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Simulating *Dictyostelium* cell deformation in amoeboid movement

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Abstract– A model system for propagating and spiral waves of phosphatidylinositol lipids observed in migrating *Dictyostelium discoideum* cell is proposed. In the model, chemical dynamics described by reaction-diffusion system is coupled with cell shape deformation represented by phase-field, which reproduces the excitability of the system and arising wave-wave and wave-cell boundary interactions. Parameter dependence of the model shows qualitative agreements with experimental perturbations, such as the loss of excitability by the excess actin in null-mutant of PIR. We also conducted non-parametric estimation of reaction diffusion equations that describe the observed spatio-temporal dynamics. In the method, Bayesian procedure for state-space model is performed by adopting a prior that assumes smooth functional form of reaction terms. Comparison of the results with the proposed mathematical model is discussed.

1. Introduction

Cell migration is one of the fundamental cellular events that underlie wide variety of biological processes. During cell migration, phosphatidylinositol (3,4,5)-triphosphate (PIP3) mediates formation of a leading edge. In spontaneously moving *Dictyostelium discoideum* cells, PIP3 appears as 2-dimensional propagating waves that correlate with spatiotemporal organization of F-actin. These waves push the cell border when reaching the cell edge and thus drive a large-scale membrane deformation. Therefore, it is critical to understand how the dynamic patterns of PIP3 waves and their transitions determine the overall extension and rotation of *Dictyostelium* cells to give rise to complex yet some coherent behavior of spontaneous cell motion. To capture relationship between the waveforms and the patterns of amoeboid shape, we have conducted phase mapping of PIP3 dynamics and traced the birth and death of topological singularities. Our analyses indicated that not the intrinsic stochasticity of chemical reactions but random firing to initiate wave nucleation is responsible for triggering the pattern switches, which underlies the complex behavior of cell migration.

To understand how molecular interactions among the phosphatidylinositol lipids and related molecules, we propose a mathematical model that is argued in this presentation. By considering the reactions and diffusions on the basal cell membrane, the system is shown to be an excitable system. The changes of dynamic behaviors by controlling the actin-mediated feedback strength are compared with perturbation experiments. To capture how the excitable dynamics of PIP3 wave regulate cell shape change, we also conducted numerical simulations that combine reaction-diffusion dynamics and cell deformation by considering cell border expansion at the high concetration of PIP3. We also try to semi-parametrically estimate the form of the reaction-diffusion systems that describe the observed spatio-temporal dynamics of PIP3 and PTEN from data. The estimated equations are compared with our model equations. These approaches

2. Mathematical Model

2.1. Model equations for reaction-diffusion

We propose a mathematical model composed of key reactions in the phosphoinositides signaling [1]. The reaction kinetics considered is the following ones (Fig. 1). (A) PI3K in the cytoplasm is recruited to the basal membrane and catalyzes phosphorylation of PIP2 to PIP3 [2]. The recruitment and activation of PI3K is enhanced by PIP3 possibly through accumulation of F-actin [3,4]. (B) Phosphatase PTEN in the cytoplasm is recruited to the site of PIP2 at the membrane [5], which then mediates dephosphorylation of PIP3 to PIP2. (C) PIP2 is produced and degraded at constant rates. (D) PIP3 is degraded at a constant rate. With assumption that phosphorylation and dephosphorylation processes (A and B) are sufficiently rapid compared with the other ones, we derived simple rate equations with respect to the concentrations of PIP2 ([PIP2]) and PIP3 ([PIP3]).

$$\frac{\partial U}{\partial t} = D_{\mathrm{U}}\Delta U - \frac{\alpha U V^2}{K_{\mathrm{K}} + A^{-1}\int_{\Omega} V^2\, d\mathbf{x}} + \frac{\beta U V}{K_{\mathrm{P}} + A^{-1}\int_{\Omega} U\, \mathrm{d}\boldsymbol{x}} + S - \gamma U,$$

$$\frac{\partial V}{\partial t} = D_{\mathrm{V}}\Delta V + \frac{\alpha U V^2}{K_{\mathrm{K}} + A^{-1}\int_{\Omega} V^2\, d\mathbf{x}} - \frac{\beta U V}{K_{\mathrm{P}} + A^{-1}\int_{\Omega} U\, \mathrm{d}\boldsymbol{x}} - \mu V.$$

Here, [PIP2] and [PIP3] are represented as U and V, respectively. By taking proper scaling of U and V, we can set $S = 1$ and $\mu = 1$ without losing generality.In addition,

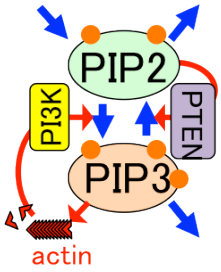

Figure 1: Reaction scheme of phosphoinositides signaling pathway. PIP2 is phosphorylated by PI3K to PIP3. PTEN desphorylate PIP3 to PIP2. Feedback via actin polymerization and PI3K enhances the phosphorylation process, while PIP2 enhances the PTEN activity of dephosphorylation. These reactions are occurred on the basal cell membrane.

we also introduced sporadic random phosphorylation from PIP2 to PIP3 that triggers the initiation of PIP3 wave.

2.2. Numerical simulation of the reaction-diffusion equation in fixed circular domain

Numerical simulations performed in circular region for immotile cells demonstrated that PIP3 shows self-organized waves such as spiral wave, traveling waves that bounces or disappears at the boundary of the cell region depending on parameters and initial conditions. These patterns are typically observed in the experiments, particularly in the circular cells by treating latrunculinA to prohibit actin polymerization. These results support the validity of the model equations.

2.3. Null-cline analysis

For spiral waves in which integral parts of the system equations are constant, reaction terms are written as $dU/dt = -\alpha_s UV^2 + \beta_s UV + 1 - \gamma U$, $dV/dt = \alpha_s UV^2 + \beta_s UV - V$. Null cline analysis of these equations indicates that the system is excitable; a stable fixed point as resting state appears at $(U,V) = (1/\gamma,0)$, and perturbation to increase V (PIP3 intensity) above a threshold value results in acceleration of phosphorylation of PIP2 to PIP3 by the actin-mediated feedback, which is followed by a large deviating orbit in the U-V plane that settles back to the original fixed point. We evaluated the threshold for excitation, Θ_s, as the smallest increment of V that could trigger firing of PIP3 in the phase plane, as given by the distance between the two branches of $dV/dt = 0$ from the fixed point in the V-direction; $\Theta_s \approx (\beta_s + \gamma)/\alpha_s$. Since α_s characterizes the strength of the positive feedback, thus decrease in the feedback strength increases the threshold and less creation of new PIP3 waves. On the other hand, when actin mediated feedback strength is getting larger by increasing α_s the model predicts another stable fixed point to appear via saddle-node bifurcation. For large value of α_s the system is attracted to this new fixed point and the excitability of the system is ceased. As a result, no wave is observed in the spatially extended system. Interestingly, consistent with this model prediction, the null-mutant strain of PIR that over-expresses actin and thus may have the stronger actin-mediate feedback strength for the phosphorylation process shows no propagating PIP3 wave despite more frequent sporadic random phosphorylation is observed.

Figure 2: Result of numerical simulation for reaction-diffusion equation with cell deformation. red: PIP3, green: PTEN (PIP2 is almost same as PTEN in signal intensity). The reaction scheme is given in Fig. 1. PIP3 wave reaching at the boundary drives cell deformation. Two arising PIP3 propagating waves collides and trigger the rapid directional cell shape change. Such behavior is also observed in experiment.

2.4 Deformable model

In the experimental observation, the PIP3 wave regulate cell shape change, thus we also conducted numerical simulations that combine reaction-diffusion dynamics and cell deformation. To model the deforming boundary, we adopted a method developed by Shao *et al.* [6]. In this scheme, phase-field $\phi(\mathbf{x},t)$ is introduces as a function of space $\mathbf{x}$ and time t that represents the cell interior as $\phi = 1$ and exterior as $\phi = 0$. By spatially restricting the rate equations within the boundary, we derived reaction-diffusion equations that couples the introduced phase-field $\phi(\mathbf{x},t)$. A boundary condition that assumes degradations of PIP2 and PIP3 are considered here. Cell is described as an abstract elastic vesicle, where the shape is determined by interactions between the surface tension, pressure, and interior chemical dynamics. To express these feature of a cell, dynamics of $\phi(\mathbf{x},t)$ obeys the following equation [6].

$$\tau\frac{\partial\phi}{\partial t} = \eta\left(\Delta\phi - \frac{G'(\phi)}{\varepsilon^2}\right) - M\left(\int\phi\,dx - A_0\right)|\nabla\phi| + (aV - bU)|\nabla\phi|$$

Here, $G(x) = 18\phi^2(1-\phi)^2$ is a basal "double well" potential of ϕ by which ϕ takes value at 0 and 1. The first term of right hand side represents effective surface tension of a cell, and the second term keeps the area of a cell around A_0 and describes effective pressure. The third term represents the rate of membrane extension and retraction proportional to the level of PIP3 and PIP2, respectively.

2.5 Numerical simulation of deformable boundary cells

Representative result of the simulated is shown in Fig. 2. In this example, two waves are initiated and collide each other. Colliding fronts of the waves merge and disappear

followed by directional change in cell shape. Such dynamics of PIP3 and cell shape is actually observed in the experiments. The results of the numerical simulations show apparent remembrance in dynamic correlation between propagating PIP3 wave dynamics and entire cell shape change. In the simulation, the arising dynamics much depends on actin-mediated feedback strength.

We also performed 1-dimensional numerical simulation to check how the stiffness of the cell boundary changes the reflectability of propagating PIP3 wave. The results shows, the reflectability depends on the stiffness not monotonically; wave reflects for low and high stiffness but disappears for intermediate stiffness. This result suggests that the interaction between PIP3 wave and cell boundary can make the wave dynamics more complex.

3. Estimation of reaction-diffusion equations

3.1 Aim of semi-parametric estimation

Current progresses of live cell imaging techniques are elucidating dynamic nature of various cellular processes. Correspondingly, developing data processing methods that fully and systematically use information involved in the spatio-temporal data, even in their fluctuation, is one of theoretical challenges. Often, mathematical models for biological behaviors are represented by the ordinary or partially differential equations. The comparison of the model equations with experimental observations is performed after the model equations are numerically solved. However, it takes numerous numerical simulations to fit the model parameters and the information involved in the fluctuation is usually not considered.

As an alternative approach, here we try to derive the functional forms of model equations from the data. The observation variables are signal intensities of PIP3 and PTEN. Our fundamental assumptions are that the system is described by two variable reaction diffusion equations, and the functional forms of the reaction terms do not have singularities but are given by rather smooth functions. We consider a way to semi-parametrically estimate the form of reaction diffusion equations here.

3.2 Estimation procedure

Here we briefly describe the procedure to estimate reaction diffusion equations from the observation data. Our aim is to detect the system equation of the form

$$\partial_t \mathbf{w} = D\Delta\mathbf{w} + \mathbf{f}\left(\mathbf{w}\right) + \xi ,$$

where $\mathbf{w} = (u, v)$ represents concentrations of PTEN (u) and PIP3 (v) and depend on the position $\mathbf{x}$ and time t, respectively. D is a diagonal matrix representing diffusion term. $\mathbf{f} = (f_u, f_v)$ is the reaction terms for PTEN and PIP3. ξ represents white Gaussian noise with intensity σ_u^2 and σ_v^2. We expand $f_i(\mathbf{w})$ (i = u,v) by radial basis functions $B_{kl}(u,v)$ that centered at ($k\Delta$u, lΔv) as $f_i\ (u,v) = \Sigma_{kl}\ \alpha^i_{kl}\ B_{kl}(u,v)$. Then $\{\alpha^i_{kl}\}$ determines the functional form of $f_i(\mathbf{w})$. Since the observations involve color degradation and inevitable errors by noise, we assume that the observed values, W($\mathbf{x}$,t) = (U($\mathbf{x}$,t), V($\mathbf{x}$,t)), are related with true ones as $\mathbf{W} = H(\mathbf{w}) + \eta(\mathbf{x},t)$ (observation equation; $\mathbf{W} = (U, V)$) where $\eta(\mathbf{x}, t)$ is white Gaussian noise with intensities Σ_i^2 (i = u, v). We model the relation as $H_i(w_i) = [a_i\exp(-k_i t) + b_i]\ w_i(t) + \eta_i.(\mathbf{x},t)$ to fit color degradation. Parameters for system and observation equations are dented as Γ in the following.

On the basis of the above arguments, we estimated all the parameters Γ as a state-space model. With the above arguments we can derive the path probability that $\mathbf{w}(t)$ and $\mathbf{W}(t)$ are simultaneously realized. This probability, $P(\mathbf{w},\mathbf{W}|\Gamma)$ is regarded as likelihood function. With prioir functions $\pi(\Gamma)$ in which we assume that second derivatives of α^i_{kl} as a (u, v)-mesh space should be zero (smoothness of the function) and noise intensities distribute following inverse Gamma function, a posteriori probability is given as $P(\mathbf{w},\Gamma\ |\mathbf{W})\ \pi(\Gamma)$. Then using MCMC technique we estimated all the related parameters to determine functional forms.

3.3 Results of estimation method

Using the results of estimation, we represented reaction terms $\mathbf{f}$ by flow diagram on the (u, v) plane. Then we compared these results and those obtained for our mathematical model. Wild type strain shows qualitatively similar nature of flow such as excitability, although some cells show unpredicted behavior from the model that has transient stable fixed point. Analysis of PIR null-mutant shows the new fixed point as is predicted by the model.

4 Summary

Our mathematical model shows good agreements with experimental observation. Phase field simulations demonstrated here could be a useful tool to describe the shape deformable migrating cell. We also performed equation estimation and compared results with the model. This estimation method, which is applicable to wide experimental data, will also be a useful tool for studying the dynamic of various cell processes.

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