Phase-Field Model of Cell Motility: Traveling Waves and Sharp Interface Limit

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Abstract

In this paper, we report our resent results on asymptotic analysis of a PDE model for motility of a eukaryotic cell. We formally derive the sharp interface limit, which describes the motion of the cell membrane. In the 1D case, we rigorously justify the limit, and, using numerical simulations, observe some surprising features such as discontinuity of interface velocities and hysteresis. We show that nontrivial traveling wave solutions appear when the key physical parameter exceeds a critical value.

Résumé

Nous présentons dans cet article des résultats récents sur l'analyse asymptotique d'un modèle EDP pour la migration de cellules eucaryotes. Nous dérivons formellement l'équation limite pour l'interface, qui décrit le mouvement de la membrane cellulaire. Dans le cas unidimensionnel, nous justifions cette limite de faqn rigoureuse, et nous observons numériquement quelques propriétés surprenantes, comme par exemple une discontinuité dans les vitesses à l'interface, et un phénomène d'hystéresis. Nous montrons l'apparition d'ondes de propagation non triviales quand le paramètre physique clé dépasse un certain seuil.

Version française abrégée

Nous considérons un modèle EDP pour la migration des cellules eucaryotes, introduit pour la première fois dans [1]. Il a été démontré numériquement que ce modèle reproduit de faqn adéquate des pénomènes observés expérimentalement, comme de brutales mises en mouvement de la cellule, et des oscillations de sa forme. Le modèle consiste en une EDP parabolique, pour la fonction scalaire décrivant la phase, couplée avec une EDP vectorielle parabolique pour le réseau de filament d'actine (cytosquelette). Tout d'abord, nous montrons que les solutions n'explosent pas en temps fini, et de plus, si la donnée initiale a une structure de type interface mince, cette structure d'interface mince est préservée au cours du temps. Ensuite, via une approche à deux échelles, dans l'esprit de [2], nous dérivons formellement la limite de l'interface mince (SIL pour Sharp Interface Limit) qui décrit le mouvement de la membrane cellulaire (interface). Nous montrons que cette interface mince a un mouvement contraint par la condition de conservation du volume avec un terme non-linéaire supplémentaire dû à l'adhérence au substrat et à la protusion du cytosquelette. Dans un cadre unidimensionnel, nous prouvons que la vitesse à l'interface satisfait une équation non linéaire simple qui est une version 1D de l'interface mince. Une approche directe serait alors de réinjecter les développements formels utilisés pour dériver la SIL dans l'EDP originelle et d'estimer le reste par des bornes sur l'énergie, mais cette approche ne résiste pas au couplage des équations. La principale astuce technique est d'introduire une représentation spéciale des solutions constituée d'une partie principale: le lieu de l'interface qui est inconnu, et d'un reste (nul dans la limite SIL) constitué d'un terme donné explicitement, et d'un terme inconnu. Cette représentation est accompagnée d'une condition supplémentaire: le terme inconnu dans le reste est orthogonal à la fonction propre de l'opérateur d'Allen-Cahn linéarisé autour de son onde stationnaire. Cette condition définit implicitement le lieu de l'interface et permet d'appliquer une inégalité de type Poincarré pour estimer le reste. En exploitant cette représentation, nous réduisons l'étude de la vitesse d'interface à une seule équation non-linéaire perturbée de faqn singulière. Nous montrons que si la vitesse à l'interface appartient à un certain domaine stable, alors, elle continue de satisfaire l'équation SIL jusqu'à ce qu'elle devienne instable. Ce résultat théorique est accompagné

par des simulations numériques qui montrent que lorsque la vitesse à l'interface devient instable, elle saute à la composante connexe la plus proche du domaine des vitesses. Les simulations numériques mettent également en évidence l'existence de boucle d'hystérésis dans le système. Enfin, nous montrons l'apparition d'ondes de propagation non triviales quand le paramètre physique clé dépasse un certain seuil et que le potentiel dans l'équation de phase a une certaine asymétrie. Nous nous ramenons pour cela à un système de dimension finie pour la vitesse à l'interface et le paramètre de conservation du volume, et nous appliquons le théorème de Schauder. Les preuves complètes et détaillées seront publiées dans [3].

1. Introduction

An initially symmetric cell on a substrate may exhibit spontaneous breaking of symmetry or self-propagation along the straight line maintaining the same shape over many times of its length [4, 5]. Understanding the initiation of steady motion of a biological cell as well as the mechanism of symmetry breaking is a fundamental issue in cell biology.

In [1, 6] a phase-field model was proposed to describe motility of a eukaryotic cell on a substrate. We consider a simplified version of that model without myosin contraction ($\gamma = 0$ in [1]), which consists of two coupled PDEs

$$\frac{\partial \rho_\varepsilon}{\partial t} = \Delta \rho_\varepsilon - \frac{1}{\varepsilon^2} W'(\rho_\varepsilon) - P_\varepsilon \cdot \nabla \rho_\varepsilon + \lambda_\varepsilon(t), \quad x \in \Omega,\ t > 0, \tag{1}$$

$$\frac{\partial P_\varepsilon}{\partial t} = \varepsilon \Delta P_\varepsilon - \frac{1}{\varepsilon} P_\varepsilon - \beta \nabla \rho_\varepsilon \tag{2}$$

in a bounded domain $\Omega \subset \mathbb{R}^2$, where the unknowns are the phase-field function ρ_ε and the vector field P_ε modeling average orientation of the actin network. System (1)-(2) is obtained by diffusive scaling of equations from [1] to study a sharp interface limit (SIL) of that model under special scaling assumptions on the parameters. We introduce the volume preservation constraint via the Lagrange multiplier

$$\lambda_\varepsilon(t) = \frac{1}{|\Omega|} \int_\Omega \left(\frac{1}{\varepsilon^2} W'(\rho_\varepsilon) + P_\varepsilon \cdot \nabla \rho_\varepsilon \right) dx \tag{3}$$

in place of the volume constraint originally introduced in the potential [1]. The function $W'(\rho)$ in (1) is the derivative of a double equal well potential. We assume that

$$W(\cdot) \in C^3(\mathbb{R}),\ W(\rho) > 0 \text{ when } \rho \notin \{0, 1\},\ W(\rho) = W'(\rho) = 0 \text{ at } \{0, 1\},\ W''(0) > 0,\ W''(1) > 0, \tag{4}$$

e.g., $W(\rho) = \frac{1}{4}\rho^2(1-\rho)^2$.

The phase-field function ρ_ε takes values close to the wells of the potential 1 and 0 for sufficiently small $\varepsilon > 0$ everywhere in Ω except for a thin transition layer. The corresponding subdomains are interpreted as the inside cell and the outside cell regions, while the transition layer models the cell membrane. In (2), $\beta > 0$ is a fixed parameter responsible for the creation of the field P_ε near the interface. The boundary conditions $\partial_\nu \rho_\varepsilon = 0$ and $P_\varepsilon = 0$ are imposed on the boundary $\partial\Omega$.

We study system (1)-(2) in the sharp interface limit $\varepsilon \to 0$. Well known approaches in the study of sharp interface limits of phase field models such as viscosity solutions techniques and the Γ- convergence method, see, e.g., [7, 8, 9, 10, 11, 12, 13], are not readily applied to (1)-(2) because of the coupling through the terms $P_\varepsilon \cdot \nabla \rho_\varepsilon$ and $\nabla \rho_\varepsilon$ (so-called *active* terms due to cytoskeleton competing with curvature driven motion). The comparison principle, necessary for the viscosity solutions technique, does not apply for (1)-(2) because of the active terms. Also the active terms prevent this system from having a gradient flow form which makes the Γ-convergence techniques developed for gradient flows [13, 14] inapplicable. Another analytical approach, based on formal asymptotic expansions was developed for different phase field models in [15, 2, 16]. Some ingredients of this approach are also used in the present study. We also mention here an alternative approach to cell motility based on numerical study of free boundary value problems developed in [4, 17, 18, 19, 20], and numerical studies of different phase field models of cell motility [21], see also [22, 23, 24, 25, 27] for other approaches.

In this work we first show that solutions of (1)-(2) do not blow up on finite time intervals for sufficiently small ε by establishing energy type and pointwise bounds, next we formally derive a law of motion of the interface postulating a

two-scale ansatz in the spirit of [2]. Then we prove the existence of nontrivial traveling waves in a one-dimensional version of (1)-(2) in the case when the potential W has certain asymmetry. This is done by an asymptotic reduction to a finite dimensional system for V and λ, and applying the Schauder fixed point theorem. Finally in a one-dimensional dynamical system we rigorously prove that the interface velocity satisfies a simple nonlinear equation and demonstrate existence of a hysteresis loop in the system by numerical simulations.

2. Existence of Solutions and Sharp Interface Limit in 2D Model

The first result of this work demonstrates that for sufficiently small $\varepsilon > 0$ a unique solution ρ_ε, P_ε of (1)-(2) exists and ρ_ε maintains the structure of a sharp interface between two phases 0 and 1, provided that initial data are well prepared. To formulate this result we introduce the following auxiliary (energy-type) functionals:

$$\begin{aligned} E_\varepsilon(t) &:= \tfrac{\varepsilon}{2}\int_\Omega |\nabla\rho_\varepsilon(x,t)|^2 dx + \tfrac{1}{\varepsilon}\int_\Omega W(\rho_\varepsilon(x,t))dx, \\ F_\varepsilon(t) &:= \int_\Omega \Big(|P_\varepsilon(x,t)|^2 + |P_\varepsilon(x,t)|^4\Big)dx. \end{aligned} \tag{5}$$

Theorem 1. *Assume that the system* (1)-(2) *is supplied with initial data that satisfy* $-\varepsilon^{1/4} < \rho_\varepsilon(x,0) < 1+\varepsilon^{1/4}$*, the double well potential* W *satisfies* (4)*, and*

$$E_\varepsilon(0) + F_\varepsilon(0) \le C_1. \tag{6}$$

Then for any $T > 0$ *there exists a solution* ρ_ε, P_ε *of* (1)-(2) *on the time interval* $(0,T)$ *when* $\varepsilon > 0$ *is sufficiently small,* $\varepsilon < \varepsilon_0(T)$*. Moreover,* $-\varepsilon^{1/4} \le \rho_\varepsilon(x,t) \le 1+\varepsilon^{1/4}$ *and*

$$\varepsilon\int_0^T\int_\Omega \Big(\frac{\partial\rho_\varepsilon}{\partial t}\Big)^2 dxdt \le C_2, \quad E_\varepsilon(t) + F_\varepsilon(t) \le C_2 \quad \forall t \in (0,T), \tag{7}$$

where C_2 *is independent of* t *and* ε*.*

This theorem shows that there is no blow up of the solution on the given time interval $(0,T)$, also it proves that if the initial data have sharp interface structure, this sharp interface structure is preserved by the solution on the whole time interval $(0,T)$. The claim of Theorem 1 is nontrivial due to the presence of the quadratic term $P_\varepsilon\cdot\nabla\rho_\varepsilon$ in (1) which, in general, could lead to a finite time blow up. The main idea behind the existence proof is to find and utilize a bound for ρ_ε in $L^\infty((0,T)\times\Omega)$, which is obtained by combining the maximum principle and energy estimates.

Next we study the SIL $\varepsilon \to 0$ for the system (1)-(2). We seek solutions in the form of ansatz (locally in a neighborhood of the interface)

$$\rho_\varepsilon = \theta_0(d/\varepsilon) + \varepsilon\theta_1(d/\varepsilon, S) + \dots, \quad P_\varepsilon = \nu\Psi_0(d/\varepsilon, S) + \dots, \tag{8}$$

where $d = d(x,t)$ is the (signed) distance to a unknown evolving interface curve $\Gamma(t)$, $S = s(p(x,t),t)$ with $p(x,t)$ being the projection of x on $\Gamma(t)$ and $s(\xi,t)$ being a parametrization of $\Gamma(t)$, $\nu = \nu(p(x,t),t)$ is the inward pointing normal to $\Gamma(t)$ at $p(x,t)\in\Gamma(t)$. The key choice here is the interface curve $\Gamma(t)$ that allows for appropriate estimates. We substitute this ansatz in (1) to find, after collecting terms (formally) of the order ε^{-2}, that θ_0 satisfies $\theta_0'' = W'(\theta_0)$. It is known that there exists a unique (up to a translation) solution (standing wave) $\theta_0(z)$ which tends to 0 or 1 when $z\to-\infty$ or $z\to+\infty$. For the potential $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2$ the function θ_0 is explicitly given by $\theta_0(z) = \frac{1}{2}\left(1+\tanh\frac{z}{2\sqrt{2}}\right)$. Then substitute (8) in (2) and consider the leading (of the order ε^{-1}) term. Denoting by $V(x,t)$ the (inward) normal velocity of the curve $\Gamma(t)$ at $x\in\Gamma(t)$ we obtain that the scalar function $\Psi_0(z)$ solves

$$-\frac{\partial^2\Psi_0}{\partial z^2} - V\frac{\partial\Psi_0}{\partial z} + \Psi_0 + \beta\theta_0'(z) = 0. \tag{9}$$

Finally, assuming that the leading term of the expansion of λ_ε is of the order ε^{-1}, $\lambda_\varepsilon = \lambda(t)/\varepsilon + \dots$, and collecting terms of the order ε^{-1} in (2) we are led to the following equation

$$-\frac{\partial^2\theta_1}{\partial z^2} + W''(\theta_0)\theta_1 = (V-\kappa)\frac{\partial\theta_0}{\partial z} - \Psi_0\frac{\partial\theta_0}{\partial z} + \lambda(t),$$

where κ denotes the curvature of $\Gamma(t)$. The solvability condition for this equation (orthogonality to the eigenfunction θ_0' of the linearized Allen-Cahn equation) yields the desired sharp interface equation

$$V(x,t) = \kappa(x,t) + \frac{1}{c_0}\Phi_\beta(V(x,t)) - \lambda(t), \quad x \in \Gamma(t), \tag{10}$$

where $c_0 = \int \left(\theta_0'\right)^2 dz$, and $\Phi_\beta(V)$ is given by

$$\Phi_\beta(V) = \int_{\mathbb{R}} \Psi_0\left(\theta_0'(z)\right)^2 dz. \tag{11}$$

From the volume preservation condition $\int_{\Gamma(t)} V ds = 0$ it follows that $\lambda(t) = \frac{1}{c_0}\int_{\Gamma(t)}(c_0\kappa + \Phi_\beta(V))ds$.

The above formal derivation of the sharp interface limit is rigorously justified in 1D (see Theorem 4 below) because of significant technical difficulties due to the curvature in 2D. Solvability of (10) was shown in [28] for β less than some critical value, moreover (10) was proved to enjoy a parabolic regularization feature. However for large β, the equation (10) might have multiple solutions. To obtain a selection criterion and elucidate the role of the parameter β in the cell interface motion we consider a 1D model of the cell-motility in the next sections.

3. Traveling wave solutions in 1D

In this section we show that solutions of system (1)-(2) exhibit significant qualitative changes when the parameter β increases and the potential $W(\rho)$ has certain asymmetry, e.g. $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2(1+\rho^2)$. Here we look for traveling wave solutions in 1D model, considering (1)-(2) with $\Omega = \mathbb{R}^1$. In other words we are interested in nontrivial spatially localized solutions of (1)-(2) of the form $\rho_\varepsilon = \rho_\varepsilon(x - Vt)$, $P_\varepsilon = P_\varepsilon(x - Vt)$. This leads to the stationary equations with unknown (constant) velocity V and constant λ:

$$0 = \partial_x^2\rho_\varepsilon + V\partial_x\rho_\varepsilon - \frac{W'(\rho_\varepsilon)}{\varepsilon^2} - P_\varepsilon\partial_x\rho_\varepsilon + \frac{\lambda}{\varepsilon}, \tag{12}$$

$$0 = \varepsilon\partial_x^2 P_\varepsilon + V\partial_x P_\varepsilon - \frac{1}{\varepsilon}P_\varepsilon - \beta\partial_x\rho_\varepsilon. \tag{13}$$

We are interested in solutions of (12)-(13) that are essentially localized on the interval $(-a, a)$, for a given $a > 0$. We look for such solutions for sufficiently small $\varepsilon > 0$ with the phase field function ρ_ε of the form

$$\rho_\varepsilon = \theta_0((x+a)/\varepsilon)\theta_0((a-x)/\varepsilon) + \varepsilon\psi_\varepsilon + \varepsilon u_\varepsilon, \tag{14}$$

where constant ψ_ε is the smallest solution of $W'(\varepsilon\psi) = \varepsilon\lambda$ and u_ε is the new unknown function vanishing at $\pm\infty$. Observe that the first term $\theta_0((x+a)/\varepsilon)\theta_0((a-x)/\varepsilon)$ has "Π" shape and becomes the characteristic function of the interval $(-a, a)$ in the limit $\varepsilon \to 0$.

Proposition 1. *For any real $\beta \geq 0$ and sufficiently small ε there exists a localized standing wave solution (with $V = 0$) of* (12)-(13) *. It is localized in the sense that the representation* (14) *holds with $u_\varepsilon \in L^2(\mathbb{R}) \cap L^\infty(\mathbb{R})$ and $\|u_\varepsilon\|_{L^\infty} \leq C$.*

Proposition 1 justifies expected existence of standing wave solutions (immobilized cells) in the class of functions with the symmetry $\rho(-x) = \rho(x)$ and $P(-x) = -P(x)$, so that the polarization field on the front and back has the same magnitude but is oriented in opposite directions. This field, loosely speaking, is trying to push front and back in opposite directions with the same velocities, thus, cell does not move. Indeed, the relation between P_ε and V can be obtained from the second equation in (8), (11) and (15).

We show, however, that not all localized solutions of (12)-(13) are necessarily standing waves. Assuming that there exists a traveling wave solution with a nonzero velocity, e.g. $V > 0$, and passing to the sharp interface limit $\varepsilon \to 0$ in (12)-(13) at the back and front transition layers ($x = \pm a$ in (14)) we formally obtain two relations for the velocity V and the constant λ

$$c_0 V = \Phi_\beta(V) - \lambda, \text{ and } -c_0 V = \Phi_\beta(-V) - \lambda. \tag{15}$$

Then eliminating λ we obtain the equation for the velocity V:

$$2c_0 V = \Phi_\beta(V) - \Phi_\beta(-V). \tag{16}$$

This equation always has one root $V = 0$ which corresponds to the standing wave solution whose existence for system (12)-(13) is established in Proposition 1. Two more roots, say V_0, and $-V_0$ appear for sufficiently large $\beta > 0$ in the case when $\Phi_\beta(V) > \Phi_\beta(-V)$ for $V > 0$, thanks to the fact that Φ_β is proportional to β (note that if $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2$ then Φ_β is an even function, so the RHS of (16) vanishes for arbitrary β and thus V is necessarily 0). This heuristic argument can be made rigorous by proving the following:

Theorem 2. *Let $W(\rho)$ and β be such that* (16) *has a root $V = V_0 > 0$ and $\Phi'_\beta(V_0) + \Phi'_\beta(-V_0) \neq 2c_0$ (nondegenerate root). Then for sufficiently small $\varepsilon > 0$ there exists a localized solution of* (12)-(13) *with $V = V_\varepsilon \neq 0$, moreover $V_\varepsilon \to V_0 \neq 0$ as $\varepsilon \to 0$ (as above localized solution means that representation* (14) *holds with $u_\varepsilon \in L^2(\mathbb{R}) \cap L^\infty(\mathbb{R})$ and $\|u_\varepsilon\|_{L^\infty} \leq C$).*

Remark. In Theorem 2, it is crucial that (16) has a non-zero solution V_0 which is impossible for the symmetric potential $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2$, but does hold for an asymmetric potential, e.g., $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2(1+\rho^2)$. In the case of smaller diffusion in equation (13) one can prove that $\int_0^1 W''(\rho)dW^{3/2}(\rho) > 0$ is a sufficient condition for existence of $V_0 \neq 0$. We conjecture that this remains true for (12)-(13).

Theorem 2 guarantees existence of non-trivial traveling waves that describe steady motion without external stimuli. Thus our analysis of (12)-(13) is consistent with experimental observations of motility on keratocyte cells [4].

The proof of Theorem 2 is carried out in two steps. In the first step we use (14) to rewrite (12)-(13) as a single equation of the form $\mathcal{A}_\varepsilon u_\varepsilon + \varepsilon B_\varepsilon(V,\lambda) + \varepsilon^2 C_\varepsilon(u_\varepsilon, V, \lambda) = 0$, where $\mathcal{A}_\varepsilon u := \varepsilon^2\partial_x^2 u - W''(\theta_0((x+a)/\varepsilon)\theta_0((a-x)/\varepsilon))u$ is the Allen-Cahn operator linearized around the first term in (14). We rewrite this equation as a fixed point problem $u_\varepsilon = -\varepsilon\mathcal{A}_\varepsilon^{-1}(B_\varepsilon(V,\lambda) + \varepsilon C_\varepsilon(u_\varepsilon, V, \lambda))$. The operator $\mathcal{A}_\varepsilon$ has zero eigenvalue of multiplicity two (up to a proper $o(\varepsilon^2)$ perturbation). This leads to solvability conditions which to the leading term coincide with (15). In the second step we apply the Schauder fixed point theorem to establish existence of solutions of (12)-(13).

4. Sharp interface limit in a 1D model problem and hysteresis

This section is devoted to the asymptotic analysis as $\varepsilon \to 0$ of the following 1D problem

$$\frac{\partial \rho_\varepsilon}{\partial t} = \partial_x^2 \rho_\varepsilon - \frac{W'(\rho_\varepsilon)}{\varepsilon^2} - P_\varepsilon \partial_x \rho_\varepsilon + \frac{F(t)}{\varepsilon}, \tag{17}$$

$$\frac{\partial P_\varepsilon}{\partial t} = \varepsilon\partial_x^2 P_\varepsilon - \frac{1}{\varepsilon}P_\varepsilon - \beta\partial_x\rho_\varepsilon, \tag{18}$$

$x \in \mathbb{R}^1$, $t > 0$, for a given function $F : (0, +\infty) \to \mathbb{R}^1$. This is a model problem to develop rigorous mathematical tools for (1)-(2), and it describes a normal cross-section of the transition layer (interface) between 0 and 1 phases. The variable $x \in \mathbb{R}$ corresponds to the re-scaled signed distance d (see Section 2). The function $F(t)$ models forces due to the curvature of the interface and the mass preservation constraint λ_ε, and for technical simplicity $F(t)$ is chosen to be independent of x.

Similar to Section 3, we seek the solution of (17)-(18) in the form

$$\rho_\varepsilon(x,t) = \theta_0(y) + \varepsilon\psi_\varepsilon(y,t) + \varepsilon u_\varepsilon(y,t), \quad y = \frac{x - x_\varepsilon(t)}{\varepsilon}, \tag{19}$$

where θ_0 and ψ_ε are known functions, and u_ε is a new unknown function. Location of the interface $x_\varepsilon(t)$ is defined implicitly via the additional condition that $u_\varepsilon(y,t)$ is orthogonal to $\theta_0'(y)$ in $L^2(\mathbb{R})$:

$$\int_{\mathbb{R}} \theta_0'(y) u_\varepsilon(y,t) dy = 0. \tag{20}$$

This orthogonality condition allows us to use a Poincaré type inequality to derive a priori bounds for u_ε. Function $\psi_\varepsilon(y,t)$ is defined by

$$\psi_\varepsilon(y,t) = \psi_\varepsilon^-(t) + \theta_0(y)(\psi_\varepsilon^+(t) - \psi_\varepsilon^-(t)), \quad \text{where} \quad \partial_t(\varepsilon\psi_\varepsilon^\pm) = -\frac{W'((1\pm 1)/2 + \varepsilon\psi_\varepsilon^\pm)}{\varepsilon^2} + \frac{F(t)}{\varepsilon},\ \psi_\varepsilon^\pm(0) = 0.$$

Existence of $x_\varepsilon(t)$ together with estimates on u_ε uniform in ε and t are established in the following

Theorem 3. *Let $\rho_\varepsilon, P_\varepsilon$ be a solution of Problem* (17)-(18) *with initial data for ρ_ε and P_ε satisfying "well-prepared" initial conditions:*

$$\rho_\varepsilon(x,0) = \theta_0(x/\varepsilon) + \varepsilon v_\varepsilon(x/\varepsilon), \tag{21}$$

where $\|v_\varepsilon\|_{L^2(\mathbb{R})} < C$, $\|v_\varepsilon\|_{L^\infty(\mathbb{R})} \le C/\varepsilon$, and $P_\varepsilon(x,0) = p_\varepsilon(\frac{x}{\varepsilon})$ such that

$$\|p_\varepsilon\|_{L^2(\mathbb{R})} + \|\partial_y p_\varepsilon\|_{L^2(\mathbb{R})} < C. \tag{22}$$

Then there exists $x_\varepsilon(t)$ such that expansion (19) *holds with $\|u_\varepsilon(\cdot,t)\|_{L^2(\mathbb{R})} < C$ for $t \in [0,T]$ and $\int_{\mathbb{R}} u_\varepsilon\theta_0' dy = 0$. Moreover, assuming that $\int_{\mathbb{R}} v_\varepsilon\theta_0' dy = 0$, the interface velocity $V_\varepsilon = \dot{x}_\varepsilon(t)$ is determined by the following system:*

$$\begin{cases} (c_0 + \varepsilon\tilde{O}_\varepsilon(t))V_\varepsilon(t) = \displaystyle\int (\theta_0')^2\Psi_\varepsilon dy - F(t) + \varepsilon O_\varepsilon(t), & (23)\\ \varepsilon\dfrac{\partial\Psi_\varepsilon}{\partial t} = \dfrac{\partial^2\Psi_\varepsilon}{\partial y^2} + V_\varepsilon(t)\dfrac{\partial\Psi_\varepsilon}{\partial y} - \Psi_\varepsilon - \beta\theta_0'(y), & (24)\end{cases}$$

where $\tilde{O}_\varepsilon(t)$ and $O_\varepsilon(t)$ are bounded in $L^\infty(0,T)$.

The reduced system (23)-(24) can be further simplified by taking the limit $\varepsilon \to 0$. Formal passing to the limit in (24) leads to equation (9) whose unique solution depends on the parameter V. Substituting this solution into (23) in place of Ψ_ε we obtain the equation

$$c_0 V_0(t) = \Phi_\beta(V_0(t)) - F(t) \tag{25}$$

for the limiting velocity $V_0 = \lim_{\varepsilon\to 0} V_\varepsilon$. However, in general, equation (25) is not uniquely solvable. The plot of the function $c_0 V - \Phi_\beta(V)$ for sufficiently large β is depicted on the Figure 1, where one sees that (25) has two or three solutions when $F \in [F_{\min}, F_{\max}]$. In order to justify (25) and select a correct solution we reduce system (23)-(24) to a single nonlinear equation substituting expression for V_ε from (23) into (24). Then rescaling time and neglecting terms of the order ε we arrive at the equation $\partial_t U = \partial_y^2 U + \frac{1}{c_0}(\int(\theta_0')^2 U dy - F)\partial_y U - U - \beta\theta_0'$ whose long time behavior has to be analyzed in order to obtain the limit of (23)-(24) as $\varepsilon \to 0$. This is done by spectral analysis of the linearized operator $\mathcal{A}_V U = \partial_y^2 U + V\partial_y U - U - \frac{1}{c_0}\partial_y\Psi_0 \int(\theta_0'(z))^2 U(z)dz$ about steady states Ψ_0 of the above nonlinear equation, where Ψ_0 are obtained by finding roots V of the ordinary equation $c_0 V = \Phi_\beta(V) - F$ and then solving the PDE (9).

Definition 1. *Define the set of stable velocities $\mathcal{S}$ by $\mathcal{S} = \{V \in \mathbb{R};\ \sigma(\mathcal{A}_V) \subset \{\lambda \in \mathbb{C}; \mathrm{Re}\lambda < 0\}\}$, where $\sigma(\mathcal{A}_V)$ denotes the spectrum of the operator $\mathcal{A}_V$ (note that $\mathcal{S}$ is an open set).*

Theorem 4. *Let $F(t)$ be a continuous function and assume that $V_0 \in \mathcal{S}$ solves $c_0 V_0 = \Phi_\beta(V_0) - F(0)$. Assume also that $\|p_\varepsilon - \Psi_0\|_{L^2} \le \delta$, where Ψ_0 is the solution of* (9) *with $V = V_0$ and $\delta > 0$ is some small number depending on V_0 but independent of ε. Then $V_\varepsilon(t) = \dot{x}_\varepsilon(t)$ defined in Theorem 3 converges to the continuous solution of the equation $c_0 V(t) = \Phi_\beta(V(t)) - F(t)$ with $V(0) = V_0$ on every finite time interval $[0,T]$ where such a solution exists and $V(t) \in \mathcal{S}$ $\forall t \in [0,T]$.*

We conjecture that stability of velocities is related to monotonicity intervals of the function $c_0 V - \Phi_\beta(V)$. This conjecture is supported by the following result.

Proposition 2. *If $c_0 \le \Phi_\beta'(V)$, then V is not a stable velocity.*

In general $\Phi_\beta'(0)$ is nonzero if the potential $W(\rho)$ is asymmetric. In particular, for $W(\rho) = \frac{1}{4}\rho^2(1-\rho)^2(1+\rho^2)$ we have $c_0 < \Phi_\beta'(0)$ when $\beta > \beta_{critical} > 0$, therefore zero velocity is not stable in this case. For 2D problem this would imply instability of initial circular shape leading to a spontaneous breaking of symmetry observed in experiments.

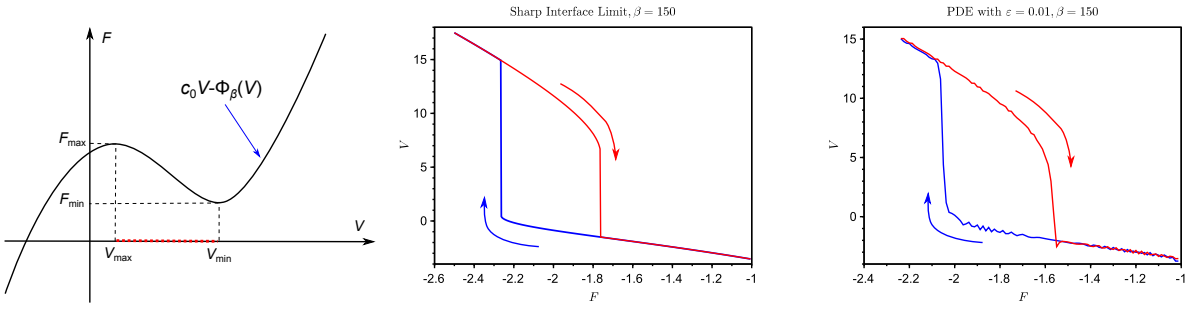

Figure 1: Hysteresis loop in the problem of cell motility. (Left) The sketch of the plot for $c_0V - \Phi_\beta(V)$; (Center,Right) Simulations of $V = V(F)$, (Center): solution of (10) (Right): solution of PDE system (17)-(18). On both figures (Center) and (Right) arrows show in what direction the system $(V(t), F(t))$ evolves as time t grows; blue curve is for $F_\downarrow(t)$, red curve is for $F_\uparrow(t)$.
Légende: Boucle d'hysteresis apparaissant dans le problème de migration cellulaire. (Gauche) Tracé de la courbe $c_0V - \Phi_\beta(V)$; (Centre,Droite) Simulations de $V = V(F)$, (Centre): solution of (10) (Droite): solution du système EDP (17)-(18). Sur les deux graphiques (Centre) et (Droite), les flèchent montrent dans quel sens $(V(t), F(t))$ évolue avec le temps t; la courbe bleue représente $F_\downarrow(t)$, la courbe rouge $F_\uparrow(t)$.

Remark 1. *In the particular case* $W(\rho) = \frac{1}{4}\rho^2(\rho-1)^2$ *we prove that* $(-\infty, \sqrt{2}) \cap \left\{V;\ c_0 > \Phi'_\beta(V)\right\} \subset \mathcal{S}$. *We also establish* $\mathcal{S} = \left\{V;\ c_0 > \Phi'_\beta(V)\right\}$ *via verifying numerically a technical inequality.*

While Theorem 4 describes local in time continuous evolution of the interface velocity according to the law $c_0V = \Phi_\beta(V) - F(t)$ until V leaves the set of stable velocities $\mathcal{S}$, we conjecture that this law remains valid even after the time when the solution V reaches an endpoint of a connected component of $\mathcal{S}$. Consider a particular example of $\beta = 150$, the corresponding plot of the function $c_0V - \Phi_\beta(V)$ is depicted on Fig. 1. Choose $F(t)$ given by $F(t) = F_\uparrow(t) := -2.25 + 1.25t$ for $t \in [0, 1]$ and $F(t) = F_\downarrow(t) := F_\uparrow(2 - t)$ for $t \in (1, 2]$. Starting with well prepared initial data we expect that the interface velocity V increases with $F(t)$ until it reaches $V_{\max}$ then it jumps to another branch and continues to vary in $(V_{\min}, +\infty)$ till the moment when it decreases to $V_{\min}$ and experiences one more jump, then it varies in $(-\infty, V_{\max})$ to return to the initial velocity at $t = 2$ see Fig. 1, left. Thus we conjecture that system has a hysteresis loop, this conjecture is verified by numerical simulations for the sharp interface limit (25) as well as the original system (17)-(18) for small ε. The results of the latter simulations with $\varepsilon = 0.01$ are depicted on Fig. 1, right.

Complete proofs of all reported results will be published in [3].

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