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Simple model of cell crawling

T. Ohta [a,b,*], M. Tarama [c], M. Sano [a]

[a] Department of Physics, The University of Tokyo, Tokyo, 606-8502, Japan
[b] Toyota Physical and Chemical Research Institute, Nagakute, Aichi 480-1192, Japan
[c] Fukui Institute for Fundamental Chemistry, Kyoto University, Kyoto, 606-8103, Japan

HIGHLIGHTS

- A simple but general model for cell crawling is derived from symmetry consideration.
- We apply the so-called coherence resonance to generate the time-dependent forces.
- The nonlinear coupling among deformations affects drastically the crawling behavior.

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ABSTRACT

Based on symmetry consideration of migration and shape deformations, we formulate phenomenologically the dynamics of cell crawling in two dimensions. Forces are introduced to change the cell shape. The shape deformations induce migration of the cell on a substrate. For time-independent forces we show that not only a stationary motion but also a limit cycle oscillation of the migration velocity and the shape occurs as a result of nonlinear coupling between different deformation modes. Time-dependent forces are generated in a stochastic manner by utilizing the so-called coherence resonance of an excitable system. The present coarse-grained model has a flexibility that it can be applied, e.g., both to keratocyte cells and to *Dictyostelium* cells, which exhibit quite different dynamics from each other. The key factors for the motile behavior inherent in each cell type are identified in our model.

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1. Introduction

Eukaryotic cell crawling has attracted much attention recently from the view point of nonlinear science and non-equilibrium statistical physics. One of the characteristic features is that the symmetry is spontaneously broken to cause the front-rear asymmetry when the cell migrates in contrast to bacterias which swim by rotary motion of flagella and hence are inherently asymmetric. The dynamics of eukaryotic cells involves the mechanical forces between cell membrane and substrate, and biochemical reaction of active molecules inside a cell.

Study of cell crawling on substrates has began rather recently compared to that of swimming bacterias. The latter has a long history of hydrodynamical approach in the limit of low Reynolds number [1–4]. Shape deformation of crawling keratocyte cells has been analyzed experimentally [5]. Classification of morphology of motile cells, correlations between shape deformation and migration of *Dictyostelium* cells and other living cells have also been investigated [6–9]. Recent advanced experimental techniques have enabled us to measure the spatial distribution of traction forces exerted by a migrating cell on substrates [10–13] and the concentration distribution of active molecules which involve cell motility [14].

Plasma membrane protrusion caused by actin polymerization in the cell interior is the essential mechanism of cell crawling. In the early 1990s, DiMilla et al. investigated persistent migration of tissue cells such as fibroblasts by a mathematical model which is essentially one-dimensional and incorporates cytoskeletal force generation, cell polarization, and dynamic adhesion [15]. Theoretical studies of cell crawling taking into account shape deformations have started recently. Modeling of cell crawling employing reaction–diffusion mechanism inside a cell or on a cell boundary and the interaction between the chemical components and the cell membrane has been proposed in two dimensions [16–18]. A phase field model for cell shape coupled with the polarization field of actin filaments has also been proposed for the cell motility. The crawling dynamics of keratocyte cells including oscillatory straight

* Corresponding author at: Department of Physics, The University of Tokyo, Tokyo, 606-8502, Japan.
E-mail address: ohta@daisy.phys.s.u-tokyo.ac.jp (T. Ohta).

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motion and bipedal motion [19] has been investigated by taking account of the density of adhesion bonds and traction forces [20,21]. A similar model in terms of the phase field has been studied in which the reaction–diffusion dynamics inside a *Dictyostelium* cell is assumed to be excitable and therefore this model is capable of investigating non-stationary motion [14]. Modeling of amoeboidal cell crawling has also been formulated by an oscillatory dynamics [22] where irregularity appears as spatio-temporal chaos [23]. These are models in two dimensions. In a slightly different approach, theory of active gels has been applied to stationary amoeba motion in one dimension to make a connection between the migration velocity and the distribution of active stress or myosin molecules [24,25]. Motility of active droplets in which active stress is generated has been studied numerically both in two and three dimensions to show that a bifurcation from a motionless state to a migrating state with shape deformations occurs due to spontaneous symmetry breaking of the polarity inversion in the absence of treadmilling [26].

It is mentioned briefly that there is another mechanism of cell motility due to plasma membrane blebbing [27]. This is not restricted to migration on substrate. Blebbing is initiated by local disruption of membrane-action cortex and internal hydrostatic pressure. It is of importance to note that actin polymerization is not involved in the initial bleb expansion. Cell motility by blebbing in three-dimensional environments has been investigated theoretically [28].

In the present paper, we study cell crawling under a homogeneous environment based on a phenomenological model in terms of migration velocity and shape deformations. A set of time-evolution equations is derived based on symmetry consideration in the same spirit as the derivation of equations for deformable self-propelled particles [29,30]. To make shape deformations, we introduce forces which act on the cell perimeter. We consider time-independent and time-dependent forces separately. The case of constant forces is regarded as a model of coherent motions, e.g., of keratocyte cells whereas the time-dependent forces are applied to motility of *Dictyostelium* cells. In the experiments of *Dictyostelium* cells, morphological change occurs repeatedly but it is not precisely periodic. To realize this behavior, we utilize the so-called coherence resonance which generates spike excitation of chemical components repeatedly in an excitable system when noise is added appropriately [31].

All the previous models mentioned above are constructed to apply to a specific system such as fish keratocyte cells and *Dictyostelium* cells. A steadily migrating keratocyte cell is elongated perpendicularly to the velocity direction [5] whereas a *Dictyostelium* cell in a starved condition has a tendency to elongate parallel to the migration direction [8]. Our model, though simple, has an advantageous feature that it is applicable to non-stationary motion of a crawling cell with general shape deformations by choosing appropriately the parameters.

One of the basic assumptions of our model in terms of the center of mass and the cell boundary is that all other degrees of freedom involving migration relax rapidly. If this is not the case, we need to add other relevant degrees of freedom as dynamical variables.

In the next section (Section 2) we start with description of our model system. The case of constant forces is analyzed in Section 3 where we obtain limit cycle oscillations of migration velocity and shape deformations. This is compared with the phase field model of keratocyte cells. Numerical results for the time-dependent forces are shown in Section 4 and are compared qualitatively with the motions of *Dictyostelium* cells. Discussion is given in Section 5.

2. Model for cell crawling

We introduce the model of cell crawling in two dimensions in terms of the velocity of the center of mass v_i, and the deformation tensors

$$v_k = \gamma S_{ij} U_{ijk}, \tag{1}$$

$$\frac{dS_{ij}}{dt} = -\kappa_2 S_{ij} + b_0 \left(v_i v_j - \frac{\delta_{ij}}{2} v_k v_k \right) + F_{ij}^{(2)}(t), \tag{2}$$

$$\frac{dU_{ijk}}{dt} = -\kappa_3 U_{ijk} + d_0 [v_i v_j v_k - \frac{v_n v_n}{4} (\delta_{ij} v_k + \delta_{jk} v_i + \delta_{ki} v_j)] + F_{ijk}^{(3)}(t), \tag{3}$$

where the repeated indices imply summation.

The tensors S_{ij} and U_{ijk} are defined as follows. Deformations of a cell around a circular shape with radius R_0 are written as

$$R(\phi, t) = R_0 (1 + \delta R(\phi, t)), \tag{4}$$

where

$$\delta R(\phi, t) = \sum_{n=-\infty}^{\infty} c_n(t) e^{in\phi}. \tag{5}$$

Since uniform expansion and contraction of a circular cell are prohibited and the translational motion of the cell has been incorporated in the variable v_k, the modes c_0 and $c_{\pm 1}$ should be removed from the Fourier series (5). The deformation tensors are given in terms of the Fourier coefficients by [32]

$$S_{11} = c_2 + c_{-2} = 2a_2 \cos 2\theta_2, \tag{6}$$

$$S_{12} = S_{21} = i(c_2 - c_{-2}) = 2a_2 \sin 2\theta_2, \tag{7}$$

$$S_{22} = -S_{11}, \tag{8}$$

$$U_{111} = -U_{122} = -U_{212} = -U_{221} \equiv W_+, \tag{9}$$

$$U_{222} = -U_{112} = -U_{121} = -U_{211} \equiv -W_-, \tag{10}$$

where

$$W_+ = c_3 + c_{-3} = 2a_3 \cos 3\theta_3, \tag{11}$$

$$W_- = i(c_3 - c_{-3}) = 2a_3 \sin 3\theta_3, \tag{12}$$

with positive a_2 and a_3.

The coefficients κ_2 and κ_3 are positive while the sign of γ in Eq. (1) will be fixed later. Here, for simplicity, we ignore other nonlinear couplings such as $U_{ijk} v_k$ and $S_{ij} v_k + S_{jk} v_i + S_{ki} v_j - (v_n/2)(\delta_{ij} S_{kn} + \delta_{jk} S_{in} + \delta_{ki} S_{jn})$ [29] but consider the coupling only with the velocity as Eqs. (2) and (3) since those terms are expected to be mostly relevant to the correlation between the elongation direction and the migration direction as shown below.

Eq. (1) implies that there is no inertia term and that the cell does not migrate if it is circular since we consider a deformation-induced migration. In our previous studies of migration-induced deformations [32,33], equation of motion of the center of mass was derived, which takes the following form

$$\frac{dv_k}{dt} = \kappa_1 v_k - g(v_i)^2 v_k + a S_{kj} v_j + \gamma' S_{ij} U_{ijk}, \tag{13}$$

where κ_1, $g(>0)$, a and γ' are constants. Eq. (1) is a special case of Eq. (13). In fact, when κ_1 is negative, that is, migration is passive, one may ignore the g-term and in the limit of $|\kappa_1| \gg 1$, the solution of Eq. (13) is given by

$$v_k = -\gamma' [\kappa_1 + aS]^{-1}_{k\ell} S_{ij} U_{ij\ell} \approx -\frac{\gamma'}{\kappa_1} S_{ij} U_{ijk}. \tag{14}$$

It is also noted here that the deformation-induced migration in the form of Eq. (1) has been introduced in a different context

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