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RESOLVING THE CHEMOTACTIC WAVE PARADOX: A MATHEMATICAL MODEL FOR CHEMOTAXIS OF DICTYOSTELIUM AMOEBAE

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ABSTRACT

The slime mould *Dictyostelium discoideum* is a widely studied paradigm for biological pattern formation. To provide an explanation for the apparently paradoxical behaviour of *Dictyostelium* amoebae in the symmetric chemoattractant waves which govern their aggregation, we extend the standard model for chemotaxis of a cell population by explicitly considering adaptation of the chemotactic signalling pathway. In the limiting cases of very fast and very slow adaptation kinetics the model equations reduce to the standard model which predicts cell movement opposite to the observed direction. Adaptation on an intermediate timescale, however, provides cells with a "short-term memory" of experienced chemoattractant concentrations which can fully account for the experimental observation of cell translocation opposite to the direction of propagation of the chemoattractant waves.

Keywords: Chemotaxis, *Dictyostelium*, receptor adaptation, mathematical model.

1. Introduction

The life cycle of the slime mould *Dictyostelium discoideum* consists of both single-cell and multicellular stages. Starvation triggers the progression from free-living amoebae to the formation of a multicellular fruiting body. Aggregation of large numbers of amoebae is directed by chemotaxis towards cyclic adenosine 3',5'-monophosphate (cAMP), which is produced by the amoebae themselves [3]. Periodic waves of cAMP propagate outwards from the aggregation centre at a speed of about 300 μm/min; the cAMP concentration profile of a single pulse is nearly symmetric [14]. Each cAMP pulse elicits a motile response. Amoebae move for about 100 s at a speed of 20–30 μm/min towards the aggregation centre. Movement then ceases until the next wave arrives.

The mechanism of chemotactic cell movement is a source of controversy. Experiments in steady cAMP gradients (at low absolute cAMP concentrations) have shown that cells are able to orient and move persistently in the direction of increasing cAMP concentration [4]. Assuming that the chemotactic drift velocity is determined in this fashion by the local cAMP gradient, one would observe during aggregation *in situ* that cells in the wavefront move opposite to the direction of wave propagation, whereas they reorient and move with the wave as the waveback is experienced. Because cells would remain longer in the waveback than in the wavefront, they should show some net translocation in the direction of wave propagation, that is, away from the aggregation centre. This is essentially what has been termed the "chemotactic wave paradox" [13].

Measurements *in situ* show that cells move in fact only in the wavefronts and remain more or less stationary in the wavebacks [11–13]. Thus *Dictyostelium* chemotaxis cannot solely be determined by the local cAMP gradient, and more complex mechanisms have to be invoked for an explanation. It is well known for the cAMP signalling system supporting wave propagation that cAMP not only activates its synthetic pathway; it also induces desensitization on a considerably slower time scale to that of the relay response, followed by resensitization as cAMP is withdrawn. This adaptation is a central component of models of the cAMP signalling system [7,8,14]. Relatively slow adaptation is also a property of the chemotactic pathway [3,10]. In the present paper we propose an extension of a classical continuum model for chemotaxis [6] which explicitly includes adaptation of the chemotactic pathway. We show that adaptation can fully account for the observed cell behaviour and thus provide a natural solution to the "chemotactic wave paradox".

2. The Model

We follow Keller and Segel [6] and model the flux of cells by the following expression

$$\boldsymbol{J} = \underbrace{-D\nabla n}_{\text{random dispersal}} + \underbrace{\chi n \nabla \gamma}_{\text{chemotaxis}}, \tag{1}$$

where n denotes the cell density and γ the chemoattractant (cAMP) concentration. The chemotactic flux is assumed to be proportional to the local gradient of the chemoattractant. The chemotactic coefficient χ measures the responsiveness of the cells to the chemotactic signal. To account for adaptation, in many models χ has been taken to be a decreasing function of the chemoattractant concentration γ [8]. Neglecting cell diffusion, Eq. (1) predicts convective cell movement with average speed $\chi(\gamma)\nabla\gamma$. Thus the cell velocity profile in a symmetric wave of the chemoattractant will also be symmetric, and the above paradoxical result of cell movement away from the aggregation centre will be obtained. Clearly, the problem with this model lies in the form of the chemotaxis term. The assumption of an instantaneous response of an amoebae to the cAMP gradient is reasonable, as the

motile machinery of a cell reacts within seconds to a cAMP stimulus [10]. (Actin polymerization, for example, peaks 3–5 s after the delivery of stimulus). Adaptation of the chemotactic pathway, however, takes place on a considerably slower time scale [3]. Therefore the sensitivity of a cell towards cAMP will depend on the cAMP concentrations experienced previously. The chemotactic coefficient χ will be a function of some measure of cellular sensitivity α, so that a more realistic expression for the cell flux should take $\chi = \chi(\alpha)$, where the time evolution of α will be governed by a *separate* equation. It is known that cAMP induces a slow transition of the cAMP cell surface receptors from an active into an inactive form [3,7]. We will therefore think of the cAMP receptors as the crucial desensitizing element. The sensitivity variable α will be identified with the fraction of active (i.e. non-desensitized) cAMP receptors per cell.

The mass balance equation governing the time evolution of the extracellular concentration of active receptors has to take into account the kinetics of adaptation and the flux of receptors. We neglect receptor diffusion in the cell membrane, since the formulation of the model implicitly involves averaging over a length at least one order of magnitude larger than a cell diameter in order to arrive at a continuous cell density. Thus the receptor flux has only a convective contribution $\alpha \boldsymbol{J}$. The extracellular concentration of active receptors is given in terms of their fraction per cell, α, by $\alpha n/(1 - nV_c)$, where V_c is the cellular volume. For low cell densities we can approximate this by αn, to obtain

$$(n\alpha)_t = nf(\alpha, \gamma) - \nabla \cdot (\alpha \boldsymbol{J}),$$

where $f(\alpha, \gamma)$ is the difference between the rates of resensitization and desensitization per cell. Aggregating amoebae do not proliferate and their death rate is negligible, so that the cell density is governed by

$$n_t = -\nabla \cdot \boldsymbol{J}. \tag{2}$$

Combining the two preceding equations one can derive the following equation for α:

$$\alpha_t = f(\alpha, \gamma) - \frac{\boldsymbol{J}}{n} \nabla \alpha. \tag{3}$$

Desensitization and resensitization involve interconversion of the cAMP receptor between an active and an inactive form, R and D, respectively. This can be represented by the following general scheme

$$R \underset{f_-(\gamma)}{\overset{f_+(\gamma)}{\rightleftharpoons}} D,$$

where a more complex reaction sequence can be hidden behind these overall reactions [7,11]. By the law of mass action, $f(\alpha, \gamma)$ takes the form

$$f(\alpha, \gamma) = -f_+(\gamma)\alpha + f_-(\gamma)(1 - \alpha), \tag{4}$$

where $R + D = R_T$ is assumed constant and α denotes the number of R receptors scaled with R_T. In the following we use the kinetic expression for cAMP receptor adaptation derived in [7]: $f_+ = \mu t_0^{-1}(1 + \kappa\gamma)/(1 + \gamma)$ and $f_- = \mu t_0^{-1}(L_1 + L_2\kappa c\gamma)/(1 + c\gamma)$, where μ, t_0, κ, L_1, L_2 and c are positive parameters.

The chemotactic response of a cell will depend on the number of active receptors. One can imagine that an appreciable response requires a minimal number of active receptors. On the other hand, for large numbers of active receptors the response might not increase linearly with α but, instead, show some "saturation". This can be accounted for by a chemotactic coefficient of the form

$$\chi = \chi_0 \frac{\alpha^m}{A^m + \alpha^m}, \quad m > 1. \tag{5}$$

Equations (1)–(5) model the motile response of a population of amoebae, capable of chemotactic adaptation, to an imposed chemoattractant pattern, $\gamma(x, t)$.

3. Analysis

We show that the model equations support cell movement towards the aggregation centre, that is, opposite to the direction of cAMP wave propagation. For simplicity, we consider (2)–(3) on a one-dimensional spatial domain $[0, l]$ and far away from the aggregation centre, where the curvature of the cAMP waves becomes negligible. Introducing (1), (4) and (5) into Eqs. (2)–(3), they take the form

$$n_t = \left(\delta n_x - \frac{\alpha^m}{A^m + \alpha^m}\gamma_x\, n\right)_x \tag{6}$$

$$\alpha_t = \mu\left(-\frac{1 + \kappa\gamma}{1 + \gamma}\alpha + \frac{L_1 + L_2\kappa c\gamma}{1 + c\gamma}(1 - \alpha)\right) + \left(\delta\frac{n_x}{n} - \frac{\alpha^m}{A^m + \alpha^m}\gamma_x\right)\alpha_x, \tag{7}$$

where cell density, cAMP concentration, time and length have been scaled by characteristic values n_0, γ_0, t_0 and $(\chi_0\gamma_0 t_0)^{-1/2}$, respectively. From experimental data we take $\gamma_0 = 10^{-7}$ M and $t_0 = 10$ min. The parameters for the receptor kinetics are taken from the cAMP signalling model [6,14], with μ ranging between 0.3 and 1.2 for the different parameter sets.

We impose a symmetric travelling wave in γ with speed v, $\gamma(x, t) = \gamma(x + vt)$. As we are not interested in boundary effects the boundary conditions are taken to be $\gamma = \bar{\gamma}$, $\gamma_x = 0$, where $\bar{\gamma}$ is the rest concentration of cAMP, that is, the wave does not reach the boundaries during an "integration experiment". Hence $\alpha = f_-(\bar{\gamma})/(f_+(\bar{\gamma}) + f_-(\bar{\gamma}))$, and $n_x = 0$, implying zero cell flux at the boundaries.

Available data from leukocytes (another amoeboid cell) suggest that $\delta = D/\chi_0\gamma_0 < 0.01$ [2], and, as we shall see below, variations in cell density are very small. Thus we can simplify Eqs. (6)–(7) by neglecting the diffusion terms ($\delta = 0$). Now (6)–(7) decouple, and $\alpha(x, t)$ can be obtained by solving (7). The characteristics of Eq. (6) (with $\delta = 0$), given by

$$\frac{dx}{dt} = \chi(\alpha(x, t))\gamma_x(x, t) \equiv \omega(x, t), \tag{8}$$

then yield the required information, as they describe the (average) cell paths in the chemoattractant landscape, where $\omega(x,t)$ is the velocity of cell migration. Finally, we can expect that, after an initial transient, α and n will take the form of travelling waves with speed v. Hence we can transform Eqs. (6)–(7) into ordinary differential equations in the independent variable $z = x + vt$. We then find the cell path by solving two ordinary differential equations, namely the travelling wave equation for $\alpha(z)$ and (8) (for details see [5]). In general this has to be done numerically. Furthermore, we obtain the travelling cell density profile explicitly,

$$n(z) = \frac{n_0 v}{v + \omega(z)}. \tag{9}$$

As $\omega \ll v$, the variations in cell density will be very small, in agreement with experimental observations [1].

If the adaptation kinetics were either very fast ($\mu \gg 1$) or very slow ($\mu \ll 1$), then we would have from (7), to a first approximation, $\alpha = f_-(\gamma)/(f_+(\gamma) + f_-(\gamma))$ and $\alpha = \bar{\alpha}$, respectively. In both cases the model equations reduce to the conventional Keller-Segel equation with $\chi = \chi(\gamma)$ obeying a "receptor law" (see e.g. [9]) and $\chi = \text{const.}$, respectively. As discussed above, both of these cases will yield net cell movement away from the aggregation centre. The interesting behaviour can be expected to occur on the intermediate time scale, $\mu = \mathcal{O}(1)$. This is illustrated in Fig. 1. It can be clearly seen that for $\mu = 1.0$, cells move in the gradient of the wavefront, desensitize and remain stationary in the waveback. Responsiveness is recovered before the next cAMP pulse arrives.

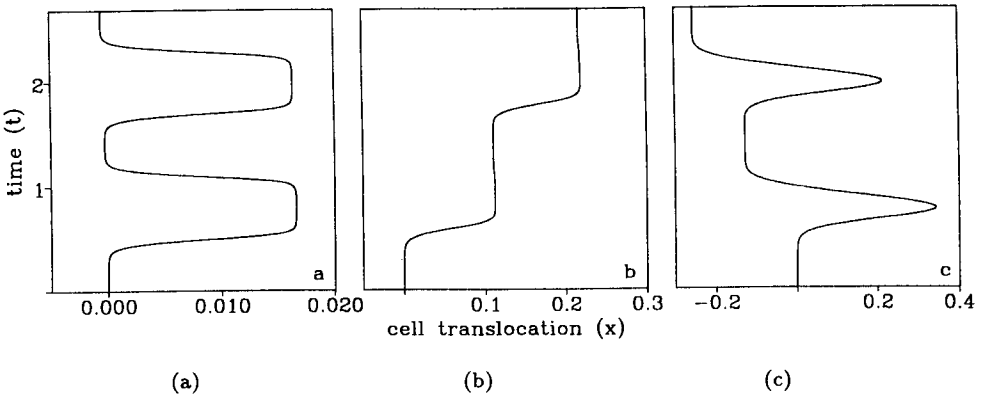

Fig. 1. Cell paths under the influence of two travelling cAMP pulses (dimensional period 10 min), moving from right to left; (a) $\mu = 10^3$, (b) $\mu = 1.0$, and (c) $\mu = 10^{-3}$. The cAMP waves travel from right to left with $v = 260$ μm/min, the concentration profile is modelled according to [14]. Parameter set C from [15] was used for the adaptation kinetics. For $\mu = 1.0$ cells only move in the wavefronts, and consequently their net translocation will be opposite to the direction of wave propagation. Contrast this with (a) and (c) which illustrate the "chemotactic wave paradox". The chosen value of the chemotactic coefficient, $\chi_0 = 11$ cm^2/M·s, which compares favourably with experimental values for leukocytes [2], yields the cell velocity observed experimentally.

4. Conclusion

Adaptation kinetics on an appropriate time scale equip *Dictyostelium* amoebae with a "short-term memory" of experienced cAMP concentrations which enables them to distinguish between front and back of symmetric waves of the chemoattractant. We find that this time scale should be roughly the same as for the adaptation of the cAMP relay response.

During slime mould aggregation, chemotaxis and cAMP signalling are interdependent processes: cell movement is governed by the local cAMP gradient, and cAMP production is dependent on the local cell density. The proposed chemotaxis-adaptation model combined with a model of the cAMP signalling dynamics can be expected to yield a realistic description of the aggregation process [16,17].

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