Inertia of Chemotactic Motion as an Emergent Property in a Model of an Eukaryotic Cell

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Abstract

Chemotaxis is widely seen in many biological systems. Among them amoebic cells from unicellular slime molds to immune cells are believed to directly sense chemical gradients. Here, we construct a model of amoebic cell by taking account of the chemical kinetics as well as a cellular body. The model is composed of discrete grids and a set of rules which define chemical and motional events on each grid. The model can explain the observed features of the cellular locomotion. We find that the simulated cell tends to keep the direction of motion, which reminds us of "inertia" of motion in Newtonian dynamics. The averaged motion of amoebic cells approximately obeys an "underdamped" equation of motion for a short time scale. "Inertia" of chemotactic motion is an emergent property of the system where motion and the signal processing are strongly coupled to each other.

Introduction

Amoebic cells in animal species have important roles. For example, a phagocyte, a defender of an animal body, is an amoebic cell that migrates and kills external microbes by phagocytosis (Roitt et al., 1998). In general, an amoebic cell does not have a definite shape, but cells that have characteristic shapes also possess the amoebic property more and less. For instance, a neuron in its developmental phase elongates an axon, which can be thought of as an amoebic motion.

It is believed that an eukaryotic cell can directly sense the small difference of chemical concentration between two points at the cellular membrane (Pollard, 2003). This ability of amoebic cells is called "chemotaxis". When external microbes invade tissues, immune cells migrate from vessels to the tissues driven by the chemotaxis: They direct their courses along the gradient of chemoattractants produced from the invaded tissues (Springer, 1994; Katanaev, 2001).

Recent studies have revealed detailed biochemical mechanisms how actins and other molecules control the chemotactic motion (Pollard, 2003; Pollard and Borisy, 2003; Pollard et al., 2000; Iijima et al., 2002). An actin monomer in the cytoplasm binds an ATP and a profilin. External signals indirectly activate the Arp2/3 complex which binds to an ATP bound actin. This Arp2/3-ATP-actin complex initiates the actin polymerization. The polymerization is terminated when a caping protein binds to the actin polymer. ATP-actin subunits in thus formed actin polymer are changed into ADP-actin by phosphate dissociation and ADP-actin subunits are severed from the actin polymer. Force acting on the cellular membrane depends on the balance between the actin polymerization and depolymerization.

We introduce a model that treats actin filaments and some chemicals as well as the cellular membrane. By using this model, we study in this paper whether there exists a simple rule to which an eukaryotic cell should be subject.

Model

Our model consists of discrete two-dimensional grids on which concentrations of relevant 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 internal of the cellular domain. When the grid is in the cellular domain, three real numbers are defined on the grid, which indicate concentrations of activator, inhibitor and actin filaments.

We give four rules in order to move the cell: Chemical Kinetics, Diffusion, Actin filaments extending the cellular domain and Keeping the cell. The following paragraphs explain those rules.

(1) **Chemical Kinetics**: Both activator and inhibitor are produced by the stimulation of the external signal (Levchenko and Lglesias, 2002). The activator enhances polymerization of actins, whereas the inhibitor suppresses the polymerization. First, this rule selects a grid in the cellular domain randomly. If concentrations 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 updated to A'_j, I'_j and G'_j obeying the following equations:

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

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

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

where α, β, γ, k_α, k_β, k_f 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 say that a grid in the cellular domain is in the membrane if at least one of the 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 chemical gradients.

(2) **Diffusion**: Only the inhibitor diffuses into the whole cytoplasm (Levchenko and Lglesias, 2002). 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 are redistributed obeying 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) **Actin filaments extending the cellular domain**: The rule randomly selects a grid from the membrane. When F_j at the selected jth grid in the membrane reaches 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. G_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 a 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:

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

where kT is a constant. We generate a random number between 0 and 1 and then compare the number with P_e. If the number is smaller than P_e, we "undo" the event of removing/adding. From the definitions of P_e 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. After the master rule selected one of the four rules, the selected rule is executed. We iterate this process several millions times.

Results

First, we try to clarify what our cell does in a simple linear gradient. We select a set of parameters to make the cell go up the gradient as follows: $\alpha = 1.0$, $\beta = 0.1$, $k_\alpha = 0.9$, $k_\beta = 0.02$, $\gamma = 4.0$, $k_f = 0.99$, $D = 0.45$, $h = 10.0$, $F_{th} = 1.0$, $P_1 = 0.0419$, $P_2 = 0.03$, $P_3 = 0.03$, $P_4 = 0.898$, $V_0 = 900$, $c = 1.2$ and $kT = 100$. The initial diameter of the cell equals to 30 grids. Although we have not yet exhaustively tried different parameter sets, we expect that the cell behaviors are robust against the parameter change. We let $S_j = -y + \text{constant}$ which indicate a linear gradient.

Figure 1 shows snapshots of our simulation, in which a cell clearly moves downward according to the gradient. First, actin filaments increases in all membrane grids, then actin filaments remains in only the "head" of the cell. Figure 2 clarifies that the cell does not move in the completely same direction as the gradient direction but motions of the cell have large fluctuations with regard to the x-direction.

Jeon et al. have succeeded in making a new device that can maintain complex but static gradients (Jeon et al., 2002). By using this device, they analyzed the locomotion of neutrophils in several patterns of gradient. They tested "Hill" gradient, for example, in which concentration initially increases then decreases at a middle point along a certain direction. Neutrophils starting form a bottom climbed up the hill, and they continued to proceed without stopping at the top until they finally returned from the downhill side. The cell of our model shows the same behavior at least qualitatively. In Figure 3 the simulated cells move beyond the top of the hill, where the gradient is drawn in the left side of the figure.

We also analyze "Flat & Drop" gradient. This gradient starts with a flat pattern. From a certain point, the concentration of chemicals drops gradually. Initially, the cell is "pushed" by an additional event defined as follows: First a membrane grid is randomly selected. If the vertical position y of the selected grid is larger than l, the grid is removed. This event has an effect as if to push the cell by a plank. l is set to 7.5, about a half of the cellular radius. Figure 4 depicts trajectories of the cells pushed. After pushed, cells move down in the decreasing y direction even though there is no gradient. After passing the line $y = -50$, the cell moves

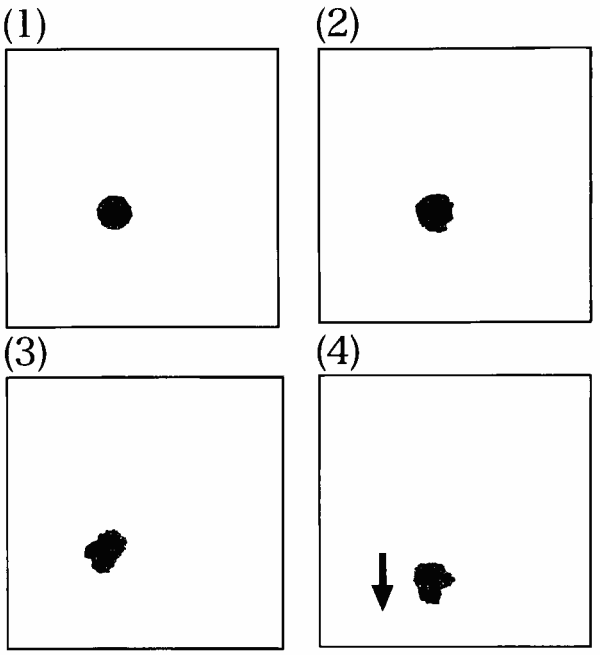

Figure 1: Snapshots of the cell moving. The gray collared area is the region of cellular grids. Dark part of the cell indicates positions where F_j is larger than $F_{th}/2.0$. S increases in the downward direction.

against an upward gradient until they finally return.

Cases of Hill and Flat & Drop gradients imply that the present model cells have a tendency to keep their motions. Figure 4 shows that cells continue to move even without gradient. The cells do not stop soon in both cases. This property of the simulated cells has some resemblance to "inertia" in Newtonian dynamics. Cells move as if balls move in the potential which has the reversed pattern of the chemical gradient. In the case of Hill gradient, for example, cells passing the top of the gradient look like balls going up an uphill by inertia. In the case of Flat & Drop gradient, cells moving the flat part look like balls rolling on a flat floor.

The cell should turn around a source point of chemoattractants if it has an inertia-like property. We define "Central" gradient as follows: Strength of signals S equals to $C - u|\vec{r} - \vec{r}_0|^2$, where C and u are constant. All gradient vectors point to the center $\vec{r}_0$. This gradient is an analogy of a linear spring that binds a material point to a fixed point. In Figure 5 we can see that a fluctuating trajectory indeed turns around a center (using $C = 4000$, $u = 1$ and $\vec{r}_0 = (70,0)$). Here, the cell was initially pushed down by calling the event procedure defined in the Flat & Drop gradient study, during a short period of starting steps. Although not all the trajectories starting with different random seeds showed the circular orbit as shown in Figure 5, most of them did not move directly toward the center but turned around the center for a while, showing the existence of the inertia effect working at least for a short time scale.

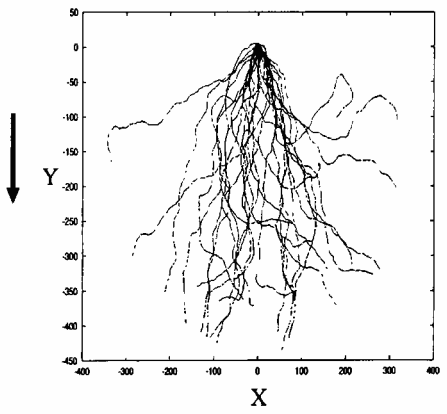

Figure 2: Trajectories of centers of cells in Linear gradient. Each trajectory starts with a different random seed but the same initial condition.

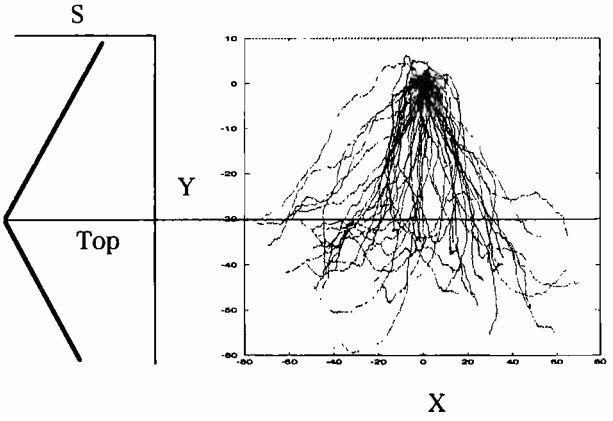

Figure 3: Motions of cells in Hill gradient. The shape of the gradient is drawn in the left.

Why does the cell have an inertia-like property? Although the definite answer is not yet known, the distribution of Inhibitor I_j gives a clue to the answer. Figure 6 indicates I_j in a cell moving linearly in a flat field without gradient. I_j tends to be concentrated on the rear of the cell. This heterogeneous distribution of Inhibitor is kept until the cell stops moving. We speculate that such heterogeneity is maintained by the following mechanism: While moving, the head of the cell is always extended, whereas the rear is always retracted. Inhibitor gradually gathers into the rear if this extending-retracting processes are slightly faster than diffusion of Inhibitor. The large concentration of Inhibitor thus accumulated suppresses increase in actin filaments F_j, which should decrease the probability that F_j at the rear exceeds the threshold. In this way motion of the cell maintains the bias

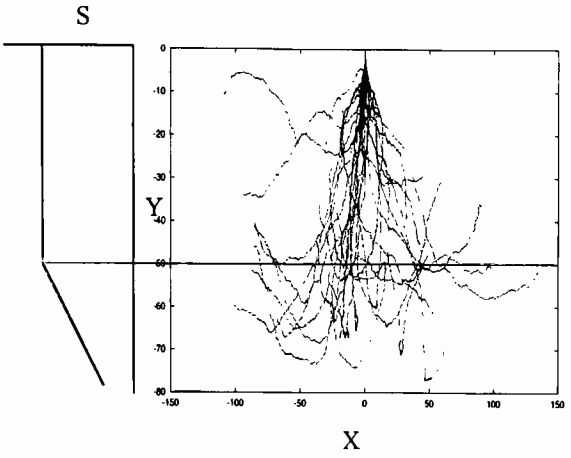

Figure 4: Behavior of cells in Flat & Drop gradient. The pattern of gradient is changed below the line $y = -50$ as is drawn in the left figure. In the area of $y < -50$ the direction of the gradient is upward. The cells move against the gradient until they finally turn to the gradient.

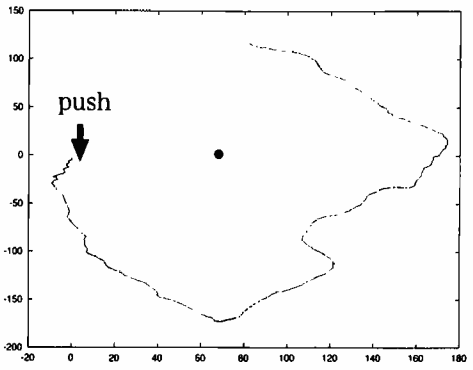

Figure 5: A trajectory in "Central" gradient. The cell starts from the point (0,0). The center is set to (70,0). The cell is pushed down during a short period of starting steps. The cell then turns around the center counterclockwise.

of Inhibitor which further stabilizes the cell motion. The cell does not stop immediately once the cell starts to move. When the gradient is opposite to the direction of cellular motion, we easily conjecture that the opposite gradient does not extinguish the bias at once.

Discussion

An inertia-like property of amoebic cells has been observed in experiments though the term "inertia" has not been used. For example, Verkhovsky et al. observed that the polarized cellular fragments undergo locomotion even without the gradient of chemoattractant (Verkhovsky et al., 1999). Those fragments sometimes stayed still but stared to undergo locomotion when a mechanical stimulus was applied. They showed that the actin-myosin II bundle is formed at one edge of the fragments associating with the locomotion. In general, cellular locomotion in a uniformed concentration is called "chemokinesis". Cells in a uniformed concentration can show long straight runs although their directions are random relative to one another in a short time scale (Wilkinson, 1998). From studies of Jeon et al., neutrophils were shown to move without changing directions immediately after the change of interleukin-8 gradient (Jeon et al., 2002).

What type of equation does the cellular motion with "inertia" should obey? Figure 7 depicts the averaged y-position of cells which move in Linear gradient as a function of time as well as a fitting curve. In this figure initial 1400 steps are shown. Data are same as those used in Figure 2 and the average was taken over all cells. Note that the total steps executed in Figure 2 are about 6000 steps. The fitting curve is a solution of the following underdamped equation:

$$\frac{d^2\vec{r}}{dt^2} = -p\frac{d\vec{r}}{dt} + q\vec{\nabla}S(\vec{r}) \tag{8}$$

where $\vec{r}$ indicates the mean position of the cell, $S(\vec{r})$ is the chemical concentration at $\vec{r}$ and p and q are unknown functions but approximately regarded as constants. This equation is a Newtonian, underdamped equation. Since the solution curve do not fit the averaged y-position of cells after about 2000 steps, Equation (8) may not hold for the long time scale. An equation that should hold for the longer time scale might be more complex.

Does inertia of cells have any biological advantage? We do not have any clear answer for this question yet. A naive idea is that cells can avoid local maxima of concentration by inertia to find out the global maximum. Another idea is that when amoebic cells catch foods or enemies by phagocytosis, they should be moving around for a moment to prevent from missing foods or enemies. Anyway, this is an open question to be investigated.

Conclusion

We succeeded in making a model that explains amoebic chemotaxis. The cellular locomotion and the chemical processes are strongly coupled to each other, which stabilizes the "inertia"-like motion of the cell. The cell in our model moves in a way similar to the motion in Newtonian underdamped dynamics.

Acknowledgments

This work was supported by ACT-JST project of Japan Science and Technology Corporation.

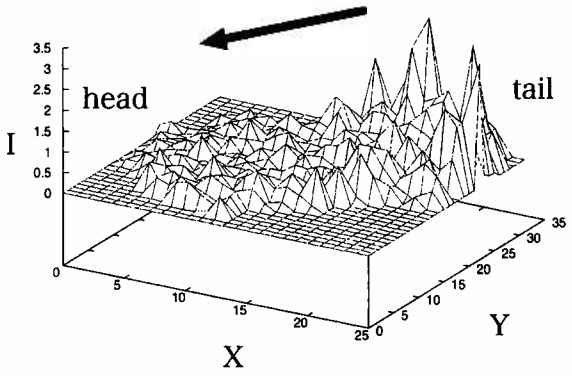

Figure 6: Distribution of Inhibitor I_j. X and Y axes indicate spatial coordinates of grids. Z axis indicates the value of I_j.

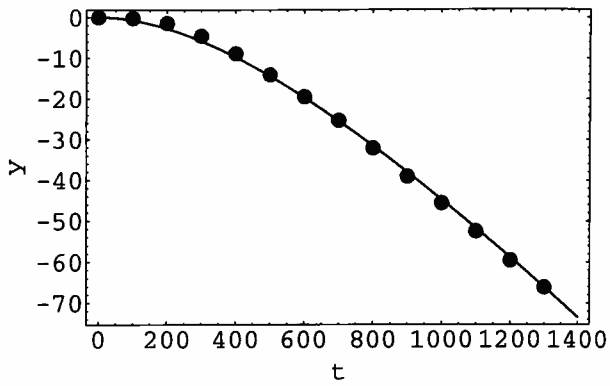

Figure 7: Horizontal and vertical axes indicate time and the y-position, respectively. Dots are sampled points of center positions averaged over all cells examined in Linear gradient. A solid curve indicates the function $y(t) = p^{-1}\{\exp(-qt) + qt - 1\}$ (which is the solution of $\ddot{y} = -p\dot{y} + q$, where $p = 0.002$, $q = -0.025$, $y(0) = 0$ and $\dot{y}(0) = 0$) that approximately fits the sampled points.

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