Patterns of Spatial Organization in Growth

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Patterns of spatial concentration profiles arising in one-dimensional reaction-diffusion systems in the course of variations of the characteristic dimension of the system (growth) are analyzed. The spatial profiles established and their changes depend on the character of the steady state pattern dependence on length. If the families of solutions (spatial profiles) arising at $L = n L_1^*$, $n L_2^*$ form closed curves, and a slow (quasistationary) linear or exponential increase of the characteristic dimension is considered, then subsequently more complex patterns of spatial concentration profiles appear regularly in a reproducible way. The system keeps every established pattern for a fixed interval of time which depends on the rate of growth. Implications for two different interpretations of the morphogen gradient formation in the models of embryogenesis are discused.

Introduction

The formation of new structures from an initially homogeneous system is a cooperative process where interaction between the basic units of the system (photons, cells, organisms) causes instability of the originally homogeneous state and evolution of spatially or spatial-temporary organized structures [1, 2]. It is a common feature of most systems that after appearance (bifurcation) of the first (most simple) structure, subsequently more complicated structures appear with a change of the value of the characteristic parameter. Very often a large number of such patterns can coexist for the same values of the governing parameters, and it depends on initial conditions which pattern will finally evolve in the system [3]. When some parameter of the system changes continuously in time (e. g. depletion of initial reaction components, change of the characteristic dimension in reaction-diffusion systems) then the question arises about what spatial structures will follow in what sequence. The answer can help e. g. in constructing reaction-diffusion models of morphogen gradient formation in embryogenesis [4, 5] and is of general interest in the study of dissipative structures in biological, chemical and physical systems.

We shall discuss several results obtained in reaction-diffusion systems. In principle we should consider the stochastic description of the process and include the description of the effect of fluctuations on the character of transitions between individual patterns. A detailed molecular theory, however, is out of question and complete microscopic simulations are not feasible. Discrete simulation methods, e. g. reactive molecular dynamics simulation [6] look promising but seem to require excessive amounts of computational work. Hence we have resorted first to the study of deterministic models, which, as we believe, should indicate qualitatively the correct macroscopic behaviour.

Dependence of patterns in reaction-diffusion systems on length

Let us consider two coupled partial differential equations of the parabolic type for the time and spatial changes (in one dimension only) of the concentrations x and y of two reaction components [1]:

$$\frac{\partial x}{\partial t} = \frac{D_x}{L^2} \frac{\partial^2 x}{\partial z^2} + f(x, y), \tag{1 a}$$

$$\frac{\partial y}{\partial t} = \frac{D_y}{L^2} \frac{\partial^2 y}{\partial z^2} + g(x, y). \tag{1 b}$$

Here D_x, D_y are diffusion coefficients; L is a characteristic length, t the time, $z \in [0,1]$ a spatial coordinate and $f(x, y)$, $g(x, y)$ are reaction rate functions. We can consider various boundary conditions, e. g. fixed concentrations at the boundaries of the system:

$$x(0, t) = x(1, t) = \bar{x}; \quad y(0, t) = y(1, t) = \bar{y} \tag{2 a}$$

or zero flux at the boundaries:

$$\frac{\partial x(0, t)}{\partial z} = \frac{\partial y(0, t)}{\partial z} = \frac{\partial x(1, t)}{\partial z} = \frac{\partial y(1, t)}{\partial z} = 0. \tag{2 b}$$

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Let $\bar{x}, \bar{y}$ denote the trivial steady state solution of the reaction diffusion system, where

$$f(\bar{x}, \bar{y}) = 0, \quad g(\bar{x}, \bar{y}) = 0. \tag{3}$$

Let us define

$$\begin{pmatrix} a_{11}, & a_{12} \\ a_{21}, & a_{22} \end{pmatrix} = \begin{pmatrix} \dfrac{\partial f(\bar{x}, \bar{y})}{\partial x}, & \dfrac{\partial f(\bar{x}, \bar{y})}{\partial y} \\ \dfrac{\partial g(\bar{x}, \bar{y})}{\partial x}, & \dfrac{\partial g(\bar{x}, \bar{y})}{\partial y} \end{pmatrix} \tag{4}$$

and consider the characteristic length L as a bifurcation parameter. The bifurcation of spatial structures from the trivial solution $x = \bar{x}, y = \bar{y}$ (homogeneous solution) will occur at the values of bifurcation lengths, where the linearized operator

$$L = \begin{pmatrix} \dfrac{D_x}{L^2}\dfrac{d^2}{dz^2} + a_{11}, & a_{12} \\ a_{21}, & \dfrac{D_y}{L^2}\dfrac{d^2}{dz^2} + a_{22} \end{pmatrix} \tag{5}$$

has an eigenvalue of an odd multiplicity with zero real part [1, 7]. If this eigenvalue is real, then nonuniform stationary solutions bifurcate from the trivial solution (real bifurcation); if the eigenvalue is purely imaginary, new time periodic (wavelike) solutions bifurcate (complex bifurcation). The eigenvalues $\lambda_n(L)$ are determined from the relation

$$\lambda_n(L) = P_n(L) \pm \sqrt{P_n^2(L) - Q_n(L)} \tag{6}$$

where

$$P_n(L) = 1/2[a_{11} + a_{22} - (D_x + D_y)E]$$
$$Q_n(L) = D_x D_y E^2 - (D_y a_{11} D_x a_{22})E$$
$$\quad + a_{11} a_{22} - a_{12} a_{21}$$

and

$$E = (n\pi/L)^2.$$

The real bifurcation occurs if $Q_n(L) = 0$ and the complex bifurcation if $P_n(L) = 0$ and $Q_n(L) > 0$. It follows from the form of $P_n(L)$, $Q_n(L)$ that we need to evaluate the bifurcation lengths from the relations (6) only for $n = 1$ ("elementary" bifurcation lengths-real: L^*, complex: L^{**}). At most one complex and two real elementary bifurcation lengths can exist. All other primary bifurcation lengths are then their multiples $L^{(n)} = n L^*$.

The conditions of existence of bifurcation lengths are given in the Table 1. Here $a = a_{11}/\sqrt{-a_{12} a_{21}}$, $b = a_{22}/\sqrt{-a_{12} a_{21}}$, $R = D_x/D_y$. As we can infer

Table 1. Elementary bifurcation lengths ($a_{12} a_{21} < 0$).

$ab < -1$	one real bifurcation length L^* exists
$a + \mathrm{R}b > 0$ $\;\;$ $\|a - \mathrm{R}b\| > 2\sqrt{R}$	two real bifurcation lengths $L^*_{1,2}$ exist
$a + b > 0$ $\;\;$ $\|a - \mathrm{R}b\| < 1 + R$	one complex bifurcation length L^{**} exists
otherwise	no bifurcation lengths exist

from Table 1, in the case where $ab < -1$ one bifurcation length always exists regardless of the ratio of the values of diffusion coefficients. The condition $ab < -1$ can be realized in systems where the homogeneous solution $\bar{x}, \bar{y}$ of the kinetic equations $f(\bar{x}, \bar{y}) = g(\bar{x}, \bar{y}) = 0$ is of the saddle type. If the solutions in the system without spatial gradients are multiple, usually one of them is of the saddle type and thus the direct connection of the multiplicity of solutions with the existence of spatial dissipative structures arises. For the fixed boundary conditions (2 a), where the uniform solution $\bar{x}, \bar{y}$ is stable for small values of the length L, thus stable nonuniform solutions (spatial patterns) can always exist [7].

The bifurcation of spatial patterns and their change in situations where the length increases slowly with time will depend on the character of the continuous dependence of the stationary spatial concentration profiles on the length. This dependence was obtained by numerical techniques for a number of reaction-diffusion models [8 – 11]. Here we shall discuss only the situations where no complex bifurcations occur. The results are shown in Figures 1 – 3.

In Fig. 1 the situation, where in the homogeneous system we have multiple solutions is illustrated. The so called SH model, proposed by Selkov [12] for the description of the changes of S-H and S-S groups concentrations has for the chosen values of parameters three trivial solutions, one of them stable, two unstable. In Fig. 1 a the dependence of the flux at the boundary, $(dx/dz)_{z=0}$, on the length is shown. Here we have only one bifurcation length (cf. Table 1 and Legend to Fig. 1), and as it follows from the results of simulation [10], the families of the solution bifurcating at L^* do not close on themselves. The solution with the wavenumber $n = 1$ (and also the other solutions with the increasing wave numbers) can continue to exist for the increasing length and will be stable until secondary bifurcation occurs. Hence if we start the
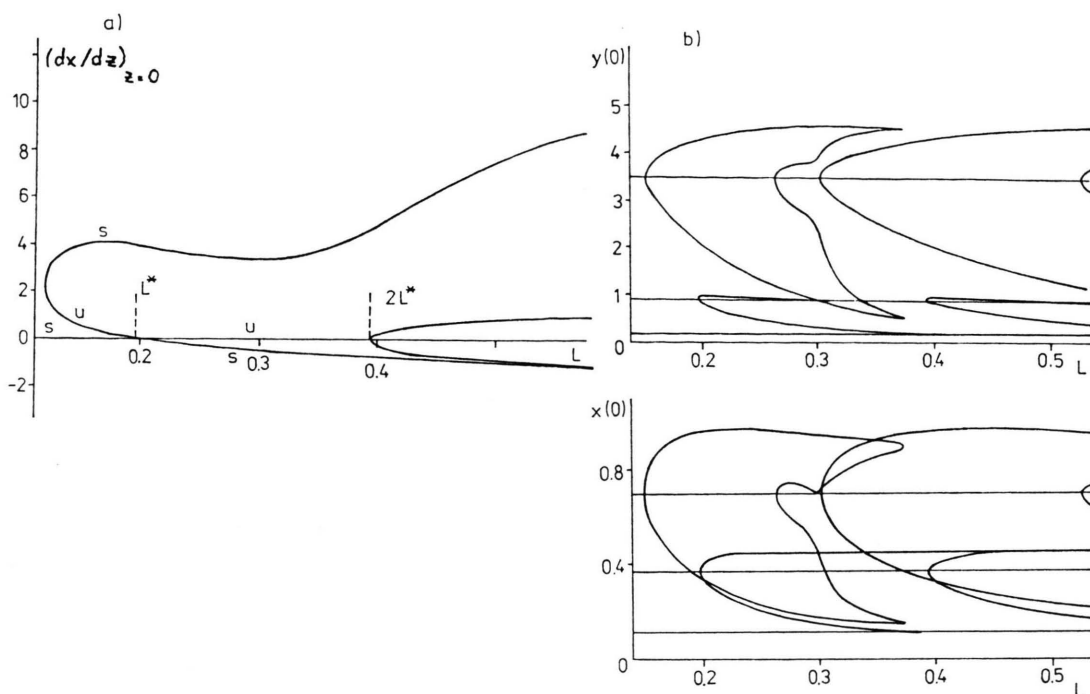
Fig. 1. Dependence of the steady state solution on the length. SH model, $f(x, y) = \alpha(\nu_0 + x^\gamma)/(1 + x^\gamma) - x(1 + g(x, y) = x(\beta + y) - \delta y$; $\alpha = 12$, $\gamma = 3$, $\delta = 1$, $\nu_0 = 0.01$, $D_x = 0.008$, $D_y = 0.004$.

Trivial solutions:

i	$\bar{x}_i$	$\bar{y}_i$	character of solution in homogeneous system	L^*
1	0.1157	0.1962	stable focus	—
2	0.3728	0.8915	saddle	0.1965
3	0.7006	3.5106	unstable node	0.2630, 0.1516

Fig. 1a. The dependence of $(\mathrm{d}x/\mathrm{d}z)_{z=0}$ on L, boundary conditions (2a);
The solutions bifurcating at x_2, y_2 (saddle). s-stable solution, u-unstable solution.

Fig. 1b. The dependence of $x(0)$ on L, boundary conditions (2b); the solutions bifurcating at $\bar{x}_2$, $\bar{y}_2$ and $\bar{x}_3$, $\bar{y}_3$.

simulation of the change of the solution with a slow increase of the length of the system (growth) the spatial profile does not change its character during the growth and the system will preserve the qualitative character of the spatial distribution attained after the first bifurcation.

The situation can be more complicated for the case shown in Fig. 1 b, where the zero flux boundary conditions (2 b) are considered. The solutions bifurcating at the different trivial solutions can be mutually interconnected and common families of solutions can arise through secondary bifurcations. The nonuniform solutions shown in Fig. 1 b are unstable for the particular case studied.

In Fig. 2 the dependence of the steady state concentrations of the components x, y at the boundary $(x(0), y(0))$ on the characteristic length is shown for the Brussellator model [1] and the zero flux boundary conditions (2 b). In this case two bifurcation lengths L_1^* and L_2^* can be observed (here $2 L_1^* > L_2^*$). The trivial (homogeneous) solution is stable for the interval of lengths $L \in (0, L_1^*)$, unstable for $L \in (L_1^*, L_2^*)$, again stable for $L \in (L_2^*, 2 L_1^*)$ and unstable for $L \in (2 L_1^*, 2 L_2^*)$. When we simulate the behaviour of spatial profiles under the conditions of the slow growth (see later), then the homogeneous (trivial) profile becomes unstable at $L = L_1^*$, changes into the spatial structure
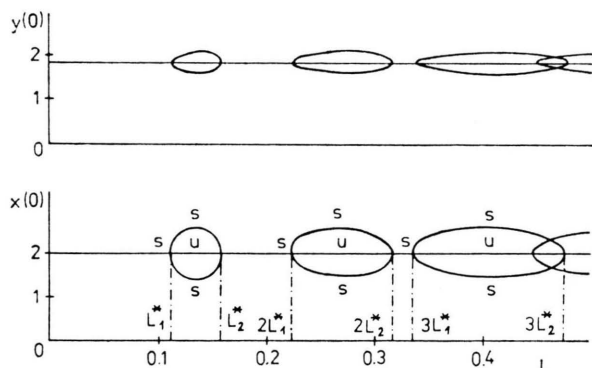
Fig. 2. The dependence of the steady state solution on the length. Brussellator.

$$f(x, y) = A + x^2 y - (B + 1) x,$$
$$g(x, y) = B x - x^2 y.$$
$$A = 2, \; B = 3.7,$$

$D_x = 0.0016$, $D_y = 0.008$, boundary conditions (2b); $\bar{x} = 2$, $\bar{y} = 1.85$; $L_1^* = 0.1115$, $L_2^* = 0.1583$; s — stable solution, u — unstable solution.

with the wavenumber $n = 1$ which between L_1^* and L_2^* will be stable and slowly change its gradient. At $L = L_2^*$ the spatial structure will change smoothly into the homogeneous solution which will become stable and will be established in the system. At $L = 2 L_1^*$ the spatial structure with wavenumber $n = 2$ becomes stable and will be preserved by the system until $L = 2 L_2^*$. The families of solutions for the higher wavenumbers can be obtained from the first family of solutions bifurcating at $L = L_1^*$, by the method of composing of solutions [8, 9].

In Fig. 3 the dependence of the concentration x at the boundary, $x(0)$ on the characteristic dimension L is presented for Meinhardt's model of morphogenesis [5, 13] and the zero flux boundary conditions (2 b). Here two bifurcation lengths L_1^* and L_2^* exist and $L_2^* > 2 L_1^*$ (cf. legend of Figure 3). The families of solutions bifurcating at $L = n L_1^*$, $n = 1, 2, \ldots$ and at $L = n L_2^*$ form closed curves. The stable solutions are shown as full lines, the unstable solutions as dashed lines. We can see from the figure that the solutions bifurcating at $n L_1^*$ are stable until the limit point of the family of solutions (LP in Fig. 3) is reached. The solutions bifurcating at $n L_2^*$ are unstable. An increasing number of stable solutions (bifurcating at $L = L_1^*$, $2 L_1^*$, $3 L_1^* \ldots$) with different wavenumbers can coexist when the dimension of the system is increased. The solutions for higher wavenumbers can again be obtained by composing from the family of solutions bifurcating at L_1^* and L_2^*.
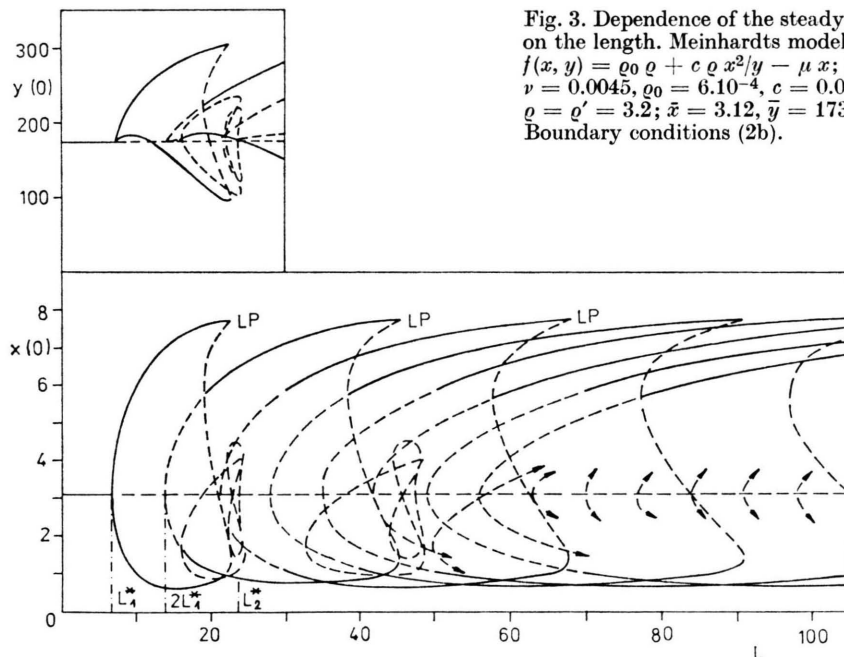

Fig. 3. Dependence of the steady state concentration at the boundary on the length. Meinhardts model.
$f(x, y) = \varrho_0 \varrho + c \varrho \, x^2/y - \mu \, x$; $g(x, y) = c' \varrho' x^2 - \nu \, y$; $\mu = 0.0035$, $\nu = 0.0045$, $\varrho_0 = 6.10^{-4}$, $c = 0.05$, $c' = 0.025$; $D_x = 0.01$, $D_y = 0.45$, $\varrho = \varrho' = 3.2$; $\bar{x} = 3.12$, $\bar{y} = 173.056$; $L_1^* = 7.0349$, $L_2^* = 23.7548$. Boundary conditions (2b).

Change of stable spatial patterns in growth

The process of differentiation in embryogenesis and other processes of evolution of spatial dissipative structures occurs in a transient situation, where the characteristic dimension L and/or other parameters change in time. We shall discuss the results of a simulation of the behaviour of the spatial concentration profiles in growth for the most interesting case of the three cases described in Figs. 1 – 3, i. e. for the case shown in Figure 3.

Let us consider two types of the functional relations describing the increase of the characteristic dimension L with the time:

a) linear growth $L = L_0 + a_1 t$,   (7)

b) exponential growth $L = L_0 e^{a_2 t}$.   (8)

In Fig. 4 the results of the following simulation experiment are shown: we have started with a small dimension of the system where the uniform profiles of the concentrations are stable and have allowed the reaction and diffusion to proceed simultaneously with an increase of the dimension of the system according to (7). The dependence of the concentration at the boundary $x(0)$ (zero flux boundary conditions (2 b) are considered) on changing L is shown in Fig. 4 together with the characteristic spatial profiles at the varying lengths (i. e. times of the growth). A relatively slow change (in comparison) with the characteristic diffusion and rection times) of L with time ($a_1 = 0.0002$) is considered. We can see from Fig. 4 that the uniform concentration profile after the loss of stability changes abruptly into a nonsymmetric spatial concentration profile which belongs to the first closed curve in Figure 3. The form of the concentration profile remains practically the same over the region of its stability. There are two possibilities for the evolution of profiles $x_{1,2}(z)$, the cases $x_1(0) > x_1(1)$ and $x_2(1) > x_2(0)$, where the profiles $x_{1,2}(z)$ are mutual mirror images. The choice of one of the two profiles is random and in the simulation depends on the numerical constants used and the round-off errors encountered. For example, the upper way was calculated for $\Delta t = 125$
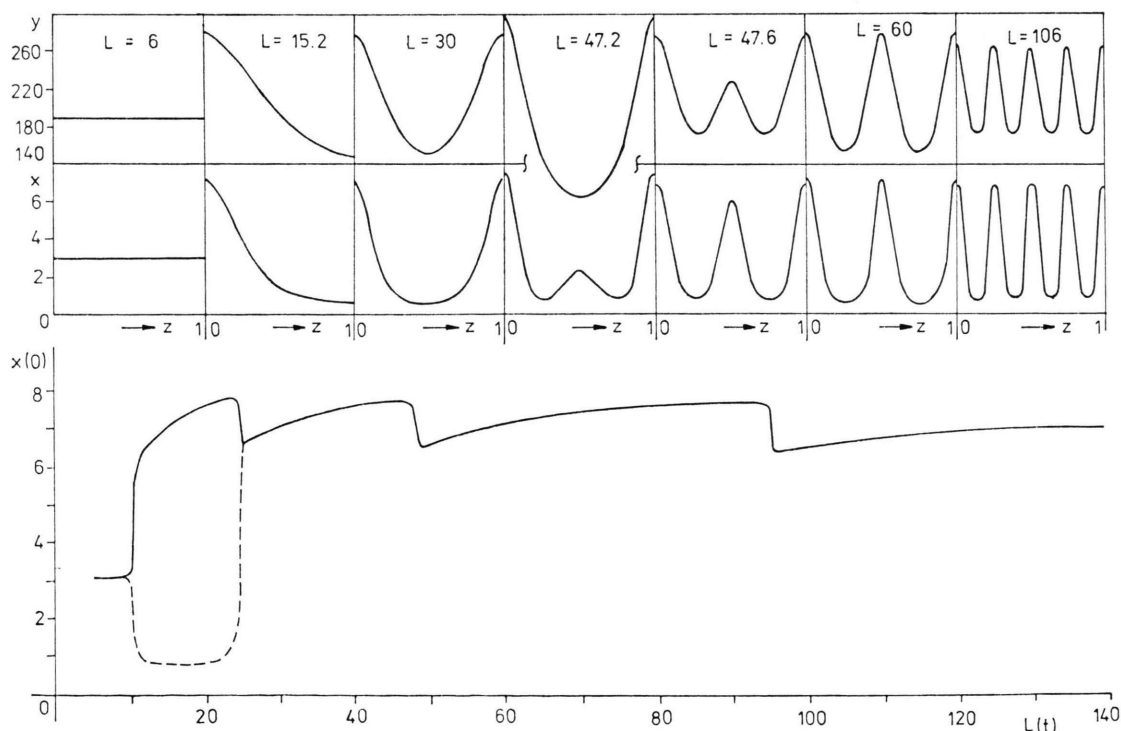

Fig. 4. The concentration x at the boundary during the linear growth. Meinhardts model, boundary conditions (2b), for the parameters see Figure 3.
$L_0 = 6$, $a_1 = 0.0002$, 48 space increments have been used for the numerical approximation, time step $\Delta t = 125$; Spatial profiles of x for several values of L are presented in the upper part of the Figure.

and the lower way resulted from the numerical calculation with $\Delta t = 250$, cf. Figure 4. In an actual physico-chemical or biological system fluctuations of concentrations which will be magnified in the neighbourhood of the bifurcation value L_1^* will determine whether $x_1(z)$ or $x_2(z)$ will appear. Also small imperfections in the system (e. g. in the symmetry etc.) can determine the choice of $x_1(z)$ or $x_2(z)$. The profile with one maximum changes into a profile with two maxima at the value of $L \doteq 25$ and the profile with three maxima appears at $L = 50$. At $L = 95$ we observe that profiles with five maxima occur. If we compare Fig. 4 with Fig. 3, we can see that the exchange of the profiles with increasing length can occur in two qualitatively different ways. The first one can be described as "travelling" on the stable branches of the steady state solutions. Here the change from one profile with a certain qualitative characteristics (e. g. number of maxima of the concentration profile, i. e. wavenumber) into the qualitatively different profile occurs at the bifurcation points, i. e. at the points of the intersection of the two branches of the solution where these branches exchange their stabilities. The second type of exchange of profiles occurs at the limit points of

branches of solutions, where the original branch of the solution ceases to exist for higher values of the length. The solution of the transient equations is then attracted by the "near" stable steady state solution. The changes of the profiles in one such transition process are also shown in Figure 4. It can be concluded from Fig. 4 that the pattern of concentration profiles is reproduced for multiples of L from the stable elementary profiles (first closed loop in Figure 3). This is true for the boundary conditions (2 b) and for the relatively slow growth rate. The case $a_1 = 0.0002$ used here can be considered as quasistationary, where the stationary states are not disturbed by the slow increase in the length. Very similar results have been obtained also for the exponential growth described by (8) with $L_0 = 6$, $a_2 = 0.00002$. For $a_1 = 0.002$ and the linear growth both processes (the transient behavior and the change of L in time) occur on a similar time scale and therefore the correspondence between transient results and steady state results for low L here does not exist. This correspondence appears for $L = 60$ and the higher values of L.

In Fig. 5 the results of the simulation for the fixed boundary conditions (2 a) are shown. The
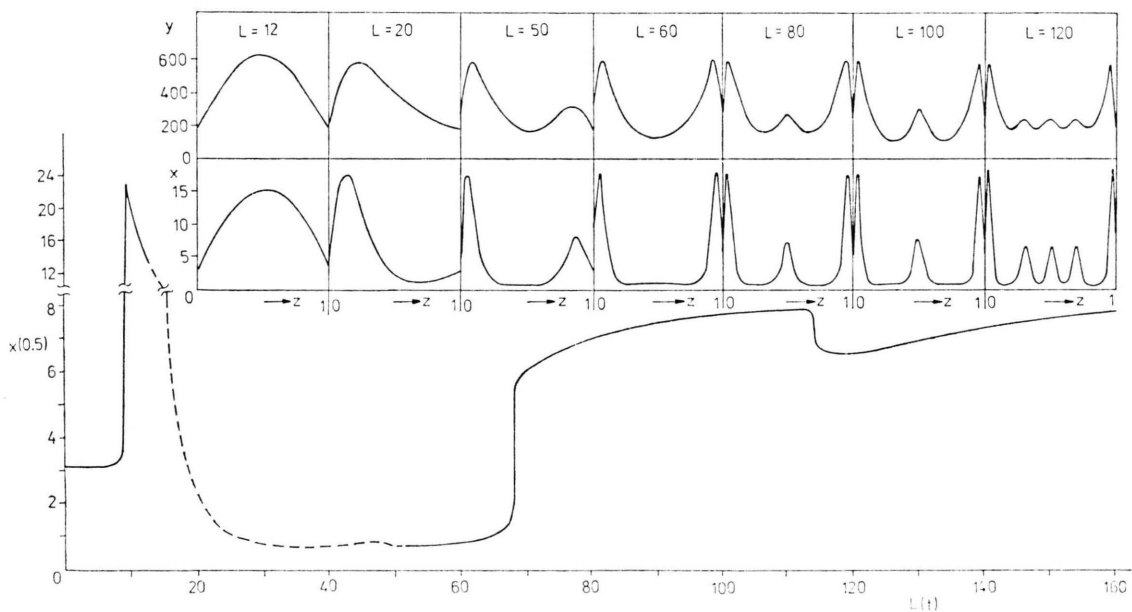

Fig. 5. The concentration x in the middle of the system ($x(0.5)$) during the linear growth. Meinhardts model, boundary conditions (2a), for the parameters see Figure 3. $L_0 = 6$, $a_1 = 0.0002$, 80 space increments have been used for the numerical approximation, time step $\Delta t = 125$, ——— symmetric spatial profiles, ····· asymmetric spatial profiles.

choice of the first nontrivial branch after $L > L_1^*$ occurs again at random. The profiles at the chosen values of the characteristic length are shown in the Figure. Similarly as for the boundary conditions (2 b) we observe that the number of maxima increases with the transition from one branch to another one. For the linear growth rate relation (7), the time interval of existence of the particular spatial profile of the morphogen doubles with every increase of the number of maxima of the profile. For the exponential growth rate (8) the time periods do not depend on the number of maxima.

Discussion and conclusions

Let us compare the results on the nonhomogeneous spatial concentration profiles established in the reaction-diffusion systems in growth with the central ideas used in the models of embryogenesis. Kauffman and coworkers [4] have used the two dimensional reaction-diffusion model for the description of the sequence and geometries of compartmental boundaries in Drosophila melanogaster. The authors [4] propose that subsequently more complex spatial concentration patterns bifurcating at different bifurcation lengths on a disc can be used for coding of the information on the development of various compartments. As we have shown for the one-dimensional example, such a sequence of the spatial concentration patterns can be generated in a reproducible way. However, the regions of existence of individual patterns are not determined by the bifurcation points, as the authors [4] consider, but can be, for example, determined by the location of the limit points in the dependence of the steady state solutions on the particular parameters.

When we are comparing our one-dimensional results for the transition between the various spatial profiles in growth with the results of models which consider two spatial dimensions, we have to discuss the question whether a similar ordering of modes occurs also in this case, where the Laplacian is not separable. The problem of the change of stability in the essentially autonomous systems (i. e. the evolution through the point of bifurcation or the point where the particular branch of the solution terminates) has not received sufficient attention in the mathematical literature. Lebovitz and Schaar [15] discuss the case where the change of stabilities occurs for the system of ordinary differential equations at the bifurcation points as a singular perturbation problem. We have not been able to locate any other work, particularly such which would be applicable to the system of partial differential equations. Haken and Olbrich [16] have used the method of generalized Ginzburg-Landau equations introduced by Haken for the solution of the two-dimensional Gierer-Meinhardt model. Within a rectangular domain with the no flux boundary conditions they have confirmed the existence of roll-type and hexagonal patterns, the complexity increasing with the mode number. In a cylindrical geometry patterns corresponding to rotation symmetric Bessel functions were determined. Erneux and Herschkowitz-Kaufman [17] have obtained for a circular reaction medium two types of spatiotemporal patterns for the Brussellator model. No studies of the change of the stationary patterns with slowly varying dimensions of the system were considered in the above papers. We can guess that the transitions between the multiple solutions will in such a case again occur at the bifurcation and limit points of the particular branches of solutions. However, the main feature which appears when the dimensionality of the medium increases is that the explicit form of the wavenumber $E = (n\pi/L)^2$ of the Laplacian operator has to be decomposed into its components along the different dimensions. In a rectangle of dimensions L_1, L_2, we shall for example have [18]

$$E = \left(\frac{n\,\pi}{L}\right)^2 = \left(\frac{n_1\,\pi}{L_1}\right)^2 + \left(\frac{n_2\,\pi}{L_2}\right)^2$$

Hence more than one eigenfunction may correspond to the same eigenvalue of the Laplacian operator, and we can expect that the transitions in growth occuring between various qualitatively different branches of solutions can be more complex than in the one-dimensional case.

Meinhardt [5] uses for coding the information on the development the single spatial asymmetric concentration profile of the morphogen (profile bifurcating at $L = L_1^*$ with the wavenumber $n = 1$). As we have shown in the paper, length limited or unlimited stable profiles can be observed in all the three cases discussed. Such a profile can also be obtained in a system with multiple steady states and finite fluxes at the boundaries, as it was proposed by the first author in other circumstances, cf. [14].

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