Coherent Oscillations in Biological Systems I

Bifurcation Phenomena and Phase Transitions in an Enzyme-Substrate Reaction with Ferroelectric Behaviour

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The concept of long range coherence in biological systems of Fröhlich and its physical basis as well as his general theoretical considerations leading to the brain wave model are reviewed. The importance of these ideas is stressed both, as a possible explanation of the increasing experimental results and as a starting point to allow a theoretical description of biological events. The brain wave model is studied in detail. All possible bifurcations and the stability of the steady states is considered. The existence, stability and direction of bifurcation of a stable limit cycle is proven. The system may exhibit different types of phase transitions when it is externally disturbed. Phase plane diagrams, arguments of catastrophe theory and approximations to the model equations give a qualitative description of the system's time behaviour. Correspondence between this limit cycle model and nerve impulse generating models is established.

1. Introduction

Biological systems exhibit stability in a way in which some modes of behaviour remain very far from thermal equilibrium. To give an interpretation of this obvious fact, one should primarily look for basical physical ideas which may serve as a starting point to establish physical theories for biological systems. One knows that a certain kind of physical order must exist which not necessarily has to be of spatial nature. This characteristic order is imposed by the supply of energy to the system. A similar situation can be found in a large number of systems in other fields, e.g. lasers, tunnel diodes, chemical reacting systems ... [1].

The functional complexity of biological materials requires the application of macroscopic theories [2]. These theories should rather describe the collective properties of the considered system than its behaviour on a molecular level. Some of the most interesting properties of biological systems are dielectric ones. These have been investigated in some detail by Fröhlich [3—6].

In his considerations a unit of a biological system consists of biomolecules surrounded by water and ions. This configuration can lead to the existence of very high internal electric fields, e.g. 10^5 V cm^{-1} in cell membranes. By this field the whole membrane is strongly polarized [3, 4]. In addition, an oscillation of parts of the membrane is connected with corresponding electric vibrations. The longest of these longitudinal electric vibrations can yield an electric dipole vibration of the whole system. Fröhlich has made two suggestions which can be taken as the physical basis for a theoretical investigation [2, 3]:

1. the long wavelength electric vibrations are very strongly and coherently excited in biological systems when the latter are active, i.e. when metabolic energy is available,

2. biological systems have metastable states with a very high electric polarization.

These rather speculative suggestions have received theoretical support through some simple model calculations. In [3] it was shown that if a system which is capable of long wave electric vibrations is supplied with energy, then a non-linear mode-mode coupling will lead to the channeling of the energy into a single coherent mode (Bose-condensation). The frequency of the longitudinal electric oscillations has been estimated to be in the 10^{11} Hz region [2].

On the other hand, if a long wave electric vibration interacts with the elastic field of the system, a metastable state with a permanent polarization is stabilized [2, 3]. Thus the nonlinear coupling of elastic and polar modes and an additional energy supply may evoke a quasi-ferroelectric behaviour, i.e. the activation of a high dipole moment [6].

Both types of activation, i.e. the coherent excitation of a single mode and the stabilization of a high dipole moment, can have far reaching consequences for the behaviour of biological systems. If, for example, the coherently excited vibration represents an oscillating giant dipole, then long range forces may be activated. Fröhlich [4] has

shown that the interaction of two giant dipole oscillations may lead to both, long range and frequency selective interactions, if one of these dipoles is coherently excited. These long range forces may lead to a selective transport of enzymes. Thus rather specific chemical reactions may become possible.

Though the above models are very simplified versions of any actual situation they may provide a basis for a search which focuses on collective properties rather than on a detailed microscopic description. Moreover, there is increasing experimental evidence for Fröhlich's initial assumptions: These are experiments on the influence of mm-band electromagnetic radiation on biological objects [8], the resonant growth rate response of yeast cells to weak microwaves [9], the possible existence of metastable states in enzymes [10] and the evidence for resonances and for non-thermal excitation of energy levels in active biological systems detected by Raman experiments [11, 12]. There is hope that in the near future new experimental results will become available, since several groups have started investigations on the basic problems and questions. On the other hand, it should be emphasized again that Fröhlich's suggestions are heavily based on general results of the physics of dielectric materials. Yet the consequences of these physical laws for biological systems are by no means unique and a matter of further laborous work.

Recently Fröhlich [7] has extended his ideas to give a possible explanation of the extraordinary high sensitivity of certain biological systems to weak electric and magnetic fields. Details of these experiments may be found in [7]. From the above considerations and model calculations he has derived a third suggestion:

3. the selective long range interaction in conjunction with the existence of highly polar metastable states and of coherent electric vibrations may be decisive for the establishment of the well known low frequency electric vibrations in the brain (EEG).

Details of this socalled brain wave model are given in [7]. The author has published some calculations on this model, in particular on the collapse of the inherent limit cycle oscillation by external stimulation [13].

It is the purpose of the present paper to extend these calculations. In the first chapter we will give a very short review of the derivation of the mathematical equations which describe the model. Subsequently we shall present the different types of steady states, their stability and phase plane behaviour. The different types of phase transitions caused by external stimulation are discussed. It will be shown that the external stimulation needs not necessarily be an electric field.

To get a better understanding of the dynamics of the model system we study so-called "energy-functions". Arguments of catastrophe theory show that Fröhlich's model exhibits a catastrophe of cusp type. We apply some approximations to overcome the restriction to a nearly time independent stimulation. Some of the approximated equations display the limit cycle collapse. The transition from an oscillating to a non oscillating state can be viewed as a transport phase transition.

2. Brain Wave Model

We apply Fröhlich's concept of long range coherence to an enzyme-substrate system [7, 13]. The suggested long range coherent interactions which are based on coherent vibrations in the 10^{11} Hz region and on the existence of a metastable state with a very high electric dipole moment could lead to collective enzymatic reactions in this system. These reactions, which take place in the Greater Membrane of the brain when they are supplied with substrate molecules, can create a chemical oscillation. It provides a slowly varying excitation and de-excitation of the system of enzymes from a weakly polar ground state to a highly polar metastable state. This slow chemical oscillation is connected to a corresponding electric vibration by means of the large dipole moments of the activated enzymes. Thus a macroscopic oscillating polarization is built up, causing large regions to oscillate coherently [14] in the 10 Hz region.

The electric dipole moment of the excited enzyme molecules is partially screened by the ions of the system. The remaining polarization causes the system to exhibit a tendency towards a ferro-electric instability.

The combination of the enzyme-substrate reaction together with the ferroelectric behaviour has led to

the following set of equations [7]

$$d_t \nu = \gamma \sigma + (c^2 e^{-\Gamma^2 \nu^2} - d^2) \nu$$
$$+ \alpha A \sigma \nu + F, \tag{2.1}$$

$$d_t \sigma = -\beta \nu - \alpha A \sigma \nu \tag{2.2}$$

with $\nu = N - \gamma/\alpha A$,

$\sigma = S - \beta/\alpha A$,

$\alpha, \beta, \gamma > 0$.

N, A are the concentrations of excited and unexcited enzyme molecules, S is the number of substrate molecules per unit volume. $\gamma \sigma$ results from the long range interaction, $\beta \nu$ and $\alpha A \sigma \nu$ originate from the nonlinear enzyme-substrate reactions. Aside from "chemical" terms we have an additional "dielectric" term which consists of two parts: a term describing the system's tendency to become ferroelectric, i.e. $c^2 e^{-\Gamma^2 \nu^2} \nu$ and frictional losses (electric resistences), i.e. $-d^2 \nu$. F results from the interaction of the system with its surrounding. It should be emphasized that F needs not necessarily be an external electric field as it was the case in [13]. It may also represent external chemical influences, e.g. input or output of enzyme molecules through transport. A more detailed derivation of Eqs. (2.1), (2.2) was given in [7, 13].

3. Steady States, Stability and Periodic Solutions

We briefly sum up those of the results of our previous paper, which are necessary for our further calculations. Depending on the parameters of the system, we have found earlier two or four steady states (SS) for our Equations (2.1), (2.2):

$$\text{SS 1}: \begin{cases} \nu_0, \\ \sigma_0 = -\beta/\alpha A; \end{cases} \qquad \text{SS 2}: \begin{cases} \nu_0 = 0, \\ \sigma_0 = -F/\gamma. \end{cases}$$

$F(t)$ is replaced by its time average, i.e. quasi-static case. The steady state value ν_0 of SS 1 is calculated from

$$F - \gamma \beta/\alpha A + (c^2 e^{-\Gamma^2 \nu_0^2} - d^2 - \beta) \nu_0 = 0. \tag{3.1}$$

Equation (3.1) has one real root for $c^2 - d^2 - \beta < 0$ and three real roots for $c^2 - d^2 - \beta > 0$.

The stability of the steady states has been proved by Ljapunov's first method. It is determined by

$$\lambda^2 - (a + \bar{d}) \lambda + a \bar{d} - b c = 0, \tag{3.2}$$

where a, b, c and $\bar{d}$ are the respective first derivatives if one expands Eqs. (2.1), (2.2) around the

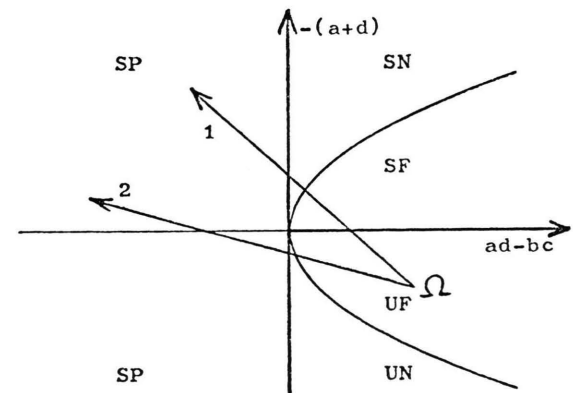steady states (vid. Figure 1). For SS 2 we have

$$a \bar{d} - b c = \beta \gamma - \alpha A F, \tag{3.3}$$
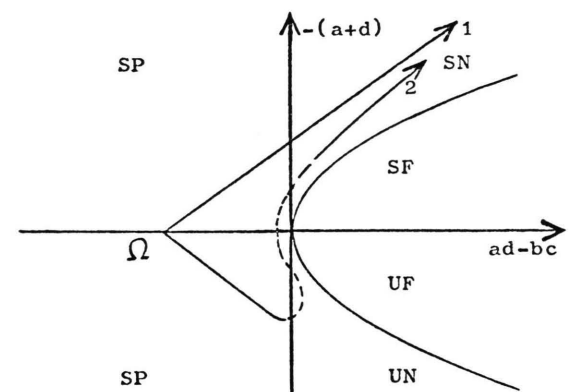
$$a + \bar{d} = c^2 - d^2 - \alpha A F/\gamma, \tag{3.4}$$

and for SS 1

$$a \bar{d} - b c = -\alpha A \nu_0 (c^2 (1 - 2\Gamma^2 \nu_0^2) \times e^{-\Gamma^2 \nu_0^2} - d^2 - \beta), \tag{3.5}$$

$$a + \bar{d} = c^2 (1 - 2\Gamma^2 \nu_0^2) \times e^{-\Gamma^2 \nu_0^2} - d^2 - \beta - \alpha A \nu_0. \tag{3.6}$$

a)

b)

Fig. 1. Stability of steady states in dependence of the external stimulation F. Ω corresponds to $F = 0$, the arrows indicate the direction of the increasing F. a) SS 2, b) SS 1; graph 1: $c^2 < d^2 + \beta$, graph 2: $c^2 > d^2 + \beta$ (SP = saddle point, SN = stable node, SF = stable focus, UN = unstable node, UF = unstable focus).

In Fig. 2 the steady states are given as a function of the external stimulation F.

Depending on the various parameters of the system on the one hand and on the external stimulation on the other hand, we have stable and
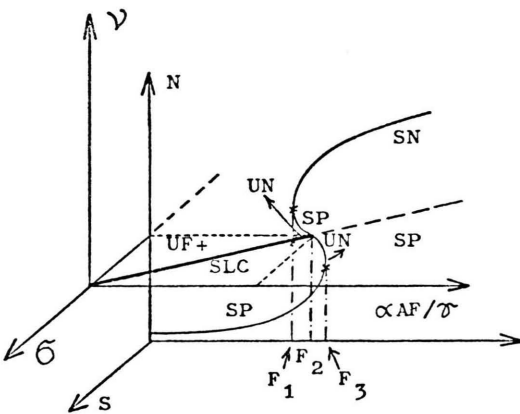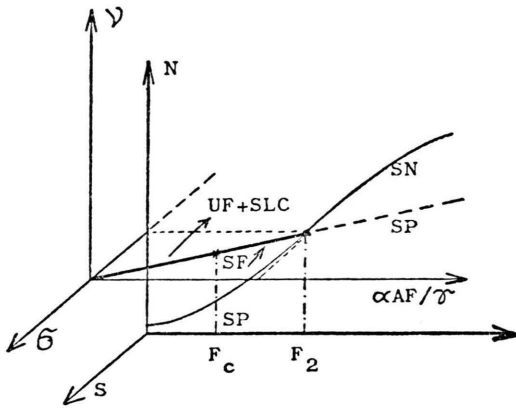
Fig. 2. Steady state solutions of Eqs. (2.1) and (2.2): a) $c^2 < d^2 + \beta$, b) $c^2 > d^2 + \beta$ (same notation as in Fig. 1, SLC = stable limit cycle).

Fig. 3. Steady state solutions ν_0 as a function of external and internal parameters. The folded surface represents the SS 1 and the plane one the SS 2 (same notation as in Fig. 1; $\Omega = \Omega$ ($\nu_0 = 0$, $F = 0$, $c^2 - d^2 - \beta = 0$)).

unstable regions (vid. Figure 3). In [13] we have found by numerical integration that a limit cycle exists. The necessary limit cycle conditions for SS 2 are:

$$a\,\bar{d} - b\,c > 0 \rightarrow \beta\,\gamma > \alpha A F , \qquad (3.7\,\text{a})$$

$$a + \bar{d} > 0 \rightarrow c^2 - d^2 > \alpha A F / \gamma , \qquad (3.7\,\text{b})$$

and

$$(c^2 - d^2 - \alpha A F / \gamma)^2 < 4\,(\beta\,\gamma - \alpha A F) . \quad (3.8)$$

To investigate the conditions for the limit cycle in more detail and to present an analytic proof for its existence and stability, we apply some results of bifurcation and focal value theory [15]. If Eqs. (3.7 a), (3.8) are valid, we have bifurcation for $c^2 - d^2 = \alpha A F / \gamma$. In this case we have a multiple focus, i.e. a transition from a stable focus to an unstable one and vice versa. The first nonvanishing
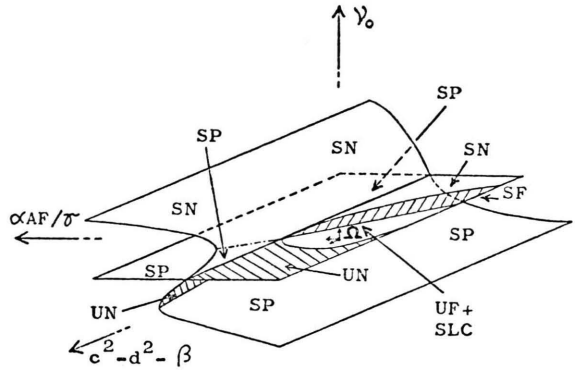
focal value (i.e. Ljapunov value) is α_3. α_3 is calculated from Eq. (76) of [15] for $F = F_c = \gamma\,(c^2 - d^2)/\alpha A$:

$$\alpha_3 = \frac{\Pi}{\Delta^3}\,c^2\,\gamma\,\Gamma^2\,(\alpha A F / \gamma - \beta) \qquad (3.9)$$

with

$$\Delta = + \sqrt{\beta\,\gamma - \alpha A F} .$$

Since we have in addition

$$\mathrm{d}_F(a + \bar{d})|_{F=F_c} = -\,\alpha A / \gamma < 0 \qquad (3.10)$$

we can make the following conclusions: For $c^2 - d^2 > \alpha A F / \gamma$ the SS 2 consists of an unstable focus (UF) surrounded by a stable limit cycle (SLC). At the bifurcation point F_c we have bifurcation to a stable focus (SF) due to the scheme:

$$\text{UF} + \text{SLC} \underset{F = F_c}{\longleftrightarrow} \text{SF} . \qquad (3.11)$$

The change in the external stimulation F modifies the stability behaviour of the steady state. With increasing F the limit cycle is absorbed by the unstable focus and a new focus is built up which takes over the stability of the limit cycle. Starting with $F > F_c$ we have the reversed situation for decreasing F: a stable focus bifurcates into a stable limit cycle around an unstable focus.

The focal value theory has proven both, the direction of bifurcation at $F = F_c$ and the existence of a single limit cycle below F_c. The details of these calculations are straightforward and need not be given in this paper. In Fig. 4 we have drawn the phase plane diagram and the limit cycle as they
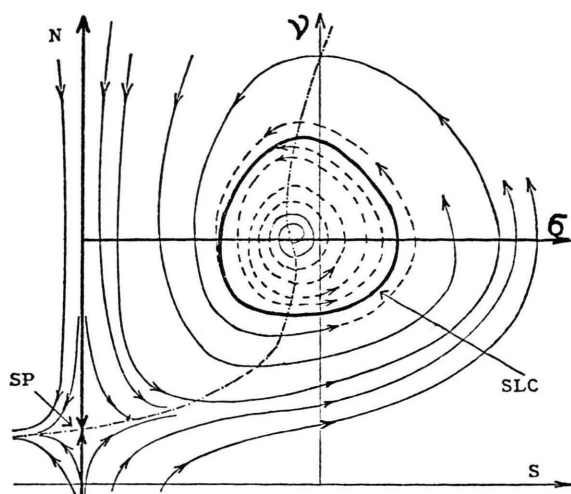
Fig. 4. Phase plane diagram for $c^2 < d^2 + \beta$ and $\beta\gamma < \alpha AF$, i.e. SS 1 is a saddle point (SP). The SS 2 is an unstable focus, surrounded by a stable limit cycle (SLC). The arrows on the trajectories define the time evolution of the system.

were found by numerical integration for

$$c^2 - d^2 - \beta < 0 \quad [13].$$

The situation with four steady states is more complicated. For $c^2 - d^2 - \beta > 0$ one gets for $F = F_c$

$$\beta\gamma < \alpha AF$$

and therefore condition (3.8) is not valid. Here, the focal value theory is not applicable; the same is the case for Hopf's bifurcation theory. Without a mathematical proof we show the results which can be derived with a detailed phase plane analysis including the slope of the trajectories in the whole plane. For $F = 0$ we start again with an unstable focus and a stable limit cycle. If F increases beyond F_1 (vid. Fig. 2b) two additional steady states appear: a stable node (SN) and a saddle point (SP), which is absolutely unstable. With some care we can deduce the following scheme of bifurcation

$$\text{UF} + \text{SLC} \underset{F \approx F_1}{\longrightarrow} \text{UN} + \text{SN} + \text{SP}. \qquad (3.12)$$

The stable limit cycle is "absorbed" by the stable node. In Fig. 5 we present some phase plane diagrams which show the qualitative behaviour (details of the phase plane analysis may be found in standard text books).

4. Catastrophe Theorie and Phase Transitions

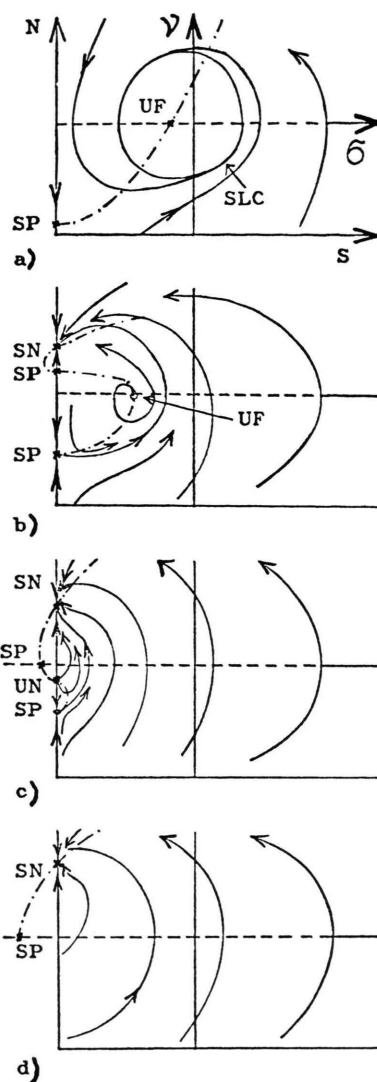In the preceeding chapter we have presented the steady state solutions and their stability. Hence-

Fig. 5. Phase plane diagrams if $c^2 > d^2 + \beta$ for different values of the external stimulation F (vid. fig. 2b): a) $F < F_1$, b) $F_1 < F < F_2$, c) $F_2 < F < F_3$, d) $F_3 < F$; ----- $d_t \sigma = 0$; -·-·-·- $d_t \nu = 0$ (same notation as in Figure 1).

forth we want to study the dynamic behaviour which is inherent in the model equations in some more detail. We start with an application of R. Thom's catastrophe theory [16].

Unfortunately Eqs. (2.1), (2.2) cannot be written in a "potential" form, i.e.

$$d_x V \neq -d_t x \qquad (4.1)$$

with $x = \nu, \sigma$.

Therefore Thom's theory cannot be applied at that stage. However, with some care the variable σ can be considered as a pool variable and may be

replaced by its steady state value σ_0 (application of adiabatic elimination principle). Equation (2.1) is then rewritten as

$$d_t v|_{\sigma=\sigma_0} \equiv g(v) = -\partial_v G(v) \qquad (4.2)$$

with

$$G(v) = \text{const} - (\gamma \sigma_0 + F) v \qquad (4.3)$$
$$+ \frac{1}{2\Gamma^2} c^2 e^{-\Gamma^2 v^2} + \frac{1}{2}(d^2 - \alpha A \sigma_0)v^2 .$$

For $\sigma_0 = -\beta/\alpha A$ (SS 1) we get

$$G_1(v) = \frac{1}{2\Gamma^2} c^2 e^{-\Gamma^2 v^2} + \frac{1}{2}v^2(d^2 + \beta) + \left(\frac{\beta\gamma}{\alpha A} - F\right)v \qquad (4.4)$$

and for $\sigma_0 = -F/\gamma$ (SS 2)

$$G_2(v) = \frac{1}{2\Gamma^2} c^2 e^{-\Gamma^2 v^2} + \frac{1}{2}v^2\left(d^2 + \frac{\alpha A F}{\gamma}\right). \qquad (4.5)$$

It has been shown that it is both sufficient for the qualitative and quantitative behaviour of our system to expand the exponential in Eq. (2.1) and to retain only the first nonlinear term [13]. The same procedure, when being applied to Eq. (4.3)

$$G(v) = \frac{1}{4}c^2\Gamma^2 v^4 - \frac{1}{2}v^2(c^2 + \alpha A \sigma_0 - d^2)$$
$$- v(\gamma\sigma_0 + F) + \text{const} \qquad (4.6)$$

or

$$\tilde{G}(v) = v^4 + a v^2 + b v \qquad (4.7)$$

with

$$\tilde{G}(v) = \frac{4}{c^2\Gamma^2} G(v)$$

$$a = -\frac{2}{c^2\Gamma^2}(c^2 + \alpha A \sigma_0 - d^2), \qquad (4.8)$$

$$b = -\frac{4}{c^2\Gamma^2}(\gamma\sigma + F). \qquad (4.9)$$

Equation (4.7) exhibits the behaviour of a cusp type of catastrophe. The steady state solutions v_0 are drawn in Figure 6. For $\sigma_0 = -\beta/\alpha A$ Eqs. (4.8), (4.9) read

$$a_1 = -\frac{2}{c^2\Gamma^2}(c^2 - d^2 - \beta),$$

$$b_1 = -\frac{4}{c^2\Gamma^2}(F - \gamma\beta/\alpha A),$$

whereas for $\sigma_0 = -F/\gamma$ we have

$$a_2 = -\frac{2}{c^2\Gamma^2}\left(c^2 - d^2 - \frac{\alpha A F}{\gamma}\right),$$
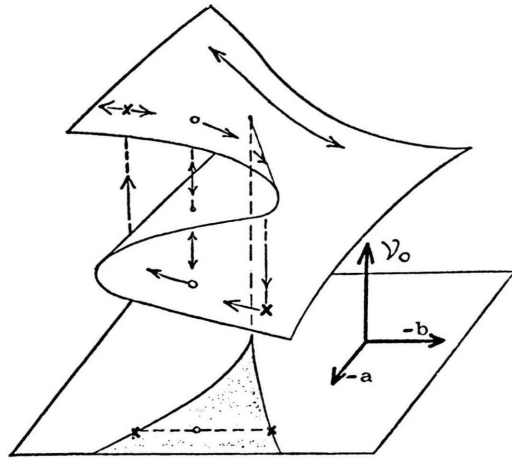
$$b_2 = 0 .$$

Fig. 6. Geometrical interpretation of the phase transitions for SS 1. The folded surface represents the steady state v_0 (i.e. behaviour variable) as a function of the control variables a and b. In the shaded region three steady states exist.

The "potential" or "energy-function" $\tilde{G}(v)$ is symmetric in the latter case, but with $b_2 = 0$ we have only a "quasi-cusp" type of catastrophe. Furthermore, for the steady state situation $d_t v = 0$ one can easily show that

$$d_t \sigma|_{\sigma=-\beta/\alpha A} = 0 \quad \text{for } v \text{ arbitrary}, \qquad (4.10)$$

$$d_t \sigma|_{\sigma=-F/\gamma} = 0 \begin{cases} \text{for } v = 0 \\ \text{for } v \neq 0 \text{ and } \gamma\beta = \alpha A F. \end{cases} \qquad (4.11)$$

In Figs. 7, 8 we have drawn $G_2(v)$ and $G_1(v)$ respectively. The two potential minima in Fig. 7 for $c^2 - d^2 - \alpha A F/\gamma > 0$ seem to indicate the existence of two stable steady states and a meta-stable one. This is misleading since only for $v_0 = 0$ we have $d_t \sigma = 0$ (vid. Equation (4.11)). Thus the double well potential reveals the existence of the limit cycle oscillation around $v_0 = 0$.

Figure 8 shows the differences in the potential function $G_1(v)$ for the two and four steady state situation. In both cases $v_0 = 0$ (i.e. the $\gamma\beta - \alpha A F$ axis) is the locus for the steady state 2.

The catastrophe theory serves as a simple tool to give a better understanding of the different types of phase transitions inherent in our Equations (2.1), (2.2).

We want to discuss the phase transition like behaviour in more detail for the respective cases $c^2 \gtrless d^2 + \beta$. a) $c^2 < d^2 + \beta$, i.e. two steady state situation. Both steady states exhibit a continuous
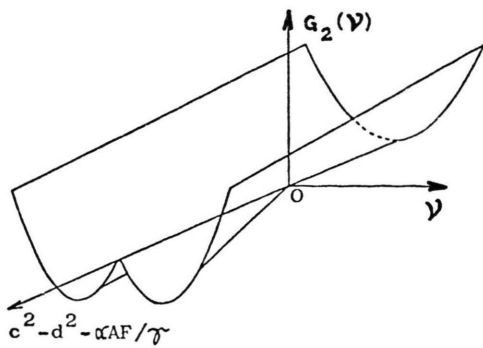
Fig. 7. Plot of the "energy-function" $G_2(\nu)$, i.e. $\sigma_0 = -F/\gamma$, as a function of the variable ν and the bifurcation parameter $c^2 - d^2 - \alpha AF/\gamma$ (for details see text).

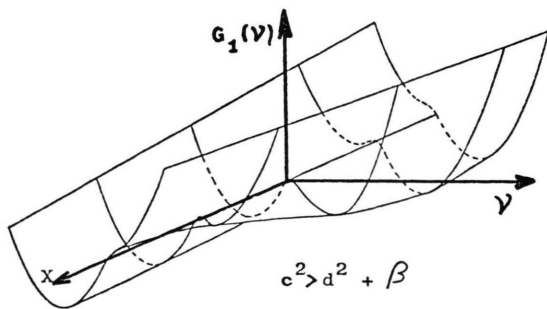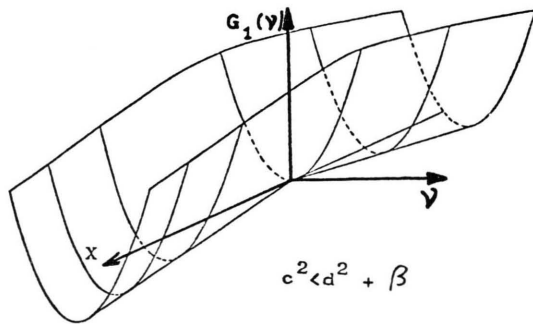

Fig. 8. Plot of the "energy-function" $G_1(\nu)$, i.e. $\sigma_0 = -\beta/\alpha A$. The SS 1 is a single ($c^2 < d^2 + \beta$, diagram a) or a threefold one ($c^2 > d^2 + \beta$, diagram b). $x = \gamma\beta - \alpha AF$.

phase transition. Starting with $F = 0$ we have the scheme (vid. Fig. 2)

$$\text{SS 1: SP} \underset{F_2}{\to} \text{SN} \tag{4.12}$$

$$\text{SS 2: UF + SLC} \underset{F_c}{\to} \text{SF} \underset{F_2}{\to} \text{SN} \to \text{SP} \tag{4.13}$$

$$(F_2 = \gamma\beta/\alpha A; \quad F_c = \gamma(c^2 - d^2)/\alpha A).$$

For $F = F_c$ we have bifurcation of a finite frequency normal mode, i.e. a hard mode instability and no softening when the mode bifurcates. With increasing F the mode softens and with $F = F_2$ we have an exchange of stabilities, i.e. a zero frequency

normal mode gets unstable. Both transitions display the behaviour of a second order phase transition.

b) $c^2 > d^2 + \beta$, i.e. four steady states exist.

This situation is a rather complicated one. Starting again with $F = 0$ one gets as bifurcation scheme

$$\text{SS 1:} \quad \begin{matrix} & \text{SN} & & \text{SN} & & \text{SN} \\ & \to \text{SP} & \to & \text{SP} & \to & , \\ & {\scriptstyle F_1} & & {\scriptstyle F_2} & & {\scriptstyle F_3} \\ \text{SP} & & \text{SP} & & \text{UN} & \end{matrix} \tag{4.14}$$

$$\text{SS 2: UF + SLC} \underset{F_1}{\to} \text{UN} \underset{F_2}{\to} \text{SP}. \tag{4.15}$$

For $F = F_1$ we have bifurcation of the stable limit cycle. The bifurcation behaviour leads to a discontinuous transition from an oscillating behaviour to a stable nonoscillating and highly excited one. This type of transition may be viewed as a special type of first order phase transition with a hard excitation. $F = F_2$ is a point of exchange of stability, a zero frequency normal mode gets unstable. This behaviour is known from second order phase transitions. With increasing F two unstable solutions coincide and disappear. They are of no relevance for our model.

The preceeding considerations do not cover the whole set of possible bifurcations and transitions. Under certain conditions (e.g. $c^2 \gg d^2 + \beta$) the critical stimulation F_1 can be zero. The steady state 1 is a threefold one for $F = 0$, the scheme (4.14) remains valid. Steady state 2 can bifurcate according to one of the three transitions:

$$\text{SF} \underset{F_2}{\to} \text{SN} \to \text{SP}, \quad \text{for} \quad c^2 < d^2, \tag{4.16}$$

$$\text{SN} \underset{F_2}{\to} \text{SP}, \quad \text{for} \quad c^2 \ll d^2, \tag{4.17}$$

$$\text{UN} \underset{F_2}{\to} \text{Sp}, \quad \text{for} \quad c^2 \gg d^2. \tag{4.18}$$

The bifurcations (4.16) and (4.17) rule out the possibility that the enzyme system can become ferroelectric, whereas (4.18) leads to a strong tendency to ferroelectric behaviour. Furthermore, all three types do not exhibit any interesting transition.

For the remainder of the present article we shall restrict ourselves to the scheme (4.12), (4.13) since these bifurcations seem to be the most relevant ones. The steady state solution for $F < F_c$ is a stable limit cycle oscillation. It represents a certain amount of energy. This stored energy can give rise to an electric signal much larger than the external stimulation when the limit cycle is caused to

collapse. Thus the system can overcome thermal noise though the external field F would be too weak to create a signal.

The condition for the breakdown of the limit cycle (i.e. $F_c = \gamma (c^2 - d^2)/\alpha A$) indicates that not only changes of the external electric stimulation can cause this collapse. Changes of either the enzyme-substrate coupling α or the concentration of unactivated enzyme A can alter the critical value F_c. A similar behaviour is achievable by a modification of the electric part of the limit cycle condition, i.e. by an influence of the ferroelectric or dielectric properties due to chemical means or changes of temperature. Furthermore, it should be emphasized again that F needs not necessarily be an electric stimulation. F may represent changes due to direct chemical influences. These influences may be caused for example by chemical substances or by auditory evoked chemical processes. However, almost nothing is known about these speculative possibilities.

Up to now we have restricted ourselves to the quasistatic case, i.e. $F(t)$ has been replaced by its time average. The different bifurcation points are thus determined by the strength of the external field. Further transitions, perhaps those of greater relevance, may occur if $F(t)$ is taken in its full time dependent form. The collapse of the limit cycle might then be determined by the frequency of the external stimulation. This problem is a rather difficult one. To get a better understanding of it, we have started investigations from quite another point of view. To apply the new method under consideration, the limit cycle which represents a coherent oscillation must be given analytically. Then after having performed a Fourier-analysis, we can couple the whole set of oscillatory components to the external stimulation. This method, which we do not present here, could be applied to give a possible explanation of the Raman and growth rate experiments, which have been cited in the introduction. In this analysis the coherent excitation in the 10^{11} Hz region will be considered as a limit cycle oscillation. Raman and Brioullin scattering as well as a direct absorption of this limit cycle are to be discussed.

5. Approximations

Hitherto we have not succeeded in solving the whole time dependent problem. Therefore we have looked for some informations which are inherent in Eqs. (2.1), (2.2) when approximations are made. We will present some of these calculations.

a) If σ and ν are small we neglect the nonlinear term $\alpha A \sigma \nu$ and expand the exponential function of Equation (2.1). The set of nonlinear differential equations then reduces to

$$d_t \nu = \gamma \sigma + (c^2 - d^2) \nu - c^2 \Gamma^2 \nu^3 + F, \quad (5.1)$$

$$d_t \sigma = - \beta \nu. \quad (5.2)$$

The only steady state for these equations is

SS 2: $\quad \nu_0 = 0, \quad \sigma_0 = - F/\gamma$

which is a stable focus for $c^2 < d^2$ and an unstable one for $c^2 > d^2$.

From Eqs. (5.1), (5.2) we can derive the second order differential equation

$$d_{\tau\tau} x + \mu (x^2 - 1) d_\tau x + x = \frac{\delta}{\omega_0} d_\tau F(\tau/\omega_0) \quad (5.3)$$

with

$$x = \delta \cdot \nu, \qquad \delta = \sqrt{3} \, c \, \Gamma (c^2 - d^2)^{-1/2},$$
$$\mu = (c^2 - d^2)/\omega_0, \quad \omega_0 = (\beta \gamma)^{1/2},$$
$$\tau = \omega_0 t.$$

This transformation is only applicable for $c^2 > d^2$. Equation (5.3) has exactly the structure of the well known Van der Pol equation (VP) [17], which has been the subject of a large number of investigations.

We only want to quote some of the relevant results.

With $\dot{F}(t) = 0$ Eq. (5.3) has a unique and stable limit cycle around the SS 2. This follows from an application of the Liénard theorem [18]. The shape of the limit cycle is determined by the parameter μ [19]. For $\mu < 1$, i.e. $c^2 - d^2 < (\beta\gamma)^{1/2}$, the oscillation is rather sinusoidal, whereas for $c^2 - d^2 > (\beta\gamma)^{1/2}$, we have an oscillation of relaxation type. The latter corresponds to the four steady state case of the exact equations. If $\dot{F}(t)$ does not vanish, again the stable limit cycle exists. Its shape (i.e. amplitude and frequency) is determined by both, the intensity and the frequency ω of the external stimulation. Depending on the detuning, i.e. $|\omega_0 - \omega|$, the amplitude either exceeds its value without external stimulation or remains below. Figure 9 shows the results when asymptotic methods are applied to the resonant and nonresonant regions respectively.
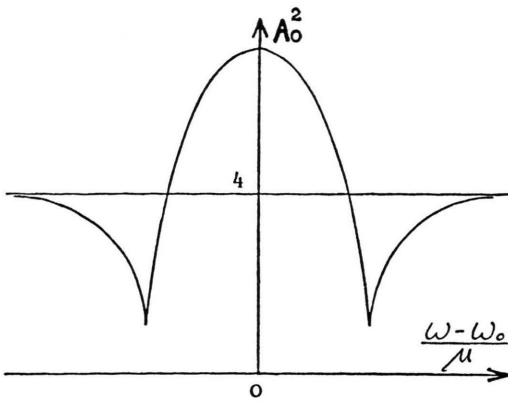
Fig. 9. The amplitude A_0 of the limit cycle as a function of the detuning parameter $(\omega - \omega_0)/\mu$ for Eq. (5.3) (Van der Pol approximation). $F(t) = F_0 \sin \omega t$.

If $\left| \int \dot{F}(t)\, dt \right|$ is bounded for $t \geqq 0$, then the solutions of Eq. (5.3) are ultimately bounded [17], i.e. there are no trajectories running to infinity. Thus the oscillation remains stable.

The Van der Pol approximation has given us some information about the system's behaviour when the external stimulation is time-dependent. The limit cycle oscillation of steady state 2 in the exact equations is still contained in the Van der Pol equation. However, in the latter case it cannot be destroyed by external means, even in the resonance regime. Thus the VP equations do neither exhibit the collapse of the limit cycle nor the existence of further steady states. Therefore this approximation is only valid in the region where the limit cycle exists.

However, the Van der Pol oscillator exhibits a rather sharp resonance and may thus lead to a possible explanation of the growth rate experiments, which have been cited in the introduction.

b) We again neglect the nonlinear term $\alpha A \sigma v$ in Eq. (2.1), whereas in Eq. (2.2) $\alpha A \sigma v$ is replaced by $\varepsilon \sigma$, i.e. the nonlinear term is traced back to a pure damping term. ($\alpha A v \to \alpha A \bar{v} = \varepsilon$.) The resulting kinetic equations

$$d_t v = \gamma \sigma + (c^2 e^{-\Gamma^2 v^2} - d^2)\, v + F , \qquad (5.4)$$

$$d_t \sigma = - \beta v - \varepsilon \sigma \qquad (5.5)$$

have one or three steady states. In the limit of a cubic approximation of the exponential, Eqs. (5.4), (5.5) are reduced to

$$d_t v = \gamma \sigma + (c^2 - d^2)\, v - \Gamma^2 c^2 v^3 + F , \qquad (5.6)$$

$$d_t \sigma = - \beta v - \varepsilon \sigma . \qquad (5.7)$$

Equations (5.4), (5.5) may be viewed as a modified Bonhoeffer-Van der Pol system (MBVP) [18], whereas Eqs. (5.6), (5.7) have the structure of the famous Fitz-Hugh equations (FH) [20], which are also of BVP-type.

It turns out that there exist neither qualitative nor relevant quantitative differences in the dynamic behaviour of the MBVP and the FH system. Therefore it is sufficient to consider Eqs. (5.6), (5.7).

For $c^2 < d^2 + \beta \gamma / \varepsilon$ we have a single steady state and for $c^2 > d^2 + \beta \gamma / \varepsilon$ the steady state is a threefold one. We find for this steady state (SS)

$$\text{SS 3}: \begin{cases} v_0 , \\ \sigma_0 = - \dfrac{\beta}{\varepsilon}\, v_0 \end{cases}$$

with v_0 given by

$$c^2 \Gamma^2 v_0^3 + (d^2 + \beta \gamma / \varepsilon - c^2)\, v_0 - F = 0 . \quad (5.8)$$

The characteristic equation from which the stability can be calculated reads

$$0 = \lambda^2 - \lambda(c^2 - d^2 - 3 \Gamma^2 c^2 v_0^2 - \varepsilon) + \varepsilon (\beta \gamma / \varepsilon + d^2 - c^2 + 3 \Gamma^2 v_0^2 c^2) . \quad (5.9)$$

For

$$c^2 - d^2 - 3 \Gamma^2 c^2 v_0^2 - \varepsilon = 0 \quad \text{and}$$
$$\beta \gamma / \varepsilon + d^2 - c^2 + 3 \Gamma^2 v_0^2 c^2 > 0$$
$$(\text{i.e. } \beta \gamma > \varepsilon^2)$$

we have bifurcation from an unstable focus to a stable one. The condition of Hopf bifurcation [21]

$$\text{Re } \lambda_{1/2} = 0 ,$$
$$d_F \text{Re } \lambda_{1/2} \neq 0$$

are fulfilled, periodic solutions do exist. The direction of the bifurcation of these periodic solutions is determined by its focal value [15]. With

$$\alpha_3 = - \Pi \varepsilon c^2 \Gamma^2 / 4 \beta \qquad (5.10)$$

and

$$d_F(a + d)\big|_{F=F_c} = - 6 c^2 \Gamma^2 v_0\, d_F v_0$$
$$= - 6 c^2 \Gamma^2 v_0 (\beta \gamma / \varepsilon - \varepsilon)$$
$$= \; < 0 \qquad (5.11)$$

we get the bifurcation scheme

$$\text{UF} + \text{SLC} \underset{F=F_c}{\longrightarrow} \text{SF} \to \text{SN} . \qquad (5.12)$$

This type of bifurcation is similar to scheme (4.15), which seems to be the most relevant one for our purposes. It is rather surprising that the approximated equations (Eqs. (5.4), (5.5) or Eqs. (5.6),
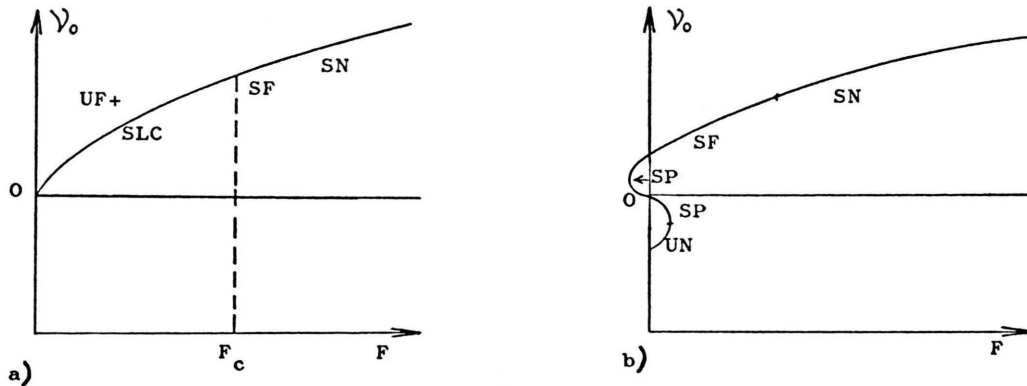
Fig. 10. Steady state solution ν_0 as a function of the external stimulation F for the approximated Fröhlich model [vid Eqs. (5.6) and (5.7)].

(5.7)) exhibit the limit cycle collapse due to external stimulation, although we have only added a small damping term $-\varepsilon\sigma$ to the VP equation. In Fig. 10 the steady state solutions of the BVP-FH equations are drawn.

The Fitz-Hugh equations were developed as a set of model equations to describe the pulse formation in the axon membrane of nerve cells. This nonlinear two-variable model was established as a simplifying model for the famous Hodgkins-Huxley equations [22]. It exhibits many of the typical effects known from experimental data. The intercorrelation between Fröhlich's brain wave model and Fitz-Hugh's nerve axon equations is rather astonishing since the meaning of the variables is a completely different one.

If one neglects the unstable solutions of saddle point type in Fröhlich's model and if one takes the approximated form which leads to Fitz-Hugh's equations one will find a good agreement between the two models (vid. Figs. 2a and 10a). For a strong external stimulation we have in both cases a highly excited branch of activated enzymes, whereas for a weak stimulation a limit cycle oscillation around a constant or a slowly increasing concentration of activated enzymes is exhibited. A qualitative picture of this behaviour is given in Figure 11.

A cubic approximation has been applied for both, the exact equations and their approximated versions. The focal value theory shows that at least this cubic nonlinearity is necessary for the limit cycle to exist (vid. Eqs. (3.9) and (5.10)). For the Fitz-Hugh type of equations thi sis quite obvious since the cubic term is the only nonlinear one, whereas in the Fröhlich model we have an additional nonlinearity, i.e. $\alpha A \sigma \nu$.

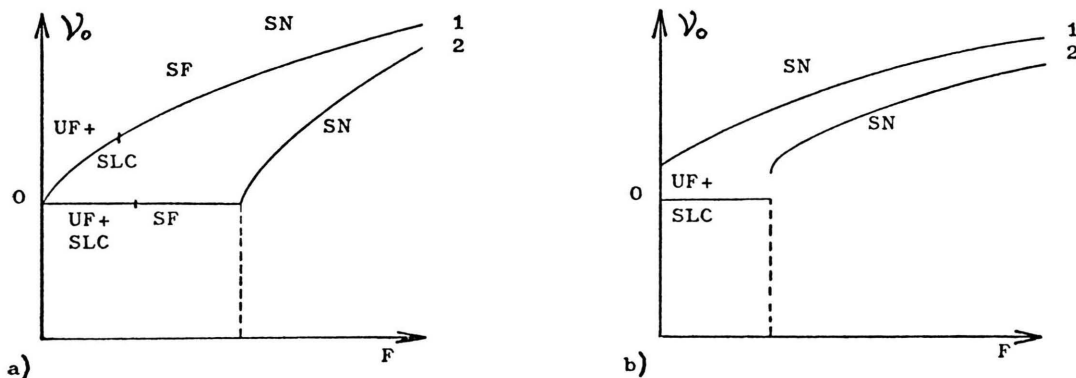Bifurcation phenomena in Fitz-Hugh's equation may be found e.g. in [23, 24].

Fig. 11. Comparison of the steady states ν_0 for the exact model [Eqs. (2.1) and (2.2); graph 2] and the approximated equations [Eqs. (5.6) and (5.7); graph 1]. Saddle point types of solutions are omitted.

6. Summary and Outlook

The existence of a coherent oscillation (limit cycle) based on a collective enzymatic reaction has been proved. This limit cycle is caused to collapse if the external stimulation exceeds a certain threshold. Aside from this sustained oscillation Fröhlich's brain wave model has shown a great variety of steady state solutions. Depending on the parameters of the system the external stimulation leads to several bifurcations, each of which may be viewed as a certain type of phase transitions.

Approximations which have been applied to the set of kinetic equations have revealed the possibility to study the action of a time dependent external stimulus. Near the critical point these approximate methods break down for a stimulus which varies with time. Thus a detailed investigation of the dynamic behaviour of the exact model equations remains to be done. Furthermore, the approximated equations show a close correlation with equations which describe the nerve action. An analysis of the relation between brain waves (EEG) and neuronal pulse propagation should be done both, experimentally and by means of a theoretical model. Obviously the brain waves may regulate and control the onset and propagation of nerve pulses.

Without more detailed information about the collective enzyme-substrate reaction one cannot solve these problems in a satisfying manner. However, just because of its rather speculative character this chemical reaction is open for a number of changes in its reaction scheme.

Although this model is far from being proved in an experimental way, it seems well suited as an example to derive biological behaviour from physical basis. Fortunately there is increasing experimental evidence which seems to indicate that the physical basis for the brain wave model is correct. Thus, the theory of long range coherence in biological systems seems to be applicable. Most of the work, however, still remains to be done.

We have extended the above calculations to find answers to some of the unsolved questions. One of the most relevant problems is concerned with the breakdown of the limit cycle by means of which a certain amount of energy is set free. We have also studied the onset of pulse propagation when the limit cycle starts to collapse [25]. These investigations require the introduction of both, the space dependence of the chemical variables and the size of the reacting and oscillating units.

Finally we want to stress that the set of differential equations that describes the brain wave model fulfills the requirements for a phase transition far away from thermal equilibrium. The system is open and nonlinear. However, it should be mentioned that already the resting state (i. e. $F = 0$) is a nonequilibrium one. It is established by the underlying physical and biological processes in which nonlinear interactions and energy supply are incorporated. From this point of view, it is not surprising that the resting state is an oscillating one i.e. we do not start from thermal equilibrium but from a nonthermodynamical branch.

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