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CHEMOTAXIS AND CHEMOKINESIS IN EUKARYOTIC CELLS: THE KELLER–SEGEL EQUATIONS AS AN APPROXIMATION TO A DETAILED MODEL

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More than 20 years after its proposal, Keller and Segel's model (1971, *J. theor. Biol.*, **30**, 235–248) remains by far the most popular model for chemical control of cell movement. However, before the Keller–Segel equations can be applied to a particular system, appropriate functional forms must be specified for the dependence on chemical concentration of the cell transport coefficients and the chemical degradation rate. In the vast majority of applications, these functional forms have been chosen using simple intuitive criteria. We focus on the particular case of eukaryotic cell movement, and derive an approximation to the detailed model of Sherratt *et al.* (1993, *J. theor. Biol.*, **162**, 23–40). The approximation consists of the Keller–Segel equations, with specific forms predicted for the cell transport coefficients and chemical degradation rate. Moreover, the parameter values in these functional forms can be directly measured experimentally. In the case of the much studied neutrophil–peptide system, we test our approximation using both the Boyden chamber and under-agarose assays. Finally, we show that for other cell–chemical interactions, a simple comparison of time scales provides a rapid check on the validity of our Keller–Segel approximation.

Introduction: General. The movement of cells in response to biochemical concentration gradients has been the subject of a great many theoretical investigations, spanning more than two decades. During this time, a number of different approaches to the problem have evolved, both at the single cell and cell continuum levels (for example, Segel, 1976; Segel *et al.*, 1986; Tranquillo *et al.*, 1988a; Rivero *et al.*, 1989; Charnick *et al.*, 1991). The more detailed models apply specifically to either eukaryotic or prokaryotic cell movement, since the underlying mechanisms responsible for chemotaxis are quite different in the two cell types, with cells responding to spatial and temporal concentration gradients, respectively, in the two cases (Devreotes and Zigmond, 1988; Berg, 1988; Pittenger and Dent, 1988). However, despite this wide range of different

modelling approaches, by far the most widely used mathematical model for cell chemotaxis and chemokinesis remains the original model of Keller and Segel (1971a,b). This very general model has been successfully applied to the movement of bacteria, eukaryotic cells and even whole organisms (Keller, 1980; Segel, 1984; Alt and Lauffenburger, 1987; Kareiva and Odell, 1987). However, before the Keller–Segel model can be used for a particular system, the variation with chemical concentration of three key coefficients must be specified; in most previous applications of the model, these parameter variations have been based directly on simple intuitive criteria such as an expected qualitative form or mathematical simplicity. Here we consider the particular case of chemical control of eukaryotic cell movement, for which Sherratt *et al.* (1993) have recently proposed a detailed model, based on the underlying receptor kinetics. We show that under an approximation that is valid for many cell–chemical interactions, including the much studied neutrophil–peptide system, this model reduces to Keller–Segel form. Our approximation gives explicit functional forms for the dependence on chemical concentration of the coefficients in the Keller–Segel model when applied to eukaryotic cells, and clarifies the way in which these functional forms depend on underlying approximations and assumptions.

Introduction: Theoretical. The Keller–Segel model consists of two coupled reaction diffusion equations with the following general form:

$$\frac{\partial n}{\partial t} = \nabla \cdot \overbrace{\{D_n(c)\nabla n}^{\text{Random cell movement}} - \overbrace{\chi(c) n \nabla c\}}^{\text{Directed cell movement}} \tag{1a}$$

$$\frac{\partial c}{\partial t} = \underbrace{D_c \nabla^2 c}_{\text{Chemical diffusion}} - \underbrace{n\,\delta(c)}_{\text{Chemical degradation by cells}} \tag{1b}$$

where $n(\underline{r}, t)$ and $c(\underline{r}, t)$ are the cell density and chemical concentration respectively, and $\underline{r}$ and t are the space and time coordinates. Detailed derivations of this model are given by Segel (1977, 1980) and Alt (1980). Alt's calculations (1980) in fact give rise to a model with an additional term, proportional to dD_n/dc, in the expression for cell flux, although in many applications this term is negligible (Rothman and Lauffenburger, 1983). Some applications of the model have included a proliferation term in the cell conservation equation (1a) (Maini *et al.*, 1991), but in most cases, including the original paper of Keller and Segel (1971b), cell division is neglected. The transport coefficients D_n and χ, and the chemical degradation rate per cell, δ,

are strictly positive functions of c, and their functional forms must be specified before the model can be applied in a particular situation. Clearly, different functional forms will be appropriate in different cases, and in the literature, particular attention has been given to the form of $\chi(c)$. The most popular expressions are a constant, a "logarithmic" form ($\chi \propto 1/c$), and a "receptor-kinetic" form ($\chi \propto 1/(\kappa + c)^2$, with κ a positive constant). The first of these is usually justified on the grounds of mathematical simplicity (Balding and McElwain, 1985; Alt and Lauffenburger, 1987). The logarithmic form is mathematically convenient because it can give rise to travelling fronts of cell density, and can be partially justified by the Weber–Fechner law of behaviour (Keller and Segel, 1971b; Keller, 1980), while the receptor–kinetic form gives a maximum chemotactic response at a particular chemical concentration $c = \kappa$, which is intuitively plausible (Lapidus and Schiller, 1976; Lauffenburger *et al.*, 1984). A more detailed form for $\chi(c)$ including a memory function was suggested by Boon and Herpigny (1986), based on intuitive assumptions concerning the force generating the chemotactic response. More recently, Rivero *et al.* (1989) proposed a continuum model in which the algebraically complex form of $\chi(c)$ is determined from a simple stochastic model for the behaviour of an individual cell; they consider separately the cases of prokaryotic and eukaryotic cells. Rivero *et al.* (1989) also derived an expression for $D_n(c)$, which reflects biochemical enhancement of random cell motility, that is chemokinesis. The simpler form $D_n(c) = 1 + 4c\hat{c}/(c + \hat{c})^2$, with $\hat{c}$ a positive constant, was proposed by Lapidus (1980), based on its qualitative agreement with experimental data. Surprisingly, almost all other applications of the Keller–Segel model have neglected variations in D_n.

Cells respond to chemoattractants via the binding of the chemical to receptors on the cell surface. The receptor–chemical complex is in many cases rapidly internalized, resulting in degradation of the chemoattractant (see below). This degradation is reflected in (1) by the term $-n\,\delta(c)$; however the vast majority of applications of the Keller–Segel model have neglected this effect and taken $\delta(c) \equiv 0$. When the term has been included, the most popular form for δ has been $\delta(c) \propto c/(k + c)$, with k a positive constant (Lauffenburger *et al.*, 1984; Ford and Lauffenburger, 1991). This implies that the degradation rate per cell is an increasing, saturating function of chemical concentration. Other forms that have been used are $\delta(c) \propto c$ (Rosen, 1985) and $\delta(c)$ constant (Keller and Segel, 1971b; Nagai and Ikeda, 1991).

Recently, Sherratt *et al.* (1993) proposed a detailed continuum model for chemotaxis and chemokinesis in eukaryotic cells, based on the underlying receptor kinetics. Here we derive an approximation to this model that is of Keller–Segel form. This enables us to use the detailed model to derive expressions for $D_n(c)$, $\chi(c)$ and $\delta(c)$ in which the parameters are related to experimentally measurable quantities.

Receptor–chemical Interactions on Eukaryotic Cells. Chemical regulation of eukaryotic cell movement occurs in response to the number and location of occupied chemical receptors on the cell surface (Van Haastert, 1983; Zigmond, 1989; Cassimeris and Zigmond, 1990). The Keller–Segel model bypasses this control mechanism, and assumes that cells respond directly to the concentration of extracellular chemicals. Here we discuss briefly a more detailed model in which receptor density is one of the variables; a more detailed derivation of the model is given by Sherratt *et al.* (1993). We take the cell flux to depend on $\rho(\underline{r}, t)$, the number of moles of occupied receptor per cell, via the expression

$$J_n = \underbrace{-D(\rho)\nabla n}_{\substack{\text{Random migration} \\ \text{and chemokinesis}}} + \underbrace{\chi_0 n \nabla \rho}_{\text{Chemotaxis}}, \tag{2}$$

where χ_0 is a positive constant. Since chemical control occurs entirely through binding to cell surface receptors, J_n has no explicit dependence on the extracellular chemical concentration. The assumption that the chemotaxis component depends on $\nabla\rho$ reflects a dependence on both the value and local gradient of extracellular chemical concentration, which is consistent with experimental observations that both quantities regulate cell speed in the neutrophil–peptide system (Tranquillo *et al.*, 1988a). In a great many cases, low concentrations of chemoattractants have a positive chemokinetic effect, while high concentrations reduce random motility. We therefore take $D(\rho)$ to be an inverted parabola, with the form $D(\rho) = D_0 + D_1\rho - D_2\rho^2$, where D_0, D_1 and D_2 are positive constants. Chemotactic peptide receptors are known to move over the cell membrane (Gex-Fabry and Delisi, 1984), but such movement occurs on a much smaller length scale than that which we are considering. Movement of receptors on the cell surface will make a negligible contribution to (2) in any situation for which a continuum approximation for cell density is appropriate. Therefore, for the purposes of our model, we can take the movement of receptors to be due entirely to passive convection with the cells, so that the flux of occupied receptors is given by ρJ_n.

The relationship between $\rho(\underline{r}, t)$ and the extracellular chemical concentration $c(\underline{r}, t)$ is determined by the kinetics of receptor–chemical binding, which can be reasonably represented as

$$\begin{array}{c}\text{Extracellular} \\ \text{chemical}\end{array} + \begin{array}{c}\text{Receptors on} \\ \text{the cell surface}\end{array} \underset{k_d}{\overset{k_a}{\rightleftharpoons}} \begin{array}{c}\text{Occupied} \\ \text{receptors}\end{array} \xrightarrow{k_i} \begin{array}{c}\text{Internalized receptor–} \\ \text{chemical complex}\end{array} \tag{3}$$

(Zigmond *et al.*, 1982; Van Haastert, 1987; Omann *et al.*, 1987). Once internalized, the chemical is degraded, but the receptors are in many cases recycled (Sullivan and Zigmond, 1980; Van Haastert, 1987). The total number

of receptors (occupied or vacant) on the cell surface varies widely. In the absence of a extracellular chemical, a relatively small number of receptors (typically a few thousand) are expressed, but binding of regulatory chemicals to these causes additional receptors to be released from an intracellular storage pool, and the maximum possible receptor number is often many times the resting value (Janssens and Van Driel, 1984; Zimmerli *et al.*, 1986). We therefore take the total number of receptors per cell to be an increasing function of the number of these receptors that are occupied, and for simplicity we use the linear function $\Gamma(1+\beta\rho)$, where β and Γ are positive constants. Here Γ is the number of moles of (vacant) receptors on an unstimulated cell. This implies that the number of moles of vacant receptor per cell is given by $\Gamma(1+\beta\rho)-\rho=\Gamma-(1-\beta\Gamma)\rho$. This is a decreasing function of ρ, reflecting the phenomenon of receptor down-regulation (Sullivan and Zigmond, 1980; Zigmond, 1981; Zigmond *et al.*, 1982).

With this expression for the number of vacant receptors per cell, (2) and the law of mass action applied to (3) together give a system of three coupled partial differential equations governing cell movement:

$$\frac{\partial n}{\partial t}=\nabla\cdot[(D_0+D_1\rho-D_2\rho^2)\nabla n-\chi_0 n\nabla\rho], \tag{4a}$$

$$\frac{\partial c}{\partial t}=D_c\nabla^2 c+k_d\rho n-k_a cn[\Gamma-(1-\beta\Gamma)\rho], \tag{4b}$$

$$\frac{\partial(\rho n)}{\partial t}=-\nabla\cdot\{\rho[(D_0+D_1\rho-D_2\rho^2)\nabla n-\chi_0 n\nabla\rho]\}$$
$$+k_a cn[\Gamma-(1-\beta\Gamma)\rho]-(k_d+k_i)\rho n. \tag{4c}$$

Here we are using the fact that ρn is the density of occupied receptors per unit volume; (4a,c) together imply that

$$\frac{\partial\rho}{\partial t}=(D_0+D_1\rho-D_2\rho^2)\frac{\nabla n\cdot\nabla\rho}{n}-\chi_0(\nabla\rho)^2+k_a c[\Gamma-(1-\beta\Gamma)\rho]-(k_d+k_i)\rho. \tag{4d}$$

The division by n in this equation is not problematic, since it is straightforward to show that sharp fronts cannot exist within the domain of solution, so that the strict inequality $n(\underline{r}, t)>0$ holds for all $t>0$.

One of the best studied chemotaxis systems is the response of neutrophils to N-formulated peptides. In this case, the receptor kinetics occur over a considerably shorter time scale than cell movement. For example, internalization of occupied receptors has a half life of about 3 min at 37°C (Sklar *et al.*, 1984; Zigmond *et al.*, 1982); even a chemically stimulated neutrophil moves

only one or two cell lengths during this time (Tranquillo *et al.*, 1988b; Rivero *et al.*, 1989). Moreover, the rate constant k_a has a value of about $10^9\ \mathrm{M}^{-1}\ \mathrm{min}^{-1}$ at 37°C (Sklar *et al.*, 1984), so that at a moderate peptide concentration such as 10^{-8} M, the half life of peptide binding to neutrophil receptors is just a few seconds. Such rapid kinetics have also been observed for chemoattractant receptors on other cells (Janssens and Van Haastert, 1987; Snyderman and Fudman, 1980; Caterina and Devreotes, 1991). We will now use this difference in time scales to derive a model that is an approximation to the full system (4).

Under the assumption of infinitely fast kinetics, (4d) implies that to a first approximation

$$\rho = \frac{\Gamma k_a c}{(1-\beta\Gamma)k_a c + k_d + k_i}. \tag{5}$$

A similar approximation in (4b) would imply that $\rho \equiv c \equiv 0$. When (4) is solved on a finite domain with moderate initial densities of both cells and chemical, this is indeed the form of the solution: the chemoattractant rapidly disappears as it is degraded by the cells. However, in almost all applications of chemotaxis models, both *in vitro* and *in vivo*, either the cells occupy only a small, localized part of the domain, into which chemoattractant rapidly diffuses as it is degraded (Lauffenburger *et al.*, 1988; Bignold, 1988; Chaplain and Stuart, 1991), or there is a source of chemical within the domain (Alt and Lauffenburger, 1987; Murray *et al.*, 1990). In both cases, these factors require that the full form of (4b) be retained in the approximate system.

The relationship (5) differs somewhat from that calculated previously for neutrophils by Zigmond (1981), because of slight differences in the assumptions concerning receptor modulation. Zigmond's (1981) calculations predict a small decrease in bound receptor number at high chemical concentrations; however, both relationships are consistent with the available data. Substituting (5) into (4a,b) gives a system of two coupled partial differential equations for $n(\underline{r}, t)$ and $c(\underline{r}, t)$ that is exactly of Keller–Segel form (1), with

$$D_n(c) = [D_0(k_d+k_i)^2 + \{2D_0(1-\beta\Gamma) + D_1\Gamma\}(k_d+k_i)k_a c + \{D_0(1-\beta\Gamma)^2 + D_1\Gamma(1-\beta\Gamma) - D_2\Gamma^2\}k_a^2 c^2]/[k_d+k_i+(1-\beta\Gamma)k_a c]^2, \tag{6a}$$

$$\chi(c) = \frac{\chi_0 k_a \Gamma(k_d+k_i)}{[k_d+k_i+(1-\beta\Gamma)k_a c]^2}, \tag{6b}$$

$$\delta(c) = \frac{\Gamma k_i k_a c}{k_d+k_i+(1-\beta\Gamma)k_a c}. \tag{6c}$$

In Fig. 1, we sketch the forms of $D_n(c)$, $\chi(c)$ and $\delta(c)$ that are implied by (6).

Comparison of the Full and Approximate Models. Chemotaxis models have a wide range of *in vivo* applications, but new models have almost always been tested by applying them to much simpler *in vitro* assays. A number of such assays have been developed over the last 30 years to enable biochemical regulation of cell movement to be quantitatively tested (see Bignold, 1988, for review). We now compare the full and approximate models, (4) and (1), (6), by applying them to two of the most popular *in vitro* assays. In both cases we will consider the much studied neutrophil–peptide system.

The Boyden chamber. In this assay, which is named after its originator (Boyden, 1962), cells crawl through a porous filter in response to gradients of a regulatory chemical. The experimental system is illustrated schematically in Fig. 2. The lower well is initially filled with a solution of the chemical under test, while the upper well is filled with a cell suspension. The cells rapidly settle onto the top of the filter, and then begin to crawl through; the porosity of the filter enables cells to crawl actively between the wells, but prevents passive falling under gravity. The cellular response to a given chemical concentration is measured in one of two ways. The first method is to use a thin filter and count the number of cells that have migrated through it in a given time period (Falk *et al.*, 1979; Bignold, 1987). Alternatively, a thicker filter is used, and the distance travelled by the leading cell front is measured (Zigmond and Hirsch, 1973; Buettner *et al.*, 1989a,b).

Here we use the thick filter system to compare the full and approximate models, (4) and (1), (6). Using the notation of Fig. 2, the chemical concentration $c(x, t)$ is defined on $h_L < x < a + h_U$, while cell density $n(x, t)$ (and thus receptor number $\rho(x, t)$) is restricted to the filter region $0 < x < a$; in the wells, $c(x, t)$ satisfies the diffusion equation. Initially, $c = c_0$, say, on

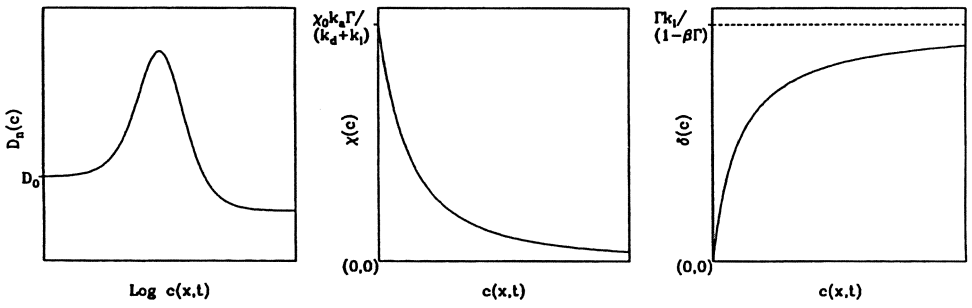

Figure 1. The qualitative form of the variation with chemical concentration $c(x, t)$ of the cell diffusion coefficient $D_n(c)$, the cell chemotaxis coefficient $\chi(c)$, and the chemical degradation rate per cell, $\delta(c)$, for the Keller–Segel approximation (1), (6) to our full model (4). The functional forms of these coefficients are given in (6). The maximum value of $D_n(c)$ occurs at $c = D_1(k_d + k_i)/[k_a\{2\Gamma D_2 - (1 - \beta\Gamma)D_1\}]$.

$-h_L \leqslant x < a$, and $c=0$ on $a < x \leqslant h_U + a$, while $n=0$ on $0 \leqslant x < a$ and $n=n_0$ at $x=a$. Here n_0 is the density of cells on the upper surface of the filter, that is $n_0 = N/(AL)$, where N is the total number of cells in the upper well, A is the cross-sectional area of the chamber, and L is a typical cell diameter. For neutrophils, $L \approx 10$ μm (Lentz, 1971; Buettner *et al.*, 1989a). The appropriate boundary conditions are $\partial c/\partial x = 0$ at $x = -h_L$ and $x = h_U + a$, $n=0$ at $x=0$ (assuming a sufficiently thick filter), and $\partial n/\partial t = J_n/L$ at $x=a$, where J_n is the cell flux. This last condition represents conservation of cells as they leave a one cell thick layer on the upper surface of the filter (Buettner *et al.*, 1989a,b; Sherratt *et al.*, 1993). In the case of the full model (4), a boundary condition for ρ at $x=a$ is also required, and we discuss this in detail in Appendix A.

Typical solutions of the two models subject to these end conditions are shown in Fig. 3; the parameter values are as discussed previously (Sherratt *et al.*, 1993), and to be specific, we take the experimental details from Harvath and Aksamit (1989). As illustrated in this figure, the two models have solutions with small, but visible, differences. As expected, the comparison improves even further if we increase the rate constants of the receptor kinetics, k_a, k_d and k_i, to a factor of 10 greater than their real values (Fig. 4). With these artificially fast kinetics, the approximate model (1), (6) is an excellent approximation to the full model (4), but even with the rate constants as observed experimentally at 37°C, the approximation is very good. Moreover, we have shown previously that the results of the full model (4) when applied to the Boyden chamber assay compare well with the corresponding experimental results (Sherratt *et al.*, 1993).

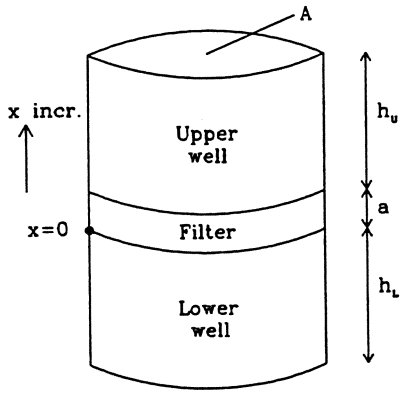

Figure 2. A schematic representation of the Boyden chamber assay. Cells are initially placed in the upper well, and crawl through the filter in response to a gradient of chemoattractant between the wells. For the solutions illustrated in Figs 3 and 4, we take the dimensions of the chamber to be as in the experiments by Harvath and Aksamit (1989), that is $h_L = 3.125$ mm, $h_U = 3.75$ mm, $a = 0.15$ mm and $A = 8$ mm^2.

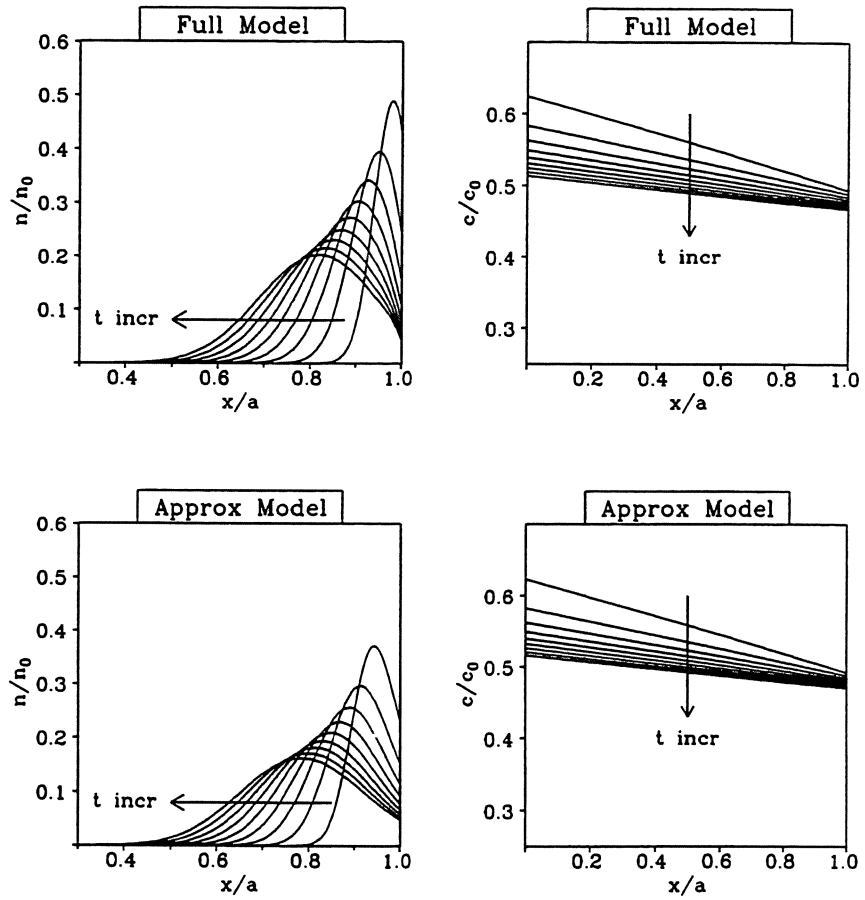

Figure 3. A comparison of the solutions of the full model (4) and our approximation to this model (1), (6) for the Boyden chamber assay. We plot the cell density $n(x, t)$ and the chemical concentration $c(x, t)$ as functions of position x in the filter at equally spaced times up to $t = 25$ min. The solution has the form of a wave of cell density moving through the filter, with the cell density on the upper surface decreasing as cells migrate into the filter. The parameter values are as discussed in detail by Sherratt *et al.* (1993), and the initial chemical concentration in the lower well, c_0, is 10^{-8} M. For internal consistency, the kinetic parameters are based on the single experimental study of Sklar *et al.* (1984). The cell transport coefficients determined by Sherratt *et al.* (1993) and used in this solution are rather different from those determined by Buettner *et al.* (1989a,b) from their Boyden chamber data, due to experimental differences such as pore size and density in the filter. The equations were solved numerically using a semi-implicit finite difference scheme.

The under-agarose assay. In this second *in vitro* assay, cells crawl under an agarose gel in response to a gradient of regulatory chemical, which diffuses through the gel. The assay was first used with small circular wells as sources of cells and chemical, resulting in a complex two-dimensional geometry (Nelson

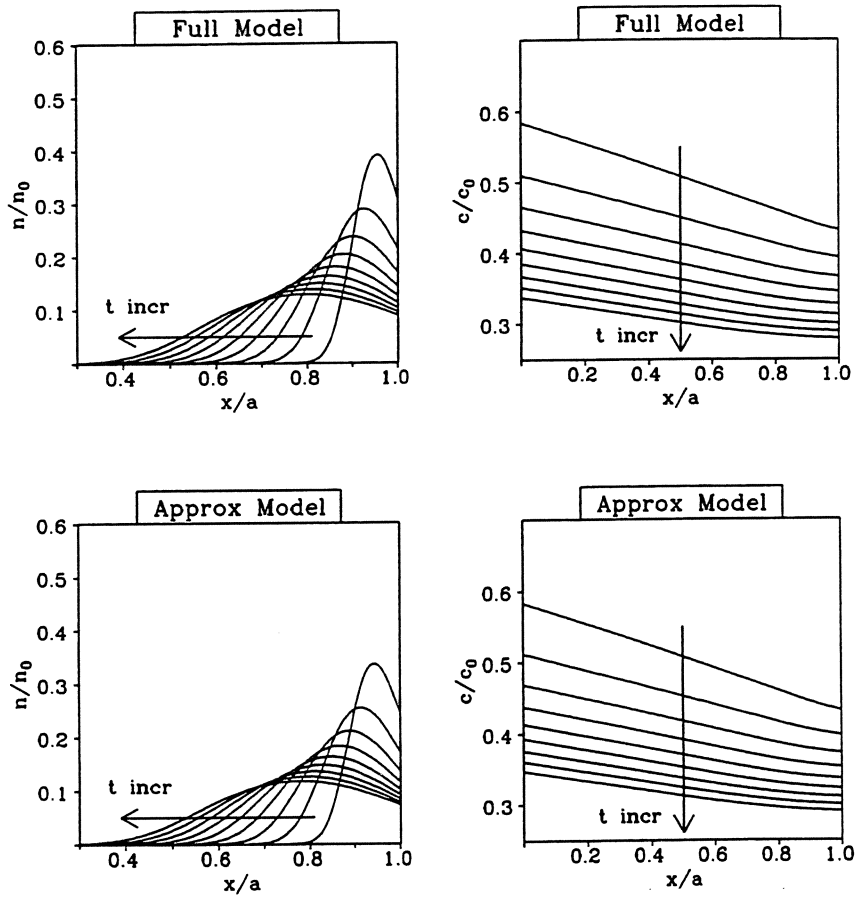

Figure 4. The effect of increasing the rate constants of the receptor kinetics on the solutions illustrated in Fig. 3. The solutions are obtained exactly as in Fig. 3, but with k_a, k_d and k_i all increased by a factor of 10. As expected, the comparison between the full and approximate models is improved with faster kinetics. Note also the much more rapid decrease in the chemical concentration in the filter, due to increased cellular degradation.

et al., 1975). However, Lauffenburger and coworkers have over the last decade developed a linear version of the assay, illustrated schematically in Fig. 5, which is much easier to model mathematically (Lauffenburger and Aris, 1979; Rothman and Lauffenburger, 1983; Lauffenburger *et al.*, 1983; Stickle *et al.*, 1985; Tranquillo *et al.*, 1988b; Farrell *et al.*, 1990). Initially the "attractant well" contains a given concentration of chemoattractant in gelled agarose, and the "cell well" contains a cell suspension which acts as a source for cells crawling under the gel. The two wells are separated simply by agarose gel.

The models (4) and (1), (6) can be applied to this assay in a straightforward

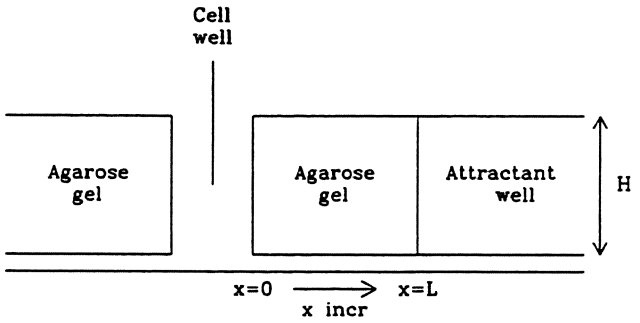

Figure 5. A schematic representation of the linear under-agarose assay. Cells crawl under the agarose gel from the cell well towards the attractant well. For the solutions illustrated in Figs 6 and 7, we take the dimensions of the assay to be as in the experiments of Tranquillo *et al.* (1988b), that is $L=6$ mm and $H=3$ mm.

way. With notation as in Fig. 5, the cell density $n(x, t)$ is defined on $[0, \infty)$ and the chemical concentration $c(x, t)$ is defined on $(-\infty, \infty)$; $c(x, t)$ satisfies the diffusion equation on $(-\infty, 0)$. Initially $c=c_0$, say, on $x>L$, and $c=0$ on $x<L$, while $n=0$ on $x>0$ and $n=n_0$ at $x=0$. Here n_0 is the cell density at the cell well boundary, which is constant because of an over-supply of cells in the well; this constancy is confirmed to be a very good approximation by direct experimental observation (Lauffenburger *et al.*, 1983; Tranquillo *et al.*, 1988b). Thus the appropriate boundary conditions are $n=n_0$ at $x=0$, $c=0$ at $x=-\infty$, and $n=0$, $c=c_0$ at $x=+\infty$. In Appendix A, we discuss the boundary condition for the receptor number $\rho(x, t)$ in the full model (4). Cellular degradation of the attractant means that the chemical concentration will vary slightly over the thickness of the agarose gel. However, we can reasonably neglect this variation and assume that the degradation rate is the same as if the receptors on the cells below the gel were distributed uniformly across the thickness of the gel. For modelling purposes, this defines n_0, as $1/(L^2H)$, where L is a typical cell diameter and H is the thickness of the gel. Usually $L \ll H$, reflecting the very small contribution of attractant degradation in this assay.

To be specific, we will consider the experimental details to be as in the study of Tranquillo *et al.* (1988b). The kinetic parameters will be the same as for the Boyden chamber, but the cell transport coefficients will be considerably higher, since cells move much faster under an agarose gel than when crawling through a low porosity filter. Assuming that $D(\rho)$ has the same shape in the two assays, there are thus two parameters to be determined: D_0 and χ_0. The former is just the cellular diffusion coefficient in the absence of attractant, which was determined by Tranquillo *et al.* (1988b) to be about 4×10^{-8} cm^2 s^{-1}. (This is about 60 times the value in the Boyden chamber used by Harvath and Aksamit,

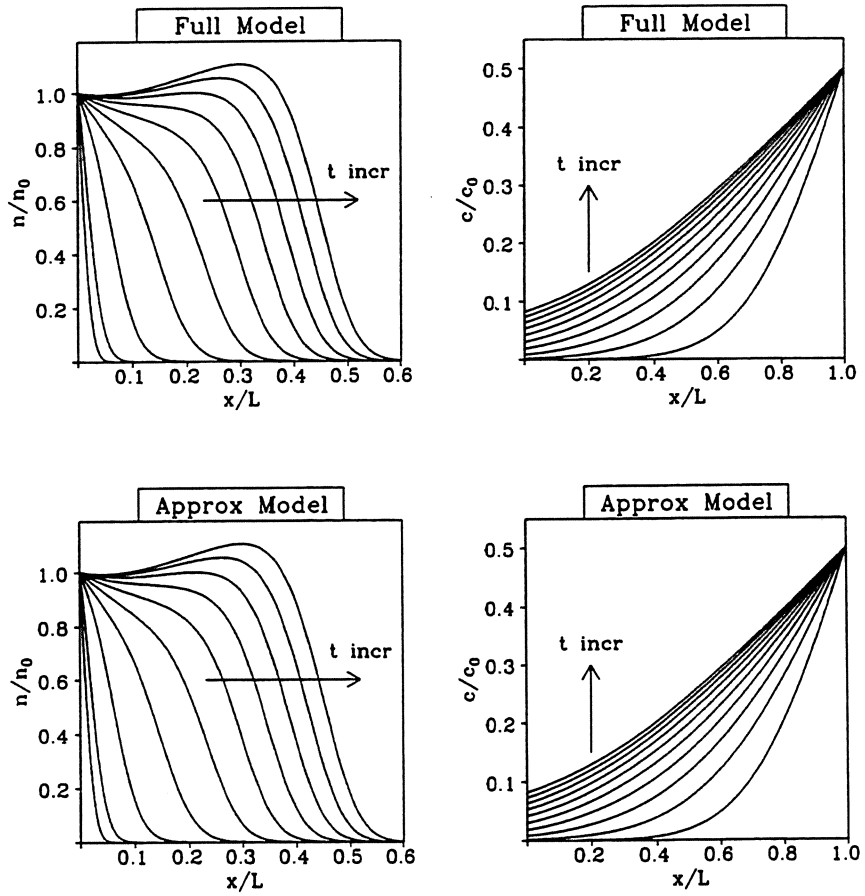

Figure 6. A comparison of the solutions of the full model (4) and our approximation to this model (1), (6) for the under-agarose assay. We plot the cell density $n(x, t)$ and the chemical concentration $c(x, t)$ as functions of position x between the cell and attractant wells, at equally spaced times up to $t = 4h$. The solution has the form of a wave of cell density moving under the gel towards the attractant well, with the cell density at the cell well boundary kept constant by an over-supply of cells in the cell well. The initial chemical concentration in the attractant well is 3×10^{-7} M. The kinetic parameter values are as discussed in detail by Sherratt *et al.* (1993), and the cell transport coefficients are $D_0 = 4 \times 10^{-8}$ cm^2 s^{-1}, $D_1 = 1.5 \times 10^{12}$ cm^2 s^{-1} mol^{-1}, $D_2 = 9.2 \times 10^{30}$ cm^2 s^{-1} mol^{-2}, and $\chi_0 = 1.2 \times 10^{14}$ cm^2 s^{-1} mol^{-1}. As expected, this value of χ_0 gives values of $\chi(c)$ of the same order of magnitude as those found by Tranquillo *et al.* (1988b), who use the same data to determine cell transport coefficients. The equations were solved numerically using a semi-implicit finite difference scheme.

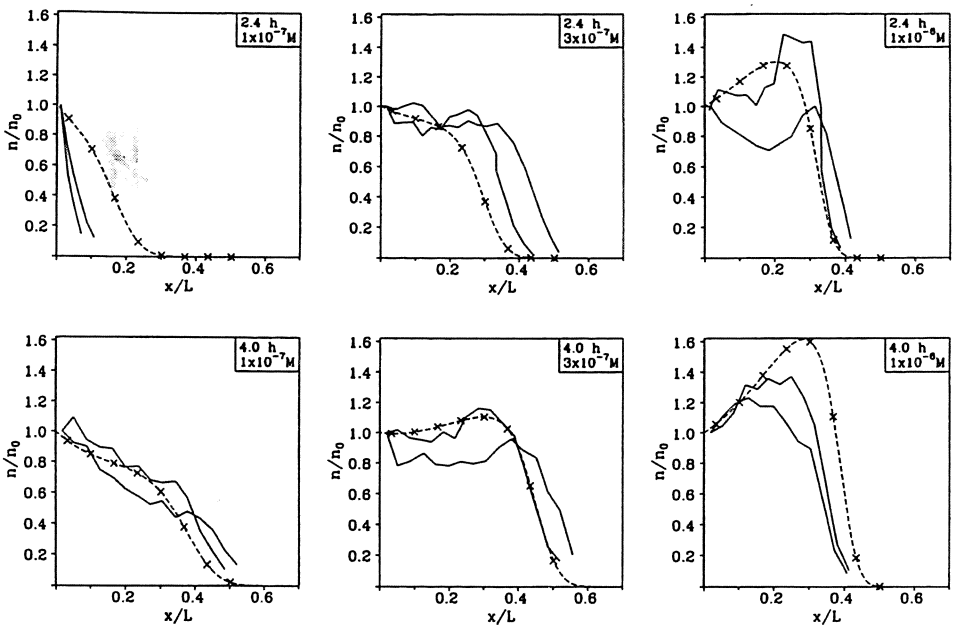

Figure 7. Comparison between the model solutions and the experimental data of Tranquillo *et al.* (1988b). We plot the cell density $n(x, t)$ as a function of distance between the cell and attractant wells for three values of the initial chemical concentration in the cell well, and in each case at 2.4 and 4.0 hr after the start of the experiment. The model parameter values and method of solution are as in Fig. 6. (——— experimental results of Tranquillo *et al.* (1988b); – – – – – solutions of the full model (4); × solutions of the approximate model (1), (6).)

1989.) We determined the remaining free parameter χ_0 by fitting the solutions of the full model to the experimental results of Tranquillo *et al.* (1988b).

As in the Boyden chamber assay, the solutions of the full and approximate models, (4) and (1), (6), compare extremely well for this assay (Fig. 6). The variation of cell density with position under the gel was actually determined experimentally by Tranquillo *et al.* (1988b), using automated cell counting. The model solutions compare well with these experimental results, as illustrated in Fig. 7.

Discussion. The general model of Keller and Segel (1971a,b) for chemotaxis and chemokinesis has been successfully applied to a wide range of biological systems. However, before the model can be used in a particular case, appropriate functional forms must be specified for the dependence on chemical concentration of the cell transport coefficients and the chemical degradation rate. In the vast majority of applications in the literature, these functional forms

have been chosen based directly on simple intuitive criteria. Here, we have focused on the case of eukaryotic cell movement, with the neutrophil–peptide system as our paradigm. We have shown that the detailed model of Sherratt *et al.* (1993) for this case can be well approximated by a simpler model of Keller–Segel form. This enables the functional forms of the transport coefficients and chemical degradation rate to be deduced from the full model.

Given the great success of the Keller–Segel approach to chemical control of cell movement, it is no surprise that a more detailed model for the phenomenon can be approximated by a simpler model of Keller–Segel form. Moreover, in the absence of a detailed quantitative experimental understanding of the underlying processes, it is inevitable that the full model is itself based to some extent on intuitive criteria, and the functional forms that the detailed model implies for $\chi_n(c)$ and $\delta(c)$ are not new, and have been used by a number of previous authors (e.g. Ford and Lauffenburger, 1991; Lauffenburger *et al.*, 1984). The contribution of our approach is threefold. Firstly, we have predicted a consistent set of functional forms for the transport coefficients and degradation rate; secondly, we have related the parameter values in these functions to experimentally measurable quantities; and thirdly, our derivation clarifies the way in which the forms of the transport coefficients depend on a variety of underlying assumptions and approximations. In the case of the neutrophil–peptide system, our approximation is validated by the good agreement between the solutions of the full and approximate models.

A crucial outstanding question is whether the approximate model will be valid for systems other than neutrophils and *N*-formylated peptides. To answer this, we must calculate and compare the time scales of cell movement, chemical diffusion and receptor kinetics. We show in Appendix B that in the absence of cell movement, the occupied receptor density approaches its equilibrium value with a half life of about $\ln 2/[k_d+k_i+(1-\beta\Gamma)k_aC]$, where C is an order of magnitude estimate for the chemical concentration. We expect the approximate model to be valid provided this half life is much shorter than the time scales of chemical diffusion and of cell movement into regions of different chemical concentration, since both of these processes tend to alter the chemical–receptor equilibrium; estimation of these time scales is discussed in Appendix B. In the case of the neutrophil–peptide system, the half life with which the occupied receptor density reaches equilibrium is about 20 sec. In comparison, the time scales of chemical diffusion and cell movement are about 2 min and 2.5 hr respectively in the Boyden chamber assay, and bout 3.5 min and 30 min respectively in the under-agarose assay (see Appendix B). However, these time scales will be different both in different experimental situations and for different cell types, and it is important to calculate them in each case. This simple calculation provides a rapid check on the validity of our Keller–Segel approximation.

APPENDIX A

When applying the full model (4) to the Boyden chamber and under-agarose assays, a boundary condition on $\rho(x, t)$ is required at the cell source ($x=a$ and $x=0$, respectively). In both cases, the cell source consists of a region of spatially homogeneous cell density, which remains spatially homogeneous throughout the experiment. This requires that $\partial J_n/\partial x=0$, where J_n is the cell flux, which implies that $\partial^2\rho/\partial x^2=0$, and we take this as the boundary condition on ρ in both cases. (For the thin filter Boyden chamber assay, in which cells and thus their receptors migrate through the filter onto the lower surface, different end conditions are appropriate (Sherratt *et al.*, 1993)). This condition can be incorporated very naturally into the numerical scheme. We use a semi-implict finite difference method, in which we evaluate $\partial\rho/\partial x$ by a one-sided difference, taken in the direction in which n is predominantly increasing; this is necessary for convergence, as expected from the theory of numerical solution of hyperbolic equations (Smith, 1985). The scheme is given explicitly in Sherratt *et al.* (1993). The boundary condition at the cell source can be most easily incorporated simply by representing $\partial\rho/\partial x$ at the boundary by a one-sided difference in the opposite direction, which implies that $\partial\rho/\partial x$ is the same at the boundary and at the adjacent space node.

APPENDIX B

Neglecting the transport term in equation (4d) gives the following equation for $\rho(x, t)$, the number of bound receptors per cell:

$$\partial\rho/\partial t=\Gamma k_a c-[k_d+k_i+(1-\beta\Gamma)k_a c]\rho.$$

Substituting the constant order of magnitude estimate C for $c(x, t)$ then gives a straightforward equation with solution:

$$\rho-\frac{\Gamma k_a C}{k_d+k_i+(1-\beta\Gamma)k_a C}\propto\exp\{-[k_d+k_i+(1-\beta\Gamma)k_a C]t\}.$$

This suggests that in the absence of cell movement, $\rho(x, t)$ will approach the value (5) implied by our assumption of infinitely fast kinetics with a half life of about $\ln 2/[k_d+k_i+(1-\beta\Gamma)k_a C]$. This must be compared with the time scales over which the chemical concentration changes in the neighbourhood of a cell. Such change occurs for two reasons: Cells move into regions of different chemical concentration, and chemical diffusion alters the concentration profile. The time scales of these processes can be estimated as L_c/S and L_c^2/D_c, respectively. Here S is an order of magnitude estimate of the cell speed. Rivero *et al.* (1989) have shown that cell speed $s(c)$ and random motility $D_n(c)$ are related by $s(c)=[2D_n(c)/P]^{1/2}$, where P is a typical time between direction changes during cell movement; for neutrophils, $P\sim 1$–5 min (Tranquillo *et al.*, 1988). Thus we can take $S=[\{D_0+D_1^2/(4D_2)\}/P]^{1/2}$, since $\{D_0+D_1^2/(4D_2)\}/2$ is the average of the unstimulated and maximum values of $D_n(c)$. L_c denotes the length scale over which the chemical concentration changes significantly, which can be calculated directly from estimates of c and $\partial c/\partial x$. Note that L_c, and thus these time scales, will be different for different experimental assays. In the Boyden chamber assay, $D_0+D_1^2/(4D_2)=1.5\times10^{-9}$ cm^2 s^{-1}, $D_c=7.3\times10^{-6}$ cm^2 s^{-1} and $L_c\sim0.03$ cm, so that $L_c/S\sim2.5$ hr and $L_c^2/D_c\sim2$ min. In the under-agarose assay, the random motility about 60 times larger and $L_c\sim0.04$ cm, so that $L_c/S\sim30$ min and $L_c^2/D_c\sim3.5$ min. In both cases we estimate L_c as the length over which c changes by about 10% of its typical value.

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