

ASYMPTOTIC METHODS IN MATHEMATICAL BIOLOGY

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ABSTRACT

In this contribution we study asymptotic methods for differential equation models of physiological and ecological phenomena. In a survey of the literature special attention is given to the Hopf bifurcation, almost linear oscillations, relaxation oscillations, nonlinear reaction-diffusion and to the change in stability of an ecological system due to periodic forcing.

1. INTRODUCTION

This paper deals with the asymptotic analysis of differential equation models of physiological and ecological phenomena. In contrast with systems in physics and engineering the elements constituting a biological system are in general not known in detail. Or, as in the case of population dynamics, the way elements have interaction may be poorly understood. Even in situations, where the biologist is aware of finer structures, one still may choose for a simple model. For example, in population dynamics problems, one may leave out the age structure of a species. The idea is to study a mathematical model exhibiting the same phenomena as the biological system. It is anticipated that in a simple mathematical model the underlying mechanism will be more easily understood. Thus, instead of modelling a physiological system with some flavor of realism, we suggest to introduce a basic model, which may function as a prototype of a biological system. In sections 8 and 9, for example, we take the Van der Pol oscillator as a model for a spontaneously oscillating element of a physiological system.

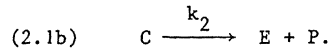
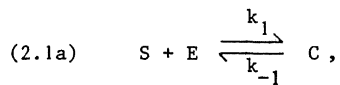
In the last decade there has grown a more or less general accepted theory of asymptotic methods for differential equations. For almost linear oscillations the method of Krylov-Bogoliubov and Mitropolsky takes this position [6]. For singular perturbation problems, there are also textbooks [16,40], which explain the techniques for that class of problems.

For one part this paper is meant as a survey of the use of standard asymptotic methods and so we will describe the biological context in which they arise, but we will not work them out, as it suffices to refer to the literature. On the other hand there are asymptotic methods, which are developed typically with an eye on biological

applications, those will be studied in more detail. We mention the change in stability of a system due to periodic forcing, the dynamics of highly nonlinear oscillators and nonlinear reaction-diffusion problems.

2. MODELLING CHEMICAL REACTIONS IN PHYSIOLOGICAL SYSTEMS

As a result of a chemical reaction concentrations of reactants will change in time. These changes can be described by a system of coupled nonlinear differential equations. Reaction mechanisms in biological systems are controlled by enzymes. The Michaelis-Menten theory gives us an example of a typical enzymatic reaction. A substrate S forms together with the enzyme E a complex C , which in turn breaks irreversibly down to form the enzyme E again and a product P . Schematically, we have



The corresponding system of differential equations for the concentrations of the reactants with given initial values becomes

$$(2.2a) \quad \frac{ds}{dt} = -k_1 es + k_{-1} c, \quad s(0) = s_0,$$

$$(2.2b) \quad \frac{de}{dt} = -k_1 es + (k_{-1} + k_2)c, \quad e(0) = e_0,$$

$$(2.2c) \quad \frac{dc}{dt} = k_1 es - (k_{-1} + k_2)c, \quad c(0) = 0,$$

$$(2.2d) \quad \frac{dp}{dt} = k_2 c, \quad p(0) = 0,$$

where the concentrations are indicated by lower casts. The rate constants $k_{\pm i}$ are nonnegative. Usually, e_0 is small compared with s_0 . Since the sum of e and c is constant in time, we may first solve the system (2.2ac). We carry out the following transformations

$$(2.3abc) \quad \tau = k_1 e_0 t, \quad \lambda = (k_2/k_1) s_0, \quad \mu = ((k_{-1} + k_2)/k_1) s_0,$$

$$(2.3def) \quad x = s/s_0, \quad y = c/e_0, \quad \varepsilon = e_0/s_0 \ll 1$$

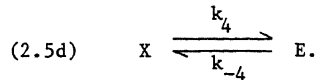
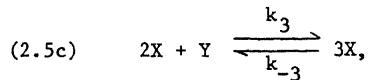
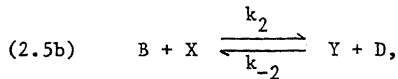
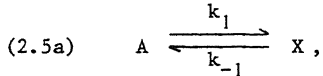
and arrive at the singularly perturbed system

$$(2.4a) \quad \frac{dx}{d\tau} = -x + (x + \mu - \lambda)y, \quad x(0) = 1,$$

$$(2.4b) \quad \varepsilon \frac{dy}{d\tau} = x - (x+\mu)y, \quad y(0) = 0,$$

The solution exhibits an initial boundary layer in y and can be expressed in an asymptotic expansion by using standard singular perturbation techniques, see [16,40].

A hypothetical chemical reaction with time periodic changes in concentrations of some of the reactants is the Brusselator [39] :



Keeping the reactants A, B, D and E at a constant level and setting the reverse reactions all zero, we obtain for the concentrations of X and Y :

$$(2.6a) \quad \frac{dx}{dt} = k_1 a - k_2 b x + k_3 y x^2 - k_4 x,$$

$$(2.6b) \quad \frac{dy}{dt} = k_2 b x - k_3 y x^2.$$

Introduction of nondimensional variables defined by

$$(2.7abc) \quad \tau = k_4 t, \quad u = k_4 x y / (k_1 a), \quad v = k_4 / (k_1 a),$$

$$(2.7de) \quad \alpha = k_3 (k_1 a)^2 / k_4^3, \quad \beta = k_2 b / k_4$$

transforms (2.6) into

$$(2.8a) \quad \frac{du}{d\tau} = 1 - (\beta+1)u + \alpha u^2 v,$$

$$(2.8b) \quad \frac{dv}{d\tau} = \beta u - \alpha u^2 v.$$

This system has the equilibrium point $(\bar{u}, \bar{v}) = (1, \beta/\alpha)$, which is stable for $\beta < 1 + \alpha$. Above the critical value $\beta_c = 1 + \alpha$ the equilibrium becomes unstable and a stable limit cycle with amplitude of order $O((\beta - \beta_c)^{1/2})$ occurs. This phenomenon is called Hopf bifurcation. We will deal with it in more detail in the context of a different problem. For β and α large the oscillation may turn into a highly nonlinear so-called relaxation oscillation. Introduction of a new dependent variable $w = u + v$

changes the system into

$$(2.9a) \quad \frac{du}{dt} = f(u,w),$$

$$(2.9b) \quad \frac{dw}{dt} = g(u,w),$$

$$(2.9cd) \quad f(u,w) = 1 - u - \beta u + \alpha u^2(w-u), \quad g(u,w) = 1 - u$$

In figure 1 we sketch the corresponding closed trajectory in the phase plane. Later on we will discuss relaxation oscillations in relation with the Van der Pol equation.

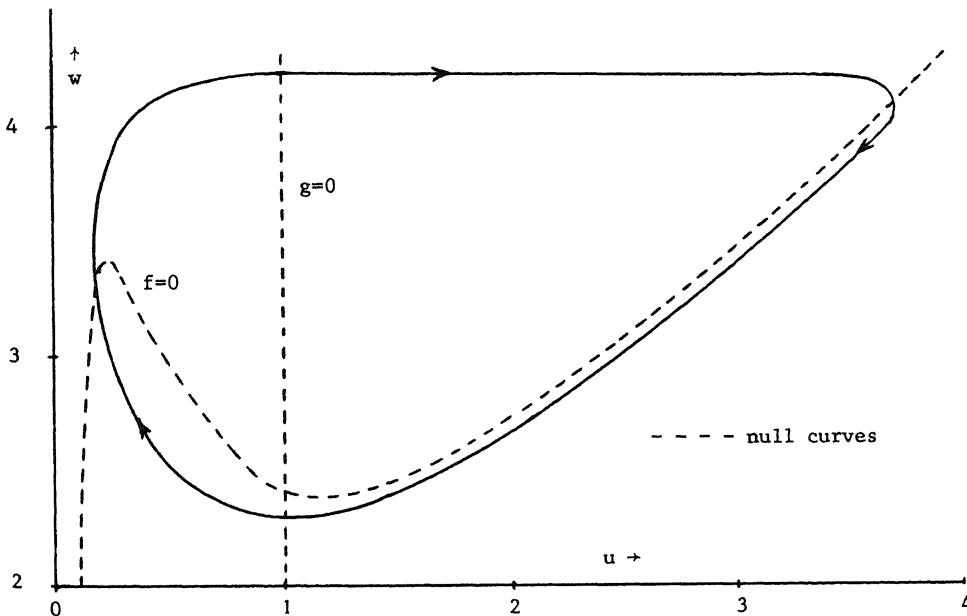


Fig. 1. Relaxation oscillation governed by the Brusselator, see (2.9) with $\alpha = 5$, $\beta = 7$.

Many types of biological system exhibit spontaneous periodic behaviour. We mention rhythmic action of cardiac tissue, the gastor-intestinal tract and the ureter. Circadian rhythms are present in organisms at all levels of evolution [49]. The physiology of these phenomena is quite complex see [10]. Writing down the equations, for all components with their interactions is, in general, not possible. The Hodgkin-Huxley equations [24] describing the propagation of electric pulses in neurons marks the progress that is made, so far at this point. Prototypes of biological oscillations are found in anorganic chemistry: the Belousov-Zhabotinskii reaction,

see [47], and in electronic circuit theory: Vand der Pol oscillator, see [48].

3. MODELLING INTERACTING BIOLOGICAL POPULATIONS

The density of a biological species X_i in a given habitat will change under the influence of available food and predation by other species. Assuming that there are no delay effects due to the influence of age structure, we model density changes of interacting species by a system of coupled nonlinear differential equations

$$(3.1) \quad \frac{dx_i}{dt} = x_i g_i(x_1, \dots, x_n), \quad i = 1, \dots, n.$$

The growth rate g_i contains information about the way X_i interacts with the other species. A negative partial derivative $\partial g_i / \partial x_j$ means that X_i experiences either competition or predation from X_j . On the other hand a positive partial derivative means that X_j is a prey for X_i or that X_i takes profit from the presence of X_j in a different way (if this profit is mutual, then the interaction is called symbiosis). In a realistic model there is also a self limitation upon the growth of X_i , that is $\partial g_i / \partial x_i$ is negative for X_i large. The generalized Volterra-Lotka system

$$(3.2) \quad \frac{dx_i}{dt} = x_i \left(a_i + \sum_{j=1}^n b_{ij} x_j \right), \quad i = 1, \dots, n$$

is the most elementary system satisfying the above conditions. The existence of stable limit solutions (equilibrium or limit cycle) is an important aspect in the analysis of this system. For $n = 1$, (3.2) with $b_{11} < 0 < a_1$ represents the Verhulst equation, which can be solved explicitly for some initial value $x_1(0) = x_{10} > 0$:

$$(3.3) \quad x_1(t) = a_1 x_{10} \exp(a_1 t) / \{a_1 + b_{11} x_{10} - b_{11} x_{10} \exp(a_1 t)\}.$$

For $t \rightarrow \infty$ $x_1(t)$ tends to the stable equilibrium $\bar{x}_1 = -a_1 / b_{11}$. For $n = 2$ and $a_2 < 0 < a_1$, $b_{12} < 0 < b_{21}$, $b_{11} = 0 = b_{22}$ we have the classical Volterra-Lotka system describing a prey-predator relation. This system has a family of neutrally stable periodic solutions. It is a conservative system which makes it less attractive in terms of its biological applicability. In [22] we dealt with asymptotic methods for this system.

The other two possibilities of interaction for $n = 2$ are competition, $b_{12}, b_{21} < 0$ and symbiosis $b_{12}, b_{21} > 0$, see Freedman [19] for the analysis of these cases and for more literature. For $n \geq 3$ the dynamics of the system (3.2) can be quite complex. Coexistence or deterministic persistence of all species is the main question at this level of complexity. In terms of the mathematical problem one tries to find conditions for the coefficients in order to have limit solutions (equilibria or limit cycles) with $x_i > 0$. A stable equilibrium may occur at any n for an appropriate

choice of a_i and b_{ij} . Limit cycles are possible for $n \geq 3$, see [26].

4. SOME REMARKS ON DIFFERENTIAL EQUATION MODELS

The models for chemical reaction and population interaction of the preceding sections all have the form

$$(4.1) \quad \frac{dx_i}{dt} = f(x_1, \dots, x_n; p_1, \dots, p_m), \quad i = 1, \dots, n \quad \text{or} \quad \frac{dx}{dt} = f(x; p),$$

where p_1, \dots, p_m denote the parameters of the system. The dynamics of this system depends upon the dimension n . For $n = 1$ equilibria are the only possible stable (and unstable) limit solutions. For $n = 2$ limit cycles may arise as well, while for $n \geq 3$ the strange attractor (see [41]) occurs as the third possibility of a stable limit solution. The values of the parameters may also influence the occurrence of certain limit solutions. At a point of bifurcation in the parameter space a limit solution may turn from stable into unstable and a new type of limit solution will branch off. For the analysis of this phenomenon for $m = 1$ we refer to [29]. The requirement of generic bifurcation (see Hale [23]) restricts the types of bifurcations that are permitted. For $n = m = 1$ a stable and unstable equilibrium may coalesce at a bifurcation point and disappear afterwards. For $n = 2, m = 1$ there are four generic bifurcations possible. With one of them, the Hopf bifurcation, we will deal in section 6. Bifurcations of (4.1) with $n = m = 2$ have been analyzed from the typical system

$$(4.2a) \quad \dot{x}_1 = x_2,$$

$$(4.2b) \quad \dot{x} = -p_2 x_1 - p_1 x_2 - x_1^3 - x_1^2 x_2,$$

see Holmes and Marsden [25]. From point of view of applications there is no reason to study bifurcations for larger values of m , as usually the behavior of the system may depend critically upon only some of the parameters.

In many cases physiological systems undergo external periodic influences such as the day-night rhythm and pace maker oscillations. Seasonal influences play a role in population dynamics. Therefore, we will also investigate periodically forced systems of the type

$$(4.3) \quad \frac{dx}{dt} = h(x, t; p), \quad h(x, t+T; p) = h(x, t; p).$$

For $n = 2$ this system may represent a periodically forced nonlinear oscillator. First of all we expect a solution with the same period as the driving force (harmonic entrainment). However, there may also occur solutions with a period being a multiple of the driving period (subharmonic entrainment) or even chaotic solutions,

see [25].

There is an extensive literature on differential equation models in physiology and ecology, we mention [8,19,27,28,37]. In the next section we will restrict our asymptotic analysis to the behavior of the system near equilibrium and to periodic solutions of (4.1) and (4.3). For periodic solutions asymptotic methods are necessarily restricted to the two extreme cases: almost linear oscillations and relaxation oscillations. In general, a quantitative analysis for the intermediate range has to be carried out with the aid of numerical methods. Perturbation methods are also important in the analysis of bifurcations. As an example, we study the Hopf bifurcation in section 6.

5. NEAR-EQUILIBRIUM ANALYSIS OF THE PERTURBED VOLTERRA-LOTKA SYSTEM

Bojadziev [6] studies the local behavior near equilibrium of a system of type (3.1) with

$$(5.1a) \quad g_1(x_1, x_2) = \alpha - \beta x_2 + e_1(x_1, x_2),$$

$$(5.1b) \quad g_2(x_1, x_2) = -\gamma + \delta x_1 + e_2(x_1, x_2).$$

with $\delta = 0$ and $e_1 = e_1(x_2)$ and $e_2 = e_2(x_1)$ being analytic functions of such a form that the system has at least one equilibrium (\bar{x}_1, \bar{x}_2) with $\bar{x}_i > 0, i = 1, 2$. Assuming that the solution remains in a small ϵ -neighborhood of $x = \bar{x}$, one may set $x(t) = \bar{x} + \epsilon v(t)$. Substitution into (3.1) with (5.1) yields a regularly perturbed system of differential equations for $v_i(t), i = 1, 2$. To this system Bojadziev applies the Krylov-Bogoliubov-Mitropolskii method leading to solutions that exhibit either damped or undamped oscillations depending on the choice of $g(x)$.

Freedman and Waltman [20] consider (3.1), (5.1) with $e_i = \epsilon d_i(x_1, x_2), i = 1, 2$ and $0 < \epsilon \ll 1$. They analyse the existence of a stable periodic solution near the equilibrium of the unperturbed system ($\epsilon=0$). Under certain conditions for $d(x)$ existence of periodic solutions can be proved by using the implicit function theorem. In this case ϵ can be seen as a bifurcation parameter and a Hopf bifurcation takes place at $\epsilon = 0$. We will deal with perturbation methods for this phenomenon in the next section.

6. THE HOPF BIFURCATION

Let us consider the system (3.2) with $b_{ij} \leq 0$. This system has an equilibrium point $x = \bar{x}$ satisfying

$$(6.1) \quad a + B\bar{x} = 0,$$

where a is a vector with entries a_i and B the matrix with entries b_{ij} . The change of variables

$$(6.2) \quad x_i = \bar{x}_i(1+v_i)$$

transforms (3.2) into

$$(6.3) \quad \frac{dv}{dt} = -Cv - N(v,v),$$

where $C = \{c_{ij}\}_{n \times n}$, $c_{ij} = b_{ij}\bar{x}_j$ and $N(v,v) = (v.Cv)$. Coste e.a. [9] analyse the behavior of the solution near equilibrium at a point in the parameter space, where a Hopf bifurcation occurs. There the equilibrium changes from stable with all eigenvalues of C positive to unstable with two complex conjugate eigenvalues crossing the imaginary axis. In order to analyse this qualitative change locally in the parameter space, we introduce ϵ as the critical parameter and take $\epsilon = 0$ at point of bifurcation. Let

$$(6.4) \quad C(\epsilon) = C_0 - \epsilon C_1 + \dots$$

Then the eigenvalues of C_0 are positive except for the conjugate imaginary eigenvalues $\lambda_{\pm} = \pm i\omega_0$. C_1 is chosen such that these two eigenvalues of $C(\epsilon)$ obtain positive real parts as ϵ is negative and negative real parts for ϵ positive. Introduction of a new time scale

$$(6.5) \quad \tau = t/\xi, \quad \xi = T/(2\pi)$$

changes (6.3) into

$$(6.6) \quad \frac{dv}{d\tau} = \xi\{-C_0 v + \epsilon C_1 v - N_0(v,v) + \epsilon N_1(v,v)\}$$

with $N_j(v,v) = (v.C_j v)$, $j = 0, 1$. It is assumed that a solution of (6.6) can be expanded as

$$(6.7abc) \quad v(\tau) = \sum_{i=1}^{\infty} \eta^i v^{(i)}(\tau), \quad \xi = \frac{1}{\omega_0} + \sum_{i=1}^{\infty} \eta^i \xi^{(i)}, \quad \epsilon = \sum_{i=1}^{\infty} \eta^i \epsilon^{(i)}.$$

Substitution into (6.6) yields after grouping terms of equal order the equations

$$(6.8a) \quad \left(\frac{d}{d\tau} + \frac{C_0}{\omega_0} \right) v_i = F_i, \quad i = 1, 2,$$

$$(6.8bc) \quad F_1 = 0, \quad F_2 = -\xi^{(1)} C_0 v^{(1)} + \frac{\epsilon^{(1)}}{\omega_0} C_1 v^{(1)} - \frac{1}{\omega_0} N_0(v^{(1)}, v^{(1)}).$$

The solution of the first equation has the form

$$(6.9) \quad v^{(1)} = \phi e^{i\tau} + \bar{\phi} e^{-i\tau},$$

where ϕ and $\bar{\phi}$ are eigenvectors of C_0 satisfying

$$(6.10ab) \quad C_0 \phi = i\omega_0 \phi, \quad C_0 \bar{\phi} = -i\omega_0 \bar{\phi}.$$

Let ψ and $\bar{\psi}$ be eigenvectors of the conjugate C_0^\dagger of C_0 satisfying

$$(6.11ab) \quad C_0^\dagger \psi = -i\omega_0 \psi, \quad C_0^\dagger \bar{\psi} = i\omega_0 \bar{\psi}.$$

Then there hold the orthogonality conditions $(\bar{\phi}, \bar{\psi}) = 0$, where $(a, b) = \sum a_i \bar{b}_i$.

To equation (6.8) with $i = 2$ the Fredholm alternative applies: a solution exists if

$$(6.12) \quad \langle F_2, (\psi e^{-i\tau} + \bar{\psi} e^{i\tau}) \rangle = 0,$$

where

$$(6.13) \quad \langle a, b \rangle = \frac{1}{T} \int_0^T (a(\tau), b(\tau)) d\tau.$$

Using the orthogonality conditions we reduce (6.12) to

$$(6.14ab) \quad \left\{ i\omega_0 \xi^{(1)} + \frac{\rho}{\omega_0} \epsilon^{(1)} \right\} (\phi, \bar{\psi}) = 0, \quad \rho = (C_1 \phi, \bar{\psi}) / (\phi, \bar{\psi}),$$

as F_2 is real valued. Assuming that $\rho \neq 0$ (6.14a) demands $\xi^{(1)} = \epsilon^{(1)} = 0$, so that $v^{(2)}$ follows from (6.8ac). In a similar way the Fredholm alternative for the equation of $v^{(3)}$ yields a value for $\epsilon^{(2)}$ which is assumed to be different from zero. For $\epsilon^{(2)} > 0$ we have the situation as sketched in fig. 2a. The other case is given in fig. 2b. For systems with a_1 equal the Hopf bifurcation breaks down. In [9] this problem is analyzed in further detail. For a textbook on bifurcation theory we refer to [29].

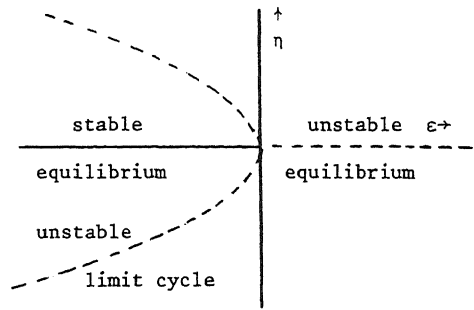
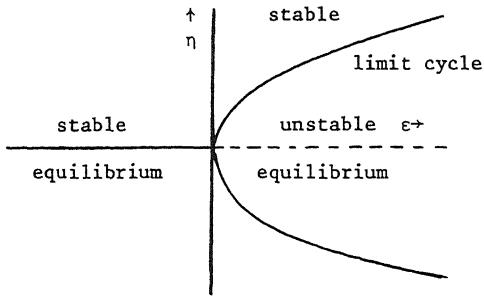


Fig. 2a. Bifurcation diagram for $\epsilon^{(2)} > 0$ Fig. 2b. Bifurcation diagram for $\epsilon^{(2)} < 0$

7. PERIODICALLY FORCED VOLTERRA-LOTKA SYSTEMS

There exists a number of papers which deal with (3.2) for $n = 2$ with time periodic coefficients, see [5,12,13,36]. We will discuss here the approach of Rosenblat [44], as it gives a good impression how asymptotic methods can be applied to this class of problems. The system of equations takes the form

$$(7.1a) \quad \frac{dx_1}{dt} = -ax_1 \left\{ 1 - \frac{x_1 - \alpha x_2}{c(t)} \right\},$$

$$(7.1b) \quad \frac{dx_2}{dt} = ax_2 \left\{ 1 - \frac{x_2 - \beta x_1}{d(t)} \right\},$$

where

$$(7.2a) \quad c(t) = c\{1 + \epsilon \phi(t)\}, \quad d(t) = d\{1 + \epsilon \psi(t)\},$$

$$(7.2b) \quad \phi(t+T) = \phi(t), \quad \langle \phi(t) \rangle = 0,$$

$$(7.2c) \quad \psi(t+T) = \psi(t), \quad \langle \psi(t) \rangle = 0$$

with

$$(7.2d) \quad \langle p(t) \rangle = \frac{1}{T} \int_0^T p(t) dt.$$

For $\epsilon = 0$ the equilibrium $(\bar{x}_1, \bar{x}_2) = \{(c - \alpha d) / (1 - \alpha \beta), (d - \beta c) / (1 - \alpha \beta)\}$ is asymptotically stable in the range of parameter values

$$(7.3abc) \quad \alpha \beta < 1, \quad \alpha < c/d \quad \text{and} \quad \beta < d/c.$$

Let us start from this situation and increase β until it passes the value d/c . Then the equilibrium representing coexistence of species becomes unstable and leaves the

positive quadrant. The effect of fluctuations in the coefficients is studied by expanding the near equilibrium solution of (7.1) as

$$(7.4) \quad x(t; \varepsilon) = \bar{x} + \sum_{n=1}^{\infty} \varepsilon^n x^{(n)}(t).$$

Substituting in (7.1) gives for the coefficients of the terms with ε

$$(7.5a) \quad \frac{dx_1^{(1)}}{dt} + \frac{a\bar{x}_1}{c} (x_1^{(1)} + \alpha x_2^{(1)}) = a\bar{x}_1 \phi(t),$$

$$(7.5b) \quad \frac{dx_2^{(1)}}{dt} + \frac{b\bar{x}_2}{d} (\beta x_1^{(1)} + x_2^{(2)}) = b\bar{x}_2 \psi(t).$$

It is noted that $\langle x_i^{(1)}(t) \rangle = 0$, $i = 1, 2$. A similar couple of equations holds for $x_i^{(2)}(t)$, $i = 1, 2$. From these equations it is derived that

$$(7.6ab) \quad \langle x_1^{(2)}(t) \rangle = \frac{M - \alpha N}{1 - \alpha\beta}, \quad \langle x_2^{(2)}(t) \rangle = \frac{N - \beta M}{1 - \alpha\beta},$$

where

$$(7.7ab) \quad M = \langle \phi(x_1^{(1)} + \alpha x_2^{(1)} - c\phi) \rangle, \quad N = \langle \psi(\beta x_1^{(1)} + x_2^{(1)} - d\psi) \rangle.$$

In order to analyse the change in the range of β values for which coexistence is possible we set

$$(7.8ab) \quad \beta = \beta_0 + \varepsilon^2 \beta_1, \quad \beta_0 = d/c.$$

The equilibrium satisfies

$$(7.9ab) \quad \bar{x}_1 = c \left\{ 1 + \frac{\varepsilon^2 c \alpha \beta_1}{c - \alpha d} + O(\varepsilon^4) \right\}, \quad \bar{x}_2 = - \frac{\varepsilon^2 \beta_1 c^2}{c - \alpha d} + O(\varepsilon^4).$$

Consequently, $x_2^{(1)}(t) = 0$ and $x_1^{(1)}(t)$ is the solution of

$$(7.10) \quad \frac{dx_1^{(1)}}{dt} + \frac{a\bar{x}_1}{c} x_1^{(1)} = a\bar{x}_1 \phi(t).$$

The average of $x_2^{(2)}$ changes into

$$(7.11) \quad \langle x_2^{(2)}(t) \rangle = -(d/c) \langle c\psi(c\psi - x_1^{(1)}) - (c\phi - x_1^{(1)})^2 \rangle / (c - \alpha d).$$

The coexistence equilibrium disappears for $\langle x_2(t) \rangle = 0$ or, taking into account terms of $O(\varepsilon^2)$, for

$$(7.12) \quad \{-\beta_1 c^2 - (d/c) \langle c\psi(c\psi - x_1^{(1)}) - (c\phi - x_1^{(1)})^2 \rangle\} / (c - ad) = 0.$$

Thus, the range of β values for which coexistence is possible is bounded above by $\beta^{(c)} = d/c + \varepsilon \beta_1^{(c)}$ with

$$(7.13) \quad \beta_1^{(c)} = - \frac{d}{c^3} \langle c\psi(c\psi - x_1^{(1)}) - (c\phi - x_1^{(1)})^2 \rangle.$$

Depending on the parameter values of c and d and the shape of the periodic functions ϕ and ψ the coefficient $\beta_1^{(c)}$ may be either positive, negative or zero. Thus, a positive $\beta_1^{(c)}$ can be interpreted as stabilizing for the coexistence of two species. Although the calculations are based upon small disturbances, it is anticipated that this tendency is also present for ε large. A similar conclusion, based on a different analysis, was made by Cushing [13].

8. COUPLED ALMOST LINEAR OSCILLATORS

As we stated in section 2 there exist many types of biological systems exhibiting spontaneous periodic behaviour, such as tissue of the heart muscle or the gastro-intestinal tracts. Such tissue consists of interconnected cells with each cell acting as an autonomous oscillator. In order to have the organ functioning in the desired way there must be some coordination in the rhythmic activity of the cells. In this section and the next one we study the phenomenon of mutual entrainment.

Modelling the contraction waves in the gastro-intestinal tract Linkens [31] uses a chain of almost linear oscillators

$$(8.1) \quad \ddot{x}_i + \lambda_i \dot{x}_{i+1} + \lambda_{i-1} \dot{x}_{i-1} - c_i (1 - x_i^2) (\dot{x}_i + \lambda_i x_{i+1} + \lambda_{i-1} x_{i-1}) + \omega_i^2 x_i = 0,$$

with $\lambda_0 = \lambda_{n+1} = 0$. Assuming that c_i is small a first order asymptotic approximation of an entrained solution will be

$$(8.2) \quad x_i(t) = A_i \cos(\omega t + \alpha_i), \quad i = 1, \dots, n$$

with $\alpha_1 = 0$. Substitution of (8.2) into (8.1) yields, after equating the coefficients of $\cos \omega t$ and $\sin \omega t$, a system of $2n$ algebraic equations for ω , a_i and α_i , which is solved by minimizing the residues of these equations for some initial estimates of a_i, α_i , and ω (the Rosenbrock Hill climbing routine). This method is quite practical and does not follow the scheme of solving the system asymptotically for c_i small as pointed out by Krylov, Bogoliubov and Mitropolsky. The results of Linkens for (8.1) agree with the observed waves in the physiological system, where the contracting oscillations at the beginning of the tract have a higher intrinsic frequency, which

results in phase waves propagating from there down the tract. In (8.1) this configuration is simulated by choosing decreasing values for ω_i as i increases. The KBM-method for two coupled almost linear Van der Pol oscillators has been worked out in Minorsky [34]. Linkens [32] gives more references to the KBM-methods for coupled Van der Pol oscillators. In a number of cases it is questionable whether almost linear oscillations are the appropriate models for biological oscillations. In the Michaelis-Menten kinetics time constants of reactions have usually quite different orders of magnitude. It is for this reason that we expect that relaxation oscillators will do much better. There are two arguments in favor of the linear oscillator which we ought to bring up before dealing with the next subject. First, in some cases oscillations may arise as fluctuations near an equilibrium, which makes them indeed almost sinusoidal. Secondly, in the case of the intestinal tract the measured potential turns out to be close to harmonic.

9. COUPLED RELAXATION OSCILLATORS

In this section we investigate the analogy between phenomena in populations of coupled biological oscillators and the behavior of systems of entrained relaxation oscillators. Using perturbation methods we will obtain quantitative results for entrainment of coupled relaxation oscillators. In the foregoing section we already mentioned one reason for using relaxation oscillators as prototypes of biological oscillations. In addition to this there are other properties of relaxation oscillators to support this idea. First, they exhibit a high orbital stability and, secondly, they are easily speeded up or slowed down on the orbit by external periodic influences.

In [21] mutual entrainment of Van der Pol relaxation oscillators is analyzed. The phenomena of mutual synchronization and propagation of phase waves, which exist in physiological systems, are also found in the behavior of these mathematical oscillators. Let us first analyse the synchronizing influence of one relaxation oscillator upon an almost identical one:

$$\begin{aligned} (9.1a) \quad \epsilon \frac{dx_0}{dt} &= y_0 - F(x_0), & (9.1c) \quad \epsilon \frac{dx_1}{dt} &= y_1 - F(x_1), \\ (9.1b) \quad \frac{dy_0}{dt} &= -x_0, & (9.1d) \quad \frac{dy_1}{dt} &= -(1-\delta p_1)x_1 + \delta x_0 \end{aligned}$$

with $0 < \epsilon \ll \delta \ll 1$ and F continuous satisfying $F(0) = 0$ and $F'(x) = \text{sign}(x^2 - 1)$. The discontinuous limit solution of (9.1ab) is $x(t) = \exp\{-(t-t_B)\}$ at the branch AB, see fig. 3a. Its period is $T_0 = 2 \ln 3$, see fig. 3b for the time dependent behavior.

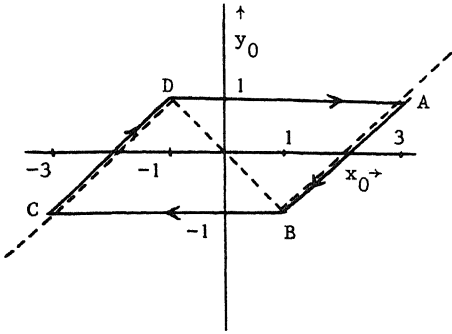


Fig. 3a. Limit trajectory of periodic solution as $\epsilon \rightarrow 0$

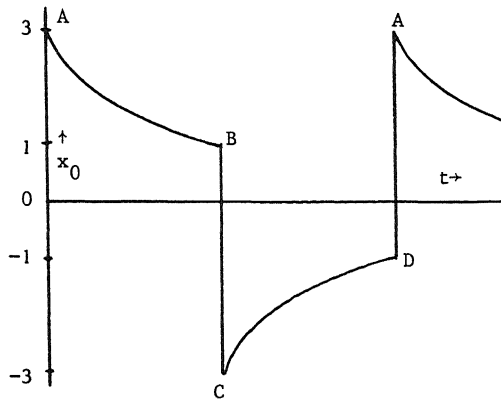


Fig. 3b. Time dependent behaviour of the piece-wise linear relaxation oscillator

Let us indicate this first order approximation of the oscillation by

$$(9.2ab) \quad x_0 = X_0(t), \quad y_0 = Y_0(t).$$

In the limit for ϵ tending to 0 the system (9.1cd) follows the same closed trajectory as (x_0, y_0) , see fig. 3a. For (9.1d) we compute the different velocity on this trajectory. Let $x_1 = X_0(\phi_1(t))$, $y_1 = Y_0(\phi_1(t))$, then

$$(9.3) \quad \frac{dY_0}{d\phi_1} \frac{d\phi_1}{dt} = - (1-\delta p_1) X_0(\phi_1(t)) + \delta X_0(t)$$

or, using (9.1b),

$$(9.4) \quad \frac{d\phi_1}{dt} = (1-\delta p_1) - \delta \frac{X_0(t)}{X_0(\phi_1(t))}, \quad \phi_1(0) = a_1.$$

The solution of this equation gives us the new phase after one period T_0 :

$$(9.5) \quad \phi_1(T_0) = a_1 + T_0(1-\delta p_1) + \delta \Psi(a_1) + 0(\delta^2)$$

with

$$(9.6) \quad \Psi(a_1) = - \int_0^{T_0} X_0(t)/X_0(t+a_1) dt.$$

The phase shift function $\Psi(a_1)$ can be calculated explicitly. It is an exponential function with $\Psi(a_1) = -\Psi(a_1+T_0/2)$, see fig. 4. For $|p_1| < T_0$ the phase shift can compensate the intrinsic frequency difference and oscillator (x_1, y_1) is synchronised by (x_0, y_0) .

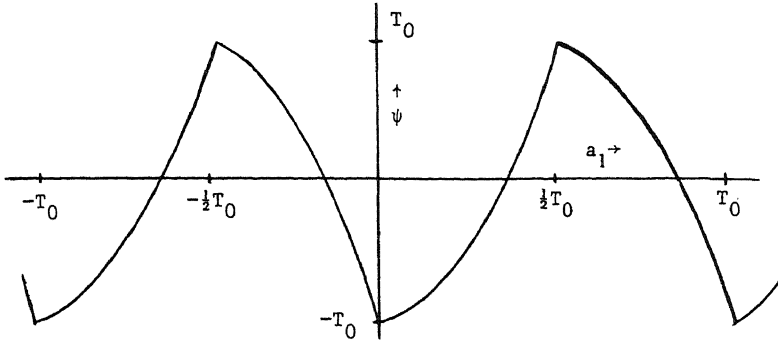


Fig. 4. The phase shift function Ψ for the piece-wise linear relaxation oscillator.

Mutual synchronization of a large system of coupled relaxation oscillators is analyzed in a similar way. Take

$$(9.7a) \quad \epsilon \frac{dx_i}{dt} = y_i - F(x_i),$$

$$(9.7b) \quad \frac{dy_i}{dt} = -(1 - \delta p_i)x_i + \delta \sum_{j \neq i} G_{ij}(x_j(t)), \quad i = 1, \dots, N$$

then the phase functions satisfy

$$(9.8) \quad \frac{d\phi_i}{dt} = 1 - \delta p_i + \delta \sum_{j \neq i} G_{ij}(x_0(\phi_j(t))/x_0(\phi_i(t))), \quad \phi_i(0) = a_i.$$

Existence of synchronized solutions of such a system can be proved by using the theory of Mishenko and Pontryagin [34,43]. The common period of the entrained system will depend upon the type of coupling. Both slowing down and speeding up of the average free running period is possible in the synchronized state. The total effect is computed from the functions G_{ij} . Simulation of spatially distributed oscillators with nearest neighbor coupling leads to bulk oscillations, stable phase waves, as well as to persistent chaotic wave patterns resembling fibrillation of heart tissue, see [21]. For different approaches to coupled highly nonlinear oscillators we refer to [38,46].

10. NONLINEAR REACTION-DIFFUSION EQUATIONS

Let us consider a chemical reaction of the type discussed in section 2, which takes place in a tube with a small cross-section. Moreover, we assume that as in (2.4) and (2.8) the dynamics can be described by a system of two coupled equations for two of the reactants. Let one of these reactants have a small diffusion coefficient then the system will have the form

$$(10.1a) \quad \frac{\partial u}{\partial t} = f(u,v) + \epsilon^2 \frac{\partial^2 u}{\partial x^2},$$

$$(10.1b) \quad \frac{\partial v}{\partial t} = g(u,v) + \frac{\partial^2 v}{\partial x^2},$$

where the independent variable x denotes the position in the tube. Fife [17] analyses a model with functions f and g having null curves as shown in fig. 5a. Then (u_{\pm}, v_{\pm}) are two stable stationary states. Let far away at one side of the infinitely long tube the system be in the state (u_-, v_-) say for $x \rightarrow -\infty$, and in state (u_+, v_+) for $x \rightarrow \infty$. There is wave front, exhibiting a gradual change in v and a sharp transition in u . It propagates slowly to either the left or the right as will turn out in the subsequent analysis. Substitution of

$$(10.2) \quad z = x - \epsilon ct$$

transforms (10.1) into

$$(10.3a) \quad \epsilon^2 \frac{d^2 u}{dz^2} + \epsilon c \frac{du}{dz} + f(u,v) = 0,$$

$$(10.3b) \quad \frac{d^2 v}{dz^2} + \epsilon c \frac{dv}{dz} + g(u,v) = 0.$$

Outside the front region, where u changes rapidly, u and v are approximated by the solutions of the reduced equations ($\epsilon=0$):

$$(10.4a) \quad f(u_0, v_0) = 0,$$

$$(10.4b) \quad \frac{d^2 v_0}{dz^2} + g(u_0, v_0) = 0.$$

From (10.4a) we conclude that $u_0 = h_{\pm}(v_0)$, see fig. 5a. Let $z = 0$ be the position of the front, where v_0 takes the (unknown) value \hat{v} , then

$$(10.5) \quad \frac{d^2 v_0}{dz^2} + g(h_{\pm}(v_0), v_0) = 0 \quad \text{for } z \gtrless 0.$$

or in the phase-plane formulation with $p_0 = dv_0/dz$:

$$(10.7a) \quad p_0 \frac{dp_0}{dv_0} = -g(h_-(v_0), v_0) \quad \text{for } v_0 < \hat{v} \quad \text{with } p_0(v_-) = 0,$$

$$(19.7b) \quad p_0 \frac{dp_0}{dv_0} = -g(h_+(v_0), v_0) \quad \text{for } v_0 > \hat{v} \quad \text{with } p_0(v_+) = 0.$$

Since $p_0 dp_0/dv_0 = \frac{1}{2} dp_0^2/dv_0$, integration of both right-hand sides gives p_0 as a function of v_0 . Moreover, as p_0 is continuous in \hat{v}

$$(10.8) \quad \int_{v_-}^{\hat{v}} g(h_-(s), s) ds = \int_{v_+}^{\hat{v}} g(h_+(s), s) ds,$$

which determines uniquely the value of \hat{v} . To find the shape of u at the front itself we use the stretched variable $\zeta = z/\epsilon$. The local approximation $u = W_0(\zeta)$ then satisfies

$$(10.9) \quad \frac{d^2 W_0}{d\zeta^2} + c \frac{dW_0}{d\zeta} + f(W_0, \hat{v}) = 0$$

and matches the outer solution u_0 , if

$$(10.10ab) \quad \lim_{\zeta \rightarrow -\infty} W_0(\zeta) = h_-(\hat{v}) \text{ and } \lim_{\zeta \rightarrow \infty} W_0(\zeta) = h_+(\hat{v}).$$

Trajectories in the phase plane should satisfy

$$(19.11) \quad Q_0 \frac{dQ_0}{dW_0} + cQ_0 + f(W_0, \hat{v}) = 0, \quad Q_0 = \frac{dW_0}{d\zeta}.$$

The phase portrait is such that for a unique $c = c^*$ a trajectory exists that connects the two stationary points $(h_-(\hat{v}), 0)$ and $(h_+(\hat{v}), 0)$, see fig. 5b. Aronson and Weinberger [2] prove that

$$(10.12) \quad c^* \geq 0 \quad \text{according as} \quad \int_{h_-(\hat{v})}^{h_+(\hat{v})} f(u, \hat{v}) du \lesseqgtr 0.$$

There exists an extensive literature on reaction-diffusion problems. Besides in chemical reactions similar mechanisms are found in population genetics and in the dynamics of interacting species, see [4,11,14,15,18,42]. The phenomenon of a traveling wave front is one aspect of the dynamics of a reaction-diffusion system. Existence of stable spatial inhomogeneities is another aspect, which is given much attention in the literature [3,30,33].

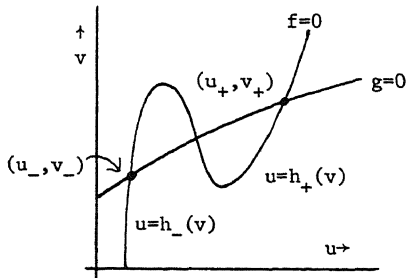


Fig. 5a. Null curves for f and g

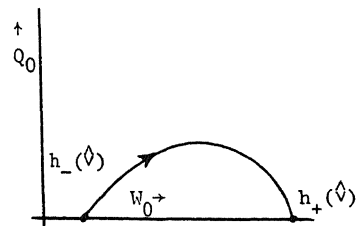


Fig. 5b. Phase plane picture of the boundary layer in u .

REFERENCES

- [1] R. ARIS., *The mathematical theory of diffusion and reaction in permeable catalysts*, vol. I & II, Clarendon Press, Oxford, 1975.
- [2] D.G. ARONSON & H.F. WEINBERGER, *Multidimensional nonlinear diffusion arising in population genetics*, Adv. in Math. 30 (1978), 33-76.
- [3] M. ASHKENAZI & H.G. OTHMER, *Spatial patterns in coupled biochemical oscillators*, J. Math. Biology 5 (1977), 1-31.
- [4] E.J. BISSET, *Interaction of steady and periodic bifurcating modes with imperfection effects in reaction diffusion systems*, SIAM J. Appl. Math. 40 (1981), 224-241.
- [5] J.G. BLOM, R. DE BRUIN, J. GRASMAN & J.G. VERWER, *Forced prey-predator oscillations*, J. Math. Biology 12 (1981), 141-152.
- [6] N.N. BOGOLUIBOV & Y.A. MITROPOLSKY, *Asymptotic Methods in the Theory of Non-linear Oscillations*, Hindustan Publ. Corps, New Delhi, 1961.
- [7] G. BOJADZIEV, *The KBM method applied to models of population dynamics*, Bull. Math. Biology 40 (1979), 335-345.
- [8] S.N. BUSENBERG & K.L. COOKE, *Differential Equations and Applications in Ecology, Epidemics, and Population Problems*, Acad. Press. New York, 1981.
- [9] J. COSTE, J. PEYRAUD & P. COULLET, *Asymptotic behavior in the dynamics of competing species*, SIAM J. Appl. Math. 36 (1979), 516-543.
- [10] B. CHANCE, E.K. PYE, A.K. GOSH & B. HESS (eds.), *Biological and biochemical oscillators*, Acad. Press, New York, 1973.
- [11] O. COPE., *Stability of limit cycle solutions of reaction-diffusion equations*, SIAM J. Appl. Math. 38 (1980), 457-479.
- [12] J.M. CUSHING., *Periodic time dependent predator-prey systems*, SIAM J. Appl. Math. 32 (1977), 82-95.
- [13] J.M. CUSHING., *Two species competition in a periodic environment*, J. Math. Biology 10 (1980), 385-400.
- [14] J.A. DESIMONE & J.A. PENNLINE, *A new asymptotic analysis of the n-th order reaction-diffusion problem: analytical and numerical studies*, Math. Biosci 40 (1978), 303-318.
- [15] M.R. DUFFY, N.F. BRITTON & J.D. MURRAY, *Special wave solutions of practical reaction diffusion systems*, 39 (1980), 3-13.
- [16] J.W. ECKHAUS., *Asymptotic Analysis of Singular Perturbations*, North-Holland Publ. Amsterdam, 1979.
- [17] P.C. FIFE., *Singular perturbation and wave front techniques in reaction-diffusion problems*, in Proc. of the AMS-SIAM Symposium on Asymptotic Methods, R.E. O'MALLEY (ed.) (1976), 23-50.
- [18] P.C. FIFE., *Mathematical aspects of reacting and diffusing systems*, Lecture Notes in Biomath. 28, Springer Verlag Berlin, 1977.
- [19] H.I. FREEDMAN., *Deterministic Mathematical Models in Population Ecology, Monographs and Textbooks in pure and appl. math.* vol. 57, M. Dekker Inc. New York, 1980.
- [20] H.I. FREEDMAN & P. WALTMAN, *Perturbation of two-dimensional predator-prey equations with an unperturbed critical point*, SIAM J. Appl. Math. 29 (1975), 719-733.
- [21] J. GRASMAN & M.J.W. JANSSEN, *Mutually synchronized relaxation oscillators as prototypes of oscillating systems in biology*, J. Math. Biology 7 (1979), 171-197.

- [22] J. GRASMAN & E.J.M. VELING, *Asymptotic methods for the Volterra-Lotka equations*, in *Asymptotic Analysis from Theory to Application*, F. Verhulst (ed.), Lecture Notes in Math. 711, Springer Verlag Berlin, 1979, 146-157.
- [23] J.K. HALE., *Remarks on bifurcation theory in differential equations*, in *New Approaches to Nonlinear Problems in Dynamics*, P.J. Holmes (ed.), SIAM Philadelphia, 1980, 379-391.
- [24] A.L. HODGKIN & A.F. HUXLEY, *A quantitative description of membrane current and its application to conduction and excitation in nerve*, *J. Physiol.*, 117 (1952), 500-544.
- [25] P.J. HOLMES & J.E. MARSDEN, *Dynamical systems and invariant manifolds*, in *New Approaches to Nonlinear Problems in Dynamics*, SIAM PHILADELPHIA, 1980, 3-25.
- [26] J. HOPFBAUER., *On the occurrence of limit cycles in the Volterra-Lotka equation*, *Nonlinear Anal.* T,M&A 5 (1981) 1003-1007.
- [27] F.C. HOPPENSTEADT (ed), *Mathematical aspects of physiology*, *Lectures in Appl. Math.* vol. 19, Am. Math. Soc., Providence, 1981.
- [28] F.C. HOPPENSTEADT (ed)., *Nonlinear oscillations in biology*, *Seminar on Appl. Math.* by Am. Math. Soc. and SIAM, AMS Lectures in Appl. Math 17, 1979.
- [29] G. IOOSS & D.D. JOSEPH, *Elementary stability and bifurcation theory*, Springer Verlag, Berlin, 1980.
- [30] J.P. KEENER., *Activators and inhibitors in patterns formation*, *Studies in Appl. Math.* 59 (1978) 1,23.
- [31] D.A. LINKENS., *Analytical solutions of large numbers of mutually coupled nearly sinusoidal oscillators*, *IEEE Trans. on Circuits and Systems* vol. CAS 21 (1974), 294-300.
- [32] D.A. LINKENS., *Modelling of gastro-intestinal electrical rhythms*, in *Biological systems, modelling and control*, D.A. Linkens (ed.). The Inst. of Electr. Engin., London (1979), 202-241.
- [33] M. MIMURA & Y. NISHUIRA, *Spatial patterns for an interaction-diffusion equation in morphogenesis*, *J. Math. Biology* 7 (1979), 243-263.
- [34] N. MINORSKY., *Nonlinear oscillations*, Nostrand, Princeton, 1962.
- [35] E.F. MISHCHENKO., *Asymptotic calculation of periodic solutions of systems of differential equations containing small parameters in the derivations*, *Am. Math. Soc. Transl.*, series 2, 18 (1961), 199-230.
- [36] P. DE MOTTONI, A SCHIAFFINO, *Competition systems with periodic coefficients: a geometric approach*, *J. Math. Biology* 11 (1981), 319-335.
- [37] J.D. MURRAY., *Lectures on nonlinear-differential-equation models in biology*, Clarendon Press, Oxford, 1977.
- [38] J.C. NEU., *Large populations of coupled chemical oscillators*, *SIAM J. Appl. Math.* 38 (1980), 305-316.
- [39] G. NICOLIS & I. PRIGOGINE, *Self-organisation in Nonequilibrium Systems*, Wiley-Interscience Publ., New York, 1977.
- [40] R.E. O'MALLEY., *Introduction to singular perturbation theory*, Acad. Press, New York., 1974.
- [41] E. OTT., *Strange attractors and chaotic motions of dynamical systems*, *Rev. Mod. Phys.* 53 (1981), 655-671.
- [42] A.S. PERELSON & L.A. SEGEL, *A singular perturbation approach to diffusion reaction equations containing a point source with application to the hemolytic plaque assay*, *J. Math. Biology* 6 (1978), 75-85.
- [43] L.S. PONTRYAGIN., *Asymptotic behaviour of solutions of systems of differential equations with small parameter in the higher derivatives*, *Am. Math. Soc. Transl.*, series 2, 18 (1961), 295-320.

- [44] S. ROSENBLAT., *Population models in a periodically fluctuating environment*, J. Math. Biology 9 (1980), 23-36.
- [45] K.E. SWINK., *A nonlinear model for human population dynamics*, SIAM. J. Appl. Math. 40 (1981), 266-278.
- [46] V. TORRE., *Synchronisation of non-linear biochemical oscillators coupled by diffusion*, Biol. Cybern. 17 (1975), 137-144.
- [47] J.J. TYSON., *The Belousov-Zhabotinski Reaction*, *Lecture Notes in Biomath.* 10, 1976.
- [48] B. VAN DER POL & J. VAN DER MARK, *The heartbeat considered as a relaxation oscillation and an electrical model of the heart*, Phil. Mag. 4 (1928), 763-773.
- [49] A.T. WINFREE., *The geometry of biological time*, Biomathematics vol. 8, Springer Verlag, Berlin, 1980.