Amoebic ability to arrive at signal sources in an obstacle-rich space

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Abstract

Amoebic cells are able to trace signal molecules and arrive at sources of those molecules. An interesting problem is on how amoebic cells can avoid obstacles and find the correct way to reach the signal source. To answer this problem, we develop a discrete model of amoeba. We put a wall in the model space with a hole through which the amoeba can migrate. The wall also has a dummy hole or "permeable membrane" through which the signal permeates but the amoeba can not pass. If we place the cell near by the permeable membrane, the cell initially tries to pass it but finally finds the true hole and succeeds in passing it.

1 Introduction

Amoebic cells are widely seen in many eukaryotic species. Cellular slime mold at the unicellular period, for example, moves and searches foods with the amoebic locomotion [1]. Human neutrophils which attack the external microbes are also well-known examples of amoebic cells [2].

One of important features of amoebae is "chemotaxis". Immune cells migrate from vessels to the inflamed tissue in order to destroy the external microbes. Cells in the inflamed tissue are known to produce signal molecules (usually called "chemokine"). Immune cells detect the gradient of the signal and move along the gradient to get to the tissue.

The mechanism that amoebae can detect the very small difference in signal density between their head and tail, which is often as small as the signal fluctuation, has been a challenge to researches, and many secrete mechanisms of chemotaxis have been brought to light through intensive studies [3, 4, 5, 6, 7].

However, many problems remain elusive. One of interesting problems is the mechanism that amoebic cells can migrate among tissue cells which are constructed as if a maze in animal bodies. There suppose to be dead-ends, narrow holes, and other unexpected difficulties. In order for amoebic cells such as immune cells to arrive at appropriate tissues, they need to avoid these difficulties. The aim of this paper is to elucidate amoebic abilities of migration in an obstacle-rich space.

2 Model

Our model has discrete two-dimensional grids on which some concentrations of molecules are defined. A cell is defined on the grids as a domain. We adopt hexagonal grids for convenience. A grid is either external or in the cellular domain. When the grid is in the cellular domain, three real numbers are defined on the grid, which indicate densities of activator, inhibitor and actin filaments. We give four rules in order to move the cell: Kinetics, Diffusion, Cellular domain extension and Keeping the cell. The following paragraphs explain those rules.

(1) **Kinetics**: Both activator and inhibitor are produced by the stimulation of the external signal[8]. The activator enhances polymerization of actins, whereas the inhibitor suppresses the polymerization. First, this rule selects a grid in the cellular domain randomly. If densities of activator, inhibitor and actin filaments at the selected grid j are expressed as A_j, I_j and F_j, respectively, those variables are changed obeying the following equations:

$$A'_j = A_j + \alpha S_j - k_\alpha A_j \quad (1)$$

$$I'_j = I_j + \beta S_j - k_\beta I_j \quad (2)$$

$$F'_j = F_j + \begin{cases} \gamma - k_f F_j & (\frac{A}{I} > h) \\ -k_f F_j & (\text{otherwise}) \end{cases}, \quad (3)$$

where α, β, γ, k_α, k_β, k_f, γ and h are constants. S_j indicates the concentration of chemoattractants or the strength of the external signal at the jth grid. Grids at the border of the cellular domain are regarded as

the cellular membrane. We call the grid in the cellular domain the membrane if at least one of its six nearest grids is external. S_j is set to zero if the jth grid is in the cellular domain but not in the membrane. The functional form of S_j represents the chemical gradient. A schematic picture of the kinetics is depicted in Figure 1

(2) **Diffusion**: Only the inhibitor diffuses into the whole cytoplasm[8]. This rule selects a grid from the whole cellular domain. At the selected jth grid and its nearest cellular lth grid, I_j and I_l obey the following equations:

$$I'_j = I_j - DI_j \quad (4)$$

$$I'_l = I_l + \frac{DI_j}{n}, \quad (5)$$

where D is the diffusion constant. n is the number of the nearest cellular grids. D should be smaller than 1 by definition.

(3) **Cellular domain extension**: The rule randomly selects a grid from the membrane. When F_j at the selected jth grid in the membrane exceeds the threshold F_{th}, an external grid in the six nearest grids of the jth grid is turned into a cellular grid. When there are two or more than two external grids around the jth grid, a grid is randomly selected. If this grid is referred to as l, $F_l = F_j/2$ and other variables are set to zero. F'_j equals to $F_j/2$ by definition, where the prime indicates the value at the next time step.

(4) **Keeping the cell**: We also give a rule to prevent cell from breaking into pieces. The cellular volume is kept and the cellular surface length is constrained to be as small as possible. This rule randomly selects a grid from the membrane. Then the rule decides either to remove the grid or to add a new cellular grid around the grid. This rule checks the cellular "tension" by calculating energy of tension as:

$$E = (V - V_0)^2 + cL^2, \quad (6)$$

where V and L are the cellular volume and length of the membrane and V_0 and c are constants. When E' denotes the energy after either removing or adding a cellular grid, we define the probability P as follows:

$$P = \exp\left(-\frac{E' - E}{kT}\right), \quad (7)$$

where kT is a constant. We generate a random number between 0 and 1 and then compare the number with P. If the number is smaller than P, we "undo" the event of removing/adding. From the definitions of P and E, the volume of the cell tends to be V_0 and the length of the membrane becomes as small as possible. Note that if removing is chosen, the values of A, I and F in the removed grid are added into the nearest cellular grid.

We also give the "master" rule that randomly selects one of the above rules. Each rule has the probability of selection. The probabilities of selection for rules from (1) to (4) are written as P_1, P_2, P_3 and P_4. $P_1 + P_2 + P_3 + P_4$ should equal to 1. When the master rule selects one of the four rules, the selected rule is executed. We iterate this process several millions times.

External signal is defined in external grids. The signal diffuses over external grids but not into cellular grids. When S_k is the signal density in the external grid k, S_k is updated to S'_k by the following equation:

$$S'_k = S_k - D_s S_k + D_s \sum_l S_l/n_l, \quad (8)$$

where l indicates the lth nearest external grid, n_l is the number of nearest external grids around the lth grid, and D_s is constant. Although this equation looks similar to Equations 4 and 5, it should be noted that signal densities are synchronously updated at all external grids. After the master rule randomly selects the rules n_c times, it executes Equation 8 once, and this cycle is repeated. The reason why we adopt the synchronous updating rule for external signal densities is that the external signal diffuses much more rapidly than intracellular molecules. External signal does not diffuse into cellular grids. We define rectangle boundary grids in which the external signal sinks: The signal flows into the boundary grids but not from the grids. When a signal source is defined at the kth grid, S_k is kept constant instead of Equation 8 as $S_k = S_0$ at the source grid.

We calibrate parameters in the model by examining how our cell moves in a simple linear gradient. The initial diameter of the cell is set to be 30 grids. The cell goes up the linear gradient as observed experimentally [9] when the following set of parameters are chosen: $\alpha = 1.0$, $\beta = 0.1$, $k_\alpha = 0.9$, $k_\beta = 0.02$, k_f, $D = 0.45$, $h = 1.0$ $P_1 = 0.0419$, $P_2 = 0.03$, $P_3 = 0.03$, $P_4 = 0.898$, $V_0 = 900$, $c = 10^5$, $kT = 100$, $D_s = 0.3$, $S_0 = 0.5$ and $n_c = 10$.

Although we have not yet exhaustively tried different parameter sets, we expect that the cell behaviors are robust against the parameter change. We use 95×95 grids in which both external and cellular grids are defined. Simulation is designed to terminate before the cell reaches the boundary of the grid space.

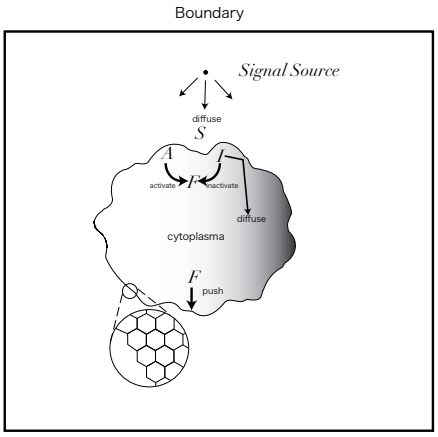

Figure 1: A schematic picture of a cell in the space with boundary through which signal drops out of the space. Both activator A and inhibitor $I$are produced by the stimulation S of the external signal. The activator enhances polymerization of actins F, whereas the inhibitor suppresses the polymerization. Only the inhibitor diffuses into the whole cytoplasm. External signal diffuses from signal sources.

3 Results

First we put a source near by the cell. When the cell touches the source, the source is eliminated from the grid space. This operation naively represents "phagocytosis" . Does the cell arrive at the source as reaching "food"? Figure 2 shows that the cell succeeds in reaching the food.

If there are multiple foods, how does the cell behave? Interestingly, the cell moves to one of foods and "eats" it. It then goes to the next one and eats all the foods in the end. (Figure 3).

Figure 4 shows that there is a wall with a hole and a "permeable membrane" through which the signal can permeate but the cell cannot pass. When the cell starts near by the permeable membrane, the cell stays at the membrane for a while then moves to the true hole and reaches the source.

4 Discussion

In actual animal bodies amoebic cells seem to select suitable paths by avoiding obstacles or local maxima of signal density. Results in the last section showed that the model amoebic cell can also choose a suitable path as natural amoebic cells do: When multiple foods are placed in the space, the simulated cell did

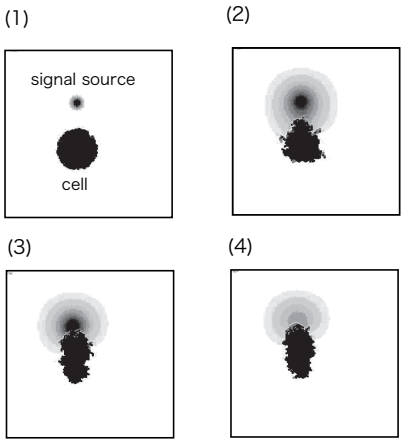

Figure 2: Snapshots of a cell moving to a signal source as if to eat a "food". A large, dark gray area is the cell. The signal density is indicated with gray scale. A sinal source is a small dark gray area. Around the source, contour lines of signal density are shown. In Subfigure (4), a dark small area has vanished because the source has been touched by the cell and removed.

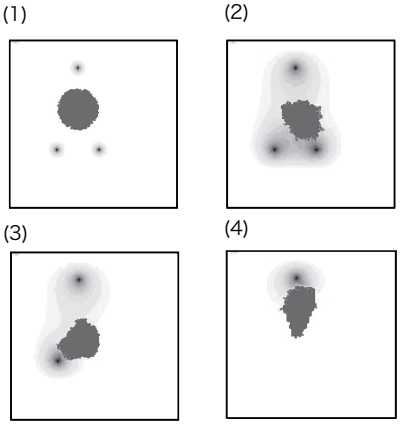

Figure 3: Snapshots of a cell "eating" three foods. The cell moves to the right bottom, then to the left bottom, and finally to the top.

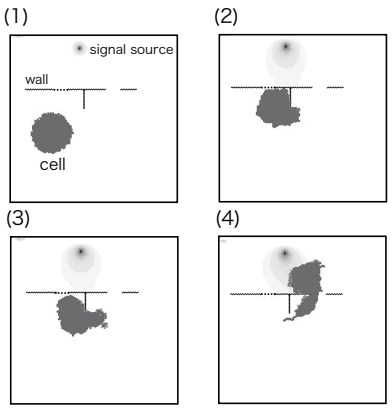

Figure 4: Snapshots of a cell moving in the space separated by a wall. The wall has a membrane indicated by a dashed line at the left part, through which the signal permeates. The wall also has a hole at the right part. A vertical part of the wall is a stand in cell's way.

not freeze but chooses one food to another to gain as much food as possible. When the obstacle is placed between the food and the cell, the cell can find out the proper way to get round the obstacle to reach the food. Simplicity of our model leads to the idea that such seemingly complex motion is based on the essentially simple mechanism. Although the real biological process is supported by enormous numbers of different types of proteins, the key mechanism underlying the behavior might be the nonlinear and history-dependent response of cell to the external stimuli as demonstrated in the model.

Our next task is to quantify the efficiency of amoebic strategy by using our model. Such works will be done in future publications.

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