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TW 230/82 DECEMBER

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THE MATHEMATICAL MODELLING OF ENTRAINED BIOLOGICAL OSCILLATORS

Preprint

kruislaan 413 1098 SJ amsterdam

Printed at the Mathematical Centre, 413 Kruislaan, Amsterdam.

The Mathematical Centre, founded the 11-th of February 1946, is a non-profit institution aiming at the promotion of pure mathematics and its applications. It is sponsored by the Netherlands Government through the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

1980 Mathematics subject classification: 92A09, 34C15, 34E10, 34E15.

The mathematical modelling of entrained biological oscillators *)

by

J. Grasman

ABSTRACT

In this paper perturbation methods are used for the mathematical analysis of coupled relaxation oscillators. The present study covers entrainment by an external periodic stimulus as well as mutual entrainment of coupled oscillators with different limit cycles. The oscillators are of a type one meets in the modelling of biological oscillators by chemical reactions and electronic circuits. Special attention is given to entrainment different from 1:1. The results relate to phenomena occurring in physiological experiments, such as the periodic stimulation of neural and cardiac cells, and in the nonregular functioning of organs and organisms, such as the AV-block in the heart and certain deviations from the regular circadian rhythm.

KEY WORDS & PHRASES: *relaxation oscillations, entrainment, synchronization, Van der Pol oscillator*

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*) This report will be submitted for publication elsewhere.

1. INTRODUCTION

Periodicity and synchrony play an important role in the temporal organization of activity in an organism. At cellular level there is synchronization of neural and cardiac oscillators by cyclic inputs as well as mutual synchronization [2,12,13,14,25,28]. At a higher level organs can be forced to follow the rhythm of an external pacemaker [20]. Finally, the organism, as a whole, exhibits periodic activity known as the circadian rhythm: the rest-activity cycle of about 24 hours, which is entrained by the external light-dark cycle [5,26,27]. In all these examples we think of 1:1 phase locking in the first place. There has grown an extensive literature on the mathematical modelling of this phenomenon, see [6,9,15,17,27]. However, entrainment with a frequency ratio different from 1:1 is also observed at all three levels of organization mentioned above. Cardiac muscle tissue may oscillate with a period being a multiple of the forcing period [12,25,28]. A heart may function in such a way that the contraction period of the ventricles and that of the atria have a ratio different from 1:1 (AV-block), see [12,16]. In experiments one was able to lock the respiratory cycle of the lungs to the phase of a mechanical ventilator in a ratio different from 1:1 [20]. The rest-activity rhythm of humans driven by the light-dark cycle can also be different from the 1:1 ratio. For enfants it may run 2:1 or higher. It is reported that such a synchrony is already present for the embryo driven by the mothers rhythm, see [5]. Moreover, some humans, isolated from external dark-light cycles, exhibit a 2:1 phase locking between their body temperature and their rest-activity cycle [26]. Compared with harmonic entrainment, there are less studies on the mathematical modelling of nonharmonic entrainment for highly nonlinear oscillators, we mention ERMENTROUT [3] and GLASS and PEREZ [7].

In this paper we analyse a system of n coupled relaxation oscillators with intrinsic frequencies close to a ratio $j_1:j_2:\ldots:j_n$ with $j_i, i=1,\ldots,n$ integer. In our analysis we use singular and regular perturbation methods. The relaxation oscillator we consider is a Van der Pol type differential equation with a small parameter ε multiplying the second derivative. This makes the system of coupled equations singularly perturbed. A second parameter δ is a measure for the deviation of the intrinsic frequencies from the ratio $j_1:j_2:\ldots:j_n$. Entrainment is possible if the coupling is at least of the same order of magnitude. It is assumed that $0<\varepsilon<<\delta<<1$. In [9] the case of weakly coupled almost idential relaxation oscillators was analyzed and it was proved that the asymptotic solution indeed approximates an exact synchronized solution of the system. This proof, based on the work of MISHENKO and PORTRYAGIN, see e.g. [18], als applies to the present configuration of coupled nonidentical oscillators. It is remarked that much of the results for harmonic entrainment of almost identical oscillators carry over to nonharmonic entrainment. There is, however, one unexpected exception: in the case of superharmonic entrainment the solution depends critically upon ε as turns out in a numerical integration of the system for different ε. The dependence is such that above a small value of ε the entrainment breaks down. This critical dependence also affects mutual nonharmonic entrainment: the entrained asymptotic solution has a low accuracy compared with the case of subharmonic entrainment.

In section 2 the discontinuous asymptotic approximation of a free relaxation oscillator is given. Furthermore, we consider the case where a periodic forcing term with an amplitude of order $O(\delta)$ is added to the equation. The forcing is of a type that does not change the limit cycle of the oscillator in the limit $\varepsilon \to 0$. In this way only the phase of the oscillator is influenced in the asymptotic approximation. Let T be the period of the driving force. Then we consider the mapping of the phase at time t to the one at time t + T. For the case of piece-wise linear relaxation oscillators one can compute this mapping explicitly. A stable fixed point of this mapping corresponds with an entrained solution. Without any difficulty this method can be extended to coupled oscillators, see section 3. In the sections 4 and 5 we deal with two examples of coupled piece-wise linear oscillators and compare the asymptotic results with entrained numerical solutions of the systems for ε and δ fixed. Then, in the example of section 4, the sensitivity of superharmonic entraiment to the value of ε is noticed. Finally, in section 6 we deal with chemical and electronic oscillators, that are frequently used for modelling biological oscillations. It is shown, that they belong to the class of relaxation oscillators, that are analyzed in this paper.

2. FREE AND FORCED OSCILLATORS

The relaxation oscillators we consider are of the type

(2.1a) $\varepsilon dx/dt = y - F(x),$

(2.1b) $dy/dt = -ax,$

where ε is a small positive parameter and F a continuous, piece-wise differentiable function satisfying $F(x) \to \pm\infty$ as $x \to \pm\infty$ and with one local maximum and minimum, see fig. 1a. Typical examples are the Van der Pol equation with $F(x) = \frac{1}{3}x^3 - x$ and the piece-wise linear differential equation with

(2.2a) $F(x) = 2 + x$ for $x \leq -1,$

(2.2b) $F(x) = -x$ for $-1 < x < 1,$

(2.2c) $F(x) = -2 + x$ for $x > 1.$

In section 6 we deal with applications in chemistry and electronic networks, then F follows, respectively, from the reaction dynamics and the diode characteristic. In this paper we concentrate on discontinuous approximations of periodic solutions of (2.1) as $\varepsilon \to 0$. In fig. 1a we sketch the corresponding closed trajectory in the phase plane. The time-dependence of the x-component is given in fig. 1b. The approximate solution over the two branches AB and CD satisfies

(2.3) $F'(X_0)dX_0/dt = -aX_0.$

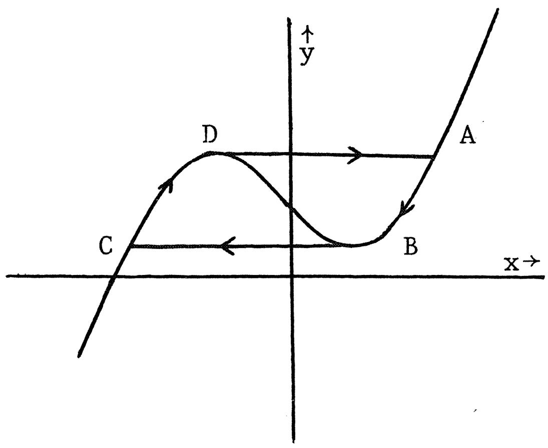
For the Van der Pol oscillator this equation can be integrated, giving an implicit expression for X_0 as a function of t. For the piece-wise linear oscillator satisfying (2.2) the approximate solution has period $T_0 = 2a^{-1}\ln 3$ and reads

$$(2.4a) \qquad X_0(t) = 3e^{-at} \quad \text{for} \quad 0 < t < a^{-1} \ln 3,$$

$$(2.4b) \qquad X_0(t) = -e^{-at} \quad \text{for} \quad -a^{-1} \ln 3 < t < 0,$$

$$(2.4c) \qquad Y_0(t) = F(X_0(t)).$$

For differentiable functions F the asymptotic stable periodic solution of (2.1) has a limit cycle $(X_\varepsilon, Y_\varepsilon)$ which approaches (X_0, Y_0) as $\varepsilon \to 0$ and the period satisfies $T_\varepsilon = T_0 + 0(\varepsilon^{2/3})$. For a proof of this we refer to MISHENKO and ROSOV [18]. STOKER [21] states that for the piece-wise linear oscillator $T_\varepsilon = T_0 + 0(\varepsilon \ln \varepsilon)$.



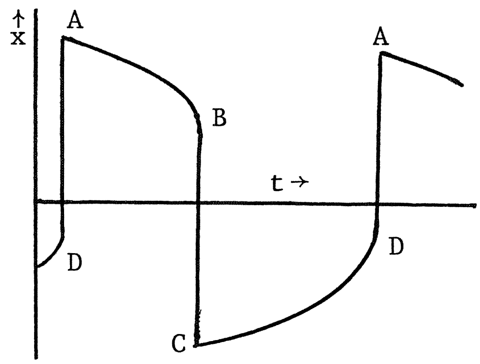


Fig. 1a The limit cycle in the phase plane as $\varepsilon \to 0$

Fig. 1b The time dependence of the x - component of the periodic limit solution.

Next we take into consideration the periodic forcing of the relaxation oscillator (2.1) through its y-component

$$(2.5a) \qquad \varepsilon \, dx/dt = y - F(x),$$

$$(2.5b) \qquad dy/dt = -ax + \delta h(t), \quad h(t+T) = h(t),$$

with $0<\varepsilon<<\delta<<1$ and $h(t)$ a piece-wise continuous function. In the limit $\varepsilon \to 0$ the forcing term h will not change the closed trajectory in the phase plane. It may only influence the velocity of the oscillator on the limit cycle. Consequently, a solution of (2.5) is approximated by

$$x = X_0(\phi(t)), \quad y = Y_0(\phi(t)), \tag{2.6}$$

where $(X_0(t), Y_0(t))$ represents a discontinuous approximation of the free oscillator, see (2.4). Substitution in (2.5) for $\varepsilon = 0$ yields

$$\frac{dY_0}{d\phi}\frac{d\phi}{dt} = -aX_0(\phi(t)) + \delta h(t) \tag{2.7}$$

or

$$\frac{d\phi}{dt} = 1 - \frac{\delta h(t)}{aX_0(\phi(t))}, \quad \phi(0) = \alpha^{(0)}. \tag{2.8}$$

Integration gives the following approximation valid for bounded t

$$\phi(t) = \alpha^{(0)} + t - \frac{\delta}{a}\int_0^t \frac{h(\bar{t})}{X_0(\alpha^{(0)}+\bar{t})}\,d\bar{t} + 0(\delta^2). \tag{2.9}$$

Over one period T the forcing causes a phase shift $\delta\psi(\alpha^{(0)})$ with

$$\psi(\alpha) = -\frac{1}{a}\int_0^T \frac{h(t)}{X_0(\alpha+t)}\,dt. \tag{2.10}$$

Considering the value of ϕ at times $t = kT$, we obtain the iteration map P for the phase, $\alpha^{(k+1)} = P\alpha^{(k)}$ or in a explicit form

$$\alpha^{(k+1)} = \alpha^{(k)} + T + \delta\psi(\alpha^{(k)})(\mathrm{mod})T_0. \tag{2.11}$$

From the iteration map we analyse the limit behavior of the system. In the simplest case it has a stable fixed point that corresponds with a periodic solution of period T. Other possibilities are higher stable subharmonic solutions, see fig. 2c, and chaotic solutions for $\delta = 0(1)$, see [10]. Clearly, a fixed point $\bar{\alpha}$ satisfies

$$\psi(\bar{\alpha}) = (mT_0 - T)/\delta \tag{2.12}$$

for some integer m and is stable if $\psi'(\bar{\alpha}) < 0$. Phase locking will only occur if

$$\min_{\alpha} \delta\psi(\alpha) < mT_0 - T < \max_{\alpha} \delta\psi(\alpha). \tag{2.13}$$

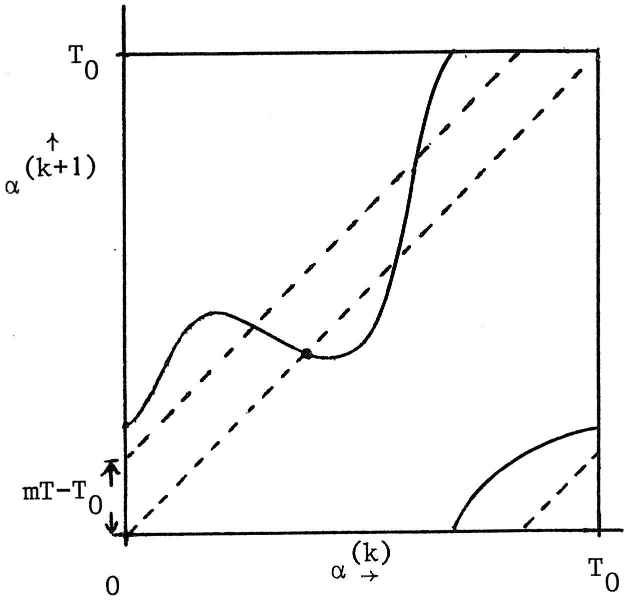


Fig. 2a. The iteration map P

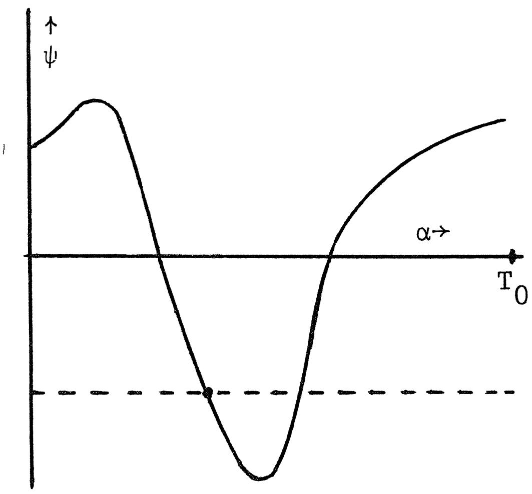


Fig. 2b. The phase shift function ψ

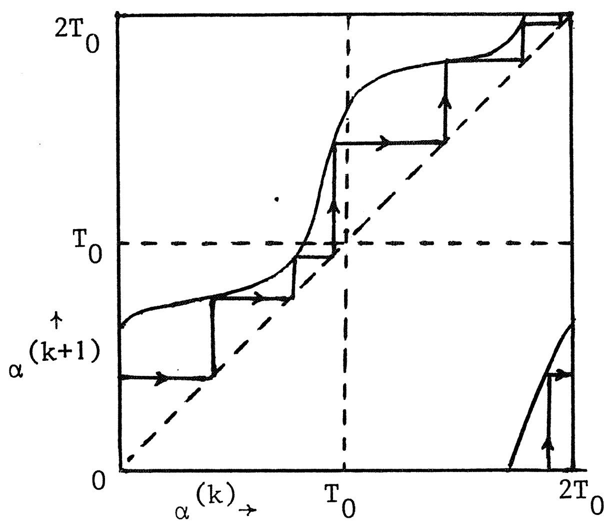


Fig. 2c. A higher order fixed point of the map P.

3. COUPLED OSCILLATORS

We are now on the position to handle systems of coupled relaxation oscillators satisfying

$$\text{(3.1a)} \qquad \varepsilon dx_i/dt = y_i - F_i(x_i)$$

$$\text{(3.1b)} \qquad dy_i/dt = -a_i x_i + \delta \sum_{j=1}^{n} H_{ij}(x_j, y_j), \qquad i = 1,\dots,n,$$

where H_{ij} is assumed to be continuous with respect to x_j and y_j. Each oscillator describes a free oscillation given by $(X_{i0}(\phi_i(t)), Y_{i0}(\phi_i(t))$ with

$$\text{(3.2)} \qquad \phi_i(t) = \alpha_i^{(0)} + t - \frac{\delta}{a_i} \int_0^t \frac{H_{ii}(X_{i0}(\alpha_i^{(0)}+t), Y_{i0}(\alpha_i^{(0)}+t))dt}{X_{i0}(\alpha_i^{(0)}+t)} + 0(\delta^2).$$

Let $H_{ii} = a_i p_i x_i$, then the phase of the free oscillation satisfies

$$\text{(3.3)} \qquad \phi_{i0}(t) = \alpha_i^{(0)} + (1-p_i\delta)t.$$

In case the oscillators are coupled the phase functions are approximated by

$$\text{(3.4)} \qquad \phi_i(t) = \phi_{i0}(t) - \frac{\delta}{a_i} \sum_{j \neq i} \int_0^t \frac{H_{ij}(X_j(\alpha_j^{(0)}+t), Y_j(\alpha_j^{(0)}+t))}{X_i(\alpha_i^{(0)}+t)} dt + 0(\delta^2).$$

Let us assume that the unperturbed oscillators (δ=0) have autonomous periods $T_{i\varepsilon}$ satisfying

$$\text{(3.5)} \qquad T_{10}:T_{20}:\dots:T_{n0} = j_1:j_2:\dots:j_n,$$

where j_i, $i = 1,\dots,n$ are integers. The fact that $H_{ii} = p_i x_i$ results in autonomous periods of the perturbed system that differ $0(\delta)$ from this ratio. Next we introduce the common unperturbed period T being the smallest number for which the quotients T/T_{i0}, $i = 1,\dots,n$ are positive integers. The phase shift function is defined by

$$\text{(3.6)} \qquad \psi_{ij}(\alpha_i,\alpha_j) = \frac{-1}{a_i} \int_0^T \frac{H_{ij}(X_j(\alpha_j+t), Y_j(\alpha_j+t))}{X_i(\alpha_i+t)} dt, \; i \neq j.$$

For the iteration map P of the phases $\alpha_i^{(k)}$ at times $t = kT$ we obtain

$$(3.7)\qquad \alpha_i^{(k+1)} = \alpha_i^{(k)} - (1-\delta p_i)T + \delta \sum_{j\neq i} \psi_{ij}(\alpha_i^{(k)},\alpha_j^{(k)}) \ (\mathrm{mod})T_{i0}$$

for $i = 1,\ldots,n$ or $\alpha^{(k+1)} = P\alpha^{(k)}$. More specifically, the phase shift function ψ_{ij} depends upon $\beta_{ij} = \alpha_i - \alpha_j$ as is seen from (3.6) by shifting the integration interal over α_j. If we set $\alpha_1 = 0$, then all phase differences β_{ij} are determined uniquely from the remaining $n - 1$ phases α_j. The system (3.4) has a periodic solution with a period of about T if the following system of n algebraic equations for $\alpha_2,\ldots,\alpha_n$ and q has a solution:

$$(3.8)\qquad p_i T + \sum_{j\neq i} \psi_{ij}(\beta_{ij}) = q, \qquad i = 1,\ldots,n.$$

The period of the approximation for $\varepsilon \to 0$ takes the value $T + \delta q$. It is more difficult to analyse the higher dimensional iteration map than the one dimensional one of the preceding section unless there is a regular structure in the coupling and the distribution of autonomous frequencies. Numerical simulation of the map P for a system of 144 coupled oscillators, see [9], suggest the existence of chaotic solutions with a domain of attraction of nonzero measure. In the numerical experiment the 144 oscillators were spread out over a two-dimensional periodic spatial structure (a torus) with coupling to the nearest neighbours and gave arise to persistent chaotic phase waves, resembling fibrillation of the ventricles.

4. ENTRAINMENT OF TWO OSCILLATORS WITH FREQUENCY RATIO 1:3

As an example we deal with two coupled oscillators, which for $\varepsilon \to 0$ have the same limit cycles in the phase plane and with autonomous frequencies that differ about a factor 3. We take a type of coupling that the simplifies computations:

(4.1a) $\varepsilon dx_1/dt = y_1 - F(x_1)$, (4.1c) $\varepsilon dx_2/dt = y_2 - F(x_2)$,

(4.1b) $dy_1/dt = -(1-\delta p_1)x_1 + \delta a_1 x_2$, (4.1d) $dy_2/dt = - 3x_2 + \delta a_2 x_1$

with $F(x)$ given in (2.2). Carrying out the computations set out in the foregoing section we arrive at the phase shift functions

(4.2a) $\qquad \psi_{21}(\beta) = \psi_{12}(-\beta), \qquad \beta = \alpha_1 - \alpha_2,$

(4.2b) $\qquad \psi_{12}(\beta) = a_2\{e^{\beta}(-4/3-\gamma) + 4/3e^{3\beta}\}$ for $0 \le \beta < 1/3 \ln 3$

with $\gamma = 3^{-1/3} + 3^{2/3} - 3^{1/3} - 3^{-2/3}$. For $1/3 \ln 3 \le \beta < 0$ we have $\psi_{ij}(\beta) = \psi_{ij}(\beta+1/3\ln 3)$.

Let us compare these asymptotic results for $\varepsilon = 0$ with numerical solutions of (4.1) for fixed small parameter values, $\varepsilon = 10^{-3}$ and $\delta = .25$. In fig. 3a we present the result for subharmonic entrainment, $(a_1,a_2) = (1,0)$. It is observed that the values of the entrained numerical solutions $(p_1,\beta(\varepsilon))$ are close to the stable branch of the phase shift function $\psi_{12}(\beta)$. The value $\beta(\varepsilon)$ is found as the difference in time at the successive intersections of $x_1(t)$ and $x_2(t)$ with the line $x = 0$. For the case of superhamonic entrainment, $(a_1,a_2) = (0,1)$, the outcome is quite different, see fig. 3b. The phase shift curve turns out to be very sensitive to the value of ε. As a result of this superharmonic entrainment is only possible when the autonomous frequencies are much closer to the ratio 1:3 than in the case of subharmonic entrainment. For $\varepsilon = .002$ this bandwith is reduced by a factor two and again at $\varepsilon = 4.10^{-3}$. At $\varepsilon = .005$ superharmonic entrainment virtually breaks down. Finally, in fig. 3c we sketch the result of mutually entrained numerical solutions, $(a_1,a_2) = (1,1)$. The values $(p_1,\beta(\varepsilon))$ for the numerical solutions are away from the stable branch of the relative phase shift function $\psi_{12}(\beta) - \psi_{21}(-\beta)$. A further comparision shows that the outcome of the numerical solutions is consistent with the results for super- and subharmonic entrainment.

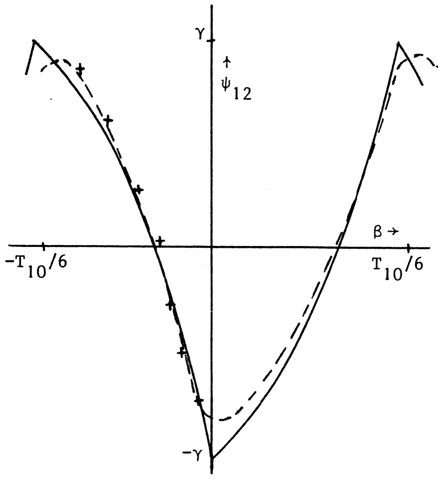


Fig. 3a. Subharmonic entrainment

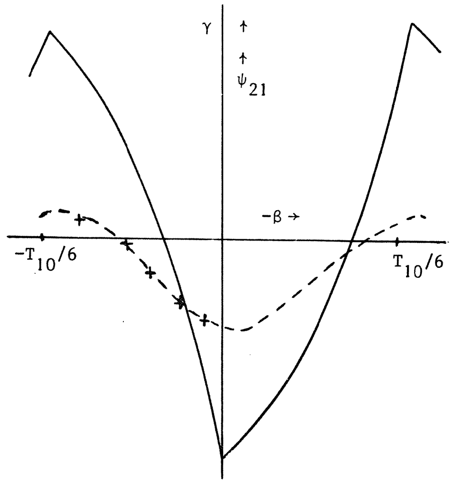


Fig. 3b. Superharmonic entrainment

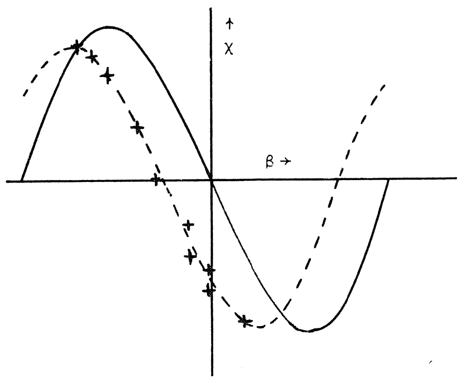


Fig. 3c. Mutual entrainment, $\chi(\beta) = \psi_{12}(\beta) - \psi_{21}(-\beta)$.

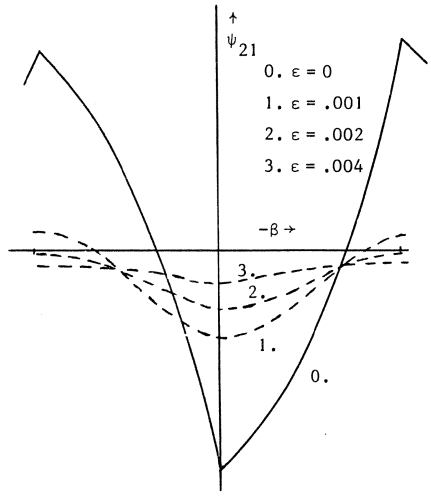


Fig. 3d. Dependence upon ε for superharmonic entrainment

5. ANOTHER EXAMPLE OF SUBHARMONIC ENTRAINMENT

When carrying out the computations of the forecoing section for autonomous frequencies with a ratio of about 1:2, the influence functions ψ_{12} and ψ_{21} turned out to be identically zero in the first order approximation with respect to δ. The computation of the next order term is possible but quite laborious. A further investigation shows that the cancellation is due to symmetry and that it occurs for any ratio containing an even integer with $F(x) = - F(-x)$. For coupled oscillators that run different, nonsymmetric limit cycles, one can compute the phase shift functions as well, as is seen in the following example:

(5.1a) $\quad \varepsilon dx_1/dt = y_1 - F_1(x_1),$ $\qquad$ (5.1c) $\quad \varepsilon dx_2/dt = y_2 - F(x_2),$

(5.1b) $\quad dy_1/dt = -(1-p_1\delta)x_1 + \delta x_2,$ $\qquad$ (5.1d) $\quad dy_2/dt = -sx_2,$

where $s = 4\ln 3/(\ln 2+\ln 3)$, $F(x)$ is given by (2,2) and $F_1(x)$ satisfies

(5.2a) $\quad F_1(x) = -2 + x \qquad$ for $\quad x \geq 1,$

(5.2b) $\quad F_1(x) = -1/3 - 2/3\,x \qquad$ for $\quad -2 < x < 1,$

(5.2c) $\quad F_1(x) = 3 + x \qquad$ for $\quad x \leq -2.$

Clearly, $T_{10} = 2T_{20} = \ln 2 + \ln 3$ for $\delta = 0$ and $\varepsilon \to 0$. The phase shift function is given by

(5.3a) $\quad \psi_{12}(\beta) = -.629\,e^{\beta} - .302\,e^{s\beta}$ for $0 \geq \beta > -3/4 \ln 2 + 1/4 \ln 3,$

(5.3b) $\quad \psi_{12}(\beta) = 8.17\,e^{\beta} - 12.86\,e^{s\beta}$ for $-3/4 \ln 2 + 1/4 \ln 2 \geq \beta > -T_{10}/4,$

(5.3c) $\quad \psi_{12}(\beta) = -\psi_{12}(\beta - T_{10}/4)$ for $0 \leq \beta < T_{10}/4,$

(5.3d) $\quad \psi_{12}(\beta) = \psi_{12}(\beta + T_{10}/2).$

In fig. 4 entrained numerical solutions are plotted for $\varepsilon = 10^{-3}$ and $\delta = .25$. Compared with the subharmonic solutions of the preceding example we note a higher sensitivity with respect to ε, probably due to the additional discontinuity in the derivative of the phase shift function.

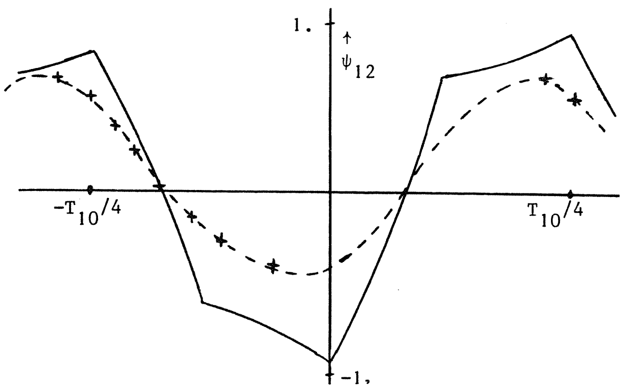


Fig. 4 . The influence function for subharmonic entrainment.

6. APPLICATIONS IN THE THEORY OF CHEMICAL AND ELECTRONIC OSCILLATIONS

The physiology of periodic phenomena in organisms can be quite complex and is in most cases not understood in sufficient detail. In the process of investigation one uses prototypes of biological oscillators in order to get more insight in the mechanism of entrainment and related phenomena. Besides abstract mathematical models there are prototypes of oscillators orginating from anorganic chemisty, e.g. the BELOUSOV - ZHABOTINSKII reaction [23] and from electronic circuit theory: the Van der Pol oscillator [24]. In this section we show that two such models can be cast in the form of relaxation oscillators of the type we study in this paper.

First we consider a hypothetical chemical reaction with periodic fluctuations in the concentration of some of the reactants: the Bruxellator, see [1]. Schematically we have the following reaction:

(6.1a) $$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X,$$

(6.1b) $$B + X \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Y + D,$$

(6.1c) $$2X + Y \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} 3X,$$

(6.1d) $\quad X \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} E.$

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

(6.2a) $\quad dx/dt = k_1a - k_2bx + k_3yx^2 - k_4x,$

(6.2b) $\quad dy/dt = k_2bx - k_3yx^2.$

Introduction of nondimensional variables defined by

(6.3a) $\quad u = k_4xy/(k_1a), \quad w = u + k_4y/(k_1a),$

(6.3b) $\quad \tau = k_4t, \quad \alpha = k_3(k_1a)^2/k_4^3, \quad \beta = k_2b/k_4$

transforms (6.2) into

(6.4a) $\quad du/d\tau = 1 - u - \beta u + \alpha u^2(w-u) = \beta f(u,w;\beta),$

(6.4b) $\quad dw/d\tau = 1 - u = g(u,w).$

This system has the equilibrium point $(\bar{u},\bar{w}) = (1,1+\beta/\alpha)$, which is stable for $\beta < 1 + \alpha$. Varying β we find that the equilibrium point is unstable above the critical value $\beta_c = 1 + \alpha$. Then a stable limit cycle with amplitude $(\beta-\beta_c)^{\frac{1}{2}}$ branches off. For $\beta > \alpha + 1 >> 1$ with $\beta-\alpha = O(1)$ the limit cycle turns into a relaxation oscillation, see fig. 5. The only difference with (2.1) is the null curve $f = 0$ with one stable branch depending strongly upon β, as it is situated in a $1/\beta$-neighborhaed of the w-axis in the u,w-plane. A local stretching transformation, e.g. $v = 1 + u - \exp(-\beta u)$, will give $f(v,w,0) = 0$ the required shape. Furtermore, we may study space dependent dynamics by diffusion coupling of a set of this chemical oscillators. Consisering diffusion of only the w-component with a diffusion coefficient δ we arrive at a type of system analyzed in section 3:

(6.5a) $\quad dv_i/dt = \beta f(v_i, w_i; 0)$

(6.5b) $\quad dw_i/dt = g(v_i, w_i) + \delta \sum_j w_j - w_i, \quad i = 1,2,\ldots,n,$

where the summation is taken over the neighboring oscillators. In [9] such a system of identical piece-wise linear oscillators was analyzed with the asymptotic method of section 4 and gave arise to bulk oscillations, stable phase wave patterns and persitent chaotic phase waves. The regular oscillatory patterns agree qualitatively with nummerical results by AUCHMUTY and NICOLIS [1] for Bruxellators with diffusion coupling. There are also other approaches to the mathematical analysis of coupled chemical oscillators, we mention [4,19,22].

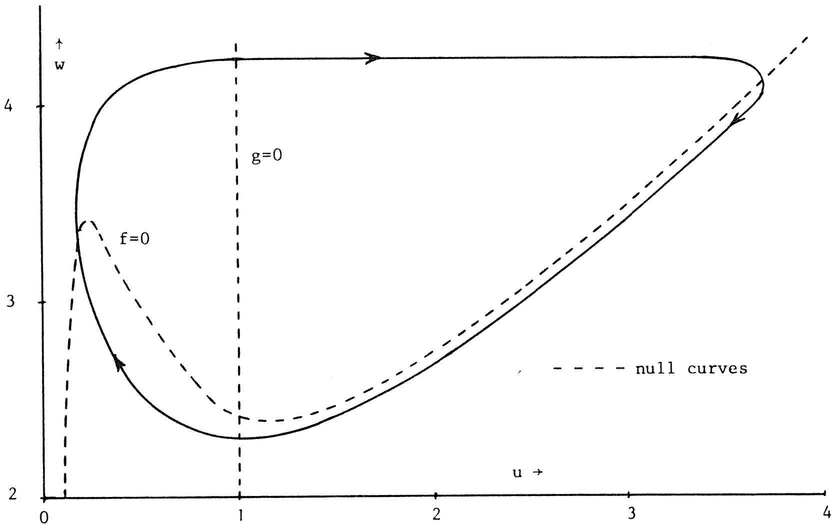


Fig. 5. Limit cycle of the Bruxellator for $\alpha = 5$ and $\beta = 7$.

Finally, we discuss the occurrence of entrained oscillations in a electronic circuit. GOLLUB e.a. [8] analyzed the circuit given in fig. 6a. The two tunnel diodes have characteristics a sketched in fig. 6b. For this circuit with $R_c = 0$ the voltage and current satisfy the system of differential equations.

(6.6a) $\quad C_1 dV_1/dt = I_1 - F(V_1),$ $\qquad$ (6.6c) $\quad C_2 dV_2/dt = I_2 - F(V_2),$

(6.6b) $\quad L_1 dI_1/dt = E - V_1 - R(I_1+I_2)$ $\qquad$ (6.6d) $\quad L_2 dI_2/dt = E - V_2 - R(I_1+I_2).$

For R small and C_1 and C_2 of even smaller order of magnitude this system is of the type we studied with asymptotic methods. In [8] the same type of entrainment is observed as we derived for the piece-wise linear oscillators. In addition they observed chaotic states for the circuit with R = 0 and $R_c \neq 0$. This choice yields differential equations for I_1 and V_i that are different from the ones of section 4.

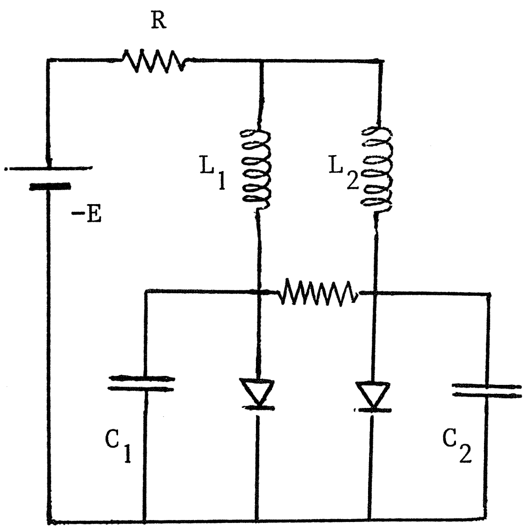


Fig. 6a. The circuit with two tunel diodes

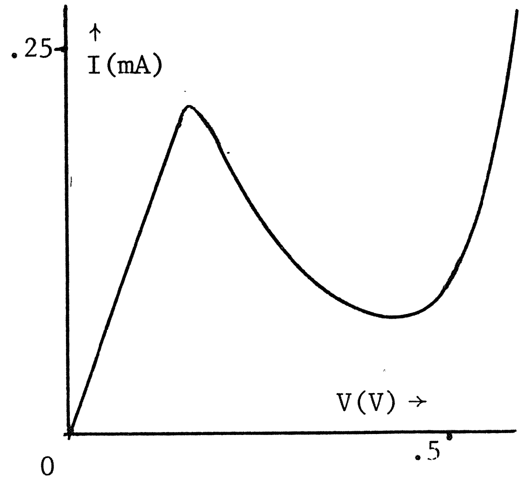


Fig. 6b. The charactiristic I = F(V) of the tunnel diode

ACKNOWLEDGEMENT

The author is grateful to Professor F.C. Hoppensteadt for bringing n:m entrainment to his attention.

REFERENCES

[1] AUCHMUTY, J.F.G. & G. NICOLIS, *Bifuration analysis of reaction diffusion equations - III, chemical oscillations*, Bull. Math. Biol. 38 (1976), 325-350.

[2] COHEN, A.H., P.J. HOLMES, & R.H. RAND, *The nature of the coupling between segmental oscillators of the lamprey spinal generator for locomotion: a mathematical model*, J. Math. Biol. 13 (1982), 345-369.

[3] ERMENTROUT, C.B., *n:m phase-locking of weakly coupled oscillators,* J. Math. Biol. 12 (1981), 327-342.

[4] ERMENTROUT, G.B. & J. RINZEL, *Waves in a simple, excitable or oscillatory reaction-diffusion model,* J. Math. Biol. 11 (1981), 269-294.

[5] GAER LUCE, C., *Biological rhythms in human and animal physiology,* Dover, New York, 1971.

[6] GLASS, L. & M.C. MACKEY, *A simple model for phase locking of biological oscillators,* J. Math. Biol. 7 (1979), 339-352.

[7] GLASS, L. & R. PEREZ, *Fine structure of phase locking,* Phys. Rev. Letters 48 (1982), 1772-1775.

[8] GOLLUB, J.P., T.O. BRUNNER & B.C. DANLY, *Periodicity and chaos in coupled nonlinear oscillators,* Science 200 (1978), 48-50.

[9] GRASMAN, J. & M.J.W. JANSEN, *Mutually synchronized relaxation oscillators as prototypes of oscillating systems in biology,* J. Math. Biol. 7 (1979), 171-197.

[10] GUCKENHEIMER, J., *Symbolic dynamics and relaxation oscillations,* Physica 1 D (1980), 227-235.

[11] GUEVARA, M.R. & L. GLASS, *Phase locking, period doubling bifuration and chaos in a mathematical model of a periodically driven oscillator: a theory for the entrainment of biological oscillators and the generation of cardiac dysrhytmias,* preprint Mc Gill University, Montreal 1981.

[12] GUEVARA, M.R. L. GLASS & A. SHRIER, *Phase locking, period-doubling bifurcations, and irregular dynamics in periodically stimulated cardiac cells,* Science 214 (1981), 1350-1353.

[13] GUTTMAN, R. L. FELDMAN & E. JAKOBSON, *Frequency entrainment of squid axon membrane,* J. Membr. Biol. 56 (1980), 9-18.

[14] HOLDEN, A.V., *The response of excitable membrane models to a cyclic input,* Biol. Cybern. 21 (1976), 1-7.

[15] HOPPENSTEADT, F.C. (ed.), *Nonlinear oscillations in biology,* Seminar

Appl. Math. by AMS and SIAM, AMS Lectures in Appl. Math. vol. 17, 1979.

[16] KEENER, J.P., *On cardiac arrythmias: AV Conduction block*, J.Math. Biol. 12 (1981), 215-225.

[17] LINKENS, D.A., *Modelling of gastro-intestinal electrical rhythms*, in Biological systems, modelling and control, D.A. Linkens (ed.), The Inst. of Electr. Engin., Londen (1979), 202-241.

[18] MISHENKO, E.F. & N.Kh. ROSOV, *Differential equations with small parameters and relaxation oscillations*, Plenum Press, New York 1980.

[19] NEU, J.C., *Large populations of coupled chemical oscillators*, SIAM J. Appl. Math. 38 (1980), 305-316.

[20] PETRILLO, G.A. L. GLASS & T. TRIPPENBACH, *Phase locking of the respiratory rhythm in cats to a mechanical ventilator*, preprint mcGill University, Montreal 1981.

[21] STOKER, J.J., *Nonlinear vibrations*, Interscience, New York 1950.

[22] TORRE, V., *Synchronization of nonlinear biochemical oscillators coupled by diffusion*, Biol. Cybern. 17 (1975), 137-144.

[23] TYSON, J.J., *The Belousov-Zhabotinskii reaction*, Lecture Notes in Biomath. vol. 10, 1976.

[24] POL, van der B. & J. van der MARK, *The heart beat considered as a relaxation oscillation and an electrical model of the heart*, Phil. Mag. 4 (1928), 763-773.

[25] TWEEL, van der L.H. F.L. MEIJLER & F.J.L. van CAPELLE, *Synchronization of the heart*, J. Appl. Physiol. 34 (1973), 283-287.

[26] WEVER, R.A., *The circadian system of man*, Springer-Verlag, New York, 1979 .

[27] WINFREE, A.T., *The geometry of biological time*, Biomath. vol. 8, Springer-Verlag, New York, 1980.

[28] YPEY, D.L. W.P.M. van MEERDIJK, E. INCE & G. GROOS, *Mutual entrainment of two pacemaker cells. A study with an electronic parallel conductance model*, J. Theor. Biol. 86 (1980), 731-755.