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Cyclic AMP oscillations in *Dictyostelium discoideum*: models and observations

Vidyanand Nanjundiah[a,b]

[a]*Developmental Biology and Genetics Laboratory, Indian Institute of Science, Bangalore 560012, India*
[b]*Jawaharlal Nehru Centre for Advanced Scientific Research, Indian Institute of Science, Bangalore 560012, India*; received in revised form 22 January 1998; accepted 13 February 1998

Abstract

Oscillations in intra- and extracellular cyclic AMP are believed to underlie aggregation and morphogenesis in *Dictyostelium discoideum*. Upon comparing mathematical models with observations we find that the models are, qualitatively speaking, quite successful. At the same time many features remain unexplained. A strong case can be made for cyclic AMP-independent oscillations whose basis remains to be explored.

Keywords: Dictyostelium; Oscillations; Cyclic AMP

1. Introduction

The rhythmic pulsations and waves displayed by amoebae of *Dictyostelium discoideum* exemplify the importance of oscillatory processes for intercellular communication. In *D. discoideum* (and in several other Dictyostelids), hitherto free-living amoebae respond to the stress of starvation by aggregating via vigorous periodic movements [1–3]. The contraction and extension that accompanies each movement step leads to the appearance of beautiful concentric waves or spirals that spread outwards from a centre [4]; the visual resemblance to the propagated waves displayed by the Beloussov–Zhabotinsky chemical oscillator is striking. The discoveries that amoebae at the right stage of development can (1) be attracted by extracellular cyclic AMP (cAMP) [5], (2) amplify and relay cAMP signals [6,7] and (3) synthesize and release cAMP in periodic pulses [8], made it plausible that cAMP was the causative agent of oscillatory aggregation in *D. discoideum*. The issue appeared to be confirmed when it was shown that aggregation patterns on plates were accompanied by concentric waves of cAMP [9]. Periodic cAMP stimuli can induce and accelerate differentiation [10,11]. It has been suggested that cAMP oscillations are similarly responsible for post-aggregative development, in particular for the undulatory and circulating movements that are seen during later morphogenesis [12,13]. This article aims to make two points. Firstly, although we have plausible models for cAMP oscillations in *D. discoideum*, many experimental observations await explanation in terms of them. Secondly, cAMP-independent oscillations exist but their basis is not understood. An intriguing possibility is that during development *D. discoideum* switches from a cAMP-based oscillatory communicating system to one that does not require cAMP.

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* Tel.: +91 80 3092608; fax: +91 80 3341683; e-mail: vidya@ces.iisc.ernet.in

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2. Oscillatory behaviour

Regular pulsations that originated in centres and moved outwards through a field of amoebae were seen in the time-lapse sequences of development on agar plates filmed by Arndt [1]. The pulsations, accompanied initially by propagating concentric or spiral waves of cellular contraction, precede the formation of streams of inwardly moving amoebae. Measurements on such films led to the inference that both the speed and the orientation of cells varied periodically in the wild-type (period approx. 5 min), and that waves of excitability propagated down streams at a speed of 40 μm/min [3,4]. A decisive advance in the study of oscillations was the discovery that well-stirred and aerated cell suspensions of *D. discoideum* exhibited developmentally regulated periodic changes in light scattering that mirrored the oscillations seen during aggregation ([14]; at least in part, the light scattering changes are caused by variations in the number of cells that form transient agglomerates [15]). Typically, 30–40 cycles can be detected before clumping (in suspensions) or the formation of tight aggregates (on plates) makes monitoring difficult (Fig. 1).

Cells in suspension are in an unnatural environment that prevents them from undergoing normal multicellular morphogenesis. However, the developmental clock appears to maintain its schedule under these conditions: this conclusion follows from measurements of variables that monitor the onset of aggregation competence [3] and oscillations [14], and of changes in gene expression that mark development [16]. We may infer that the behaviour monitored in cell suspensions is a consequence of the same cellular properties that drive development on a two-dimensional substrate. The earliest oscillations in suspension cultures are seen at a time corresponding to the appearance of pre-aggregation waves on plates, and the number of oscillations that can be seen in suspensions is large enough for it to be assumed that the later ones correspond to post-aggregative developmental stages (Fig. 1).

The suspension technique came to be widely used to monitor a number of other oscillatory changes that were exhibited at times corresponding to the onset of aggregation and beyond. These included periodic changes in extracellular H^+ [17], K^+ [18] and Ca^{2+} [19], in CO_2 production [20], in the reduced state of cytochrome *b* [14]; in intracellular levels of cyclic GMP (cGMP [21]; and in intra- and extracellular levels of cAMP [8]. It seemed that the cAMP oscillator was fundamental, with the others being derived from it. The reasons that favoured such a hypothesis were: (1) application of extracellular cAMP to competent cells could elicit a transient response (an increase in intracellular cAMP, an uptake of Ca^{2+}, a release of K^+ and H^+, and a burst of CO_2 production) resembling that observed during one oscillatory cycle of the corresponding variable [6,7,14,18–22]; (2) plausible schemes that accounted for spontaneous cAMP oscillations were soon at hand. Besides, cAMP was known to be a naturally-produced chemo-attractant [5]. Thus one could imagine that oscillations in all other variables were passive responses to the autonomous production and release of cAMP by starved amoebae of *D. discoideum*.

3. The case for a cAMP oscillator

Cells were shown to amplify and relay cAMP (cAMP-induced cAMP release) under natural conditions [6] and in suspensions [7]. Relay implied that the mechanism involved in cAMP production, release and sensing had an autocatalytic step, namely a step that could potentiate oscillatory behaviour. Spontaneous oscillations of intra- and extracellular cAMP in cell suspensions [8] could be explained on the basis of self-stimulation of excitable cells by the cAMP released by them, along with the enzymatic degradation of intra- and extracellular cAMP [23,24]. Initial models required much larger fluctuations in the level of cellular ATP (the substrate for the production of cAMP catalysed by adenylyl cyclase) than found experimentally [25,26]. Subsequent work [27] showed that the need for significant ATP consumption during an oscillatory cycle could be eliminated by taking into account the desensitisation of the cAMP receptor caused by cAMP binding [28]. In some cases there is a discrepancy between the range of parameter values that permit oscillations in suspensions and those that are necessary to account for wave propagation on plates [29]. Oscillations can be modelled without incorporating a desensitisation step at the level of the receptor if adenylyl cyclase is inhibited either by the mobilisation of intracellular calcium [30] or via a G protein [31] that is activated by cAMP binding, but there are problems with the details of the latter scheme [32]. Halloy et al. [33] should be consulted for an update on models.

An important point to emphasise is that we have good models for cAMP oscillations. They differ in their assumptions and do not relate in every respect to known ‘facts’. Further study is needed to determine whether this means that a particular model will eventually need to be discarded, or our perception of the experimental system will change, or whether minor tinkering will make the model agree with observations. Any model for cAMP oscillations would seem to require the following minimal components [34]: (1) adenylyl cyclase which, via transient stimulation by binding of extracellular cAMP to (2) cell surface cAMP receptors, is activated to produce (3) intracellular cAMP which is (4) secreted by the cell (thereby ‘closing the loop’). cAMP levels are continually depleted by (5) intra- and extracellular phosphodiesterases and diffusion. Oscillations can be blocked if receptors are continually occupied by cAMP [14,35]. It appears to be the membrane-bound phosphodiesterase (and not so much the secreted enzyme), along with diffusion, that is primarily responsible for keeping receptor occupancy low and steepening chemotactic gradients [36–38]. Calcium can interact with the oscillating system: the chelators EDTA and EGTA decrease the light-scattering response to cAMP and Ca^{2+} restores them [41], and when Ca^{2+} is added to a suspension just before cAMP, the cAMP-induced production of cAMP and cGMP is monophasic rather than biphasic [39,40]. The observation that caffeine leads to a decrease in excitability [41] suggests that intracellular Ca^{2+} may be an inhibitor of adenylyl cyclase.

4. Models for cAMP oscillations in the light of experimental data

Considering that the models were designed to account for the observed intra- and extracellular oscillations of cAMP in cell suspensions, it is no surprise that they do so [23,24,27,30,31]. They can also describe the appearance on a surface of propagated concentric waves and spirals of cAMP concentration [29,42–45]. The streams that are formed by inwardly moving amoebae can be shown to be a generic consequence of cell-to-cell relay of the chemoattractant; thus, stream formation does not need to be explained by a specific model for oscillations or aggregation [46,47]. Quantitative analysis of wave propagation speeds (which range from 144 to 714 μm/min before stream formation) are in accord with an intracellular delay of about 15 s between a cell’s sensing the signal and relaying it [48]. The analysis accounts for the seemingly paradoxical observation that waves speed up as they move outwards from the centre and 15 s is consistent with the time required for synthesising cAMP at the maximal possible rate by fully stimulated adenylyl cyclase.

However there are other features of the oscillatory behaviour exhibited by amoebae of *D. discoideum* regarding which the models have nothing to say or require modification. (1) Observations made on plate cultures as well as in suspension show that there is a secular increase in frequency which on occasion occurs abruptly and is correlated with the onset of multicellularity or with the spike-to-sinusoid transition (Fig. 1; also see below and [14,49–52]). The explanation could lie in an increase or decrease in the activity of one of the oscillator components, perhaps as a fall-out of the oscillation itself, but this needs to be demonstrated. Interestingly, a mutant defective in chemotaxis, and so unable to aggregate, exhibited an unvarying frequency for over 3 h [4]. (2) The oscillator can be phase-shifted by cyclic AMP [14] and models can account for the phase-response curve, at least qualitatively, though there are points of difference (Fig. 2). (3) The oscillation frequency is an increasing function of temperature both on plates and in suspensions (Fig. 3; [53–55]). Typical periods on plates are 12 min at 8°C and 12 min at 22°C and the activation energy in an Arrhenius plot is 15–17 kcal/mol. Temperature-dependence remains unexplored in models. (4) Rhythmic behaviour persists over approximately three decades in cell density (from about 3.10^8/ml down to 3×10^5/ml) without any systematic variation in frequency. Two models predict a strong frequency-dependence, or no oscillations at low cell densities, or both (Fig. 4). (5) The question of whether an isolated amoeba can oscillate (on plates or in suspension) is related to density-dependence in suspensions. Single cells can display periodic variations in

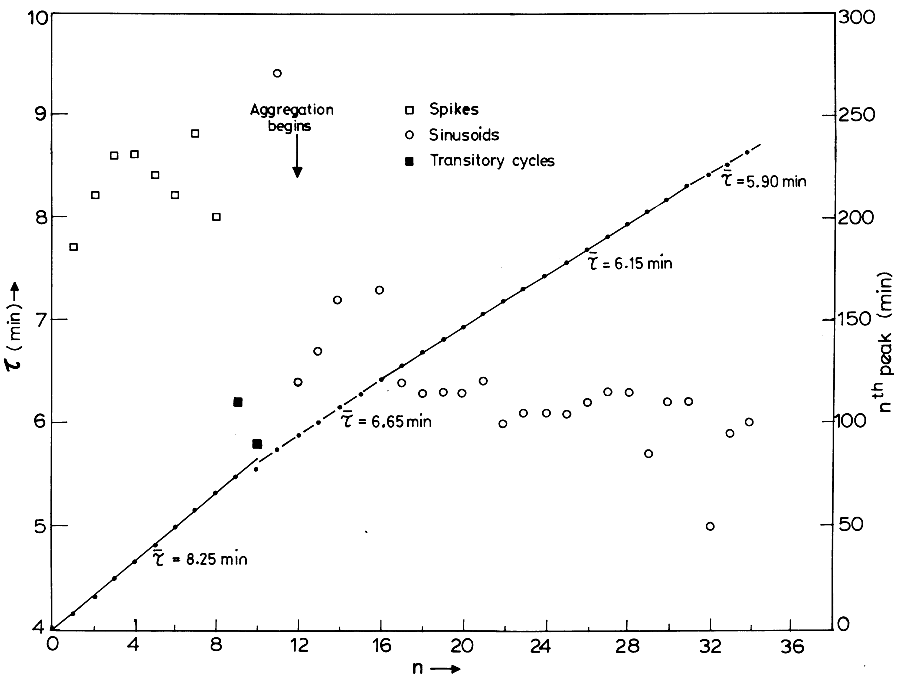

Fig. 1. A typical time-course of light scattering oscillation periods displayed by a clone of starved *D. discoideum* Ax-2 amoebae in suspension (2.10^7 cells/ml, 23°C, 500 nm; for details of method see [14]). An aliquot of the same suspension was observed on a plate. Abscissa, cycle number (*n*), left ordinate, period (squares and circles); right ordinate, time of *n*th peak (plotted as dots). The peak of cycle number 1 corresponds to 3 h 22 min after starvation. By the time aggregation began on the plate, the oscillation morphology had turned sinusoidal (also see [52]). The alternating straight and broken line segments were drawn by eye. τ is the average period within each such segment.

shape and size [56], and one can model a unicellular cAMP oscillator in which the binding of extracellular cAMP to the surface receptor is affected by diffusion away from the cell as well as by enzyme hydrolysis [57,58]. What may need to be taken into account, however, is the possibility that the cAMP level at the cell surface might be significantly depleted both by binding and by rapid diffusion. A one-dimensional approximation to the real situation, which assumes that the cAMP is released in a single burst and that most receptor sites remain unoccupied, shows that diffusion can lower peak binding by a factor $\{(l^2k_{-1})/\pi D\}^{1/3}$ where l is cell size, k_{-1} is the 'off' rate for cAMP-receptor binding and D is the diffusion coefficient of cAMP. Using reasonable numbers, this can be as small as 0.1 [58]. The point is that in the models as they exist, self-stimulation of a cell by released cAMP might be too weak to permit oscillatory behaviour. If this is a general feature common to all models requiring self-stimulation via a released chemical, the implication would be that the basic oscillator is an intracellular one. (6) The mechanism of cAMP secretion remains un-known: cAMP might be packaged in intracellular vesicles prior to release [59]. Simultaneous measurements of intra- and extracellular cyclic AMP [8], and of cAMP hydrolysis during oscillations enable one to model secretion in terms of a concentration difference multiplied by an effective transport coefficient *P*. It turns out that *P* can increase from approximately 0.05–0.22/min, i.e. by a factor of about four, during a pulse. If confirmed this will need to be incorporated into existing models. (7) Models implicitly assume that aggregation-competent cells must be physiologically identical ([45] is an exception), but this may not be correct. Cells harvested immediately after the completion of exponential growth oscillate (after starvation) with periods up to three times that of cells harvested 10 h later (10

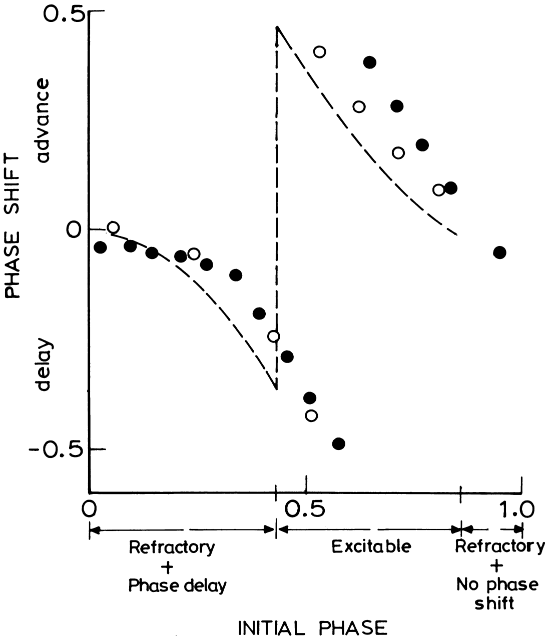

Fig. 2. Experimental and theoretical phase responses curves (PRCs). The broken line is the prc obtained after a 5–10 nM extracellular cAMP stimulus, measured using the pH oscillation as an indicator and replotted with respect to light-scattering. Phases 0 and 1 refer to successive peaks of decreased light scattering intensity [17]. ‘Excitable’ means that a precocious cellular cAMP pulse can be induced by the stimulus, ‘Refractory’, that it cannot [40]. The symbols are drawn after carrying out simulations using, for illustrative purposes, the models in [27] (o) and [30] (●), respectively. The strength of the instantaneous cAMP stimulus was assumed to be 25–37.5% of the peak extracellular cAMP level. Note the small discrepancy between theory and experiment in respect of the singularity (the phase at which a phase delay abruptly changes to a phase advance). Also, stronger stimuli elicit significantly larger phase shifts in the models.

vs. 3 min; [4]). Cells starved when they are around the S phase of the cell cycle, or after growth in the absence of glucose, give rise to aggregation centres, and begin oscillating in suspensions, earlier than those that are starved when in mid-late G2 ([60] and VN, unpublished data). Also, cells harvested when in S/early G2 display a higher light-scattering oscillation frequency than those harvested when in mid-late G2 [61].

5. The possibility of cAMP-independent oscillatory behaviour

The preceding points lead one inevitably to consider whether *D. discoideum* can exhibit cAMP-independent oscillations [52]. The points in favour of such a possibility are many. (1) Light scattering oscillations change (in phase and wave-form) from a spike-like to a sinusoidal profile after about 20 cycles [14]. The latter are accompanied by a sinusoidal oscillation in extracellular calcium but without measurable cAMP (or cGMP) changes [19]. While an externally applied pulse of cAMP cannot shift the phase of sinusoidal oscillations, the continuous addition of cAMP or the addition of purified phosphodiesterase can quench them [14,52]. This indicates that sinusoidal oscillations can be influenced by cAMP but may not depend on it. It should be emphasised that the morphology of

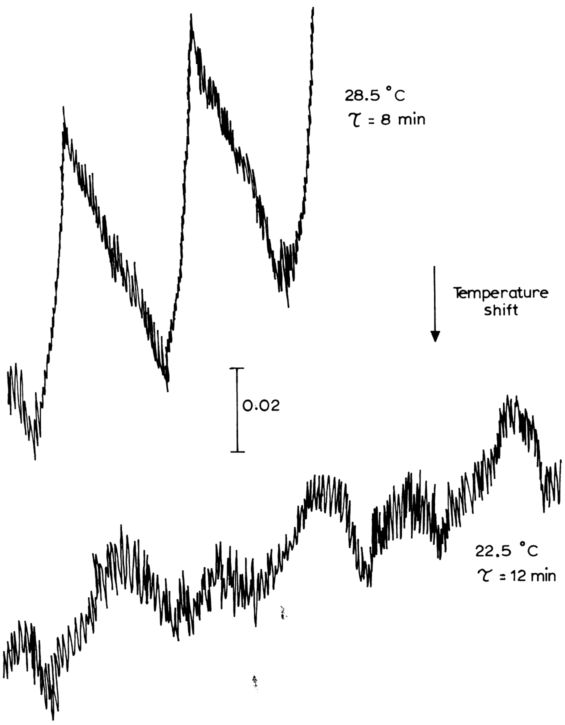

Fig. 3. Light scattering traces monitored in a suspension of wild-type *D. discoideum* initially at 28.5°C and then shifted to 22.5°C. τ is the period. Peaks of decreased light scattering occur towards the top of each trace (scale shown). Note that the waveform, amplitude and period all change. (The cycles at the lower temperature suggest that the population is undergoing a spike-to-sinusoidal transition. Spikes predominate at higher temperatures).

oscillation and its time-course is generally as stated but by no means exclusively so. On occasion one sees irregular light-scattering waveforms and sometimes sinusoids precede spikes. Spikes appear to be the rule at high temperatures (Fig. 3). (2) The non-aggregating mutant Agip43 exhibits spontaneous spike-shaped oscillations in light scattering without measurable variations in cAMP; but an external cAMP pulse can phaseshift the oscillator to a unique final phase irrespective of when it is applied. This could imply that not just the putative sinusiodal oscillators but also the 'spike-oscillator' is coupled to the cAMP oscillator in the wild-type, but decoupled from it in Agip43 [62,63]. (3) In Agip20, another non-aggregating mutant, adenylyl cyclase activity oscillates (with a 4–6-fold variation in amplitude and a period of 6–7 min) but cAMP levels do not, meaning that something other than cAMP can form part of an oscillatory loop that is linked to the cAMP system but is independent of it. Cell populations oscillate in phase, indicating the presence of a synchronizer [64]. Interestingly, similar oscillations were also detected in undifferentiated wild-type cells [65]. (4) Cells lacking in the aggregation-specific adenylyl cyclase, and demonstrably unable to make cAMP after starvation, can nevertheless develop and differentiate (apparently normally) if they are transformed so as to over-produce the catalytic subunit of protein kinase A [66]. Streams are said to be formed during aggregation, indicating that a cell-to-cell relay system must be involved [46]; but then the relayed signal has to be something other than cAMP. One does not know whether the cells can oscillate, but the implication that there is a relay mechanism favours such a possibility.

There are other arguments in favour of a cAMP-independent oscillator in *D. discoideum* (species that aggregate rhythmically but do not use cAMP as a chemoattractant testify to the possibility of such oscillations). Approximately hourly changes in respiratory activity and protein content occur during growth [67], when the cAMP signalling system is inoperative. From measurements of rhythmic variations in cell

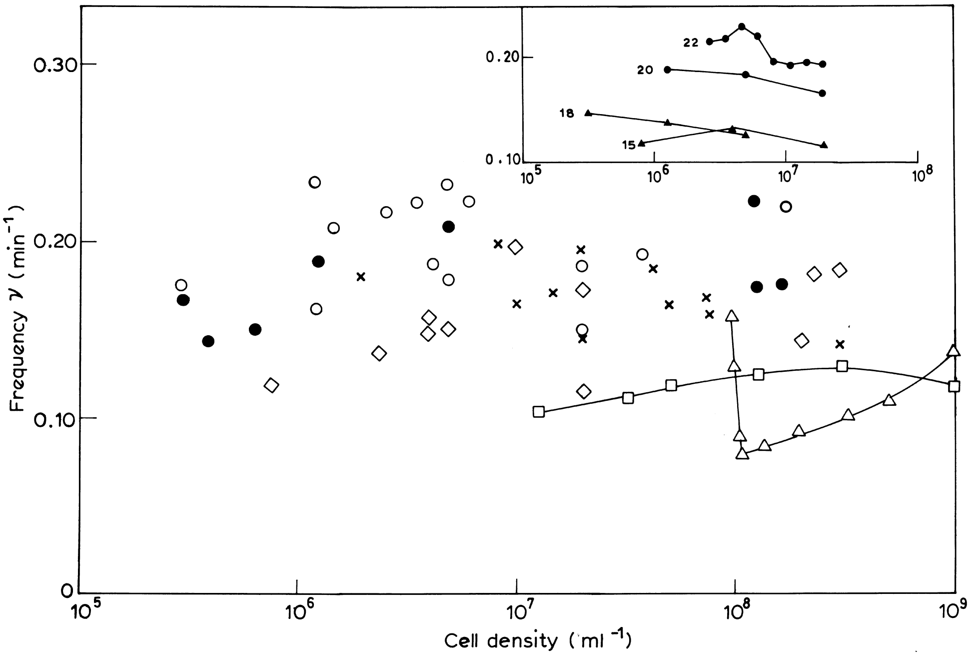

Fig. 4. Light scattering oscillation frequencies measured in suspension of wild-type (Ax-2) amoebae at 23°C as a function of cell density. Two sub-clones were tested and it can be seen that they differ. Each symbol represents an average of about five cycles. Some readings were from a suspension monitored all along at the same density and others from ones that were diluted after starting with a higher density. The inset shows results of four experiments in which frequencies were measured after a succession of dilutions in the same suspension and indicates the absence of systematic effects. x, spikes (sub-clone B2); ◇, spikes (sub-clone C1); ○, sinusoids (B2); ●, sinusoids (C1). The continuous lines are drawn after simulations based on the models in [27] (△) and [30] (□) (from [52]).

orientation and movement during aggregation it can be inferred (on the basis of differences in the reaction of wild-type amoebae to different mutant centres) that aggregation centres can release at least two distinct factors in a pulsatile manner, the two serving to guide locomotion and orientation, respectively [68,69]. A calcium-based oscillator is a specific possibility worth considering [70]: not only does Ca^{2+} oscillate in the absence of cAMP changes, but the calcium ionophore A23187 can phase-shift sinusoidal light scattering oscillations [71]. Jaffe [72] has recently proposed that stretch-propagated calcium waves might be responsible for the optical density oscillations seen during and after aggregation.

6. Discussion

Taken individually, the models that have been proposed for cAMP oscillations account reasonably well for the range of observed behaviours. Indeed, they predict qualitatively new behaviours, for example, dynamical chaos and birhythmicity [73,74], that have not yet been observed. Clearly this is a matter that needs exploring, as is cell-to-cell heterogeneity (but see [45]). Under natural conditions, not all cells acquire the competence to relay, or to oscillate autonomously, at the same time [75]. So also, a substantial proportion of cells in a population may never attain oscillatory autonomy [76]. On comparing models with observations it is obvious that even to the extent presently understood, the system is far more complex than any single model requires [34]: for example there could be more than one oscillatory loop involving cAMP. A combination of genetic analysis, biochemistry and, eventually, reconstitution of the native system will be required before we can be certain. Further, given that the comparison between models and experiments has been based solely on waveforms, amplitudes and frequencies, a plausible and apparently successful model does not imply that the molecular assumptions underlying it are both necessary and sufficient to explain the observed behaviour. Indeed, based on the data presented earlier, it is arguable that at least two oscillators subserve communication in *D. discoideum*. A cAMP-based oscillator could be responsible for the long-range wave propagation that precedes aggregation, with the periodic stimuli serving to prime the system in some manner. Post-aggregation oscillations on the other hand might be driven differently: the case for a Ca^{2+}-based oscillator is a strong one [70], though it is uncertain whether Ca^{2+} could act as an extracellular synchronizer as well. Finally, it is important to start exploring the ramifications of possible cAMP-independent oscillatory behaviour. In terms of constructing models, this means that formal schemes that are not tied down to cAMP remain important [77].

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