Stochastic microswimming model for the average translational velocity of the ribosome

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The motion of the ribosome is modeled here, assuming that its two subunits are subject to stochastic rearrangements, thus producing different conformations constituting its deformation cycle, or swimming stroke. Using a general statistical mechanical formulation, the mean propulsion velocity of the ribosome is obtained as a function of the transition rates among the different conformations and of the relevant deformation variables. A calculation with reasonable parameter estimations shows that the ribosome can match the average protein synthesis speed with deformations of a size comparable to its radius.

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I. INTRODUCTION

The ribosome is a roughly globular nanoparticle, with an average diameter ranging from 20 to 25 nm [1] composed of the loose association of two subunits, one larger than the other. Chemically, it is a tangle of a special kind of RNA—the ribosomal RNA—with more than 50 varieties of proteins. An important advance in this field of physicochemical studies has been the determination of the x-ray structure of the whole ribosome and its subunits [2]. The main biological function of the ribosome is that of a catalyst, where major precursors, such as aminoacyl-tRNA and mRNA, meet with other factors to synthesize a protein.

With respect to its dynamics, there are two main reasons behind the current conceptualization of the ribosome as a macromolecular machine [3,4]. First, the complex and iterative process of protein synthesis (where the ribosome sequentially reads every codon in the mRNA molecule to link the corresponding amino acids into a protein) can be carried out in vitro by the ribosome alone, only in the presence of the major biochemical precursors [5]. Second, during the process of protein synthesis, the ribosome undergoes many molecular rearrangements to both its internal structure [6] and the relative positions of its two subunits. Regarding the latter, mutual rearrangements of ribosome’s subunits have been reported, including the joining and separation of both subunits relative to each other during the translocation phase of protein synthesis [7], and a small rotation of the small subunit with respect to the large subunit around an axis approximately perpendicular to the subunit’s interface [8]. The hybrid site model of protein synthesis also suggests a mutual displacement of the ribosomal subunits, one sliding over the other, producing a “dislocated” ribosome during translocation [9].

It has also been shown that intersubunit movement is required for ribosomal translocation [10]. In addition to giving an account for the universal two-subunit architecture of ribosomes [10], this result is consistent with several old hypotheses, such as the idea of a pulsating ribosome, which suggested an alternate contraction and expansion of the ribosome during translation [11].

The fact of the matter is that periodic shape changes of significant portions of the ribosome, even if they are stochastically generated, can set the surrounding fluid in motion—causing net displacement of one body with respect to the other in the ribosome-mRNA system. That there is motion of the ribosome along an mRNA molecule during in vitro protein synthesis has been demonstrated by recent experiments using sensitive optical trapping techniques, where ribosome movement is observed as a series of pauses and codon-sized translocation events [12].

Our main hypothesis is that the flow generated by a successful stochastic sequence of conformational changes of the ribosome is an essential component of the motion dynamics in the ribosome-mRNA system during protein synthesis. Due to the small geometric and dynamic scales in which these events take place, we assume that the conformational changes of the ribosome occur in a stochastic manner at a low Reynolds number $Re = RV/v$ (where $R$ and $V$ are typical length and speed values of the body, respectively, while $v$ is the constant kinematic viscosity of the fluid). In this dynamic regime, viscous forces prevail over inertial ones, and, without inertia, a deformable body only has shape changes in order to obtain net translation [13]. An asymmetric particle such as the ribosome has a good chance of generating enough thrust (out of viscous drag) to propel itself after each deformation cycle because, in a viscous regime, taking advantage of asymmetries is a common way to obtain propulsion [14].

To begin testing our hypothesis, we presume the ribosome is free to move as a swimmer along the path set by the mRNA and calculate its average translational velocity $\bar{V}$ following a general statistical mechanical procedure [15]. Such procedure involves two steps. First, assume a prescribed (deterministic) sequence of conformational changes to obtain $\bar{V}$ as a function of the relevant deformation parameters, which is the subject of the next section. Then, find the propulsion velocity as a function of the rate constants of the stochastic transitions among the different ribosomal configurations, which is the main purpose of this investigation and is explained in Sec. III. In Sec. IV we discuss several relevant issues about the dynamics of the ribosome during
protein synthesis and its relationship with the free-swimming hypothesis.

II. DETERMINISTIC SWIMMER

The model ribosome is a unit sphere \( S \) cut from side to side by a plane, producing two spherical segments representing its subunits. In spherical coordinates, \( S = \{ \sin(\theta)\cos(\varphi), \sin(\theta)\sin(\varphi), \cos(\theta) \} \), where \( \theta \) and \( \varphi \) are the azimuthal and polar angles, respectively. The cutting plane is parallel to the \((x, y)\) plane and produces a circle on the sphere located at a latitude \( \theta = \alpha \) where \( \alpha \in [\pi/2, \pi] \). It is assumed that the mRNA will lie in the \( x \) direction (see Fig. 1).

The general expression for a periodic sequence of infinitesimal shape changes is

\[
S(t) = RS + R\varepsilon \sum_{i=1}^{n} a_i(t)w_i,
\]

where \( \varepsilon \) is a small positive number that measures the size of a typical deformation relative to a characteristic length scale \( R \) of the basic shape \( S \); \( a_i(t) \) are time periodic coefficients, and each \( w_i \) is an autonomous vector field defined on \( S \) [13]. The set \( \{ w_i \} \) defines the swimming strategy and is a basis for vector fields on \( S \). To have the possibility of net motion, one needs \( i \geq 2 \); otherwise, a reciprocal strategy is produced—one that only retraces its initial sequence of deformations, thus producing no net motion [14]. A single swimming stroke is described by \( S(t) \) when \( 0 \leq t \leq T \); where \( T = 2\pi/\omega \) is the period of the oscillation and \( \omega \) is its angular frequency.

The chosen vector fields \( w_i \) are rigid motions of one or both subunits, defined in general as follows: \( w_1 = f_1(\theta)i \), \( w_2 = f_2(\theta)k \), where \( i, k \) are the Cartesian basis vectors while \( f_1(\theta) \) are real step functions: \( f_1(\theta) = b_1 + (b_2 - b_1)U(\theta - \alpha) \), \( f_2(\theta) = c_1 + (c_2 - c_1)U(\theta - \alpha) \). Here \( c_1 > 0, c_2 < 0; b_1, b_2 \), are dimensionless real numbers and \( U \) is the Heaviside unit step function.

The vector field \( w_1 \) represents the displacement of one subunit relative to the other along the \( x \) direction (dislocation), while vector field \( w_2 \) designates the separation of one subunit relative to the other along the \( z \) direction (Fig. 1).

The temporal order in which the vector fields \( w_i \) appear in a swimming stroke and their magnitude and direction at each instant \( t \) are given by the periodic coefficients \( a_i(t) \). For the ribosome to start at a partially unlocked state [4] and move in the \( x \) direction we set \( a_1(t) = \cos(\omega t) \), \( a_2(t) = 1 + \sin(\omega t) \), where adding a 1 in the last equation avoids the clashing of subunits during the swimming stroke.

Thus, a periodic sequence of deformations \( S(t) \) of the sphere \( S \) with radius \( R \) is defined with \( n = 2 \) in Eq. (1):

\[
S(t) = RS + R\varepsilon[a_1(t)w_1 + a_2(t)w_2].
\]

As such, the swimming stroke starts with both subunits moving along the horizontal \( x \) direction and is followed by its separation over the vertical \( z \) direction until they reach the maximum amplitude of motion in each direction. From there, both subunits return to the initial undeformed shape by mirroring the first half of the motions. It is important to note that the above description of the swimming strategies is given relative to a frame attached to the ribosome.

To solve the problem of self-propulsion at low Reynolds number (microswimming) it is necessary to assume that the swimmer can squirm, but without exerting net forces and torques on itself—the so-called nonbootstrap condition [13]. Thus, a sequence of deformations (2) does not necessarily specify a possible motion, for it will involve net forces and torques on the swimmer. The allowed motion is a superposition of the given deformations \( S(t) \) given by (2) and counterflows corresponding to additional rigid displacements canceling all forces and torques [13].

To calculate the counterflow, one has to find the response of the fluid to the trial motions \( S(t) \) by solving Stokes equations: \( \nabla^2(\nabla \cdot v) = 0, \nabla \cdot v = 0 \) with the nonslip boundary condition, \( v|_S = \frac{\partial S}{\partial n} \equiv v' \). Note that it is implicit in (1) that deformations changing both the volume and surface area of the swimmer are also allowed [13], but the boundary conditions of the solution of Stokes equations must match the swimmer deformation. In particular, the condition \( \nabla \cdot v = 0 \) implies, according to the divergence theorem, that \( 0 = \oint_S v \cdot \mathbf{n} dS + \oint_{S_S} v \cdot \mathbf{n} dS = \oint_{S} v' \cdot \mathbf{n} dS + \oint_{S_S} v' \cdot \mathbf{n} dS \), where \( S_S \) represents an arbitrary large sphere containing the unbounded fluid. The asymptotic behavior of \( v \) at infinity gives the force and torque associated with the trial motion. The rigid displacements necessary to cancel these must have the same leading behavior at infinity as the trial solution. Using this fact [13], Lorentz’s reciprocity theorem, [16] or the linearity of the self-adjoint dissipation operator [17], one can arrive at the formula giving the translational velocity of a spherical swimmer as a function of the instantaneous surface speed \( v' \):

\[
\mathbf{V}(t) = -\frac{1}{4\pi R^2} \int_S v' dS.
\]

Let \( \mathbf{F} \) and \( \mathbf{n} \cdot \mathbf{\dot{v}} \) be the drag force and surface stress on the sliced sphere, respectively, when rigidly translated through the fluid at a velocity \( \mathbf{U} \). Let \( d = \max(d_x, d_z) \) be the size of a typical deformation. Here \( d_x \) and \( d_z \) are the maximum absolute
displacements of the subunits along the horizontal and vertical directions, respectively, during a swimming stroke, and let \( \varepsilon = d/R \). If \( d \) is sufficiently small compared to the radius \( R \) of the sphere, then \( \mathbf{F} \approx -6\pi\mu\mathbf{R}\mathbf{U} \) and \( \mathbf{n} \cdot \mathbf{a} \approx [3\mu/(2R)]\mathbf{U} \) up to \( O(\varepsilon^2) \). Under these conditions, one can use formula (3) for the model ribosome as follows.

Let \( r_m, \theta_m, \) and \( \phi_m \) be the coordinates of the position of a material point on the deformed sphere. The general expression for deformations in terms of the given spherical coordinates is \( r_m = R[1 + \psi_1(\theta, \phi, t)], \theta_m = \theta + \psi_2(\theta, \phi, t), \) and \( \phi_m = \phi + \psi_3(\theta, \phi, t) \), where \( \theta, \phi \) are the coordinates of a material point in the undeformed sphere. The deformations \( \psi_1, \psi_2, \psi_3 \) (1, 2, 3) are periodic functions in \( t \) of fixed period \( T \). The components of the vector field \( \psi = e(a_1(t)\mathbf{w}_1 + a_2(t)\mathbf{w}_2) \) are obtained after expressing \( \mathbf{I}, \mathbf{k} \) (which are present in the definition of the vector fields \( \mathbf{w}_i \)) in terms of the spherical base vectors \( \mathbf{e}_r, \mathbf{e}_\theta, \mathbf{e}_\phi \). The deformation velocity \( \mathbf{v} \) in Cartesian coordinates is

\[
\mathbf{v} = \frac{\partial}{\partial t}[r_m \sin(\theta_m) \cos(\phi_m), r_m \sin(\theta_m) \sin(\phi_m), r_m \cos(\theta_m)],
\]

and the material area element is

\[
dS_m = r_m^2 \sin(\theta_m) d\theta_m d\phi_m.
\]

Solving (3) with the expressions just given, calculating the surface integral accurate to \( O(\varepsilon^2) \), and averaging in the time over the period of the swimming stroke leads to the general average linear velocity vector:

\[
\langle \mathbf{V} \rangle = \frac{1}{T} \int_0^T \mathbf{V}(t) dt = \left\{ \frac{1}{16} Rbc\varepsilon^2 \omega \sin^2(\omega)[1 + \sin(\omega)], 0, 0 \right\},
\]

where \( b = (b_1 + b_2), c = (c_1 - c_2) \) are factors related with some measure of deformation size in the \( x \) and \( z \) directions, respectively. Thus, on average, the deterministic ribosome only translates along the local \( x \) axis after each swimming stroke, with velocity

\[
\mathbf{V} = \frac{1}{16} Rbc\varepsilon^2 \omega \sin^2(\omega)[1 + \sin(\omega)].
\]

A. From prescribed to stochastic deformations

According to the general geometric theory of microswimming \([13,18]\) the displacement \( \mathbf{D} \) generated after each stroke by the coupling of any two members (oscillation modes) \( \mathbf{v}_m, \mathbf{v}_n \) of the deterministic swimming strategy is

\[
D = \sum_{m,n} \int_0^T a_m \delta_m F_m^{ir} dt = \frac{1}{2} \sum_{m,n} \int_0^T (a_m \delta_n - a_n \delta_m) F_m^{ir} dt,
\]

where \( a_m, a_n \) are time dependent periodic coefficients and the \( F_m^{ir} \) are the components of the translational part of the curvature tensor \( \mathbf{F}[\mathbf{v}_m, \mathbf{v}_n] \), giving the infinitesimal translation produced by the coupling of modes \( \mathbf{v}_m, \mathbf{v}_n \). According to Green’s theorem, the integral \( \int_0^T (a_m \delta_n - a_n \delta_m) dt \) gives the area of the projected closed trajectory in the parameter plane \( a_m - a_n \). In the case of just two vector fields, Eq. (6) becomes

\[
D = \frac{1}{2} R^2 \varepsilon^2 F^{ir}[v_1^h, v_2^k] \int_0^T (a_1 \delta_2 - a_2 \delta_1) dt,
\]

where the superscript \( h \) indicates the horizontal parts of the given deformations, that is, the ones satisfying the nonbootstrapping condition \([18]\). As such, the average speed over the time lapse \( T \) of a swimming stroke is \( \langle \mathbf{V} \rangle = D/T \), which, in this particular case, is given by (4). For a stochastic swimmer, this average aging over prescribed configurations must be substituted by an average over the probabilistic space of conformations that the swimmer can adopt \([15]\).

III. CONFORMATION SPACE

At the molecular level, one has to take into account the stochastic nature of the conformational changes and not prescribe a deterministic trajectory for the deformation of the system under study. The geometric information embodied in the deterministic formula for the average speed given by (5) is going to be a part of the final expression for the average velocity under stochastic conditions, which also must include the rate constants among the different ribosomal configurations.

Let \( C_n \) denote the different conformations of the ribosome and \( P_n \) the probability that the ribosome is at conformation \( C_n \). The rate of transition from \( C_m \) to \( C_n \) is denoted by \( k_{mn} \). The conformational space of the ribosome is defined by the variables \( d_1, d_2 \) describing the displacements of the subunits along the \( x \) and \( z \) directions, respectively, relative to the radius of the ribosome. Thus, variables \( d_1 \) and \( d_2 \) can only take the values \( d_1 = 0, \pm e_1, d_2 = 0, e_2 \) where \( e_1 = d_1/R, e_2 = d_2/R, d_1, d_2 \) are the maximum absolute displacements along the horizontal and vertical directions, respectively, and \( R \) is the radius of the ribosome—as before. The conformation space has four states (see Fig. 2). The key assumption here is that the ribosome can transit from one state to another in an almost instantaneous way. The cycle pictured in Fig. 2 is a good discrete representation of the continuous stroke given by...
Eq. (2), which is symmetrical along the local vertical axis and produces net motion provided \( b_1 \neq -b_2 \) [see Eq. (5)].

The transition rates among the different configurations in the cycle are

\[
\begin{align*}
C_1 & \xrightarrow{k_{12}} C_2 & C_2 & \xrightarrow{k_{23}} C_3 & C_3 & \xrightarrow{k_{34}} C_4 & C_4 & \xrightarrow{k_{41}} C_1.
\end{align*}
\]

The probability current at every link in the cycle is \( J_{mn} = k_{mn} P_m - k_{nm} P_n \) (\( m, n = 1, \ldots, 4 \)). In the steady state, all currents are equal to a single steady state current \( J \) that can be found by solving the system of four linear current equations plus the normalization condition \( \sum_{n=1}^{4} P_n = 1 \), giving the result

\[
J = \frac{k_{12}k_{23}k_{34}k_{41} - k_{14}k_{43}k_{32}k_{21}}{(k_{12}k_{23}k_{34} + k_{23}k_{34}k_{41} + k_{34}k_{41}k_{12} + k_{41}k_{12}k_{23})}.
\]

Since, for a one-loop cycle in the conformation space, the time average of the incomplete differential has to be substituted by \( AJ \), where \( A \) is the area enclosed by the cycle in the conformation space [15], the time average of the velocity as a function of the rate constants is

\[
\bar{V} = K \varepsilon_1 \varepsilon_2 J.
\]

The product \( \varepsilon_1 \varepsilon_2 \) gives the area of the cycle in the discrete conformation space \( (d_1, d_2) \), and \( K = \frac{2}{9} b c e^2 \sin^2(\alpha)[1 + \sin(\alpha)] \) is a constant term obtained after canceling in (4) the deterministic period \( T \) and the area enclosed by the coefficients \( a_1(t), a_2(t) \) in the continuous parameter space \( (a_1, a_2) \). Equations (7) and (8) give the average swimming speed of the model ribosome. The average time taken to complete a motion cycle \( C_1 \rightarrow C_2 \rightarrow C_3 \rightarrow C_4 \rightarrow C_1 \) is related to the probability flux \( J \) by \( T = J^{-1} \) [15].

A. Calculations

According to Eq. (5), the fastest ribosomal morphology has \( \alpha = \pi/2 \); that is the equatorial ribosome—the one with equally sized subunits. By making \( d_1 = d_2 \equiv d \) in the conformation space and establishing symmetry in the deformations along the \( x \) and \( z \) axis with \( c_1 = -c_2 \equiv C, b_1 = b_2 \equiv B > 0 \) and \( C = B \equiv k, bc = 4k^2 \) in (5) and Eq. (8) becomes

\[
\bar{V} = k^2 \varepsilon^4 RJ
\]

for the equatorial ribosome.

In vivo assays of protein synthesis rate give ranges from 2–4 to 20–40 amino acids per second [19]. Since codon length \( l_c \approx 1.0 \text{ nm} \) [19], it yields an average protein synthesis speed of \( V_p \approx 3–30 \text{ nm/s} \). At such a speed, the corresponding Reynolds number will be \( \text{Re} \approx 10^{-11}–10^{-10} \). This is a very low Reynolds number indeed considering, for example, that bacteria move at \( \text{Re} \approx 10^{-5} \) [14].

Let period \( T \) be given by \( T = nl_c/V_p \) where \( n \) is the average number of codons traversed by the ribosome in the forward direction per deformation cycle. If one amino acid is added to the protein chain per cycle, then \( n = 1 \)—resulting in \( T = 1/30 \text{ s} \) for the average fast rate of protein synthesis—which implies \( J = 30 \text{ s}^{-1} \). It is interesting to observe that the previously calculated value of \( T \approx 33 \text{ ms} \) has the same order of magnitude as the average duration of the translocation step found experimentally [20].

The magnitude of separation between the two ribosomal subunits upon aminoacyl-tRNA starvation is 3 nm [7]. Let \( d = 3 \text{ nm} \) be a typical deformation size. With \( R = 10 \text{ nm} \), one finds, using formula (9), that a deformation \( dk \approx 12 \text{ nm} \) is needed to reach the average speed \( \bar{V} \) of 30 nm/s. A slightly higher value for \( d \) will make the deformation size smaller than \( R \) but, in any case, one obtains reasonable ribosomal deformation sizes calculating with Eq. (9). Another way of producing the same speed with a smaller deformation size is with a shorter period \( T \), for example, if more than one amino acid is incorporated into a protein per ribosomal deformation cycle.

IV. DISCUSSION

A. Detailed balance

If detailed balance holds, then \( \bar{V} = 0 \), since the numerator in (7) would be zero. But molecular machines such as the ribosome work in out-of-equilibrium situations, both thermodynamically and mechanically speaking. This is because during the process of peptide biosynthesis and tRNA site
changes, the ribosome is moved along the mRNA a distance that, in the end, is equal to one codon with the addition of each amino acid. This translocation step is catalyzed in vivo by the complex formed by a protein [elongation factor (EF)] with GTP, which is hydrolyzed to provide the required energy [21]. Since the ribosome can also synthesize a protein in vitro, even in the absence of all elongation factors [5], another possible source of energy for translocation is the energy of peptide bond formation [12].

In the absence of an external energy source such as GTP, the distance a bead is displaced outside of an optical trap is smaller than in the presence of an energy source during the motion of the ribosome along a linear mRNA strand [22]. In our model this result can be interpreted as due to an increase in the amplitude and/or frequency of ribosomal deformations when the source of chemical energy is in the reaction mixture, producing a more powerful swimming stroke after completing each deformation cycle in a shorter time. Since \( T = J^{-1} \), a shorter period \( T \) for the deformation cycle can be produced if the forward rate constants become higher than their backward counterparts [see Eq. (7)]. Then the deformation cycle will go counterclockwise more times than clockwise. Higher deformation amplitude is obtained in our model when the product \( bc \) in Eq. (5) is also higher. This in turn increases the value of \( K \) in (8) and, together with the increase in frequency (meaning a higher value for the probability flux \( J \)), will lead to a faster speed. Since at low Re, force is proportional to velocity, this would mean that the ribosome applies more force on the bead in this situation, resulting in larger and more frequent displacements of the bead outside of the optical trap after each translocation phase.

Another simple and interesting unbalanced situation is when all the reverse rate constants are smaller than their forward counterparts \( (k_{12} \gg k_{23}, \text{ etc.}) \). This case (hereafter referred to as “forward dominance”) is a situation closer to the structuralist view of a ribosome working cycle, which is completely mechanistic and is embodied in the classical textbook pictures of the process of protein synthesis. It is also the case in which the ribosomal motion would produce protein synthesis in the most efficient way, since the ribosome aims to read the complete message in the mRNA molecule in a preferred direction. Calculating (7) in the limit of forward dominance and, since \( T = J^{-1} \), one obtains

\[
T = k_{12}^{-1} + k_{23}^{-1} + k_{34}^{-1} + k_{41}^{-1}.
\]

(10)

This means that the period for a full cycle is the sum of the time intervals needed to complete each leg of the cycle [15].

According to experimental results, the translocation step consists of several substeps (most likely three) with an equal mean lifetime of \( \approx 25 \text{ ms} \) [20]. Since only part of the total lifetime can be due to configuration change, \( 25 \text{ ms} \) sets an upper boundary to the duration of each ribosomal configuration—at least under forward dominance conditions. These results can be interpreted in our model as if, for example, each deformed configuration \( (C_2, C_3, C_4) \) belongs to one of the reported substeps, and the transition back to the undeformed configuration \( C_1 \) (given by the rate constant \( k_{41} \)) is quite fast—possibly on the order of microseconds.

### B. Mechanics of motion

The complete ribosome only exists as such during the process of protein synthesis, since it is assembled and attached to the mRNA right before starting the process and disassembled after it has finished reading the message in the mRNA [19]. Therefore, its motion is restricted to the local direction set by the mRNA, with which it strongly interacts. On the grounds of abundant biochemical and structural data, it has been proposed that in order to efficiently perform its biochemical work, the ribosome must oscillate between a locked and an unlocked state [4]. In the latter, the ribosome is able to accept a large ligand (such as tRNA) or allow movement of macromolecules inside it, while in the former, the ribosome immobilizes the chemical reactants to promote its reaction or allow for molecular recognition (e.g., codon-anticodon).

Large intersubunit rearrangements would have to occur in order to produce one state or the other. Our suggestion here is that during such conformational changes, the ribosome lowers the strength of its interaction with mRNA, allowing the mechanism for configuration change to be released. This is a key assumption in our model (and also for ratchet models of ribosome dynamics [12,23]), and in fact there is experimental evidence supporting it. Force measurements in single-molecule experiments have shown that the energy liberated by peptide bond formation weakens the ribosome-mRNA interaction right before the translocation step [23]. Furthermore, it has also been found that at a certain level of tension force applied by the optical trap on a linear mRNA strand, the ribosome slips back during translocation steps [22]. This phenomenon has been proposed as a physical explanation to \(-1\) frame shifting [22]. As such, in our model it can be interpreted as if the force applied by the optical trap has just reached a level over the ribosome-mRNA interaction force and matched the force generated by the swimmer, canceling it out completely and causing the ribosome to slip back to the 5' end by pulling the messenger towards the optical trap during ribosomal unlocked states.

Following the release of the mechanism for configurational change and after one or more unlocked states, the ribosome would be able to complete its deformation cycle—producing a net force on the fluid of a sufficient magnitude to offset the ribosome-mRNA interaction force and generating the necessary impulse to move the ribosome along the mRNA. According to our model, this propulsive hydrodynamic force would be a part of the total force responsible for the displacement—measured in any single-molecule experiment using optical tweezers [12]—which a bead suffers as it is being pulled out of the optical trap at each translocation step.

When the strain on the linear mRNA goes above the slip-back threshold, the ribosome actually reverses its direction of translocation [22]. One interpretation of this result consistent with our model is that the high tension force on the mRNA affects the horizontal displacements of the subunits in both magnitude and direction—changing the quantitative characteristics of the dislocated ribosomal configurations \( C_2 \) and \( C_4 \). Such change is mathematically reflected in our model as an inversion in the order relation between the deformation parameters \( b_1, b_2 \), which are measures of the size and direction of the horizontal displacement of the large and small subunits, respectively (see Fig. 1). For example, \( b_1 > 0 > b_2 \) gives a
positive value to parameter $b$ in Eq. (5) and to the constant $K$ in (8), while $b_2 > 0 > b_1$ gives the opposite result, reversing the sign of the velocity given by (8).

Although precisely how domain and subunit movements are coupled to the chemical steps of translation and its dynamics remains unclear [12]; here we suggest that, for example, each configuration $C_n$ could have both a locked and an unlocked state, and the transition between configurations could take place in the unlocked state. In this way, one achieves certain compatibility between ribosomal conformations and their biochemical function. This dynamic, with periods of motion (translocation) followed by pauses, is actually what is observed experimentally [12,20] and would not affect the final average position of the ribosome after each motion cycle: $C_1 \rightarrow C_2 \rightarrow C_3 \rightarrow C_4 \rightarrow C_1$, since at low $Re$ it does not matter if the swimming strokes are performed at a slow or fast speed [13].

If it is assumed that the mRNA is free to move in certain lapses of the protein synthesis process while the ribosome is held in a roughly fixed position (as it is supposed to be in the endoplasmic reticulum), then the state of motion of the swimming ribosome would be transmitted by the fluid to the mRNA, which would now move with respect to the fixed ribosomes.

V. CONCLUSION

The main objective of this paper has been fulfilled with the derivation of expression (8) giving the mean linear speed $\bar{V}$ of a ribosome subject to a cycle of stochastic deformations. We have shown that the prescribed swimming strategy, embodied in Eq. (5) and stochastically reflected in the conformational space, is successful because it can produce net ribosome motion. Furthermore, the ribosome reaches the reported average velocity of protein synthesis with deformations of reasonable size and several experimental results on ribosome dynamics can coherently be interpreted inside the frame of the model. As such, these results suggest that the ribosomal deformations during translation could serve a dual function, the first being biochemical, in the cycle of protein synthesis (as is originally believed) and the second being dynamical, to impulse the ribosome along the mRNA.