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Chemotaxis with directional sensing during *Dictyostelium* aggregation

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ABSTRACT

We show that the chemotactic movements of colonies of the starving amoeba *Dictyostelium discoideum* are driven by a force that depends on both the direction of propagation (directional sensing) of reaction-diffusion chemotactic waves and on the gradient of the concentration of the chemoattractant, solving the chemotactic wave paradox. It is shown that the directional sensing of amoebae is due to the sensitivity of the cells to the time variation of the concentration of the chemoattractant combined with its spatial gradient. It is also shown that chemotaxis exclusively driven by local concentration gradient leads to unstable local motion, preventing cells from aggregation. These findings show that the formation of mounds, which initiate multicellularity in *Dictyostelium discoideum*, is caused by the sensitivity of the amoebae due to three factors, namely, to the direction of propagation of the chemoattractant, to its spatial gradient, and to the emergence of cAMP "emitting centres", responsible for the local accumulation of the amoebae.

1. Introduction

Chemotaxis is the phenomenon in which cells or microorganisms direct their movement as a response to the local variation of the concentration of some chemical substance. For example, in colonies of *Dictyostelium discoideum* (Dd), localised groups of starving amoebae initiate the production of cyclic adenosine monophosphate (cAMP) that spreads in space as reaction-diffusion travelling chemical waves. In the vicinity of these spontaneously formed cAMP emission centres, the amoebae sense cAMP and direct their chemotactic movements towards the initiation centres [1]. Near these centres, amoebae rotate around a spontaneously formed hole (i.e. a zone depleted from cells), where the cell density increases locally to form aggregates (Fig. 1). At a later stage of development, aggregates are transformed into a simple multicellular organism with two main kinds of differentiated cells [2]. This is one of the simplest known mechanisms of transition from colonies of unicellular to multicellular organisms. For a detailed description of *Dictyostelium* aggregation and open questions on the involved biochemical mechanisms, see [2–4].

Experimental observations show that Dd cells move towards a region where cAMP chemical waves are produced, and the speed of cells is proportional to the slope or gradient of the concentration of cAMP [1,5]. On the other hand, it has been observed that cells move as long as the gradient is positive, when measured along the direction of the wave source [2,6]. "When the slope reverses, Dd cells stop moving and await for the next wave." [2, p. 101] This fact shows that the chemotactic cell response cannot solely be determined by the local cAMP gradient [7].

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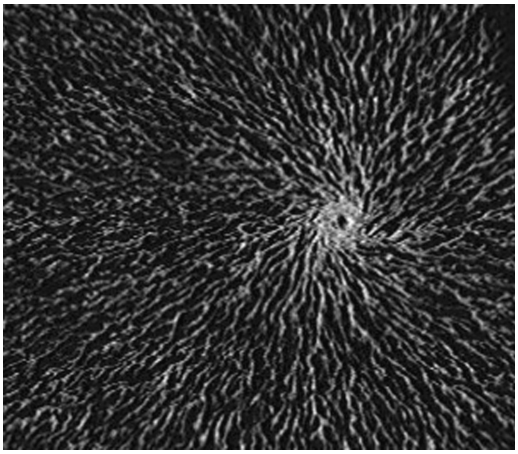

Fig. 1. Aggregation of a colony of *Dictyostelium discoideum* towards a spontaneously formed aggregation "centre". Near the aggregation centre, amoebae begin to rotate around a spontaneously formed hole. This hole is characterised by a depletion of cells. (Data from Christiane Hilgardt [25]).

Here, we investigate whether the force that drives the chemotaxis of Dd cells is solely proportional to the gradient of the chemotactic substance or whereas it also depends on the direction of propagation (directional sensing) of the time varying chemotactic signal.

If the chemotactic substance is produced at a localized source and disperses monotonically along space, the question of directional sensing is meaningless. However, if the chemoattractor propagates along space as periodically repeating wave, the hypothesis that the chemotactic motion of cells is driven by a local concentration gradient implies that the existence of a periodic variation in time of the direction of motion of the cells. This simple gradient hypothesis induces motion of the amoebae in the direction opposed to the source of the chemotactic signal, leading, asymptotically in time, to dispersive motion, preventing the amoebae from aggregation (Appendix A). This oscillatory behaviour in the aggregation pattern of *Dictyostelium discoideum* has never been observed and this effect is called the chemotactic wave paradox [7,8].

In the experimentally oriented literature, it is implicitly assumed that Dd cells are sensitive to the direction of propagation of the cAMP wave [9–12]. On the other hand, in simulation studies, it is generally assumed that cell chemotaxis is only driven by the sensitivity of the cells to the gradient of the chemotactic substance [13–17], and directional sensing is not included in models. Early studies have shown that the amoebae motility is also sensitive to temporal gradients [18]. However, sensitivity to temporal gradients have never been considered in mathematical models of *Dictyostelium* aggregation. One of the results we derive here (Appendix A) is that the introduction of directional sensing leads to the sensitivity to the temporal gradient of the chemoattractant.

Since we are interested in unravelling the importance of the effects of the gradient and of the directional sensing in the Dd aggregation phenomena, we will let the cells propagate in a cAMP concentration field with a prescribed dynamics. In this paper, we omit some well-known properties of Dd aggregation, like the fact that Dd amoebae produce and relay cAMP upon sensing of an external concentration of the chemoattractant [19], and the phenomenon of streaming [2]. While the production and relay of cAMP is necessary for the establishment of a gradient field of cAMP, these effects are independent of the mechanisms responsible for chemotaxis and directional sensing.

2. Chemotaxis with directional sensing

We denote by $X(x,y,t)$ the local concentration of some chemotactic substance. The equation of motion of an amoeba under the influence of a chemoattractant has the form:

$$m\ddot{\vec{r}} = -\lambda\dot{\vec{r}} + \vec{F}(X(x,y,t)) \tag{1}$$

where, as usual, the dots represent time derivatives, $\vec{r} = (r_x, r_y)$ are the spatial position coordinates of the amoeba, λ is a damping coefficient, m is the mass of the amoeba and $\vec{F}$ represents a generic chemotactic force field. The term $-\lambda\dot{\vec{r}}$ describes the damped motion of the cells and has been measured experimentally, [20].

As it is shown in the Appendix A, the direction dependent chemotactic force field is:

$$\vec{F} = \begin{cases} \overrightarrow{gradX} \quad if \quad \mathrm{sign}\left(\dfrac{\partial X}{\partial t}\right) > 0 \\ \vec{0} \quad if \quad \mathrm{sign}\left(\dfrac{\partial X}{\partial t}\right) \leq 0 \end{cases} \tag{2}$$

Introducing (2) into (1), the equations of motion of an amoeba under the influence of the chemotactic signal $X(x,y,t)$ are:

(i) if sign $(\frac{\partial X}{\partial t}) > 0$,

$$\begin{cases} m\ddot{r}_x &= -\lambda\dot{r}_x + \mu\dfrac{\partial X}{\partial x} \\ m\ddot{r}_y &= -\lambda\dot{r}_y + \mu\dfrac{\partial X}{\partial y}\,. \end{cases} \tag{3}$$

(ii) if sign$(\frac{\partial X}{\partial t}) \leq 0$,

$$\begin{cases} m\ddot{r}_x &= -\lambda\dot{r}_x \\ m\ddot{r}_y &= -\lambda\dot{r}_y\,. \end{cases} \tag{4}$$

The equations of motion (3)–(4) have been derived under the assumption that amoebae are sensitive to the direction of propagation of a chemotactic wave, together with the condition that if the slope of the gradient reverses sign, there is no chemotactic motility.

To describe the spatial variation of the chemoattractant $X(x,y,t)$, we consider the Ginzburg–Landau reaction-diffusion equation [21]:

$$\begin{cases} \dfrac{\partial X}{dt} &= \nu\bar{X} - \beta\bar{Y} + (\bar{X}^2 + \bar{Y}^2)(a\bar{X} - b\bar{Y}) + D_X\Delta X \\ \dfrac{\partial Y}{dt} &= \beta\bar{X} + \nu\bar{Y} + (\bar{X}^2 + \bar{Y}^2)(a\bar{Y} + b\bar{X}) + D_Y\Delta Y \end{cases} \tag{5}$$

where $\bar{X} = X - X^*$, $\bar{Y} = Y - Y^*$, $\Delta = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2}$ is the two-dimensional Laplace operator, D_X and D_Y are the diffusion coefficients, and ν, β, a, b, X^*, and Y^* are parameters. The functions X and Y represent chemical variables. In bounded two-dimensional domains with zero-flux