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A Resolution of the Chemotactic Wave Paradox

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Abstract—We propose an extension of the standard model for cell chemotaxis which explicitly accounts for the adaptation of the chemotactic response. We show that this model resolves the "chemotactic wave paradox" of slime mould aggregation in a natural way.

1. A CHEMOTAXIS MODEL INVOLVING ADAPTATION

Cell migration plays a central role in biological pattern formation. A widespread mode of cellular movement is (positive) chemotaxis: cells move up gradients in concentration of a chemical, called a chemoattractant. Keller and Segel [1] proposed the following expression for the chemotactic flux:

$$J = -D\nabla n + \chi n \nabla \gamma, \tag{1}$$

where n, γ, D and χ denote the cell density, chemoattractant concentration, cell diffusion and chemotactic coefficients, respectively. Based on (1), the standard model system for cell chemotaxis

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takes the form

$$n_t = p(n) - \nabla \cdot J, \tag{2}$$

$$\gamma_t = q(n, \gamma) + D_\gamma \nabla^2 \gamma, \tag{3}$$

where $p(n)$ and $q(n, \gamma)$ denote the cell proliferation and chemoattractant production kinetics, respectively, and D_γ is the chemoattractant diffusion coefficient. This model has been successfully applied to a variety of chemotaxis systems [2].

For one of the most-studied examples of chemotaxis, however, applicability of (1)–(3) is limited. This is the aggregation of amoebae of the cellular slime mould, *Dictyostelium discoideum*, a paradigm model system for biological pattern formation. On the one hand, the form of the chemotactic drift term in (1) is consistent with experimental data obtained in stationary, monotonic gradients of the chemoattractant, cAMP[1] [3]. Application of the model (1)–(3) to aggregation *in situ*, on the other hand, leads to a paradoxical result (the so-called "chemotactic wave paradox" [4]). Aggregation is directed by periodic waves of cAMP, travelling from the aggregation centre outwards and attracting the cells towards the centre. The concentration profile of a single cAMP pulse is nearly symmetric [5]. Thus, the chemotactic velocity profile under the influence of such a pulse, $\chi(\gamma)\nabla\gamma$, would also be approximately symmetric, resulting in cell movement opposite to the direction of wave propagation in the wavefront and with the wave in the waveback. As amoebae would remain longer under the influence of the waveback than of the wavefront, they would show some net translocation in the direction of wave propagation, *away* from the aggregation centre. Experimental measurements *in situ* demonstrate that amoebae move in fact only in the wavefronts and remain more or less stationary in the wavebacks [4,6]. Thus, the chemotactic cell response cannot solely be determined by the local cAMP gradient.

It is well known that the chemotactic machinery of slime mould cells, as well as many other chemotactic organisms, adapts to a given stimulus [7]. The molecular mechanisms of adaptation involve the desensitization of an element of the chemotactic signal transduction pathway by the chemotactic signal, followed by resensitization upon withdrawal of the chemoattractant. The chemotactic coefficient χ will, therefore, depend on some measure of cellular sensitivity towards the chemoattractant, α, that is, $\chi = \chi(\alpha)$. If the characteristic times for the adaptation reaction and the change in chemoattractant concentration are of comparable magnitude, the basic model (1)–(3) is not sufficient to describe the chemotactic response. It must incorporate the time dynamics of the sensitivity variable α. This is the case with slime mould aggregation, where both characteristic times are roughly of the order of 1 min [7]. In the following, we show that such an extension of the basic model can resolve the "chemotactic wave paradox" in a natural way.

To derive an equation governing adaptation, we need to be more specific about the underlying mechanisms. Although they are not completely understood in the case of slime mould chemotaxis, it is reasonable to assume that an adapting element of the chemotactic pathway (probably the cAMP cell surface receptor and/or associated G-protein) can be found in two conformations, active, R, and inactive (desensitized), D [7]. Binding of cAMP favours the $R \to D$ transition (desensitization), and generally also affects resensitization, $D \to R$, that is,

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

We now identify the sensitivity variable α with the fraction of the active component per cell, $\alpha = R/R_T$, where $R_T = R + D =$ constant. By the law of mass action, the adaptation rate per cell is

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

Neglecting diffusion of the active component within the cell, its flux has only a convective contribution, αJ. The mass balance for the extracellular concentration of the active component takes

[1]Cyclic adenosine 3'5'-monophosphate.

the form

$$(n\alpha)_t = nf(\alpha,\gamma) - \nabla\cdot(\alpha J). \tag{5}$$

Aggregating amoebae do not proliferate and their death rate is negligible, that is, $p(n) \equiv 0$ in (2). Combining (2) and (5), we have the following equation for α:

$$\alpha_t = f(\alpha,\gamma) - \frac{J}{n}\cdot\nabla\alpha. \tag{6}$$

We can imagine that an appreciable chemotactic response requires a minimal fraction of the adapting component to be in the active state. On the other hand, for a large active fraction of the component, the response will not increase linearly with α but, instead, show some "saturation." This can be accounted for by a chemotactic coefficient of the form

$$\chi = \chi_0 \frac{\alpha^m}{A^m + \alpha^m}, \qquad m > 1, \tag{7}$$

where χ_0 and A are positive constants. Equations (2) and (6), together with (1), (4) and (7) model the motile response of a population of amoebae, capable of chemotactic adaptation, to an imposed spatio-temporal chemoattractant pattern, $\gamma(x,t)$.

2. MODEL ANALYSIS

We shall 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) and (6) on a one-dimensional spatial domain $[0,l]$, and far from the aggregation centre, where the curvature of the chemoattractant waves becomes negligible. Introducing (1), (4) and (7) into equations (2) and (6), these take the form

$$n_t = \left(\delta n_x - \frac{\alpha^m}{A^m+\alpha^m}\gamma_x\, n\right)_x \tag{8}$$

$$\alpha_t = \mu\Big[-f_+\gamma)\alpha + f_-(\gamma)(1-\alpha)\Big] + \left(\delta\frac{n_x}{n} - \frac{\alpha^m}{A^m+\alpha^m}\gamma_x\right)\alpha_x, \tag{9}$$

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. For the adaptation kinetics, we use the kinetic expression derived for cAMP receptor adaptation in [8], namely $f_+(\gamma) = (1+\kappa\gamma)/(1+\gamma)$, $f_-(\gamma) = (L_1 + L_2\kappa c\gamma)/(1+c\gamma)$, where κ, L_1, L_2 and c are positive parameters. The parameter μ which, in a crude sense, determines the rate of adaptation, ranges between 0.3 and 1.2 for the different parameter sets analyzed in [9] (for a characteristic time of $t_0 = 10\,\text{min}$).

Instead of considering the chemoattractant production kinetics in detail, we simply impose a symmetric travelling wave in γ with speed v, $\gamma(x,t) = \gamma(x+vt)$. As we are not concerned with boundary effects, the boundary conditions are chosen as follows: $\gamma(0) = \gamma(l) = \bar\gamma$, $\gamma_x(0) = \gamma_x(l) = 0$, $\alpha(0) = \alpha(l) = f_-(\bar\gamma)/(f_+(\bar\gamma) + f_-(\bar\gamma)) \equiv \bar\alpha$ and $n_x(0) = n_x(l) = 0$, where $\bar\gamma$ is the rest concentration of cAMP. That is, the wave does not reach the boundaries during an "integration experiment," and cells do not leave the domain.

Available experimental data from other amoeboid cells suggest that $\delta = D/\chi_0\gamma_0 < 0.01$ [10], and, as we shall see below, variations in cell density are very small. Thus, we can simplify equations (8)–(9) by neglecting the diffusion terms ($\delta = 0$). Now (8)–(9) decouple, and $\alpha(x,t)$ can be obtained by solving (9). The characteristics of equation (8) (with $\delta = 0$), given by

$$\frac{dx}{dt} = \chi(\alpha(x,t))\gamma_x(x,t) \equiv w(x,t), \tag{10}$$

then yield the required information, as they describe the (average) cell paths in the chemoattractant landscape, where $w(x,t)$ is the velocity of cell migration. Finally, we can expect that,

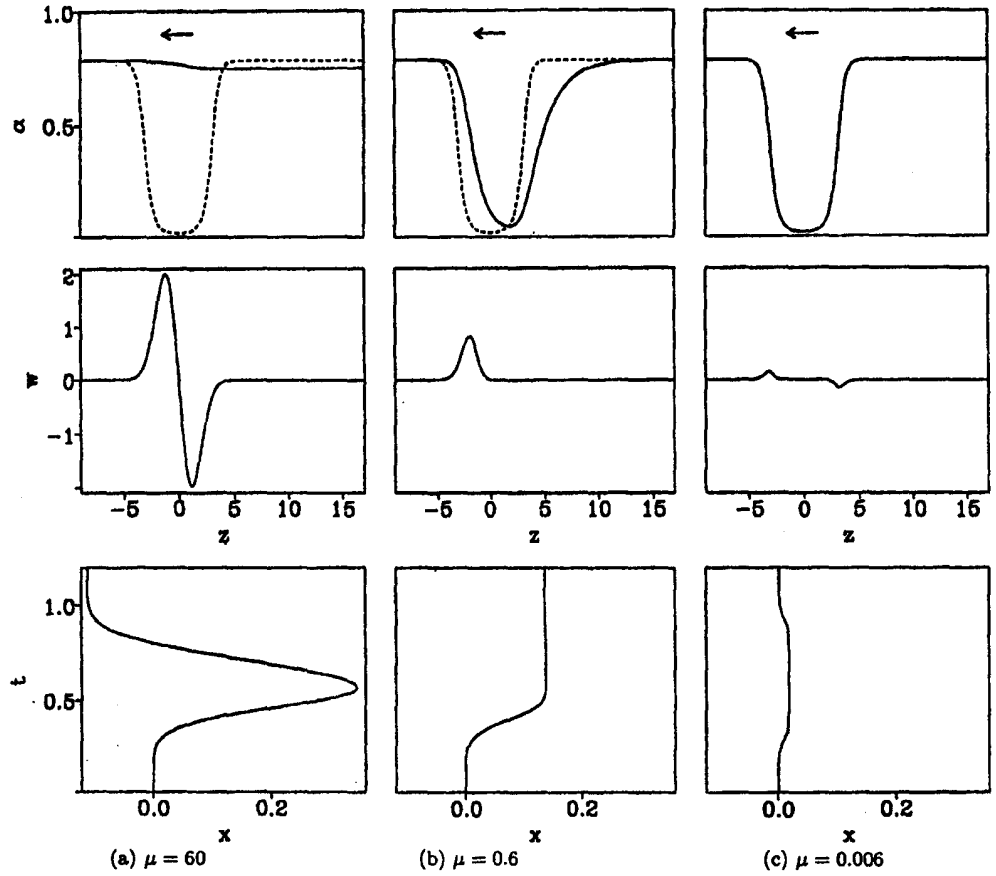

Figure 1. Active receptors, $\alpha(z)$, cell velocity, $w(z)$, and cell paths, $x(t)$, under the influence of a travelling cAMP pulse; (a) $\mu = 60$, (b) $\mu = 0.6$, and (c) $\mu = 0.006$. Direction of propagation, half-width and position of the cAMP pulse in the z-frame are indicated by direction, length and position of the arrows; the concentration profile is modelled according to [5], $v = 260\,\mu$m/min. Parameter set C from [9] was used for the adaptation kinetics; the broken line for $\alpha(z)$ indicates the quasi-steady state profile, corresponding to $\mu \to \infty$. For $\mu = 0.6$ cells only move in the wavefronts, and consequently their net translocation is opposite to the direction of wave propagation (essentially the same result is obtained for $0.3 < \mu < 1.2$). Contrast this with (a) and (c), which illustrate the "chemotactic wave paradox." The chosen dimensional value of the chemotactic coefficient, $\chi_0 = 10\ \mathrm{cm}^2/\mathrm{M}\cdot\mathrm{s}$, which compares favourably with experimental values for leukocytes [10], yields the cell velocity observed experimentally.

after an initial transient, α and n will take the form of travelling waves with speed v. Hence, we introduce the independent travelling wave variable $z = x + vt$. With suitable scaling of γ, the travelling wave equation for $\alpha(z)$ takes the form

$$\left(\epsilon\frac{\alpha^m}{A^m+\alpha^m}\gamma' + 1\right)\alpha' + \frac{\mu}{v}\Big[(f_+(\gamma)+f_-(\gamma))\alpha - f_-(\gamma)\Big] = 0, \qquad \alpha \to \bar{\alpha} \text{ as } z \to \pm\infty, \tag{11}$$

where $' \equiv \frac{d}{dz}$, and the small parameter $\epsilon = w_0/v \approx 0.1$ is the ratio of typical cell velocity, w_0, to wave speed.

The travelling cell density profile is given explicitly by

$$n(z) = \frac{n_0 v}{v + w(z)}. \tag{12}$$

As $w \ll v$, the variations in cell density will be very small, in agreement with experimental observations [11].

Determining the adaptation profile $\alpha(z)$ from (11) is the key step of the analysis, yielding in turn both the cell path and the cell density profile, from (10) and (12), respectively. Equation (11) is a regular perturbation problem as $\epsilon \to 0$, and its solution can be sought in the form $\alpha(z) = \alpha_0(z) + \epsilon\alpha_1(z) + \epsilon^2\alpha_2(z) + \cdots$. The (dominant) $\mathcal{O}(1)$ term is given by

$$\alpha_0' + \frac{\mu}{v}\Big\{\big[f_+(\gamma(z)) + f_-(\gamma(z))\big]\alpha_0 - f_-(\gamma(z))\Big\} = 0, \tag{13}$$

which has the solution $\alpha_0(z) = \bar{\alpha} + \exp\left\{-\frac{\mu}{v}F(z)\right\}\int_{-\infty}^{z}\frac{\mu}{v}f_-(\gamma(\xi))\exp\left\{\frac{\mu}{v}F(\xi)\right\}d\xi$, where $F(z) = \int^z \big[f_+(\gamma(\xi)) + f_-(\gamma(\xi))\big]\,d\xi$. Thus, $\alpha_0(z)$ is solely determined by the adaptation kinetics; the higher order terms account for the effect of convection. It can be seen from (13) that the effective rate of cell adaptation is given by μ/v, that is, the reaction rate over wave speed.

If the adaptation kinetics were either very fast ($\mu \gg 1$) or very slow ($\mu \ll 1$), we would have from (11), 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 standard model with $\chi = \chi(\gamma)$ obeying a "receptor law" (see, e.g., [2]) and $\chi =$ constant, 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 Figure 1. It can be clearly seen that for $\mu = 0.6$, cells move in the gradient of the wavefront, desensitize and remain stationary in the waveback. Responsiveness is recovered before the next cAMP pulse arrives.

3. CONCLUSION

When the characteristic times of the cell adaptation kinetics and of the changes in chemoattractant concentration are of the same magnitude (in our case $\mu/v = \mathcal{O}(1)$), qualitatively new phenomena can occur which cannot be captured by the standard chemotaxis model (1)–(3). In particular, adaptation provides cells with a "short-term memory" for chemoattractant concentrations. This allows slime mould amoebae to distinguish between front and back of symmetric chemoattractant waves and to choose their migration direction opposite to the direction of wave propagation. To investigate the relationship between cAMP signalling and motile response, we will combine the chemotaxis-adaptation model with a model of cAMP signalling; this will result in an integrated description of the aggregation process.

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