in the cell. Assuming that the system is closed then leads to network of interconnected RFMRs.

The RFMR may be used in the future for analyzing novel synthetic circular DNA or mRNA molecules for protein translation in-vitro or in-vivo. Such devices have potential advantages with respect to linear mRNA, since they do not include free ends and may thus be more stable. For example, in E. coli RNA degradation often begins with conversion of the 5’-terminal triphosphate to a monophosphate, creating a better substrate for internal cleavage by RNase E [37]. In eukaryotes, such as Saccharomyces cerevisiae, intrinsic mRNA decay initiate with deadenylation that causes the shortening of the poly(A) tail at the 3’ end of the mRNA, followed by the removal of the cap at the 5’ end by the decapping enzyme, which leads to a rapid 5’ $\rightarrow$ 3’ degradation of the mRNA by an exoribonuclease [40]. In eukaryotes, the canonical scanning model requires free ends of the mRNA [21]. However, it may be possible to design circular DNA or mRNA molecules by using Internal Ribosome Entry Sites (IRESes) [47]. Such an experimental system (or a similar system) can be used in the future for evaluation the theoretical results reported in this study.

APPENDIX A: PROOFS

Proof of Prop. 1. Write the RFMR (1) as $\dot{x} = f(x)$. The Jacobian matrix $J(x) := \frac{\partial f}{\partial x}(x)$ is given in (21). This matrix has nonnegative off-diagonal entries for all $x \in \mathbb{C}^n$. Thus, the RFMR is a cooperative system [42], and this implies (3). Furthermore, it is straightforward to verify that $J(x)$ is an irreducible matrix for all $x \in \text{int}(\mathbb{C}^n)$, and this implies (4) (see, e.g., [42], Ch. 4).

Proof of Thm. 1. Since the RFMR is a cooperative irreducible system with $H(x) = 1_n^t x$ as a first integral, Thm. 1 follows from the results in [32] (see also [31] and [22] for some related ideas).

Proof of Prop. 2. Recall that the matrix measure $\mu_1(x) : \mathbb{R}^{n \times n} \rightarrow \mathbb{R}$ induced by the $L_1$ norm is

$$\mu_1(A) = \max\{c_1(A), \ldots, c_n(A)\},$$

where $c_i(A) := a_{ii} + \sum_{k \neq i} |a_{ki}|$, i.e. the sum of entries in column $i$ of $A$, with the off-diagonal entries taken with absolute value [48]. For the Jacobian of the RFMR, we have $c_i(J(x)) = 0$ for all $i$ and all $x \in \mathbb{C}^n$, so $\mu_1(J(x)) = 0$. Now (8) follows from standard results in contraction theory (see, e.g., [38]).

Proof of Thm. 2. Write the PRFMR as $\dot{x} = f(t, x)$. Then $f(x, y) = f(t + T, y)$ for all $t$ and $y$. Furthermore, $H(x) = 1_n^t x$ is a first integral of the PRFMR. Now Thm. 2 follows from the results in [45] (see also [20]).

Proof of Corollary 1. Let $s := 1_n^t a$. Then $L_a$ contains $\text{Ave}(a) 1_n$ and this is an equilibrium point. The proof now follows immediately from Thm. 1.

APPENDIX B: SOLUTION OF THE RFMR WITH $n = 2$

Consider (1) with $n = 2$, i.e.

$$\begin{align*}
\dot{x}_1 &= \lambda_2 x_2(1 - x_1) - \lambda_1 x_1(1 - x_2), \\
\dot{x}_2 &= \lambda_1 x_1(1 - x_2) - \lambda_2 x_2(1 - x_1).
\end{align*}$$

(22)

We assume that $x(0) \neq 0_2$ and $x(0) \neq 1_2$, as these are equilibrium points of the dynamics. Let $s := x_1(0) + x_2(0)$. Substituting $x_2(t) = s - x_1(t)$ in (22) yields

$$\begin{align*}
\dot{x}_1 &= \lambda_2 (s - x_1)(1 - x_1) - \lambda_1 x_1(1 - s + x_1) \\
&= \alpha_2 x_1^2 + \alpha_1 x_1 + \alpha_0,
\end{align*}$$

(23)

where

$$\begin{align*}
\alpha_2 &:= \lambda_2 - \lambda_1, \\
\alpha_1 &:= (\lambda_1 - \lambda_2)s - \lambda_1 - \lambda_2, \\
\alpha_0 &:= s \lambda_2.
\end{align*}$$

If $\lambda_1 = \lambda_2$ then (23) is a linear differential equation and its solution is

$$x_1(t) = \frac{s}{2}(1 - \exp(-2\lambda_1 t)) + x_1(0) \exp(-2\lambda_1 t),$$

(24)

so

$$x_2(t) = s - x_1(t)$$

$$= \frac{s}{2}(1 + \exp(-2\lambda_1 t)) - x_1(0) \exp(-2\lambda_1 t)$$

$$= \frac{s}{2}(1 - \exp(-2\lambda_1 t)) + x_2(0) \exp(-2\lambda_1 t).$$

(25)

In particular,

$$\lim_{t \to -\infty} x(t) = (s/2) 1_2,$$

(26)

i.e., the state-variables converge at an exponential rate to the average of their initial values.
In the context of translation on a circular mRNA/DNA this means that uniform translation rates are expected to yield a steady-state of uniform ribosomal distributions along the transcript, and that the convergence to this steady-state is fast.

If \( \lambda_1 \neq \lambda_2 \) then (23) is a Riccati equation (see, e.g. [12]), whose solution is

\[
x_1(t) = \frac{-\alpha_1 - \sqrt{\Delta} \coth(\sqrt{\Delta} (t - t_0)/2)}{2\alpha_2},
\]

where

\[
\Delta := \alpha_1^2 - 4\alpha_2\alpha_0 = (s - 1)^2(\lambda_1 - \lambda_2)^2 + 4\lambda_1\lambda_2,
\]

\[
t_0 := \frac{2}{\sqrt{\Delta}} \coth^{-1} \left( \frac{2x_1(0)\alpha_2 + \alpha_1}{\sqrt{\Delta}} \right).
\]

Note that since the \( \lambda_i \)'s are positive, \( \Delta > 0 \). Also, a straightforward calculation shows that \( t_0 \) is well-defined for all \( x_1(0) \in [0, 1] \). Note that (27) implies that

\[
\lim_{t \to \infty} x(t) = \frac{1}{2\alpha_2} \left[ -\alpha_1 - \sqrt{\Delta} \right] \left( 2\alpha_2 s + \alpha_1 + \sqrt{\Delta} \right).
\]

The identity

\[
\coth \left( \frac{t}{2} \sqrt{\Delta} \right) = 1 - \frac{2}{\exp(\sqrt{\Delta} t) - 1}
\]

implies that for sufficiently large values of \( t \) the convergence is with rate \( \exp(-\sqrt{\Delta} t) \). Thus, the convergence rate depends on \( \lambda_1, \lambda_2, \) and \( s \).

Summarizing, when \( n = 2 \) every trajectory of the RFMR follows the straight line from \( x(0) \) to an equilibrium point \( e = e(\lambda_1, \lambda_2, s) \). In particular, if \( a, b \in C^2 \) satisfy \( 1'_{\theta}a = 1'_{\theta}b \) then the solutions emanating from \( a \) and from \( b \) converge to the same equilibrium point. Fig. 8 depicts the trajectories of the RFMR with \( n = 2, \lambda_1 = 2 \) and \( \lambda_2 = 1 \) for three initial conditions.

To study entrainment in this case, consider the RFMR with \( n = 2, \lambda_1(t) = 3q(t)/2, \) and \( \lambda_2(t) = q(t)/2, \) where \( q(t) \) is a strictly positive and periodic function. Then (25) becomes

\[
\dot{x}_1 = (-x_1^2 + (s - 2)x_1 + s/2)q.
\]

Assume that

\[
x_1^2(0) < s/2.
\]

It is straightforward to verify that in this case the solution of (29) is

\[
x_1(t) = (s/2) - 1 + z \tanh \left( k + z \int_0^t q(s)ds \right),
\]

where

\[
z := \sqrt{3 + (s - 1)^2}/2, \quad k := \tanh^{-1} \left( (x_1(0) + 1 - s/2)/z \right).
\]

Note that (30) implies that \( k \) is well-defined. Suppose, for example, that \( q(t) = 2 + \sin(t) \). Then \( \lambda_1(t) \) and \( \lambda_2(t) \) are periodic with period \( T = 2\pi \). In this case,

\[
x_1(t) = (s/2) - 1 + z \tanh \left( k + z(2t + 1 - \cos(t)) \right),
\]

and

\[
x_2(t) = s - x_1(t) = (s/2) + 1 - z \tanh \left( k + z(2t + 1 - \cos(t)) \right).
\]

Thus, for every \( a \in L_s, \lim_{t \to \infty} x(t, a) = \phi_s(t), \) where \( \phi_s(t) := \left( [(s/2) - 1 + z(s/2) + 1 - z] \right) ^ t \) (which is of course periodic with period \( T \)).

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