Impaired Diffusion Coupling-Source of Arrhythmia in Cell Systems

Igor Schreiber, Milan Kubíček, and Miloš Marek
Department of Chemical Engineering, Prague Institute of Chemical Technology, 16628 Prague 6, Czechoslovakia

Z. Naturforsch. **39 c,** 1170–1179 (1984); received December 3, 1982/May 16, 1984

Reaction-Diffusion Systems, Dissipative Structures, Oscillations, Synchronization, Arrhythmias

A detailed analytical and numerical analysis of a simple reaction-diffusion model of the source of non-homogeneities and arrhythmias in an originally homogeneous reaction system is presented. Solution, bifurcation and evolution diagrams are used to describe the behaviour of the model. It is shown that under certain conditions steady and/or oscillatory nonhomogeneous states are the only stable solutions of the model. These phenomena are essentially not dependent on a particular reaction kinetics. A possible relevance to some biological situations is discussed.

I. Introduction

Cell systems with intercellular communication and properly defined set of chemical reactions occurring in individual cells serve as widely studied models of tissues and cell populations. Thus Turing [1] has formulated well known reaction-diffusion model of morphogenesis on the basis of coupled cell systems with mutual mass exchange by diffusion. Gmitro and Scriven [2] and Othmer and Scriven [3] have studied various problems of stationary and dynamic patterns in cellular networks and started a renewal of interest in the theoretical aspects of Turing's theory. A model of chemical oscillators confined to two boxes coupled by diffusion through a semipermeable membrane has been used by Tyson and Kauffman [4] to describe biochemical control of the mitotic cycle in the acellular slime mold Physarum polycephalum. The kinetic mechanism of chemical oscillations was described by a set of equations used by Prigogine and Lefever [5] in the original study of two box diffusion problem (Brusselator model). Tyson and Kauffman have found that both homogeneous and inhomogeneous (different in the two cells) steady states and limit cycles can exist for specific values of reaction and diffusion parameters. The authors have stressed that the existence of inhomogeneous limit cycles is of considerable theoretical significance in the understanding of cellular differentiation, which requires both "a map", to provide positional information and "a clock" to coordinate activities of the cell system in time [6]. Tyson [7] has used a special case of coupling between two boxes, somewhat similar to our model. Landahl and Licko [8] also studied coupled cells with other kinetic systems.

Ashkenazi and Othmer [9] discussed the effects of diffusion on the dynamics of biochemical oscillators for general kinetic mechanism and for a simplified model of glycolysis. They have found that if the diffusion is sufficiently rapid, the population of oscillators relaxes to a globally synchronized oscillation, but if the diffusion is slow enough, the synchronized oscillation can be unstable and a nonuniform (inhomogeneous) steady state or an asynchronous oscillation can arise. The authors have stressed the significance of these results for models of contact inhibition and for the formation of zonation patterns. The effects of cell density and metabolic flux between cells on the collective dynamics of a cell population have been studied by Othmer and Aldrige [10]. For diffusion coupled glycolysis see also [21–23]. Shapiro and Horn [11] have studied analytical criteria relating statics and dynamics of a reaction-diffusion cell system to the algebraic structure of the underlying reaction mechanism. Ross and coworkers [12] discussed cooperative instability phenomena in arrays of catalytic sites. They have also used Prigogine-Lefever Brusselator reaction mechanism and predicted conditions necessary for occurrence of oscillations. Experimental results on oscillatory behaviour in the system of two coupled cells with mutual mass exchange and the complex Belousov-Zhabotinski

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reaction have been reported by Marek and Stuchl [13]. Relative stability of coexisting steady states in two coupled cells has been investigated recently [14], and coexistence of various inhomogeneous steady states in the hexagonal system of seven reaction-diffusion cells has been established experimentally [15].

II.1. The Model

In this paper we study a special case of the reaction-diffusion cell system, *i.e.* that of a single compartment with diffusional coupling to a homogeneous environment. We assume that large number of reaction cells with intensive mutual coupling surround a single cell or a small assemblage of cells with low (impaired) linear diffusion coupling to the environmental cells. This model corresponds, for example, to the appearance of an inhomogeneity in otherwise homogeneous tissue, *cf.* [16]. We study particularly an appearance of non-homogeneous solutions in the cells with low coupling, assuming that the transport of reaction components from the inhomogeneity will not affect the course of concentrations in the homogeneous environment.

Let us assume that no spatial gradients of concentrations of characteristic reacting components exist among the cells within a homogeneous environment of volume V and also within an inhomogeneity of volume v. Then the system can be described as two compartments with a mutual mass exchange characterized by a mass transport coefficients, with the rates of reactions dependent on concentrations $U = (U_1, \ldots, U_n)$ and $u = (u_1, \ldots, u_n)$, *cf.* Fig. 1:

$$\dot{U} = f(U) + \frac{1}{V} K(u - U), \tag{1a}$$

$$\dot{u} = f(u) + \frac{1}{v} K(U - u). \tag{1b}$$

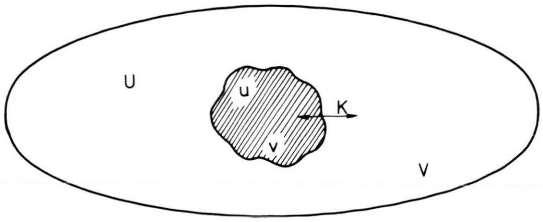

Fig. 1. Two-compartment model of inhomogeneity.

Here U is an n-vector of concentrations in the environment (medium), u is an n-vector of concentrations of the same chemical components in the inhomogeneity, f includes kinetic relations and inlets of the reacting components, and $K = \{k_{ij}\}$ is a diagonal $n \times n$ matrix of transport (diffusion) coefficients.

If the volume V of the environmental compartment is large and the mass transport relatively weak (*i.e.* $0 < k_{ii} \ll 1$), then $K/V \to 0$ and we obtain the model equations in the form

$$\dot{U} = f(U); \tag{1c}$$

$$\dot{u} = f(u) + D(U - u). \tag{1d}$$

Here non-zero elements of the diagonal matrix D, $d_{ii} = k_{ii}/v$ need not be necessarily small as both the volume v and k_{ii} can be comparable.

The boundary between the compartments can be formed, for example, by a semipermeable membrane or by a scar in the tissue, etc.

Our objective is to follow the behaviour of the solution of systems of Eqns. (1 c, d) in dependence on the change of the matrix of transport coefficients D. The change in D can be, for example, interpreted in the following way: the transport coefficients d_{ii} can be written in the form $d_{ii} = k_{ii}/v = k'_i S/v \sim l^{-1}$, $i = 1, \ldots, n$; here k'_i describes the permeability of the boundary between the inhomogeneity and the environment, S denotes the inhomogeneity surface area, v inhomogeneity volume and l is a characteristic dimension (S/v is proportional to $1/l$); the change in d_{ii} can thus originate either from the change of the characteristic dimension l (caused *e.g.* by growth of the inhomogeneity) or from the change in the permeability k'_i of the boundary.

II.2. Kinetic Mechanism

We have chosen Brusselator kinetic mechanism, because it has been widely used in the studies of dissipative structures, both steady state and oscillatory behaviour are possible in a single compartment, and it is sufficiently simple to enable us to obtain at least part of the results analytically. The Eqns. (1 c, d) are with the Brusselator mechanism in the form

$$\dot{X} = A - (B+1)X + X^2 Y;$$
$$\dot{Y} = BX - X^2 Y; \qquad (2\,a)$$
$$\dot{x} = A - (B+1)x + x^2 y + D_1(X - x);$$
$$\dot{y} = Bx - x^2 y + D_2(Y - y). \qquad (2\,b)$$

Here $U = (X, Y)$ are concentrations of two chemical components in the homogeneous medium, $u = (x, y)$ concentrations in the inhomogeneity, A, B reaction parameters and D_1 and D_2 diffusion coefficients for the components x and y, respectively. The ratio $D_1/D_2 = q$ will be assumed constant.

If three steady state solutions of Eqns. (2) exist, then in addition to SH also a pair of nonhomogeneous solutions SN_1, SN_2 exists. They are determined as:

$$X^S = A;$$
$$Y^S = B/A;$$
$$x^S_{1,2} = [(D_2 B/(D_1+1)A \pm \sqrt{(D_2 B/(D_1+1)A)^2 - 4D_2})]/2;$$
$$y^S_{1,2} = (D_1+1)(A - x^S_{1,2})/D_2 + B/A. \qquad (3\,b)$$

III.1.1. Stability of Steady States

Using linearization of Eqns. (2) in the neighbourhood of SH and SN_1, SN_2, we obtain the characteristic equation in the form

$$\chi(\lambda) = \det \begin{bmatrix} B-1-\lambda & A^2 \\ -B & -A^2-\lambda \end{bmatrix} \cdot \det \begin{bmatrix} -(B+1) + 2x^S y^S - D_1 - \lambda & (x^S)^2 \\ B - 2x^S y^S & -(x^S)^2 - D_2 - \lambda \end{bmatrix} = 0. \qquad (4)$$

III.1. Steady State Solutions

Steady state (S) and periodic (P) solutions which occur for model (2) are summarized in Table I. One or three steady state solutions can exist.

Single steady state solution is homogeneous (SH) and it holds

$$X^S = x^S = A,$$
$$Y^S = y^S = B/A. \qquad (3\,a)$$

Four eigenvalues $\lambda_1, \ldots, \lambda_4$ (roots of Eqn. (4)) determine stability of the steady state solution in question. If the real parts of all eigenvalues are negative, the steady state solution is stable. Two eigenvalues $\lambda_{1,2}$ are determined from the quadratic equation

$$\lambda^2 + (A^2 - B + 1)\lambda + A^2 = 0. \qquad (5\,a)$$

Table I. Possible steady-state and periodic solutions of the model (2).

Steady-state solutions	*Existence*	*Stability*
homogeneous solution SH	exists for all A, B, D_1, q	stable or unstable
pair of non-homogeneous solutions SN_1, SN_2	exists for $B > \frac{2A\sqrt{q}(D_1+1)}{\sqrt{D_1}}$	stable or unstable
Periodic solutions		
A: Synchronized oscillations in the medium and the inhomogeneity with zero or small constant phase shift.		
homogeneous solution PH	exists for $B > 1 + A^2$	stable or unstable
pair of non-homogeneous solutions PN_1, PN_2	necessary condition of existence $B > 1 + A^2$	stable or unstable
B: Medium is in a steady state and inhomogeneity oscillates		
a) Stable steady state in the medium and oscillations in the inhomogeneity have not been found.		
b) Unstable steady state in the medium and stable or unstable oscillations in the inhomogeneity exist (*cf.* complex bifurcations in bifurcation diagram, Fig. 2). These solutions are unstable as a whole.		

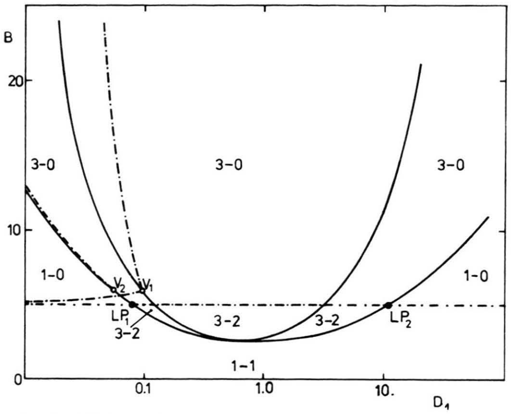

Fig. 2. Bifurcation diagram; ——— real bifurcations; —·—·— complex bifurcations; $A = 2$, $q = 0.1$, $m - n$, m – number of steady state solutions, n – number of stable steady state solutions.

These eigenvalues determine the stability of steady states in the medium. The eigenvalues are the same as are those for a single reaction cell. When $B > 1 + A^2$, the steady state is unstable and stable periodic solution bifurcates *via* Hopf bifurcation. For $B < 1 + A^2$ the steady states are stable.

The remaining two eigenvalues $\lambda_{3,4}$ can be obtained by solving another quadratic equation resulting from the second determinant in Eqn. (4). The eigenvalues are determined for homogeneous solutions from the relation.

$$\lambda^2 + [A^2 - B + 1 + (D_1 + D_2)]\,\lambda + (D_1 + 1)(A^2 + D_2) - D_2 B = 0\,. \tag{5 b}$$

These two eigenvalues will have negative real parts if the conditions

$$B < \frac{(D_1 + 1)(A^2 + D_2)}{D_2} \quad \text{and}$$
$$B < 1 + A^2 + (D_1 + D_2) \tag{6}$$

are satisfied simultaneously.

If the conditions (6) hold and $B < 1 + A^2$, the homogeneous solution SH is stable. Then the second condition in (6) is satisfied always, while the first condition is satisfied only for properly chosen values of D_1 and D_2. If it holds

$$\frac{D_1 + 1}{D_2}(A^2 + D_2) < B < 1 + A^2\,, \tag{7}$$

then the diffusion interaction causes instability of SH even if $B < 1 + A^2$. Small perturbations of the system will then cause transition to a non-homogeneous solution (SN).

III.1.2. Real Bifurcations from SH

The situation, where a branch of non-homogeneous solutions crosses a branch of homogeneous solutions will occur if at least one of the eigenvalues in (5) is zero (we shall call it "real bifurcation"), *i.e.* if

$$B = \frac{(D_1 + 1)}{D_2}(A^2 + D_2)\,. \tag{8}$$

At the points determined by (8) either the branch of solutions SN_1 or the branch SN_2 pass through the branch of homogeneous solutions SH. Both branches SN_1 and SN_2 join at the limit points (*cf.* Fig. 2). The limit points satisfy the condition of zero discriminant in Eqn. (3 b),

$$B = 2A\,(D_1 + 1)/\sqrt{D_2}\,. \tag{9}$$

Stability of non-homogeneous solutions SN_1 and SN_2 can be determined, *e.g.*, numerically from Eqn. (4) after substitution from (3 b). It has been found that for $B < 1 + A^2$ either unique and stable SH solution exists or there are three steady states SH, SN_1, SN_2 and two of them are stable.

III.2. Hopf (Complex) Bifurcations

Bifurcation of periodic solutions from SH, SN_1 and SN_2 takes place when a pair of complex conjugate eigenvalues crosses the imaginary axis (Hopf or "complex bifurcation").

Bifurcation from SH occurs if one of two conditions is satisfied. The first one follows from Eqn. (5 a)

$$B = 1 + A^2\,, \tag{10 a}$$

and from Eqn. (5 b) we obtain second condition

$$B = 1 + A^2 + D_1 + D_2\,,\; B < \frac{D_1 + 1}{D_2}(A^2 + D_2)\,. \tag{10 b}$$

If condition (10 a) is satisfied, homogeneous periodic solution PH ($X = x$, $Y = y$) appears. When D_1 and D_2 are chosen in such a way that the condition (7) is not satisfied, then PH bifurcates supercritically from the stable SH and PH is stable. If the condition (7) is fulfilled, then in a certain range of values of D_1 and D_2 SH is unstable and therefore the homogeneous periodic solution PH is also unstable.

For $B > 1 + A^2$ SH (and generally all steady state solutions) is unstable (*cf.* Eqn. (5a)) and thus periodic solutions appearing through condition (10b) are also unstable.

Complex bifurcations from non-homogeneous solutions SN_1 and SN_2 (secondary bifurcations) can be of two types:

a) Direct bifurcations, caused by passing of a pair of eigenvalues in the second determinant in Eqn. (4) through imaginary axis. Concentrations in the homogeneous medium are in a steady state (which can be either stable or unstable), and only the concentrations x and y in the inhomogeneity oscillate. However, periodic solutions thus obtained for model (2) are limited to small intervals of the values of D_1 and D_2 and, moreover, are unstable.

b) Induced bifurcations; here concentration oscillations in the inhomogeneity are induced by the oscillations in the medium. These oscillations are nonhomogeneous ($X \neq x$ and $Y \neq y$) and bifurcate from SN_1 and SN_2 when the condition (10a) is satisfied. The solutions are stable if they branch from stable SN_1 or SN_2 as this bifurcation is always supercritical.

III.3. Bifurcation, Solution and Evolution Diagrams

As a "bifurcation diagram" we denote the diagram, where the points of real bifurcations and the points of complex bifurcations are depicted in dependence on one or more parameters. An example of such a diagram is shown in Fig. 2. The parameters A and $q = D_1/D_2$ are fixed at $A = 2$ and $q = 0.1$, respectively, and the values of B and D_1 are varied. The points of real bifurcation (*cf.* conditions (8) and (9)) are here depicted in the parameter plane $B - D_1$ as full lines. Hopf bifurcations from SH (*cf.* Eqns. (10a, b)), numerically determined Hopf bifurcations from SN_1 and SN_2, and points of induced bifurcations of periodic solutions are all shown as dash-and-dotted lines. The choice $A = 2$ and $q = 0.1$ satisfies the inequality (7) for a certain region in the $B - D_1$ plane. (This is important for bifurcation of induced oscillations, see below.)

The curves of real and complex bifurcations divide the plane $B - D_1$ into parts, where different number of steady state and periodic solutions exist. The first number written in the sectors of Fig. 2 denote the total number of steady state solutions and the second one denotes the number of stable ones. When the curve of the complex bifurcations is crossed, stability of certain solution can change; when the curve of the real bifurcations is crossed, both the stability and the total number of solutions may change.

The condition for complex bifurcation given by (10a) defines the straight line parallel to the axis D_1 in Fig. 2. This line divides the plane $B - D_1$ into two parts, in the upper part all steady state solutions are unstable. The curve of complex bifurcations given by (10b) ends at the curve of real bifurcations defined by the condition (8), where the corresponding eigenvalues have zero imaginary parts (the point V_1 in Fig. 2).

At this point starts one of the two curves of the secondary bifurcations (the second curve of secondary bifurcations starts at the point V_2, close to the curve of the limit points).

The curve of induced complex bifurcations from the non-homogeneous solutions SN_1 and SN_2 corresponds to the abscissa $\overline{LP_1 LP_2}$, coinciding with the line $B = 1 + A^2$.

"Solution diagrams" – dependences of steady state solutions (here characterized by values of x) on the values of the parameter D_1 at constant values of B are given in Figs. 3a, b, c. The curve of non-homogeneous steady state solutions crosses the curve of homogeneous steady state solutions at the points of real bifurcation. When $B < 1 + A^2$, the bifurcation is transcritical (*cf.* point BP in Fig. 3a) and exchange of stability between SH and SN_1 or SN_2 occurs. For $B > 1 + A^2$ (*cf.* Fig. 3b, $B = 6$) are all steady state solutions unstable. At the limit points (*LP* in Figs. 3), defined by condition (9), coalesce the non-homogeneous solutions SN_1 and SN_2. The curves of non-homogeneous solutions SN_1, SN_2 are closed (*cf.* Figs. 3a, b, c). For sufficiently low values of B is the curve of non-homogeneous solutions isolated, *i.e.* it does not intersect the curve of homogeneous solutions (*cf.* Fig. 3c).

From the point of view of formulation of the models of inhomogeneities and, generally, in any study of dissipative structures, it is most important to study the evolution of steady state and periodic solutions with a change of characteristic parameter in time [18]. Dependence of a characteristic norm of the solution on a changing parameter is then called "evolution diagram". The example of such an evolution diagram is shown in Fig. 4, which cor-

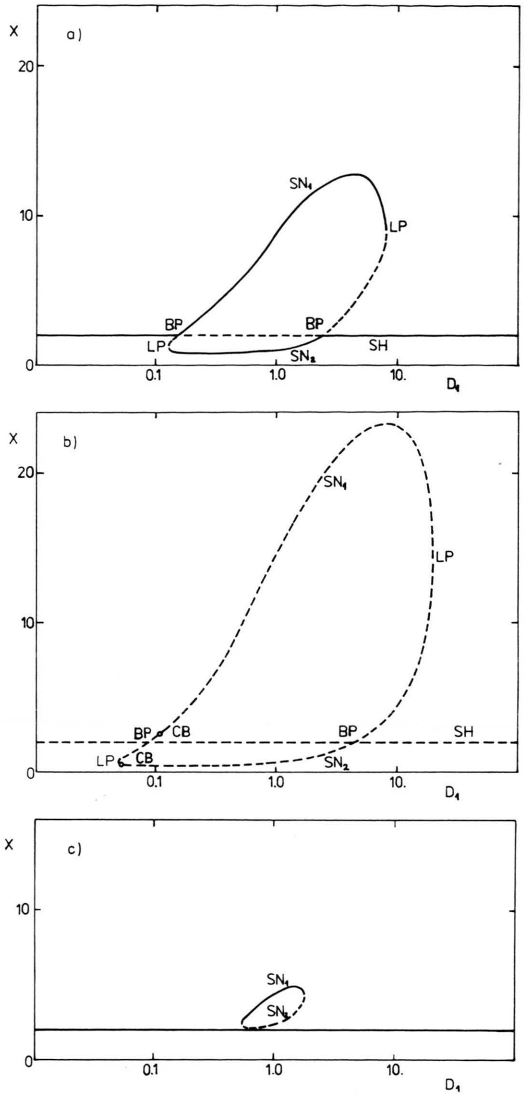

Fig. 3. Steady state solution diagram; ——— stable solutions, ---- unstable solutions, $A = 2$, $q = 0.1$. a) $B = 4$, b) $B = 6$, c) $B = 2.65$; BP – bifurcation point; LP – limit point, CB – complex bifurcation point.

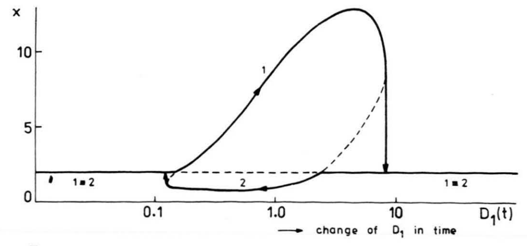

Fig. 4. Evolution diagram; $A = 2$, $B = 4$, $q = 0.1$; 1 – increase of D_1; 2 – decrease of D_1.

responds to the situation shown in the solution diagram 3a. We can observe hysteresis, *i.e.* different course of the concentration in the inhomogeneity when D_1 increases with time (curve 1) and when D_1 decreases with time (curve 2). The decrease of D_1 may, for example, correspond to the cell growth (increase of linear dimension l, *cf.* section II). Isolated solutions SN_1 (*cf.* solution diagram 3c) can be reached in the course of evolution only if sufficiently large perturbations around SH occur.

IV. Periodic Solutions

Periodic solutions of Eqn. (2) can be either homogeneous ($X(t) = x(t)$, $Y(t) = y(t)$) or non-homogeneous. The uni-directional coupling in the model (2) causes that oscillations in the medium and the inhomogeneity will be always periodic and synchronized with a small phase-shift in the case of non-homogeneous oscillations. Only in the case where the values of parameters A and B differ in the medium and the inhomogeneity, we may expect quasiperiodic and chaotic behaviour. Different combinations of oscillatory and steady state solutions which can exist in the medium and the inhomogeneity are summarized in the Table I. Numerical analysis of the case B in the Table (*i.e.* periodic solutions) has shown that only unstable solutions can occur for model (2). We shall not present any results for this alternative, as these are of theoretical interest only.

Homogeneous periodic solution PH bifurcates from the steady state solution (SH) under condition (10a). The regions of existence and stability of homogeneous solutions are schematically shown in the bifurcation diagram $B - D_1$ (*cf.* Fig. 5). The periodic solution PH exists always when $B > 1 + A^2$ and it can be stable or unstable. It was found numerically that for higher values of B this solution is always stable.

Non-homogeneous periodic solutions PN_1 and PN_2 arise *via* an induced Hopf bifurcation from SN_1 and SN_2.

As they are induced by the oscillations occurring in the medium, they bifurcate for $B > 1 + A^2$. Similarly as in the case of PH it holds that only bifurcations from the stable SN_1 and SN_2 give stable periodic solutions (supercritical bifurcation), *cf.* Fig. 6. As all three periodic solutions PH, PN_1 and PN_2 are generated through the same pair of

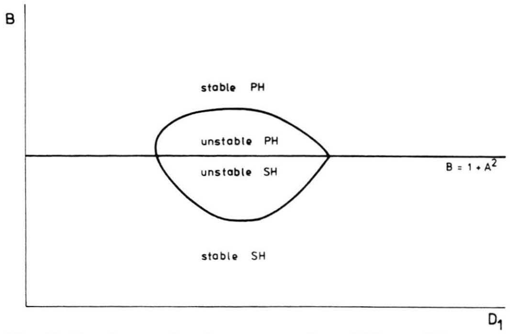

Fig. 5. Regions of existence and stability of homogeneous solutions in a schematic bifurcation diagram; $A = 2$, $q = 0.1$, PH – periodic homogeneous solution, SH – stationary homogeneous solution.

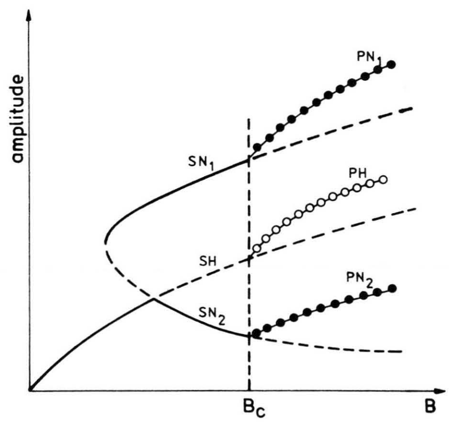

Fig. 6. Schematic solution diagram with bifurcations of non-homogeneous periodic solutions. PN_1 and PN_2 bifurcate *via* induced bifurcation at $B_c = 1 + A^2$.

purely imaginary eigenvalues corresponding to Hopf bifurcation in the medium (see Eqn. (5a)), they have the same period. The course of oscillations in the medium is the same for PH, PN_1 and PN_2, *i.e.* $X^{PH}(t) = X^{PN_1}(t) = X^{PN_2}(t)$ (the same holds for $Y(t)$); however, the periodic solutions differ in the time course of oscillations in the inhomogeneity. When SH is unstable the bifurcated PH is also unstable and system must switch to one of the non-homogeneous states PN_1 or PN_2. The phase shift between the oscillations in the medium and the inhomogeneity is constant and relatively small.

However, the amplitudes A of oscillations in the inhomogeneity $A_x^{PN_{1,2}} = x_{max}^{PN_{1,2}} - x_{min}^{PN_{1,2}}$, $A_y^{PN_{1,2}} = y_{max}^{PN_{1,2}} - y_{min}^{PN_{1,2}}$ may differ substantially from the amplitudes of oscillations in the medium. The periodic solutions are shown in Figs. 7a, b ($y \sim x$ plot and $x \sim t$ plot). PN_2 has lower amplitude of oscillations than PH (and at the same time also lower than has the medium). The other non-homogeneous solution PN_1 has far higher amplitude of the component x ($A_x^{PN_1} \gg A_x^{PH}$), while the amplitude $A_y^{PN_1}$ of the component y is very low.

To obtain more complete picture of the behaviour of periodic solutions far from the bifurcation point, an algorithm for continuation of a branch of (stable or unstable) periodic solutions in dependence on a characteristic parameter has been used [19]. We have chosen two paths, corresponding to line $B = 6$ and $D_1 = 0.5$ in the $B - D_1$ parametric plane (*cf.* Fig. 2) and continued periodic solutions PH, PN_1 and PN_2 along these paths. The results are given in Figs. 8 and 9 in the form of the dependence of A_x on D_1 and B, respectively. Let us consider dependence on D_1 shown in Fig. 8, first. The branch of PN_1 (oscillations with large amplitude in the inhomogeneity) is stable; the solution PN_2 is stable only if solution PH is unstable. Both periodic solutions, PH and PN_2, exchange their stability at two transcritical branching points. The non-homogeneous solutions PN_1 and PN_2 coalesce at the limit points.

Similar situation can be observed in Fig. 9, where dependence A_x on B is shown. Stable non-homo-

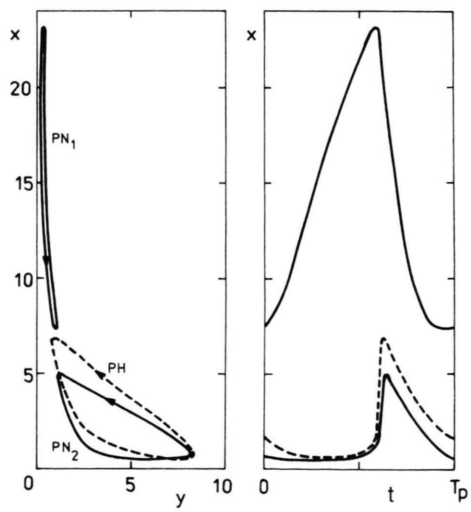

Fig. 7. Projection of periodic solutions into the phase plane $x - y$ and time dependence of x; $A = 2$, $B = 6$, $q = 0.1$, $D_1 = 0.5$.

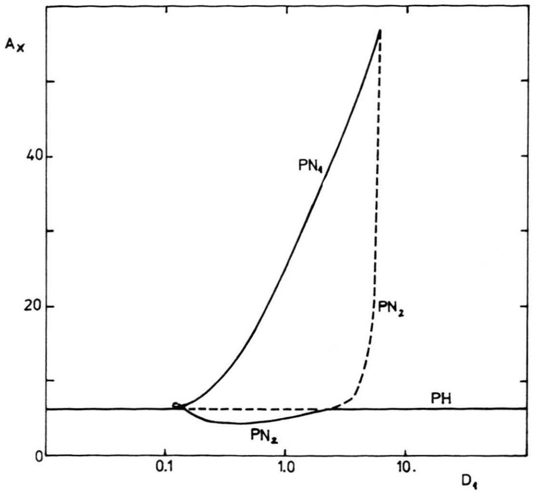

Fig. 8. Dependence of the amplitude of PH, PN_1 and PN_2 on D_1; $A = 2$, $B = 6$, $q = 0.1$; ——— stable periodic solutions; - - - - unstable periodic solutions.

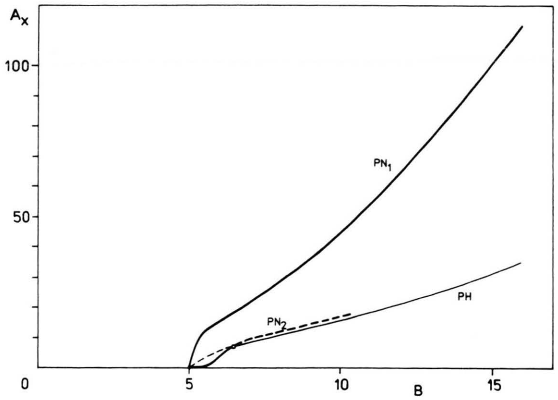

Fig. 9. Dependence of the amplitude of PH, PN_1 and PN_2 on B; $A = 2$, $D_1 = 0.5$, $q = 0.1$; ——— stable solutions; - - - - unstable solutions.

geneous periodic solutions PN_1 and PN_2 and unstable PH bifurcate at the critical point $B = 1 + A^2$. The branch PN_2 crosses transcritically the branch of PH with the exchange of stability. The amplitude $A_x^{PN_1}$ increases sharply with the increasing value of B and the oscillations become relaxational (for relaxation oscillations regime in a single Brusselator cell see *e.g.* [7]).

According to our computations both branches PN_1 and PN_2 will not join for some value of B as might be expected. We have followed these solutions in dependence on B for several values of D_1 and found no limit points for reasonably high values of B. The overall picture of existence of periodic solutions in $B - D_1$ plane is (together with representative solution diagrams) shown in Fig. 10. All steady state solutions in the region $B < 1 + A^2$ (this condition admits some of them to be stable) are also shown, for comparison. Stability of solutions in individual regions is given in Table II.

V. Evolution of Non-Homogeneous Periodic Solutions-Arrhythmias

We have discussed the existence of non-homogeneous periodic solutions with amplitudes which can be considerably different from the amplitudes of homogeneous periodic solutions. The non-homo-

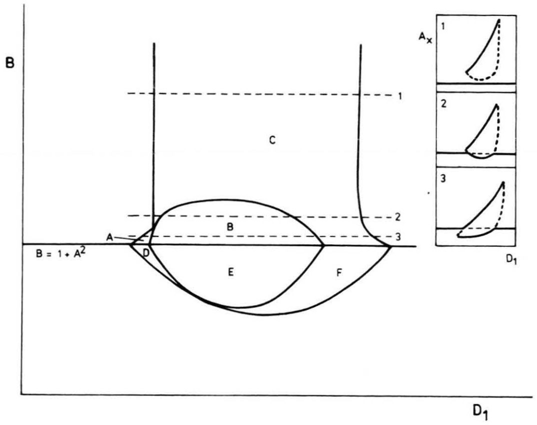

Fig. 10. Regions of existence of steady state solutions SH, SN_1 and SN_2 for $B < 1 + A^2$ and periodic solutions PH, PN_1 and PN_2, schematically; for stability of solutions in regions A, B, C, D, E, F see Table II. Three possible types of a periodic solution diagram are schematically shown for cross-section 1, 2 and 3.

Table II. Stability of stationary and periodic solutions in the bifurcation diagram $B \sim D_1$ (see Fig. 10). S-stable, N-nonstable.

		A	*B*	*C*
$B > 1 + A^2$	PN_1	N	S	S
	PN_2	S	S	N
	PH	S	N	S
		D	*E*	*F*
$B < 1 + A^2$	SN_1	N	S	S
	SN_2	S	S	N
	SH	S	N	S

geneity thus can become a source of high amplitude concentration pulses which can have effects on some other properties of the inhomogeneity-environment system (*i.e.* the properties which have not been modelled by the present model). One of the important questions to answer is then the following one: What will be the behaviour of the system in the course of change of the parameter (*i.e.* evolution) and under what conditions the large amplitude oscillations in the inhomogeneity can settle in. These questions can be answered by a construction of appropriate evolution diagram. We have considered, as an example, the effect of the change of the size l of the inhomogeneity associated with the change of D_l in time (D_l is proportional to l^{-1}) on the oscillatory behaviour of the system. We have chosen the following time dependence of D_l:

$$D_l(t) = D_{l0}\, 2^{\pm t/c}, \quad D_2 = D_l/q . \tag{11}$$

Here c is the time interval for doubling (or halving) of the diffusion coefficients. This exponential change has the property that relative changes of the parameter D_l are constant over the same time intervals.

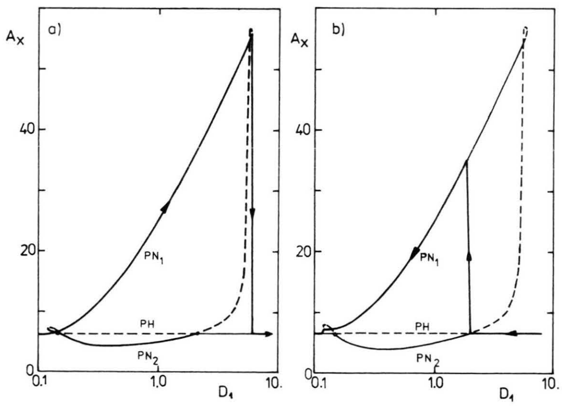

Fig. 11. Evolution diagram – dependence of the amplitude of oscillations in the non-homogeneity on D_l. $D_l(t)$ is changed in time according to Eqn. (11) with $c = 500$. $A = 2$, $B = 6$, $q = 0.1$, noise level 0.05. a) D_l increasing in time, b) D_l decreasing in time.

In the real biological system we have to consider effects of noise, *i.e.* concentration fluctuations. In our modelling studies we have subjected the right hand sides of the Eqn. (2) to an additional random noise with an amplitude ranging from 10^{-4} to 10^{-1}.

The results for high noise level are shown in Figs. 11 a, b. Both for D_l increasing (Fig. 11 a) and for D_l decreasing (Fig. 11b) large amplitude oscillations of x in the inhomogeneity settle in. Evolution of the behaviour of the system (2) with noise level close to 10^{-4} is somewhat indeterminate. System sometimes jumps from PH to PN_1 but sometimes undergoes a smooth transition from PH to PN_2. However, when the noise level is higher, the jumps from PH to PN_1 are preferred.

VI. Conclusions

Reaction-diffusion model of the formation of steady state ($SN_{1,2}$) and oscillatory ($PN_{1,2}$) inhomogeneities has been studied and the conditions of existence of non-homogeneous solutions have been determined. Construction of bifurcation, solution and evolution diagrams has been used to illustrate the effects of parameter variations on the behaviour of the model system. Choice of the simple reaction model – Brusselator – has enabled us to perform at least part of the analysis analytically. The results are not specific for this kinetic scheme; any scheme with proper feed-back mechanism will render similar results. The entire analysis can be also performed numerically [20].

Evolution of non-homogeneous oscillations in an originally homogeneous system caused by a change of permeability of the boundary of a certain region (*e.g.* by a change of D_l) can be for example, taken as one of the possible mechanisms of generation of arrhythmias in excitable tissues.

Acknowledgements

We wish to express our thanks to Martin Holodniok for his help with numerical parts of the work.

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