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NERVE IMPULSE EQUATIONS

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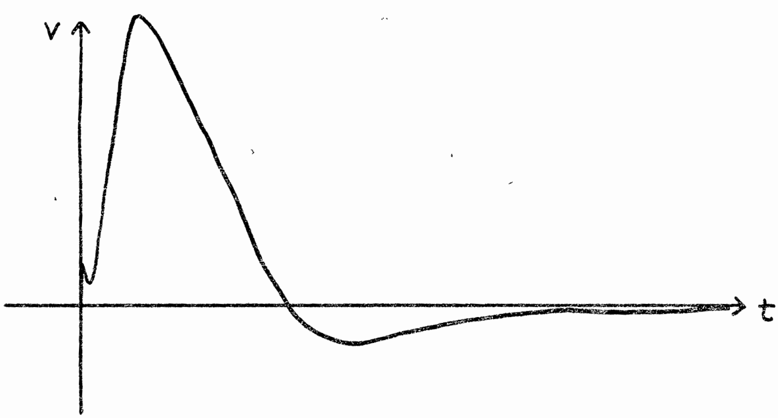
THE HODGKIN-HUXLEY MODEL

The Hodgkin-Huxley [5] model for nerve impulse transmission consists of a long thin cylindrical membrane (axon) containing axoplasm and bathed in an ionic solution. If the nerve is stimulated above a threshold, the permeability of the membrane increases rapidly, allowing sodium ions to rush in. Diffusion of electrons within the axon raises the membrane potential (V) above threshold farther down the axon, where more sodium ions enter, and the impulse proceeds in a wavelike manner. Two slower processes (inhibition of sodium entrance and exit of potassium ions) return the axon to its original resting state.

The impulse, or action potential, depends upon the distance (x) from the point of stimulus and the time (t) since the stimulus.



t) is described by a nonlinear diffusion equation coupled with nary differential equations describing sodium (m activation, iactivation) and potassium (n activation):

$$\frac{1}{R}\frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} + g(V,m,n,h)$$

$$\frac{\partial n}{\partial t} = \gamma_n(V) \quad (n_\infty(V) - n)$$

$$\frac{\partial h}{\partial t} = \gamma_h(V) \quad (h_\infty(V) - h) \qquad \text{(HH)}$$

$$\frac{\partial m}{\partial t} = \gamma_m(V) \quad (m_\infty(V) - m) \; ,$$

re $0 < \gamma_n, \gamma_h << \gamma_m$; $0 < n_\infty, h_\infty, m_\infty < 1$; and all functions are

TRAVELING WAVE SOLUTIONS

Let us consider a phenomenon (e.g. nerve impulse, muscle ntraction, heartbeat, chemical reaction) whose principal process described by a nonlinear diffusion equation and whose subprosses are described by ℓ "slow" and m "fast" equations:

$$\frac{\partial^2 V}{\partial x^2} = \frac{\partial V}{\partial t} + g(V,y,z)$$

$$\frac{\partial y}{\partial t} = \epsilon h(V,y,z) \qquad \text{(P)}$$

$$\frac{\partial z}{\partial t} = \delta^{-1} q(V,y,z) \; ,$$

ere $V \in [V\ ,V\ ] \subset \mathbb{R}$, $y \in \Omega \subset \mathbb{R}^\ell$; $z \in \Omega_z \subseteq \mathbb{R}^m$; ϵ, δ are small; and all functions are C^2. Note that two slow [or fast] variables may be slow or fast relative to one another. This is the case, for example, in a model for the heart muscle and pacemaker which we shall discuss later.

We now consider traveling wave solutions of (P) with speed $\theta > 0$. If $s = x + \theta t$ and $\cdot = \frac{d}{ds}$, (P) becomes the system in $\mathbb{R}^{2+\ell+m}$:

$$\begin{aligned} \dot{V} &= W \\ \dot{W} &= \theta W + g(V,y,z) \\ \dot{y} &= \theta^{-1}\epsilon h(V,y,z) \\ \dot{z} &= \theta^{-1}\delta^{-1}q(V,y,z) \quad . \end{aligned} \tag{**,θ}$$

We proceed by analyzing the V-W, y, and z systems separately and patching together these solutions to form singular solutions of (**,θ) . Isolating block techniques [1,2,3] prove that the existence of a singular solution of (**,θ) implies the existence of a true solution for certain ranges of the θ , δ , ϵ parameters.

We shall assume that the equation $q(V,y,z) = 0$ defines a function $z(V,y)$ and that, if δ is small, solutions of (**,θ) are strongly attracted to the surface $z = z(V,y)$.

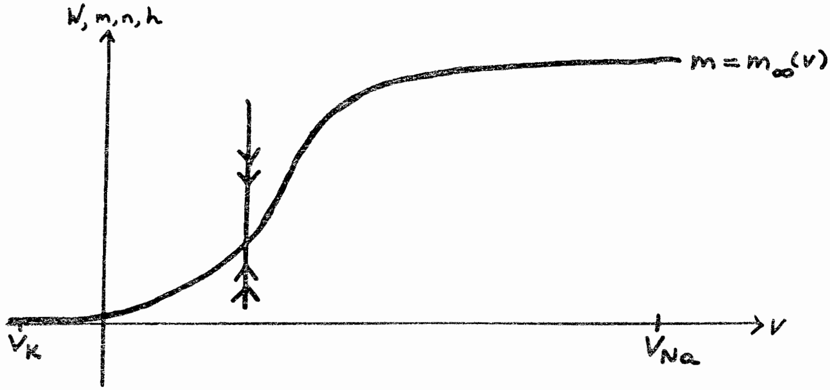


Figure 2: (HH,θ) with $\gamma_m >> 1$.

ore precisely, we assume:

(A) There exists a function $z(V,y): [V_\alpha, V_\beta] \times \Omega_y \to \Omega_z$ such hat $q(V,y,z) = 0$ iff $z = z(V,y)$.

(B) For fixed $\langle V,y \rangle$, the eigenvalues of $D_z q(V,y,z)$ at $= z(V,y)$ have negative real parts.

Let (*,θ) be the system in $\mathbb{R}^{2+\ell}$ associated with (**,θ):

$$\dot{V} = W$$

$$\dot{W} = \theta W + G(V,y) \qquad (*,\theta)$$

$$\dot{y} = \theta^{-1} \epsilon H(V,y) ,$$

here $G(V,y) \equiv g(V,y,z(V,y))$ and $H(V,y) \equiv h(V,y,z(V,y))$. All he following results, stated for (*,θ), are true for (**,θ) rovided (A) and (B) are satisfied and δ is small.

THE FITZHUGH-NAGUMO EQUATIONS

Observing that the rates of the n,h variables of (HH) are about equal, FitzHugh [4] and Nagumo, et al. [6] considered a system with one slow variable:

$$\dot{V} = W$$

$$\dot{W} = \theta W - f(V) + y \qquad (F\text{-}N,\theta)$$

$$\dot{y} = \epsilon\theta^{-1}(V-\gamma y) \ ,$$

where $f \epsilon C^2$ is "cubic"; $f(0) = 0$; $f'(0) < 0$; and $\gamma \geq 0$. (See Figure 5.) Solutions of (F-N,θ) have many of the same "nerve-like" properties as those of (HH), but the uncoupling of the two slow variables in (HH) leads to new types of solutions, such as finite wave train and "plateau" solutions, not seen in the (F-N) model.

SINGULAR SOLUTIONS

Definitions

For the moment, consider the system:

$$\dot{x} = F(x) \ , \qquad (\dagger)$$

where $x \in \Omega \subseteq \mathbb{R}^k$ and $F \in C^1$. Let <u>$x \cdot t$</u> denote a solution of (†) for $t \in J$, a subinterval of $\mathbb{R}$. If $M \subseteq J$, let <u>$x \cdot M$</u> $\equiv \{x \cdot t : t \in M\}$.

$\overline{x}$ is a rest point of (†) if $F(\overline{x}) = 0$. If $\overline{x}$ is a rest int whose eigenvalues have j positive and $(k-j)$ negative real rts, <u>$U(\bar{x})$</u> $\equiv \{x \in \Omega : x \cdot t \to \bar{x}$ as $t \to -\infty\}$ is a j-manifold (the stable <u>manifold</u> of $\bar{x}$); and <u>$S(\bar{x})$</u> $\equiv \{x \in \Omega : x \cdot t \to \bar{x}$ as $t \to \infty\}$ is $(k-j)$-manifold (the <u>stable manifold</u> of $\bar{x}$). If $\bar{x}, \bar{\bar{x}}$ are rest ints of (†) a solution $x \cdot \mathbb{R} \subseteq U(\bar{x}) \cap S(\bar{\bar{x}}) - \{\bar{x}, \bar{\bar{x}}\}$ is <u>homoclinic</u> $\bar{x} = \bar{\bar{x}}$; <u>heteroclinic</u> if $\bar{x} \neq \bar{\bar{x}}$. A solution $x \cdot \mathbb{R}$ is <u>periodic</u> $x \cdot T = x$ for some $T \neq 0$.

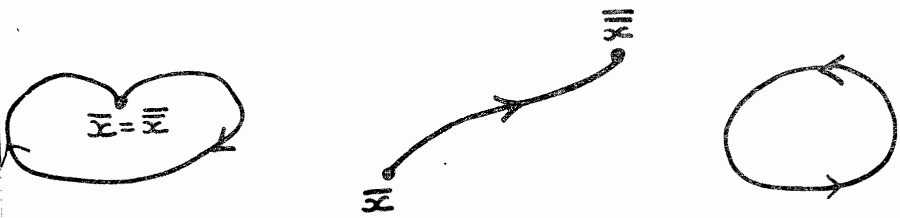


Figure 3: Homoclinic, heteroclinic, and periodic solutions.

We now return to $(*,\theta)$. If ϵ is small, $(*,\theta)$ is appro- nated by the system:

$$\begin{aligned} \dot{V} &= W \\ \dot{W} &= \theta W + G(V,y) \qquad\qquad (*,\theta)_0 \\ \dot{y} &= 0 . \end{aligned}$$

$\langle V, W,y\rangle$ is a rest point of $(*,\theta)_0$ iff $W = G(V,y) = 0$. Hence- th we assume that for fixed $y \in \pi \subseteq \Omega_y$, G is "cubic" and three zeros.

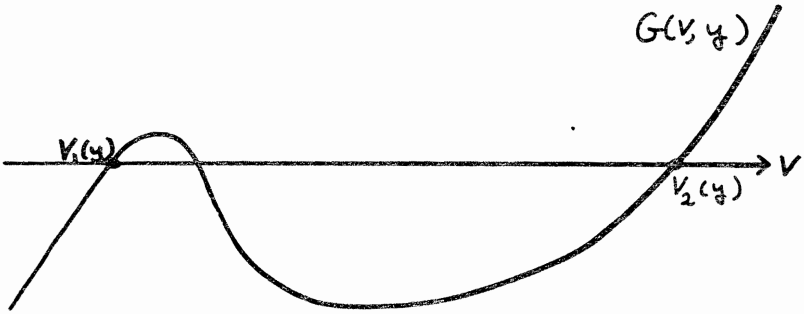


Figure 4: Cubic G for $y \in \pi$.

The first $(V=V_1(y))$ and last $(V=V_2(y))$ zeros are saddle points of $(*,\theta)_0$. Moreover, there exists $\theta = |\theta(y)|$ such that $(*,\theta)_0$ admits a heteroclinic solution from $\langle V_1(y),0,y\rangle$ to $\langle V_2(y),0,y\rangle$ if $\int_{V_1(y)}^{V_2(y)} G(V,y)\,dV \leq 0$ $[\theta(y) \geq 0]$; or from $\langle V_2(y),0,y\rangle$ to $\langle V_1(y),0,y\rangle$ if $\int_{V_1(y)}^{V_2(y)} G(V,y)dV \geq 0$ $[\theta(y) \leq 0]$. (See figures 5,6.)

<u>The (F-N) example</u>

There exists $\bar{\theta} > 0$ such that $(F\text{-}N,\bar{\theta})_0$ admits a solution from $\langle 0,0,0\rangle$ to $\langle V_2(0),0,0\rangle$. In addition, for some $\bar{y} > 0$, $(F\text{-}N,\bar{\theta})_0$ admits a solution from $\langle V_2(\bar{y}),0,\bar{y}\rangle$ to $\langle V_1(\bar{y}),0,\bar{y}\rangle$.

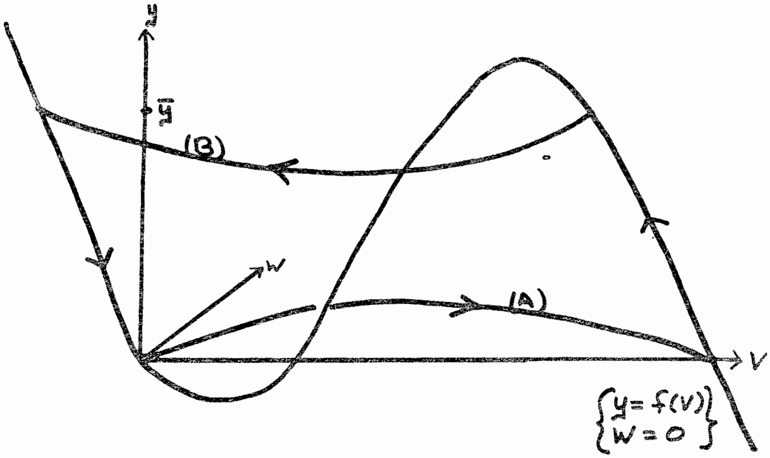


Figure 5: Homoclinic singular solution of (F-N) . (A) and (B) are solutions of $(F\text{-}N,\theta)_0$. $\theta(\bar{y}) = -\theta(0)$.

Let us now re-examine the statement "$(*,\theta)$ is approximated by $(*,\theta)_0$ when ϵ is small". This is accurate unless a trajectory is near $\{\dot{V} = \dot{W} = 0\}$; in this case, $|\dot{y}| >> |\dot{V}|, |\dot{W}|$ no matter how small ϵ is.

If $V_1(y)$ $[V_2(y)]$ is the left [right] zero of $G(V,y)$ for $\epsilon\ \pi_1[\pi_2] \subseteq \Omega_y$, let $(*)_i$ be the system on π_i :

$$\dot{y}^i = H(V_i(y),y) . \qquad (*)_i$$

for $\langle V,W,y\rangle$ near $\langle V_i(y),0,y\rangle$, then, solutions of $(*,\theta)$ are governed by $(*)_i$. A singular solution consists of solutions of of $(*,\theta)_0$ connected by solutions of $(*)_i$. Figure 5 illustrates a homoclinic singular solution of (F-N) . If γ is large, (F-N) has more than two rest points and admits two heteroclinic singular solutions.

HOMOCLINIC SOLUTIONS

Assume:

(A) $\bar{y}$ is a rest point of $(*)_1$ whose eigenvalues have negative real part.

(B) The solution of $(*)_2$ containing $\bar{y}$ crosses $\{y:\theta(y) = -\theta(\bar{y})\}$ transversely at $y = \bar{\bar{y}}$.

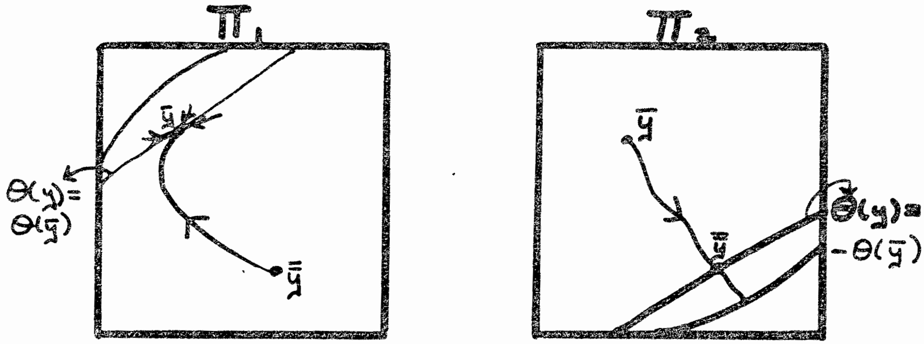


Figure 6: Homoclinic singular solution, $\ell = 2$.

(C) The solution of $(*)_1$ containing $\bar{\bar{y}}$ is contained in $S(\bar{y})$. Then $(*,\theta)$ admits a homoclinic solution for $\langle\theta,\epsilon\rangle$ in a continuum (figure 7(A)).

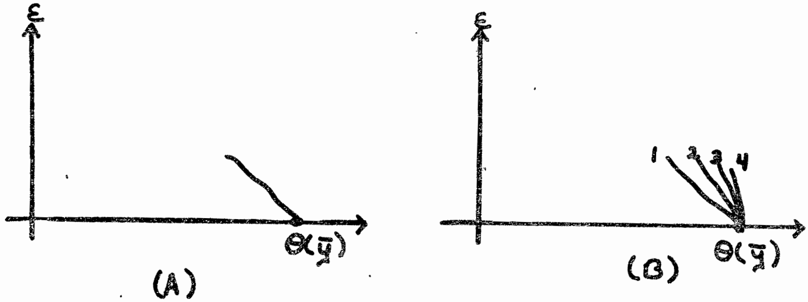


Figure 7: Parameter ranges for existence of homoclinic (A) and wave train (B) solutions of $(*)$.

Remarks

(1) The last section contains hypotheses which imply (A) - (C) generically for (HH).

(2) The existence theorem generalizes easily to include a finite number of "jumps" between π_1 and π_2. If $\ell \geq 2$, then, $(*,\theta)$ admits finite wave train solutions provided the solution in π_1 containing $\bar{\bar{y}}$ crosses $\{\theta(y) = \theta(\bar{y})\}$ transversely.

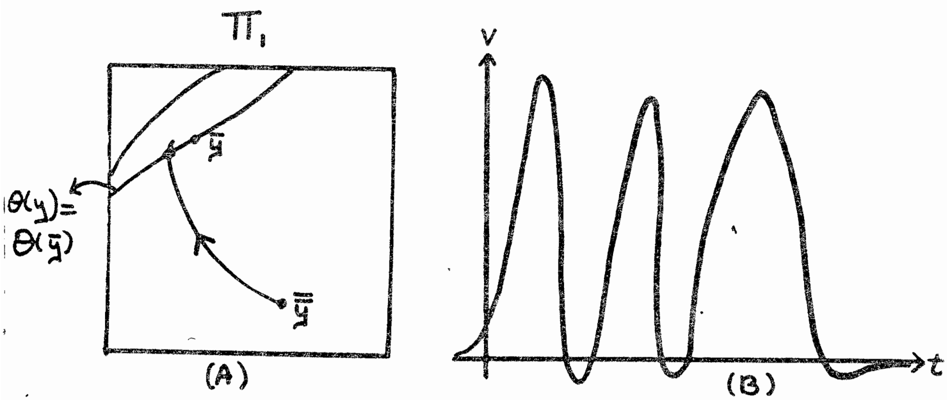


Figure 8: (B)A three-fold wave train, $V(t)$ for fixed x.

If this is the case, $(*,\theta)$ admits a double wave train solution for $\langle\theta,\varepsilon\rangle$ in a continuum (figure 7(B)). In fact, for fixed small $\varepsilon > 0$, if $(*,\theta)$ admits a singular k-fold wave train, then there exist $\theta_1 <\ldots< \theta_k$ such that $(*,\theta_j)$ admits a k-fold wave train $(j = 1,\ldots,k)$.

(3) If $\ell = 2$; $\dot{\theta}^2(y) < 0$ when $\theta(y) = \theta(\bar{y})$; and $\dot{\theta}^1(y) > 0$ when $\theta(y) = -\theta(\bar{y})$, then $(*,\theta)$ admits singular k-fold wave trains for all $k = 1,2,\ldots$ iff $(*,\theta)$ admits a singular 1-fold wave train.

(4) Solutions of $(*,\theta)$ converge to the singular solution as $\langle\theta,\varepsilon\rangle \to \langle\theta(\bar{y}),0\rangle$.

(5) Detailed analysis of $(*)_i$ may provide further qualitative information. For example, consider (HH) with

$$\dot{n} = \epsilon_n \gamma_n(V)(n_\infty(V)-n)$$

$$\dot{h} = \epsilon_h \gamma_h(V)(h_\infty(V)-h) \quad .$$

An approximate model for the contraction of the heart muscle consists of (HH) with $\frac{\epsilon_n}{\epsilon_h}$ small. In this case, solutions of $(*)_i$ appear as in 9(A), and solutions of $(*,\theta)$ appear as in 9(B).

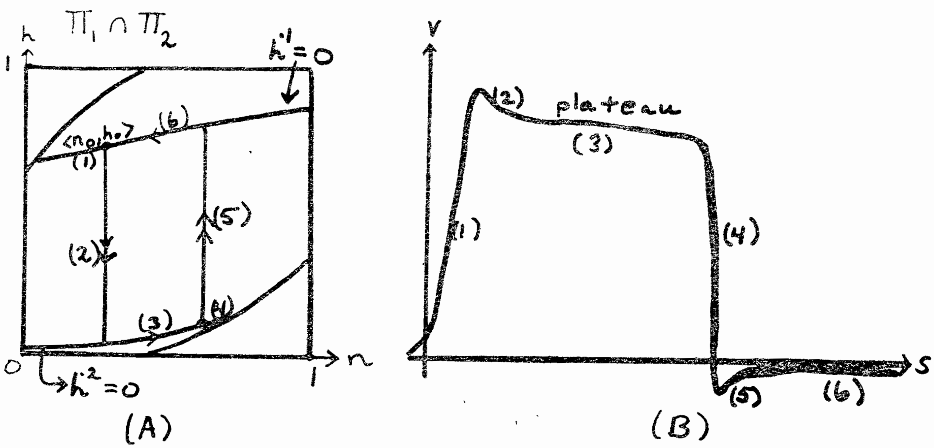


Figure 9: Plateau homoclinic singular solution

(1) Jump to π_2 . (2) Move rapidly to $\{\dot{h}^2 = 0\}$ in π_2 . (3) Move to $\{\theta(y) = -\theta(y)\}$ in $\pi_2 \cap \{\dot{h}^2 = 0\}$. (4) Jump to π_1. (5) Move rapidly to $\{\dot{h}^1 = 0\}$ in π_1 . (6) Move to rest in $\pi_1 \cap \{\dot{h}^1 = 0\}$.

The shape of the action potential of the heart muscle is as seen in Figure 9(B); a nerve exhibits similar behavior if injected with tetraethylammonium chloride (TEA) [7].

(6) Analogous results hold for heteroclinic solutions.

PERIODIC SOLUTIONS

Periodic singular solutions may be defined as solutions of $(*,\theta)_0$ connected by finite solution segments of $(*)_i$.

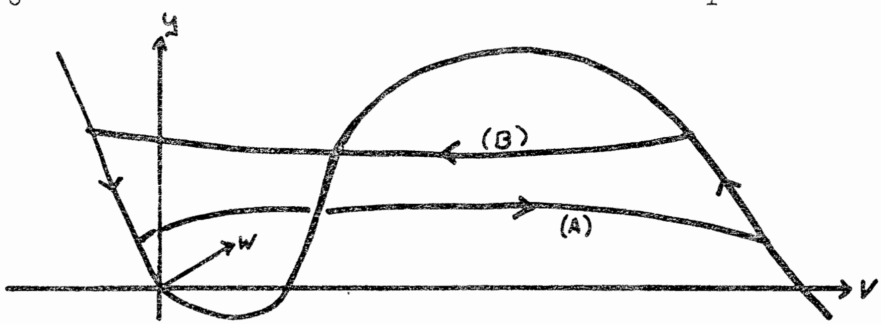


Figure 10: Periodic singular solution of (F-N) . (A) and (B) are solutions of $(*,\tilde{\theta})_0$ and $0 < \tilde{\theta} < \theta(0)$.

A fixed point theorem implies that $(*,\tilde{\theta})$ admits a periodic solution for all small $\epsilon > 0$ provided $\ell = 1$ and $H(V_1(y),y) < 0 < H(V_2(y),y)$ for $|\theta(y)| \leq \tilde{\theta}$.

If $\ell \geq 2$, $(*,\tilde{\theta})$ may admit a plateau periodic solution provided that one slow variable is much slower than the others. For example, let $\ell = 2$ and consider (HH) with $\frac{\epsilon_n}{\epsilon_h} << 1$. If $\epsilon_n = 0$, $\langle V,0,n,h \rangle$ is a rest point of (HH) iff $G(V,n,h) = 0$ and $h = h_\infty(V)$. $(HH,\tilde{\theta})$ admits two heteroclinic singular solutions, one from π_1 to π_2 [(1), (2) of figure 11(A)]; the other from π_2 to π_1 [(4), (5)].

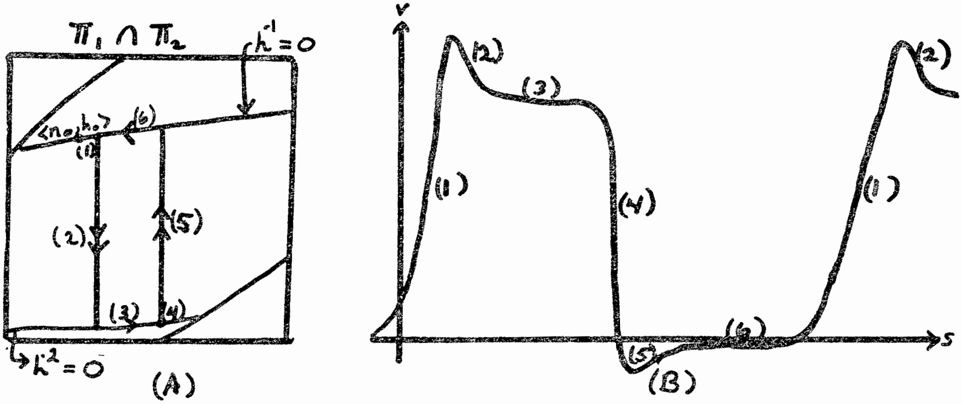


Figure 11: Singular plateau periodic solution of (HH) .

If these solutions are connected in π_1 , π_2 [(6),(3)], there exists a periodic plateau solution (figure 11 (B)) of $(*,\tilde{\theta})$ if ϵ_h and ϵ_n/ϵ_h are small.

As in the previous section, plateau solutions model "heart-like" behavior, with periodic solutions corresponding to pacemaker activity. In nerves, however ϵ_n and ϵ_h are about equal; hence we seek a definition of periodic singular solution which will imply the existence of periodic solutions of $(*,\tilde{\theta})$ for all small $\epsilon > 0$. The appropriate notion is an ℓ-dimensional singular solution [2].

Fix $\tilde{\theta} > 0$ and assume that $\ell \geq 2$ and that all solutions of $(*)_1$ $[(*)_2]$ cross $\{\theta(y) = -\tilde{\theta}\}$ $[\{\theta(y) = \tilde{\theta}\}]$ transversely. Assume also that there exists $M \subseteq \{\theta(y) = \tilde{\theta}\}$ such that (A) - (C) hold:

(A) M is homeomorphic to $[0,1]^{\ell-1}$.

(B) If $y \in M$ the solution of $(*)_2$ through y crosses $\{\theta(y) = -\tilde{\theta}\}$ transversely in a point $F_2(y)$. Moreover the solution of $(*)_1$ through $F_2(y)$ crosses $\{\theta(y) = \tilde{\theta}\}$ transversely in a point $F_1 \circ F_2(y)$.

(C) $F_1 \circ F_2(M) \subseteq \text{int}\ (M)$.

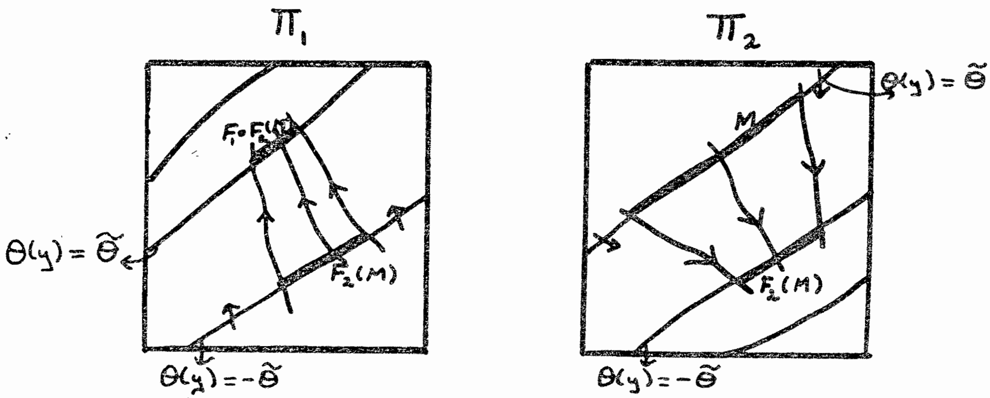


Figure 12: Singular periodic solution, $\ell = 2$.

Notice that $F_1 \circ F_2|M$ admits at least one fixed point (Brouwer fixed-point theorem) and hence $(*,\widetilde{\theta})$ admits a singular periodic solution in the previous sense. $(*,\widetilde{\theta})$ admits a periodic solution for all small $\varepsilon > 0$ if (A) - (C) are satisfied.

Remarks

(1) The natural choice of M is $\{\theta(y) = \widetilde{\theta}\}$ (assuming that this set is homeomorphic to $[0,1]^{\ell-1}$, as it is for (HH)). If no solution of $(*)_1$, $(*)_2$ leaves π_1, π_2 in $\partial(\Omega_y)$, (C) is satisfied; again (HH) satisfies this criterion (with $\Omega_y = [0,1]^2$) since $0 < n_\infty, h_\infty < 1$. (B), however, may not be an appropriate assumption if $F_2(\{\theta(y) = \widetilde{\theta}\}) \cap \{\dot{\theta}^2(y) > 0\} \neq \emptyset$ or $F_1 \circ F_2(\{\theta(y) = \widetilde{\theta}\}) \cap \{\dot{\theta}^1(y) < 0\} \neq \emptyset$, as illustrated in Figure 13.

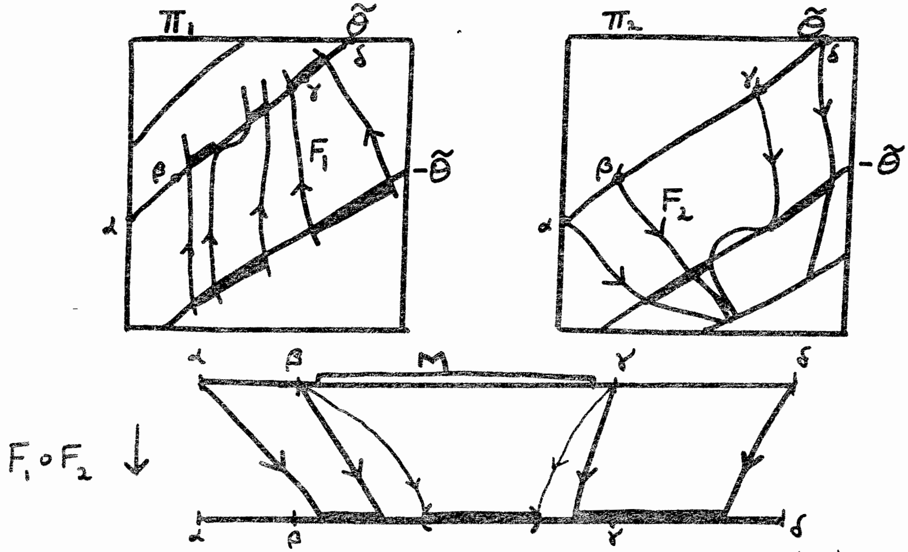


Figure 13: $F_1 \circ F_2$ piecewise-continuous. $M \subseteq (\beta\gamma)$.

$F_1 \circ F_2$ is discontinuous at β and γ. However, if M is chosen to be a closed interval such that $F_1 \circ F_2((\beta\gamma)) \subseteq M \subseteq (\beta\gamma)$, M then satisfies (B) and $(*,\tilde{\theta})$ admits a periodic solution. In fact, induction on the number of points of discontinuity of $F_1 \circ F_2$ proves that (A) - (C) are satisfied if $\ell = 2$ and $F_1 \circ F_2$ is piecewise-continuous.

(2) If $\ell = 1$, $(*,\tilde{\theta})$ admits at most one periodic singular solution for each $\tilde{\theta}$. (It seems likely, too, that for each small $\epsilon > 0$ $(*,\tilde{\theta})$ admits a unique periodic solution.) If $\ell \geq 2$, however, $(*,\tilde{\theta})$ may admit N periodic singular solutions; in this case $(*,\tilde{\theta})$ admits at least N periodic solutions for small $\epsilon > 0$. These solutions may not be locally unique.

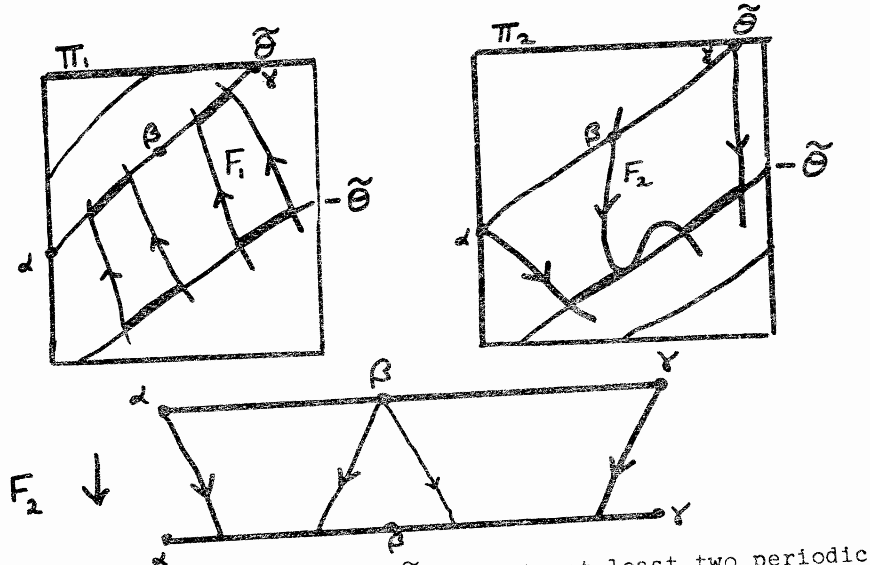


Figure 14: $\ell = 2$. $(*,\tilde{\theta})$ admits at least two periodic solutions.

(3) If $(*)_1$ admits a rest point, y_0 , $(*,\tilde{\theta})$ admits gular periodic solutions only if $\tilde{\theta} < \theta(y_0)$ when $\ell = 1$ (or he plateau case). If $\ell \geq 2$, $(*,\tilde{\theta})$ may admit periodic solu- s for $\tilde{\theta} \geq \theta(y_0)$ as illustrated in Figure 15.

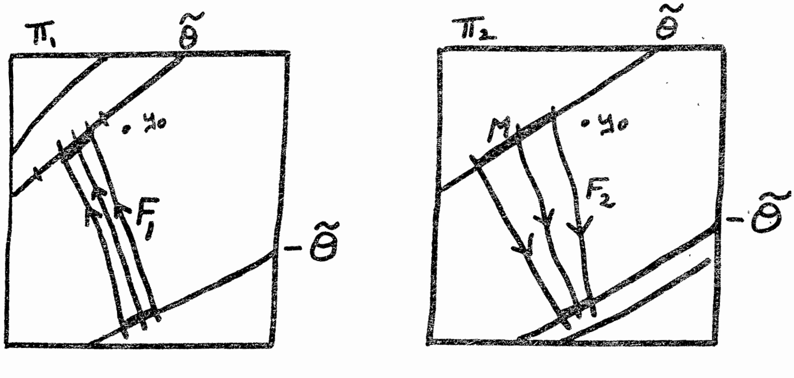


Figure 15: Singular periodic solution of (HH) with $\tilde{\theta} > \theta(y_0)$

Again note that (HH) admits solutions of a type not seen in the (F-N) system.

(3) If $\ell \geq 3$, $(*,\tilde{A})$ may admit "finite wave train" periodic solutions as illustrated in Figure 16.

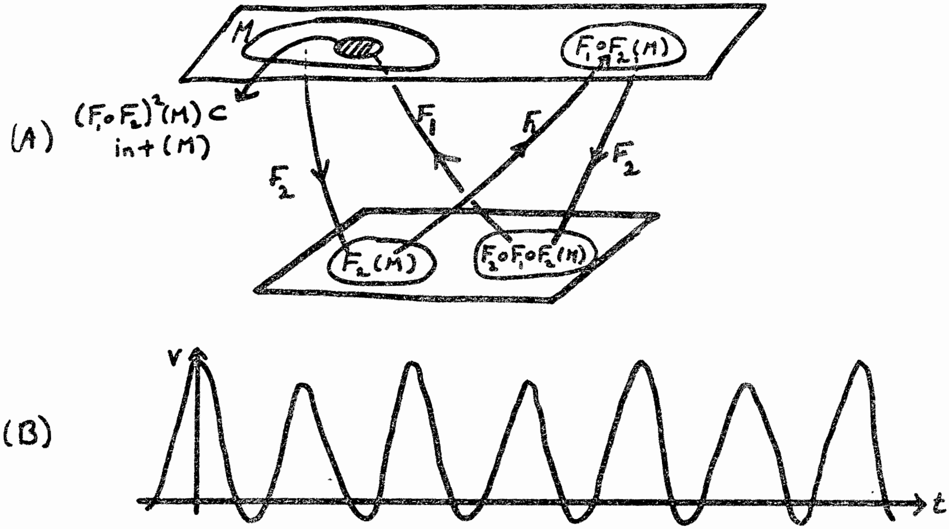


Figure 16: A 2-fold periodic wave train, $\ell = 3$. (A) Singular solution. (B) V(t) for fixed x .

Problems of transversality (condition (A)) may become complex for $\ell \geq 3$.

HYPOTHESES ON THE HODGKIN-HUXLEY EQUATIONS

In the original Hodgkin-Huxley model of the squid giant axon,

$$g(V,m,n,h) = \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_K n^4 (V - V_K) + \bar{g}_\ell (V - V_\ell) ,$$

where $\bar{g}_{Na}, V_{Na}, \bar{g}_K, V_K, \bar{g}_\ell$ and V_ℓ are constants. Also, $n_\infty', m_\infty' > 0$

nd $h_\infty' < 0$, corresponding (respectively) to potassium and sodium activation and sodium inactivation with maintained depolarization (i.e., if V is fixed, as in a voltage clamp experiment, $n \to n_\infty(V)$, $h \to h_\infty(V)$, and $m \to m_\infty(V)$). In order that the model describe nerve activity of nearly every species, as well as other excitable membrane phenomena, hypotheses on (HH) should be mild and qualitative. We impose the following conditions on *(HH)*, where $G(V,n,h) \equiv g(V,m_\infty(V),n,h)$, $n_0 \equiv n_\infty(0)$, $h_0 \equiv h_\infty(0)$, and $m_0 \equiv m_\infty(0)$.

HH) Hypotheses

There exist $V_K < 0 < V_{Na}$ such that for every $V \epsilon [V_K, V_{Na}]$ nd $n,h \,\epsilon\, [0,1]$:

(A) $G(V_K,n,h) < 0 < G(V_{Na},n,h)$.

(B) *There exist at most three* $V \epsilon (V_K, V_{Na})$ such that $G(V,n,h) = 0$. Moreover, if $G(V,n,h) = \frac{\partial G(V,n,h)}{\partial V} = 0$, $\frac{\partial^3 G(V,n,h)}{\partial V^3} \neq 0$ *and* $V > 0$ if $\frac{\partial^2 G(V,n,h)}{\partial V^2} > 0$.

(C) $\frac{\partial G}{\partial V}(0,n_0,h_0) > 0$, and there exists $V_2 > 0$ such that $G(V_2,n_0,h_0) = 0$ *and* $\int_0^{V_2} G(V,n_0,h_0)dV < 0$.

(D) $\frac{\partial G}{\partial n} > 0$ and $\frac{\partial G}{\partial h} < 0$.

(E) $G(V,n_\infty(V),h_\infty(V)) = 0$ iff $V = 0$.

(F) $n_\infty' > 0$ and $h_\infty' < 0$. ///

arks

(A) and (D) are clearly true of the original (HH). (E) es that $\langle 0,0,n_0,h_0,m_0 \rangle$ is the unique rest point of (HH,θ) any θ (i.e. the nerve has a unique rest state). (B) and (C) the "cubic" conditions on G and depend upon the function) especially the fact that $m_\infty' > 0$

Note that we nowhere assume that g is linear in V or that the activity of Na^+ and K^+ are independent.

These assumptions give π_1, π_2 the phase portraits seen in figures 6, 8, 9, 11, and 12.

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