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Development of a three-dimensional dynamic model for chemotaxis

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Abstract. In this study, we proposed a three-dimensional dynamic model under the diffuse interface description for the single crawling cell. From the developed model, we described the clear evolution processes for crawling neutrophil and assessed the reliable quantitative chemotactic property, which confirmed the high possibility of adequate predictions. To establish the system considering of multiple mechanisms such as, diffusion, chemotaxis, and interaction with surface, a diffuse interface model is employed.

Keywords: chemotaxis; crawling cell; interface energy; cell migration; diffuse interface model.

1. Introduction

The directional movement of cells responding to a chemoattractant gradient is called chemotaxis (Berg and Brown 1972, Adler 1969). Early experimental studies demonstrated this directional movement of a cell responding to an attractant gradient field (Adler 1973, Zigmond 1977, Robert *et al*. 1975, Lauffenburger *et al*. 1983, Tranquillo *et al*. 1988). However, these studies mostly had difficulties in obtaining a clear observation of cell migration due to the unstable gradient of chemoattractant. Recently developed microfluidic gradient-making networks which lead more incisive experiment can generate stable concentration profiles with linear or polynomial shapes, such as a cliff gradient or a hill gradient of chemoattractant (Adler 1973, Zigmond 1977, Ford *et al*. 1991, Jeon *et al*. 2002, Lewus and Ford 2001). Moreover, the recent development of observation techniques enable us to trace a single cell crawling over the surface and obtain more precise kinetic traits of the crawling cell, such as velocity and mobility (Frevert *et al*. 2006, Rot 1993, Tharp *et al*. 2006). On the other hand, some transport coefficients related with the cell migration, such as the diffusivity and the chemotaxis sensitivity of cell, were investigated in the various chambers (Adler 1973, Ford *et al*. 1991, Lewus and Ford 2001). Especially, the single cell studies can provide detailed information for chemotactic properties than the studies with the level of cell population, measuring the average velocity of the neutrophil, which was around 5~20 μm/min (Jeon *et al*. 2002, Frevert *et al*. 2006, Tharp *et al*. 2006).

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With the development of experimental techniques for the observation of cell dynamics, mathematical modeling of cell migration becomes increasingly necessary to interpret and understand experimental phenomenon. A classical chemotaxis model had been proposed by Keller and Segel, which described macroscopically the aggregation process of the cells by the averaged local density of the cells (Keller 1971). The classical Keller-Segel model has been extensively studied over the years (Rivero 1989, Ford and Lauffenburger 1991, Painter and Sherratt 2003, Lapidus and Schiller 1976). However the Keller-Segel's model has the possibility of blow up of solutions in a finite time. To overcome this intrinsic limit of Keller and Segel model, which is the blow up due to the overcrowded cells, researchers proposed various approaches. For instance, one- or two-dimensional models developed for an individual cell to avoid overcrowding of cell (Ben-Jacob *et al.* 2000, Stokes *et al.* 1991, Brenner *et al.* 1998). Also, a volume filling method or a multi-scale method combining multi-description which approaches with different respect to model the chemotaxis phenomenon was adopted from the classical Keller-Segel model (Lushnikov *et al.* 2008, Alber *et al.* 2007, Alber *et al.* 2006, Wang 2007). On the other hand, a model with pointwise presentation for a cell was simulated to simulate individual cell migration incorporating resolved attractant field (Stokes *et al.* 1991, Jabbarzadeh and Abrams 2005). However, assessments of chemotactic cell migration require taking into account the finite size of the cell, and much less work has been done on deriving models which treat the single cell as a three-dimensionally extended object.

Here, we proposed a three-dimensional dynamic model for a single crawling cell under the diffuse interface description. From the results of our study, we confirmed the high possibility of adequate predictions. Furthermore, we also prevent the intrinsic limit of blow up and provide the realistic simulation results of a crawling cell. The dynamically evolving surface incorporating the contact effect and the chemotactic mechanism poses a computational challenge. In this study, a diffuse interface framework is adopted to model the system. In the diffuse interface framework, an interface is represented by a thin continuous transition region. With the diffuse interface framework, we secure the stability of solution effectively in the computational process. This paper emphasizes the modeling issues involved in describing a single crawling cell as an extended three dimensional object, and implements experimentally motivated simulations with the chemoattractant gradient fields.

2. Model

Here, we consider a single crawling cell as neutrophil. Fig. 1 shows the schematic draw of three-dimensional dynamic mode for the single crawling neutrophil. We assume a well-defined gradient of chemoattractant on the surface. In the chemotactic condition, the cell migrates in a straight line in the direction of the chemoattractant gradient by sensing of gradient. This directional movement of the crawling cell is caused by small fluctuations around the cell. It systematically occurs as a result of the cell's minimized free energy. Although the biochemical phenomenon occurs through a complex pathway, as we confirmed in previous studies (Song and Kim 2009, Zhang *et al.* 2010), for simplicity, we ignore these processes and assume that the chemical gradient is uniformly generated only in the x_2 direction. Also, we applied a periodic boundary condition in the x_1 and x_3 directions to ensure straight crawling of the neutrophil in the x_2 direction.

The migration of a crawling cell is related with multiple mechanisms, such as diffusion, chemotaxis, and adhesion play of cell. To obtain the computational efficiency and to avoid evolving cells related to multiple driving forces, a diffuse interface approach is adopted. Similar approaches

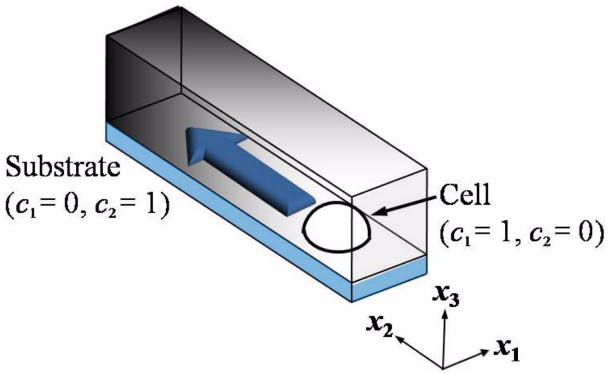

Fig. 1 A schematic drawing represents neutrophil chemotaxis on a substrate. The darker region corresponds to the higher concentration of chemoattractant

have been applied in previous studies regarding the morphological evolutions of nano- and microstructures and their reliability and effectiveness have been demonstrated (Song and Kim 2009, Lu and Kim 2006, Zhang *et al.* 2008, Kim 2009, Kim and Lu 2004, Kim and Lu 2006, Kim and Lu 2006, Lu and Kim 2004, Lu and Kim 2005). Here, we define three concentration fields, c_1, c_2, and c_3 to represent the cell, the substrate, and the solution, respectively. A concentration c_1 which is for the cell is defined by the volume fraction of the cell and a concentration c_2 is defined by the volume fraction of the substrate. The solution in the domain is represented by c_3, which is $1 - c_1 - c_2$. Each component is separated by the equilibrium state of the system with the minimum chemical energy in the diffuse interface framework. For example, we define the concentration c_1 by the volume fraction of the neutrophil, $c_1 = 1$ for inside the neutrophil and $c_1 = 0$ for outside the cell. We describe other components in the same way as the neutrophil. The concentration that represents the cell, $c_1(x_1, x_2, x_3, t)$, is regarded as a spatially continuous and time-dependent function. The concentration of the substrate, $c_2(x_1, x_2, x_3)$, does not evolve during the process.

Keller and Segel have proposed the mathematical model for the chemotaxis phenomenon, which is most widely used (Keller 1971). They proposed an expression for the cell flux induced by the response of taxis, $\mathbf{J}_c = \chi c \nabla \phi$, where χ is the taxis sensitivity, $c(\mathbf{x})$ is the density of cells centered at x, and ϕ is the attractant concentration. Thus, the cell flux $\mathbf{J}_c$ describes the movement of the cell responding to the attractant gradient. On the other hand, in our study, we define the mobility as $M_1(c) = M_0\{\int c_1^2(1-c_1)^2 dc_1 / \int_0^1 c_1^2(1-c_1)^2 dc_1\}$, which is distributed in the interfacial region throughout the cell. The material constant M_0 is proportional to the diffusivity of the cell, which is the cell property. Note that $M(c_1)$ vanishes outside the interfacial region of the cell. The cell with high mobility will migrate faster than that with low mobility. Since the mobility is proportional to the taxis sensitivity χ (Alber *et al.* 2006), we define the cell flux induced by the chemotactic response as $\mathbf{J}_c = M\beta\nabla\phi$, where β is the sensitivity constant and $M_0\beta$ corresponds to the taxis sensitivity χ in the model by Keller and Segel (Keller 1971). The chemical potential is defined by $\mu_0 = \delta G / \delta c_1$ and it is related to the driving forces that could be represented by $\mathbf{F}_{d1} = -\nabla\mu_1^0$. Using the driving force induced by the chemical potential, we obtain the cell flux related to the surface energy of the cell as $\mathbf{J}_{d1} = -M\nabla\mu_1^0$. Thus, the net flux can be expressed by $\mathbf{J}_1 = -M_1\nabla\mu_1^0 + M_1\beta\nabla\phi$.

In our study, we adopted the expression of free energy for a system with multiple components in

the diffuse interface framework, which is standard in the Cahn–Hilliard model (Cahn 1958), that is

$$G = \int_V \{f(c_1, c_2) + h_{11}(\nabla c_1)^2 + h_{22}(\nabla c_2)^2 + h_{12}(\nabla c_1 \nabla c_2)\} dV \tag{1}$$

The free energy is used to describe the thermodynamic properties of the system in diffuse interface modeling. The surface energy of the cell and the interaction between the cell and the substrate were incorporated by the Cahn numbers in our model, which were normalized based on the physical detail and which can provide specific information on the adhesion of a cell. The Cahn number is defined as $Ch = (\sqrt{h/f_0})/L_c$.

When the mass is transported, the net flux along the interface relies on the gradient of chemical potential and external stimuli, which is conserved in the system. This conservative evolution obeys a Cahn-Hilliard equation (Cahn 1958), namely

$$\frac{\partial c_1}{\partial t} = -\nabla \cdot (-M_1 \nabla \mu_1^0 + M_1 \beta \nabla \phi) \tag{2}$$

The governing equations are normalized with a characteristic length L_c and time, $t_c = L_c^2/M_0 f_0$. The choice of the magnitudes of the characteristic quantities depends on the physical detail to resolve and computational convenience. Then, dimensionless equations are

$$\frac{\partial c_1}{\partial t} = \nabla \cdot (M_1 \nabla \mu_1) \tag{3}$$

$$\mu_1 = (2c_1 + c_2 - 1)(2c_1^2 - 2c_1 + 2c_1 c_2 - c_2 + 2c_2^2) - Ch_{11}^2 \nabla^2 c_1 - \frac{1}{2} Ch_{12}^2 \nabla^2 c_2 - \alpha\phi \tag{4}$$

where α is $\beta\phi_0/f_0$ and represents the significance of the chemotaxis. The mobility M_1 and the initial chemoattractant concentration ϕ are dimensionless numbers normalized by those of the cell M_0 and ϕ_0. In this study, we have multiple components so we derived three different Cahn numbers $Ch_{11} = \sqrt{h_{11}/f_0}/L_c$, $Ch_{12} = \sqrt{h_{12}/f_0}/L_c$, and $Ch_{22} = \sqrt{h_{22}/f_0}/L_c$ related to each material coefficient h_{11}, h_{12}, and h_{13}.

3. Results and discussion

3.1 The velocity of chemotactic cell migration

We simulated a series of simulations with the same material parameters. We choose the characteristic length L_c and the Cahn number to be 0.5 μm and $Ch_{11} = 1$, $Ch_{12} = 1$ respectively. Then, the characteristic time becomes $t_c = L_c^2/(M_0 f_0) : 10^{-4}$ s and α becomes $\beta\phi_0/f_0 \sim 1.5$, which correspond an experiment value of 50 ng/mlg500 μm. The calculation domain size is $60 \times 140 \times 40$. A spherical cell with a radius of 20 is initially positioned at (30, 35, 0). These simulations give quantitative information of neutrophil chemotaxis. The results are visualized by three-dimensional surface plots. The surface of cell is defined by the concentration of 0.5.

Fig. 2 shows the snapshots of cell crawling at chosen time steps. Since the characteristic length is 0.5 μm, the corresponding radius of the cell becomes 10 μm. The concentration fields are visualized by grayscale graph. The darker region corresponds to higher concentration and the brighter region

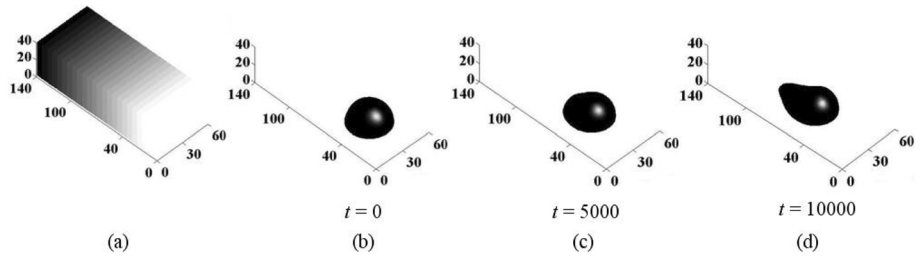

Fig. 2 The evolution sequence of a crawling cell in the chemotactic condition. (a) The cell is subjected to the linear chemoattractant gradient field where α is 1.5. The cell crawls to the region with the higher chemoattractant concentration during the simulation

corresponds to lower concentration. As shown in Fig. 2(a), the chemoattractant is supplied from the top of the domain and a linear chemoattractant gradient field from the bottom to the top is assigned by α that is 1.5. From Figs. 2(b) to (d), an evolution sequence of the cell from $t = 0$ to $t = 10000$ is presented. As presented by the experiments, the cell migrates to the higher chemoattractant concentration region in the simulation. In contrast with the existing results for the population of cells which had limit to present the migration of cells, our result describes the detailed evolution processes of cell crawling especially in a three dimensional domain. We assess the chemotactic velocity of the crawling neutrophil from the tracked displacement of the cell in Fig. 2. The linear gradient of chemoattractant generates a constant cell flux, which gives a linearly changing displacement of the cell. Thus, the cell migrates with a constant velocity of 9.8ìm/min when the chemoattractant concentration is distributed from zero to 50 ng/mlg500 μm, which is consistent with the experimental observation presented the velocity of around 5~20 μm/min (Frevert *et al*. 2006, Jeon *et al*. 2007).

4. Conclusions

In this study, we showed high possibility of adequate prediction for the dynamics of crawling neutrophil through the developed three-dimensional model. We considered the chemotaxis of single crawling cell, which has an advantage over previous studies with the population of cells in accurate assessments of chemotaxis providing a clear observation of cell migration. To establish reliable modeling system of cell dynamics, the diffuse interface model is adopted. The diffuse interface approach incorporates the cell flux relates with the surface energy and the chemotactic response of the cell. The developed model is numerically solved by the semi-implicit Fourier spectral method. The result has shown that the neutrophil migrates toward the region with the high chemoattractant concentration as an experimental observation. From the result, we obtained the chemotactic velocity of crawling cell and it is consistent with the experimental observation.

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