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Self-organization and advective transport in the cell polarity formation for asymmetric cell division

Sungrim Seirin Lee [a,*], Tatsuo Shibata [b,c]

[a] Department of Mathematical and Life Sciences, Hiroshima University, Kagamiyama 1-3-1, Higashi-hiroshima 739-8530, Japan
[b] RIKEN Quantitative Biology Center, 6-2-3 Furuedai, Suita, Osaka 565-0874, Japan
[c] RIKEN Center for Developmental Biology, Minatojima-Minamimachi 2-2-3, Kobe 650-0047, Japan

HIGHLIGHTS

- We explored the mechanism of AP polarity formation using self-recruitment model.
- Advective transport increases the robustness in the AP polarity formation.
- The total mass to cell size robustly regulates the length scale of polarity pattern.

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ABSTRACT

Anterior–Posterior (AP) polarity formation of cell membrane proteins plays a crucial role in determining cell asymmetry, which depends not only on the several genetic process but also biochemical and biophysical interactions. The mechanism of AP formation of *Caenorhabditis elegans* embryo is characterized into the three processes: (i) membrane association and dissociation of posterior and anterior proteins, (ii) diffusion into the membrane and cytosol, and (iii) active cortical and cytoplasmic flows induced by the contraction of the acto-myosin cortex. We explored the mechanism of symmetry breaking and AP polarity formation using self-recruitment model of posterior proteins. We found that the AP polarity pattern is established over wide range in the total mass of polarity proteins and the diffusion ratio in the cytosol to the membrane. We also showed that the advective transport in both membrane and cytosol during the establishment phase affects optimal time interval of establishment and positioning of the posterior domain, and plays a role to increase the robustness in the AP polarity formation by reducing the number of posterior domains for the sensitivity of initial conditions. We also demonstrated that a proper ratio of the total mass to cell size robustly regulate the length scale of the posterior domain.

1. Introduction

The body of animals is composed of many kinds of cells with different functions and sizes, which are diversified from a single cell during development. One of the widespread mechanisms for generating cell diversity is asymmetric cell division. A mother cell divides into two dissimilar daughter cells, which subsequently develop completely different properties. The mechanism of asymmetric cell division has been well studied experimentally in yeast, *Caenorhabditis elegans*, and *Drosophila* (Betschinger and Knoblich, 2004; Gönczy, 2005; Knoblich, 2008; Pruyne and Bretscher, 2000). In *C. elegans*, a single fertilized egg cell and its daughter cells form two exclusive domains of different PAR proteins on the membrane. PAR-3/6 and PKC-3 proteins (anterior proteins) are distributed on one side and PAR-1/2 and LGL-1 (posterior proteins) are distributed on the other side, resulting in anterior–posterior polarity (AP polarity) that determines an anterior–posterior axis. Such asymmetry formation depends not only on several genetic processes but also on biochemical and biophysical interactions.

Before the *C. elegans* embryo is fertilized, the anterior protein, PAR-6, is distributed uniformly in the membrane, while the posterior protein, PAR-2, is located in the cytosol. After fertilization, the acto-myosin cortex starts contracting and then the posterior protein exhibits membrane translocation from the

* Corresponding author.
E-mail addresses: seirin@hiroshima-u.ac.jp, seirin.lee@gmail.com (S. Seirin Lee), tatsuoshibata@cdb.riken.jp (T. Shibata).

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cytosol at the sperm entry point. As the posterior protein spreads over the membrane from the posterior side to the anterior side, the domain of the anterior protein shrinks in the same direction. When the length of the anterior and posterior domains reaches to approximately half size of a cell, the boundary of the domains stop and is maintained until cell cleavage starts. These process are called the establishment and maintenance phases, respectively. The establishment phase lasts for approximately a few minutes to 8 min, and is followed by the maintenance phase, which lasts for another 16 min (Gönczy, 2005).

Asymmetry formation of *C. elegans* embryo is characterized by the following three processes: (i) membrane association and dissociation of proteins (Gönczy, 2005), (ii) diffusion into the membrane and cytosol (Goehring et al., 2011a), and (iii) active cortical and cytoplasmic flows induced by the contraction of the acto-myosin cortex (Goehring et al., 2011b; Mayer et al., 2010; Niwayama et al., 2011). The advective transport induced by acto-myosin contraction has been shown to play a crucial role in AP polarity formation (Goehring et al., 2011b; Howard et al., 2011).

Several theoretical approaches have been used to study cell polarity. Marco et al. (2007) considered the maintenance mechanism of yeast polarity and proposed that the translocation of the membrane proteins between the membrane and the cytosol, with a balance of diffusion, is sufficient to explain the mechanism of polarity patterning without the advective effect. Dawes and Munro (2011) also has shown that cortical flow is not required for the establishment of the AP polarity pattern, but a bistable switch mechanism of PAR proteins are important. Mori et al. (2008) and Otsuji et al. (2007) have suggested the mathematical structure for cell polarity patten, and showed that the mass-conservation and the bistability in chemical reaction are sufficient, in the absence of the advective transport. Tostevin and Howard (2008) have considered the formation of the anterior–posterior polarity pattern using a model combined with the effect of acto-myosin contraction which directly influences a biochemical reaction of polarity proteins, but the effect of advective transport was not supposed into the model. On the other hand, Goehring et al. (2011b) has proposed that a passive advective transport of par proteins by active cortical flow triggers AP polarity in *C. elegans* both experimentally and theoretically with a model satisfying the properties of mass conservation and bistability.

Accumulation of molecular knowledge and development of imaging technologies enable us to study how these proteins are coordinated to establish and maintain asymmetry formation in individual cells (Betschinger and Knoblich, 2004; Hoege and Hyman, 2013). Mathematical studies for the bifurcation structure of cell polarity models also suggest that the properties of bistability and mass conservation are sufficient for inducing symmetry breaking and cell polarity formation (Mori et al., 2011; Trong et al., 2014). However, many questions are still remained in the process of establishing and maintaining cell asymmetry where molecular interactions and physical dynamics are mutually related. Furthermore, it is not obvious how the three properties play an important role in AP polarity formation. In particular, the role of cytoplasmic flow has not been considered in any previous model. Thus, we include the three characterized properties into a model and capture the core dynamics of AP polarity formation using a model reduction.

We first formulate a mutually inhibited anterior and posterior proteins model, from which we induce a self-recruitment model of anterior/posterior protein. In order to explore the effect of the biophysical dynamics in the cytosol on AP polarity formation, we do not assume the infinite diffusion rate in cytosol in contrast to the previous models of Goehring et al. (2011b) and Trong et al. (2014), so that we explore how the ratio of diffusion rates in the cytosol to the membrane and the cytoplasmic flow directly influence AP polarity formation.

Using this model, we first investigate how the self-recruitment property with either or both active and passive transports plays a role for establishing and maintaining AP polarity pattern. Then, we explore the role of cortical and cytoplasmic flows and how the flows are related to the robustness of domain numbers and time scale of establishment of the AP polarity pattern. Finally, we focus on the regulation of the length scale of the posterior domains with respect to cell size and discuss the robustness of the regulation of the domain length to the variation of total mass.

2. Methods

2.1. Mutual inhibition model

The dynamics of AP polarity formation is characterized by the chemical reactions of posterior and anterior proteins and the biophysical processes of diffusion and advection. These are described by three processes: (i) translocation of posterior and anterior proteins between the membrane and cytosol by association and disassociation, (ii) diffusion in both the membrane and cytosol, and (iii) advection by cortical and cytoplasmic flows. In order to capture the essential mechanism of AP polarity formation in the membrane, we consider a mathematical model in one dimensional circular space, $[0, L]$, as shown in Fig. 1A.

For the concentrations of posterior proteins in the membrane and cytosol, $[\mathrm{P_m}]$ and $[\mathrm{P_c}]$, respectively, and the concentrations of anterior proteins in the membrane and cytosol, $[\mathrm{A_m}]$ and $[\mathrm{A_c}]$, respectively, the evolution equations describing (i)–(iii) are given by

$$\frac{\partial[\mathrm{P_m}]}{\partial t}+\frac{\partial}{\partial x}(\nu_m[\mathrm{P_m}])=D_m\frac{\partial^2[\mathrm{P_m}]}{\partial x^2}+\mathcal{F}_{on}(x,t)[\mathrm{P_c}]-\mathcal{F}_{off}(x,t)[\mathrm{P_m}], \tag{1}$$

$$\frac{\partial[\mathrm{P_c}]}{\partial t}+\frac{\partial}{\partial x}(\nu_c[\mathrm{P_c}])=D_c\frac{\partial^2[\mathrm{P_c}]}{\partial x^2}-\mathcal{F}_{on}(x,t)[\mathrm{P_c}]+\mathcal{F}_{off}(x,t)[\mathrm{P_m}], \tag{2}$$

$$\frac{\partial[\mathrm{A_m}]}{\partial t}+\frac{\partial}{\partial x}(\nu_m[\mathrm{A_m}])=D_m\frac{\partial^2[\mathrm{A_m}]}{\partial x^2}+\overline{\mathcal{F}}_{on}(x,t)[\mathrm{A_c}]-\overline{\mathcal{F}}_{off}(x,t)[\mathrm{A_m}], \tag{3}$$

$$\frac{\partial[\mathrm{A_c}]}{\partial t}+\frac{\partial}{\partial x}(\nu_c[\mathrm{A_c}])=D_c\frac{\partial^2[\mathrm{A_c}]}{\partial x^2}-\overline{\mathcal{F}}_{on}(x,t)[\mathrm{A_c}]+\overline{\mathcal{F}}_{off}(x,t)[\mathrm{A_m}]. \tag{4}$$

The second terms on the left hand side represent the advection term with the velocities of cortical and cytosol flows, ν_m and ν_c. The first terms on the right hand side describe the diffusional transport with diffusion coefficients in the membrane and cytosol, D_m and D_c, respectively. The diffusion coefficient in the membrane is smaller than that in the cytoplasm, i.e., $D_m < D_c$.

The second and third terms on the right hand side are the association and dissociation reactions with the membrane concentration-dependent on- and off-rates, $\mathcal{F}_{on}(x,t)$, $\overline{\mathcal{F}}_{on}(x,t)$, $\mathcal{F}_{off}(x,t)$ and $\overline{\mathcal{F}}_{off}(x,t)$. The posterior and anterior PAR proteins have regulatory effects on each other in dissociation from the membrane (Gönczy, 2005; Cuenca et al., 2002), as shown in Fig. 1B, left panel. Thus, we consider the off-rates, which are dependent on the membrane concentration of the other protein, with basal constant off-rates, α and $\overline{\alpha}$, given by

$$\mathcal{F}_{off}(x,t)=\alpha+\frac{K_1[\mathrm{A_m}]^n}{K+[\mathrm{A_m}]^n}, \tag{5}$$

$$\overline{\mathcal{F}}_{off}(x,t)=\overline{\alpha}+\frac{\overline{K}_1[\mathrm{P_m}]^n}{\overline{K}+[\mathrm{P_m}]^n} \tag{6}$$

where $K, K_1, \overline{K}$ and $\overline{K}_1$ are positive constants, and $n(>1)$ is the Hill coefficient that specifies the sensitivity of change in the off-rate to the change in the membrane concentration of the protein. The off-rate functions, (5) and (6), imply that the anterior and posterior proteins in the membrane mutually inhibit. The on-rates are given