DYNAMICS of CELL and TISSUE MOTION

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Introduction

Self-organization is a fundamental widespread process occurring in morphogenesis, wound healing and population dynamics. For example, in embryology, cell-cell interactions play a key role in tissue formation and cell aggregation prior to the formation of structures, such as skeletal elements in the limb, or skin organ formation, such as hair, teeth and feathers. In wound healing, cells respond to external guidance cues, as well as orientation cues from each other, to move into a wound and effect its closure. In populations, aggregation may be essential for shelter, reproduction, safety, etc, or to resist starvation conditions.

Recent advances in biotechnology have led to a great increase in experimental data on the biochemical and mechanical aspects of cell-cell interactions and mathematical modelling has a crucial role to play in providing a theoretical framework in which to interpret this data, as well as investigating the potential of hypothesized interactions to account for experimental observations. In this way, modelling can help elucidate the underlying processes involved in aggregation phenomena. In turn, there is the need to develop more sophisticated mathematical modelling, and analytical and computational techniques to account for the detailed observations at the cellular level. Phenomenological models, such as those of reaction-diffusion type, which have played an essential role in understanding processes at a gross level, have to be replaced by more detailed models to reflect the complexity of the underlying processes.

This Chapter contains four contributions which illustrate a number of different types of interactions that can lead to self-organization in cell populations. The interactions can be due purely to cell-cell contact cues, or can be mediated through substances secreted by cells which effect the motion of other cells. The papers also illustrate a number of different modelling strategies, ranging from pure continuum models, to hybrid models with discrete, stochastic, or cellular automaton components.

The paper by Mogilner, Deutsch & Cook (III.1) reviews a number of recently proposed models by the authors which try to capture different aspects of the general problem of spatio-angular self-organization of cells by mutual interaction and successive (gradual or abrupt) alignment. The authors briefly present their modelling approach and simulation/analysis results for a common class of stochastic diffusion/migration processes with interactions, each elucidating a different level of approximation by a nonlinear evolution system. An integro-partial-differential equation system is presented in which the independent variables are space and orientation angle (as well as time). Linear stability analysis reveals the possibility that model simulations can lead to simultaneous spatial aggregation of cells and alignment. This type of model can be analysed using the orientation tensor approach

which approximates the full system by a system of reaction-diffusion-advection equations. It is shown that the model can exhibit total alignment. Finally, a stochastic model is considered using a lattice-gas cellular automaton approach.

The paper by Stevens & Schweitzer (III.2) models a very different type of cell-cell interaction, namely that of trail following wherein certain biological species, for example myxobacteria, can interact by laying down a substance that changes the substratum on which the bacteria are moving, thus influencing the motion of other bacteria. The model is based on a reinforced random walk description of cells moving on a two-dimensional lattice. The direction of motion is influenced by the concentration of the substance the cell experiences. Computer simulations of the model are presented, showing clustering, swarming and cell streaming. It is shown that this discrete interacting particle model can be approximated by a continuous model which can also exhibit the phenomena of blow-up and collapse.

A composite contribution follows (III.3), modelling cell streaming and aggregation in the slime mould *Dictyostelium discoideum*. Here, amoebae secrete the chemoattractant, cAMP, and aggregate under appropriate conditions. Three different approaches to modelling cell movement and chemical dynamics are presented together with simulations demonstrating that each model can account for the experimentally-observed phenomenon of cell streaming. At first, Dallon & Othmer describe a discrete-continuum model in which the chemoattractant concentration is modelled as a continuum field, while the amoebae are considered as discrete sources and sinks of the chemical. Model assumptions also include the adaptation of the cAMP signalling pathway. Simulations show spontaneous generation of spiral waves.

The model of Van Oss, Panfilov & Hogeweg is also of a hybrid discrete-continuum form but differs from that of Dallon & Othmer as it uses the model of Martiel & Goldbeter for cAMP relay and incorporates cAMP secretion and degradation via a discrete description of the amoebae. Analysis of the model shows the importance of the turnover rate of intracellular cAMP for cell streaming.

Höfer & Maini present a pure continuum model for *Dictyostelium* streaming and aggregation. This model shows behaviour consistent with two key experimental observations – first, during aggregation *in situ* the frequency of cAMP spiral waves increases while the speed of subsequent cAMP waves decreases; second, the appearance of a cell-free zone in the spiral core in the presence of caffeine which is thought to lower the excitability of the medium. This behaviour is also exhibited by the discrete-continuum hybrid models.

Finally, the paper by Savill & Hogeweg (III.4) considers a cellular automaton model in which cells are attached to each other by energy bonds which can be broken according to a certain probability function. By varying the key parameters, the model can simulate engulfment, cell dispersal and cell sorting. By coupling this model to a continuum model for chemical dynamics, it is shown that the composite model exhibits a number of key features. In particular, it can simulate a number of steps in the morphogenesis of *Dictyostelium discoideum*, including cell locomotion, mound formation, slug crawling, and cell sorting.

III.3

Models of *Dictyostelium discoideum* Aggregation

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Catelijne Van Oss, Alexandre Panfilov, Paulien Hogeweg (Utrecht)
Thomas Höfer, Philip K. Maini (Oxford)

1 Introduction

Philip Maini & Thomas Höfer

Since its discovery in the 1940's, the life cycle of the cellular slime mould *Dictyostelium discoideum* has attracted the interest of developmental biologists. It involves a relatively simple transition from unicellular to multicellular organization. Briefly, amoebae feed on bacteria in the soil and divide. Exhaustion of the food supply triggers a developmental sequence which leads, via cell aggregation, to the formation of a migrating slug-like "organism". The slug eventually culminates into a fruiting body, aiding the dispersal of spores from which, under favourable conditions, new amoebae develop. To date a variety of species in different taxonomic groups are known whose life cycles follow a similar pattern (Margulis & Schwartz 1988). Over the past fifty years, many of the molecular and cellular mechanisms which are involved in cell aggregation, collective movement and differentiation have been identified, and much work is devoted to the understanding of the interaction of these mechanisms in shaping *Dictyostelium* development. Mathematical modelling has proved a useful tool with which to study these interactions on a quantitative basis.

A typical aggregation sequence in *Dictyostelium discoideum* begins by the formation of concentric and spiral concentration waves of the extracellular messenger cyclic 3'5'-adenosine monophosphate (cAMP) which induce cell chemotaxis in periodic steps towards the aggregation centre (Alcantara & Monk 1974, Tomchik & Devreotes 1981). The onset of multicellularity is marked by the establishment of a branching pattern of cell streams in which direct cell-cell contacts are established.

The first attempt to develop a quantitative theory of slime mould aggregation was made by Keller & Segel (1970). They proposed a system of two coupled partial differential equations for the dynamics of the cell density, incorporating an advective chemotaxis term as suggested earlier by Patlak (1953), and for the change of cAMP. The emergence of aggregation centres is linked to a chemotaxis-driven instability in the model which leads to cell clustering. While this description appears to be valid for *Dictyostelium* species without periodic chemoattractant waves, such

as *D. minutum* and *D. lacteum*, the situation for *Dictyostelium discoideum* is now known to be more complex. Cohen & Robertson (1971a) developed a rule-based model of cAMP signal relay which accounted for its pulsatile wave-like character, and they considered cell movement in a subsequent paper (Cohen & Robertson, 1971b). Nanjundiah (1973) carried out a stability analysis of the Keller-Segel system on a circular domain with a signalling centre and found unstable "azimuthal" modes which he linked to the occurrence of cell streaming. cAMP signalling and cell movement was combined in the rule-based computer simulations of *Dictyostelium* aggregation by Parnas & Segel (1977, 1978) and MacKay (1978). In particular, the two-dimensional simulations by MacKay appear to be the first demonstration of cell streaming in an aggregation model.

While these earlier rule-based models largely relied on phenomenological observations on the aggregation dynamics, the elucidation of the molecular mechanisms of the cAMP signalling dynamics since the 1980's (e.g. Devreotes 1989 and references therein) was accompanied by the development of mechanistic models of cAMP signalling. The models incorporate the detailed biochemical dynamics of both the activation and desensitization of the adenylate cyclase pathway by binding of extracellular cAMP to its surface receptors, and concentrate in detail on the temporal aspects of signalling as revealed by experiments on stirred cell suspensions. The models essentially differ with respect to the presumed mechanisms of cAMP-induced desensitization. These include receptor phosphorylation (Martiel & Goldbeter 1987), desensitization through inhibition of adenylate cyclase via external calcium influx (Rapp *et al.* 1985, Othmer *et al.* 1985, Monk & Othmer 1989) and G-protein mediated desensitization (Tang & Othmer 1994, Goldbeter 1996). Although these and other mechanisms have been implicated by experiments, the question of which of these play the dominant role *in situ* remains a source of controversy. It is not unlikely that multiple mechanisms operate concomitantly (Van Haastert *et al.* 1992). Current evidence suggests that the G-protein mechanism is the primary one.

Incorporation of diffusion of extracellular cAMP into these models yields a description of the signalling dynamics in a stationary cell layer, which turns out to be a valid approximation for the situation at the beginning of aggregation (Tyson *et al.* 1989, Monk & Othmer 1990, Tang & Othmer 1995). With the help of these reaction-diffusion models, the experimentally observed cAMP waves have been characterized as a particular case of chemical wave patterns in so-called excitable media (Tyson & Murray 1989). However, the signalling models neglect cell movement and thus can not describe the actual aggregation process and in particular cell streaming.

This contribution consists of three models that couple cell movement with the chemical dynamics leading to cell streaming. The models of Dallon & Othmer (Sect. 2) and Van Oss *et al.* (Sect. 3) consider cells as discrete entities responding to a continuum field of chemoattractant concentration. Höfer & Maini (Sect. 4) model the cell distribution as a continuous density, coupled with the chemical dynamics.

2 A discrete cell model with adaptive signalling

John C. Dallon and Hans G. Othmer

In this section we describe a model in which *Dictyostelium discoideum* cells are treated as discrete points that detect and respond to the continuum field of the chemoattractant. This model, details of which can be found in Dallon & Othmer (1996) (I hereafter), is comprised of two main parts: (i) the mechanism for signal transduction and cAMP relay response, and (ii) the cell movement rules. The transduction of the extracellular cAMP signal into the intracellular signal is based on the G-protein model developed in Tang & Othmer (1994, 1995), and the reader is referred to those papers for details. The equations for the intracellular dynamics of the i^{th} cell can be written as a system of the form

$$\frac{d\mathbf{w}^i}{d\tau} = \mathbf{G}^i(\mathbf{w}^i, w_5), \tag{1}$$

where $w_5(\mathbf{x}, \tau)$ is proportional to extracellular cAMP, the components w_j^i, j = 1,$\cdots$,4, represent intracellular quantities in the signal transduction and cAMP production steps, and $\mathbf{w}^i$ is a vector of these four internal variables for the i^{th} cell. When the cells are treated as discrete points the evolution of extracellular cAMP is governed by the partial differential equation

$$\begin{aligned}\frac{\partial w_5(\mathbf{x},\tau)}{\partial \tau} &= \Delta_1 \nabla^2 w_5(\mathbf{x},\tau) - \hat{\gamma_9}\frac{w_5(\mathbf{x},\tau)}{w_5(\mathbf{x},\tau)+\gamma_8} \\ &\quad + \sum_{i=1}^{N} \frac{V_c}{V_o}\delta(\mathbf{x}-\mathbf{x}_i)\left(sr(w_4^i) - \gamma_7 \frac{w_5(\mathbf{x},\tau)}{w_5(\mathbf{x},\tau)+\gamma_6}\right).\end{aligned} \tag{2}$$

Here $\mathbf{x}_i$ denotes the position of the i^{th} cell, the first term represents diffusion of cAMP, the second represents the degradation of cAMP by extracellular phosphodiesterase, and the summation represents the localized sources and sinks of cAMP at the cells. The precise definitions of the variables and the parameter values can be found in Tang & Othmer (1995).

The second part of the model involves the cell movement rules, the following two of which are common to most of the simulations. They are (i) the cell moves in the direction of the gradient of cAMP when the motion is started; (ii) the cell moves at a speed of 30 microns per minute (Alcantara & Monk 1974). Various rules for initiating movement and determining its duration were explored.

As we show in I, formal rules based on a fixed duration of movement can produce aggregation. However, if the duration is too short aggregation does not occur, but by adding other mechanisms such as directional persistence the problem can be corrected. For example, when the duration is set at 20 seconds, which is the experimentally observed turning time (Futrelle *et al.* 1982), the cells do not aggregate successfully. By adding cell polarization (Varnum-Finney *et al.* 1987) or a memory of recently encountered gradients, the aggregation patterns are restored.

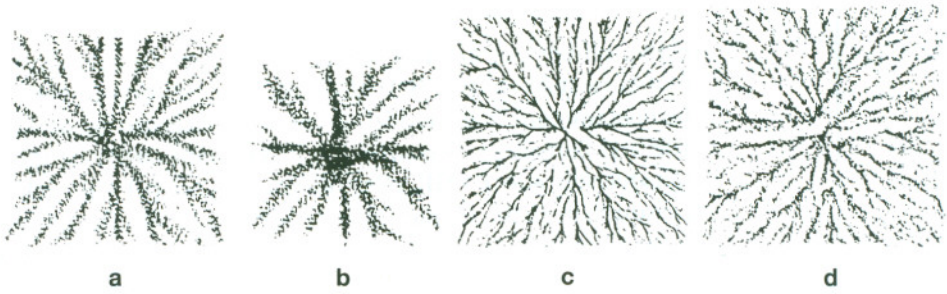

Figure 1: Aggregation patterns which formed with a pacemaking region at the centre and different rules for the duration of movement. Cells move for 100 seconds (a), 500 seconds (b), and according to an internal variable (c). In (d) the direction of movement is randomly perturbed by up to 90 degrees from the direction of the local gradient. All simulations are shown at 150 minutes. Eqn. 2 is solved using an Alternating Direction Implicit method with the intercellular variables lagged in time. The domain is 1 cm by 1 cm with 200 grid points in each direction. The number of cells used was 10089, each weighted by 16, which corresponds to a volumetric density of about 0.2.

Because the cAMP signal a cell sees is very rough, the cell may move away from the aggregation centre, and our simulations indicate that the cell must commit to a direction for a sufficient length of time to aggregate successfully.

These formal rules based on a fixed duration of movement ignore some essential biological facts. For example, if the profile of the cAMP wave is altered the 100 second rule used in Fig. 1a will certainly not be applicable. A detailed model of how a cell chooses the direction of motion and the length of a "run" is not available, nor would it be feasible to use such a model at present. However we have developed more realistic rules based on internal variables as follows. It is known (see I) that cAMP activates the cGMP pathway via G-proteins in addition to activating the cAMP production pathway (Newell *et al.* 1990). It is also known that cGMP is near the beginning of the chemotactic response pathway and that cGMP production adapts to the cAMP stimulus on a time scale of about 30 seconds. If cGMP adapts then downstream components will also adapt except in unusual circumstances, perhaps on a longer time scale. Thus we assume that there is a downstream "motion controller", the identity of which is not known. However, it must be used in such a way that the cell moves only when cAMP is increasing, for it is known that cells only move in the rising phase of the cAMP wave. In the absence of detailed information about the controller dynamics, we used as a stand-in a quantity in the cAMP pathway that has the appropriate time course. This mechanism is biologically more realistic than the *ad hoc* rules and it gives results which match very well with experimental results (cf. Fig. 1c). This

rule shows how a cell can respond to temporally-increasing cAMP levels by predicating motion on a threshold of an intracellular variable. Our simulations agree with the conclusion reached by Soll *et al.* (1993), that cells seem to orient during the beginning of the wave of cAMP and then move in a relatively blind fashion. We also show in I that aggregation is very robust under the combination of our signal transduction mechanism and the movement rule is based on an internal variable. For example, Fig. 1d shows that successful aggregation can occur as long as the cells choose their direction within the correct half space determined by the gradient and a line orthogonal to it. Our simulation indicates that many strategies can lead to successful aggregation.

This model also gives insight into the occurrence of target pattern waves *vs.* spiral waves. In particular we have found that spiral waves can arise spontaneously at higher densities when cells are initially distributed randomly, and that they may coexist with target patterns. This is in agreement with the results of recent laboratory experiments (Lee *et al.* 1996).

Finally, the simulations give a compelling argument that the mechanisms which are relevant in stream formation are finite amplitude instabilities. There are many factors involved in stream formation including random density variations, random cell parameter variations and variations in cell speeds. Each of these have a host of consequences which contribute to stream formation.

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3 Streams and spirals in a discrete cell model of *Dictyostelium* aggregation

Catelijne Van Oss, Alexandre Panfilov, Paulien Hogeweg

We have modelled the aggregation of *Dictyostelium discoideum* (*Dd*) considering the *Dd* cells as discrete points that move in a continuous cAMP field (Van Oss *et al.* 1996). In the model, the process of cAMP production is described by the Martiel-Goldbeter (MG) equations for cAMP relay (Martiel & Goldbeter 1987, Tyson *et al.* 1989). Discrete cells are added to the MG equations in the following way. The position of cell i in space is given by $\vec{R}_i(t) = (x_i, y_i)$. By using the delta function $\delta(\vec{r} - \vec{R}_i)$, where $\vec{r} = (x, y)$, we can write down the equations governing

cAMP production as follows:

$$\begin{aligned} \frac{\partial \rho}{\partial t} &= [-f_1(\gamma)\rho + f_2(\gamma)(1-\rho)] \sum_{i=0}^{N} \delta(\vec{r} - \vec{R}_i) \\ \varepsilon_i \frac{\partial \beta}{\partial t} &= [s_1 \Phi(\rho, \gamma) - \beta] \sum_{i=0}^{N} \delta(\vec{r} - \vec{R}_i) \\ \frac{\partial \gamma}{\partial t} &= D\nabla^2 \gamma + \tfrac{1}{\varepsilon_e}[s_2\beta - \gamma] \sum_{i=0}^{N} \delta(\vec{r} - \vec{R}_i), \end{aligned} \tag{3}$$

where $f_1(\gamma) = \frac{1+\kappa\gamma}{1+\gamma}$; $f_2(\gamma) = \frac{L_1 + \kappa L_2 c\gamma}{1+c\gamma}$; $\Phi(\rho, \gamma) = \frac{\lambda_1 + Y^2}{\lambda_2 + Y^2}$; $Y = \frac{\rho\gamma}{1+\gamma}$, $\rho(\vec{r}, t)$ is the fraction of active cAMP receptors, $\beta(\vec{r}, t)$ is intracellular cAMP, $\gamma(\vec{r}, t)$ is extracellular cAMP and N is the number of cells. Chemotaxis can be written as:

$$\frac{d\vec{R}_i}{dt} = \mu \vec{\nabla} \gamma(\vec{r}, t)\Big|_{\vec{R}_i}. \tag{4}$$

The parameter μ=0 if one of the following conditions is satisfied:

1. $\rho < 0.7$. In other words, to explain the fact that amoebae do not respond to cAMP gradients in the back of the cAMP wave, we assume that the chemotactic apparatus becomes desensitized as a result of prolonged $\text{cAMP}_{[ex]}$ stimulation.
2. $\vec{\nabla}\gamma(\vec{r}, t) < \theta$, where θ is a threshold value preventing motion towards very small gradients.
3. $\vec{R}_i(t + \Delta t) = \vec{R}_j(t + \Delta t)$, $i = 1, \ldots, N; i \neq j$, where Δt is the time step of the simulations. Two cells cannot be at the same position at the same time.

Otherwise, μ=1.

The results show that the parameter ε_i, which is inversely proportional to the turnover rate of internal cAMP, is important for the spatial pattern that arises. Cell streams do not form at the experimentally determined parameter setting used by Martiel & Goldbeter (1987) and Tyson *et al.* (1989) (Fig. 2a). However, if ε_i is decreased, streams do form (Fig. 2b). The smaller the value of ε_i, the faster the streams form and the more pronounced they are, culminating in the case where ε_i is so small that β can be assumed to be at quasi steady state and (1) reduces to two equations for ρ and γ ("the two-variable model"). In the simulations in which no streams were formed (ε_i is high), the speed of the cAMP wave does not depend on the cell density. Interestingly, the decrease in ε_i leads, in addition to stream formation, to a dependence of the cAMP wave speed on cell density: wave speed is high at high density and *vice versa*. Our hypothesis is that this dependence of wave speed on cell density is the underlying mechanism for stream formation (for further details see Van Oss *et al.* 1996). This view is supported by Vasiev *et al.* (1994), who showed that cell streaming in their (much more simplified) model

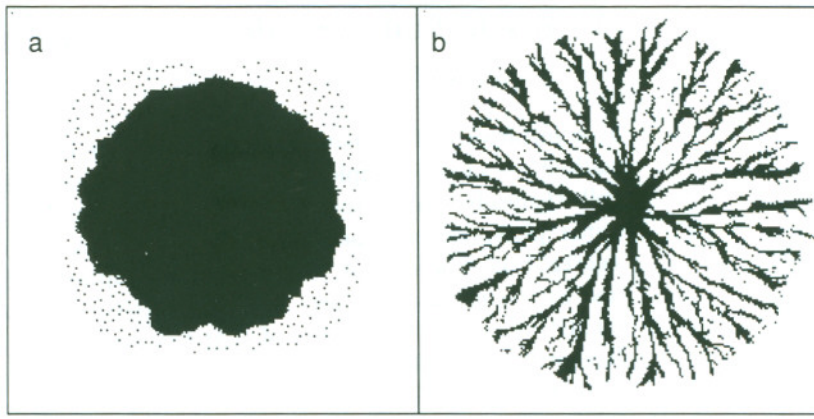

Figure 2: Aggregation in the model defined by Eqns. 3 & 4, (a) ε_i=0.019 and (b) ε_i=0.0038. Time $\approx$ 200 min. Cells are shown in black. Initially, cells are randomly distributed on a circular domain, stimulation occurs by periodically raising γ in the centre of the field, period 8.3 min. To integrate the explicit Euler method is used, space step 0.01 and time step 0.001 (space scale 4.5 mm, time scale 8.3 min), field size is 200 $\times$ 200 meshpoints $\sim$ 1 $\times$ 1 cm^2, boundary conditions are zero Dirichlet. The number of cells is $1.8{\cdot}10^4$, c=10, s_1=950, s_2=0.05, λ_1=10^{-3}, λ_2=2.4, κ=18.5, ε_e=0.002, L_1=10, L_2=$5{\cdot}10^{-3}$, D=0.01, θ=1.

of *Dd* aggregation is due to the density-dependent wave speed. Experiments of Siegert & Weijer (reported in Van Oss *et al.* 1996) on the aggregation phase of *Dd* show that the speed of the cAMP wave at high cell density is higher than at low density, indicating that wave speed is indeed dependent on cell density. The stability analysis of the cell distribution carried out by Höfer & Maini (see Sect. 4) is derived from a two-variable caricature of Eqn. 3 which does not contain the parameter ε_i. An interesting open question concerns the role of ε_i in the stability criterion if a similar analysis was made of Eqn. 3.

Besides aggregation due to concentric waves, we also studied aggregation due to a spiral wave. Simulations (using the two-variable model) show that the spiral wave behaviour depends strongly on the initial cell distribution and shows a great amount of variability. The spiral wanders or anchors, sometimes breaks up and forms several spirals or a double-armed spiral, or an empty (no cells present) core is formed around which the spiral rotates. This diverse behaviour of the spiral wave, which is also observed experimentally (Durston 1973, 1974) is due to the continuously changing excitable medium, which is caused by chemotaxis. During aggregation, the increasing cell density (and thus increasing excitability) in the aggregation centre leads to the experimentally often observed (Gross *et al.* 1976, Siegert & Weijer 1989) decrease in spiral wave period.

4 A continuum model of slime mould aggregation

Thomas Höfer and Philip K. Maini

It is intuitively clear that the dynamics of the cell distribution and of cAMP signalling are closely coupled: cell movement is induced by the cAMP waves, while cells themselves act as sources for extracellular cAMP and also for its degrading enzyme, phosphodiesterase; hence they also act as cAMP sinks. Thus a model of the aggregation process must 1. include a description of (chemotactic) cell movement and the resulting dynamics of the cell distribution, and 2. extend the model of the cAMP dynamics to the case of spatially and temporally varying cAMP sources. Recently, this problem has been tackled in two different ways. The first approach consists in modelling discrete cells equipped with cAMP-dependent movement rules and coupled to a finite-difference approximation for the continuous cAMP dynamics (Dallon & Othmer 1996, Van Oss *et al.* 1996, Kessler & Levine 1993). In a second approach, the cell distribution is approximated by a continuous density, resulting in a system of coupled partial differential equations for the cell density and the cAMP dynamics. (Vasiev *et al.* 1994, Höfer *et al.* 1995a,b). Höfer *et al.* (1995a) propose the following continuum model of the aggregation process

$$\frac{\partial n}{\partial t} = \nabla \cdot (\mu \nabla n - \chi(v) n \nabla u) \tag{5}$$

$$\frac{\partial u}{\partial t} = \lambda[\phi(n) f_1(u,v) - (\phi(n) + \delta) f_2(u)] + \nabla^2 u \tag{6}$$

$$\frac{\partial v}{\partial t} = -g_1(u) v + g_2(u)(1 - v), \tag{7}$$

where n, u and v denote cell density, extracellular cAMP concentration and fraction of active cAMP receptors, respectively. The cell density dynamics (Eqn. 5) include random cell movement with a cell diffusion coefficient μ, and chemotactic drift in gradients of cAMP. The magnitude of the chemotactic response is assumed to depend on the cellular sensitivity towards cAMP, measured by the fraction of active cAMP receptors per cell. Accordingly, the chemotactic coefficient is taken to be of the form $\chi(v) = \chi_0 v^m/(N^m + v^m)$, $m > 1$ (Höfer *et al.* 1994). The following functional forms are used for the rates of cAMP synthesis and degradation per cell: $f_1(u,v) = (bv + v^2)(a + u^2)/(1 + u^2)$, and $f_2(u) = du$. These are somewhat simplified versions of the kinetic terms derived by Martiel & Goldbeter (1987). The cell density dependence of the local rates of synthesis and degradation is reflected in the factor $\phi(n) = n/(1 - \rho n/(K + n))$. Similarly, the rate functions of receptor desensitization and resensitization are simplified expressions of the corresponding terms in the Martiel-Goldbeter model, $g_1(u) = k_1 u$, and $g_2(u) = k_2$.

This relatively simple continuum model yields a good description of the key features of the aggregation process. A typical aggregation sequence is shown in Fig. 3. Linear stability analysis predicts the break-up of the initially homogeneous cell density distribution perpendicular to the direction of wave propagation on

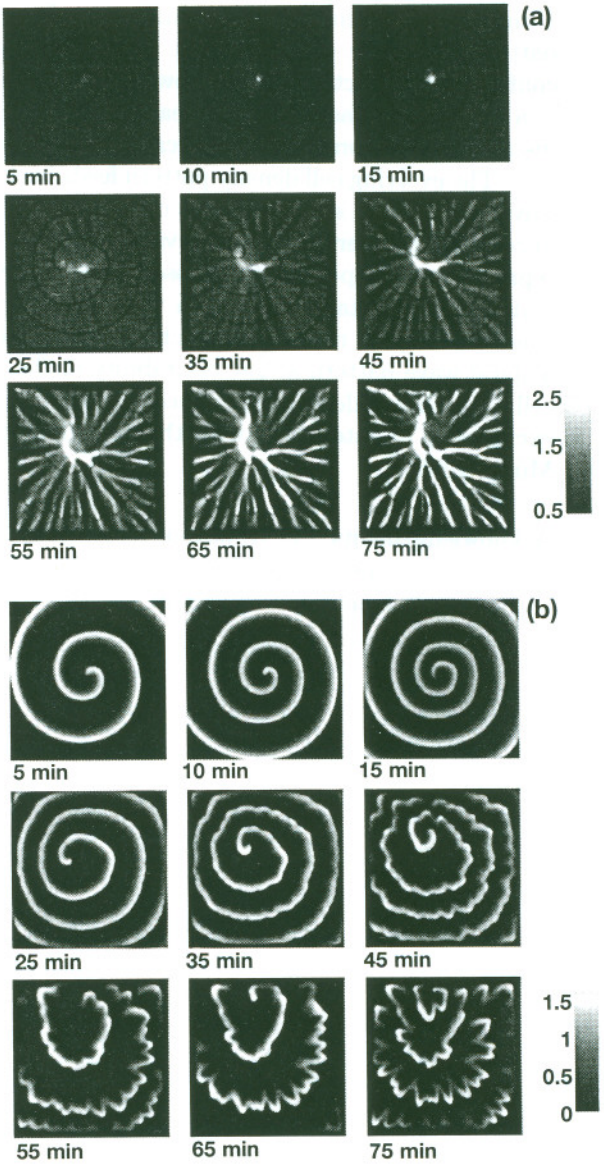

Figure 3: Spatio-temporal evolution of (a) cell density, and (b) cAMP concentration in a numerical simulation of system (5)–(7). The dimensional domain size is 6.5 mm × 6.5 mm, and snapshots are taken at the times indicated. Initial conditions were chosen to be a plane wavefront with a free end at the centre of the domain and homogeneous cell density (1.0) with a random perturbation between -0.075 and 0.075 added at every mesh point. Boundary conditions are zero-flux. Parameter values: $\lambda = 70.0$, $a = 0.014$, $b = 0.2$, $\rho = 0.7$, $K = 8.0$, $d = 0.0234$, $\delta = 0.11$, $k_1 = k_2 = 2.5$, $\mu = 0.01$, $N = 1.2$, $\chi_0 = 0.5$, $A = 0.72$, and $m = 10.0$.

a characteristic length scale, causing the formation of a branching cell stream pattern, cf. Höfer *et al.* (1995b). Detailed computational studies (unpublished) confirm the prediction of the growth of a small-amplitude pattern in cell density in a quantitative fashion. The linear analysis of a model caricature gives an explicit instability criterion which is typical of a chemotaxis-driven instability.

The evolving cell density pattern feeds back into the cAMP wave dynamics, as wave propagation speed depends on cell density. This can explain two apparently unconnected experimental observations (Höfer *et al.* 1995a,b). First, the model reproduces the experimentally observed decrease in cAMP wave propagation speed and the concomitant increase in wave frequency as a cAMP spiral evolves with time. Second, the model predicts the formation of closed cell loops in the centre of a spiral wave pattern at low excitability of the medium. The formation of central cell loops has indeed been induced by the application of caffeine, which lowers excitability by interfering with the adenylate cyclase pathway (e.g. Steinbock & Müller 1995).

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