Biophysical Chemistry 4 (1976) 151–157

INHOMOGENEOUS STATIONARY STATES IN REACTION–DIFFUSION SYSTEMS

Stephen M. McPHAIL, Michael A. COLLINS and Robert G. GILBERT
Department of Theoretical Chemistry, University of Sydney, N.S.W., Australia 2006

Received 8 September 1975
Revised manuscript received 20 November 1975

Inhomogeneous stationary solutions for reaction–diffusion equations are of interest with regard to the chemical basis of morphogenesis. Numerical means of determining such solutions and of testing their stability to small perturbations are examined, and applied to shape formation in three systems: the "Brusselator" and "Lotka–Volterra" mechanisms, and a simple model for slimemould aggregation.

1. Introduction

Chemical systems which give rise to spontaneous shape formation and which may be described in terms of reaction-diffusion equations are of considerable biological interest, in terms of a chemical basis for cell differentiation, formation and morphogenesis: the establishment and maintenance of structure [1,2]. Such "symmetrybreaking" systems result in spatially nonuniform concentrations, the best-understood experimental example of which is the Belousov–Zhabotinskii reaction [3]. On the theoretical side, considerable progress has been made in establishing general criteria for the instability of homogeneous *initial* conditions for a given reaction scheme [2,4,5] and in the actual solution of the partial differential equations describing its evolution [2,6]. In the present paper we examine means of calculating the *final inhomogeneous stationary states* (ISS) which such systems can attain in one dimension, and since not all stationary states are stable to small fluctuations, we also examine how the stability of these states may be determined. These procedures enable us, for example, to see if a postulated mechanism is, indeed, capable of describing a particular experimental observation without doing a complete numerical solution of the coupled partial differential equations for reaction and diffusion. The general numerical techniques discussed here complement results obtained by analytical solutions for particular systems, such as the elegant work of Auchmuty and Nicolis [7].

In section 2 we set up a computational technique for determining one-dimensional inhomogeneous stationary states, as solutions to coupled ordinary differential equations with double-ended boundary conditions. In section 3 we examine necessary and sufficient conditions for the stability of these states to small disturbances. In section 4 we apply these methods to several simple systems of interest: the Brusselator mechanism [2,3] (to confirm our results by comparison with the approximate analytical solutions of Auchmuty and Nicolis [7]), the Lotka–Volterra mechanism with diffusion included [2], and a simple model describing the aggregation of cellular slimemoulds in response to a chemotactic signal [8–10].

2. Inhomogeneous stationary states

We confine ourselves here to a one-dimensional system, although the methods discussed below can be extended to higher dimensions using hyperbolic or elliptic partial differential equation techniques [10]. We assume that the temporal and spatial development of the system is described by a set of coupled parabolic partial differential equations of the form:

$$\frac{\partial \phi}{\partial t} = f[\phi] + D\frac{\partial^2 \phi}{\partial x^2}, \qquad (1)$$

where $\phi \equiv (\phi_1, \ldots, \phi_k, \ldots, \phi_K)$ is the K-dimensional

vector of concentrations, $f[\phi] \equiv (f_1, \ldots, f_K)$ a nonlinear vector function describing the kinetics, and $\mathbf{D}$ the matrix of diffusion coefficients. The inhomogeneous stationary state, ϕ^0, is defined by

$$f[\phi^0] + \mathbf{D}\frac{d^2\phi^0}{dx^2} = 0, \tag{2}$$

with appropriate boundary conditions. These conditions are usually constant concentrations or zero flux at the two boundaries. The latter corresponds to active transport across the membrane within the cell walls. Such boundary conditions are inapplicable to several problems of interest, such as the Belousov–Zhabotinskii reaction or the slimemould aggregation investigated in section 4: in both cases we have a closed system in lieu of an open system with appropriate boundary conditions. However, it is reasonable in such cases to suppose that the semi-quantitative form of the solutions can be reproduced by judicious selection of boundary values in an open system; a test of the validity of such procedures would be to see whether the solutions so obtained were drastically different for slightly altered boundary conditions.

Under certain conditions it is possible to derive an analytic solution for the ISS by a perturbation expansion near the first bifurcation [7]. Beyond this region, however, numerical methods must be used. This involves the solution of nonlinear differential equations with double-ended boundary values, a problem whose numerical difficulties are well appreciated. The difficulty lies in the nonlinearity which often causes the divergence of solutions with boundary values only slightly different from those required. We have used an algorithm based on one of the standard methods of solving this type of problem [12], which converges for most problems attempted. We take the set of K coupled second order differential equations for ϕ^0, eqs. (2), and convert them to a set of $2K$ first-order equations by the substitution:

$$y_k = \phi_k^0, \qquad y_{k+K} = d\phi_k^0/dx, \qquad k = 1, \ldots, K.$$

The values of y_k $(k = 1, \ldots, K)$ at, say, the left-hand boundary are known. Values of y_{k+K} at this boundary, y_{k+K}^{L}, are estimated, and using these initial conditions the equations are integrated to obtain y_k at the other boundary. Denoting those values obtained at the other boundary by y_k^{obt} and those required by the boundary conditions by y_k^{req}, we then minimize the function

$$g(y_{k+K}^{\mathrm{L}}, k = 1, K) = \sum_{k=1}^{K} (y_k^{\mathrm{obt}} - y_k^{\mathrm{req}})^2,$$

with respect to the difference between the required values and those actually obtained.

The minimization of this function of the slopes at the first boundary is best performed using the simplex method [12]. The convergence of this procedure is strongly dependent on the initial estimates of y_{k+K}^{L}. We have found that divergence can usually be avoided by first solving the simpler problem of finding values for y_{k+K} that can be integrated to yield y_k^{req} over a smaller region of space. The values of y_{k+K}^{L} thus obtained are used as the initial estimates for an extended region, the process being repeated until the required distance is covered. Even using this method, it still proved possible for the estimates indicated by the minimization procedure to lead to divergence. This divergence is often associated with the transition from a length of region with one charactistic solution to another [7] (e.g., to solutions which differ greatly in initial slope but with shape similar to other solutions). The problem was overcome in two ways: (i) by having the integration subroutine halt and return a large number to the function $g(y_{k+K}^{\mathrm{L}})$ if either y_k began to diverge or the error became large and (ii) by including a facility which enabled the first region examined to be of sufficient length that transitions were avoided during the extension process. Initial estimates obtained by, e.g., the zeroth order analytical approximation of Auchmuty and Nicolis [7] could also be used, although no attempt was made to do this for the problems solved here.

3. Stability criteria

Criteria for the stability of an ISS that have been used previously have been confined either to linearized kinetics or have referred to *local* stability [13]. By local stability one refers to stability with respect to a perturbation confined to a small region, so that the stability at a given distance x may be examined independently of the behaviour for other values of x. We consider here *global* stability, i.e., stability with respect to *any* small perturbation, including those which affect the whole region of space considered. We first derive a straightforward necessary and sufficient con-

dition based on the set of ordinary differential equations obtained by writing eq. (1) in a way suitable for solution by a second order difference method [10]. We break the region of space under consideration into N compartments each of width h. Each compartment is assumed to be homogeneous in space. Further assuming that the spacial dependence of $\phi(x,t)$ between any three adjacent compartments defines a parabola, the Fick's law diffusion term in eq. (1) may be rewritten, for the kth species in the nth compartment, ϕ_{kn}, as

$$D_k\,\partial^2\phi_{kn}/\partial x^2 = D_k(\phi_{k,n-1}+\phi_{k,n+1}-2\phi_{k,n})/h^2,$$

where for convenience we have assumed the diffusion matrix to be diagonal with non-zero elements D_k. Hence, if the boundary conditions are constant concentration, eq. (1) is equivalent to the $K\times(N-2)$ set of equations of the form

$$\mathrm{d}\phi_{kn}/\mathrm{d}t = f_k(\phi)+D_k(\phi_{k,n-1}+\phi_{k,n+1}-2\phi_{k,n})/h^2,$$

in the limit of small h [we have $K\times(N-2)$ rather than $K\times N$ equations since it is clear that there can be no variation in the first and last compartments, these being the boundaries]. Standard methods for the numerical solution of eq. (1) are based on this procedure [10]. Similar sets of equations result from the use of other boundary conditions, such as zero flux. To derive the stability criterion, we linearize eq. (2) about one of its ISS solutions, $\phi^0(x)$, which has component ϕ^0_{kn} for the kth species in the nth compartment. Consider a small perturbation of $\phi^0(x)$:

$$\phi(x,t) = \phi^0(x)+\delta\phi(x,t).$$

Writing the column vector ψ as:

$$\psi = (\delta\phi_{1,2},\ldots,\delta\phi_{K,2},\ldots,\delta\phi_{K,N-1}),$$

we have from eq. (2):

$$\frac{\mathrm{d}\psi}{\mathrm{d}t} = \Omega\psi,$$

where Ω is a $K(N-2)\times K(N-2)$ matrix whose elements are:

$$\Omega_{ll} = \partial f_k/\partial\phi_k - 2D_k/h^2, \qquad l = iK+k,\ i \text{ an integer},$$

$$\Omega_{lm} = D_k/h^2, \qquad m = l+K, l-K \text{ for } 0<m\leqslant(N-2)K,\ m\neq l,$$

$$\Omega_{lm} = \partial f_{m'}/\partial\phi_k, \qquad m = jK+m',\ i \text{ and } j \text{ integers},$$

$$m\neq l,\ l = iK+k,\ m = (l-K+1),\ldots,(l+K-k),$$

$$\Omega_{lm} = 0, \qquad \text{otherwise.}$$

A necessary and sufficient condition for the global stability of ϕ^0 is that $\psi\to 0$ as $t\to\infty$. Hence eq. (4) implies that ϕ^0 will be globally stable if all the eigenvalues of Ω have only negative real parts in the limit of small h. This condition is necessary and sufficient as long as h is small enough that the finite difference equations are equivalent to the partial differential equations. A numerical test for this equivalence is to see if any appreciable change in the solutions is obtained by reducing h.

Since this result is valid only for large N, an analytic solution cannot be expected. Numerical determination of stability requires finding the largest eigenvalue of a very large non-hermitian matrix. The numerical problem may be reduced since we require only the largest eigenvalue and since the matrix is banded (all elements $K+1$ or more away from the diagonal are zero). Although the numerical difficulties are by no means trivial, finding the eigenvalues using even standard techniques [14] requires only about as much computer time as determining the ISS itself.

One alternative to actually solving the eigenvalue problem is to use the ISS plus some small perturbation as the initial input to a numerical solution of eq. (1) (by finite difference) to see if the ISS is re-attained. Although not a rigorous demonstration of stability, a rapid divergence does indicate instability, and this method requires much less computer time and storage than the full eigenvalue approach. It is also a convenient means of separating quasi-stable states (i.e., those where the largest eigenvalues are positive but very small) from truly unstable ISS. A quasi-stable state would be indistinguishable from one that is truly stable in a real system.

A third global stability criterion is through the existence of the vector function $\psi_s(x) = \int_0^\infty \delta\phi(x,t)\mathrm{e}^{-st}\,\mathrm{d}t$, where $\delta\phi$ is an arbitrary small perturbation on the ISS ϕ^0. Since our boundary conditions require that $\delta\phi$ be zero at the boundaries, we then have

$$\frac{\mathrm{d}^2\psi}{\mathrm{d}x^2} = -\mathbf{D}^{-1}\mathbf{G}(x) - \delta\phi(x,t=0), \tag{7}$$

where the elements of the matrix $\mathbf{G}(x)$ are $G_{kk'}$ =

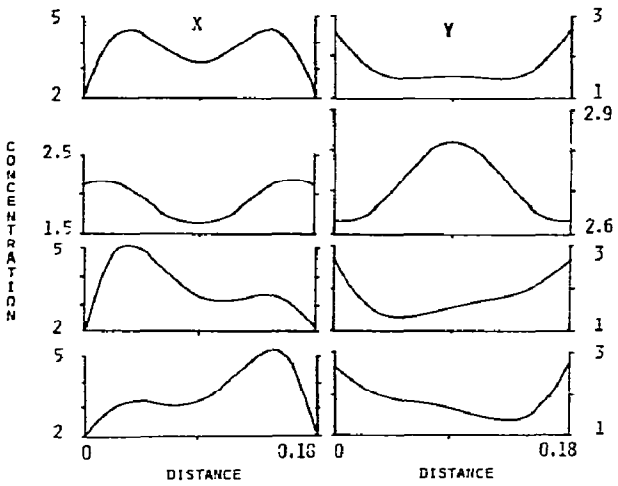

Fig 1. Stable and unstable inhomogeneous stationary state concentrations of X and Y for the Brusselator mechanism.

$\partial f_k/\partial\phi_{k'} - s\delta_{kk'}$. The existence of a solution of eq. (7) for an arbitrary $\delta\phi(x, t=0)$ and $s = 0$ obeying the conditions of $\delta\phi = 0$ at both boundaries is a sufficient (but not necessary) condition for global stability, and is necessary but not sufficient for $s > 0$.

4. Applications

4.1. The Brusselator mechanism

This hypothetical reaction scheme has been the subject of extensive investigation [2,7,15]. We apply our methods to it as a check on our analysis. The dimensionless reaction–diffusion equations are

$$\partial X/\partial t = X^2 Y - (B+1)X + A + D_X \partial^2 X/\partial x^2,$$

$$\partial Y/\partial t = BX - X^2 Y + D_Y \partial^2 Y/\partial x^2.$$

Stationary states for $A = 2$, $B = 5.24$, $D_X = 1.6\times10^{-3}$, $D_Y = 8\times10^{-3}$, with boundary values of $X = 2.1$, $Y = 2.63$, over a length of 0.18, are shown in fig. 1 (note that solutions may exist in addition to those obtained by the computer using a particular error tolerance and allowed range of initial gradients; no special significance should be attached to the fact that only solutions with positive gradients in X were found). Our results are similar to the approximate analytical solutions derived by Auchmuty and Nicolis for the case where $A(x) = A^0 \cosh[2\alpha(x-\frac{1}{2})]/\cosh\alpha$, for $\alpha > 0$. In confirmation of the conclusions of ref. [7], it is of interest to note (a) that of the four stationary states found by the computer for this particular set of parameters, only the first is stable, and is the only one to which a numerical solution of the complete partial differential equations evolves, and (b) that *asymmetric* stationary states are possible. This last result is of interest with regard to the formation of asymmetry in natural systems [16].

4.2. The Lotka–Volterra mechanism

This has also been extensively studied theoretically [2,15]; it is well known that the *homogeneous* system cannot give rise to a stable limit cycle. The dimensionless reaction–diffusion equations are:

$$\partial A/\partial t = -AB + k'A + D_A \partial^2 A/\partial x^2,$$

$$\partial B/\partial t = AB - kB + D_B \partial^2 B/\partial x^2.$$

Our results for the stationary states of this system show that a stable stationary structure may be formed. In fig. 2 we show the results of a stationary state computation with $k' = 0.09$, $k = 0.9$, $D_A = D_B = 1$, with boundary values $A = 1$, $B = 0.1$. This shape is stable. It is of course primarily a boundary-layer effect; no oscillatory spatial structure has been found using this mechanism.

4.3. Slime mould aggregation

The spontaneous aggregation of a culture of *D. discoidium* amoeba is one of the simplest examples of morphogenesis, and is the precursor of cell differentation in the species. The mechanism for this aggregation is fairly well established, several detailed mathematical models having been developed [8,9,11,17]. An amoeba emits a series of pulses of a chemotactic agent, cAMP, that stimulate neighbouring amoebae to emit pulses themselves and then to migrate towards the first amoeba, provided that the concentrations of both cAMP and the amoebae are sufficiently high. The cAMP is also degraded by reaction with an enzyme.

We procede to show that the average spacing between clumps of aggregated amoebae can be deduced by a simple application of the theory developed above. Because of the limited quantitative data available for

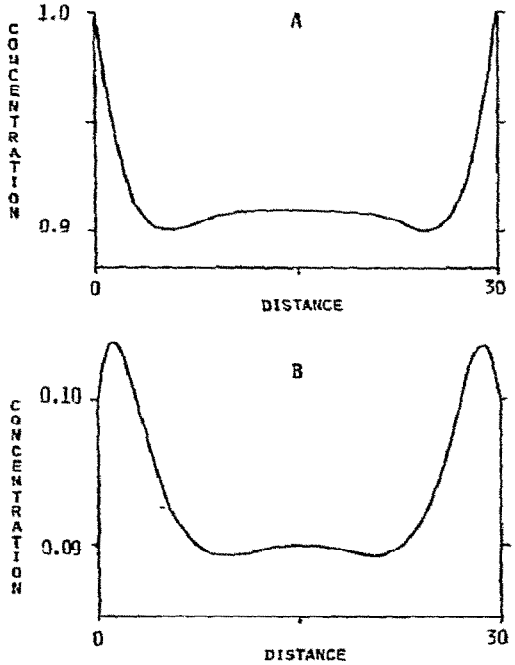

Fig. 2. Stationary state concentrations of A and B for the Lotka–Volterra mechanism.

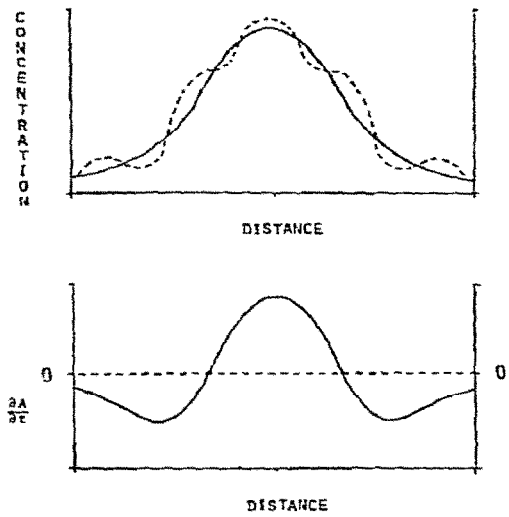

Fig. 3. Upper diagram: schematic variation of pulsatile concentration (----) and averaged concentration (——) of cAMP with distance. Lower diagram: schematic variation of the time differential of averaged amoeba concentration with distance.

the system, we are forced to make crude estimates for several of the parameters involved, but fortunately our final result depends only weakly on these estimates. Our simplified model is adapted from that of Keller and Segel [8]. We do not consider the detailed pulsatile emission of cAMP and pulsatile migration of amoebae; instead we replace these rapidly varying concentrations (in space) by concentrations averaged over a length greater than that of pulsatile variation but short compared to the overall aggregation length (see fig. 3). These smoothly varying concentrations are denoted C and A respectively. We assume that no other variables need be considered.

We next assume that the diffusion of cAMP follows Fick's Law with diffusion coefficient D_C. Following Robertson and Cohen [9], we estimate this coefficient from the Stokes–Einstein relation to be $4 \times 10^{-10} \mathrm{m^2 s^{-1}}$. We further assume that cAMP is emitted by amoebae with first-order rate constant f, with respect to amoeba concentration above a critical value A^0; below this critical value, cAMP is absorbed by amoebae, perhaps by complexing with an enzyme, with the same first-order rate constant f. A^0 is about 10^{-14} M [18], and we have estimated f from the data of Malkinson and Ashworth [19] to be $1.5 \times 10^2 \mathrm{s^{-1}}$. The self-diffusion of amoebae is taken to have a simple Fick form with diffusion coefficient D_A, estimated from the Stokes–Einstein equation to be $\sim 2 \times 10^{-13} \mathrm{m^2 s^{-1}}$, for an amoeba radius of 1 μm. The movement of amoebae under a chemotactic gradient is also given a Ficks' law dependence, with a negative diffusion coefficient $-D_{AC}$ considered as an off-diagonal element of the matrix of diffusion coefficients [20]. Thus chemotactic diffusion considered in isolation from the other processes obeys the equation:

$$\partial A/\partial t = -D_{AC}\partial^2 C/\partial x^2. \tag{8}$$

This form is physically quite reasonable (although somewhat different from that assumed by Keller and Segel). Suppose the smoothed concentration of cAMP emitted from a small group of amoebae centered about the origin has the gaussian form illustrated in fig. 3. Amoebae near the origin will move towards it, whereas those further away (where the cAMP concentration falls below the critical value) will not move. Thus A should increase in time near the origin and decrease in time further away; this gives an x dependence of $\partial A/\partial t$ with the qualitative form of the negative of the second

differential of a gaussian, as illustrated. An estimate for the value of D_{AC} is obtained as follows. Consider a single amboeba near a group of amoebae emitting cAMP, and consider a small time interval, say 10 s, when the single amoeba migrates to join the group but as yet does not influence its neighbours, so that its motion is governed by eq. (8) alone. The local value of A has then dropped from its homogeneous value of $\sim 1.5 \times 10^{14}$ M [21] to zero; thus locally $\partial A/\partial t \approx 1.5 \times 10^{15}$ M s^{-1}. The velocity of amoeba under such conditions is observed to be $\sim 2 \times 10^{-5}$ m s^{-1} [9], and thus the distance involved is $x \approx 2 \times 10^{-4}$ m. Assuming that C diffuses from an initial gaussian distribution of the form $C(t=0) = B \exp(-\beta x^2)$, we have:

$$C(t) = B(1+4D_C\beta t)^{-1/2} \exp[-\beta x^2/(1+4D_C\beta t)], \quad (9)$$

where B is the initial pulse, approximately 2×10^{-7} M [21]. We estimate β by assuming that the initial shape corresponds to spontaneous emission by a small number of amoeba: $\beta \approx 2 \times 10^7$ m^2 is a rough value. We may then substitute eq. (9) into eq. (8), and use the above values to obtain a value of 3×10^{-16} m^2 s^{-1} for D_{AC}. This is obviously a very primitive estimate, but it is found to vary only by about a factor of 2 if our estimates of range or β are changed by an order of magnitude.

We then have the following over-all reaction–diffusion equations for the system:

$$\partial A/\partial t = -D_{AC}\partial^2 C/\partial x^2 + D_A \partial^2 A/\partial x^2,$$

$$\partial C/\partial t = D_C \partial^2 C/\partial x^2 + f(A - A^0).$$

The stationary state form of these equations has a simple sinusoidal analytical solution. Choosing the boundary conditions to be such that the minimum amoeba concentration is zero, we have:

$$A = A^0(1 - \cos kx), \qquad k^2 = D_{AC} f / D_A D_C. \quad (10)$$

Using the values of the constants f, D_A, D_{AC}, D_C found above, this gives a spacing between the clumps of the order of 1 mm, corresponding to that observed experimentally.

This solution can be directly shown to be stable using the sufficient stability criterion of eq. (7). Putting $a = \int_0^\infty \delta A(x,t)\,dt$, and letting $p(x)$ be the initial perturbation in A, we see that a general solution to eq. (7) obeying the left-hand boundary condition $a(x=0) = 0$ is [22]:

$$a(x) = k^{-1} \int_0^\infty p(\xi) \sin k(x-\xi)\,d\xi + E \sin kx,$$

where E is a constant to be fixed by the right-hand boundary condition. The required boundary condition $a(x=L) = 0$ can always be obtained by choosing

$$E = (k \sin kL)^{-1} \int_0^L p(\xi) \sin k(L-\xi)\,d\xi,$$

except for the special case where L is an integral multiple of $2\pi/k$. Since we may write down a general solution of eq. (7) obeying the required boundary conditions for an arbitrary perturbation, the inhomogeneous stationary state of eq. (10) is stable.

Obviously as the amoebae approach the maximum concentration of $2A^0$ predicted by the above, additional kinetic terms will come into effect, and the simple sinusoidal concentration predicted by our treatment will break down. However, since the concentration of amoebae between clumps will then be practically zero, the average spacing between clumps will have been determined in accordance with the simple mechanism given above. Since the initial homogeneous distribution is unstable, we have a true dissipative structure [2].

The above examples illustrate the general usefulness and applicability of the computation of stationary states and the determination of their stability.

Acknowledgement

A helpful discussion with Professor P. Fife is gratefully acknowledged.

References

[1] A.M. Turing, Phil. Trans. Roy. Soc. (London) B237 (1952) 37.
[2] P. Glandsdorff and I. Prigogine, Thermodynamic Theory of Structure, Stability and Fluctuation (Wiley–Interscience, London, 1971).
[3] E. Körös, M. Burger, V. Friedrick, L. Ladanyi, Z. Nagy and M. Orban, Faraday Symp. 9 (1974)
[4] J.J. Tyson and J.C. Light, J. Chem. Phys. 59 (1973) 4164.
[5] B.L. Clarke, J. Chem. Phys. 62 (1975) 3726.

[6] M.A. Collins and R.G. Gilbert, Chem. Phys. 5 (1974) 49; G. Rosen, J. Chem. Phys. 63 (1975) 417.
[7] G. Nicolis and J.F.G. Auchmuty, Proc. Nat. Acad. Sci. USA 71 (1974) 2748; J.F.G. Auchmuty and G. Nicolis, Bull. Math. Biol., in press.
[8] E.F. Keller and L.A. Segel, J. Theor. Biol. 26 (1970) 399.
[9] M.H. Cohen and A. Robertson, J. Theor. Biol. 31 (1971) 101.
[10] M.H. Cohen and A. Robertson, J. Theor. Biol. 31 (1971) 119.
[11] A. Ralston and H.S. Wilf, Mathematical Methods for Digital Computers (Wiley, New York, 1960).
[12] J.A. Nelder and R. Mead, Computer J. 7 (1965) 308.
[13] G.R. Gavalas, Nonlinear Differential Equations of Chemically Reacting Systems (Springer, Berlin, 1968).
[14] J.H. Wilkinson, The Algebraic Eigenvalue Problem (Clarendon Press, Oxford, 1965).
[15] G. Nicolis and J. Portnow, Chem. Rev. 73 (1973) 365.
[16] A. Babloyantz and J. Hiernaux, Faraday Symp. 9 (1974).
[17] A. Robertson and M.H. Cohen, Ann. Rev. Biophys. Bioeng. 1 (1972) 409.
[18] T.M. Konyn and K.B. Raper, Devl. Biol. 3 (1961) 725.
[19] A.M. Malkinson and J.M. Ashworth, Biochemical J. 134 (1971) 311.
[20] D. Fitts, Nonequilibrium Thermodynamics (McGraw–Hill, New York, 1962).
[21] G. Gerisch, H. Fremm, A. Huesgen and U. Wick, Nature 255 (1975) 547.
[22] R. Courant, Differential and Integral Calculus (Blackie, London, 1956).