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THE MATHEMATICAL MODELLING OF ENTRAINMENT IN PHYSIOLOGICAL SYSTEMS

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The mathematical modelling of entrainment in physiological systems*)

by

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ABSTRACT

In this paper we study oscillatory phenomena in physiological systems from differential equation models. Special attention is given to numerical and asymptotic methods for the analysis of entrainment and the occurrence of travelling phase waves in model problems such as coupled Van der Pol oscillators.

KEY WORDS & PHRASES: *Mutual entrainment, Coupled Van der Pol oscillators*

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1. INTRODUCTION

In this paper we describe the role of mathematical models in the investigation of a physiological system given by n state variables $(x_1(t),\ldots,x_n(t))$ depending continuously on time t and satisfying a vector differential equation of the form

$$(1) \qquad \frac{dx}{dt} = f(x).$$

The Hodgkin-Huxley equations [8] and the Van der Pol equation [4] are two examples of systems having this form. In the first the state variables represent some physical quantities; the second equation is often used as a simple theoretical model of a physiological system exhibiting a self sustained oscillation.

In experiments the characteristic features of a biological system are understood from the system's response under a periodic stimulus, see [7]. In that case mathematical methods, such as correlation techniques, are used to analyse this response.

In this paper we follow a different approach. We will try to predict the occurrence of phenomena such as entrainment from a study of the mathematical model. Fore more complex problems (n large or complicated functions f_i) we will rely upon numerical methods, while for a simpler model problem as the Van der Pol oscillator analytical methods may learn us about the properties of the system. Thus, we study a system of differential equations (1) augmented with time dependent periodic coefficients. Such a system we write as

$$(2) \qquad \frac{dx}{dt} = g(x,t,b)$$

with

$$(3ab) \qquad g(x,t,0) = f(x) \quad \text{and} \quad g(x,t,b) = g(x,t+2\pi,b).$$

Clearly, the period of the stimulus is taken 2π and the parameter b is a measure for its intensity.

2. A NUMERICAL METHOD FOR FINDING PERIODIC SOLUTIONS

It is expected that the solution of (2) has a periodic solution with the same period as the stimulus. If this is the only periodic solution and if it is also stable, then this solution is usually easily detected. However, it may be quite well possible that one or more stable solutions with different periods also exist, e.g. subharmonic solutions with different periods being a multiple of the driving period. Each of these stable solutions will have its own domain of attraction. By just integrating the system numerically for some starting value we may arrive at one periodic solution without having any idea about the existence of others. In order to deal with this problem more systematically, we integrate the system over the time interval 2π for a large number of starting points within the operational domain of the state space. This integration procedure provides us with an approximation of the mapping P of the state space into itself:

$$(4) \qquad P: x(0) \longmapsto x(2\pi).$$

If for some starting value x the solution returns after k iterations of the map P in x, we have obtained a periodic solution with period $2\pi k$. Such a point is found as the value of x where the positive semi-definite function

$$(5) \qquad V_k(x) = \|P^k x - x\|$$

vanishes. In (5) the symbol $\|\cdot\|$ denotes the Euclidean norm of a vector.

We will illustrate this method by the following example, for which other approaches such as the Galerkin method [12] did not turn out to be appropriate for finding the subharmonic solutions. We consider the Volterra-Verhulst equations with a periodically varying coefficient (see [1]):

$$(6a) \qquad \frac{dx_1}{dt} = 4.539x_1(1 + b\cos t - x_2 - .0025x_1),$$

$$(6b) \qquad \frac{dx_2}{dt} = 1.068x_2(-1+x_1), \quad b = .25.$$

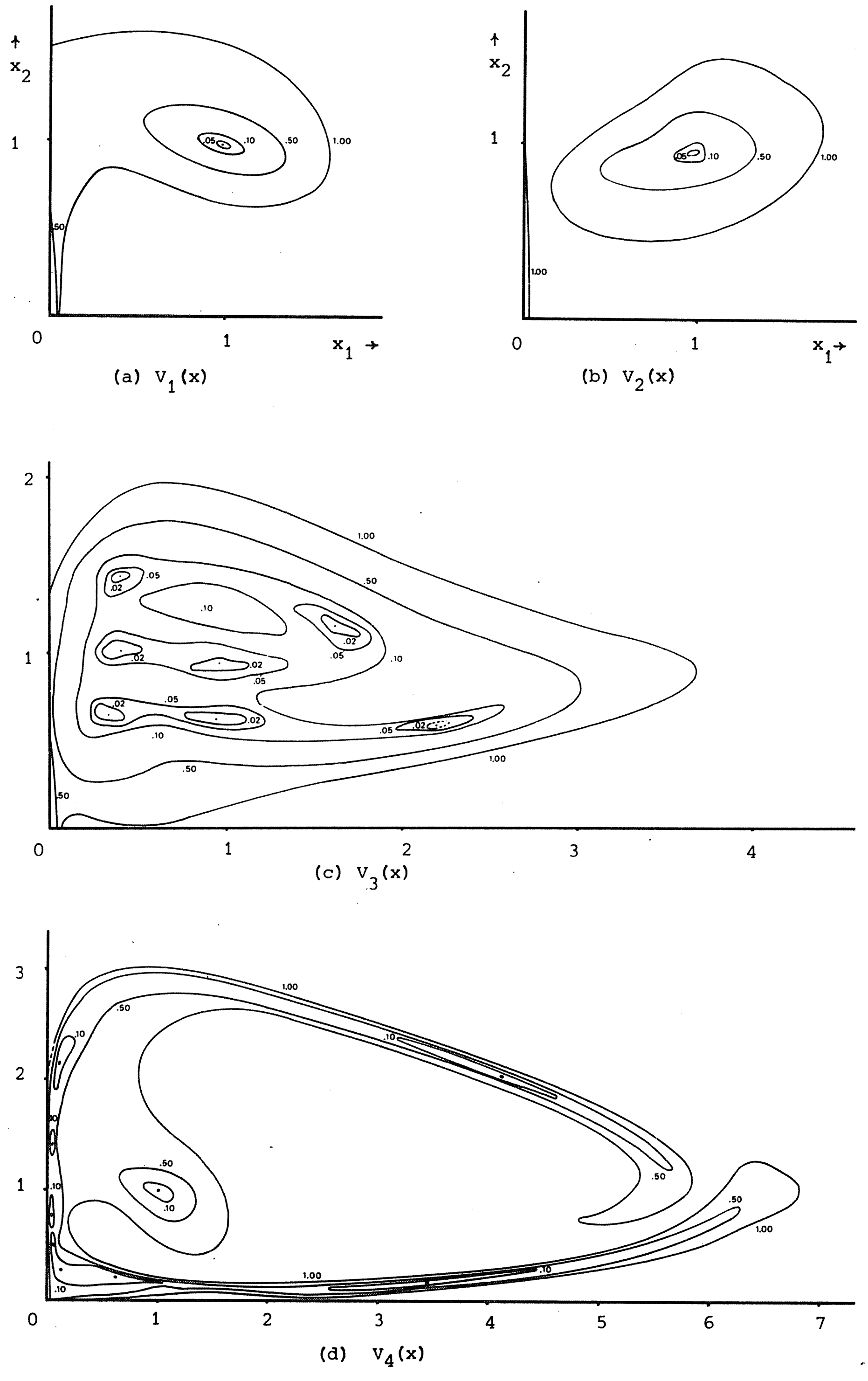

Fig.1. Level lines of the functional V_n, n = 1,2,3,4.

In Figure 1 we depicted the functional $V_k(x)$, $k = 1,\dots,4$, while in Figure 2 the domain of attraction of the stable periodic solutions is constructed with the method of Hayashi [6]. For other numerical and analytical approaches to this problem we refer to [11,13].

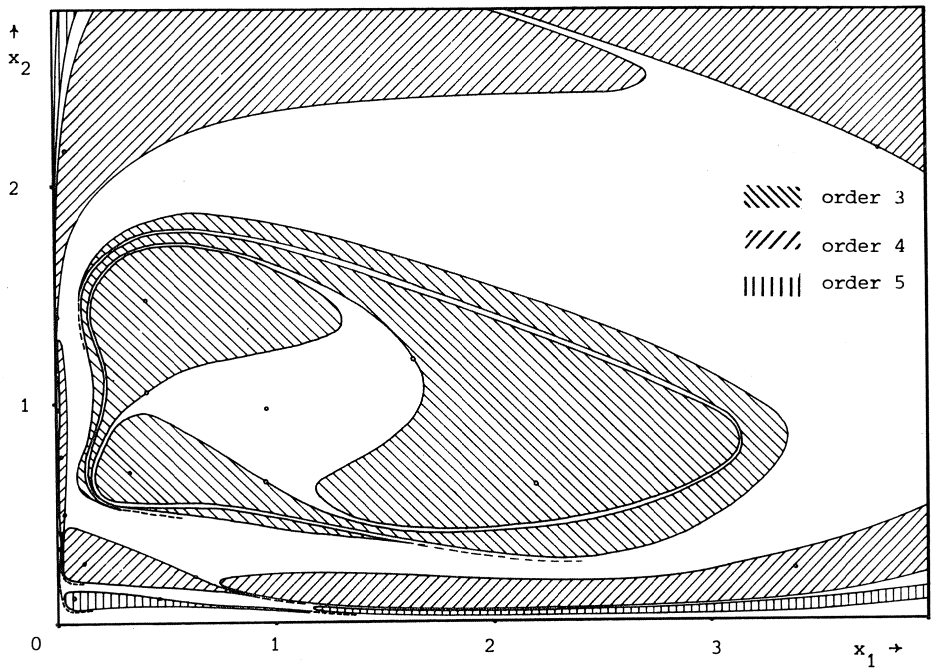

Fig.2. Attraction domains of the subharmonic solutions

3. ANALYTICAL RESULTS FOR FORCED OSCILLATIONS

For the "simple" model problem of the Van der Pol oscillator with a sinusoidal forcing term, that is

(7a) $$\frac{dx_1}{dt} = x_2 - \nu(\tfrac{1}{3}x_1^3 - x_1),$$

(7b) $$\frac{dx_2}{dt} = -x_1 + b(\nu)\nu\cos t,$$

we apply asymptotic methods to analyze the existence of periodic solutions. Asymptotic methods are a well-known tool in the analysis of almost linear systems such as (7) with $0 < \nu << 1$. However, oscillating systems in biology tend to be highly nonlinear and highly stable in their orbit, although within their orbit they may be easily speeded up or slowed down. The system (7) with $\nu >> 1$ indeed has this properties. In [3,5] this problem is analyzed for $b(\nu) = \alpha + \beta\nu^{-1}$, $0 \leq \alpha \leq 2/3$. It turns out that for some (α, β_1) one stable subharmonic solution exists, while for some nearby value (α, β_2) two stable subharmonics with period differing 4π are found.

4. MODELLING MUTUAL ENTRAINMENT

Finally, we consider a specific structure of (1); we analyse the behaviour of a system of weakly coupled piece-wise linear oscillators

$$\text{(8a)} \qquad \frac{dx_{k1}}{dt} = \{x_{k2} - F(x_{k1})\}/\varepsilon$$

$$\text{(8b)} \qquad \frac{dx_{k2}}{dt} = (1-\delta g_k)x_{k1} + \delta \sum_{j=1}^{n} a_{jk}x_j, \qquad k = 1,\dots,n,$$

$$\text{(8c)} \qquad F(x) = x \pm 2 \text{ for } x \lesseqgtr \mp 1, \; F(x) = -x \text{ for } |x| \leq 1,$$

ith $0 < \varepsilon << \delta << 1$. In [4] we investigated systems of such oscillators arranged in geometrical structures with nearest neighbour coupling ($a_{jk} = 1$, if oscillators j and k are neighbours, otherwise $a_{jk} = 0$). Concentrating upon the phases of the oscillators as a function of time and position we observe the occurrence of wave phenomena. We studied the following configurations:

(a) *Oscillators on a line*

We consider a string of 51 oscillators with each oscillator coupled to its two neighbours. In this example we also introduce a dependence of the autonomous period upon the position on the line: it is assumed that it increases from one side to the other ($g_k = -1.25+(k-1)/20$, $T_{k0} = 2(1+\delta g_k)\ln 3 + O(\delta^2) + O(\varepsilon \ln \varepsilon)$). In this way we have constructed an idealization of the gastro-intestinal tract, see [9]. In Figure 3 we give the state variable x_{k1} of an oscillator as a function of its position k after a time being the length of 200 periods of the average autonomous oscillator. It is assumed that initially the oscillators are all in the same phase (bulk oscillation). We find that the system tends to a state of partial entrainment, but looking globally to the phases of the oscillators we see a wave travelling from the inherently faster oscillators towards the slower ones. This result agrees with electronic simulations by BROWN et al. [2].

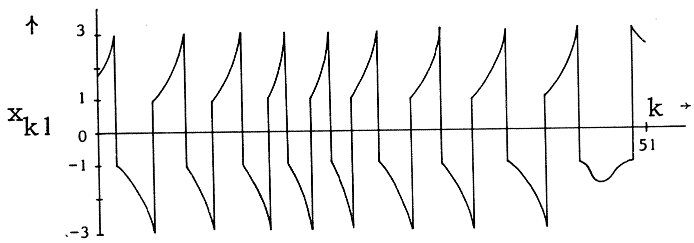

Fig.3. Piecewise linear oscillators on a line (continuous representation) at time t = 4001n3; initially all oscillators were running in the same phase.

(b) *Oscillators on a torus*

Next we investigate a set of identical oscillators (g_k = 0) arranged on a two-dimensional torus with coupling between neighbours. A numerical experiment was done with 144 oscillators starting in phases being randomly distributed. After a time equivalent with 50 periods of the autonomous oscillators, the system arrived in a state with phase waves running over the torus braking down when meeting each other and with wave centres appearing and disappearing spontaneously. The system did remain in this state for an extended period of time, see Figure 4. This chaotic pattern resembles fibrillation of the heart's ventricles, a state in which the coordination of the fibres of the heart muscle decreases rapidly with increasing distance. Experiments of this type might possibly add to a better understanding of this phenomenon.

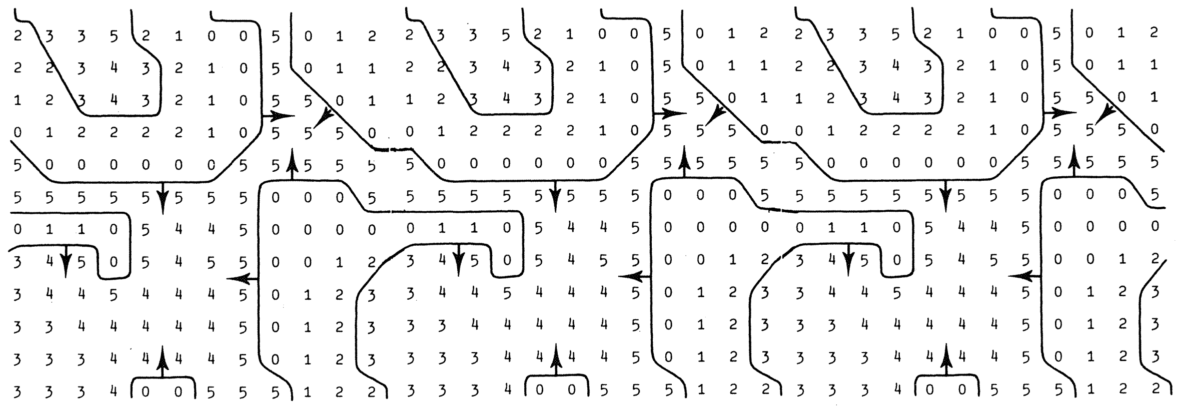

Fig.4. Piecewise linear oscillators on a torus, illustrating numerical experiment. The right and left boundaries are connected, as well as the upper and lower boundaries. The phase ϕ of each oscillator is indicated by the rounded off value of $3\phi/\ln 3$. Wave fronts and their direction are indicated by lines and arrows. At the start of the experiment phases were assigned randomly. The figure represents the state after 50 iterations of the Poincaré map and is repeated two times in the horizontal direction.

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