A mathematical analysis of excitable membrane phenomena

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This work defines and analyzes the dynamics of a general excitable membrane. The definition generalizes such special cases as the Hodgkin-Huxley and FitzHugh-Nagumo models of nerve impulse transmission. It describes how any number of microscopic membrane processes are synthesized by a macroscopic potential which, in turn, influences the microscopic processes by feedback. Each microscopic process corresponds to the statistics of switching on and off suitable membrane sites. The macroscopic potential obeys a nonlinear diffusion equation.

The mathematical results classify the types of solutions that can be achieved by particular statistical rules and potential functions. Of critical importance is the number of independent phenomena responsible for the return to rest. The Hodgkin-Huxley model postulates two such processes, the inhibition of Na^+ and K^+ activation; the FitzHugh-Nagumo model combines these two into one. Both models exhibit a single pulse solution (Fig.6A) as well as a continuous family of periodic solutions which converge to the single pulse as the period becomes infinite. The Hodgkin-Huxley model, however, may exhibit plateau and finite wave train solutions (Fig.6A); solutions consisting of periodic bursts; periodic solutions with speed which is greater than that of the single pulse; and even two or more stable pulse solutions, traveling at different speeds. If three or more inhibitory processes occur, there may be periodic wave trains of any length (Fig.7) and yet more complex behavior. This approach illuminates the underlying topological structure of particular models, and helps one to visualize the types of microscopic events that can lead to a given class of observed phenomena. Of particular interest is the qualitative nature of the hypotheses, which allow for the vast array of data one would hope to include in a model which describes the nerve impulse, muscle contraction, and the heartbeat in all species. While the spirit of our analysis is reminiscent of the catastrophe theory methods of Zeeman [1] *et al.*, we associate a global dynamic with its microscopic realization and prove existence theorems rigorously.

We begin with a detailed description of the Hodgkin-Huxley model, as a typical excitable membrane process. We then generalize this system to allow any number of fast or slow subprocesses. Geometric hypotheses are placed on the system as

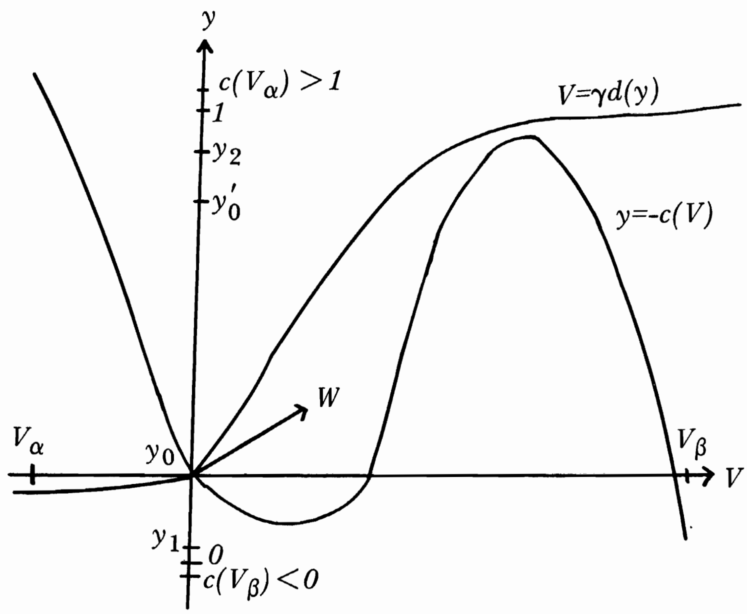

Fig.1 The phase space of the (FN) system. The 'cubic' curve represents the rest points when $\epsilon = 0$

the need for them develops. Our goal in each case is to find a 'singular solution', arising from the different time scales involved. Proofs that the existence of a singular solution implies the existence of a true solution are contained in [2,3]. One proof is sketched at the end of the chapter in order to introduce the methods used.

The Hodgkin-Huxley model

The Hodgkin-Huxley [4,5] equations summarize a model of the nerve impulse in which the axon is taken to be a long cylindrical membrane containing axoplasm (with high K^+ concentration) and bathed in a solution with high Na^+ concentration. When the nerve is stimulated above a threshold sodium ions rush in and dramatically shift the membrane potential, V, from its rest state. Two slower processes, inhibition of sodium entrance and potassium exit, return V to rest. Diffusion of electrons within the axon induces the process to repeat itself in a wavelike manner.

The Hodgkin-Huxley system consists of a nonlinear diffusion equation coupled with equations describing changes in membrane permeability as V varies:

$$\frac{1}{R}\frac{\partial^2 V}{\partial x^2} = C\frac{\partial V}{\partial t} + \bar{g}_{Na} m^3 h(V - V_{Na}) + \bar{g}_K n^4 (V - V_K) + \bar{g}_L(V - V_L)$$

$$\begin{aligned}\frac{\partial m}{\partial t} &= (1-m)\alpha_m(V) - m\beta_m(V)\\ \frac{\partial h}{\partial t} &= (1-h)\alpha_h(V) - h\beta_h(V)\\ \frac{\partial n}{\partial t} &= (1-n)\alpha_n(V) - n\beta_n(V)\end{aligned} \qquad (1)$$

where x is the distance from the stimulus; t the time since the stimulus; and $\alpha_m, \beta_m \ldots > 0$. Ohm's law, Kirchoff's law, and the Nernst-Planck equations for ionic flux across a membrane are used to derive the first equation. The total membrane current ($\frac{1}{R}\frac{\partial^2 V}{\partial x^2}$, where R is the axoplasmic resistance) is set equal to the capacitance current ($C\frac{\partial V}{\partial t}$) plus the sodium ($\bar{g}_{Na} m^3 h(V - V_{Na})$), potassium ($\bar{g}_K n^4 (V - V_K)$), and leakage ($\bar{g}_L(V - V_L)$) currents. The equation for m describes the statistics of switching on ($m = 1$) or off ($m = 0$) of the active sodium sites. Sodium inactivation (h) and potassium activation (n) are described similarly. The rate ($\alpha_m(V) + \beta_m(V)$) at which m tends to an asymptotic value $\left(\frac{\alpha_m(V)}{\alpha_m(V) + \beta_m(V)}\right)$ for fixed V is large compared to the rates of n and h. Since m represents activation, $\alpha'_m > 0$ and $\beta'_m < 0$.

Similarly, $\alpha_n' > 0$, $\beta_n' < 0$, $\alpha_h' < 0$ and $\beta_h' > 0$.

A traveling wave solution of (2) satisfies a system of five ODE's, where $s = x + \theta t$, $\dot{} = \frac{d}{ds}$, and θ is the (leftward) speed of the wave:

$$
\begin{aligned}
\dot{V} &= W \\
\dot{W} &= \theta W + f(V,m,n,h) \\
\dot{m} &= \delta^{-1}\theta^{-1}((1-m)\alpha_m(V) - m\beta_m(V)) \\
\dot{h} &= \epsilon\theta^{-1}((1-h)\alpha_h(V) - h\beta_h(V)) \\
\dot{n} &= \epsilon\theta^{-1}((1-n)\alpha_n(V) - n\beta_n(V))
\end{aligned}
\tag{2}
$$

In (2) we have set $R = C = 1$; let $f(V,m,n,h)$ represent the ionic current; and introduced δ^{-1}, ϵ to represent the 'fast' and 'slow' rates when δ, ϵ are small.

Generalizing the model

We may now ask: what hypotheses on (2) generate a 'nerve-like' solution, that is, a solution which tends to the (unique) rest state of the nerve as $s \to \pm\infty$? Is it necessary, for example, to assume that f is linear in V or that the Na^+ and K^+ currents are independent, as implied by the form of f in (1)? The answer is no; in fact it is misleading to think of f as linear in V, and the validity of the Nernst-Planck equations (for *flat* membranes) is questionable in the first place. If (2) is to describe the nerve impulse in all species, we would expect a wide range of functions and parameters to yield nerve-like solutions. Moreover, if (2) is generalized to include other excitable membrane phenomena any number of subprocesses should be allowed. The analysis should include not only homoclinic solutions (from a rest point to itself) but also heteroclinic (between two rest points) and periodic solutions.

In order to study this general setting, we replace (2) by (3):

$$
\begin{aligned}
\dot{V} &= W \\
\dot{W} &= \theta W + f(V,y,z) \\
\dot{y} &= \epsilon\theta^{-1} g(V,y,z) \\
\dot{z} &= \delta^{-1}\theta^{-1} h(V,y,z)
\end{aligned}
\tag{3}
$$

where $V \in [V_\alpha, V_\beta] \subseteq \mathbb{R}$, $y \in [0,1]^l$, and $z \in [0,1]^k$; $\delta, \epsilon > 0$ are small; and $f,g,h \in C^2$.

We first consider the 'fast' equation:

$$\delta\dot{z} = \theta^{-1} h(V,y,z) \tag{4}$$

As $\delta \to 0$, (4) makes sense only if $h(V,y,z) = 0$.

Hypothesis (Fast)
There exists $z_\infty(V,y)$ such that $h(V,y,z) = 0$ iff $z = z_\infty(V,y)$. Moreover the eigenvalues of

$$\left.\frac{\partial h_i(V,y,z)}{\partial z_j}\right|_{z = z_\infty(V,y)} \quad \text{are negative.}$$

(FAST) is satisfied, for example, if $h_i(V,y,z) = (1 - z_i)\alpha_i(V,y) - z_i\beta_i(V,y)$, in which case $z_{\infty i} = \dfrac{\alpha_i}{\alpha_i + \beta_i}$ and the eigenvalues are $\{-(\alpha_i + \beta_i) : i = 1 \ldots k\}$.

If δ is small, then, it is reasonable to study the system (5) in which $z \equiv z_\infty(V,y)$:

$$
\begin{aligned}
\dot{V} &= W \\
\dot{W} &= \theta W + F(V,y) \\
\dot{y} &= \epsilon\theta^{-1} G(V,y)
\end{aligned}
\tag{5}
$$

where $F(V,y) \equiv f(V,y,z_\infty(V,y))$ and $G(V,y) \equiv g(V,y,z_\infty(V,y))$. We shall henceforth consider (5), since it can be shown [2] that all solutions of interest correspond to solutions of (3) for δ small.

Let us now examine the statement: 'A solution of (5) with ϵ small stays close to a solution of (5) with $\epsilon = 0$.' This statement is true *provided* the solution avoids the set where $\dot{V}$ and $\dot{W}$ are near zero. If $\dot{V}$ and $\dot{W}$ become very small, y eventually changes rapidly relative to V, W. Using (1) as a guide, it is reasonable to assume that $F(V_\alpha,y) < 0 < F(V_\beta,y)$ if $y \in [0,1]^l$. If this is the case, interesting solutions of (5) require that F be essentially nonlinear in the sense that, for some fixed y, $F(V,y)$ have at least two (and hence three) zeroes in (V_α, V_β). We shall assume that F has at most three zeroes. This case is often observed experimentally and can be easily extended to include more complicated nonlinearities. [Notice that we are now considering $f(V,m_\infty(v),n,h)$ of (2).] We shall be interested in bounded solutions

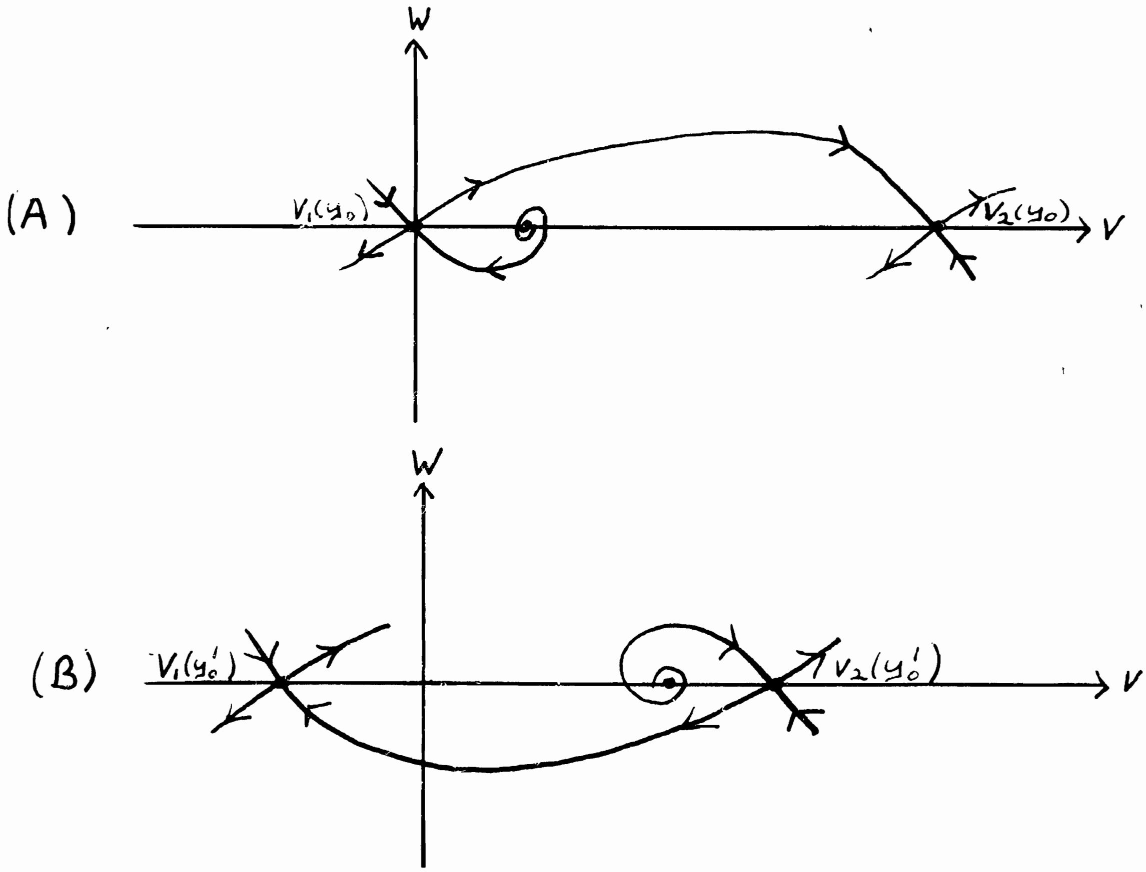

Fig.2 Phase portrait of (5) with $\epsilon = 0$, $\theta = \theta(y_0)$. (A) $y = y_0$; (B) $y = y_0' > y_0$.

of (5) which are alternatively dominated by the V- W and y systems.

Example: The FitzHugh-Nagumo equations.
It is instructive to examine the FitzHugh-Nagumo [6,7] model, in which $l = 1$. The equations represent the tunnel diode system used by Nagumo *et al.* to simulate the nerve.

$$\dot{V} = W$$

$$\dot{W} = \theta W + c(V) + y \qquad (6,\text{FN})$$

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

where $c(V)$ is the 'cubic' depicted in Fig.1 and $\gamma, d' > 0$.

$\dot{V} = \dot{W} = 0$ precisely along the curve $y = -c(V)$, $W = 0$. If γ is small, $\langle 0, 0, y_0 \rangle$ is the unique rest point of (6). As γ increases (6) acquires a rest point in the right branch of $\{W = c(V) + y = 0\}$. Note that $F(V_\alpha, y) = c(V_\alpha) + y < c(V_\alpha) + 1 < 0 < c(V_\beta) < c(V_\beta) + y = F(V_\beta, y)$ for $y \in [0,1]$.

Let us examine $\{V = W = 0,\ c'(V) > 0\}$. This set has two components which form the left and right branches of the cubic curve in Fig.1. Restricting attention to the left branch, for each $y \in [y_1, 1]$ there is a unique $V \equiv V_1(y)$ such that $y = -c(V)$. That is, $V_1(y)$ is the lefthand zero of $c(V) + y$ for fixed y. Similarly, $V_2(y)$ may be defined as the righthand zero when $y \in [0, y_2]$. $c(V) + y$ has three zeroes precisely when $y \in (y_1, y_2)$.

Returning to (5), we assume that for fixed $y \in [0,1]^l$ the equation $F(V,y) = 0$ defines a 'cubic' function of V.

Hypothesis (Cubic)

(A) $F(V_\alpha,y) < 0 < F(V_\beta,y)$.

(B) For every y there exist at most *three* V such that $F(V,y) = 0$; for some y there exist exactly three.
Moreover, $\frac{\partial^2 F}{\partial V^2}(V,y) \neq 0$ if $F(V,y) = \frac{\partial F}{\partial V}(V,y) = 0$. (That is, F admits double but not triple zeroes and $\{\dot V = \dot W = 0, \frac{\partial F}{\partial V} > 0\}$ has two components.)

(C) $\frac{\partial F}{\partial y_j} > 0$ for some j. [(C) may be replaced by a hypothesis on $\langle \frac{\partial F}{\partial y_1} \dots \frac{\partial F}{\partial y_l} \rangle$.]

(CUBIC) allows us to define $V_1(y)[V_2(y)]$ to be the left [right] zero of $F(V,y)$ for $y \in \Pi_1[\Pi_2] \subseteq \subseteq [0,1]^l$. It can be shown [2] that for each $y \in \Pi_1 \cap \Pi_2$ there exists $\theta(y) \geqslant 0$ such that $(5, \theta = \theta(y), \epsilon = 0)$ admits a heteroclinic solution from $\langle V_1(y), 0, y\rangle$ to $\langle V_2(y), 0, y\rangle$ if $\int_{V_1(y)}^{V_2(y)} F(V,y)\,dV \leqslant 0$; or from $\langle V_2(y), 0, y\rangle$ to $\langle V_1(y), 0, y\rangle$ if $\int_{V_1(y)}^{V_2(y)} F(V,y)\,dV \geqslant 0$.

Solutions of this system are completely understood; the form of G and choice of parameters θ, ϵ, δ now determine solutions of (3) and (5). We examine a few of the possibilities.

Our attention will focus on the two systems:

$$\dot y^1 = G(V_1(y), y), \quad y \in \Pi_1 \qquad (7.1)$$

$$\dot y^2 = G(V_2(y), y), \quad y \in \Pi_2 \qquad (7.2)$$

When V and W are small, (7.1) or (7.2) dominates (5).

In the (FN) example, y_0 is a global attractor for the system:

$$\dot y^1 = V_1(y) - \gamma d(y), \quad y \in [y_1, 1] \qquad (8.1)$$

If γ is small, the system:

$$\dot y^2 = V_2(y) - \gamma d(y), \quad y \in [0, y_2] \qquad (8.2)$$

has no rest point and $\dot y^2 > 0$. Thus all solutions leave $\Pi_2 = [0, y_2]$ in $\{y = y_2\}$. As γ increases, (8.2) acquires a global attractor, y_γ.

Let us consider the case $y_0' < y_\gamma < y_2$, where $\theta(y_0') = \theta(y_0)$.

In the nerve, this corresponds to the case where two stable potential states exist. If $\theta = \theta(y_0)$ and $\epsilon = 0$, one solution of (6) runs in $\{y = y_0\}$ from $\langle V_1(y_0), 0, y_0\rangle$ to $\langle V_2(y_0), 0, y_0\rangle$. If ϵ is small, the corresponding branch of the unstable manifold of $\langle 0, 0, y_0\rangle$ will stay near this solution *until* $\dot V$ and $\dot W$ become small, that is, until the solution approaches $\langle V_2(y_0), 0, y_0\rangle$. If (8.2) then dominates, the solution will move up to the rest point $\langle V_2(y_\gamma), 0, y_\gamma\rangle$. The solution of $(6, \epsilon = 0, \theta = \theta(y_0))$ and the positive half solution of (8.2) from $\langle V_2(y_0), 0, y_0\rangle$ to $\langle V_2(y_\gamma), 0, y_\gamma\rangle$ together form a *heteroclinic singular solution.* There is another possibility, as seen in Fig.3A. If the solution of (6) were to be dominated by (8.2) only up to the point where $y = y_0'$ it could jump back to the left branch, that is, stay close to the solution of $(6, \epsilon = 0, \theta = \theta(y_0))$ running from $\langle V_2(y_0'), 0, y_0'\rangle$ to $\langle V_1(y_0'), 0, y_0'\rangle$. Once the solution approaches $\langle V_1(y_0'), 0, y_0'\rangle$, then, (8.1) dominates and pulls it down to the rest point $\langle 0, 0, y_0\rangle$. This sequence of solutions of $(6, \epsilon = 0, \theta = \theta(y_0))$ and solution segments of (8.1) and (8.2) is a *homoclinic singular solution.* The existence of a singular solution implies the existence true solution of (5) or (6) for small $\epsilon > 0$. Whether the unstable manifold of $\langle 0, 0, y_0\rangle$ forms a homoclinic or heteroclinic solution depends upon the choice of parameters.

In fact, a parameter in a curve (A) (Fig.4) yields a homoclinic solution; and one in (B) yields a heteroclinic solution, where for fixed $\epsilon > 0$ a heteroclinic solution requires a faster wave speed. We note also that there exists a heteroclinic singular solution from $\langle V_2(y_\gamma), 0, y_\gamma\rangle$ to $\langle 0, 0, y_\gamma\rangle$, and a corresponding family of heteroclinic solutions for parameter values in the curve (C).

Periodic singular solutions may be constructed in a similar way (Fig.3B). Fix any $y_p > y_0$ such that $\int_{V_1(y_p)}^{V_2(y_p)} (c(V) + y_p)\,dV < 0$. Then there exist $y_p' > y_p$ such that $\theta(y_p') = \theta(y_p)$. The heteroclinic solutions of $(6, \theta = \theta(y_p), \epsilon = 0)$, linked by finite

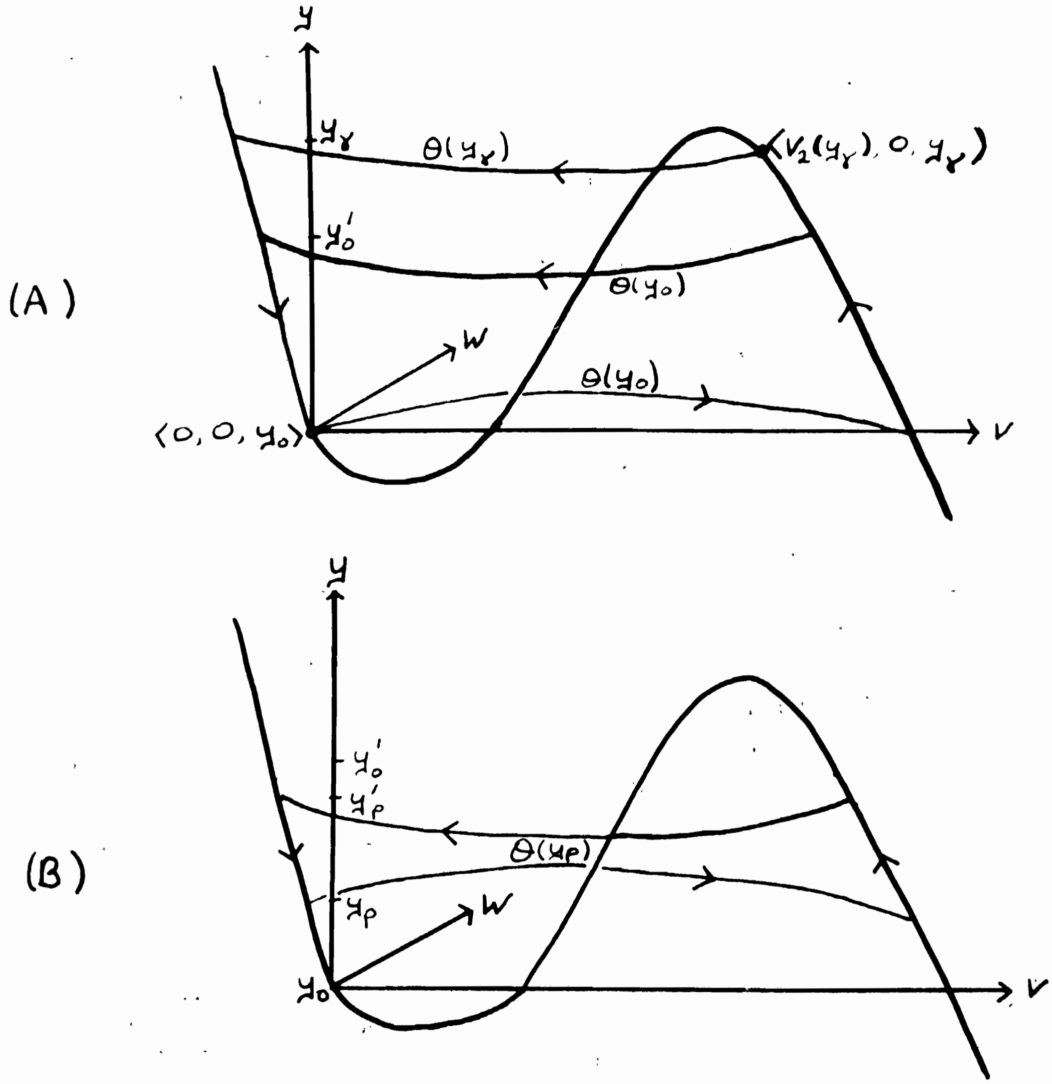

Fig.3 (A) A homoclinic singular solution of (FN) and two heteroclinic singular solutions. (B) A periodic singular solution.

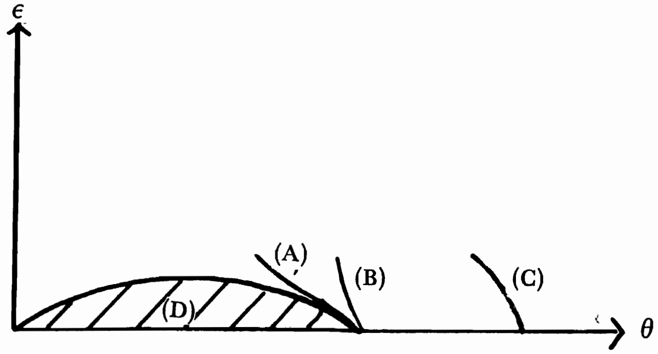

Fig.4 Parameter values for which (FN) admits a homoclinic (A), heteroclinic (B) or (C) or periodic (D) solution.

solution segments of (8.1) and (8.2), form a periodic singular solution. In fact, for any $\langle \theta, \epsilon \rangle$ in the open set (D) of Fig.4 (6) admits a periodic solution. For fixed small $\epsilon > 0$, there exists a continuous family of periodic solutions whose periods range from small (for θ small) to infinite, as θ approaches the value which yields a homoclinic solution. The proof that a singular periodic solution yields a true periodic solution depends critically upon the assumption that $l = 1$, that is, that (5) contain only one slow variable. The correct notion for $l \geqslant 2$ is that of an l-dimensional singular solution, discussed in [3].

The slow manifold

We shall now give examples of hypotheses on the general system (5) which imply the existence of singular solutions. When $l \geqslant 2$, some possible solutions arise which were not seen in the (FN) example.

Hypothesis (Slow)

(A) $G_j(V,y) < 0$ if $y_j = 1$ and

$G_j(V,y) > 0$ if $y_j = 0.$

Hence solutions of $(6, i)$ enter Π_i on $\partial [0,1]^l$.

(B) y_0 is globally asymptotically stable in (7.1). That is, all solutions of (7.1) approach y_0 as $s \to \infty$.

(C) $$\int_{V_1(y_0)}^{V_2(y_0)} F(V,y_0)\, dV < 0.$$

(D) No positive half solution of (7.2) is contained in Π_2.

(B) and (D) are usually verified by means of a Liapunov function.

Hypothesis (SLOW) implies that (5) admits a homoclinic solution for a curve of parameters [Fig.4(A)]. Slightly more restrictive hypotheses, which are satisfied, for example, if (5) is an analytic system, imply the existence of a family of periodic solutions for $\langle \theta, \epsilon \rangle$ in an open set [Fig.4(D)].

Figure 5 illustrates the phase portrait of (7.1) and (7.2) with $l = 2$, e.g. the Hodgkin-Huxley system.

A homoclinic singular solution consists of a jump from $\langle V_1(y_0), 0, y_0 \rangle$ to $\langle V_2(y_0), 0, y_0 \rangle$; the segment (A) from y_0 to y_0'; the jump back; and the segment (B) from y_0' to y_0. Note, however, that (B), instead of returning to rest, may 'decide' to jump back to Π_2 at y_1, i.e. real parameters may be chosen for (5) to yield a solution with more than one jump. y_1 travels in Π_2 to y_1' (C); jumps back to Π_1; and either returns to y_0 (D) *or* jumps back to Π_2 at y_2. In fact, if the phase portrait is as illustrated, once the extra jumps begin there may be any number of them and hence there exist *finite wave train* solutions of any length $k \geqslant 1$. Similar reasoning shows that periodic solutions may exist for $\theta \geqslant \theta(y_0)$. Neither of these cases is observed if $l = 1$, e.g. in the (FN) example.

Detailed analysis of (7.1) and (7.2) yields further qualitative results. For example, suppose one variable y_j is much slower than the others, as is the case if K^+ exit is inhibited in the nerve [8] or in models of the heart. A long plateau is observed in both the homoclinic and periodic solutions.

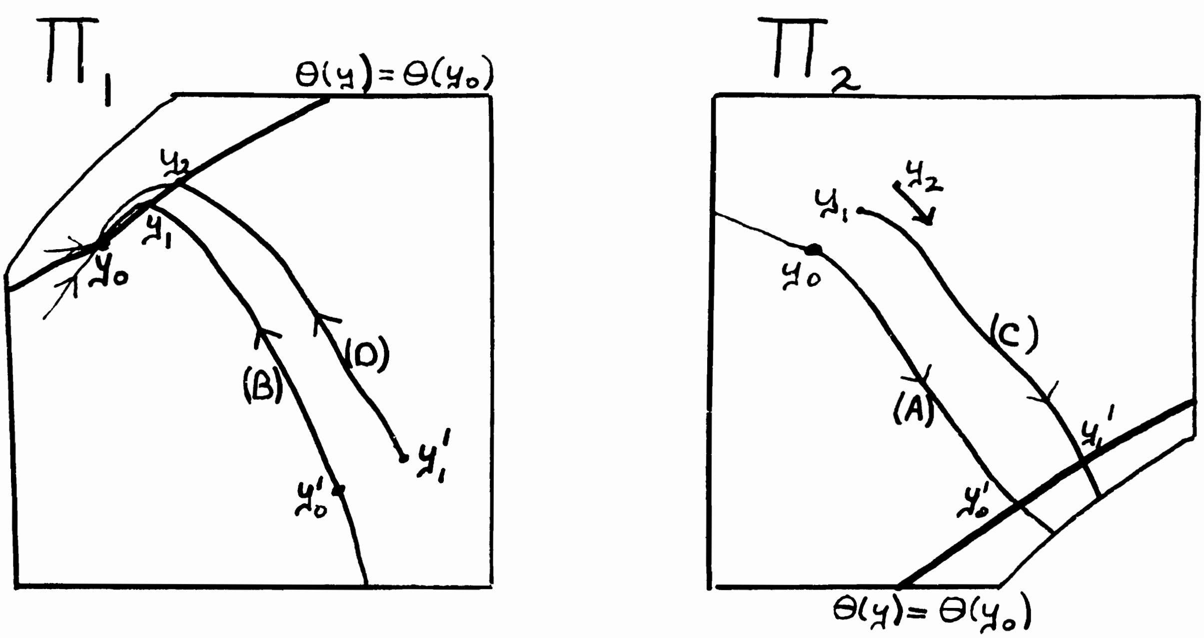

Fig.5 Phase portraits of (7.1) and (7.2) with $l = 2$

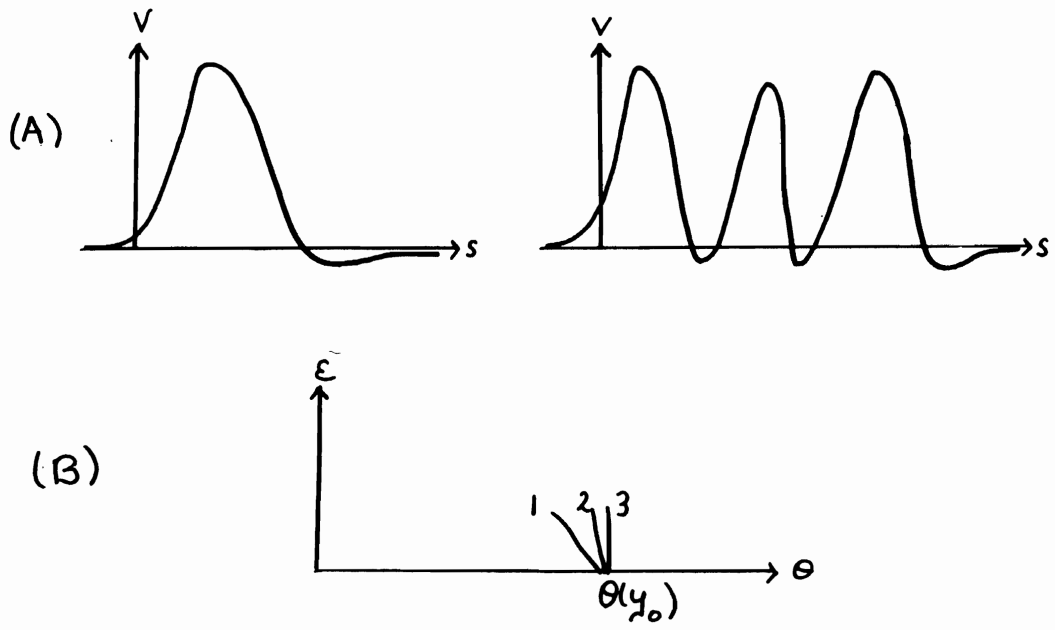

Fig.6 (A) A single pulse solution and a wave train of length three. (B) Parameter values which yield wave train solutions of length 1,2,3...

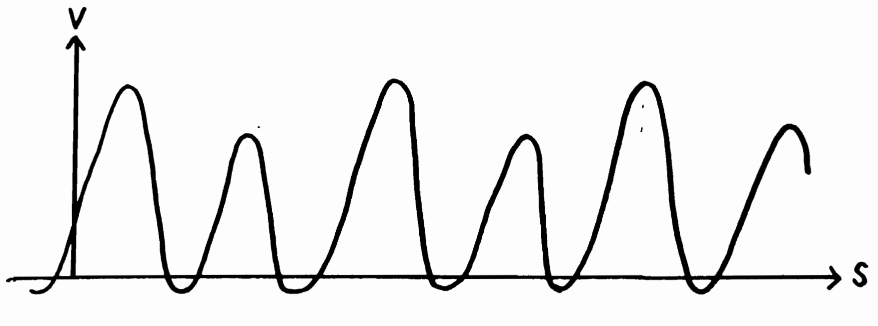

Fig.7 A periodic wave train which may occur if $l \geqslant 3$

A proof

We conclude with an outline of the proof that the existence of a singular periodic solution implies the existence of a periodic solution when $l = 1$. We introduce the notion of an *isolating block*, or *block*, as first used by Wazewski [9] and developed by Conley *et al.* [10, 11]. A periodic solution will correspond to a fixed point of a certain map whose existence is established using *Leray-Schauder degree* which, if $l = 1$, reduces to the winding number [12].

Consider the periodic singular solution depicted in Fig.3(B). We construct two blocks B_1 and B_2 about the left and right legs. For $\theta = \theta(y_p)$ and ϵ small, a periodic solution runs through these blocks and approaches the singular solution as $\epsilon \to 0$.

Let B_1 be diffeomorphic to $[0,1]^3$, as in Fig.8. B_1 may be constructed such that points on the front, bottom, and back of B_1 leave the block in forward time. These points form the exit set, b_1^-.

Points on the rest of ∂B_1 leave in backward time, and form the entrance set, b_1^+. The crucial property of a block is that the map, ϕ_1^-, which sends a point in B to the first point on its forward trajectory in b_1^- is continuous *where defined* [11]. (Observe Fig.9, in which B is a block and A is not.)

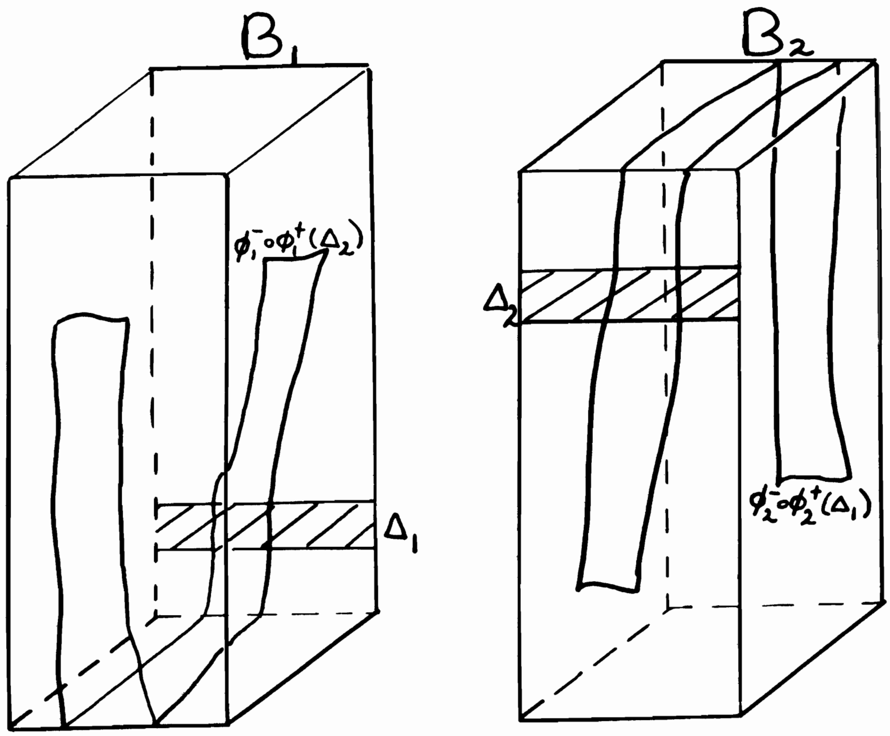

Fig.8 Blocks B_1, B_2 about the left and right legs of the periodic singular solution

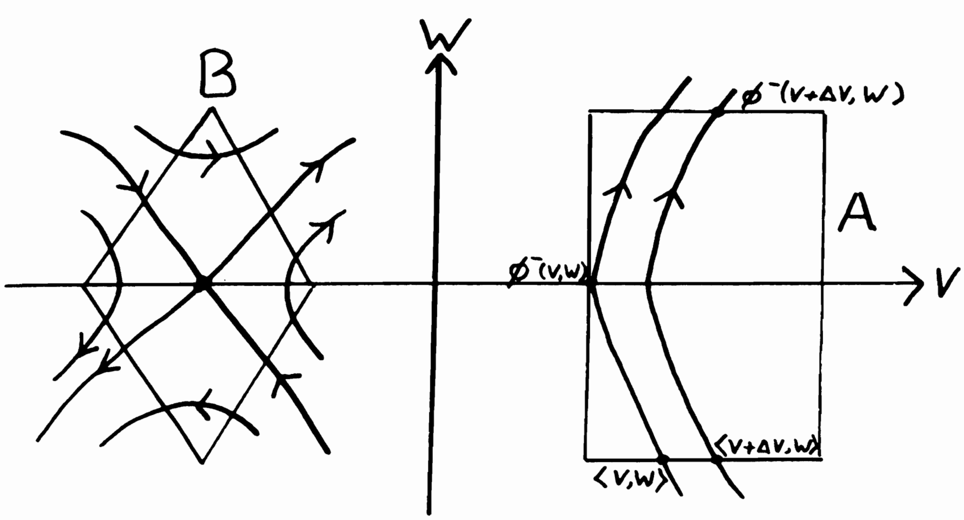

Fig.9 (A) ϕ^- is discontinuous at $\langle V,W\rangle$, and $a^+ \cup a^- \subsetneq \partial A$.
(B) ϕ^- is continuous but defined only off the stable manifold of the rest point

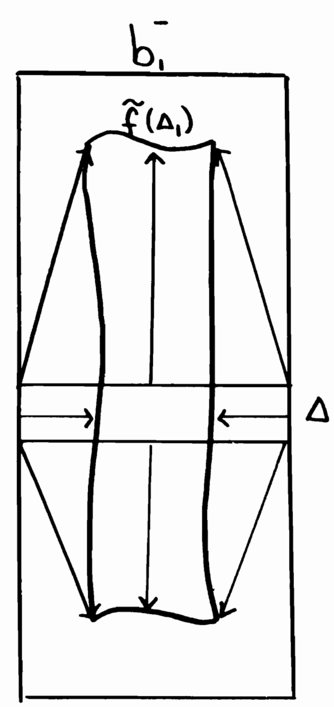

Fig.10 Projection of b_2^- onto $\mathbb{R}^2$

B_1 may be constructed so that no solution stays in it, so ϕ_1^- is defined in all of B_1. ϕ_1^+, similarly, is the map sending a point (in $\mathbb{R}^3$) to the first point if any in b_1^+. ϕ_1^+ is continuous at u if $\phi_1^+(u) \notin b_1^-$. B_2 is constructed symmetrically, with b_2^- the front, top, and back.

The fact that, when $\epsilon = 0$, there exists a solution from $\langle V_1(y_p), 0, y_p \rangle$ to $\langle V_2(y_p), 0, y_p \rangle$ allows us to construct a set Δ_1 spanning b_1^- with the property that ϕ_2^+ maps Δ_1 into $b_2^+ - b_2^-$. Moreover, the *top* of Δ_1 is mapped by $\phi_1^+ \circ \phi_2^-$ into the *back* of b_2^-; and the *bottom* of Δ_1 is mapped into the *front* of b_2^- (and well below $\{y = y_0'\}$). The continuity of $\phi_2^- \circ \phi_2^+$ then implies that $\phi_2^- \circ \phi_2^+(\Delta_1)$ forms a 'ribbon' running over the top of b_1^-; in particular it runs across Δ_2. Again, Δ_2 is defined symmetrically.

We now show that the map $f \equiv \phi_1^- \circ \phi_1^+ \circ \phi_2^- \circ \phi_2^+$ has a fixed point $\bar{u} \in \Delta_1$, i.e. $f(\bar{u}) = \bar{u}$. $\bar{u}$ is then contained in a periodic solution of the system (6)! Let π be a continuous map from b_2^- onto Δ_2 such that π is the identity on Δ_2, and points of $b_2^- - \Delta_2$ are mapped to $\partial\Delta_2$. Then $\tilde{f} \equiv \phi_1^- \circ \phi_1^+ \circ \pi \circ \phi_2^- \circ \phi_2^+$ maps Δ_1 into b_1^-. Project b_1^- onto the plane, as in Fig.10.

Associated with each $u \in \Delta_1$ is a vector $(\tilde{f}(u) - u)$. This vector field is nonzero on $\partial\Delta_1$ and has winding number ± 1. Thus the vector field has a zero in Δ_1, that is $\tilde{f}(\bar{u}) = \bar{u}$ for some $\bar{u} \in \Delta_1$. Since $\phi_1^- \circ \phi_1^+$ maps the top and bottom of Δ_2 into $b_1^- - \Delta_1$, $\bar{u}$ must have been mapped by $\phi_2^- \circ \phi_2^+$ into Δ_2. Thus $f(\bar{u}) = \tilde{f}(\bar{u}) = \bar{u}$.

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