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Theoretical estimate of the effect of thermal agitation on ribosome motion generated by stochastic microswimming

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ABSTRACT

The effect of thermal agitation on ribosome motion is evaluated through the Péclet number, assuming that the ribosome is self-propelled along the mRNA during protein synthesis by a swimming stroke consisting of a cycle of stochastically-generated ribosome configurations involving its two subunits. The ribosome velocity probability distribution function is obtained, giving an approximately normal distribution. Its mean and variance together with an estimate of the *in vivo* free diffusion coefficient of the ribosome and using only configuration changes of small size, give a Péclet number similar to motor proteins and microorganisms. These results suggest the feasibility of the stochastic microswimming hypothesis to explain ribosome motion.

1. Introduction

The ribosome is a roughly globular nanoparticle, with an average diameter of 20 *nm* [1], comprised of the loose association of two subunits of different sizes. Its main biological function is to be a catalyst where major precursors, such as aminoacyl-tRNA and mRNA, meet with other factors to synthesize a protein. It sequentially reads the genetic message codified in the mRNA, adding one amino-acid to the growing polypeptide chain before moving three nucleotides to the next codon during the translocation phase [2].

During protein synthesis, the ribosome experiences many rearrangements in both its internal structure [3], and the relative positions of its two subunits [4]. With respect to the latter, it has been shown that intersubunit movement is required for ribosomal translocation, thus explaining the universal two-subunit architecture of ribosomes [5]. This is also consistent with the old idea of a pulsating ribosome which alternates contraction and expansion during translation [6].

With respect to motion, there is now substantial experimental evidence showing that the ribosome moves itself along the mRNA during protein synthesis, both *in vitro* [7–9] where it is characterized as a series of pauses and codon-sized translocation events, and *in vivo* where even individual ribosome trajectories can be followed in the cellular cytoplasm, allowing the calculation of diffusion coefficients [10,11].

Subcellular particles move at very low Reynolds number $Re = RV/\nu$, where R is a typical length of the body, V its velocity and ν the constant kinematic viscosity of the fluid. A spherical particle the size of the ribosome with radius $R = 10\ nm$ and $V = 800\ nm/s$ (typical of motor proteins [2]) in water at normal conditions has $Re \approx 10^{-9}$. Whereas for swimming bacteria, $Re \approx 10^{-5}$[12].

Moving at low Re is the realm of very viscous fluids, very slow motions, or flow fields of small extent. Viscous forces prevail over inertial ones, and the total force acting on an object is not proportional to acceleration but rather to velocity [13,14]. The motion of a microswimmer (swimmer at low Re) in a fluid is completely determined by the geometry of the sequence of shapes that it assumes, independent of any variation in the rates at which different parts of the sequence are run through (as long as these rates are slow) [15]. The stochastic microswimming model of ribosome motion [16] summarized in Section 2, assumes that the ribosome is self-propelled along the mRNA during protein synthesis by a swimming stroke consisting of a cycle of stochastically-generated conformational changes involving the relative position of its two subunits.

At the small scales in which the events of protein synthesis take place, thermal fluctuations play an important role in the dynamics of a microswimmer [17,18], whose swimming stroke produces a rather coherent motion of fluid particles (flow) around the body in motion. The impact of diffusion caused by thermal noise (Brownian motion) on self-propelled motion can be evaluated with the Péclet

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number *Pe*. This is a dimensionless ratio of the rate at which a particle moves a distance *L* after being carried along by a coherent flow of the fluid over the rate at which it diffuses the same distance *L* [19]. Thus $Pe = LV/D$, where *V* is a typical speed of the particle, and *D* is its diffusion coefficient. A sound estimate of ribosome typical speed during protein synthesis can be obtained from its velocity probability distribution function (PDF), which is calculated in Section 3 under the hypothesis of stochastic microswimming. The complete estimation of the effect of thermal agitation on ribosome-directed motion is presented in Section 3 and discussed in Section 4.

2. Materials and methods

2.1. Ribosome model

The ribosome is supposedly in an unbounded fluid domain and is modeled by a solid sphere *S* with radius *R*, cut from side to side thus producing two spherical segments representing its subunits with the intersubunit channel, where the mRNA lies, located at an azimuth angle $\theta = \alpha$, $\alpha \in [\pi/2, \pi]$ (Fig. 1).

2.2. Conformational space

Only two subunit motions that appear during translation are included in the configurations cycle or ribosome conformational space (Fig. 2). The first is the joining and separation of both subunits relative to each other (C_1 and C_3), which is an experimentally-detected ribosome conformational change [20]. The other is the mutual displacement of the ribosomal subunits, where one slides over the other along the intersubunit channel producing a "dislocated" ribosome (C_2 and C_4). This is a rearrangement of ribosomal subunits suggested from biochemical information by the hybrid site model of protein synthesis [21]. The permitted transitions between configurations C_m and C_n are presumed to be instantaneous, as they occur one at a time, do not overlap and have first order equilibrium rate constants k_{mn}. The cycle portrayed in Fig. 2 has the characteristic of connecting the four proposed configurations with the minimum number of bonds.

Because the shape of the object and its conformational changes are sufficiently symmetric, the ribosome swims in a rectilinear fashion [16,22]. As shown elsewhere [16], this cycle of deformations is a successful swimming strategy for the spherical ribosome at low *Re*, and it is moved along the *x*-axis at an average speed $\overline{V}$:

$$\overline{V} = C\bar{J}, \tag{1}$$

where *C* is a constant depending on the ribosome relevant deformation parameters, including the total area enclosed by the loop in the conformational space (Fig. 2), and $\bar{J}$ is the net mean number of cycles completed per unit of time at a steady state in the counterclockwise, positive direction [23]. Following the method in Ref. [22], *C* was obtained in Ref. [16] after the calculation of $\overline{V}$ in the deterministic case, where ribosome motion obeys the Stokes equation and it goes through a cycle of prescribed deformations. This cycle is identical to the one in Fig. 2 but with only one arrow linking neighboring configurations and all pointing in the counterclockwise direction.

3. Results

3.1. Velocity PDF

Let $V = CJ_t$ be the random variable given the ribosome velocity, where *C* is as in Eq. (1) and J_t is the net number of cycles in the plus direction per unit of time that the ribosome has completed at time *t*. The distribution of *V* is approximately normal because the frequency J_t is also approximately normally-distributed: $J_t \sim N(\bar{J}, \sigma_J)$ (Appendix A). Then the expected value of *V* is given by Eq. (1), with standard deviation $\sigma_V = C\sigma_J$:

$$\sigma_V = C\sqrt{\bar{J}^+ + \bar{J}^-}\, t^{-1/2}. \tag{2}$$

where $\bar{J}^+, \bar{J}^-$ are the mean number of cycles completed at a steady state per unit of time in the counterclockwise or clockwise direction, respectively. Since $V \sim N(\overline{V}, \sigma_V)$, then $\overline{V}$ is the value with highest probability density in the distribution and is the best representative of ribosome speeds at all times during the process of protein synthesis. Therefore, about 99.7% of all speed values are in the interval $\overline{V} \pm 3\sigma_V$ for each $t > 0$. Since $\sigma_V \approx t^{-1/2}$, the velocity distribution is widespread for short times and becomes thinner as time goes on.

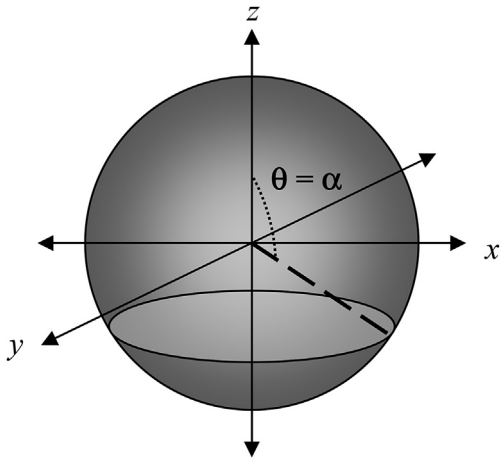

Fig. 1. The model ribosome is a sliced sphere with the two spherical segments representing its subunits and the intersubunit channel between them, which is located at an azimuth angle $\theta = \alpha$, where $\pi/2 \leq \alpha \leq \pi$.

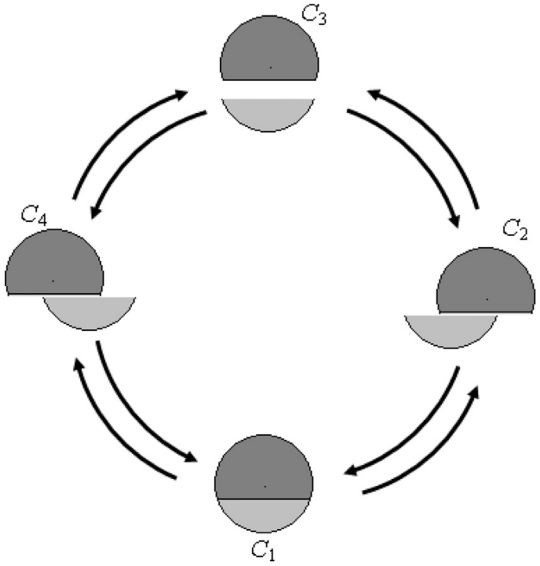

Fig. 2. Ribosome conformational space. C_n denotes the different configurations, and the arrows connecting them are the permissible transitions $C_m \rightarrow C_n$ which occur at first order rates k_{mn}. Net swimming to the right requires the system to make more cycles in the counterclockwise direction than in the clockwise direction.