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COMPUTER SIMULATION OF AGGREGATION IN *DICTYOSTELIUM DISCOIDEUM*

STEVEN A. MACKAY
Department of Biophysics and Theoretical Biology, University of Chicago, Chicago, Illinois 60637, *U.S.A.*

SUMMARY

The aggregation phase of development of the cellular slime mould *Dictyostelium discoideum* is simulated on a computer. The simulation is performed in 2 dimensions, and produces animated graphical output similar to time-lapse films. It is based on observations of cell behaviour as expressed by a set of rules for each cell, involving cell movement and release of and response to chemical signals. Following these rules, the simulation has reproduced many observed aggregation patterns: propagating waves of cell movement; formation of branching streams; entrainment of slower centres; and spiral centre formation. The simulation has proved to be an important adjunct to experimental work.

INTRODUCTION

A primary goal of developmental biologists is the understanding of the control of developing tissue. One approach used in reaching this goal is to explain how activities of individual cells (growth, cell division, movement, secretion, differentiation, etc.) produce spatial and temporal organization (Robertson & Cohen, 1972). A basic idea behind this approach is that if it is possible to specify the rules governing the behaviour of a given cell, then the observed global, multicellular behaviour can be explained by superposition of the individual cell activities. Thus, the first step in this approach is to devise a set of rules, consistent with observation, which govern the behaviour of individual cells and their responses to changing external conditions. This set of rules comprises the system *model*, and the transformation of this model into a structure suitable for execution on a computer is *simulation* (Zeigler, 1976). The output of a well designed simulation should be comparable with the real behaviour that the model is attempting to explain. In this way, simulation becomes a tool for checking the *validity* of the model upon which it is based. But effective simulation will not impose structures or behaviours not present in the original model. If the simulation is to be a tool for comparing different models, or for determining the effects of altering parts of a model, the structure of the simulation programme must allow for easy implementation of the new models.

Several simulations have been developed to study biological systems. For example, a 1-dimensional simulation has been used in studies of algae and *Hydra* (Herman & Shiff, 1975), and is based on the concept of linear iterative arrays. Using a model incorporating the activities of cell division, flattening and differentiation, Bezem & Raven (1975) presented a simulation of early embryonic development. These studies

adopt the approach described above of attempting to explain multicellular behaviour in terms of the activities of individual cells.

In the cellular slime moulds, these activities exist in simple form, with growth, differentiation and cell division well separated temporally from movement and secretion (Bonner, 1967), yet the organisms progress through a complex and interesting morphogenesis. One phase of morphogenesis, *aggregation*, has been extensively studied in one species, *Dictyostelium discoideum*.

In the laboratory, *D. discoideum* cells feed on bacteria, either on agar plates or in suspension culture. The cells grow and divide until the bacteria are withdrawn (by washing and centrifugation) and starvation appears to be the trigger for subsequent development (Loomis, 1975).

After approximately 9 h, aggregation begins. In time-lapse films of aggregating amoebae, *waves* are seen propagating outward from *centres*. These waves are regions of coordinated, inward cell movement. Thus, cells eventually form *aggregates* near the centres. The central part of the aggregate forms a *tip*, and eventually a *slug*, with the tip at the anterior end. After a period of migration, a fruiting body is erected, the head of which contains spores. Under favourable conditions, the spores will germinate to form new amoebae.

Relatively simple models have been developed describing how the behaviour of individual slime mould cells interacts to cause the patterns seen in aggregation. Simulation of these models and comparison of the simulation output with observed aggregation patterns can be useful for hypothesis testing. In this paper, simulations are described which examine some factors affecting wave propagation and centre behaviour during aggregation of *D. discoideum*. The simulations are based on variations of the model described below.

SYMBOLS USED IN TEXT

C	Concentration of cAMP	r	Distance from a source of cAMP
D	Diffusion constant of cAMP	t	Time elapsed since the release of a pulse of cAMP
K_m	Michaelis-Menten constant for PDE	τ_0	K_m/V_{max}
∇C	Spatial gradient of cAMP concentration	V_{max}	Maximum activity of PDE
η	No. of molecules in a pulse released by a cell		

DESCRIPTION OF THE MODEL

Aggregation is mediated by the release of and response to a *chemical signal*, 3′-5′-cyclic adenosine monophosphate (cAMP) (Konijn, Van de Meene, Bonner & Barkley, 1967; Robertson, Drage & Cohen, 1972). The concentration profiles of cAMP are determined by diffusion away from the sources and by degradation by a phosphodiesterase (PDE) enzyme released by the cells (Chang, 1968). The rate of PDE secretion depends on cell density (Gingle, 1976).

Interphase, the period before aggregation, begins when the cells are separated from their food source. During interphase, the cells move about randomly, without forming

significant cell–cell contacts. Also during interphase, the cells develop *competences* required for later activity. Before aggregation can begin, the cells must be able to: (*a*) respond chemotactically to cAMP (Robertson & Cohen, 1974) and (*b*) release a pulse of cAMP in response to a sufficient stimulus (*relaying*) (Gingle & Robertson, 1976).

The *chemotactic response* is a movement step by the cell of about 20 μm over a period of about 100 s (Cohen & Robertson, 1971*b*; Alcantara & Monk, 1974). Several explanations of the nature of the *chemotactic stimulus* have been offered: a concentration threshold (Cohen & Robertson, 1971*a*); a spatial concentration gradient threshold (Mato, Losada, Nanjundiah & Konijn, 1975; Nanjundiah & Malchow, 1976); a temporal gradient (Parnas & Segel, 1977; Gerisch & Hess, 1974). This model assumes that cells are stimulated to move by a cAMP concentration above a threshold of 10^{-9} M, and oriented by the direction of the maximum spatial gradient. An investigation is in progress to determine the effects of using other rules for chemotaxis.

The *relaying response* consists of: (*a*) a delay period of about 12–15 s between receipt of the signal and beginning of the movement step (Alcantara & Monk, 1974); (*b*) the release of a pulse of cAMP of about 6×10^6–10^7 molecules (Roos, Nanjundiah, Malchow & Gerisch, 1975; Grutsch, 1977), postulated to take place about the time of the beginning of the movement step (Cohen & Robertson, 1971*a*); and (*c*) a refractory period during which the cell is insensitive to further stimulus. The existence of the refractory period is necessary to account for the unisensal propagation of waves (Cohen & Robertson, 1971*a*), since cells do not sense reflexion of their signal from their nearest neighbours. The length of the refractory period declines from 10 to about 2 min (Robertson & Drage, 1975). Relaying is stimulated by a concentration above about 8×10^{-9} M (Gingle, 1976; Grutsch, 1977).

The *action of the PDE and diffusion away from the source* cause the concentration of cAMP to decrease with distance from the signalling cell. At a certain distance, the *relaying range*, the concentration falls below the relaying threshold. If the average distance between cells is greater than the relaying range, long-range relaying cannot occur. Since the intercell distance is related to cell density, there exists a *critical density* below which relaying is not seen (Konijn & Raper, 1961; Cohen & Robertson, 1971*a*; Gingle, 1976).

Certain areas of a field of cells, called *pacemaker regions* (Durston, 1974) are the origins of the signalling phenomenon, and become aggregation centres. Centres pulse signals at different frequencies, giving rise to behaviours observed on films, e.g. *gating* of centres by the refractory period of the field (only every other pulse being propagated), *entrainment* of slower centres by faster ones, etc. (Durston, 1974). There are 2 types of pacemakers; those which propagate *concentric circular waves*, and those which propagate spiral waves (Gerisch, 1965).

DESCRIPTION OF SIMULATION

A system has been designed to simulate this model of *D. discoideum* signalling behaviour. Typically, 1000 cells are randomly distributed within a circle in 2 dimen-

sions. This number of cells is characteristic of that in an actual 'small drop' experiment (Konijn & Raper, 1961). The drop has a diameter of up to 1 mm, which when displayed on the CRT screen of our DEC PDP 11/40 GT-44 graphics system corresponds to 1 μm per screen position. Cell densities involved are thus between 5×10^4 and 2×10^6 cells/cm^2, which are in the range for normal aggregation. The cells are considered to be 10 h into interphase, so that all are able to move and relay in response to signals (Gingle & Robertson, 1976).

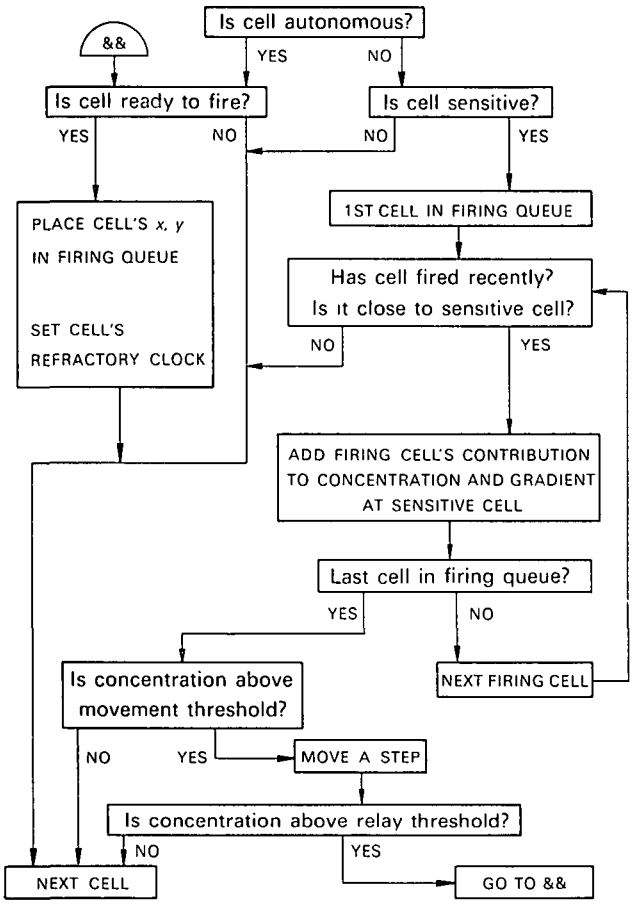

Fig. 1. Simulation algorithm for one cell (see text for details).

One or more cells are chosen to pulse the signal autonomously. The periods of these centres range from 2 to 7 min as measured in films of real centres (Durston, 1973; Gross, Peacey & Trevan, 1976). All the other cells are able to respond to the signals from these centres by chemotaxis or relaying, depending upon the local cAMP concentration. After a cell has responded to a stimulus above relaying threshold, it becomes refractory. All cells have the same refractory period at a given time. This does not imply that all cells are at the same *phase* in their refractory cycle, for each cell becomes refractory as soon as it is stimulated, and this response is independent of the

response of all other cells. The refractory period of all the cells decreases with age, as has been measured (Robertson & Drage, 1975).

All cells follow an identical algorithm describing their behaviour (Fig. 1). The state of each cell is represented by the current x,y position and the time when the cell was last signalled. The cell first calculates the elapsed time since it was last signalled, and if this time is greater than the refractory period, it tests whether at its position there is a concentration of cAMP above either the chemotactic or the relaying threshold. If this concentration is above the chemotactic threshold, the cell moves 20 μm in 100 s in the direction of the maximum cAMP spatial gradient. If above the relaying threshold, the cell becomes refractory, undergoes a delay period of 15 s, releases a pulse of cAMP, then makes the movement step. In addition all cells continually have a component of random motion, with mean velocity of 5 μm/min corresponding to a diffusion constant (Gail & Boone, 1970) of 4×10^{-8} cm^2/s, as measured in films of actual slime mould amoebae (R. K. Raman & L. E. King, unpublished observations).

The diffusion of the cAMP signals from firing cells and the continual degradation of cAMP by PDE follow values reported by Cohen & Robertson (1971*a*, *b*), as extended by Gingle (1976). An analytic solution of the diffusion equation has been used, assuming hemispherical diffusion of cAMP into the substrate and standard first-order Michaelis-Menten enzyme kinetics. The quantity $\tau_0 = K_m/V_{max}$ gives a measure of PDE activity. In order to use the analytic solution, the cells are assumed to be point sources of cAMP and the pulse is assumed to be an instantaneous delta function. The solution thus obtained is then fitted to measured relay ranges. If the number of molecules released by one cell is η, and the diffusion constant of cAMP is D, then the concentration of cAMP at a distance r from the firing cell and time t after the cell has fired is (Gingle, 1976):

$$C(r,t) = \frac{\eta}{(4\pi Dt)^{\frac{3}{2}}} \exp(-r^2/4Dt)\exp(-t/\tau_0). \tag{1}$$

The spatial gradient can be calculated from equation 1:

$$\vec{\nabla}\mathrm{C} = \frac{-2C}{4Dt}\vec{\mathrm{r}}. \tag{2}$$

When a cell is stimulated to release a pulse of cAMP, the simulation places that cell's current location and firing time as an x,y,t triple on the firing *queue*. Cell triples are continually added to the end of the queue as they fire, so as simulation time proceeds, the queue grows. However, after a certain time has elapsed since a cell has fired, the strength of its signal is everywhere negligible ($< 0{\cdot}1\%$ relaying threshold) because of diffusion and degradation. Thus, cell triples which have been on the firing queue a certain amount of time are removed from the front of the queue.

When a cell determines that it is sensitive to detect cAMP signals, it evaluates equations 1 and 2 using each cell on the firing queue as a source. The contribution from each of these cells is summed and the resultant concentration and gradient values are used by the simulation to guide the actions of that detecting cell. Thus,

instead of examining all other cells, a detecting cell need only perform the concentration calculations for those other cells which will make a non-trivial contribution to the signal at its location. Such computational optimizations have been essential for the performance of these simulations on our equipment. These changes are somewhat model-dependent, however, and therefore some trials have been made to determine what effects these optimizations have on the simulation output. Results indicate that for the types of simulations already produced, the effects are insignificant, but that for some proposed simulation experiments (e.g. testing effects of the duration of the released pulse), the optimizations will have to be abandoned, and the simulations run on a faster computer.

It is desirable to develop the simulation so that the output can easily be compared with the actual behaviour. In our laboratory, most of the information regarding slime mould aggregation behaviour is gathered from time-lapse films (taken at 2–8 frames per min) of fields or drops of *D. discoideum* cells. Much of the behaviour studied by this simulation is not of a static nature, that is, visible in one frame of a film, but of a dynamic nature, that is, visible only over several frames or when the films are moving. Thus the output of the simulation is in the form of graphical animations.

The typical simulation animation consists of about 400 frames, and is displayed on our CRT screen at 18 frames per s. In each frame, the x,y coordinates of each cell are plotted as a point. Additional information about the cell (firing status, refractory state, etc.) is indicated by variation in the intensity of the dot. Each frame of the simulation corresponds to 20 s of real time, so that the resulting animation is directly comparable to the time-lapse films in our library.

Some phenomena in the simulation occur over the duration of several frames, such as the 100-s movement step. However, most critical phenomena in the simulation concern the dynamics of wave propagation and signal detection, which occur on a time scale much less than a frame. The speed of the chemical diffusion has been analysed to determine that these processes must be evaluated with a time grain of about 200 ms to constitute a sufficiently accurate representation. Therefore, at each cell the cAMP concentration and its spatial gradient are computed by integrating the contributions from all the other cells once in a *subframe*, where there can be up to 100 subframes per animation frame. Hence, the clock that governs all internal aspects of the simulation is advanced in subframe units (Fig. 2).

The result of the simulation computation phase is a large data file, containing the x, y position of each cell and its basic status of firing, for each animation frame. Another procedure in the overall simulation system generates from this file another large file containing the display code for each animation frame. A special real-time playback utility programme (Potel, 1977) has been designed to show these sequences of display frames back at animation rates. Playback may be at variable speeds either forwards or in reverse. The animations thus produced are directly comparable to time-lapse films of real aggregation.

Table 1 is a summary of the parameters used in the simulation, and gives some typical values.

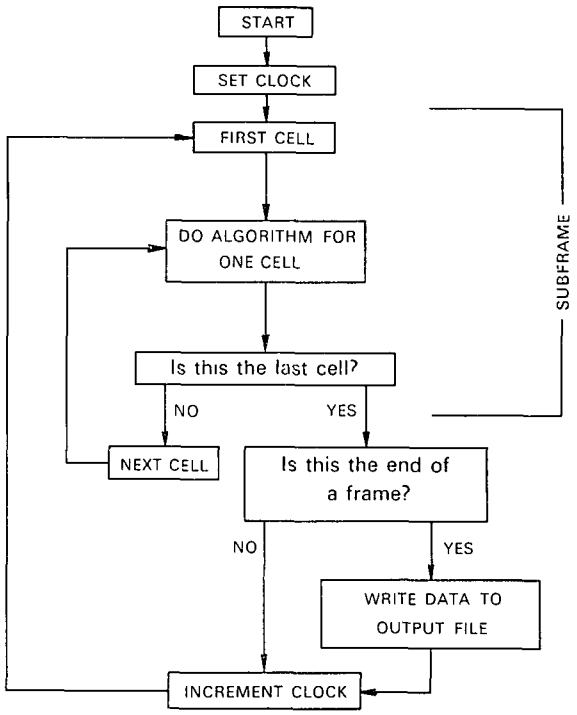

Fig. 2. Algorithm for one frame of simulation.

Table 1. *Simulation parameters*

Parameter	Typical value
No. of molecules released by a cell	10^7
Diffusion constant of cAMP	$9{\cdot}7 \times 10^{-6}$ cm^2/s
$\tau_0 = K_m/V_{max}$ mean cAMP lifetime (a measure of PDE activity) varies with cell density	1–10 s
Threshold for relaying	8×10^{-9} M
Threshold for chemotaxis (direction given by maximum spatial gradient)	10^{-9} M
Delay time for relaying	15 s
Refractory period for relaying (decreases with age)	10–3 min
Refractory period for chemotaxis	100 s
Chemotactic step	20 μm in 100 s
Random motion speed	5 μm/min
No. of cells	Up to 1600
Area	Up to 1 mm^2

SIMULATION RESULTS

An important use of simulations is the validation of the models upon which they are based (Zeigler, 1976). The results obtained from this simulation show that the model outlined above is sufficient to produce many of the observed slime mould

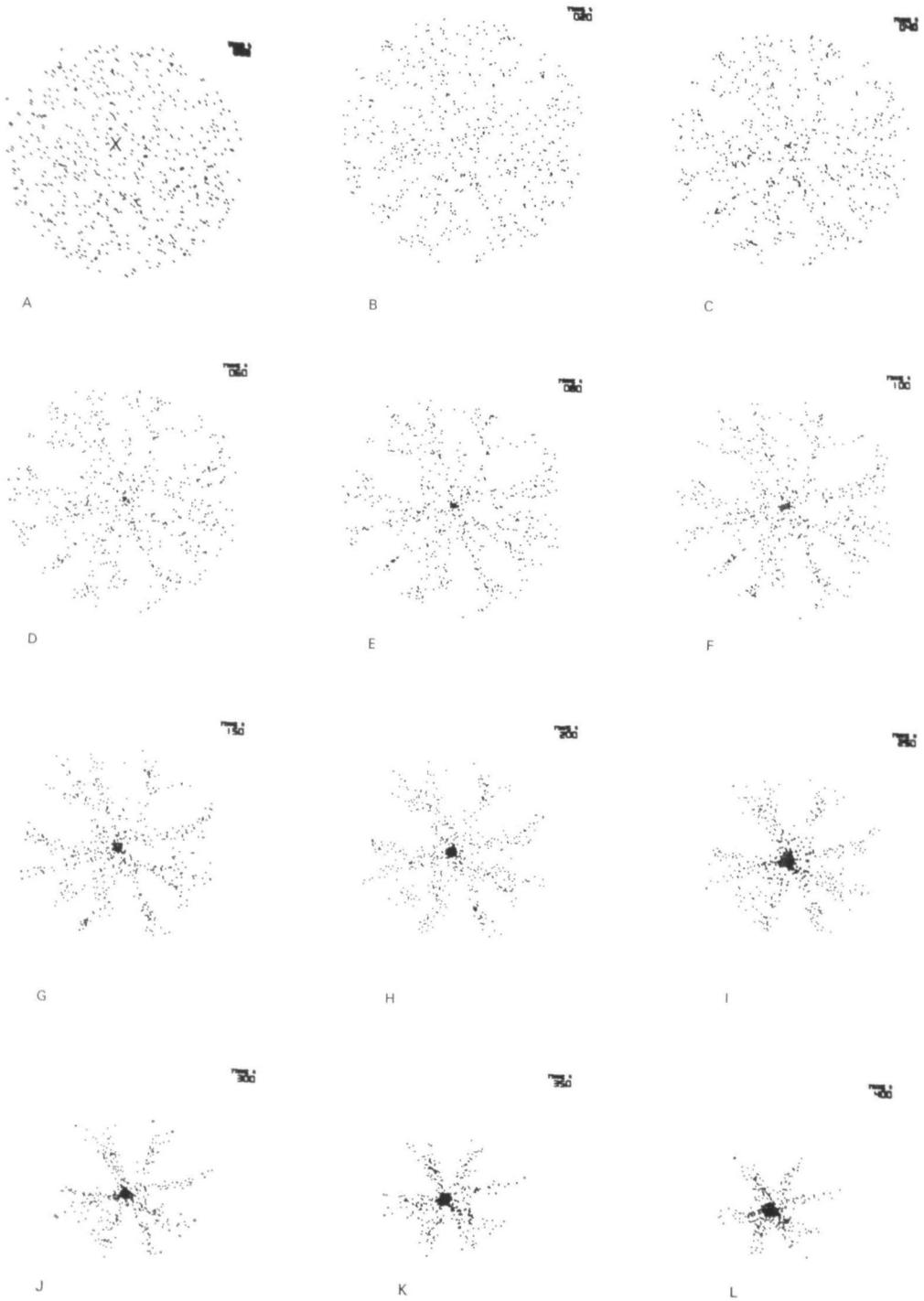

Fig. 3. Frames from a simulation with 1 centre. In all simulations shown, one frame corresponds to 20 s of real time. The centre is marked with X. A–L are frames 0, 20, 40, 60, 80, 100, 150, 200, 250, 300, 350, and 400, respectively.

aggregation features. The simulation animations are strikingly similar to films of slime moulds. The wave patterns, stream formation, effects of competing centres and cell movement reproduce behaviours observed in films.

Fig. 3 shows the simplest simulation behaviour. A single cell in the centre of this drop of 800 cells releases a periodic signal. All the other cells in the drop are competent to chemotax and relay. Fig. 3A shows the initial configuration, while B–L show later frames. The simulation reproduces the wave propagation, periodic movement and stream patterns which are characteristic of *D. discoideum* aggregation as observed in time-lapse films.

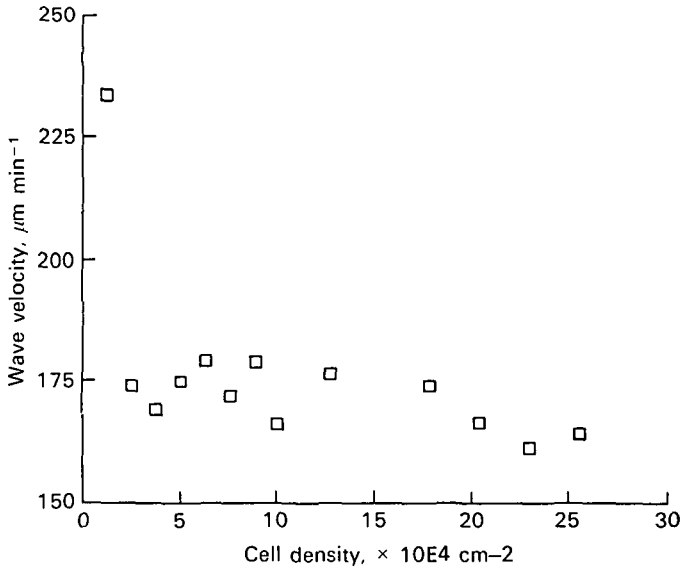

Fig. 4. Wave velocity as measured from simulations *vs.* cell density.

In all the simulations described, cells which are firing (releasing their signal) in a frame are displayed as a brighter point than those cells which are not firing. This difference is not apparent in still photographs, but in the animations, bands of firing cells are clearly seen propagating outward from the centre. Also visible in the animations are bands of cells moving in toward the centre after firing. The simulation animations thus show much the same wave propagation features as reported by Alcantara & Monk (1974).

This type of single-centre simulation has been repeated for several different starting cell densities and the qualitative behaviour has been the same. The velocities of the waves propagated can be calculated by measuring the average distance travelled by the wave in one frame using the Galatea film analysis system (Potel & Sayre, 1976). A plot of wave velocity *vs.* cell density is shown in Fig. 4. Except at low cell densities, the velocity shows a slight decrease with increasing density, which is essentially the same behaviour observed by Alcantara & Monk (1974).

Simulations with 2 centres have been produced to study the effects of competition between centres. Fig. 5 shows the results of one such simulation. The centre on the

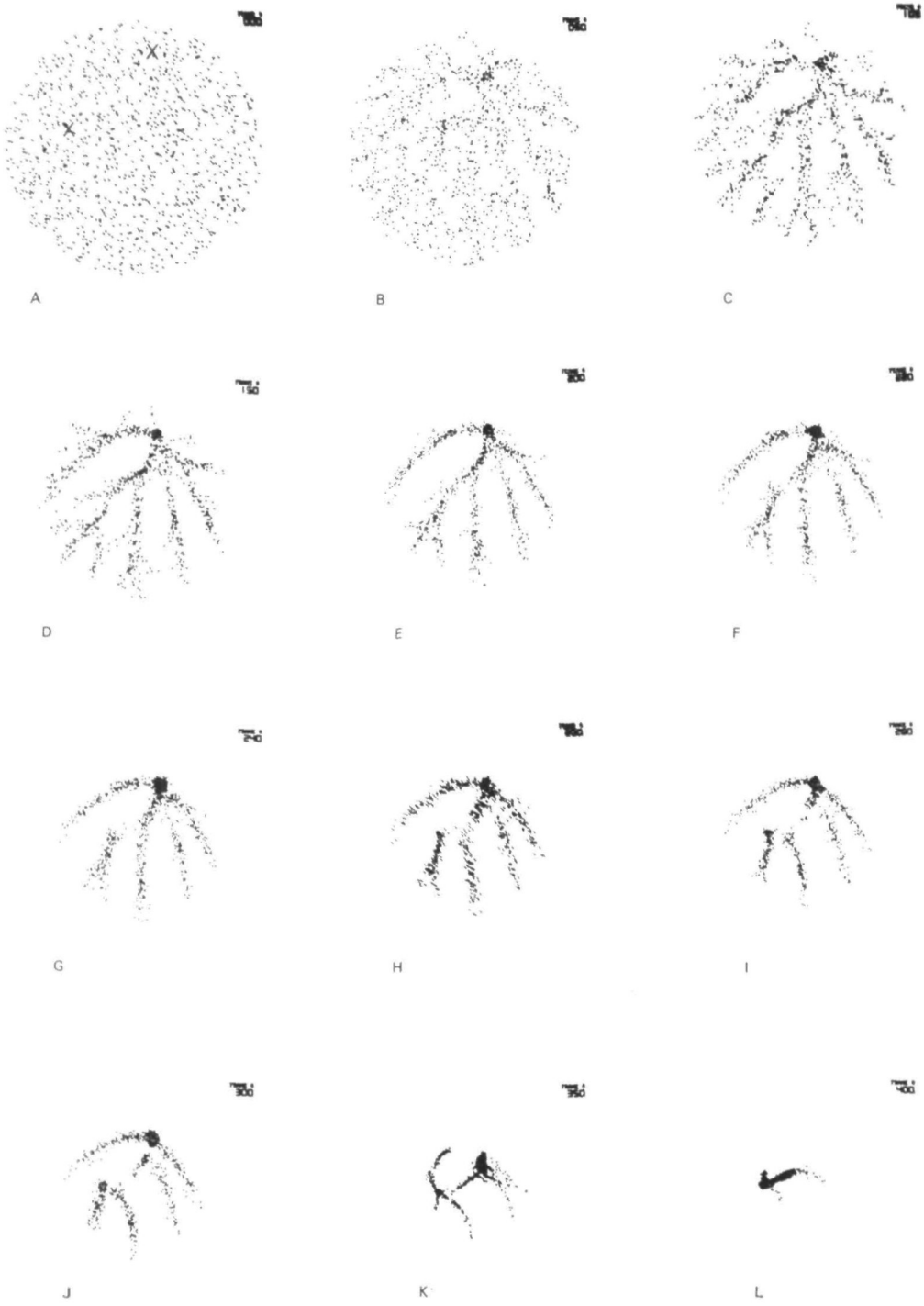

Fig. 5. Frames from a simulation with 2 centres. The centres are marked with X. A–L are frames 0, 50, 100, 150, 200, 220, 240, 260, 280, 300, 350, and 400, respectively.

right was given a longer period than the centre on the left, but the signals for the left centre were initially gated by the refractory period of the field (i.e. only every other pulse from this centre was propagated), thus the left centre initially had a longer effective period than the right centre. The right centre therefore entrains the left centre, as seen in Fig. 5B–F. After Frame 240 (G), however, the refractory period of the field of cells, which decreases with age, has become less than the period of the left centre. This centre now entrains all the cells in the field (Fig. 5J–L). The entrainment and gating behaviour, which is observed in films (Durston, 1974) is caused simply by the interaction between the periods of the centres and the field of cells.

Two-centre simulations have been run which are identical to the one just described except for the amount of PDE present. The simulation pictured in Fig. 5 has a level of PDE predicted by one analysis of relay range measurements (Gingle, 1976). The velocity of waves in this simulation was measured using the same method as for Fig. 4 and is 200 μm/min. Fig. 6 depicts a simulation with less PDE present. The wave velocity is higher (300 μm/min) and the bands of firing cells, those which appear bright in the animation, are much wider than in the simulation with medium amounts of PDE. Fig. 7 shows the results of a simulation with more PDE, causing slower wave velocities (180 μm/min) and much narrower firing bands. A comparison of Figs. 6 and 7 reveals that the streaming morphology is affected by changing PDE. The low PDE simulation shows little streaming with cells moving in radially to the centre, while the high PDE simulation has very thin streams.

The above simulations involved one or more cells pulsing periodic signals into a field of cells uniform in their refractory and relaying properties. The wave forms produced were of the concentric, circular type. The other type of wave form noticed in *D. discoideum* is the spiral wave (Gerisch, 1965; Durston, 1974) and several explanations have been offered for their behaviour (Winfree, 1972; Durston, 1973).

The simulation shown in Fig. 8 was produced by introducing a phase difference in the refractory state of the cells. The cells on the left side of the drop were sensitive at the beginning of the simulation, while the cells on the right side were insensitive (refractory) at the beginning of the simulation, and remained insensitive until frame 12 (representing 4 min of real time). One cell near the centre of the drop was chosen to fire only once, starting the signal propagation. The wave propagated through cells on the left side until frame 12, then spread into the cells on the right side, which just became sensitive. By the time the wave returned to the original centre, the cells in this area became sensitive again (Fig. 8B) and were able to sustain the propagation. Two such stable areas were set up (C–F) with waves propagating in opposite directions around a central hole. This type of spiral centre is like that observed in films (Durston, 1973). The size of the central hole decreased slightly after several revolutions of the wave, but eventually became constant.

The initial conditions outlined for the above simulation, with the 2 populations of cells (sensitive and refractory) separated spatially, is quite artificial. Thus a somewhat more realistic situation was set up for the simulation shown in Fig. 9. Again, half the cells were sensitive and half were refractory at the beginning of the simulation. However, in this simulation, the 2 populations of cells were mixed randomly in the drop.

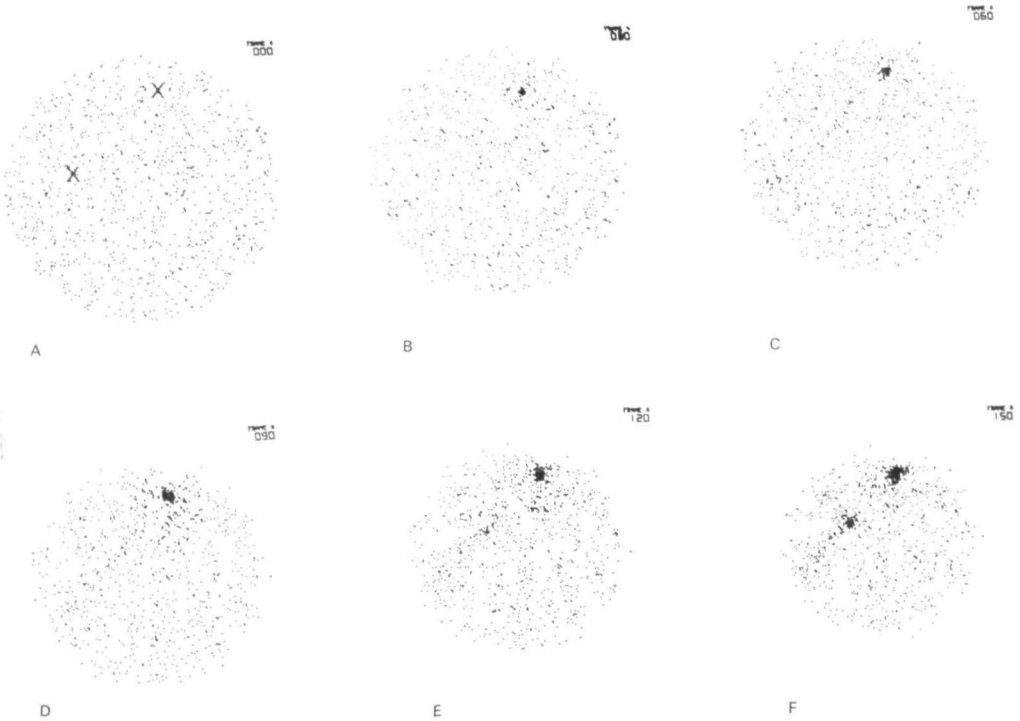

Fig. 6. Frames from a simulation with low PDE activity. Beginning cell locations are the same as for Figs. 5 and 7. Centres marked with X. A–F are frames 0, 30, 60, 90, 120, and 150, respectively.

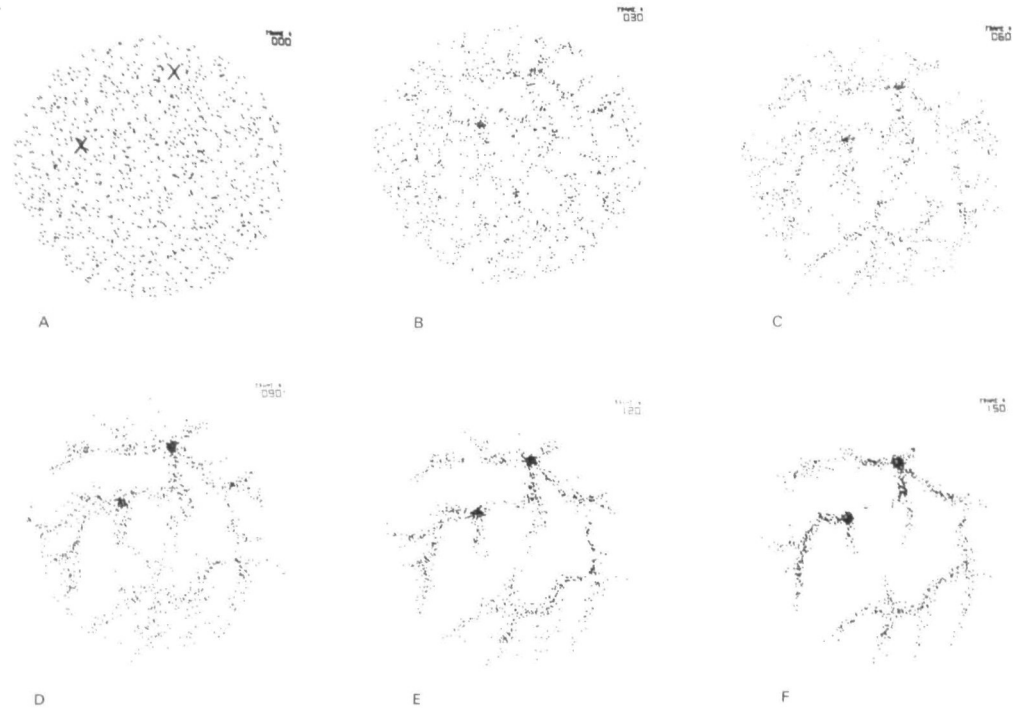

Fig. 7. Frames from a simulation with high PDE activity. Beginning cell locations are the same as for Figs. 5 and 6. Centres marked with X. A–F are frames 0, 30, 60, 90, 120, and 150, respectively.

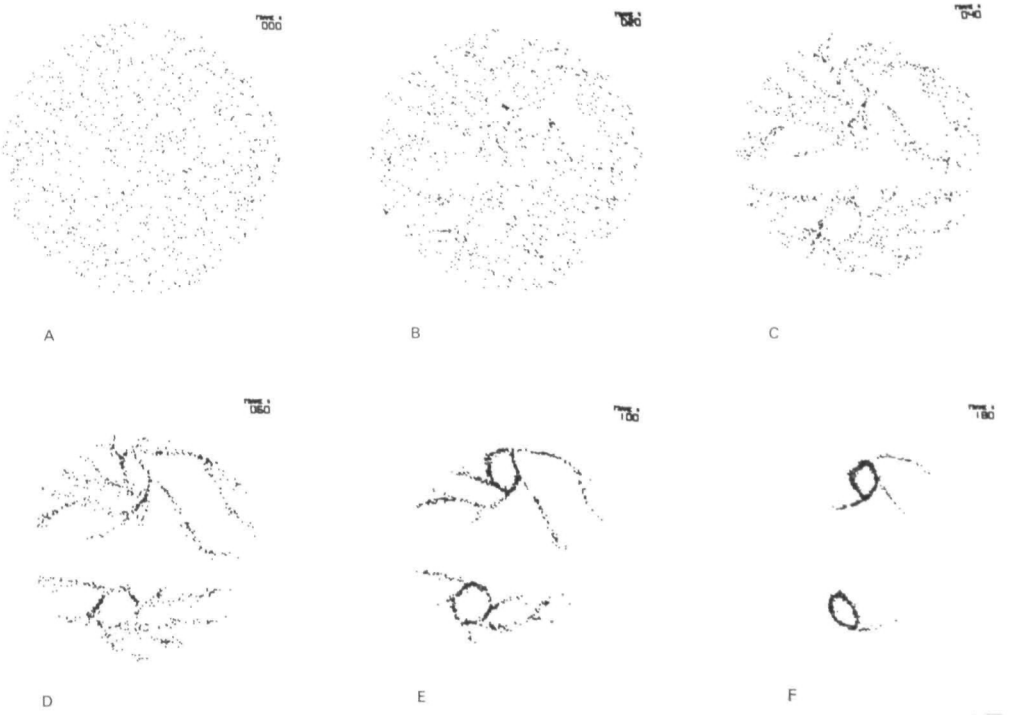

Fig. 8. Frames from a simulation producing spiral centres (see text for details). A–F are frames 0, 20, 40, 60, 100, and 180, respectively.

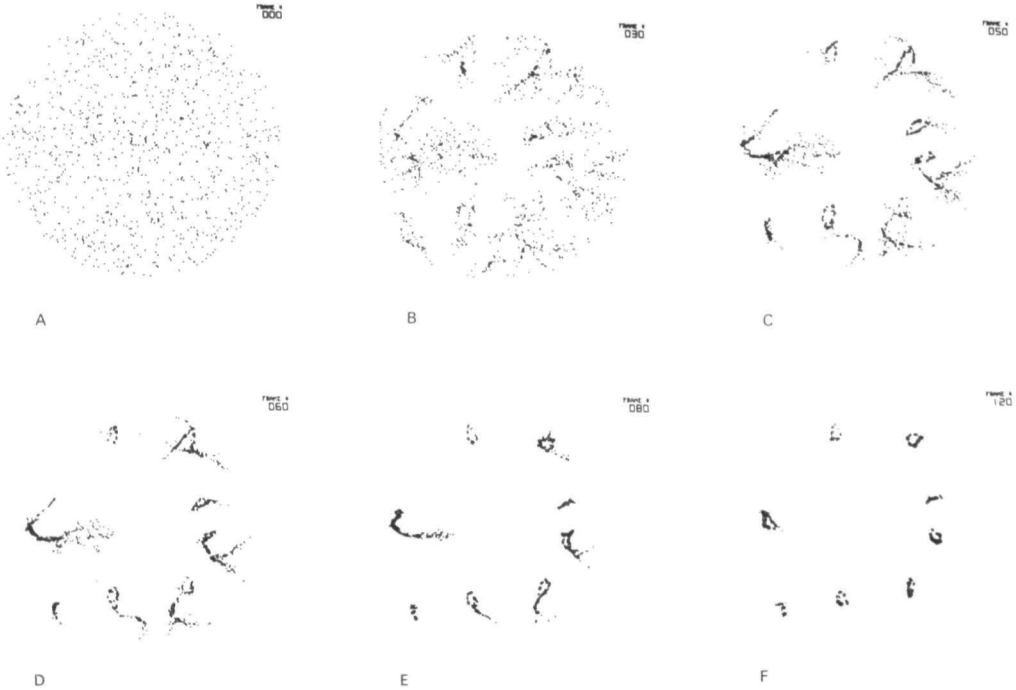

Fig. 9. Frames from a simulation producing spiral centres (see text for details). A–F are frames 0, 30, 50, 60, 80, and 120, respectively.

As in the previous simulation, one cell fired once only, to start the signal propagation. The result was that the field broke up into several spiral centres, located in the area occupied by the wave when the initially refractory cells became sensitive.

An interesting feature of these simulations can be seen by close examination of one of the spiral centres of Fig. 9F. The cells in this centre formed small clumps, with all the cells in a clump firing at the same time. The rules followed by the cells here resulted in cells being spatially organized on the basis of some common trait (in this case, similar refractory phase).

DISCUSSION

The simulation outlined in this paper provides a useful tool for studying the aggregation phase of slime mould development. Although one particular model of slime mould aggregation has been most extensively simulated, the simulation has been designed to allow changes in the particular model examined to be made without major changes in the simulation itself. This is important because one of the intended uses of the simulation is the examination of aggregation-defective mutants which have been collected in this laboratory. This will require alterations in the basic aggregation model to see what phenotypic effects these cause.

The model upon which these simulation results are based is expressed in terms of activities of individual cells, especially movement and secretion. The rules are effected at the cellular level, and no attempt is made (at this point) to extend the rules to the subcellular level. The rules are thus of a descriptive rather than a mathematical nature. The basic simulation algorithm consists of interpreting these descriptive rules, rather than solving equations. The simulation can thus handle many more cells at a much finer grain than those simulations in which sets of equations are solved (e.g. Novak & Seelig, 1976).

During the early work on this simulation, the cells were located only on the lattice points of a 2-dimensional grid, as is common in many simulations, especially those based on solving sets of difference equations, or using finite-element methods. However, it was soon discovered that this introduced serious artifacts into the simulation output (e.g. streams forming only on the x or y axes). Therefore the grid system was replaced by the procedure of allowing cells to occupy any position down to a grain of 1 μm. Since a primary feature of the simulation is to produce output directly comparable to time-lapse films, it was necessary to perform the simulation in 2 dimensions. Much of the interesting behaviour of the simulation (e.g. stream formation, spiral centre formation) would be lost if the simulation were restricted to one dimension. The elimination of the spatial grid and the format of 2 dimensions distinguish this simulation from that of Parnas & Segel (1977). Except for the rules regarding chemotaxis (which was the primary focus of their study), the model used here and the one outlined by Parnas & Segel are similar.

The global, multicellular behaviours produced by the simulation arise solely as a result of the interactions between individual cells. For example, the streaming phenomena observed in the simulation occur even though there are no rules instructing

cells to form streams. Cells in the simulation are not oriented in any respect (i.e. they are equally receptive to signals from any direction). Streaming arises because of the responses of cells to cell-to-cell relaying (Nanjundiah, 1973).

Similarly, the simulation contains no rules specifically causing spiral-centre formation. The spiral centres arise because of the interaction between populations of cells distinguished by the phase of their refractory period. The simulation shows that it is possible that spiral centres could arise from inhomogeneities in refractoriness (Durston, 1973).

Because this simulation reproduces behaviour observed in real *D. discoideum* aggregation, it provides evidence that the set of rules which comprise the model upon which it is based is *sufficient* to explain many aspects of *D. discoideum* aggregation. It provides no direct evidence for the biological or chemical factors required to cause real slime moulds to respond according to these rules. Evidence for that can be provided by studying mutants deficient in various aspects of aggregation and the simulation can be a useful tool in that activity.

The simulation's greatest use is in interacting with experimental research. In this context, it is necessary for the simulation to be extended beyond its present state. For example, several parameters in the model upon which the simulation is based are assumed to be constant for all cells. It is more likely that these parameters (length of refractory period, threshold values, length of delay time, etc.) actually vary, with some distribution, from cell to cell, and simulations will be performed using distributions of parameters. The first simulations for this type are those which produced spiral centres (Fig. 8 and 9), where the parameter which varied was the refractory phase. Other types of extensions to the simulation would be: non-analytic solutions to the diffusion equations, which do not require the assumptions that the cAMP pulse is released from the cell instantaneously; mechanical interaction between cells (contact formation); cell polarity; finite cell size; and rules regarding formation of autonomous centres. These extensions may allow the simulation to reproduce other observed slime mould aggregation behaviours – for example, the variation with time of the period and velocity of waves from spiral and concentric centres (Gross *et al.* 1976).

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