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

Aakash Basu$^{1}$ and Debashish Chowdhury$^{*1}$

$^1$Department of Physics, Indian Institute of Technology, Kanpur 208016, India.
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Proteins are polymers of amino acids. These macromolecules are synthesized by intracellular machines called ribosome. Although, traditionally, the experimental investigation of protein synthesis has been an active area of research in molecular cell biology, important quantitative models of this phenomenon have been reported mostly in the research journals devoted to statistical physics and related interdisciplinary topics. From the perspective of a physicist, protein synthesis is a phenomenon of classical transport of interacting ribosomes on a messenger RNA (mRNA) template that dictates the sequence of the amino acids on the protein. Here we bring this frontier area of contemporary research into the classroom by appropriate simplification of the models and methods. In particular, we develop a simple toy model and analyze it by some elementary techniques of non-equilibrium statistical mechanics to predict the average rate of protein synthesis and their spatial organization in the steady-state.

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I. INTRODUCTION

Physical frontiers in biology [1] and biological frontier of physics [2] are now active areas of interdisciplinary research. There are journals like Physical Biology whose aim is to foster “the integration of biology with the traditionally more quantitative fields of physics”, etc. Biological physics is also one of the interdisciplinary topics on which very interesting papers are published regularly in high-impact research journals like Physical Review Letters. However, often the original theoretical works are too technical to be accessible to those who are not expert in theoretical modeling of biological systems.

Our main aim in this paper is to bring such a piece of contemporary research into the classroom by appropriate simplification of the models and methods. In particular, we develop a simple toy 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 [3, 4]. In spite of its extreme 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 get a glimpse of a frontier of contemporary research into the classroom by appropriate simplification of the models and methods.

The paper is organized as follows: Because of the interdisciplinary nature of the topic investigated in this paper, we present in section II a summary of the essential biochemical and mechanical processes involved in protein synthesis. In section III we present our toy model and highlight its main features. We report our results in sections IV and V. We compare the model and the results with those for some other similar systems in section VI.

Finally, in section VII we draw our conclusions.

II. PROTEIN SYNTHESIS: ESSENTIAL MECHANO-CHEMICAL PROCESSES

A protein is a linear polymer of amino acids which 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 [3, 4]. An mRNA is a linear polymer of nucleotides and 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.

A given codon on the mRNA is decoded and the corresponding amino acid, required for the corresponding polypeptide, is delivered by an adapter molecule called transfer RNA (tRNA)(see fig.1). One end of a tRNA molecule consists of an anti-codon (a triplet of nucleotides) while the other end carries the cognate amino acid (i.e., the amino acid that corresponds to its anti-codon). Since each species of anti-codon is exactly complimentary to a particular species of codon, each codon on the mRNA gets translated 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. Three sites (called E, P, A), which are located in the larger subunit of a ribosome, bind to an aminoacyl-tRNA (aa-tRNA) (see fig.1). A fourth binding site, which is located on the smaller subunit of the ribosome, binds to the mRNA template strand. The movement of the smaller subunit of a ribosome on the mRNA track is coupled to the biochemical processes occurring in its larger subunit.

Three major steps in the biochemical cycle of a ribosome are sketched schematically in fig.1. In the first, the ribosome selects an aa-tRNA whose anticodon is exactly

*Corresponding author (E-mail: debch@iitk.ac.in)
amino acid mRNA strand subunit smaller chain base growing polypeptide complex aa tRNA

FIG. 1: A pictoral depiction of three major steps in the chemo-mechanical cycle of a single ribosome. The larger and smaller subunits have been represented by two rectangles. The complementary shapes of the vertical tips and dips merely emphasize the codon-anticodon matching.

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.

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 as a one-dimensional lattice where each site corresponds to one single codon. The smaller subunit of each ribosome covers \(\ell\) codons \((\ell = 2\) in this figure\) at a time.

III. PROTEIN SYNTHESIS: A TOY MODEL

In all the theoretical models, \([7, 8, 9, 10, 11, 12, 13, 14, 15, 16]\) 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). Moreover, in all these models, the steric interactions among the ribosomes are taken into account by imposing the condition of mutual exclusion, i.e., no codon can be covered simultaneously by more than one ribosome.

In their pioneering work, MacDonald, Gibbs and coworkers \([7, 8]\) modelled each ribosomes by an extended particle (effectively, a hard rod) of length \(\ell\) in the units of a codon \((\ell\) is an integer). But, 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 \([9]\).

Very recently, we have reported elsewhere \([16]\) a detailed quantitative theory of protein synthesis. Our theoretical treatment is based on standard methods of non-equilibrium statistical mechanics. Our model differs from all 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 detailed model developed in ref.\([16]\).

Our model is shown schematically in fig.3. We represent the single-stranded mRNA chain, consisting of \(L\) codons, by a one-dimensional lattice of length \(L + \ell - 1\) where each of the first \(L\) sites from the left represents a single codon. We label the sites of the lattice by the
integer index $i$; the site $i = 1$ represents the start codon while the site $i = L$ corresponds to the stop codon. In our model, the small subunit of each ribosome covers $\ell$ codons at a time; no lattice site is allowed to be covered simultaneously by more than one overlapping ribosome. Irrespective of the length $\ell$, each ribosome moves forward by only one site in each step as 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 \[17\]. In the "particle-hopping" models of vehicular traffic \[18\] \[19\], each vehicle is modelled 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 some other vehicle in front of it.

We’ll 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. Borrowing the terminology of traffic science \[18\] \[19\], we shall 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, i.e., 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 a numerical approach which we used in ref. \[16\]. But, for the sake of simplicity, here we’ll consider only a homogeneous lattice.

In order to test the accuracy of our approximate analytical results, we have also carried out computer simulations of our model. Since we found very little difference in the results for systems size $L = 300$ and those for larger systems, all of our production runs were carried out using $L = 300$. We have used random sequential updating. In this scheme a ribosome is picked up randomly for updating its state; completion of updating the states of $N$ ribosomes 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 five million time steps were discarded to ensure that the system, indeed, reached a steady state. In the steady state, data were collected over the next five million time steps. Thus, each simulation run extended over a total of ten million time steps. For example, the average steady-state flux was obtained by averaging over the last five million time steps.

IV. RESULTS UNDER PERIODIC BOUNDARY CONDITIONS

Typically, a single ribosome itself covers about twelve codons (i.e., $\ell = 12$), 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. Mean field analysis under periodic boundary conditions

Let $P_\mu(i)$ be the probability of finding a ribosome at site $i$, in the chemical state $\mu$. Then, $P(i) = \sum_{\mu=1}^5 P_\mu(i)$, is the probability of finding a ribosome at site $i$, irrespective of its chemical state. Let $P(j|j)$ be the conditional probability that, given a ribosome at site $i$, there is another ribosome at site $j$. Then, $Q(j|j) = 1 - P(j|j)$ is the conditional probability that, given a ribosome in site $i$, site $j$ is empty. The periodic boundary conditions (PBC) 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. This assumption is known in statistical physics as the mean-field approximation. Under this approximation, the biochemical cycle shown in fig.\[2\] implies that the corresponding equations for the probabilities $P_\mu(i)$ are

$$\frac{\partial P_1(i)}{\partial t} = \omega_f P_3(i-1)Q(i-1) - \omega_a P_1(i), \quad (1)$$

$$\frac{\partial P_2(i)}{\partial t} = \omega_a P_1(i) - \omega_f P_2(i), \quad (2)$$

and

$$\frac{\partial P_3(i)}{\partial t} = \omega_f P_2(i) - \omega_f P_3(i)Q(i), \quad (3)$$

respectively. In the literature on non-equilibrium statistical physics, equations of the type \[11\] \[13\], which govern the time-evolution of probabilities, are known as Master equation \[20\]. The positive and negative terms on the
right hand sides of these equations are often referred to as the gain and loss terms, respectively.

Note that not all of the three equations (11)-(13) are independent of each other because of the condition

$$P(i) = \sum_{\mu=1}^{3} P_{\mu}(i) = \frac{N}{L} = \rho$$  \hspace{1cm} (4)$$

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

For the sake of 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 [16].

B. Steady state properties under periodic boundary conditions

In the steady state, all the $P_{\mu}(i)$ become independent of time. Moreover, because of the PBC, 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

$$J = \omega_{fs} P_3 Q(|i| + \ell).$$  \hspace{1cm} (5)$$

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

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

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

Solving the equations (2), (4) in the steady state under PBC, we get

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

where,

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

with

$$\frac{1}{k_{eff}} = \frac{1}{\omega_{fs}} + \frac{1}{\omega_a}$$  \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, $k_{eff} \to \infty$ 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 $\omega_{fs}$.

Using expressions (6) and (7) in (5) and the definition $\rho = N/L$ for the number density, we get

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

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

The flux obtained from (10) has been plotted against density in figure (4) for three values of $\omega_{a}$, namely, $\omega_{a} = 2.5$ s$^{-1}$, $\omega_{a} = 25$ s$^{-1}$ and $\omega_{a} = 250$ s$^{-1}$. Comparisons of these curves with the corresponding simulation data (represented by discrete points in figure (4) establishes that our approximate theory overestimates the flux. This quantitative difference, in spite of qualitative similarities, between the mean-field theoretic predictions and the simulation data arises from the correlations in the states of the interacting ribosomes which are neglected in the mean-field approximation.

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 biccular traffic as well as those observed in real traffic on highways [18]. Average flux is the product of 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 $\rho$. However, on further increase of density, 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 its variation with of the average velocity with $\rho$.

Next, let us 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, i.e., the overall rate of protein synthesis is dominantly controlled by $\omega_a$. On the other hand, 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 $\omega_a$; the smaller is the rate $\omega_a$, the higher is the magnitude of $\rho_m$. 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 increase of $\omega_a$ can also be viewed as decrease of $\rho_m$ with increase of effective $V_{\text{max}}$ of the ribosomes. A similar trend of variation of $\rho_m$ with $V_{\text{max}}$ has been observed also in the fundamental diagrams of the “particle-hopping” models of vehicular traffic [18]. This is a consequence of the increase of the effective range of sensing mutual hindrance with increasing $V_{\text{max}}$.

V. RESULTS UNDER OPEN BOUNDARY CONDITIONS

Open boundary conditions (OBC) are more realistic than PBC for modeling protein synthesis as OBC 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, in our toy model, the effects of all the biochemical processes involved in the initiation of translation are captured by a single parameter $\alpha$. Similarly, 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, i.e., the ribosome is bound to the stop codon, the ribosome gets detached from the mRNA with probability $\beta$ in the time interval $\Delta t$. Since $\alpha$ is the probability of attachment in time $\Delta t$, the probability of attachment per unit time (which we call $\omega_a$) is the solution of the equation $\alpha = 1 - e^{-\omega_a \times \Delta t}$. Similarly, we also define $\omega_\beta$ which is the probability of detachment of a ribosome from the stop codon per unit time.

A. Steady state properties under open boundary conditions

It is possible to carry out a mean-field analysis of the model under open boundary conditions even for arbitrary $\ell$. The method is similar to the one presented above for the same model under periodic boundary conditions. However, we leave these analytical calculations as an exercise for the reader and present here only the results of computer simulations in the special case $\ell = 1$.

The flux $J$ computed numerically by computer simulations are plotted against $\alpha$ (in (a)) and $\beta$ (in (b)) for three different values of $\omega_a$. The discrete data points have been obtained by carrying out 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 topmost density profile corresponds to $\beta = 0.0002$, and the lowermost one corresponds to $\beta = 0.001$; $\beta$ varies from one profile to the next in steps of 0.0002.
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 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 [16] which takes into account most of the important steps in the biochemical cycle of a ribosome during elongation stage of protein synthesis. However, another version, which is much simpler than even our toy model, has been studied extensively over the last four decades [7, 8, 9, 10, 11, 12, 13, 14, 15]. In those earlier models, each ribosome is represented by a hard rod of length $\ell$ and the effects of the entire mechano-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). TASEP is the simplest model of systems of interacting “self-propelled” particles [21, 22].

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

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

(11)

Note that, for our toy model, in the special situation where $\ell = 1$ and $k_{\text{eff}} \to \infty$, but $\omega_f = q$ remains non-zero and finite, $\Omega_f \to 0$ and, consequently, the approximate expression (11) for the flux reduces to the expression (11).

TASEP and its various extensions have been used successfully over the last two decades to model various aspects of vehicular traffic [18, 19] as well as many traffic-like phenomena in biological systems [17, 23, 24, 25, 26, 27, 28]. Our toy model can be viewed also as a biologically motivated extension of TASEP to an exclusion process for extended particles with “internal states” [29, 30].

A statistical distribution which is used widely to characterize the nature of vehicular traffic is the distance-headway (DH) distribution. In vehicular traffic, the DH is defined by the spatial gap between two successive vehicles [18]. Therefore, in any “particle-hopping” model, the number of empty sites in front of a vehicle is taken to be a measure of the corresponding DH [31, 32]. For ribosome traffic, we define the DH as the number of the codons in between two successive ribosomes which are not covered by any ribosome. In the steady state of our toy model the DH distribution is expected to be independent of the detailed internal biochemical dynamics. Therefore, the DH distribution in our toy model is identical to that derived earlier [10] for a TASEP-like model for ribosome traffic. The expression is extremely simple in the special case $\ell = 1$ under mean-field approximation. We leave it as a simple exercise for the reader as it can be written down directly on purely physical grounds.

VII. SUMMARY AND CONCLUSION

Recently we have developed a detailed model for quantitative studies of various aspects of protein synthesis by ribosomes [16]. In this paper we have presented a simplified version of this model and analyzed it using some elementary methods of statistical physics that are easily accessible to undergraduate students in colleges and universities. 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 their close superficial similarities with vehicular traffic on highways. We have discussed these similarities and crucial differences to put our work on a broader perspective.

For the sake of simplicity, throughout this paper, 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 [16] to capture the sequence inhomogeneity is to assume that the rate constant $\omega_a$ is site-dependent (i.e., dependent on the codon species). Following this prescription, we have already 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.

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