Surfing on Protein Waves: Proteophoresis as a Mechanism for Bacterial Genome Partitioning

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Efficient bacterial chromosome segregation typically requires the coordinated action of a three-component machinery, fueled by adenosine triphosphate, called the partition complex. We present a phenomenological model accounting for the dynamic activity of this system that is also relevant for the physics of catalytic particles in active environments. The model is obtained by coupling simple linear reaction-diffusion equations with a *proteophoresis*, or "*volumetric*" chemophoresis, force field that arises from protein-protein interactions and provides a physically viable mechanism for complex translocation. This minimal description captures most known experimental observations: dynamic oscillations of complex components, complex separation, and subsequent symmetrical positioning. The predictions of our model are in phenomenological agreement with and provide substantial insight into recent experiments. From a nonlinear physics view point, this system explores the active separation of matter at micrometric scales with a dynamical instability between static positioning and traveling wave regimes triggered by the dynamical spontaneous breaking of rotational symmetry.

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Controlled motion and positioning of colloids and macromolecular complexes in a fluid, as well as catalytic particles in active environments, are fundamental processes in physics, chemistry, and biology with important implications for technological applications [1,2]. In this Letter, we focus on an active biological system for which precise experimental results are available. Our work is fully inspired by studies of one of the most widespread and ancient mechanisms of liquid phase macromolecular segregation and positioning known in nature: bacterial DNA segregation systems. Despite the fundamental importance of these systems in the bacterial world and intensive experimental studies extending over 30 years [3–5], no global picture encompasses fully the experimental observations.

Partition systems encode only three elements that are necessary and sufficient for active partitioning: two proteins ParA and ParB, and a specific sequence *parS* encoded on DNA. The pool of ParB proteins is recruited as a cluster of spherical shape centered around the sequence *parS* forming the ParB*S* partition complex [4]. These ParB*S* cargos interact with ParA bound onto chromosomal DNA (ParA-slow) [6,7], triggering unbinding of ParA by inducing conformational changes through stimulation of adenosine triphosphate (ATP) hydrolysis and/or direct ParB-ParA contact [8], and thereby allowing ParA diffusion in the cytoplasm (ParA-fast) [5]. This process entails the oscillation of ParA from pole to pole and the separation of the ParB*S* partition complex into two complexes with distinct subcellular trajectories and long-term localization. Overall, these interactions result in an equidistant, stable positioning of the duplicated DNA molecules along the cell axis.

The specific modeling of ParAB*S* systems falls into two categories: either "filament" (pushing or pulling the cargos, similar to eukaryotic spindle apparatus [3]) or reaction-diffusion models [8–15]. Recent super-resolution microscopy experiments have been unable to observe filamentous structures of ParA [5,13], disfavoring polymerization-based models [12]. Reaction-diffusion models have been mainly investigated numerically to describe experimental observations like single or multiple ParB*S* complex positioning. In most cases, these models require other assumptions—such as DNA elasticity [13,14]—as simple reaction-diffusion mechanisms are not sufficient to predict proper positioning. Other reaction-diffusion models considered the dynamics of the partition complex on the surface of the nucleoid [8–11]. Recent experiments, however, demonstrate that partition complexes and ParA translocate through the interior of the nucleoid, not at its surface [5].

Recently, in the context of the active colloids literature, there have been attempts to describe the ParAB*S* system using models inspired by the diffusiophoresis [16,17] of active colloidal particles in solute concentration gradients [2,18]. These works have several important limitations for applications to ParAB*S*, such as rigid spherical particles (with surface reactions only), the steady-state approximation, only one ParA population, or reproducing equilibrium positioning only. The full dynamical behavior of the coupled system (ParB*S* cargo coupled to ParA) has, thus, not been elucidated.

Here we propose a general model of reaction-diffusion for ParA coupled to the overdamped motion of ParB*S*. Our continuum reaction-diffusion approach goes beyond the previous diffusiophoretic mechanisms [11,12,14,18] by accounting for the finite diffusion of ParA-slow and ParA-fast, as well as the interaction of ParA-slow with the entire volume of ParB*S* partition complexes. Volumetric interactions are suggested by our recently developed "nucleation and caging" model [4,19], which accounts for both the formation of ParB*S* and the distribution of ParB in the spatial vicinity of *parS*-specific DNA sites: the conformation of the plasmid is well described by a fluctuating polymer and the weak ParB-ParB interactions lead to foci of low density [4,19]. The chromosome is, thus, likely to enter ParB*S* with bound ParA-slow, thereby allowing for volumetric interactions. Such a volumetric interaction should also find useful applications in the field of porous catalytic particles. On the other hand, allowing for finite diffusion coefficients permits us to describe analytically the global dynamical picture of the model, contrary to previous numerical studies often restricted to a limited range of parameters. In particular, this enables us to predict a dynamical transition between stable and unstable regimes. We observe that biological systems are generally close to the instability threshold. The ParAB*S* system of the F-plasmid lies just below, enabling efficient positioning and precursor oscillations of ParA. Other ParAB*S* systems ([14] and references therein) could be just above, providing an explanation for the observed out-of-phase ParB*S* and ParA oscillations. Our model accounts for both these regimes.

The model.— The ParA protein population is described by two coupled density fields: $u(\mathbf{r},t)$ for the hydrolyzed ParA-fast proteins assumed to be unbound and diffusing rapidly within the nucleoid, and $v(\mathbf{r},t)$ for the nonhydrolyzed ParA-slow molecules, which are bound dynamically to the nucleoid and diffuse more slowly. These two species are coupled via a system of reaction-diffusion equations: the rapid species u converts into the slow one with a constant rate k_1, while the slow species v is hydrolyzed in the presence of the ParB*S* partition complexes located on DNA, with a rate k_2 (typically $k_1 \approx 0.02\ \mathrm{s}^{-1}$ [9] and $k_2 \approx 68.5\ \mathrm{s}^{-1}$ [12]). The ParB*S* assemblies form 3D-foci complexes [4] and interact with the ParA-slow proteins. The interaction probability is described by the profiles $S(\mathbf{r}-\mathbf{r}_i(t))$ centered around the ParB*S* positions $\mathbf{r}_i(t)$. These profiles play a double role: (i) they act as catalytic sources in the reaction-diffusion equations, triggering ParA-slow hydrolysis with the rate k_2, and (ii) they determine a feedback "proteophoresis" (volumetric) force, in contrast with chemophoresis forces that occur in general only at the complex surface. In what follows, the function $S(\mathbf{r})$ representing an idealized density profile of ParB*S* is assumed to be symmetric with a compact support of width σ and a unit value at its maximum. The dynamics of the protein population is, therefore, described by the coupled reaction-diffusion equations:

$$\frac{\partial u}{\partial t} = D_1\Delta u - k_1 u(\mathbf{r},t) + k_2 v(\mathbf{r},t)\sum_i S(\mathbf{r}-\mathbf{r}_i(t)),$$
$$\frac{\partial v}{\partial t} = D_2\Delta v + k_1 u(\mathbf{r},t) - k_2 v(\mathbf{r},t)\sum_i S(\mathbf{r}-\mathbf{r}_i(t)). \quad (1)$$

In these equations, in which we do not invoke the steady-state approximation (cf. Ref. [2]), D_1 and D_2 represent the diffusion constants of the fast and slow species, respectively, u and v. The sum runs over the ParB*S* positions $\mathbf{r}_i(t)$. The density fields are subjected to reflecting boundary conditions $\nabla u\cdot\mathbf{n}|_{\partial V}=0$ and $\nabla v\cdot\mathbf{n}|_{\partial V}=0$, where $\mathbf{n}$ is a unit vector normal to the cell boundary ∂V. The system described by Eqs. (1) together with these boundary conditions on u and v ensure total ParA protein number conservation. Note that ParA proteins can freely penetrate the partition complexes, which do not form barriers for diffusion.

The nonlinear coupling in the system is introduced by the forces driving the partition complexes, which are modeled as Brownian particles in an active medium. The backreaction on each complex is described by a "proteophoresis force" due to the ParA-slow concentration gradient acting on the whole volume of the complex. In the viscous medium prevailing in a cell, we do not expect inertial terms to be important. Neglecting in the first approximation the stochastic and confining forces, the dynamic equation for the ith complex then reads

$$m\gamma\frac{d\mathbf{r}_i}{dt}(t) = \varepsilon\int_V \nabla v(\mathbf{r},t)S(\mathbf{r}-\mathbf{r}_i(t))d^3\mathbf{r}. \quad (2)$$

Note that no direct coupling between complexes has been introduced. The constant ε represents the energy of interaction between a single ParA-slow protein and the ParB*S* partition complex. Hence, the order of magnitude of ε is a fraction of the energy released by the ATP hydrolysis ($\simeq 10k_BT$). The drag force coefficient $m\gamma$ is related to an effective diffusion constant of the complex D_{pc} by the Einstein relation $m\gamma = k_BT/D_{\mathrm{pc}}$. Thanks to attractive protein-protein interactions (leading to hydrolysis energy consumption) the interaction energy ε in Eq. (2) is positive, and the corresponding proteophoresis force and resulting motion is in the direction of increasing ParA density gradient. In the following, we will use the dimensionless coupling constant: $\alpha\equiv\varepsilon/m\gamma D_2=(\varepsilon/k_BT)(D_{\mathrm{pc}}/D_2)$. From numerical simulations, it appears that the stochastic force does not affect crucially the main system dynamics. Super-resolution microscopy [5] indicates that the partition complex motion is confined to the cell symmetry axis, i.e., within the bacterial nucleoid. Therefore, in the minimal model, we limit the study of its dynamics to one dimension and denote by x the coordinate along the cell axis, $-L\le x\le L$, where $2L$ is the cell length.

Restoring proteophoresis force positions the partition complexes symmetrically along the nucleoid axis.— The

model provides all the necessary ingredients for proper partition complex positioning. We first look for stationary solutions when a single partition complex is present within the cell at position x_1. In order to keep the algebra simple, we approximate the profile function $S(x-x_1)$ by a Dirac-delta distribution $\sigma\delta(x-x_1)$ [20], where the amplitude σ is the typical interaction volume of the complex. The stationary solutions of Eqs. (1) with reflecting boundary conditions then read

$$u(x) = A\frac{\cosh\left(q(L+x)\right)}{\cosh\left(q(L+x_1)\right)} \text{for } -L \le x < x_1,$$
$$u(x) = A\frac{\cosh\left(q(L-x)\right)}{\cosh\left(q(L-x_1)\right)} \text{for } x_1 < x \le L,$$
$$v(x) = C - \frac{D_1}{D_2}u(x), \tag{3}$$

where $q \equiv \sqrt{k_1/D_1}$. The x_1-dependent constants A and C in Eq. (3) can (see the Supplemental Material [21]) be easily computed by the gradient discontinuity at x_1,

$$D_1(\partial_x u|_{x_1^+} - \partial_x u|_{x_1^-}) = -k_2\sigma v(x_1), \tag{4}$$

and by the conservation of the total number of ParA monomers. For a deltalike complex profile, the force acting on a static partition complex located at x_1 is proportional to the mean value of the ParA-slow density gradient at x_1:

$$F(x_1) = \frac{\varepsilon\sigma}{2}(\partial_x v|_{x_1^+} + \partial_x v|_{x_1^-}),$$
$$= \frac{1}{2}\alpha m\gamma\sigma D_1 qA\big(\tanh q(L-x_1) - \tanh q(L+x_1)\big). \tag{5}$$

This result shows that the unique equilibrium position of the complex is located at the cell center, i.e., $x_1 = 0$. An important feature of the resulting force mediated by the ParA density distribution gradient is its finite range. Its screening length given by $\eta = 1/q = \sqrt{D_1/k_1}$ is illustrated in Fig. 1, where the force $F(x)$ is plotted for different values of η. Clearly, the proteophoresis force, here estimated of the order of the piconewton ($\approx$0.25 kT/nm) is sensed by the partition complex only if its distance to the cell boundary or to a neighboring complex is less than η. Note that the above quasistatic (adiabatic) analysis is valid only when the ParA distribution instantaneously adapts to the complex position (cf. Ref. [2]). The restoring character of the force Eq. (5) then makes the symmetric position $x_1 = 0$ stable.

For bacterial cells containing several partition complexes, the sum over their positions in Eqs. (1) generates an effective indirect interaction among them that, together with the boundary conditions and protein number conservation, brings the system to an equilibrium state with highly symmetric complex positions. For instance, when two complexes are present within the cell (as would be the case after a DNA replication event), the equilibrium positions are found to be located at $x_1 = -L/2$ and $x_2 = L/2$, i.e., the "1/4" and "3/4" positions in terms of the cell axis length $2L$. A phase portrait of the system in the (x_1, x_2) coordinates (see inset of Fig. 1) clearly indicates the stable nature of these positions. This result is in excellent agreement with experimental observations [5,29] and can describe even more complex experimental situations with multiple ParB*S*; see some examples in Fig. 2. Interestingly, as we show below, when the evolution time scale of the ParA distribution is shorter than that of the partition complex, the symmetric static positions become unstable and the steady-state approximation breaks down, leading to oscillatory behavior of the complexes.

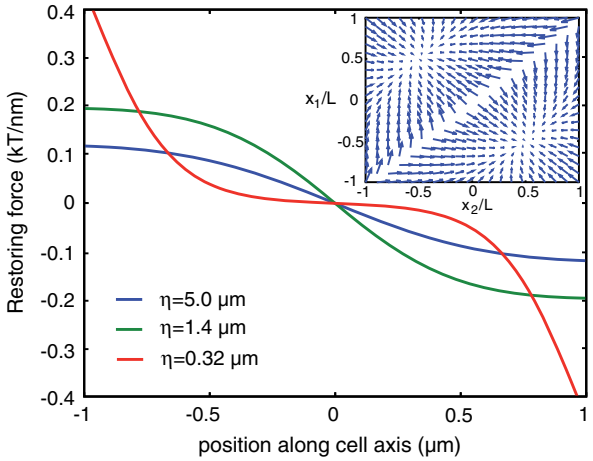

FIG. 1. Proteophoresis force [Eq. (5)] for different values of the screening length η (variable k_1) with the other biological parameters fixed (see the Supplemental Material [21]). The curve in blue is plotted using physiological values ($k_1 = 0.04$ s^{-1}) and shows a marked restoring force gradient toward midcell positions: for $\eta = 0.32$, 1.4, and 5 μm, the force produces a parabolic potential well of depth ~0, 6, and 4 kT, respectively, over a half-width of 0.25 μm (note the nonmonotonic behavior with the equilibrium position restoring force vanishing for both zero and infinite k_1; see the Supplemental Material [21]). Inset: Proteophoresis force field in the phase space $(x_1/L,\ x_2/L)$ of two partition complex positions.

The translocation-segregation mechanism can become unstable with respect to ParA traveling waves.— Analytical and numerical studies of Eqs. (1) and (2) show that stationary solutions (irrespective of the number of complexes) become unstable in cells where the ParA density profiles can develop large gradients. The concentration profiles and the partition complex start traveling together at a constant velocity c_{TW}, as if partition complexes were self-propelled by "surfing" on the ParA distribution wave they have themselves generated (see the Supplemental Material [21]) to eventually bounce back and forth in the presence of cell boundaries. This strongly suggests the existence of traveling waves (TWs) in an unbounded system or in finite-size cells whose length $2L$ is

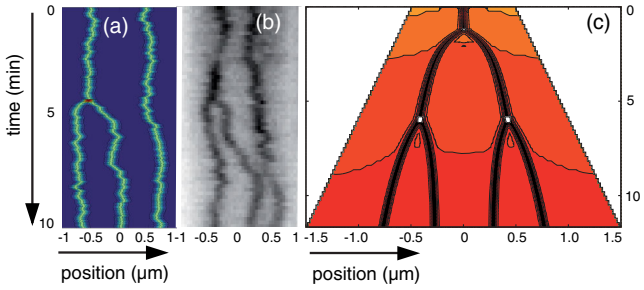

FIG. 2. (a) Kymograph obtained from the model using an additional Brownian force acting on ParB*S*: the model describes ParB*S* equilibrium, segregation, and positioning. (b) Example of an experimental kymograph obtained from 10 min time lapse microscopy (frame every 10 sec) of F-plasmids in *E.coli*, displaying a segregation event from two to three ParB*S* over the length of the nucleoid. (c) Theoretical kymograph obtained with growing cell (with an average over the stochastic noise). Trajectories are similar to experimental ones [5]. For details, see the Supplemental Material [21].

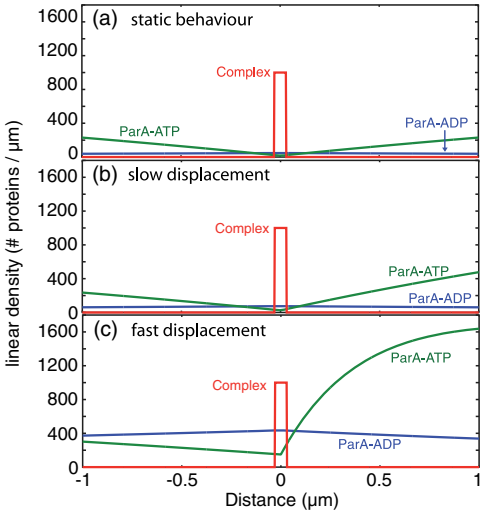

FIG. 3. Density profile of ParA-slow v (green), ParA-fast u (blue), and ParB*S* (red). (a) $\alpha < \alpha_c$: positioning in the middle of the cell. (b) Weak coupling $\alpha_c \lesssim \alpha$: ParB*S* moves as a TW and is surfing to the right on a protein wave. (c) Strong coupling $\alpha_c \ll \alpha$: large asymmetry between the two sides of ParB*S* implying fast surfing. See the Supplemental Material [21] for details.

much larger than the screening length η. For one complex, we look for solutions of Eqs. (1) and (2) in the TW form $u(x,t) = u(\xi)$; $v(x,t) = v(\xi)$, where $\xi = x - c_{\mathrm{TW}}t$ is the wave comoving reference coordinate, with the asymptotic conditions $u(\xi) \to 0$ and $v(\xi) \to v_\infty$ when $\xi \to \pm\infty$. The resulting system of ordinary differential equations admits analytical solutions for a Dirac partition complex profile $S(x - x_1) \propto \delta(x - x_1)$. For more general shapes, solutions are easily obtained numerically. Typical TW-like snapshots of ParA distributions calculated for a rectangular complex profile are displayed in Figs. 3(b) and 3(c). The equation of motion of the partition complex (2) takes the form $c_{\mathrm{TW}} = \alpha D_2 \int \partial_\xi v(\xi) S(\xi) d\xi$ and provides a nonlinear relation for determining the wave celerity c_{TW}.

The existence of traveling waves with nonzero velocity is concomitant with the loss of stability of the equilibrium positions of the partition complexes discussed above. Thus, we distinguish two dynamical regimes: (1) A *stable* regime without TWs ($c_{\mathrm{TW}} = 0$), with stable (equidistant, if more complexes are present) equilibrium complex positions independent of the initial conditions if the screening length η is large with respect to the cell size; see Fig. 3(a) and the Supplemental Material [21]. This implies a transient translocation when the initial conditions do not correspond to stable positions. This regime occurs for small values both of the coupling constant α (obtained, e.g., for large values of the limiting diffusion constant D_2) and the ParA concentration, C_0. When the screening length η is small, then ParB*S* cargos remain at their initial positions, not necessarily equidistant and without interaction between complexes. (2) A *dynamical* regime ($c_{\mathrm{TW}} \neq 0$) with unstable equilibrium positions of the complexes and ParA density oscillations in the cell corresponding to TWs in an unbounded domain; see Figs. 3(b) and 3(c) and the Supplemental Material [21]. This occurs for large values of both α and the initial ParA concentration C_0. Since α is large for small values of the diffusion constant D_2, there results an apparently surprising phenomenon, namely, that slower ParA-slow kinetics leads to faster complex dynamics. This regime occurs because the ParA-slow distribution variation in time is not rapid enough to follow the partition complex and trails behind it. Indeed, the stability threshold corresponding to the appearance of TWs at $c_{\mathrm{TW}} = 0^+$ can be written as $V_S < V_v$, where V_S is the escape velocity of the complex and V_v the speed of spatial rearrangement of the ParA-slow distribution (see the Supplemental Material [21] for details). When $V_v > V_S$, the ParA distribution rapidly reequilibrates its symmetric profile with respect to the complex position and the system tends to the stable stationary regime, while in the opposite case, spontaneous symmetry breaking and TW behavior occur. Using the expressions for V_S and V_v, we obtain the stability condition in the form $\alpha < \alpha_c \approx 1/(\sigma C_0)$. This reveals that large complex sizes, interaction energies ϵ, and ParA densities, as well as low ParA-slow diffusion coefficients lead to the instability of the partition complex positioning. Importantly (see the Supplemental Material [21]), a biologically reasonable choice of model parameters shows that the system is not far below the instability threshold, leading to a not only robust but also relatively fast segregation process, in agreement with experiment.

Discussion.— Our model for bacterial DNA segregation is able to account for the whole of the experimental phenomenology of segregation and positioning of the replicated DNA molecules. This is possible because of the careful definition of reaction-diffusion equations for the

two species of ParA (slow and fast) coupled to the overdamped motion of the ParB*S* cargo.

Our continuum reaction-diffusion approach significantly extends previous work [11,12,14,18]. Some of these [11,14] failed to observe a stable equipositioning regime because ParA-slow was not allowed to diffuse ($D_2 = 0$); thus, α diverges, setting the system in the unstable regime. In Ref. [14], relative positioning occurs only with multiple cargos as a crowding effect, whereas it is known that positioning can occur even with a single plasmid [30], as predicted by certain modeling studies [12,18]. In line with the most recent experimental findings [5], we assume that partition complexes evolve within the nucleoid volume near the axis of the rod-shaped bacterial cells, in contrast with the translocation surface mechanism presented in Refs. [8–11] performed on large surfaces coated by ParA, lacking the confinement necessary for equipositioning. Our proposed mechanism integrates explicitly a volumetric interaction [4] with the partition complex (i.e., a length in 1D), placing the system close to the stability threshold for the biological range of parameters. In the case of a surface interaction, for which the volume is limited to the boundaries of the surface complex, α_c would, thus, take much higher values. This argument can be easily generalized to higher dimensions D. Our approach also allows us to clarify analytically the physical mechanism at play, by going beyond the numerical simulations usually performed in a limited range of parameters and to show explicitly that other effects like polymerization [12] and DNA elasticity [13,14] are not needed to account for segregation.

These elements make the active system considered in our work unprecedented, with genuine size- and bulk-dependent effects, like the emergence of a critical coupling constant controlling the stability and the TW regimes. Moreover, when multiple complexes are present, they generate indirect intercomplex interactions mediated solely by the "perturbed" medium. This leads naturally to proper equilibrium partition complex positioning, as well as to spontaneous (left or right in 1D) symmetry breaking in the traveling wave regime. To our knowledge, this is the first model, in the context of active bacterial segregation via ParAB*S* systems, possessing very good qualitative and semiquantitative agreement with all experimental observations, including segregation and position control of single and multiple partition complexes (see, also, the Supplemental Material [21]). The model robustness also suggests its application to other biological processes, like macromolecule and organelle positioning in intracellular dynamics.

Beyond its biological inspiration, this model is a novel one for active particle dynamics (accounting for proteophoresis) and nonlinear physics with a very rich phenomenology. Indeed, our model falls in the class of active particles (partition complexes in the present case) which locally "perturb" a medium (composed here of ParA proteins) that acts back on their dynamics and, thus, gives rise to particle self-propulsion. Such a behavior also provides similarities with classical polaron systems [31]. In contrast with previous works [2,12,18] on the subject, as well as on the self-propulsion of catalytic particles in active environments under chemical gradients [1], we do not invoke specifically the well-known mechanism of diffusiophoresis (or chemiphoresis) [16,17,32] or autochemotaxis, which involve surface interactions and (possibly asymmetric) catalytic surface reactions [18] coupled to surrounding hydrodynamic fluid flow relative to the particle surface (see Refs. [1,2]). Future perspectives will include more refined comparisons with experimental observations and biological parameters and a generalization to higher dimensions.

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