Modeling protein synthesis from a physicist’s perspective: A toy model

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Abstract

Proteins are polymers of amino acids. These macromolecules are synthesized by intracellular machines called ribosomes. Although the experimental investigation of protein synthesis has been a traditional area of research in molecular cell biology, important quantitative models of protein synthesis have been reported in research journals devoted to statistical physics and related interdisciplinary topics. From the perspective of a physicist, protein synthesis is the classical transport of interacting ribosomes on a messenger RNA (mRNA) template that dictates the sequence of the amino acids on the protein. We discuss appropriate simplification of the models and methods. In particular, we develop and analyze a simple toy model using some elementary techniques of nonequilibrium statistical mechanics and predict the average rate of protein synthesis and the spatial organization of the ribosomes in the steady state.
I. INTRODUCTION

Physical frontiers in biology\textsuperscript{1} and biological frontiers of physics\textsuperscript{2} are now active areas of interdisciplinary research. There are journals such as Physical Biology whose aim is to foster “the integration of biology with the traditionally more quantitative fields of physics,...”\textsuperscript{3}. Biological physics is also one of the interdisciplinary topics on which papers are published regularly in high-impact research journals such as Physical Review Letters. However, often the work is too technical to be accessible to those who are not expert in modeling of biological systems.

The main aim of this paper is to bring a piece of contemporary research into the classroom by appropriate simplification of the models and methods. In particular, we develop a simple model for the collective movement of ribosomes when these macromolecular machines move along a template messenger RNA (mRNA) strand, each separately synthesizing one copy of the same protein\textsuperscript{4,5}. In spite of its simplicity, this toy model captures the most essential steps in the process of protein synthesis. Because of the simplicity of the model and the pedagogical presentation of the calculations, even senior undergraduate students can obtain a glimpse of a frontier of current interdisciplinary research involving biology and physics.

Because of the interdisciplinary nature of the topic, we present in Sec. II a summary of the essential biochemical and mechanical processes involved in protein synthesis. In Sec. III we present the model and highlight its main features. We report our results in Secs. IV and V. We compare the model and the results with those for some other similar systems in Sec. VI. Finally, in Sec. VII we draw our conclusions.

II. PROTEIN SYNTHESIS: ESSENTIAL MECHANO-CHEMICAL PROCESSES

A protein is a linear bio-polymer whose monomeric subunits, called amino acids, are linked together by peptide bonds. A polypeptide, a precursor of a protein, is synthesized from the corresponding messenger RNA (mRNA) template by a machine called ribosome\textsuperscript{4,5}. An mRNA is also a linear bio-polymer whose monomeric subunits are the nucleotides. Triplets of nucleotides form one single codon. The sequence of amino acids in a polypeptide is dictated by the sequence of codons in the corresponding mRNA template.

The amino acid, corresponding to a given codon, is delivered by an adapter molecule called
transfer RNA (tRNA) (see Fig. 1). One end of a tRNA molecule consists of an anticodon (a triplet of nucleotides), and the other end carries the cognate amino acid (that is, the amino acid that corresponds to its anticodon). Because of the codon-anticodon complementarity, each codon on the mRNA becomes converted into a particular species of amino acid on the polypeptide. A tRNA molecule bound to its cognate amino acid is called aminoacyl-tRNA (aa-tRNA).

Each ribosome consists of two subunits. The mechano-chemical processes in these two subunits are coupled and maintain proper coordination for the overall operation of the ribosome. Each of the three binding sites (E, P, and A), which are located in the larger subunit of a ribosome, can bind to a tRNA (see Fig. 1). The binding site on the smaller subunit of the ribosome can bind to the mRNA template strand.

Three major steps in the biochemical cycle of a ribosome are sketched in Fig. 1. In the first, the ribosome selects an aa-tRNA whose anticodon is exactly complementary to the codon on the mRNA. Next, it catalyzes the formation of the peptide bond between the existing polypeptide and the newly recruited amino acid resulting in the elongation of the polypeptide by one monomer. Finally, it completes the mechano-chemical cycle by translocating itself completely to the next codon and is ready to begin the next cycle. In the next section we develop a toy model to capture these three steps in the chemo-mechanical cycle of a ribosome (see Fig. 2).

III. PROTEIN SYNTHESIS: A TOY MODEL

In all the theoretical models, including our toy model proposed here, the sequence of codons on a given mRNA is represented by the corresponding sequence of the equispaced sites of a regular one-dimensional array or lattice. In all these models, the steric interactions among the ribosomes are taken into account by imposing the condition of mutual exclusion; that is, no codon can be covered simultaneously by more than one ribosome.

In their pioneering work, MacDonald, Gibbs, and coworkers modeled each ribosome by an extended particle (effectively, a hard rod) of length $\ell$ in the units of a codon ($\ell$ is an integer). In reality, a ribosome is a complex macromolecular aggregate of proteins and RNA. It is not an inert rod, but a machine whose mechanical movements along an mRNA
strand is coupled to its biochemical cycle.

Recently, we have reported a detailed quantitative theory of protein synthesis. Our theoretical treatment is based on standard methods of non-equilibrium statistical mechanics. Our model differs from earlier models in the way we capture the structure, biochemical cycle, and translocation of each ribosome. The toy model we propose here is a simplified version of the model developed in Ref. 17.

Our model is shown schematically in Fig. 3. We represent the single-stranded mRNA template chain, by a one-dimensional lattice. We label the sites of the lattice by the integer index \( i \) (by convention, from left to right). Each of the sites from \( i = 1 \) to \( i = L \) represent a single codon, where \( i = 1 \) represents the start codon and \( i = L \) corresponds to the stop codon. In our model, the small subunit of each ribosome covers \( \ell \) codons at a time; the position of each ribosome is denoted by the integer index of the lattice site covered by the leftmost site of the smaller subunit. Thus, the allowed range of the positions \( j \) of each ribosome is \( 1 \leq j \leq L \). No lattice site is allowed to be covered simultaneously by more than one overlapping ribosome. Irrespective of the length \( \ell \), each ribosome can move forward by only one site in each step because it must translate successive codons one by one.

There are close similarities between the collective movements of the ribosomes along the template mRNA strand and those of vehicles on highways. Therefore, from the perspective of statistical physics, protein synthesis is also a problem of ribosomal traffic. In the particle-hopping models of vehicular traffic, each vehicle is modeled by a particle. Moreover, a single lane of a highway is represented by a lattice of equispaced points (or, equivalently, a lattice of boxes each centered around a lattice site) none of which can accommodate more than one particle at a time. Each of these self-propelled particles can move forward by a maximum of \( v_{\text{max}} \) lattice sites, unless hindered by another vehicle in front of it.

We will compare and contrast some of the characteristic features of ribosomal traffic with the corresponding features of vehicular traffic. In analogy with vehicular traffic, we define the flux \( J \) as the average number of the ribosomes crossing a specific codon (selected arbitrarily) per unit time. We borrow the terminology of traffic science and refer to the flux-density relation as the fundamental diagram.

In the context of ribosomal traffic, the position, average speed, and flux of ribosomes have interesting interpretations in terms of protein synthesis. The position of a ribosome on the mRNA also gives the length of the nascent polypeptide it has already synthesized. The
average speed of a ribosome is also a measure of the average rate of elongation of a single polypeptide. The flux of the ribosomes gives the total rate of polypeptide synthesis from the mRNA strand, that is, the number of polypeptides synthesized completely per unit time interval.

In a real mRNA the nucleotide sequence is, in general, inhomogeneous, but far from random. Different codons appear on an mRNA with different frequencies. Moreover, in a given cell, not all the tRNA species, which correspond to different codon species, are equally abundant. It is possible to extend our toy model to capture these inhomogeneities following the numerical approach which we used in Ref. [17]. For simplicity, we will consider here only a homogeneous lattice.

To test the accuracy of our approximate analytical results, we have also carried out computer simulations of our model. Because we found very little difference in the results for systems of size $L = 300$ and those for larger systems, all of our production runs were done for $L = 300$. We used random sequential updating. In this scheme, a lattice site is picked at random, and if it is occupied by the left edge of a ribosome the corresponding ribosome is considered for updating; completion of updating the states of $L$ lattice sites increases time by one step. This scheme of updating corresponds to the master equations formulated for the analytical description in our model. Each run begins with a random initial state, but the data for the first $5 \times 10^6$ time steps were discarded to ensure that the system had reached a steady state. In the steady state, data were collected over the next $5 \times 10^6$ time steps. An outline of the main steps of the algorithm used for the simulation of the toy model for periodic boundary conditions is given in the Appendix.

IV. RESULTS FOR PERIODIC BOUNDARY CONDITIONS

Typically, a single ribosome itself covers about twelve codons (that is, $\ell = 12$), and interacts with others by mutual exclusion. The position of such a ribosome will be referred to by the integer index of the lattice site covered by the leftmost site of the smaller subunit.
A. Theoretical formulation under periodic boundary conditions

Let $P_\mu(i)$ be the probability of finding a ribosome at site $i$, in the chemical state $\mu$ where $\mu = 1, 2, 3$ represents the three chemical states in each mechano-chemical cycle of the ribosome which is shown in Fig. 1. Hence, $P(i) = \sum_{\mu=1}^{3} P_\mu(i)$, is the probability of finding a ribosome at site $i$, irrespective of its chemical state. Let $P(i|j)$ be the conditional probability that, given a ribosome at site $i$, there is another ribosome at site $j$. Then, $Q(i|j) = 1 - P(i|j)$ is the conditional probability that, given a ribosome at site $i$, site $j$ is empty. The periodic boundary conditions are somewhat artificial as, effectively, the mRNA takes the shape of a closed ring.

We assume that the probability of finding a ribosome at site $i$ is statistically independent of that of the presence or absence of other ribosomes at other sites. Under this approximation, the biochemical cycle shown in Fig. 2 implies that the corresponding equations for the probabilities $P_\mu(i)$ are

$$\frac{\partial P_1(i)}{\partial t} = \omega_{fs}P_3(i-1)Q(i-1|i-1+\ell) - \omega_aP_1(i), \quad (1)$$

$$\frac{\partial P_2(i)}{\partial t} = \omega_aP_1(i) - \omega_{fl}P_2(i), \quad (2)$$

$$\frac{\partial P_3(i)}{\partial t} = \omega_{fl}P_2(i) - \omega_{fs}P_3(i)Q(i|i+\ell), \quad (3)$$

respectively, where the symbols $\omega_a$, $\omega_{fl}$, and $\omega_{fs}$ are the rate constants shown in Fig. 2. Equations of the type $(1) - (3)$, which govern the time-evolution of probabilities, are known as master equations. The positive and negative terms on the right hand sides of these equations are often referred to as the gain and loss terms, respectively.

The three equations $(1) - (3)$ are not all independent of each other because of the condition

$$P(i) = \sum_{\mu=1}^{3} P_\mu(i) = \frac{N}{L} = \rho,$$  

where $\rho$ is the number density of the ribosomes on the mRNA strand. In our calculations, we have used Eqs. $(2) - (4)$ as the three independent equations.

For simplicity, we report here the results for only $\ell = 1$; the derivation of the corresponding results for an arbitrary $\ell$ is left as an exercise for the reader (see Problem 1).
B. Steady state properties under periodic boundary conditions

In the steady state, all the $P_\mu(i)$ become independent of time. Because of the periodic boundary conditions, no site has any special status and the index $i$ can be dropped. The corresponding flux of the ribosomes $J$ can then be obtained from

$$J = \omega_{fs} P_3 Q(i|i + \ell),$$

using the steady-state expressions for $Q(i|i + \ell)$ and $P_3$.

In the special case $\ell = 1$, $Q(i|i + 1)$ takes the simple form

$$Q(i|i + 1) = 1 - \rho.$$  \hspace{1cm} (6)

The solution of Eqs. (2)–(4) in the steady state for periodic boundary conditions is

$$P_3 = \frac{\rho}{1 + \Omega_{fs}(1 - \rho)},$$  \hspace{1cm} (7)

where,

$$\Omega_{fs} = \omega_{fs}/k_{eff},$$  \hspace{1cm} (8)

with

$$\frac{1}{k_{eff}} = \frac{1}{\omega_{fl}} + \frac{1}{\omega_a}.$$  \hspace{1cm} (9)

Note that $k_{eff}^{-1}$ is an effective time that incorporates the delays induced by the intermediate biochemical steps in between two successive hoppings of the ribosome from one codon to the next. Therefore, $k_{eff} \rightarrow \infty$ implies short-circuiting the entire biochemical pathway so that a newly arrived ribosome at a given site is instantaneously ready for hopping onto the next site with the effective rate constant $\omega_{fs}$.

If we use Eqs. (6) and (7) in Eq. (5) and the definition $\rho = N/L$ for the number density, we obtain

$$J = \frac{\omega_{fs}\rho(1 - \rho)}{1 + \Omega_{fs}(1 - \rho)}.$$  \hspace{1cm} (10)

Note that $J$ vanishes at $\rho = 0$ and at $\rho = 1$ because at $\rho = 1$ the entire mRNA is fully covered by ribosomes.

The flux obtained from Eq. (10) is plotted against density in Fig. 4 for $\omega_a = 2.5 \text{ s}^{-1}$, $\omega_a = 25 \text{ s}^{-1}$, and $\omega_a = 250 \text{ s}^{-1}$. Comparisons of these curves with the corresponding simulation data (represented by discrete points in Fig. 4) shows that our approximate theory
overestimates the flux. This quantitative difference, in spite of qualitative similarities, between our theoretical predictions and the simulation data arises from the correlations in the states of the interacting ribosomes that are neglected in our approximate analysis.

The qualitative shape of the fundamental diagrams shown in Fig. 4 for ribosomal traffic is very similar to those derived from similar particle-hopping models of vehicular traffic as well as those observed in real traffic on highways. The average flux is the product of the density and average velocity of the ribosomes. At very low densities, the ribosomes are sufficiently far apart so that each one can move freely without hindrance. In this regime, the average velocity remains practically unaffected by the increase of density and the flux increases almost linearly with \( \rho \). As the density is increased further, the average velocity begins to decrease. Beyond a certain density, the average velocity decreases so sharply with increasing density that the overall flux decreases with increasing density beyond \( \rho_m \), where the flux exhibits a maximum. We leave it as an exercise for the reader to extract the average velocity from the flux plotted in Fig. 4 and to see the variation of the average velocity with \( \rho \).

We next interpret the \( \omega_a \)-dependence of the fundamental diagrams. When \( \omega_a \) is sufficiently small, the availability of the cognate tRNA molecules is the rate-limiting process; that is, the overall rate of protein synthesis is dominantly controlled by \( \omega_a \). In contrast, when \( \omega_a \) is so large that the availability of tRNA is no longer the rate limiting process, the flux becomes practically independent of \( \omega_a \). Therefore, for a given density \( \rho \), the flux increases with increasing \( \omega_a \), but the rate of this increase slows down with increasing \( \omega_a \) and eventually the flux saturates.

Another interesting feature of the fundamental diagrams is the variation of the peak position \( \rho_m \) with \( \omega_a \). As the rate \( \omega_a \) decreases, the magnitude of \( \rho_m \) increases. Let us define \( v_{\text{max}} \) to be the maximum possible velocity of an isolated ribosome moving along a mRNA template unhindered by any other ribosome. If \( \omega_a \) is small, a ribosome has to wait on each codon for a longer time and the corresponding \( v_{\text{max}} \) would be low. Thus, the decrease of \( \rho_m \) with an increase of \( \omega_a \) can also be viewed as a decrease of \( \rho_m \) with an increase of the effective value of \( v_{\text{max}} \) of the ribosomes. A similar trend for the variation of \( \rho_m \) with \( v_{\text{max}} \) also has been observed in the fundamental diagrams of the particle-hopping models of vehicular traffic. This trend is a consequence of the increase of the effective range of sensing mutual hindrance with increasing \( v_{\text{max}} \).
V. RESULTS FOR OPEN BOUNDARY CONDITIONS

Open boundary conditions are more realistic than periodic boundary conditions for modeling protein synthesis because open boundary conditions properly capture the initiation and termination of synthesis of proteins by each ribosome. Whenever the first $\ell$ sites on the mRNA in our model are vacant, this group of sites is allowed to be covered by a fresh ribosome with the probability $\alpha$ in the time interval $\Delta t$ (in all our numerical calculations we take $\Delta t = 0.001$ s). Thus the effects of all the biochemical processes involved in the initiation of translation are captured in our toy model by a single parameter $\alpha$. Similarly, the termination of translation is also captured by a single parameter $\beta$; whenever the rightmost $\ell$ sites of the mRNA lattice are covered by a ribosome, that is, the ribosome is bound to the stop codon, the ribosome is detached from the mRNA with probability $\beta$ in the time interval $\Delta t$. Because $\alpha$ is the probability of attachment in time $\Delta t$, the probability of attachment per unit time $\omega_\alpha$ is the solution of the equation $\alpha = 1 - e^{-\omega_\alpha \Delta t}$. Similarly, we also define $\omega_\beta$ ads the probability of detachment of a ribosome from the stop codon per unit time.

A. Steady state properties with open boundary conditions

It is possible to do an analysis of the model with open boundary conditions even for arbitrary $\ell$. The method is similar to the one presented previously for the same model with periodic boundary conditions. We leave these analytical calculations as an exercise for the reader (see Problem 2) and present here only the results of computer simulations for the special case $\ell = 1$.

The flux $J$ found by computer simulations is plotted against $\alpha$ and $\beta$ in Figs. 5(a) and 5(b), respectively. The average density profiles observed for several values of $\alpha$ and $\beta$ are also shown in the insets of Figs. 5(a) and (b). Note that small $\beta$ effectively creates a bottleneck at the stop codon and would lead to a high average density profile. In contrast, the ribosomes do not pile up if $\beta$ is sufficiently large. For $\alpha < \beta = 1$, the flux gradually increases and saturates as $\alpha$ increases (see Fig. 5(a)), because a larger number of ribosomes initiate translation per unit time interval at higher values of $\alpha$. This increase of flux with increasing $\alpha$ is also consistent with the corresponding higher average density profile shown in the inset of Fig. 5(a). For $\beta < \alpha = 1$, the flux increases and eventually saturates with
increasing $\beta$ because of the softening of the bottleneck and, hence, the weakening of mutual hindrance of the ribosomes. This trend of variation of flux with $\beta$ is also consistent with the gradual lowering of the average density profile with increasing $\beta$ as shown in the inset of Fig. 5(b).

VI. COMPARISON WITH VEHICULAR TRAFFIC

Our toy model is a simplified version of a more realistic model which takes into account most of the important steps in the biochemical cycle of a ribosome during the elongation stage of protein synthesis. Another version, which is much simpler than even our toy model, has been studied extensively over the last four decades. In these earlier models, each ribosome is represented by a hard rod of length $\ell$ and the effects of the entire mechano-chemical cycle of a ribosome are captured by a single parameter $q$, which is the probability of hopping of the ribosome from one codon to the next per unit time. The trend of variation of $J$ with $\rho$ in those earlier models is qualitatively similar to that observed in our toy model (see Fig. 4). In the special case $\ell = 1$ the hard rods reduce to particles of unit size and the earlier models of ribosomal traffic become equivalent to the totally asymmetric simple exclusion process (TASEP). In fact, TASEP is the simplest model of systems of interacting self-propelled particles.

It is known that for periodic boundary conditions, the exact expression for the flux $J$ in the TASEP is given by

$$J = q\rho(1 - \rho). \quad (11)$$

For our toy model in the special case for which $\ell = 1$ and $k_{\text{eff}} \to \infty$, but $\omega_{fs} = q$ is nonzero and finite, $\Omega_{fs} \to 0$ and, consequently, the approximate expression (10) for the flux reduces to Eq. (11).

TASEP and its various extensions have been used successfully over the last two decades to model various aspects of vehicular traffic as well as many traffic-like phenomena in biological systems. Our toy model can be viewed also as a biologically motivated extension of TASEP to an exclusion process for extended particles with “internal states.”

A statistical distribution which is used widely to characterize the nature of vehicular traffic is the distance-headway distribution. In vehicular traffic, the distance-headway is
defined by the spatial gap between two successive vehicles. In any particle-hopping model, the number of empty sites in front of a vehicle is taken to be a measure of the corresponding distance-headway. For ribosome traffic we define the distance-headway as the number of the codons in between two successive ribosomes that are not covered by any ribosome.

In the steady state of our toy model the distance-headway distribution is expected to be independent of the detailed internal biochemical dynamics. Therefore, the distance-headway distribution in our toy model is identical to that derived earlier for a TASEP-like model for ribosome traffic. The expression is particularly simple in the special case $\ell = 1$. We leave it as a exercise (see Problem 3) because it can be written down directly on purely physical grounds.

VII. SUMMARY AND CONCLUSIONS

We have presented a simplified version of protein synthesis by ribosomes and analyzed our toy model using some elementary methods of statistical physics that are accessible to undergraduate students. This model captures the essential steps in the mechano-chemical cycle of each individual ribosome as well as the steric interactions between ribosomes that move simultaneously along the same mRNA template strand. In particular, we have reported the rates of protein synthesis and the average density profiles of ribosomes on their mRNA templates.

We have investigated how the rate of protein synthesis is affected by the availability of the cognate tRNA molecules. We have demonstrated that, with the increase of the corresponding rate constant $\omega_a$, the flux saturates when the availability of cognate tRNA is no longer the rate limiting step in the synthesis of proteins.

The collective movement of ribosomes during protein synthesis is sometimes referred to as ribosome traffic because of its close superficial similarities with vehicular traffic on highways. We have discussed these similarities and crucial differences to put our work in a broader perspective.

For simplicity we have ignored the effects of sequence inhomogeneities of real mRNA tracks on which ribosomes move. It is straightforward to extend our model to take into account the actual sequence of codons on a given mRNA. The simplest way to capture the sequence inhomogeneity is to assume that the rate constant $\omega_a$ is site-dependent, that is,
dependent on the codon species. By using this assumption, we have computed the rate of protein synthesis when two specific genes of a particular strain of Escherichia coli bacteria are expressed. The lower flux observed for real genes, as compared to that for a homogeneous mRNA, is caused by the codon specificity of the available tRNA molecules.

The dynamics of interacting ribosomes during protein synthesis may be viewed as a biologically motivated extension of TASEP. These systems are never in thermodynamic equilibrium, but can attain non-equilibrium steady-states. The physical properties of models of interacting self-propelled particles have been investigated extensively in the recent years using concepts and techniques of non-equilibrium statistical mechanics.

APPENDIX A: ALGORITHM FOR THE SIMULATION OF THE TOY MODEL WITH PERIODIC BOUNDARY CONDITIONS

Step 1 (Initialization)

(a) Label the lattice sites by the integers 1, 2, . . . , L from left to right and assign occupation number 0 to each site.

(b) Put \( N \) ribosomes, each of length \( \ell \), randomly on the lattice without overlap.

(c) Change the occupation number of the lattice sites covered by the left edge of each ribosome to 1.

(d) To each ribosome, assign the chemical state \( \mu = 1 \). (Alternatively, draw \( \mu \) randomly from the three allowed integers 1, 2, 3.)

Step 2 (Random selection). Using a random number generator, choose one of the \( L \) sites and if the corresponding occupation number is 1, go to step 3; else, go to step 4.

Step 3 (Updating mechano-chemical states). The chemical state of the randomly selected ribosome is updated with the transition probability \( W(1 \rightarrow 2) = 1 - e^{-\omega_1 \Delta t} \), or \( W(2 \rightarrow 3) = 1 - e^{-\omega_2 \ell \Delta t} \), or \( W(3 \rightarrow 1) = 1 - e^{-\omega f_s \Delta t} \), depending on whether it is in the state \( \mu = 1 \), 2, or 3, respectively. In the last case (i.e., corresponding to the transition \( 3 \rightarrow 1 \)), reset the occupation number of the old position of the ribosome to 0 and that of its new position to 1 if the transition takes place.
Step 4. Go to step 2. $L$ iterations of step 4 corresponds to one time step, which is equivalent to the real time $\Delta t$).

Iterate steps 2–4 up to $\text{ITERMX}$ number of time steps so that the duration of the simulation in real time is $\text{ITERMX} \times \Delta t$, where $\Delta t$ is a sufficiently small time interval. The first $\text{ITST}$ time steps are used to ensure that the system settles to a steady-state. The steady-state properties are computed over the next $\text{ITERMX} - \text{ITST}$ time steps.

**APPENDIX B: SUGGESTED PROBLEMS**

Problem 1. (a) Derive analytically the expression for the flux $J$ in the steady-state for $N$ identical ribosomes of arbitrary size $\ell$ with periodic boundary conditions. Verify that the result reduces to Eq. (10) for $\ell = 1$. Plot $J$ against the coverage density

$$\rho_{\text{cov}} = N\ell/L = \rho\ell,$$

(B1)

and suggest a physical interpretation of the variation of $J$ with $\ell$. (b) Imagine that the reverse transition from the state 2 to the state 1 is possible, that is, an aa-tRNA selected by the ribosome can detach prematurely from site A. Assume that the corresponding rate constant is $\omega_p$ and repeat the calculations of part (a) and interpret the results physically.

Problem 2. Write a computer program to simulate the model. Use open boundary conditions and compute $J$ and the average density profiles for arbitrary $\ell$.

Problem 3. Use purely heuristic arguments (without detailed calculations) to derive Eq. (11) for $J$ and the distance-headway distribution in the steady-state of TASEP for periodic boundary conditions.

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FIG. 1: Cartoons showing the three major steps in the mechano-chemical cycle of a single ribosome. The larger and smaller subunits are represented by two rectangles. The vertical “tips” and “dips” emphasize the codon-anticodon complementarity. The uppermost cartoon depicts a freshly selected aa-tRNA whose anticodon is complementary to the codon on the mRNA. The middle cartoon captures the situation where, following the formation of the peptide bond between the existing polypeptide and the newly recruited amino acid and the subsequent forward movement of the tRNA molecules from P and A to E and P sites respectively, the larger subunit has stepped ahead by one codon. The lowermost cartoon depicts the penultimate step of a cycle when the smaller subunit has also translocated to the next codon and the tRNA bound to the E site is about to exit the ribosome.
FIG. 2: A schematic representation of the simplified biochemical cycle of a single ribosome during protein synthesis in our toy model. Each box represents a distinct state of the ribosome. The integer index $i$ below the box labels the codon on the mRNA with which the smaller subunit of the ribosome binds. The number above the box labels the biochemical state of the ribosome. Within each box, 1(0) represents presence (absence) of tRNA on binding sites E, P, A, respectively. The symbols accompanied by the arrows define the rate constants for the transitions from one biochemical state to another; $\omega_a$ corresponds to the selection of the aa-tRNA, and $\omega_{fl}$ and $\omega_{fs}$ correspond, respectively, to the forward movements of the large and small subunits of the ribosome. In our numerical calculations, we use the values of the rate constants for E.coli available in the literature.\textsuperscript{6,7}
FIG. 3: A schematic representation of the model. (a) A cartoon of a single ribosome that explicitly shows the three binding sites E, P, and A on the larger subunit which is represented by the upper rectangle. The rectangular lower part represents the smaller subunit of the ribosome. (b) The mRNA is represented by a one-dimensional lattice where each site corresponds to a single codon. The smaller subunit of each ribosome covers $\ell$ codons ($\ell = 2$ in this figure) at a time.
FIG. 4: Flux of ribosomes for periodic boundary conditions plotted against the density for three values of $\omega_a$. The curves correspond to the approximate analytical expression (10), whereas the discrete data points were obtained by carrying out computer simulations. The values of all the parameters are the same as those in Table I.
FIG. 5: Flux of ribosomes under open boundary conditions plotted against $\alpha$ in (a) and $\beta$ in (b) for three values of $\omega_a$. The discrete data points were obtained by doing computer simulations, and the curves are merely guides to the eye. The average density profiles are plotted in the insets. In the inset of (a) the lowermost density profile corresponds to $\alpha = 0.0002$, and the topmost one corresponds to $\alpha = 0.001$; $\alpha$ varies from one profile to the next in steps of 0.0002. In the inset of (b) the lowermost density profile corresponds to $\omega_a = 0.25 \text{ s}^{-1}$, and the topmost one corresponds to $\omega_a = 250 \text{ s}^{-1}$; $\omega_a$ varies from one profile to the next in steps of 25 \text{ s}^{-1}.}