# Coherent Oscillations in Biological Systems II
# Limit Cycle Collapse and the Onset of Travelling Waves in Fröhlich's Brain Wave Model

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A brief description of the model equations and their underlying physical basis is given. The space independent problem of a previous paper is extended to include diffusive processes. Travelling wave solutions are introduced, the stability of the steady states and the different bifurcation schemes are discussed. The collapse of the limit cycle, by means of an external stimulation or by internal constraints as well as the onset of propagating pulses is considered. Phase portraits are discussed in great detail. Correspondence between some approximated versions of the model equations and nervous pulse propagation equations is established. Furthermore, some suggestions for an experimental proof of the model are made.

## 1. Introduction

In a recently published paper [1] (henceforth referred to as I) we have presented some studies on Fröhlich's brain wave model [2]. The physical basis of this model is the concept of long range coherence in biological systems. Starting from the dielectric properties of biological materials, Fröhlich [3] has shown by a mere application of physical laws that such systems may be capable of coherent electric vibrations in the $10^{11}$ Hz region. The existence of a metastable state with a very large electric dipole moment and long range selective interactions can lead to a collective enzymatic reaction. This reaction should take place in the greater membrane of the brain [4] if supplied with substrate molecules. It can create a chemical oscillation of parts of the membrane and a corresponding electric oscillation which is coherent over large regions.

The model has been suggested to explain the extraordinarily high sensitivity of biological systems to weak electromagnetic signals. In I we have studied the set of nonlinear differential equations which describes the model. The most relevant result is the existence of a limit cycle (sustained oscillation) and its collapse when it is exposed to an external stimulation of sufficient strength. The limit cycle stores the signal energy until the breakdown occurs. This reveals the possibility to create a response signal (i.e. nerve impulse) even though the energy which is available from the external stimulation would be too weak to cause this. The onset of a response signal necessitates the introduction of space dependent variables. In order to describe spatial non-homogeneous solutions (i.e. propagating pulses) diffusive processes have to be added to the other processes.

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In the present paper we discuss the space dependent problem in some detail. The diffusive processes are discribed by a simple application of Fick's law of diffusion. The prerequisites for the emergence of spatio-temporal patterns of organization are open systems, nonlinear kinetics and stabilization of these patterns sufficiently far away from thermal equilibrium. Fröhlich's model displays these properties (vid. I).

The bifurcation of the limit cycle, i.e. the instability of the time-periodic steady state solution may lead to another solution which is stable in space and time. These spatio-temporal dissipative structures [5] can be of various types. In this paper we shall restrict ourselves to travelling wave solutions. Other types of solutions (e.g. more complex space- and time dependent structures, localized structures, almost periodic solutions, ...) which can branch off from the homogeneous solution by means of specific constraints are more difficult to be handled. These solutions rather depend on the detailed structure of the boundaries than on the bulk properties. Work on these subjects has been done in many branches of natural sciences such as: chemical reactions, shock waves, fluid dynamics, biological evolution, ecology and in other fields, e.g. sociology [24].

An important reason to extend the calculations of our previous papers [1, 6, 7] is the increasing experimental work which has been done to test the conclusions which have been drawn from Fröhlich's suggestions. An interpretation of the known experimental results by means of some simple but convincing model calculations provides considerable evidence for Fröhlich's rather speculative suggestions (vid. I).

We start with a brief description of the model equations and their extension to the nonhomogeneous problem. Travelling wave solutions are then introduced. They allow to transform the set of nonlinear parabolic differential equations into a set of ordinary differential equations. Subsequently we study the stability of the steady states and the different bifurcation schemes. Special attention is given to the existence of periodic solutions. The resulting phase portraits are discussed in great detail. They show the dynamic behaviour of the model equations, in particular the different types of travelling waves that can exist.

Finally we briefly comment on the relations which exist between nervous pulse propagation equations and our approximated equations.

## 2. Limit Cycle and Travelling Waves

In paper I we have studied the steady state behaviour of the following set of equations

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

$$\mathrm{d}_t \sigma = -\beta \nu - \alpha A \sigma \nu\,. \tag{2.2}$$

The first two terms on the r.h.s. of both equations describe the nonlinear collective enzymatic reaction. The third term of Eq. (2.1) is the "dielectric" term. It describes the competition between the system's tendency to become ferroelectric and inherent losses due to "electrical" resistances. $F$ is the external stimulation, $\nu$ and $\sigma$ are the excess concentrations of activated enzyme and substrate molecules respectively beyond their equilibrium values $N = \nu + \gamma/\alpha A$ and $S = \sigma + (\beta/\alpha A)$. $\alpha$, $\beta$ and $\gamma$ are positive parameters and $A$ is the concentration of unexcited enzyme molecules.

Equations (2.1) and (2.2) exhibit a limit cycle oscillation if the conditions

$$\beta\gamma > \alpha A F\,, \tag{2.3}$$

$$c^2 - d^2 > \alpha A F/\gamma\,, \tag{2.4}$$

and

$$(c^2 - d^2 - \alpha A F/\gamma)^2 < 4(\beta\gamma - \alpha A F) \tag{2.5}$$

are fulfilled.

In order to look for space dependent solutions a diffusive process must be incorporated in Eqs. (2.1) and (2.2). We take the axial direction $\bar{x}$ to be the only important space dimension and apply Fick's law of diffusion. However, we do not add a "diffusive" term in Equation (2.2). On one hand we make this restriction for mathematical convenience but also to account for the fact that $\sigma$ partially plays the role of a pool-variable (i.e. a slow variable in our case). This has the effect of replacing Eqs. (2.1) and (2.2) by

$$\partial_t \nu = \gamma\sigma + \alpha A \sigma \nu + (c^2 e^{-\Gamma^2 \nu^2} - d^2)\nu + F + \partial_{xx}\nu\,, \tag{2.6}$$

$$\partial_t \sigma = -\beta\nu - \alpha A \sigma \gamma \tag{2.7}$$

(the diffusion constant $D$ is incorporated in the variable $x$, $\bar{x} = \sqrt{D}\,x$).

Assuming the membrane to be of infinite length, we study Eqs. (2.6) and (2.7) on the planar quadrant $x \geqq 0$, $t \geqq 0$. Equations (2.6) is classified as a nonlinear parabolic partial differential equation of the general form

$$\partial_{xx}\nu = \partial_t \nu + f(\nu)\,, \tag{2.8}$$

where $f(\nu)$ is nonlinear. This equation is known to have travelling wave solutions. Such a behaviour is not possible if $f(\nu)$ is linear (vid. e.g. the heat equation). Equation (2.8) is supplemented by a kinetic equation for the additional variable $\sigma$. We expect this addition to give rise to a significant new behaviour. As stated in the introduction we will restrict ourselves to travelling wave solutions of Eqs. (2.6) and (2.7). A solution of this type only depends on the variable $s = x + \Theta t$, where $\theta$ is the wave velocity; it plays the role of a parameter here. We substitute

$$\nu = \psi(x + \theta t) \equiv \psi(s)\,,$$

$$\sigma = \varphi(x + \theta t) \equiv \varphi(s)$$

in Eqs. (2.6) and (2.7), respectively.

The transformed equations read

$$\Theta\,\partial_s \psi = \gamma\varphi + \alpha A \psi\varphi + F + (c^2 e^{-\Gamma^2 \psi^2} - d^2)\psi + \partial_{ss}\psi\,, \tag{2.9}$$

$$\Theta\,\partial_s \varphi = -\beta\psi - \alpha A \psi\varphi\,. \tag{2.10}$$

Introducing $\partial_s \psi = \chi$, the Eqs. (2.9) and (2.10) can be written as a first order system

$$\partial_s \psi = \chi \,, \tag{2.11}$$

$$\partial_s \chi = \Theta \chi - \gamma \varphi - (c^2 e^{-\Gamma^2 \psi^2} - d^2) \psi - \alpha A \psi \varphi - F \,, \tag{2.12}$$

$$\Theta \, \partial_s \varphi = - \beta \psi - \alpha A \psi \varphi \tag{2.13}$$

with the steady states (equil. points):

$$\text{SS 1:} \begin{cases} \psi_0 \\ \varphi_0 = - \beta / \alpha A \\ \chi_0 = 0 \end{cases}$$

and

$$\text{SS 2:} \begin{cases} \psi_0 = 0 \\ \varphi_0 = - F/\gamma \\ \chi_0 = 0 \end{cases}$$

We expand the nonlinearities of Eqs. (2.11) to (2.13) in a Taylor series around the two steady states. The linearized equations then determine the stability of the steady state solution near this critical point [8]. For the SS 1 we get the characteristic equation

$$\begin{aligned} &\lambda^3 - \lambda^2 (\Theta - \alpha A \psi_0/\Theta) + \lambda (c^2 (1 - 2\Gamma^2 \psi_0^2) \\ &\quad \cdot e^{-\Gamma^2 \psi_0^2} - d^2 - \beta - \alpha A \psi_0) \\ &\quad + \alpha A \psi_0 (c^2 (1 - 2 \Gamma^2 \psi_0^2) \\ &\quad \cdot e^{-\Gamma^2 \psi_0^2} - d^2 - \beta)/\Theta = 0 \end{aligned} \tag{2.14}$$

and for the SS 2

$$\lambda^3 - \Theta \lambda^2 + \lambda (c^2 - d^2 - \alpha A F/\gamma) - (\beta \gamma - \alpha A F)/\Theta = 0 \,. \tag{2.15}$$

### 3. Stability of Steady State 2

The eigenvalues of Eq. (2.15) are real or complex, depending on the parameters and on the external stimulation. If the conditions (2.3) and (2.4) are fulfilled, we have an unstable node (UN) if Eq. (2.15) has three positive real roots and an unstable focus (UF) if there is a positive real root and complex roots with positive real parts. For $c^2 - d^2 - \alpha A F/\gamma = 0$ and $\beta \gamma > \alpha A F$ (i.e. $c^2 - d^2 - \beta < 0$) we have the bifurcation scheme

$$\text{U F} \underset{F_c}{\longrightarrow} \text{S P} \tag{3.1}$$

with

$$F_c = \gamma (c^2 - d^2)/\alpha A$$

[under these conditions the critical point is an unstable focus, which follows from a calculation of the discriminant of Equations (2.15)]. For

$$c^2 - d^2 - \alpha A F/\gamma > 0 \quad \text{and} \quad \beta \gamma = \alpha A F$$

(i.e. $c^2 - d^2 - \beta > 0$) we have the scheme

$$\text{U F} \underset{F_2}{\longrightarrow} \text{S P} \tag{3.2}$$

with

$$F_2 = \beta \gamma / \alpha A \,.$$

If one of the conditions (2.3) or (2.4) or both are not valid, the real parts of the eigenvalues do not have the same sign. All these cases exhibit a saddle point behaviour. The existence of a negative real eigenvalue together with a complex root with negative real parts is ruled out by the Hurwitz criterion [9]. An asymptotically stable steady state (i.e. stable node or stable focus) does not exist.

If we compare the stability conditions for the SS 2 of the space independent problem (vid. I) with those of the space dependent one, we can derive the following scheme:

stable focus (stable node) in I $\leftrightarrow$ saddle point,

saddle point in I $\leftrightarrow$ saddle point,

unstable focus (unstable node) in I $\leftrightarrow$ unstable focus.

The saddle point belongs to a one-dimensional family of solutions which tend to the steady state for $s \to + \infty$ (i.e. stable) and to a two-dimensional family of solutions which tend to the steady state for $s \to - \infty$ (i.e. unstable). This holds for

$$c^2 - d^2 - \frac{\alpha A F}{\gamma} > 0; \quad \beta \gamma - \alpha A F < 0$$

or

$$c^2 - d^2 - \frac{\alpha A F}{\gamma} < 0; \quad \beta \gamma - \alpha A F < 0 \,.$$

The reversed situation, i.e. two stable and one unstable families of solutions, is given when

$$c^2 - d^2 - \frac{\alpha A F}{\gamma} < 0; \quad \beta \gamma - \alpha A F > 0 \,.$$

The most interesting problem concerns the limit cycle oscillation around the unstable focus in the homogeneous case. This sustained oscillation can only exist if at least the conditions (2.3) and (2.4) are valid. We apply a generalized Hopf bifurcation theorem [9] to Equation (2.15). This equation has two simple, complex conjugate nonzero eigenvalues $\lambda_{1/2}$. They cross the imaginary axis if

$$\alpha A F_c/\gamma = (\beta\gamma - \Theta^2(c^2 - d^2))/(\gamma - \Theta^2). \quad (3.3)$$

Furthermore we can calculate the "speed" with which $\lambda_1$ and $\lambda_2$ bifurcate:

$$\partial_{\alpha AF/\gamma} \operatorname{Re}(\lambda_{1/2})|_{F=F_c} = \tfrac{1}{2}(\gamma^2 - \Theta^4)/ \cdot ((c^2 - d^2 - \beta)\gamma - 6\,\Theta^3(\gamma - \Theta^2)). \quad (3.4)$$

For the real root one gets $\lambda_3 = \Theta > 0$. For $\gamma \neq \Theta$ the conditions of the generalized Hopf bifurcation

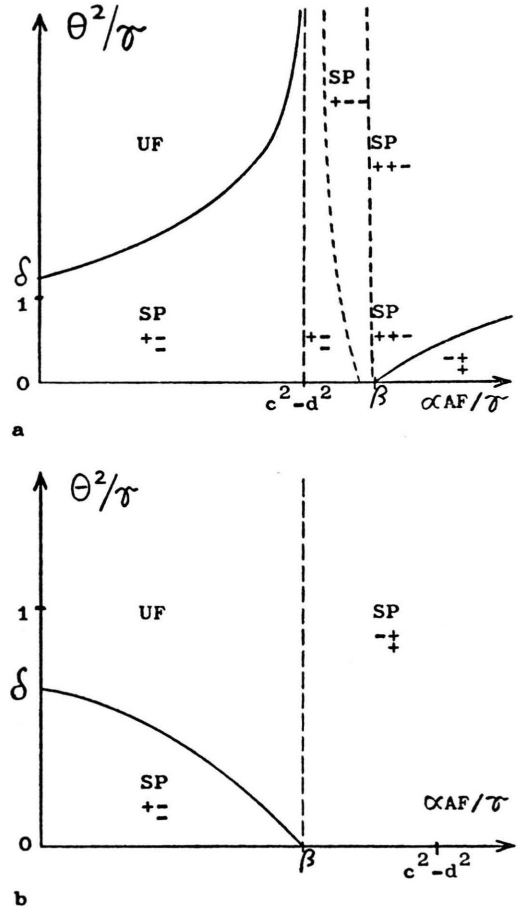



Fig. 1. Stability of steady state 2 (SS 2) in dependence of the external stimulation $F$ and of the travelling wave velocity $\theta$ The solid line represents condition (3.3), $\delta = \beta/(c^2 - d^2)$. The + and − sign correspond to a positive and a negative eigenvalue, respectively; $\ddagger$ or $=$ refer to the sign of the real part of a complex eigenvalue. (SP = saddle point, UF = unstable focus.)
a) $c^2 - d^2 - \beta < 0$; b) $c^2 - d^2 - \beta > 0$.

theorem are fulfilled, i.e. periodic solutions do exist. The existence of only one positive real root follows from a calculation of the so-called Sturm's functions. For

$$\Theta^2/\gamma < \beta(c^2 - d^2)^{-1} \quad (3.5)$$

there exists a region where the steady state solution is a saddle point. If we restrict ourselves to the most promising transition in the space-independent case [vid. Equation (I, 4.13)]:

$$\mathrm{U\,F} + \mathrm{S\,L\,C} \underset{F_c}{\rightarrow} \mathrm{S\,F} \quad (3.6)$$

we find from condition (2.4) and Eq. (3.3)

$$\Theta^2/\gamma \geqq 1. \quad (3.7)$$

We thus have a lower limit for the velocity of the travelling wave

$$\Theta_{\min} = \sqrt{\gamma}.$$

An analysis of the phase plane shows that there are no nonconstant bounded solutions, if the critical point is a saddle point. Accordingly, no stable travelling wave solutions can exist. The situation, where SS 2 is an unstable focus which is surrounded by a limit cycle, will be discussed in more detail after having studied the SS 1. A graphic representation of the conditions (3.3) is given in Figure 1.

## 4. Stability of Steady State 1

The critical value $\psi_0$ is calculated from $G(\psi_0, F) = 0$, with

$$G(\psi_0, F) = (c^2 e^{-\Gamma^2\psi_0^2} - d^2 - \beta)\,\psi_0 - \beta\gamma/\alpha A + F. \quad (4.1)$$

This equation has one real solution for

$$c^2 - d^2 - \beta < 0$$

and three roots in the opposite case.

The characteristic equation [Eq. (2.14)] can be separated in two parts:

$$\lambda_1 = -\,\alpha A\,\psi_0/\Theta, \quad (4.2)$$

$$\lambda^2 - \Theta\lambda + c^2(1 - 2\,\Gamma^2\psi_0^2) \cdot e^{-\Gamma^2\psi_0^2} - d^2 - \beta = 0. \quad (4.3)$$

The latter equation is rewritten in the form

$$\lambda^2 - \Theta\lambda - (\partial_F\,\psi_0)^{-1} = 0 \quad (4.4)$$

with $\partial_F\,\psi_0$ derived from Equation (4.1). It allows a geometrical interpretation of the stability behaviour since the sign of $\partial_F \psi_0$ can be taken from the $\psi_0 - F$-diagram (vid. Figure 2). We get critical points of different types. Both, for $\psi_0 < 0$ (i.e. $\lambda_1 > 0$), $\partial_F \psi_0 > 0$, and for $\psi_0 > 0$ (i.e. $\lambda_1 < 0$), $\partial_F \psi_0 \gtrless 0$ the critical points are of saddle point type. $\psi_0 < 0$, $\partial_F \psi_0 <$ lead to a unstable focus or an unstable node. The additional condition for the steady state to be a focus is $\Theta^2 + 4(\partial_F \psi_0)^{-1} < 0$. No asymptotically stable solutions can exist. This follows from the Hurwitz criterion [9]. The correlation which exists between the homogeneous and inhomogeneous case is the same as for steady state 2. Both results are drawn in Figure 2.

A bifurcation to a periodic solution is not possible, since the necessary conditions of a generalized Hopf bifurcation theorem are not fulfilled. The necessary condition for two purely imaginary roots reads

$$\Theta^2(\alpha A \psi_0 + (\partial_F \psi_0)^{-1}) = (\alpha A \psi_0)^2 . \quad (4.5)$$

This is the same form as Eq. (4.4) if one replaces $\alpha A \psi_0$ by $\Theta \lambda$. Hence the solutions of Eq. (4.5) and of Eq. (4.4) are not independent from each other, i.e.

$$(\alpha A \psi_0)_{1,2} = \Theta \lambda_{2,3} .$$

But since the eigenvalues $\lambda_{2,3}$ are purely imaginary, $\psi_0$ also has to be purely imaginary. However, an imaginary steady state solution $\psi_0$ is not relevant. The complete stability behaviour of the steady states 1 and 2 is shown in Figure 3.

As seen, the region where an unstable node or an unstable focus exists is rather restricted. Furthermore, only for SS 2 periodic solutions exist. However, a further analysis is required to determine the stability of the periodic solution and the direction of bifurcation. The theory of one-parameter transformation groups seems to be an appropriate and possible method [10].

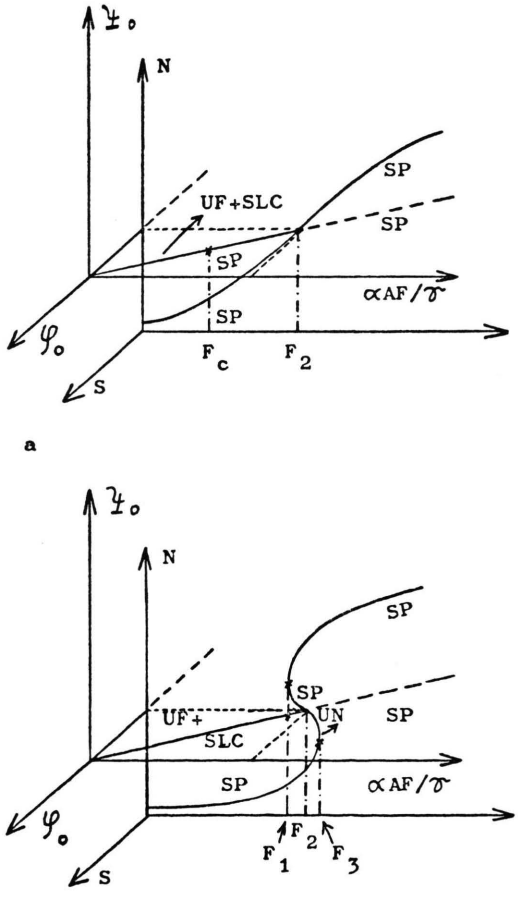



Fig. 2. Steady state solutions of Eqs. (2.9) and (2.10): a) $c^2 - d^2 - \beta < 0$; b) $c^2 - d^2 - \beta > 0$. (SP = saddle point, SLC = stable limit cycle, UF = unstable focus, UN = unstable node.)

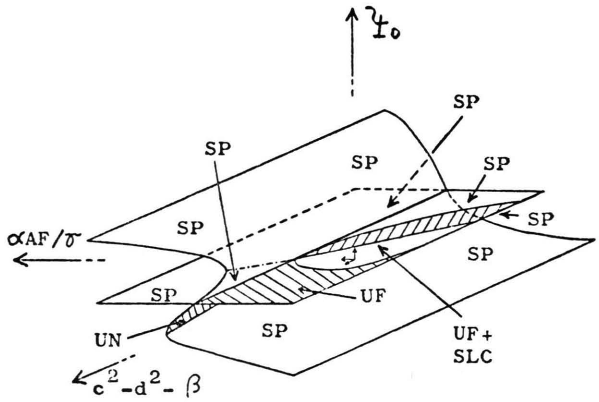



Fig. 3. Steady state solutions $\psi_0$ as a function of the external and internal parameters. The folded surface represents SS 1 and the plane one SS 2 (same notation as in Fig. 2), $\Theta^2/\gamma > \beta/(c^2 - d^2)$.

## 5. Phase Portrait

The phase portrait of Eqs. (2.11) to (2.13) changes qualitatively when relevant parameter values cross the locus of bifurcation in their parameter space. Since these loci are known, we can discuss in principle the complete phase portraits for any value of external constraints. This analysis exhibits the possible kinds of travelling waves.

Unfortunately the phase space of our dynamic system is three dimensional. In order to keep the investigations in a reasonable limit and for the clarity of the portraits we confine ourselves to an analysis in two dimensions, i.e. in the phase plane. This has the effect that one studies a system of lower dimension which now depends on an additional parameter $\varphi = \varphi_c$. We restrict ourselves to the $\chi - \psi$-plane. This limitation seems to be reasonable since the variable $\varphi$ is a slow variable and plays the role of a pool-variable ($\varphi_c$). However, we must be aware that only for $\varphi_c = \varphi_0 = -\beta/\alpha A$ (i.e. SS 1) we have $\partial_s \varphi = 0$. Then all the trajectories lie entirely in the $\chi - \psi$-plane. For $\varphi_c \neq -\beta/\alpha A$ the trajectories have a component in the $\varphi$-direction. A similar consideration has been undertaken in I, where we have discussed the "energy-function".

We now discuss the phase portrait in more detail [vid. Eqs. (2.11) to (2.13)]

$$\partial_s \psi = \chi \, , \quad (5.1)$$

$$\partial_s \chi = \Theta \chi - f(\psi) \quad (5.2)$$

with

$$f(\psi) = (c^2 e^{-\Gamma^2 \psi^2} - d^2)\psi + \alpha A \varphi_c \psi + \gamma \varphi_c + F \, . \quad (5.3)$$

The slope of the trajectories

$$\partial_\psi \chi = \chi^{-1}(\Theta \chi - f(\psi)) \quad (5.4)$$

and of the separatrices [11]

$$m_{1,2} = \tfrac{1}{2}(\Theta \pm (\Theta^2 - 4\, \partial_\psi f(\psi)|_{\psi=\psi_0})^{1/2}) \quad (5.5)$$

yields the essential features of the phase plane portraits. The critical points are given as the points of the intersection of $\chi = 0$ and $f(\psi) = 0$.

*1.* $\varphi_c = -F/\gamma$

The nonlinear function $f(\psi)$,

$$f(\psi) = (c^2 e^{-\Gamma^2 \psi^2} - d^2 - \gamma^{-1} \alpha A F)\psi \quad (5.6)$$

simulates the existence of three steady states. But only for $\psi_0 = 0$ we have $\partial_s \varphi = 0$. Then the two quasi-steady states are (vid. Fig. 4)

$$\psi_0{}^2 = \frac{1}{\Gamma^2} \ln \frac{c^2}{d^2 + \alpha A F/\gamma} \quad (5.7)$$

which, since $\psi_0$ is real, yields $c^2 > d^2 + \alpha A F/\gamma$. Then a bounded solution exists.

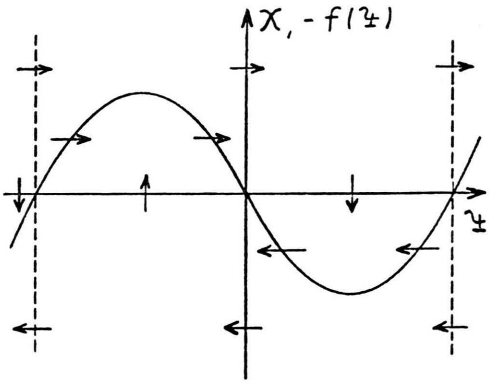



Fig. 4. Phase plain for SS 2. The arrows indicate the slope and the direction of the trajectories; $\partial_\chi \psi = \infty$ for $\chi = 0$. $f(\psi) = 0$ yields the SS 2 and the two quasi steady states.

*2.* $\varphi_c = -\beta/\alpha A$

The nonlinear function $f(\psi)$, which is given by

$$f(\psi) = (c^2 e^{-\Gamma^2 \psi^2} - d^2 - \beta)\psi - \beta\gamma/\alpha A + F \quad (5.8)$$

is neither an even nor an odd function of $\psi$ (vid. Figure 5). The phase portrait for $\Theta = 0$ is drawn in Figure 6.

A closed orbit corresponds to a standing pulse (vid. Fig. 6c), a loop to a standing periodic wave

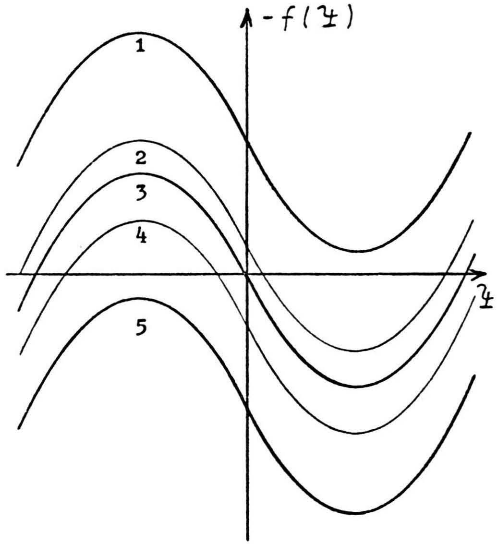



Fig. 5. Function $f(\psi)$ (vid. Eq. (5.8)) in dependence of the external stimulation $F$ for $c^2 - d^2 - \beta > 0$.
1. $0 \leqq F < F_1$,
2. $F_1 < F < F_2$,
3. $F = F_2 = \beta\gamma/\alpha A$,
4. $F_2 < F < F_3$,
5. $F_3 < F$,
$f(\psi) = 0$ are the SS 1.

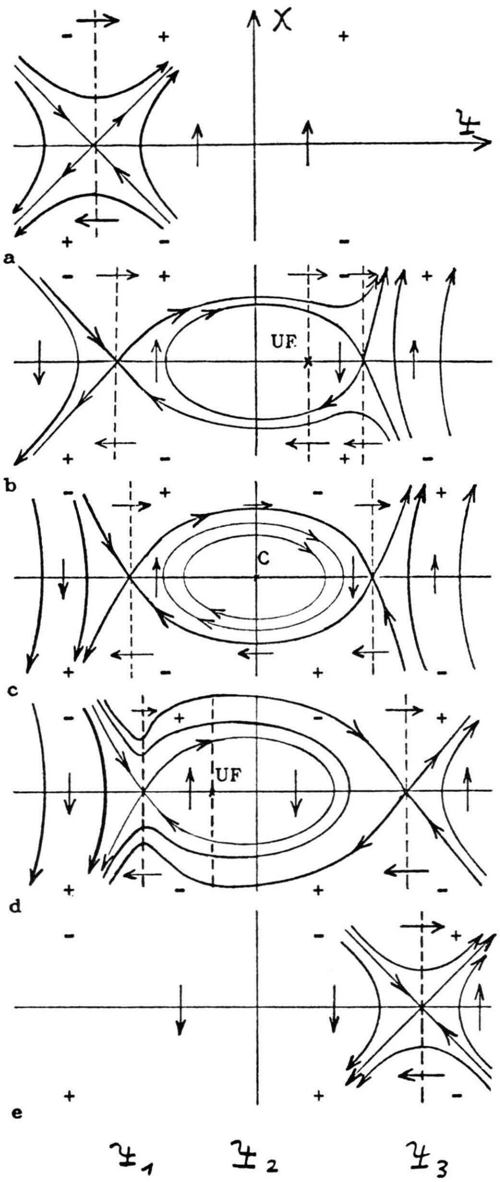



Fig. 6. Phase plain diagrams of SS 1 if $c^2 - d^2 - \beta > 0$ and $\theta = 0^+$. The singular points $\psi_1$ and $\psi_3$ are saddle points, $\psi_2$ is an unstable focus (UF) in case b and d and a centre (C) in case c. The $+$ and $-$ signs refer to a positive and a negative slope of the trajectories. Figures a to e correspond to the graphs 1 to 5 of Fig. 5, respectively.

(vid. Figure 6b, d). The stability of the loop reflects the stability of the standing periodic wave in this loop [12]. For both cases (i.e. Fig. 6b, d) we have orbital stability for the standing periodic wave. This behaviour results from the fact that for $\Theta = 0$ Eqs. (5.1) and (5.2) form a Hamiltonian system with

$$H(\chi, \psi) = \tfrac{1}{2}\chi^2 - \frac{1}{2\Gamma^2} c^2 e^{-\Gamma^2 \psi^2} - \tfrac{1}{2}\psi^2 (d^2 + \beta) - \psi\left(\frac{\beta\gamma}{\alpha A} - F\right). \tag{5.9}$$

It should be stressed that, in the $\psi - \chi$-plane, the internal steady state of the triplet is an unstable node or an unstable focus, i.e. the eigenvalues are positive. If, in addition, the time dependence of $\varphi$ is taken into account, the additional eigenvalue is negative for $\psi_0 > 0$ and positive for $\psi_0 < 0$. Thus, in three dimensions we have for $\psi_0 > 0$ a saddle point behaviour, whereas for $\psi_0 < 0$ the steady state is an unstable focus (vid. Figure 2). A saddle point type of behaviour is not possible in the two dimensional case (vid. Figure 6). Such a different behaviour in the two and three dimensional case is a typical one. A critical point that seems absolutely unstable in three dimensions can exhibit a rather different behaviour if it is not only analyzed as an isolated singular point. Examples for this behaviour are homoclinic and heteroclinic orbits. In the latter case at least one additional critical point must exist.

For $\Theta \neq 0$, i.e. the travelling wave case, the position of the steady states is not changed against the situation $\Theta = 0$. However, the slope of the trajectories and of the separatrices is altered, and thus the stability behaviour depends on $\Theta$. The direction of these changes is determined by Eqs. (5.4) and (5.5), e.g. a positive slope of the separatrices increases and vice versa.

The transition from the single to the triple steady state 1 with increasing $F$ is influenced by the periodic oscillation around the steady state 2. Details are only obvious if the phase plane portrait in three dimensions is considered. The threefold steady state which is defined by

$$\{\chi_0 = 0, \psi_{0,1} < \psi_{0,2} < \psi_{0,3}, \varphi_0 = -\beta/\alpha A\},$$

exhibits only a periodic oscillation around $\psi_{0,2}$ with $\psi_{0,1}$ and $\psi_{0,3}$ in the exterior of the cycle. This has been shown by simple phase plane arguments. For $\Theta \neq 0$ Eqs. (5.1) and (5.2) constitute no longer a Hamiltonian system. The Hamilton function $H(\psi, \chi)$ of Eq. (5.9) must be supplemented by an additional term $R$, which is inprinciple unknown. The dynamic behaviour for $\Theta$ being small is shown in Figure 7. The trajectories, which start at the same critical points for $\Theta = 0$ and $\Theta \neq 0$, differ in

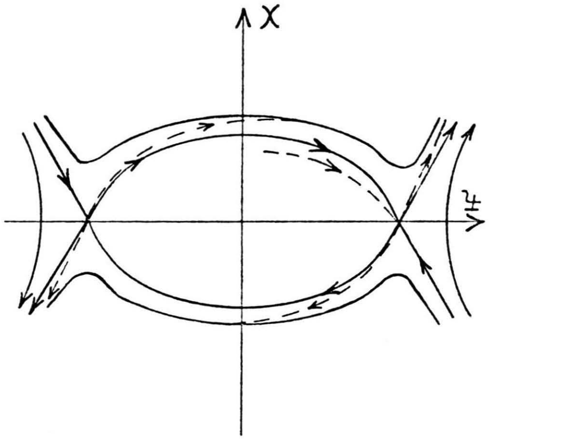



Fig. 7. Phase plain diagram of SS 1 for $\beta\gamma/\alpha A = F$ (vid. Figures 6c). The dashed lines show the changes in the slope of the trajectories for $\Theta \neq 0$.

their paths. Closed paths of the Hamiltonian system are opened, it is said that $H$ "increases on orbits". This increase corresponds to a negative friction, a behaviour which becomes obvious if the two first order Eqs. (5.1) and (5.2) are written as a second order differential equation. It reads

$$\partial_{ss}\psi - \Theta\,\partial_s\psi + f(\psi) = 0\,. \qquad (5.10)$$

The influence of $\Theta$ on the complete phase portrait is shown in Fig. 8 for $\gamma\beta/\alpha A > F$.

## 6. Discussion of the Phase Portraits

The idea of the collapse of the limit cycle oscillation and a subsequent onset of propagating pulses has been the starting point of the present work. Therefore we restrict ourselves to a discussion of the phase portraits for $\beta\gamma/\alpha A > F$. The other case, $\beta\gamma/\alpha A < F$, does not show any stable oscillating or nonoscillating solutions.

A travelling wave $(\psi(s), \varphi(s), \chi(s))$ is a nonconstant solution of Eqs. (2.9) and (2.10). The critical points (i.e. steady states) of Eqs. (2.11) to (2.13) are the identical constant solutions. A periodic solution of the latter equations corresponds to a periodic travelling wave of Eqs. (2.9) and (2.10). Travelling waves can be roughly classified into three groups: periodic waves — solitary waves and transition waves.

The most interesting problem for our purpose is the response of the system to an external stimulation which exceeds its critical value $F_c$. This response may create a pulse travelling along the membrane. The answer to this problem generally relies on a solution of the partial differential equations (Eqs. (2.9) and (2.10)). It should include the type, shape,

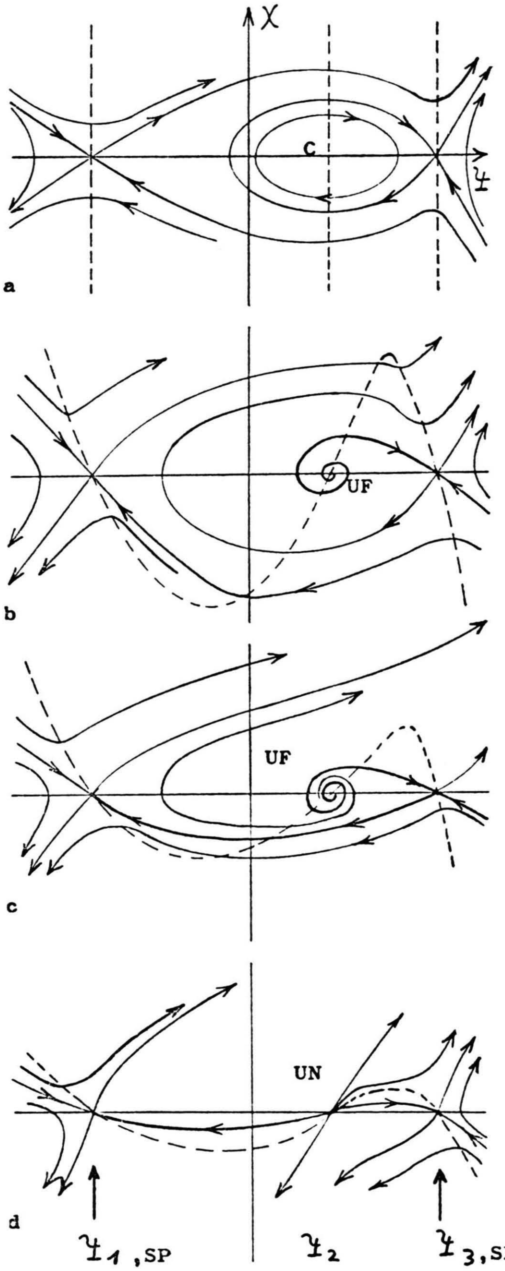



Fig. 8. Phase plain diagram of SS 1 for $F_1 < F < F_2$ for different values of wave velocity $\Theta$ if $c^2 - d^2 - \beta > 0$.

a) $\Theta = 0$ (vid. Fig. 6b);

b) to d) correspond to increasing values of $\Theta$. The dashed lines (-----) represent $d_s\chi = 0$; for $\chi = 0$ we will have $d_s\psi = 0$ (same notation as in Figs. 2 and 6).

velocity and stability of the travelling wave. A complete mathematical formulation leads to a boundary value problem with data given at $x = x_0$ and specified for all times together with an appropriate initial stimulus at $t = 0$. This combined boundary and initial value problem can only be solved in a numerical way. There the temporal and the spatial stability are determined by the initial and the boundary value problem, respectively.

Up to now we have not succeeded in solving the complete problem. Hence we will restrict ourselves to results which one can deduce from a phase plane analysis. The trajectories describe the shape of the travelling front from one singular point to another one.

*a) Unique steady state 1*

We start with a discussion of the results which we have found for $c^2 - d^2 - \beta < 0$, i.e. if the SS 1 is a single one. We may represent this case by the scheme (vid. Table 1).

It is rather instructive to have a closer look at the region $F \approx F_c$. The limit cycle collapse at $F \to F_c$ coincides with the breakdown of the limit cycle in the space independent problem: Consequently we have the bifurcation schemes:

*space independent problem*

stable oscillating solution $\xrightarrow[F \approx F_c]{}$ stable nonoscillating solution,

*space dependent problem*

stable oscillating solution $\xrightarrow[F \approx F_c]{}$ propagating pulse in space and time.

The energy which is stored in the limit cycle oscillation by chemical reactions and external stimulation, is transferred into the propagating signal. The critical value for the external stimulation is

$$F_c = \gamma (c^2 - d^2)/\alpha A \,. \tag{6.1}$$

We note that this is determined by the parameters of the kinetic equations (Eqs. (2.1) and (2.2)). $\gamma/\alpha A = N_0$ stems from the substrate-enzyme reaction. $N_0$ is that part of the excited enzyme concentration whose dipole moment is screened by the surrounding water molecules and ions and which therefore does not contribute to the ferroelectric

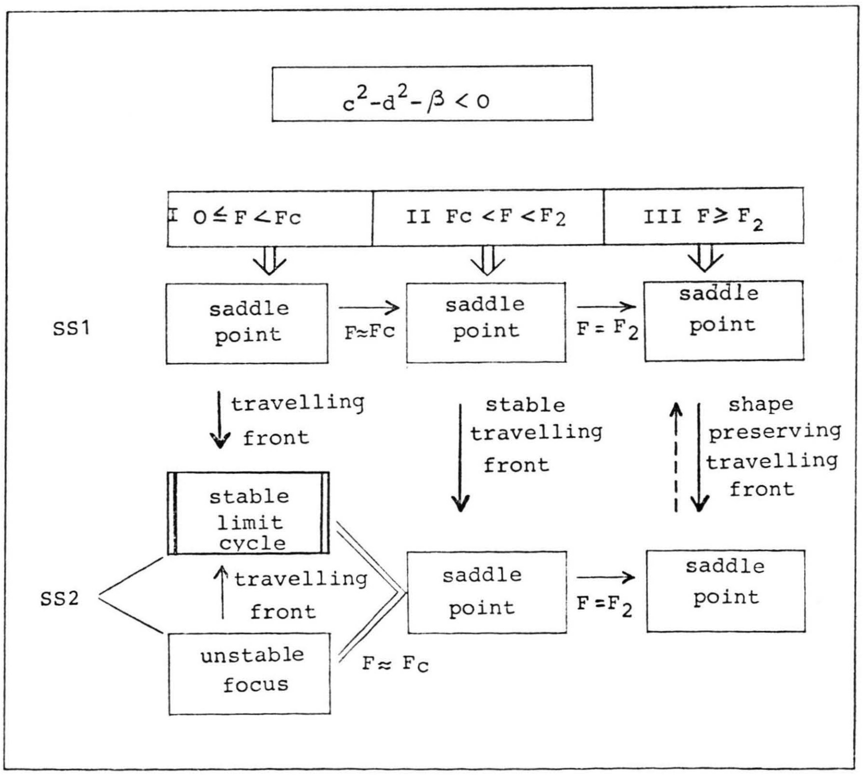



Table. 1. Bifurcationscheme for the single SS 1 (i.e. $c^2 - d^2 - \beta < 0$) and the SS 2, if $\Theta^2/\gamma > \beta/(c^2 - d^2)$. Trajectories which start from the unstable saddle point and the unstable focus, approach the stable limit cycle with velocity $\Theta$. The shape of these travelling fronts depends on the parameters of the system. For increasing external stimulation $F$ ($F > F_c$) there are bifurcations to other steady states, thus creating other types of travelling waves. The most important regions are those with $F < F_c$ and $F_c < F < F_2$ with the limit cycle collapse at $F \to F_c$ (vid. Figure 2). $F_c = \gamma (c^2 - d^2)/\alpha A$; $F_2 = \beta \gamma / \alpha A$.

behaviour (vid. I). Its value increases if there is a large input of substrate molecules e.g. through autocatalytic production or if there is a small concentration of weak polar enzyme molecules (A). $\alpha$ represents the strength of the nonlinear enzyme-substrate reaction. For increasing strength we have a decreasing concentration of screened excited enzyme molecules, $N_0$. Small values of $N_0$ in turn reduce the threshold value $F_c$ for the external stimulation to achieve the limit cycle collapse. The second essential parameter which determines $F_c$ is $c^2 - d^2$. This term represents the competition between the ferroelectric tendencies of the unscreened part of the highly polar enzyme molecules and the dielectric losses. A large sensitivity of the biological system to external stimulation requires a small critical value $F_c$ which can be achieved by small values either of $N_0$ or of $c^2 - d^2$. The last condition requires a soft ferroelectric material which seems to be present in biological systems. Furthermore, since $c^2 - d^2 < \beta$ is required, we should have a large decay rate $\beta$ for the excited enzyme molecules. This means that the chemical damping should dominate over the dielectric terms (e.g. over the ferroelectric tendencies). Since the collapse of the limit cycle is determined by all parameters of the kinetic equations there is a wide variability for experimental investigations, whence it should not be too difficult to decide whether the model may serve as a starting point to describe the function of the Greater Membrane.

Above $F_c$, a detailed discussion with respect to the existence of a homoclinic or heteroclinic orbit is necessary. Only then the form of the pulse which propagates along the membrane can be given. However, we may state that there is a bifurcation to a saddle point which contains two stable and one unstable family of solutions. This behaviour is valid in the region $F_c < F < F_2$ and one can show that the travelling wave has a shape preserving tendency when it propagates.

The critical value $F_c$ of the external stimulation has a certain value for fixed internal parameters. However, changes of these parameters by internal or external means may lead to a sequence of several critical values $F_c$. Large values of $F_c$ may thus perhaps play the role of the threshold which is known from nerve excitation. This behaviour seems to manifest the close connection which exists between brain waves (i.e. electroencephalographic oscillation) nad nerve action [21]. Furthermore, the existence of different types of travelling and standing waves indicates that there are changes in both, the amplitude and frequency of the brain wave oscillations, if $F_c$ is changed. The emergence of spatial and spatio-temporal behaviour by means of the bifurcation of the homogeneous state at $F_c$ can thus be caused by critical changes of the internal parameters. It seems possible that $F_c$ is lowered to a value which is comparable with always existing internal fields. Without an external stimulation dramatic changes of behaviour may then occur. The resulting internally caused instabilities may give rise to a collapse of the limit cycle oscillation. Quite new phenomena may result, e.g. an elliptic seizure. The latter is a coherent oscillation with a large amplitude which may be seen by electroencephalographic activity [22]. A more detailed investigation of this problem which should include the correlation between individual units of nerve cells in the brain and the EEG activity, is beyond the scope of this work.

*b) Threefold steady state 1*

The situation with $c^2 - d^2 - \beta > 0$, where the SS 1 is a threefold one, is more complicated. We can draw the scheme (vid. Table 2):

For $\Theta = 0$ we have a complete separation of the phase space for the SS 1 from that of the SS 2. Besides one looses the time dependence of the variables $\psi$, $\chi$ and $\varphi$. We do not want to discuss this situation in more detail. Different types of travelling waves between the split SS 1 solutions are shown in Figure 9. A possible type of transitions from SS 1 to SS 2 is drawn in Figure 10. A more detailed phase analysis which includes $\chi - \varphi$ and $\varphi - s$ diagrams and the different types of transitions from SS 1 to SS 2 is postponed to a later study.

For $F > F_3$ no stable space dependent solution exists. The behaviour of the system is the same as that for $c^2 - d^2 < \beta$. A pulse propagates from the region where the stable limit cycle has collapsed. After a recreation period, the limit cycle can be built up again. Details of these processes require a complete calculation of the whole dynamic behaviour of the system. This should include the size of the reacting (i.e. oscillating) and of the pulse propagating regions of the Greater Membrane and is beyond the scope of the present paper. Finally it should be stressed that the limit cycle which

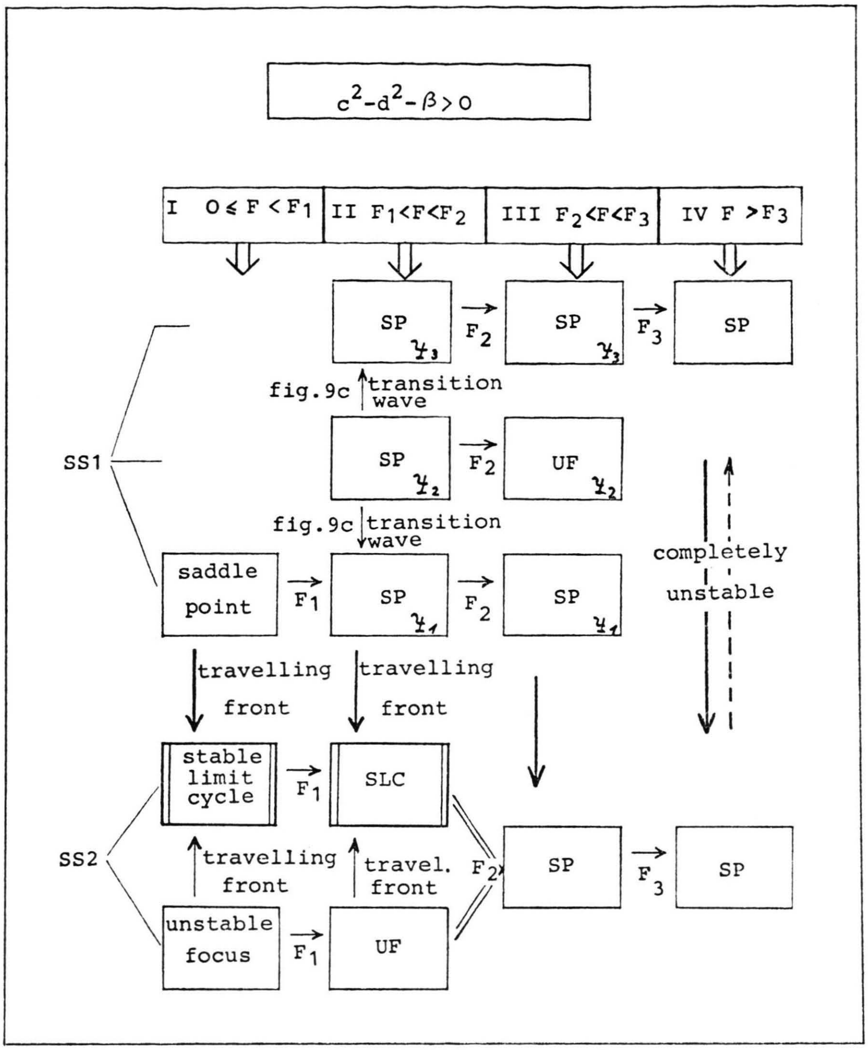



Table 2. Bifurcation scheme for the threefold SS 1 (i.e. $c^2 - d^2 - \beta > 0$) and the SS 2, if $\Theta^2/\gamma > \beta/c^2 - d^2$). There are four different regions of behaviour (vid. Figure 2): $F < F_1, F_1 < F < F_2$, $F_2 < F < F_3$ and $F_3 < F$. The behaviour of region I corresponds to that of region I in Table 1. In region II there are trajectories which connect singular solutions of SS 1 (vid. Fig. 9c) or the limit cycle of SS 2. Regions III and IV lead to different travelling waves, the details of which are unknown.

represents a stable oscillation in space and time, may be viewed as a standing periodic wave. The existence of the limit cycle is related with the condition

$$\Theta^2/\gamma > \beta/(c^2 - d^2) \tag{6.2}$$

which follows from Equation (3.3). This restriction seems plausible since a travelling wave can only exist if its velocity is large enough to overcompensate the diffusion. Furthermore, the diffusion constant $D$ is incorporated in $\Theta$, since the real travelling wave speed is $\bar{\Theta} = \sqrt{D}\,\Theta$.

## 7. Approximations

We will briefly comment on the relations which exist between nervous pulse propagation equations and our equations, if the latter are simplified. The nonlinear term $\alpha A \sigma \nu$ of Eq. (2.1) is neglected, whereas the nonlinearity of Eq. (2.2) is replaced by $-\varepsilon\sigma$. This approximation is an appropriate one for small values of $\nu$ and $\sigma$ and for $\alpha A \ll \gamma, \beta$, $c^2 - d^2$. The same approximations have been performed in I, where they turned out to exhibit a rather good description of the steady state behaviour. Furthermore, we expand the exponential of Equation (2.1). Then we end up with a Bonhoefer-Van der Pol/Fitz-Hugh system, which has been discussed in I (vid. Eqs. (I 5.6) and (I 5.7)). In the space dependent case these equations read

$$\partial_s \psi = \chi\,, \tag{7.1}$$

$$\partial_s \chi = \Theta\,\chi - \gamma\,\varphi - (c^2 - d^2)\,\psi + c^2\,\Gamma^2\,\psi^2 - F\,, \tag{7.2}$$

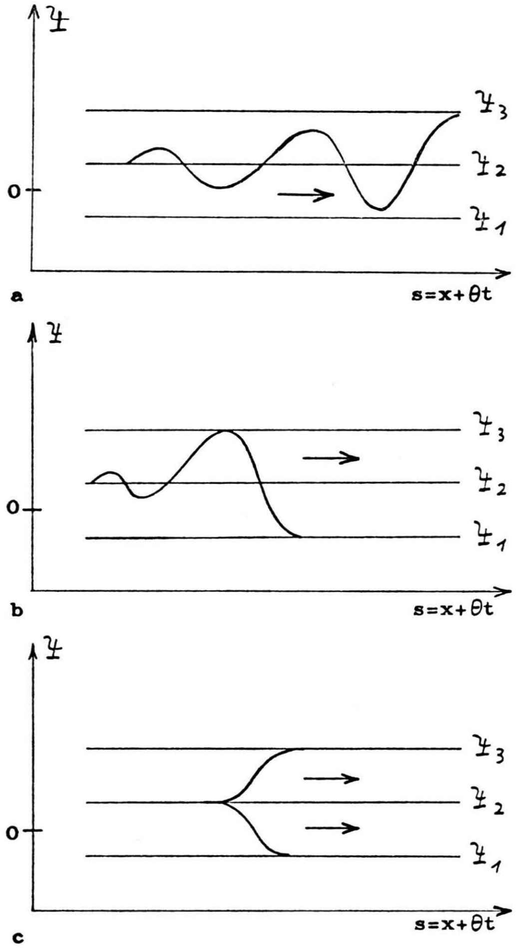
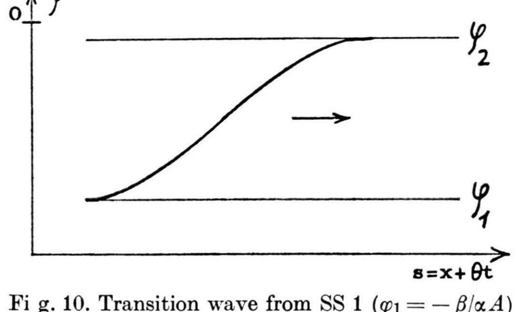



Fig. 9. Travelling waves within SS 1 for different values of $\Theta$ ($\Theta_1 < \Theta_2 < \Theta_3$).
a) For $\Theta_1$ an oscillating nonconstant solution unwinds from the unstable focus $\psi_2$ and tends to $\psi_3$ (vid. Figures 8b);
b) for $\Theta_2$ there is a transition from $\psi_3$ to $\psi_1$ (transition wave) and an oscillating transition from $\psi_2$ to $\psi_3$ (vid. Figure 8c);
c) for $\Theta_3$ we have an upward transition from $\psi_2$ to $\psi_3$ and a downward one from $\psi_2$ to $\psi_1$ (vid. Figure 8d).




Fi g. 10. Transition wave from SS 1 ($\varphi_1 = -\beta/\alpha A$) to SS 2 ($\varphi^2 = -F/\gamma$) for $0 < F < F_2$.

$$\Theta\,\partial_s\varphi = -\beta\,\psi - \varepsilon\,\varphi\,. \tag{7.3}$$

The steady state for these equations is given by

$$\text{SS 3}: \quad \chi_0 = 0\,, \quad \varphi_0 = -(\beta/\varepsilon)\,\psi_0\,.$$

where $\psi_0$ is the solution of

$$\psi_0(c^2 - d^2 - \beta\gamma/\varepsilon) - \Gamma^2 c^2 \psi_0^3 + F = 0\,. \tag{7.4}$$

It is a single ($c^2 - d^2 - \beta\gamma/\varepsilon < 0$) or a threefold one ($c^2 - d^2 - \beta\gamma/\varepsilon > 0$).

The stability of the steady state is calculated from

$$\lambda^3 - \lambda^2(\Theta - \varepsilon/\Theta) - \lambda(\varepsilon - \beta\gamma/\varepsilon + (\partial_F\psi)^{-1}) - \varepsilon/\Theta(\partial_F\psi)^{-1} = 0\,, \tag{7.5}$$

where $\partial_F\psi$ can be derived from Equation (7.4). The results are drawn in Figure 11.

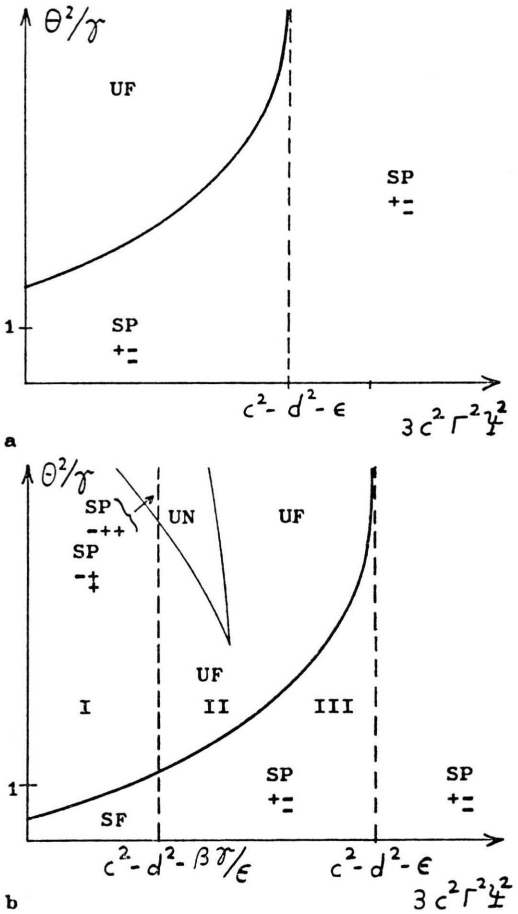



Fig. 11. Stability of SS 3 (Eqs. (7 1) to (7.3)) in dependence of the steady state solution $\psi_0$ and of the travelling wave velocity $\Theta$ The solid line represents the condition (3.3), if the latter is applied to the approximated equations.
a) $c^2 - d^2 - \beta\gamma/\varepsilon < 0$; b) $c^2 - d^2 - \beta\gamma/\varepsilon > 0$, there is one steady state $\psi_{0.i}$ ($i = 1, 2, 3$) in each of the three regions (I, II, III).

Equations (7.1) to (7.3) have the same structure as the wellknown Fitz-Hugh-Nagumo equations [14]. These equations have been established to give a simpler description of the Hodgkin-Huxley equations [15]. The latter describe a model for the "propagated action potential", in which a signal is created by means of an external stimulation and moves along the axon without loss of its waveform.

The behaviour of the Fitz-Hugh-Nagumo equations has been investigated by many authors. Since these equations are so closely related to our own ones, it is worth citing those results which also apply to our system.

Hasting [16] proofs the existence of homoclinic orbits for $\Theta = \Theta_1, \Theta_2$ and the possibility of periodic travelling waves for $\Theta_1 < \Theta < \Theta_2$. Single pulses and periodic travelling waves can exist, if a more generalized system is considered (Rinzel [17]). Spatial and temporal stability has been discussed [17, 20] as well as the necessary conditions for the threshold and the onset of pulses. A rather detailed calculation which includes the direction of bifurcation and the existence of periodic solutions has been given for the space independent problem in [19, 23].

The results of these articles are applicable to the Equations (7.1) to (7.3). But, without a detailed calculation of the whole time and space dependent problem, including the boundaries of the membrane system, it is not possible to decide which one of the solutions is relevant. However, since our results exhibit pulse propagation, single and repeated pulses (wave trains) and threshold behaviour, which is wanted for biological ystems, our equations may be expected to have significance for biological purposes.

## Conclusion

The brain wave model has been suggested by Fröhlich in order to give an explanation of the extraordinary high sensitivity of certain biological systems to weak electromagnetic waves. This experimental result seems to be in an appreciable agreement with our results.

The resting state of the nonlinear system has turned out to be an oscillating one (i.e. a limit cycle). External electrical or chemical constraints can cause this limit cycle to collapse. The results reported here show that after the breakdown propagating pulses are created. Depending on the internal parameters of the system on one hand, and on the external stimulation on the other hand, several types of travelling waves are possible. Their speed, waveform and stability are governed both, by the size of the membrane system itself and the internal parameters.

The extreme low frequency oscillations (10 Hz region) thus make the Greater Membrane respond to very weak signals. Furthermore, this oscillating resting state rather than a static (nonoscillating) one, forms the nonequilibrium energy source for the onset of propagating pulses. The entire brain wave model is based on a state far from thermal equilibrium. The latter is stabilized by the long range coherent behaviour of the substrate-enzyme system. From this point of view it is rather obvious that there are relations between neuronal activities (i.e. nerve pulses) and brain waves (i.e. low frequency oscillations) [21]. The close connection which exists at least for the approximated brain wave equations and the Fitz-Hugh Bonhoeffer and Fitz-Hugh Nagumo equations, seems to support this concept.

A number of equations remain unsolved. From a mathematical point of view it would be interesting to know which kind of initial and boundary conditions produce travelling waves. A relevant question from a physical point of view is to ask whether a microscopic basis for the phenomenological concept can be given. Fröhlich's very simple theoretical models may serve as a starting point to consider actual biological systems.

Experimental evidence is now increasing which seems to support the theoretical prediction for a longitudinal polarization oscillation in the $10^{11}$ Hz region as well as for the oscillations found in the EEG. More refined experimental methods could lead to a specification of the parameters of the model and to an indication of the parameter regions which are of relevance.

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