Nerve Impulse Equations.

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under the supervision of
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Contents.

I - Aknowledgments.

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II - Introduction.

The nervous system of animals contains certain specialized cells, called nerve cells or neurones, that are responsible for the transmission of information within the body. Those cells consist of an enlarged part containing the nucleus, and cytoplasmatic processes extending from it.(fig 1). The processes are classified by hystological criteria as axons or dendrites. Neurones of vertebrates usually have only one axon, and it rarely branches except at its termination.

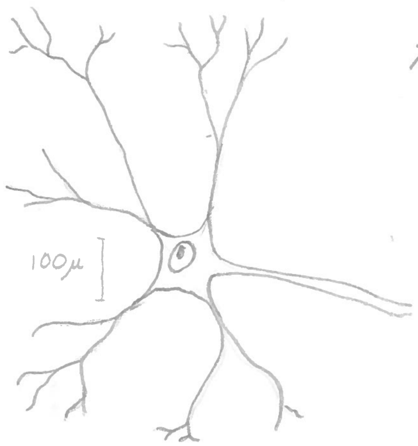

Fig 1- A "typical" neurone. The axon is the process extending to the right.

The whole neurone is surrounded by a thin membrane which is selectively permeable to ions present in the physiological environment. The cell uses energy to keep the concentration of some of these ions, like Na^+, K^+ and Cl^-, away from thermodynamic equilibrium, giving rise to a difference of electric potential across the membrane of around $-70\,mV$, the inside of the cell being electronegative with respect to the outside. This steady state situation is called the rest state of the nerve cell.

Other neurones and sensory receptors can induce fluctuations on the membrane potential. A weak stimulus produces only a locally observable disturbance, but if the perturbation reaches a certain threshold value it triggers a transient reversal of potential difference with a peak value of about 100 mV that travels as a wave along the axon (fig 2). These waves, or action potentials, have roughly constant size, form and propagation speed in each neurone, and because of these properties physiologists describe it as an "all-or-none" event.

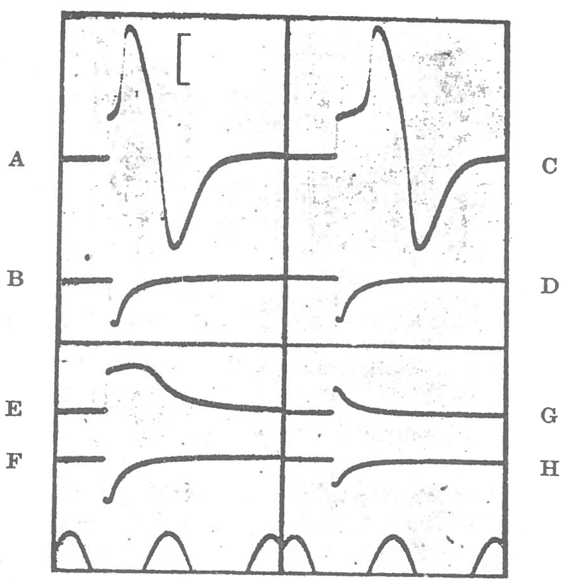

Fig 2 - Electrical changes produced by shocks in axons from shore crab, Carcinus maenas recorded at stimulating electrode. Relative strenght of shocks: A 1.05; B -1.05; C 1.00; D -1.00; E 1.00; F -1.00; G 0.61; H -0.61. Scale 15 mV. Reproduced from [7].

The threshold depolarization for triggering an action potential is not constant, its value can be lowered by subthreshold stimulation and raised by the passage of an action potential

(this accounts for the difference between fig 2 C and E).
Both effects last only a few msec. Repetitive, strong or maintained stimulation may give rise to long trains of waves (fig 3).

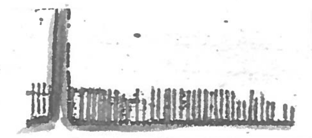

Fig 3. Repetitive firing on an axon of the optic nerve of frog Rana pipiens. The blue line marks stimulation period. From [15]

The generally accepted physico-chemical explanation for these phenomena, due to Hodgkin, Huxley and Katz ([8],[9],[10],[11],[12],[13]) can be summarized as follows:

1) At the rest state the cell concentrates K^+ in its interior and pumps out Na^+.
2) Depolarization of the membrane over threshold induces a quick increase of its permeability to Na^+, leading to further depolarization. After reaching a definite value the conductance of sodium decreases slowly.
3) Depolarization also starts a slow increase in permeability to K^+ that moves out of the neurone bringing the membrane potential back to rest (see fig 4).
4) The depolarization from 2 flows as a capacitance current to nearby parts of the membrane, starting

the same process at another point. this causes the depolarization wave to travel along the axon.
5) these events take place uniformly around the circumference of the axon.

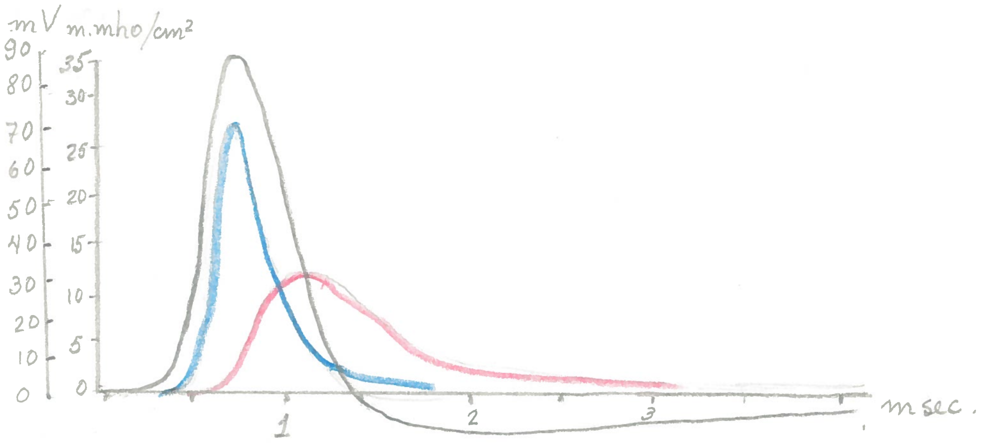

Fig 4- Membrane conductance to Na^+ and K^+ during propagated action potential. Results of theorectical prediction, redrawn from [11]

We will call this series of events the nerve impulse. It is a model well supported by experimental evidence and a quantitative version of it was formulated by Hodgkin an Huxley ([11]) using a non linear diffusion equation to descibe the behaviour of the electric potential, coupled with three more equations for the ionic conductances. the equations are:

$$\frac{a}{2R_2}\frac{\partial^2 V}{\partial x^2} = C_M\frac{\partial V}{\partial t} + \bar{g}_K n^4 (V-V_K) + \bar{g}_{Na} m^3 h (V-V_{Na}) + \bar{g}_L (V-V_L)$$

$$\frac{\partial n}{\partial t} = \alpha_n(V)\,(1-n) - \beta_n(V)\,n$$

$$\frac{\partial m}{\partial t} = \alpha_m(V)\,(1-m) - \beta_m(V)\,m$$

$$\frac{\partial h}{\partial t} = \alpha_h(V)(1-h) - \beta_h(V)h$$

where a is the radius of the axon, R_2 is the specific resistance of the axoplasm, C_M is the membrane capacity per unit area, all taken to be constant; V is the displacement of the membrane from its resting value (depolarization negative), x is distance along the fibre, t is time; V_{Na}, V_K and V_l are the equilibrium potentials for sodium, potassium and other ions(l); and $\bar{g}_{Na}$ $\bar{g}_K$ and $\bar{g}_L$ are constants with the dimensions of conductance/cm². The functions α and β, obtained from indirect experimental measure are:

$$\alpha_n = 0.01\,(V+10)\left(\exp\frac{V+10}{10} - 1\right)^{-1}$$

$$\beta_n = 0.125\,\exp(V/80)$$

$$\alpha_m = 0.1\,(V+25)\left(\exp\frac{V+25}{10} - 1\right)^{-1}$$

$$\beta_m = 4\,\exp(V/18)$$

$$\alpha_h = 0.07\,\exp(V/20)$$

$$\beta_h = \left(\exp\frac{V+30}{10} + 1\right)^{-1}.$$

Numerical solutions of these equations fit remarkably well the experimental results. The main objection they find among biologists is due to the fact that there is no physiological interpretation for the variables h, m, n, and the three equations they satisfy. Although some general form of explanation is suggested in [11] there is no experimental evidence to substantiate it, and the main justification for the use of these variables is the good numerical fit they provide. For a more detailed discussion of this point see, for instance, [6], chapter 2, and bibliography quoted there.

For the mathematician the problem is to check if solutions of these equations mimic the behaviour of the nerve in a reasonable way. The existence of a solution was initially proved by Evans and Shenk [4]. The next two chapters are an account of the proof given by Carpenter ([1], [2]) that the Hodgkin and Huxley equations have solutions with one of the characteristics of nerve impulse, of being a transient travelling wave. This means that we will be looking for solutions that stay close to the rest state for large values of $|t|$.

III Singular Solutions.

In order to look for travelling wave solutions of the Hodgkin and Huxley equations (HH) we start working with the system:

$$\mathcal{S}\quad\begin{cases} \dfrac{\partial^2 V}{\partial x^2} = \dfrac{\partial V}{\partial t} + g(V,y,z) \\ \dfrac{\partial y}{\partial t} = \varepsilon\, h(V,y,z) \\ \dfrac{\partial z}{\partial t} = \delta^{-1} q(V,y,z) \end{cases}$$

where g, h, q are C^1 maps $g:\Omega \longrightarrow \mathbb{R}$, $h:\Omega \longrightarrow \mathbb{R}^k$; $q:\Omega \longrightarrow \mathbb{R}^\ell$; $\Omega_V \subset \mathbb{R}$, $\Omega_y \subset \mathbb{R}^k$, $\Omega_z \subset \mathbb{R}^\ell$ and $\Omega = \Omega_V \times \Omega_y \times \Omega_z$ are domains; $\varepsilon > 0$, $\delta > 0$ are small.

If the solution is a travelling wave, it depends only on $s = x + \theta t$, not on x or t directly. Substitution on $\mathcal{S}$ with $\cdot = \frac{\partial}{\partial s}$ yelds:

$$** \quad\begin{cases} \dot V = W \\ \dot W = \theta W + g(V,y,z) \\ \dot y = \theta^{-1}\varepsilon\, h(V,y,z) \\ \dot z = \theta^{-1}\delta^{-1} q(V,y,z). \end{cases}$$

A step further in simplification is to consider $**$ as an equation of the form

$\dot x = \varphi(x,y)$

$\dot y = \delta^{-1}\psi(x,y)$ where $\delta > 0$ is small, $(x,y) \in \mathbb{R}^n$.

For a point (x,y) far away from the surface $\psi(x,y) = 0$, $\dot y$ is far bigger than $\dot x$, and therefore the orbit will be approximately vertical, with its speed determined by the "fast equation" $\dot y = \delta^{-1}\psi(x,y)$ (see fig 1). The set of points where $\psi(x,y) = 0$

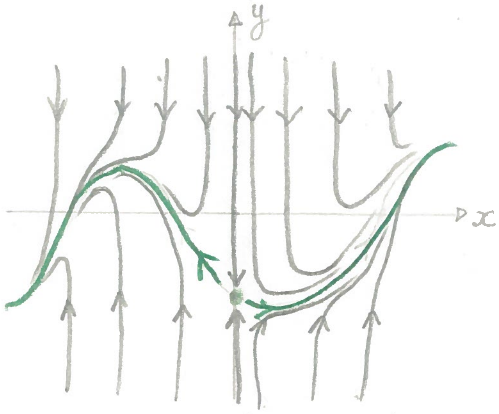

Fig 1 - example of system in $\mathbb{R}^2$. Orbits run quickly towards the slow manifold and then follow it slowly.

we call the slow manifold because near it, no matter how small δ is, the fast equation contributes very little and the behaviour of orbits is dominated by the other, slow, equation. therefore in a system similar to the example above, in which the slow manifold never has a vertical tangent, our chief concern is to study the slow equation. this eliminates the variable z in ** that accounts for fast sodium conductance, and we are left with an equation of the form:

$\dot{v} = f(v, w)$ fast

$\dot{w} = \varepsilon\, g(v, w)$ slow for small $\varepsilon > 0$.

An analogous discussion of these equations will lead to a different picture, like fig. 2. the slow manifold will have a vertical tangent at two points, giving rise to what appears to be a cycle. the arguments here are somewhat similar to those presented by Zeeman on [19], the difference being that

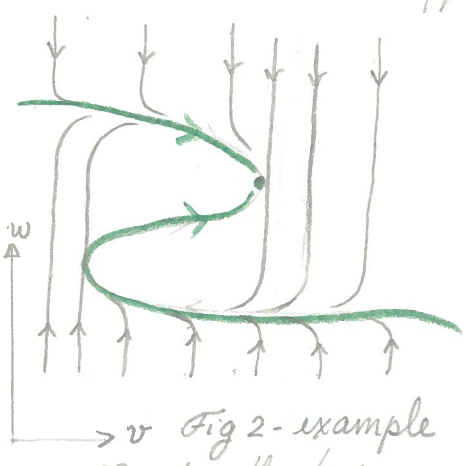

Fig 2 - example in $\mathbb{R}^2$, where the slow manifold has a vertical tangent at two points.

he is looking for equations with solutions of a given form, while we start from a given equation and check that it has the desired kind of solution.

In the remainder of this chapter we will work only on the slow manifold $q(V,y,z)=0$, where the behaviour of the slow equation $\dot{y}=\theta^{-1}\varepsilon h(V,y,z)$ is studied and some hypothesis are made concerning the (not so much) fast equations $\dot{V}=W$, $\dot{W}=\theta W+g(V,y,z)$. The solutions are then patched together to obtain a "singular solution" of the desired kind. In the next chapter we use isolating blocks to deduct the existence of a nearby true solution of the equation with the same properties.

1- General assumptions about $**$

Referring back to H-H, where $l=1$, $q(V,y,z)=\delta[\alpha_n(V)-(\alpha_n(V)+\beta_n(V))z]$, we note that $\frac{\partial q}{\partial z}(V,y,z)=-\delta[\alpha_n(V)+\beta_n(V)]<0$, so that the surface $q(V,y,z)=0$ is a strong attractor. We can assume then that $**$ satisfies:

$$h\begin{cases} ① \ \exists Z:\Omega_V\times\Omega_y\longrightarrow\Omega_z \text{ a } C^1 \text{map, s.t. } q(V,y,z)=0\Leftrightarrow z=Z(V,y). \\ ② \ \forall(V,y)\in\Omega_V\times\Omega_y, \text{ the eigenvalues of } \frac{\partial q}{\partial z} \text{ have} \\ \text{nonzero real part.}\end{cases}$$

From now on we turn our attention to the slow manifold $z=Z(V,y)$ where $**$ has the form:

$$
* \begin{cases} \dot V = W \\ \dot W = \theta W + G(V,y) \\ \dot y = \theta^{-1}\varepsilon H(V,y). \end{cases} \qquad \begin{aligned} G(V,y) &= g(V,y,z(V,y)) \\ H(V,y) &= h(V,y,z(V,y)). \end{aligned}
$$

the results obtained for * may be carried over to ** as a consequence of Lemma 3 (pag 20)

Clearly HH also satisfies (see fig 3)

g
- A) $\exists\ V_\alpha < 0 < V_\beta$ such that for every $y \in \Omega_y$ $G(V_\alpha, y) < 0$ and $G(V_\beta, y) > 0$.
- B) For some point $\bar y \in \Omega_y$ there are exactly three values of V in (V_α, V_β) for which $G(V,y) = 0$.
- C) For any given $y \in \Omega_y$ there are at most three points V in (V_α, V_β) such that $G(V,y) = 0$.
- D) $\forall\ (V,y) \in (V_\alpha, V_\beta) \times \Omega_y$, $G(V,y) = 0 = \frac{\partial G}{\partial V}(V,y) \Rightarrow$ $\Rightarrow \frac{\partial^2 G}{\partial V^2}(V,y) \neq 0$ (fig 3b).
- E) $\exists\ k \leq l$ such that $\frac{\partial G}{\partial y_k}(V,y) \neq 0\ \forall (V,y) \in (V_\alpha, V_\beta) \times \Omega_y$.

Conditions D and E ensure that the graph of G is transversal to the plane $G = 0$.

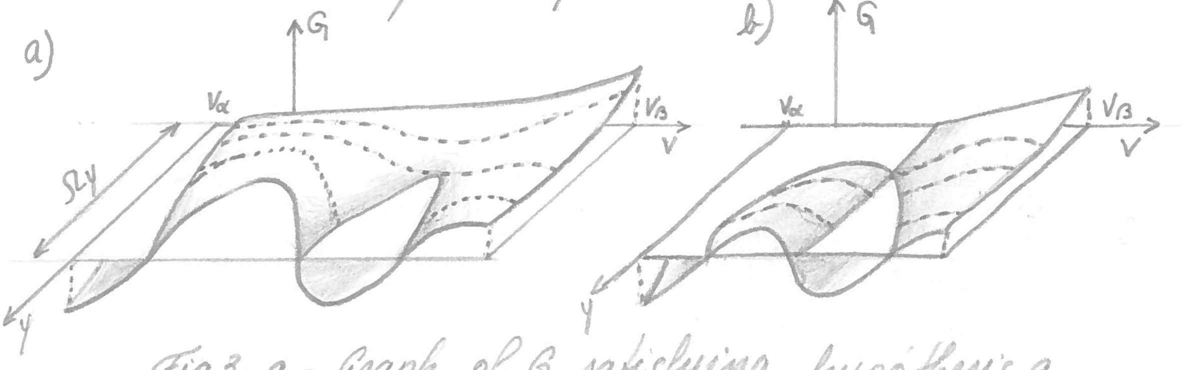

Fig 3- a- Graph of G satisfying hypothesis g.
b- the possibility of a graph like this is ruled out by condition D.

Now let $X = \{(V,W,y) : W = 0 = G(V,y) \text{ and } \frac{\partial G}{\partial V}(V,y) = 0\}$. X has two components; X_1 and X_2 (fig 4). Let Π_1 and Π_2 be their projection by the map $(V,W,y) \longrightarrow y$.

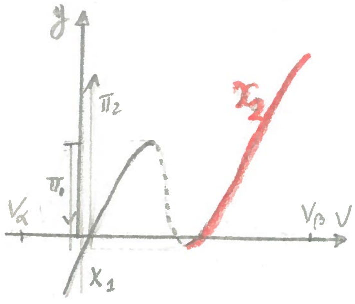

Fig 4 - the set of zeros of G

Condition g(E) and the implicit function theorem guarantee that for $i = 1, 2$ there are maps $V_i : \Pi_i \longrightarrow (V_\alpha, V_\beta)$ such that $(V, 0, y) \in X_i \Leftrightarrow y \in \Pi_i$ and $V = V_i(y)$.

If a solution of * is to mimic the nerve impulse, it should approach a stable rest point as t tends to $\pm\infty$. A solution with this property we call homoclinic. If A and B are rest points, a heteroclinic solution from A to B will be one that is both in the unstable manifold of A † (denoted $\mathcal{U}(A)$) and in the stable manifold of B. ($S(B)$)

2 - the fast equation

Since we are interested in solutions of * for small ε we begin with the case $\varepsilon = 0$. this leads to the equation $(\dot V, \dot W) = F(V, W, y, \theta) = (W, \theta W + G(V,y))$. therefore $DF(V,y) = \begin{pmatrix} 0 & 1 \\ \frac{\partial G}{\partial V}(V,y) & \theta \end{pmatrix}$ has at $(V_i(y), 0)$

† the stable manifold of a fixed point A is defined as $S(A) = \{x : \lim_{t \to \infty} x \cdot t = A\}$ where $x \cdot t = x(t)$ is the solution satisfying $x \cdot 0 = x$. the unstable manifold is defined as $\mathcal{U}(A) = \{x : \lim_{t \to -\infty} x(t) = A\}$. For a proof of their local existence see [14]

two real eigenvalues of opposite signs.

Let $\Lambda^+(y,\theta) = \{(V,W,y) \in \mathcal{U}(V_1(y),0,y,\theta)\ V \in (V_1(y),V_2(y))$ and $W>0\}$

$V^+(y,\theta) = \sup\{V : \exists W : (V,W,y) \in \Lambda^+(y,\theta)\}$ and

$W^+(\cdot,y,\theta) : (V_1(y), V(y,\theta)) \longrightarrow (0,\infty)$ be the C^1 map (fig 5)

such that $\Lambda^+(y,\theta) = \{(V, W^+(V,y,\theta),y) : V \in (V_1(y), V^+(y,\theta))\}$.

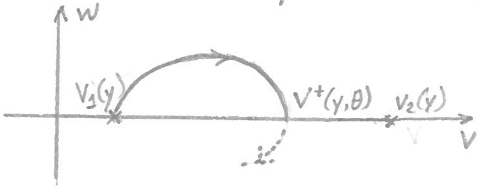

Fig 5- $\Lambda^+(y,\theta)$.

W^+ is well defined, since $\dot V = W$.

Analogously define $\Lambda^-(y,\theta)$ as the largest negative half solution of $(\dot V,\dot W) = F(V,W,y,\theta)$ contained in $\mathcal{U}(V_2(y),0,y,\theta)$ and in the half plane $W<0$; $V^-(y,\theta)$ as the smallest value of V in $\Lambda^-(y,\theta)$ and $W^- : (V^-(y,\theta), V_2(y)) \to (-\infty,0)$ $W^-(V,y,\theta)$ the unique $W<0$ such that $(V,W,y) \in \Lambda^-(y,\theta)$.

Clearly W^+ and W^- satisfy

$$\frac{dW}{dV} = \frac{\dot W}{\dot V} = \frac{\theta W + G(V,y)}{W} \Rightarrow \frac{1}{2}\left(W^+(V,y,\theta)\right)^2 = \int_{V_1(y)}^{V} \left[G(v,y) + \theta W^+(v)\right] dv$$

and $\frac{1}{2}\left(W^-(V,y,\theta)\right)^2 = \int_{V_2(y)}^{V} \left[G(v,y) + \theta W^-(v)\right] dv.$

The first direct consequence of this integral formula is that for fixed V, W^+ (W^-) is an increasing (decreasing) function of θ, and so is V^+ (V^-). Let $I(y) = \int_{V_1(y)}^{V_2(y)} G(V,y)\,dV$.

If $I(y)=0$ we can define

$$W^+(V,y,0) = +\sqrt{2\int_{V_1(y)}^{V} G(v,y)\,dv} \qquad W^-(V,y,0) = -\sqrt{2\int_{V_2(y)}^{V} G(v,y)\,dv}$$

so that $V^+(y,0) = V_2(y)$, $V^-(y,0) = V_1(y)$. Moreover,

$$\lim_{V\to V_1(y)} W^-(V,y,0) = 0 = \lim_{V\to V_2(y)} W^+(V,y,0).$$

If $I(y)<0$ the same constuction for W^- will do, but not for W^+, since if W^+ were defined for all $(V_1(y), V_2(y))$, $\frac{1}{2}(W^+(V_2(y), y, 0))^2 = I(y) < 0$, so that $V^+(y,0) < V_2(y)$. The case $I(y)>0$ is similar, and the three cases are ilustrated in fig 6.

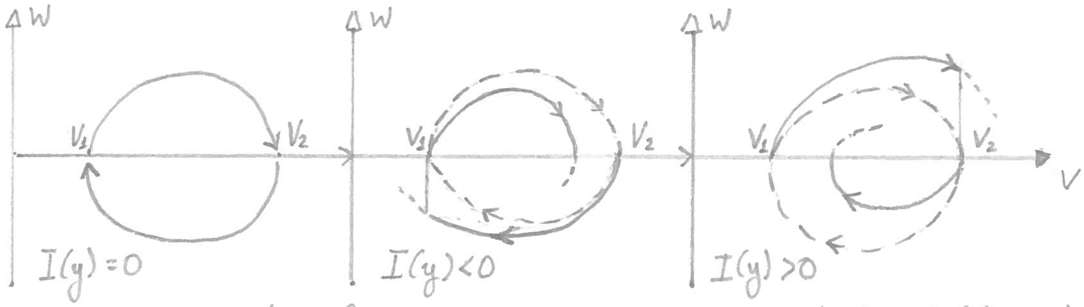

Fig 6. Graphs of $W^+(V,y,0)$ and $W^-(V,y,0)$ for different values of $I(y)$. In dotted lines, heteroclinic solutions of $*$, $\theta \neq 0$ joining $(V_1(y), 0, y)$ and $(V_2(y), 0, y)$.

For $\theta > 0$ $\mathcal{U}(V_i(y), 0, y)$ moves away from the $W=0$ axis. To get a heteroclinic solution joining the rest points let

$$\theta(y) = \begin{cases} \sup\{\theta \geq 0 : V^+(y,\theta) < V_2(y)\} & \text{if } I(y) \leq 0 \\ -\sup\{\theta \geq 0 : V^-(y,\theta) > V_1(y)\} & \text{if } I(y) \geq 0. \end{cases}$$

<u>Lemma</u>. A) $\theta : \Pi_1 \cap \Pi_2 \longrightarrow \mathbb{R}$ is a continuous map, C^1 in the regions where $I(y) \neq 0$. If $I(y) \leq 0$, $W^+(V, y, \theta(y))$ is a heteroclinic solution of $(\dot V, \dot W) = F(V, W, y, \theta)$ joining $(V_1(y), 0, y)$ to $(V_2(y), 0, y)$. If $I(y) \geq 0$, $W^-(V, y, -\theta(y))$ is a solution joining $(V_2(y), 0, y)$ to $(V_1(y), 0, y)$.

B) $\dfrac{\partial \theta}{\partial y_K} \neq 0$ and $\forall r \in \mathbb{R}$ $\theta^{-1}(r)$ is a $(l-1)$ manifold.

C) $\theta(y) \longrightarrow \infty$ as $\dfrac{\partial G}{\partial V}(V_1(y), y) \longrightarrow 0$

$\theta(y) \longrightarrow -\infty$ as $\dfrac{\partial G}{\partial V}(V_2(y), y) \longrightarrow 0$.

An analogous result could be obtained for negative speed, i.e. a C^1 map $\rho : \Pi_1 \cap \Pi_2 \to \mathbb{R}$ such that for $I(y) > 0$ $*$ will have a heteroclinic solution, with speed $\rho(y)$, from $(V_1(y), 0, y)$ to $(V_2(y), 0, y)$; and for $I(y) \leq 0$, $W^-(V, y, -\rho(y))$ will provide us with a solution from V_2 to V_1. For $I(y) = 0$ $\theta(y) = \rho(y) = 0$. Of course there is no a priori reason why $\rho(y)$ should equal $-\theta(y)$.

3- The slow equation.

Until now we have worked on the assumption that $(\dot V, \dot W) = F(V, W, y, \theta)$ is a good approximation for $*$ when ε is small. This is reasonable, unless we are near the singularities $\dot V = \dot W = 0$, where $H(V, y)$ will dominate the behaviour.

To start with, we need more knowledge of H. It is possible to prove ([1], [5], [11]) that it satisfies the following properties:

P_1) $y_0 = (\alpha_m(0), \alpha_h(0)) \in \Pi_1 \cap \Pi_2$; $H(0, y_0) = 0$; $V_1(y_0) = 0$; $\frac{\partial H}{\partial y}(0, y_0)$ is non singular and its eigenvalues have negative real part.

Let $\bar\theta$ be $\theta(y_0)$ and $*_i$ be the equation $\dot y = H(V_i(y), y)$ $i = 1, 2$, for $y \in \Pi_1 \cap \Pi_2$. Also, given $C \subset \mathbb{R}$ let $y *_i C = u(C)$ where $u : J \subset \mathbb{R} \to \Omega_y$ is the solution of $*_i$ such that $u(0) = y$.

P_2) $\forall y \in \Pi_1 \cap \Pi_2$ $\exists t \geq 0$ such that $\theta(y *_2 t) < -\bar\theta$.

Let $T_2 = \inf \{t > 0 : \theta(y_0 *_2 t) < -\bar\theta\}$

$T_1 = \inf \{t' \leq T_2 : \forall t \in [t', T_2]\ \theta(y_0 *_2 t) = -\bar\theta\}$

and $\Psi = y_0 *_2 [T_1, T_2]$ (see fig 7). Generically $T_1 = T_2$.

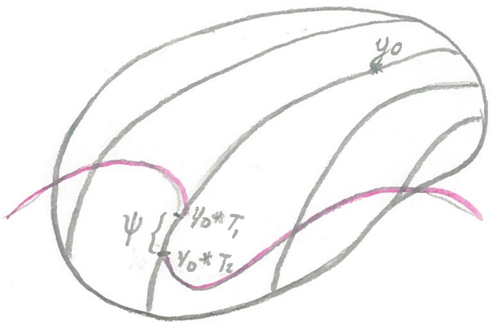

Fig 7 - flow of $*_2$ in π_1.

$\theta(y) = -\bar{\theta}$.

If we also assume:

H_1) $\psi \subset S(y_0)$ in $*_1$

H_2) $\displaystyle\int_0^{V_2(y_0)} G(V, y_0)\, dV < 0$,

starting from $(0,0,y_0)$ we can go to $(V_2(y_0), 0, y_0)$ with speed $\theta(y_0)$. From there we move about the manifold $V = V_2(y)$, until we reach ψ and are sent back to the surface $V = V_1(y)$, again with speed $\theta(y_0)$. Once there, H_1 guarantees that we go back to $(0,0,y_0)$ (fig 8). This is the singular solution we were looking for.

Now, to prove that there is a solution of $*$ that really behaves like that (approaches $(0,0,y_0)$ as $t \longrightarrow \pm\infty$) we need some results about isolating blocks.

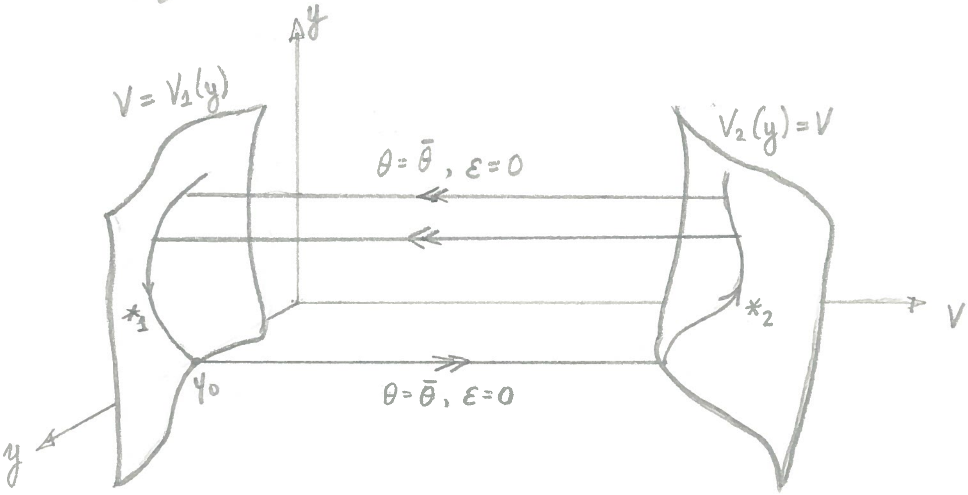

Fig 8 - homoclinic singular solution for $*$ with speed $\bar{\theta}$ images of ψ by V_1 and V_2.

IV. Isolating blocks.

1. Methods

Instead of looking at $\Omega_V \times \Omega_Y$, in this section we study the behaviour of solutions on C^1 hypersurfaces which are transversal to the flow of $*$ and form the boundary of compact sets. Such sets are called isolating blocks and the hypersurfaces are surfaces of section.

Let $\Omega \subset \mathbb{R}^n$ be a domain, $G \in C^1(\Omega, \mathbb{R}^n)$.

Δ If $A \subset \mathbb{R}^n$ is connected, $f \in C^1(A, \mathbb{R})$ defines a surface of section for $\dot{u} = G(u) \overset{def}{\Longleftrightarrow} f^{-1}(0) \neq \emptyset$ and $f(u) = 0 \Longrightarrow \langle \nabla f(u), G(u) \rangle \overset{def}{=} \dot{f}(u) \neq 0$.

Δ A compact set $B \subset \Omega$ with non empty interior is a block (or isolating block) for $\dot{u} = G(u) \overset{def}{\Longleftrightarrow}$ $\exists f_1, \ldots, f_K$ surfaces of section such that

$$B = \bigcap_{i=1}^{K} f_i^{-1}[0, \infty).$$

Δ In this case let $B^+ \overset{def}{=} \{u \in B : \exists i \ f_i(u) = 0 \text{ and } \dot{f}_i(u) > 0\}$ i.e. the part of ∂B where G points in. Also let $B^- \overset{def}{=} \{u \in B : \exists i \ f_i(u) = 0 \text{ and } \dot{f}_i(u) < 0\}$.

Δ For any $A \subset \Omega$ let $I^+(A) \overset{def}{=} \{u \in A : u \cdot [0, \infty) \subseteq A\}$

$I^-(A) \overset{def}{=} \{u \in A : u \cdot (-\infty, 0] \subseteq A\}$.

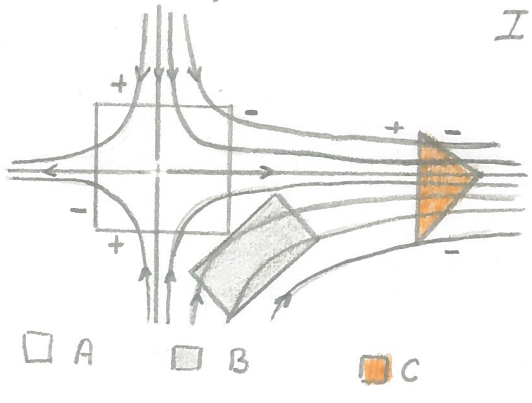

Fig 1. Example: $\Omega = \mathbb{R}^2$

$G(x, y) = (x, -y)$; A and C are blocks, B is not. $I^+(B) = I^-(B) = I^+(C) = I^-(C) = \emptyset$

$I^-(A) = \{(0, y)\} \cap A$

$I^+(A) = \{(x, 0)\} \cap A$

It is always possible to surround a hyperbolic fixed point by a block like the A in fig 1.

<u>Lemma 1</u> If $\bar{u} \in \Omega$ is a rest point of $\dot{u} = G(u)$ and its eigenvalues have nonzero real part, $\forall c > 0\ \exists B$ block for $\dot{u} = G(u)$, $\bar{u} \in B \subset \{u : |u - \bar{u}| \le c\}$ such that $I^+(B) \cap I^-(B) = \{\bar{u}\}$.

<u>Lemma 2</u> If $G(\bar{u}) \neq 0$ $\forall T_1 \le 0 \le T_2$ $\exists f$, surface of section defined in a neighbourhood of $\bar{u}$ and blocks B_1, B_2 for $\dot{u} = G(u)$ satisfying: (see fig 2).

$\bar{u} \in B_1 \cap B_2$

$B_1, B_2 \subset f^{-1}(0) \cdot [T_1, T_2]$

$B_1^+ \subseteq f^{-1}(0) \cdot T_1$; $B_2^- \subseteq f^{-1}(0) \cdot T_2$.

Given $c > 0$, B_1 and B_2 may be chosen so that $\forall t \in [T_1, T_2]$, $\forall u \in B_1 \cup B_2$, $f(u) = 0 \Rightarrow |u \cdot t - \bar{u} \cdot t| < c$.

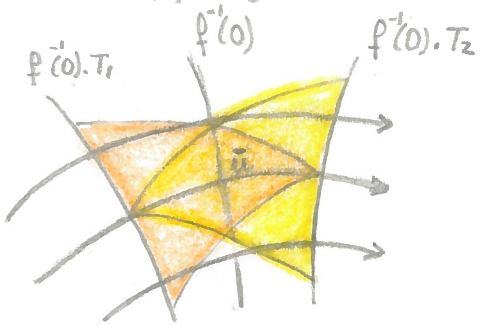

Fig 2 - B_1, B_2.

If, in addition, $\forall t \in [T_1, T_2]$ $\bar{u} \cdot t \neq \bar{u}$, B_1 and B_2 may be chosen so that $I^+(B_1) = I^+(B_2) = \emptyset$.

We now define blocks for parametrized families of differential equations. Let $C \subset \mathbb{R}^k$ be a domain, $G \in C^1(\Omega \times C, \mathbb{R}^n)$.

Δ $B \times \Sigma \subset \Omega \times C$ is a block for $\dot{u} = G(u, \sigma)$, $\dot{\sigma} = 0 \overset{def}{\Longleftrightarrow}$ Σ is compact and $\forall \sigma \in \Sigma$, B is a block for $\dot{u} = G(u, \sigma)$

Δ $(B \times \Sigma)^{\pm} \overset{def}{=} B^{\pm} \times \Sigma$.

In the preceding sections we studied

the behaviour of one equation at a time, in the regions where the others gave small contributions. So now we need a result relating blocks in an attractor surface (the slow manifold) to blocks for the whole system. In other words, given a block A for $\dot{u} = F(u)$ we want a way of obtaining from it a block for $\dot{u} = f(u,z)$, $\dot{z} = \delta^{-1} q(u,z)$, $\dot{\delta} = 0$, $(\oplus)$ where $F(u) = f(u, z(u))$, $q(u,z) = 0 \iff z = Z(u)$.

If the hypothesis of lemma 1 are satisfied by $\bar{u} = Z(u)$, $G(z) = q(u,z)$ $\forall u \in A$, we get, given $c > 0$, a block B_{uc} for the fast equation $\dot{z} = q(u,z)$, with $z(u) \in B_{uc} \subseteq \{z : |z - z(u)| \leq c\}$. Let $B_c = \{(u,z)\ u \in A, z \in B_{uc}\}$.

<u>Lemma 3</u> If A is a block for $\dot{u} = F(u)$ and $\forall u \in A$ $\frac{\partial}{\partial z} q(u, z(u))$ is non singular having eigenvalues with nonzero real part, $\exists\ \bar{c} > 0, \bar{\delta} > 0$ such that $\forall c \in (0, \bar{c}]$ $\forall \delta \in (0, \bar{\delta}]$ $B_c \times [\delta, \bar{\delta}]$ is a block for $\oplus$ with the following properties:

A) $B_c^{\pm} = \{(u,z) \in \partial B_c,\ u \in A^{\pm}$ or $z \in B_{uc}^{\pm}\}$

B) $I^+(A) = \emptyset \Rightarrow I^+(B_c) = \emptyset$.

C) If $\bar{u}$ is a rest point of $\dot{u} = F(u)$ whose eigenvalues have nonzero real part and $I^+(A) \cap I^-(A) = \{\bar{u}\}$, then $I^+(B_c) \cap I^-(B_c) = \{(\bar{u}, Z(\bar{u}))\}$.

D) For every $\eta > 0$, A is also a block for $\dot{u} = \eta F(u)$ with $D^{\pm}$ remaining constant as η varies (see bellow).

Δ Given a block $B \times \Sigma$ for $\dot{u} = G(u,\sigma)$, $\dot{\sigma} = 0$ define, $\forall (u,\sigma) \in \Omega \times C$:

$\rho^+(u,\sigma) =$ the point with smallest t in $(B^+ \times \Sigma) \cap (u,\sigma).(0,\infty)$

$\rho^-(u,\sigma) =$ the point with smallest t in $(B^- \times \Sigma) \cap (u,\sigma).(0,\infty)$

$D^+ = \{(u,\sigma) \in$ domain of $\rho^+ : \rho^+(u,\sigma) \notin B^-\}$
$D^- = \{(u,\sigma) \in$ domain of $\rho^- : \rho^-(u,\sigma) \notin B^+\}$.

<u>Lemma 4</u> $\rho^\pm$ are continuous maps on $D^\pm$
$D^\pm$ are open subsets of $\Omega \times \Sigma$.

As an example, suppose $\bar{u} \in \mathcal{U}$ is a rest point of $\dot{u} = G(u)$ and B a block, as in lemma 1. Let P be a path in D^+. Since ρ^+ is continuous, $\rho^+(P)$ is a path in B^+. Since ρ^- is also continuous, if $\rho^+(P) \subset D^-$ then $\rho^-\rho^+(P)$ will be a path in B^-. Thus $\rho^+(P)$ is <u>not</u> contained in D^- if two points of $\rho^+(P)$ are mapped by ρ^- into different components of B^-. In this case, at least one positive half solution beginning at a point in ρ^+ will be contained in B (see fig 4).

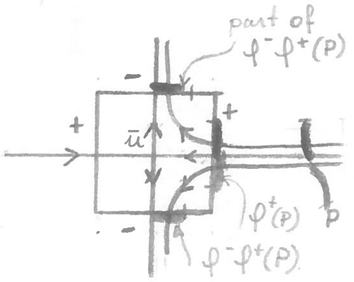

Fig 4 - behaviour of a path near a singularity.

If we assume $P \subset \mathcal{U}(\bar{u})$ this will give us a sufficient condition for the existence of a homoclinic solution.

<u>Lemma 5</u> The following is a sufficient condition for the existence of a homoclinic solution of $\dot{u} = G(u,\sigma), \dot{\sigma} = 0$.

$\exists\, B_1 \times \Sigma$, $B_2 \times \Sigma$, disjoint blocks for $\dot{u} = G(u,\sigma)$, $\dot{\sigma} = 0$, satisfying:

A) $\exists\, \bar{u} \in B_1$, $\forall \sigma \in \Sigma$ $(\bar{u},\sigma)$ is a rest point of $\dot{u} = G(u,\sigma)$, $\dot{\sigma} = 0$, and its eigenvalues have nonzero real part.

B) $I^+(B_1 \times \Sigma) \cap I^-(B_1 \times \Sigma) = \{\bar{u}\} \times \Sigma$ (fig 5)
$I^+(B_2 \times \Sigma) = \emptyset$

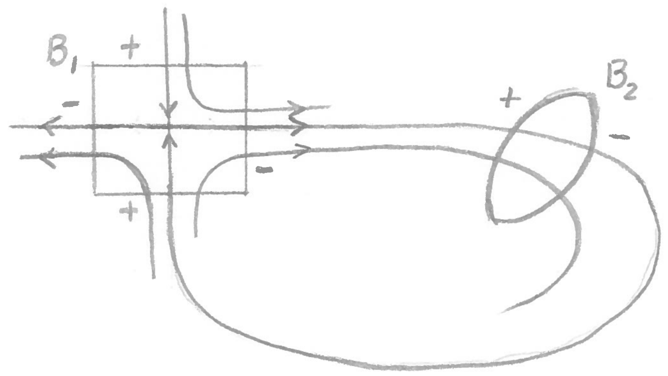

Fig 5 - conditions A and B.

C) $\exists \Delta \subset B_2^-$, closed, such that $\Delta \times \Sigma \subseteq D_1^+$; $\Delta \cap cl(B_2^- - \Delta)$ has two components, δ_0 and δ_1; $\delta_0 \times \Sigma$ and $\delta_1 \times \Sigma \subset D_1^+$; $\varphi_1^+(\delta_0 \times \Sigma)$ and $\varphi_1^-(\delta_0 \times \Sigma) \subset D_1^-$; and $\varphi_1^- \varphi_1^+(\delta_0 \times \Sigma)$ are contained in distinct components of B_1^- (fig 6, 7)

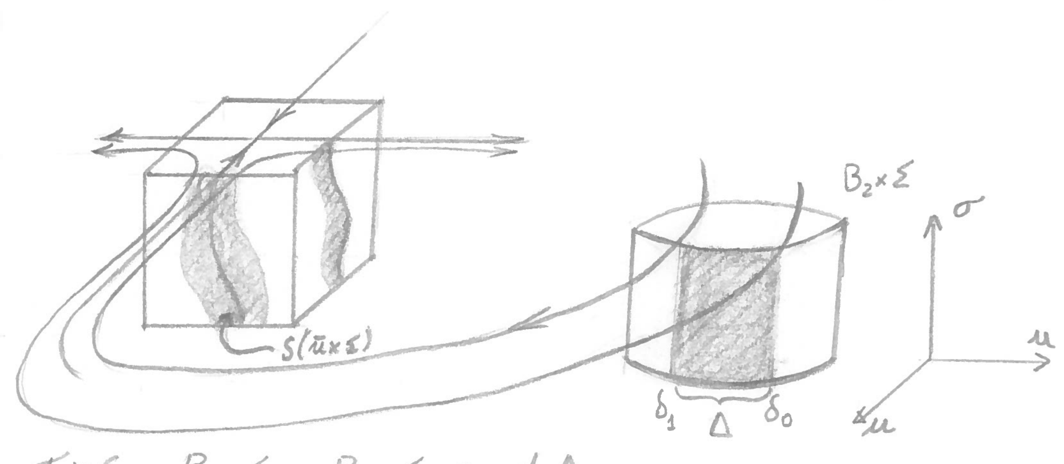

Fig 6 - $B_1 \times \Sigma$, $B_2 \times \Sigma$ and Δ.

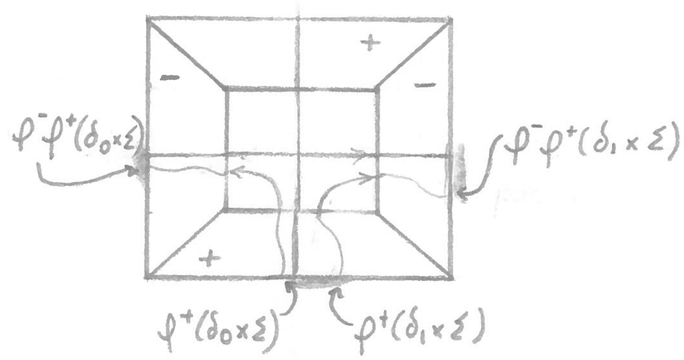

Fig 7 - $B_1 \times \Sigma$ seen from above, showing images of δ_i and Δ by $\varphi^\pm$

D) $\exists P : [0,1] \longrightarrow D_2^+$ such that $\forall s \in [0,1]$, $P(s) \in \mathcal{U}(\bar{u}, \sigma_1)$ and $\varphi_2^- \varphi_2^+ P(0)$, $\varphi_2^- \varphi_2^+ P(1)$ are contained in distinct components of $(B_2^- - \Delta) \times \Sigma$ (fig 8).

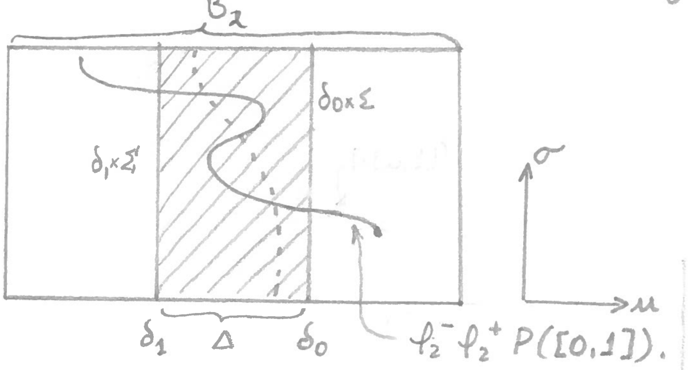

Fig 8 - $B_2^- \times \Sigma$, showing Δ and $P[0,1]$. The dotted line represents $S(\bar{u}, \sigma) \cap B_2^- \times \Sigma$. In this example there are three values of σ providing homoclinic solutions, corresponding to the points wher the dotted line and $\varphi_2^- \varphi_2^+ (P[0,1])$ meet.

2- Homoclinic solutions.

Now we can use the guidance of the singular solution to find the two blocks for $*$ as in lemma 5. First, use lemmas 1 and 2 to obtain a block A_1 for $*_1$ containing ψ, $A_1 \subset \Pi_1 \cap \Pi_2$ and $I^+(A_1) \cap I^-(A_1) = \{y_0\}$. The construction is indicated in fig 9. This we extend to a block B_1 for $*$, $\varepsilon \in (0, E]$, $|\theta - \bar{\theta}| \leq T$ using lemma 3 with

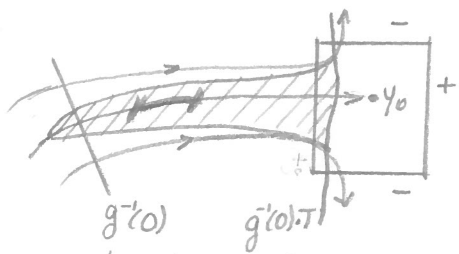

Fig 9 - Construction of $A_1 = A' \cup A''$
▨ A'' from lemma 2 g-surface of section
□ A' from lemma 1 $= \psi$.

$z = (v, w)$, $u = y$, $\delta = \varepsilon$; B_1 will contain $V_1(\psi)$ and if $\Sigma = \{\theta : |\theta - \bar{\theta}| \leq T\}$, $I^+(B_1 \times \Sigma) \cap I^-(B_1 \times \Sigma) = \{(0,0,y)\} \times \Sigma$. Moreover B_1^- will have two components, contained in $\{W>0\}$ and $\{W<0\}$.

Similarly, to construct B_2, we apply lemma 3 to a block A_2 for $*_2$. this is obtained from lemma 2 such that for some surface of section f and some $t_2>t_1>t_0>0$ we have:

$A_2 \subseteq f^{-1}(0)*_2[0,t_2)$

$y_0 \in f^{-1}(0)*_2(0,t_0)$

$\psi \subseteq f^{-1}(0)*_2(t_0,t_1)$

$f^{-1}(0)*_2 t_0 \subseteq \{y\in\pi_2 : \theta(y) > -\bar\theta\}$

$f^{-1}(0)*_2 t_1 \subseteq \{y\in\pi_2 : \theta(y) < -\bar\theta\}$.

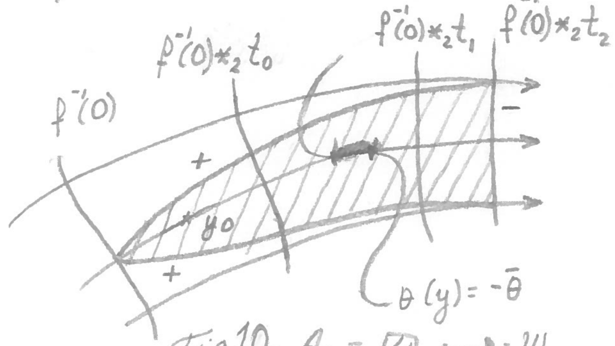

Fig 10. $A_2 =$ [hatched] $\longrightarrow = \psi$

therefore, B_2 will contain $\{(V_2(y),0,y) : y\in\psi\}$ and $(V_2(y_0),0,y_0)$; also $I^+(B_2)=\emptyset$, so that B_1 and B_2 satisfy the first two conditions on lemma 5.

Let $\Delta = \{(V,W,y)\in B_2^- : y \in f^{-1}(0)*_2[t_0,t_1]$ and $W<0\}$ $\delta_i = \{(V,W,y)\in\Delta : y\in f^{-1}(0)*_2 t_i\}$. Clearly Δ satisfies the third condition on lemma 5.

For condition D let $\lambda(\theta,\varepsilon)$ be the largest eigenvalue of $*$ (positive for small ε) and $s(\theta,\varepsilon)$ the solution on $\mathcal{U}(0,0,y)$ in the direction of $\lambda(\theta,\varepsilon)$, $W>0$.

Choose $\gamma>0$ so that $V\leq V_2(y)-\gamma$ implies $(V,W,y_0)\notin B_2$, and let $F(V,W,y) = V - V_2(y) - \gamma$. F defines a surface of section for $*$ near $s(\bar\theta,0)\cap F^{-1}(0)$. Let $p(\theta,\varepsilon) = s(\theta,\varepsilon)\cap F^{-1}(0)$, well defined for (θ,ε) near $(\bar\theta,0)$.

If $|\theta-\bar\theta|\leq J$, $\varepsilon\in(0,E]$, for suitably small J, E, the orbit of $p(\theta,\varepsilon)$ by $*$ will be attracted to the surface $V=V_2(y)$, i.e. $p(\theta,\varepsilon)\in D_2^+$, and will leave this surface (and B_2) as soon as it reaches a point where $\theta(y) = -\theta$ (fig 11).

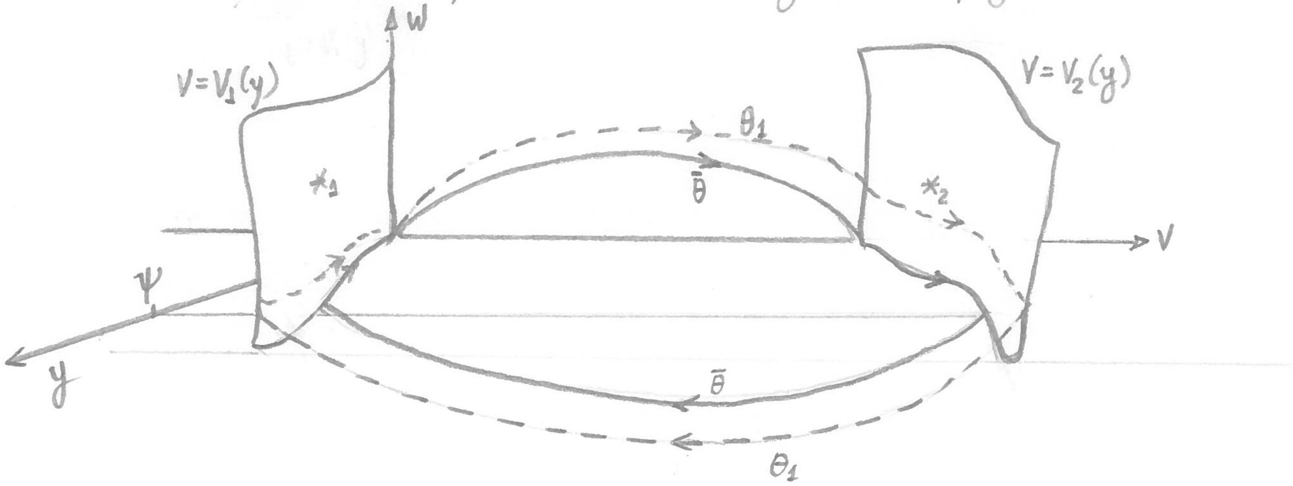

Fig 11. singular solutions of $*$. full line-homoclinic solution for $\theta=\bar{\theta}$. dotted line. solution for $\theta=\theta_1>\bar{\theta}$.

If Δ is thin enough (i.e. $t_1 - t_0$ small enough) $\varphi_2^- \varphi_2^+(p(\theta-J,0)\ \theta-J,0)$ and $\varphi_2^- \varphi_2^+(p(\theta+J,0),\theta+J,0)$ are contained in different components of $B_1^- \times \Sigma \times \{\varepsilon\} - \Delta \times \Sigma \times \{\varepsilon\}$, so that the path $P(s)=p(\bar{\theta}+(2s-1)J,\varepsilon)$ satisfies the last condition in lemma 5, and we have proved:

<u>theorem</u>. If hypothesis, g (page 12) and H_1, H_2 (page 17), are satisfied, $\exists\, E>0$, such that $\forall \varepsilon \in (0,E]$, $\exists\, \theta>0$ such that $*$ admits a homoclinic solution from and to $(0,0,y_0)$.

With some minor alterations an analogous reasoning may provide a proof of the existence of a homoclinic solution to and from $(0,0,y_0)$ with negative speed θ.

Using lemma 3 again, we have:

Corolary If hypothesis g, h (page 11), H_1 and H_2 are satisfied $\exists E>0$, $D>0$ such that $\forall \varepsilon \in (0, E]$, $\delta \in (0, D]$ $\exists \theta > 0$ $(\rho < 0)$ such that ** admits a homoclinic solution from and to $(0, 0, y_0; z(y_0))$. Consequently the Hodgkin and Huxley equations have a travelling wave solution with speed θ (ρ) that approaches $(0, \alpha_m(0), \alpha_h(0), \alpha_n(0))$ as $x \longrightarrow \pm\infty$.

V- Discussion.

Numerical analysis by Cooley [5] and Nagumo [16] indicates that at each temperature in a certain range there are two travelling wave solutions with positive speed for the Hodgkin and Huxley equations. (fig 1) It is conjectured that the slow pulse is unstable, and Rinzel and Keller [18] provided numerical evidence for this on a simplified form of the equations.

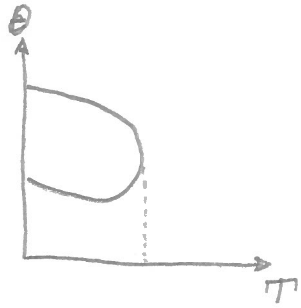

fig 1. Propagation speed θ versus temperature for solitary pulse solutions (from [17])

The existence of a second solution may be argued for from symmetry considerations, since the nerve impulse is known to propagate in both directions in the axon, but a more careful study of the equations is necessary for this.

The problem of an overall picture of the orbit structure of ** (and of H-H) is still open, as well as that of the stability of the solutions. A more detailed discussion of the single pulse and wave train solutions described by Carpenter in ([1]) is also needed in order to verify if they have some of the physiologically significant characteristics of the nerve impulse like, for instance, the threshold fluctuations described in the introduction.

Finally, a comment about the fast and slow equations. The singular solution we constructed looks somewhat like fig 2a. This seems to contradict Zeeman's reasoning in [19], but the main problem is that the fast equation is not uniformly fast, so that our picture could perfectly well look like fig. 2b. A more serious shortcoming is the possible absence of a threshold, which again may prove not true.

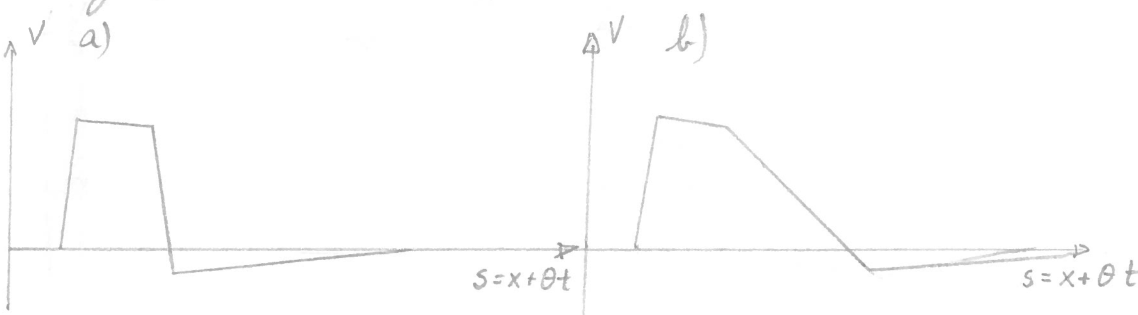

Fig 2. Schematic representations of the singular solutions for $*$.

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