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Stochastic modelling for gradient sensing by chemotactic cells

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Abstract

Chemotaxis, the process by which cells move toward attractant molecules, operates in a range of biological processes including immunity, neuronal patterning, and morphogenesis. *Dictyostelium discoideum* cells display a strong chemotactic response to cyclic adenosine 3′,5′-monophosphate (cAMP), which binds to a cell surface receptor. Each *Dictyostelium* has ca. 80000 cAMP receptors, and can transduce shallow spatial chemoattractant gradients into strongly localized intracellular responses in spite of large statistical fluctuation of receptor occupancy even in the case of very low cAMP concentration. In this study, we develop a stochastic model for gradient sensing by chemotactic cells. We simulate the binding of cAMP molecules to receptors by a Monte-Carlo method in order to account for statistical fluctuation of receptor occupancy and treat intracellular signal processing by a diffusion–translocation model, which includes the production of second-messenger molecules and positive feedback mechanisms mediated by effector molecules. Our simulation results show that the fluctuation of second-messenger concentration is much smaller than that of receptor occupancy, and that a shallow chemoattractant gradient are transduced into a large second-messenger concentration gradient through nonlinear signal amplification.

Keywords: Chemotaxis; *Dictyostelium*; Reaction–diffusion; Nonlinear signal amplification

1. Introduction

Extracellular cAMP induces directed cell locomotion (*chemotaxis*) in *Dictyostelium* cells [1–3]. Binding of cAMP to G-protein-coupled receptors leads to the activation of second-messenger pathways, including the activation of adenylyl cyclase, guanylyl cyclase, phospholipase C [1]. Thus *Dictyostelium* can transduce spatial chemoattractant gradients into intracellular responses. The measurement of the sensitivity of cells in cAMP gradients [1] has revealed that *Dictyostelium* can respond to a gradient as small as 4.0×10^{-12} M/μm in the mean concentration of 8.0×10^{-10} M. It should be noted that in such a situation the number of cAMP-coupled receptors fluctuates much and that this may obscure the difference in concentration between the two ends of the cells as we will see later in Fig. 1. Existing theoretical study such as Ref. [4], however, does not take this into account. The issue of how the gradient sensing by chemotactic cells functions despite large fluctuation also concerns the development of nanoscience and nanotechnology, since nano-scale systems are inevitably subject to large thermal and stochastic fluctuation.

In this study we develop a stochastic model for gradient sensing by *Dictyostelium*. In order to account for stochastic fluctuation in receptor occupancy, we treat the binding of cAMP molecules to receptors by a Monte-Carlo approach. Intracellular signal processing is simulated with a diffusion–translocation model [4], which includes the production of second-messenger molecules and positive feedback mechanisms.

2. Model

Let us assume that a cell has one-dimensional geometry in x-direction with a length l of 10 μm. 80 000 cAMP receptors are immobile and located on the cell surface with equal spacings. Ligand (cAMP) molecules (L) binds to

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receptors (R) with a rate constant $k_1 = 0.7 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$, and a cAMP-receptor complex (LR) dissociates with a rate constant of $k_{-1} = 0.7\ \mathrm{s}^{-1}$:

$$\mathrm{L} + \mathrm{R} \rightleftharpoons \mathrm{LR}. \tag{1}$$

In order to account for the discreteness and statistical fluctuation of receptor occupancy properly, we simulate the dynamics of each receptor described by Eq. (1) using a Monte-Carlo method: a ligand molecule binds to the receptor if a random number $p \in [0,1]$ is smaller than the binding probability $1 - \exp(-k_1[\mathrm{L}]\Delta t)$ during a time step Δt, and the ligand–receptor complex dissociates if a random number $P' \in [0,1]$ is smaller than $1 - \exp(-k_{-1}\Delta t)$, where the cAMP concentration [L] is treated as a continuous quantity, and is assumed to be constant in time and to have a linear gradient along the cell of the form,

$$[\mathrm{L}](x) = L_{\mathrm{av}} - \Delta L \cdot x. \tag{2}$$

Activation of receptors induces production of second-messenger molecules. After its production, a second-messenger molecule will diffuse in the membrane, and, ultimately, it will be degraded. This general process is described by [5]

$$\frac{\mathrm{d}m}{\mathrm{d}t} = D_m \nabla^2 m - k_{\mathrm{deg}} m + P, \tag{3}$$

where m is the second-messenger concentration, D_m the diffusion coefficient, $k_{\mathrm{deg}} = 1.0\ \mathrm{s}^{-1}$ the degradation rate constant [4], and P the production rate. We solve Eq. (3) with the reflective boundary condition using a method elaborated based on the Crank–Nicholson scheme [6].

3. Fluctuation of receptor occupancy

In order to obtain an insight into the stochastic fluctuation of the receptor occupancy, we show in Fig. 1 a typical temporal evolution of the numbers of the ligand-coupled receptors at $x < 0$ (*the front half*), where the ligand concentration is the higher, and at $x > 0$ (*the back half*). All the receptors are assumed to be initially unoccupied,

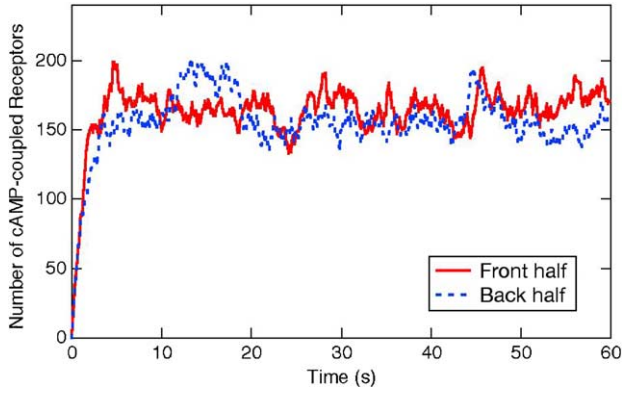

Fig. 1. Temporal evolution of receptor occupancy in the front half, where the ligand concentration is the higher, and in the back half of the cell.

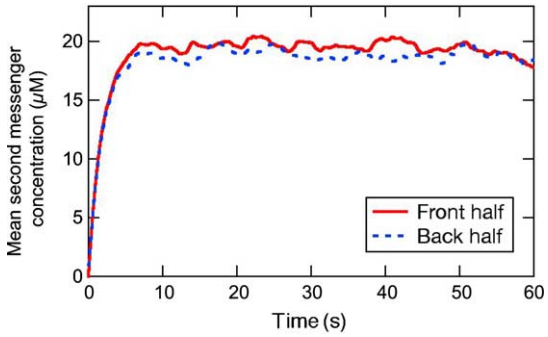

Fig. 2. Temporal evolution of second-messenger concentration in the front and back halves of the cell without nonlinear signal amplification.

and the used parameter set is:

$$L_{\mathrm{av}} = 4.0 \times 10^{-10}\ \mathrm{M}, \quad \Delta L = 5.0 \times 10^{-12}\ \mathrm{M/\mu m}. \tag{4}$$

The small difference between the two halves is scratched out by large fluctuation, and we cannot tell in which part the cAMP concentration is higher at a glance.

4. Second-messenger production and diffusion in chemoattractant gradients

In this section we examine the concentration of second-messenger molecules in case where the production rate P is linear in local receptor occupancy: when a receptor is occupied, second-messenger molecules are produced at its position with $P = 1.0\ \mu\mathrm{M\ s}^{-1}$. We set the total number of receptors to 4000 for the reduction of computational time, and in order to keep the mean number of ligand-coupled receptors to the same value as in Section 3 we scale Eq. (4) to $L_{\mathrm{av}} = 8.0 \times 10^{-9}\ \mathrm{M}$ and $\Delta L = 1.0 \times 10^{-10}\ \mathrm{M\ \mu m}^{-1}$.

In Fig. 2 we show a typical temporal evolution of second-messenger concentration in each half for the case of $D_m = 1.0\ \mu\mathrm{m}^2\ \mathrm{s}^{-1}$. Large stochastic fluctuation in Fig. 2 is strongly suppressed at the level of the second-messenger concentration. From Eq. (3), one can easily show that the second-messenger molecules act as a low pass filter $\propto [\omega^2 + (k_{\mathrm{deg}} + k^2 D_m)^2]^{-1}$, where ω and k are the frequency and wave number, respectively, of the receptor occupancy fluctuation.

5. Signal amplification with effector translocation

In Section 4, we have seen that large stochastic fluctuation in receptor occupancy is efficiently suppressed at the level of the second-messenger. The difference between the two halves is, however, very small in Fig. 2. This, along with many experimental results, indicates that signal amplification is essential. Postma and Van Haastert [4] have developed a gradient amplification model that is based on translocation experiments of PH

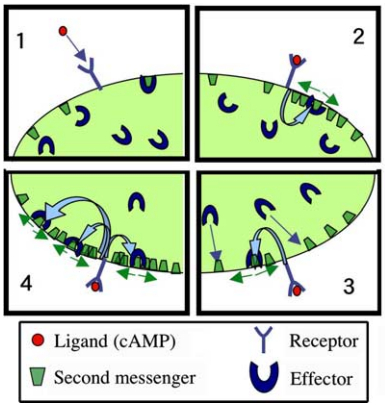

Fig. 3. The signal amplification model [4]. The figure depicts four steps in the model: (1) receptor activation, (2) second-messenger production, (3) effector translocation, and (4) amplification.

domain-containing proteins in Dictyostelium, neutrophils, and fibroblasts [5]. In this section we examine whether this model works even in the presence of stochastic fluctuation.

To introduce a nonlinearity in the system, the model assumes that one essential component (*effector*) that translocates between the cytosol and the second-messenger. Haugh et al. [5] have proposed that PI3′-kinase may play such a role. The model [4] is depicted in four steps (Fig. 3): (1) before receptor stimulation only a small number of effector molecules are bound to the membrane and are inactive; (2) after receptor activation the membrane-bound effector molecules will be stimulated leading to production of second-messengers; (3) because the second-messenger concentration increases, more effector molecules will translocate from the cytosol to the membrane; and (4) because the receptor now can signal to more effector molecules, this rapidly leads to stronger second-messenger production. The amplification can be considered as a positive feedback mechanism. The production rate P of second-messenger is written as,

$$P(x) = k_{\mathrm{peb}} + k_{\mathrm{pe}}[\mathrm{SE}], \tag{5}$$

if the nearest receptor is occupied, and otherwise,

$$P(x) = k_{\mathrm{peb}}. \tag{6}$$

where k_{peb} is the basal production rate, k_{pe} is the maximum production rate per effector molecule, and [SE] is the effector concentration in the membrane. We further assume that effector molecules in the cytosol can diffuse much faster than second-messenger and that its concentration is uniform along the cell. They can reversibly bind to second-messenger with forward binding rate constant k_{b1} and release-rate constant k_{-b1}.

In concrete simulations, we set the total number of receptors to 4000 as in the Section 4, and use the following parameter values: $k_{b1} = 1.0 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$, $k_{-b1} = 1.0\ \mathrm{s}^{-1}$, $k_{\mathrm{pe}} = 200$ molecules $\mu\mathrm{m}^2\ \mathrm{s}^{-1}$, $k_{\mathrm{peb}} = 10$ molecules $\mu\mathrm{m}^2\ \mathrm{s}^{-1}$ and the total effector concentration in the cytosol is 0.045 μM. The other parameters are the same as in Section 4.

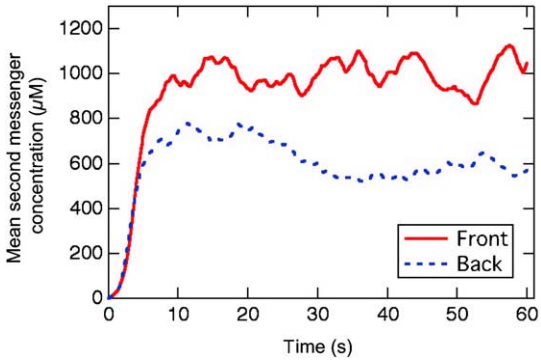

Fig. 4. Temporal evolution of second-messenger concentration in the front and back halves of the cell with nonlinear signal amplification.

In Fig. 4 we show a typical temporal evolution of second-messenger concentration in the front and back halves. We can see that the difference between the two halves is efficiently increased compared with the case where no amplification mechanism is present (Fig. 2). As a consequence, small difference in receptor occupancy with large fluctuation as in Fig. 1 can be transduced into a large second-messenger density gradient, and a shallow cAMP gradient can be detected with no ambiguity.

6. Conclusions

We have developed a stochastic model for gradient sensing by chemotactic cells, specifically *Dictyostelium discoideum*. Special attention has been given to how they detect a small signal (cAMP concentration gradient) in the presence of large stochastic fluctuation, which also concerns the development of nano-scale technology and advanced materials. We have simulated the dynamics of ligand–receptor binding and dissociation by the Monte-Carlo method and intracellular signal processing by the diffusion–translocation model [4] including positive feedback mechanisms. Our simulation results have shown that stochastic fluctuation in receptor occupancy is much reduced at the level of second-messenger concentration, and hence that nonlinear signal amplification leading to a large intracellular second-messenger gradient works even in the presence of large stochastic fluctuation. This feature may help *Dictyostelium* to detect a shallow cAMP concentration gradient with no ambiguity.

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