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Abstract

We study the bifurcation of equilibrium points for a class of differential equations extending the Hodgkin and Huxley equations for the nerve impulse. The equations studied model the behaviour of a large class of excitable biological systems, allowing for an arbitrary number of ionic channels. We obtain a geometrical description of the subset in parameter space where there is a local bifurcation of the equilibrium points of the equation for generic functions governing ionic dynamics.

The set of local bifurcation parameter values is shown to be a singular ruled submanifold in parameter space. In particular we show that for an equation with generic ion dynamics and N channels, i.e. with $2N + 3$ parameters, there is at most a multiple equilibrium of order $2N + 2$. The bifurcation set is also studied numerically for the original Hodgkin and Huxley equations.

1 Introduction

The Hodgkin and Huxley equations [5] are one of the most successfull models in mathematical biology, providing good qualitative predictions of a nerve cell's behaviour in reasonable quantitative agreement with experimental observations. The equations are not entirely based on first principles but they correspond to the generally accepted biochemical description of nerve cell activity.

We study here the bifurcation of equilibria of a natural generalization, that we call *equations of Hodgkin-Huxley type with N channels*, of the form:

$$\begin{cases} \dfrac{dv}{dt} &= I + g_0(v - V_0) + \displaystyle\sum_{i=1}^{N} g_i u_i(y_i)(v - V_i) \\ \dfrac{dy_i}{dt} &= (\gamma_i(v) - y_i)\,\tau_i(v) \end{cases} \tag{1}$$

Each of the terms $g_i u_i(y_i)(v - V_i)$ in (1) refers to an *ionic channel.* The dynamics of the i-th channel depends on *gate variables* $y_i \in \mathbf{R}^{n_i}$ through a smooth function $u_i(y_i)$, $u_i : \mathbf{R}^{n_i} \longrightarrow \mathbf{R}$. The dynamics of each gate variable y_i depends only on itself and the voltage v through smooth functions $\gamma_i : \mathbf{R} \longrightarrow \mathbf{R}^{n_i}$ and a smooth diagonal matrix $\tau_i(v)$ with $\tau_{ij}(v) \neq 0$ for all v. We use the notation:

$$g = (g_1, \ldots, g_N) \qquad \text{and} \qquad V = (V_1, \ldots, V_N)$$

and we assume $g_j \neq 0$, for all $j \geq 0$, otherwise we have a Hodgkin-Huxley type equation with less than N channels.

The original Hodgkin and Huxley equations only involve two ionic channels plus the leakage channel responsible for the term $g_0(v - V_0)$ in (1). The equations describe a particular type of cell of a particular species, the giant axon of the squid, and have to be modified if they are to apply to another type of cell in the same species or to other animals. Models of the type above with a larger number of channels are used for many types of excitable tissue as for instance the crustacean motor axon [7], the pancreatic β-cell [1] or the cardiac cell [3].

Let $\psi_i : \mathbf{R} \longrightarrow \mathbf{R}$ be given by $\psi_i(v) = u_i(\gamma_i(v))$. The equilibrium points

of (1) are solutions of the equation:

$$\eta(v, g_0, g, V_0, V, I) = I + g_0(v - V_0) + \sum_{i=1}^{N} g_i \psi_i(v)(v - V_i) = 0 \qquad (2)$$

For a fixed value of the parameters (g_0, g, V_0, V), let η_0 be the function $v \mapsto \eta_0(v) = \eta(v, g_0, g, V_0, V)$. The number of zeros of η_0 depends on (g_0, g, V_0, V) and changes at parameter values where η_0 has a multiple zero. We show in Theorem 1 that if η_0 has a zero of order $k \leq 2N + 2$ at v_0 for some value of g_0, g, V_0 and V, then, under generic assumptions on the functions ψ_j, there are parameter values arbitrarily close to the initial one, where η has a zero of order l at a point v near v_0 for any $l < k$. In particular it follows that there are nearby parameter values where η_0 has k simple zeros near v_0. In this case we say that η is a versal unfolding of η_0 near v_0.

Theorems 2 and 3 describe the geometry of the sets S_L of parameter values where η_0 has a zero of order at least $L + 2$, again under generic assumptions on the $2N + 2$ first derivatives of the maps ψ_i. We show that S_L is empty for $L > 2N$.

When $g_k = 0$ for some k, the expression for η becomes independent of both g_k and V_k, yelding an equation with fewer channels. In this case, we prove that generically, the singular set $\mathbf{S}_L$, $L \leq 2N-2$ meets each hyperspace $g_k = 0$ transverselly at the singular set of the Hodgkin-Huxley equation with $N - 1$ channels, obtained when the k-channel is ommitted.

In the last section, we include a numerical study of the singular sets S_L for the original Hodgkin-Huxley equation. We verify that Hodgkin-Huxley's original data imply genericity and, moreover, there are no singularities of type $(v - v_0)^{2N-2} = (v - v_0)^6$, as the set $\mathbf{S}_{2N} = \mathbf{S}_4$ is empty.

2 Versality

When can a multiple zero of $\eta(v, g_0, g, V_0, V, I)$ be separated into simple zeros with an arbitrarily small change of parameters? This question can be answered within the framework of elementary singularity theory [2, 6]. Let η_0 be, as before, the function $v \mapsto \eta_0(v) = \eta(v, g_0, g, V_0, V)$, for a fixed value of the parameters. The equivalence class of C^∞ functions that agree with η_0 in a neighbourhood of a point $v = v_o$, called the germ of η_0 at $v = v_0$, is denoted by $\eta_0 : \mathbf{R}, v_0 \longrightarrow \mathbf{R}$.

Two germs η_0 at $v = v_0$ and $\bar{\eta}_0$ at $v = \bar{v_0}$ are contact equivalent or $\mathcal{K}$-equivalent, (denoted $\eta_0 \approx \bar{\eta}_0$) if there exists a germ of diffeomorphism $h : \mathbf{R}, \bar{v_0} \longrightarrow \mathbf{R}, v_0$, and a germ of a non-zero function $S : \mathbf{R}, v_0 \longrightarrow \mathbf{R}$ such that $S(v) \cdot \eta_0(h(v)) = \bar{\eta}_0(v)$.

Suppose $v \mapsto \eta(v, g_0, g, V_0, V, I) = \eta_0(v)$ has a zero of order k at $v = v_0$ for some value of the parameters (g_0, g, V_0, V, I), i.e. η_0 is contact-equivalent to $\pm(v - v_0)^k$. Let $\mathcal{E}(v - v_0)$ be the set of all germs at v_0 of smooth functions and let $T\mathcal{K}\eta$ be the tangent space of the contact-equivalence class of η_0. This is defined as the real vector space of germs given by:

$$T\mathcal{K}(\eta_0) = \{\phi \in \mathcal{E}(v - v_0) : \phi(v) = \eta'(v)\lambda(v) + \mu(v)\eta(v) \text{ with } \lambda, \mu \in \mathcal{E}(v - v_0)\}$$

We may obtain k simple zeros of η in a neighbourhood of v_0 and for nearby values of (g_0, g, V_0, V, I) if $\mathcal{E}(v - v_0) = T\mathcal{K}\eta + \Delta(\eta)$ where $\Delta(\eta)$ is the real vector space generated by the derivatives of η with respect to all the parameters, i.e. by the functions $\partial\eta/\partial g_j$ and $\partial\eta/\partial V_j$, $j = 0, 1, \ldots, N$ and $\partial\eta/\partial I$.

Showing that $\mathcal{E}(v - v_0) = T\mathcal{K}\eta + \Delta(\eta)$ is equivalent to showing that $\Delta(\eta)$ contains all the germs of monomials $(v - v_0)^j$, $j = 0, \ldots, k - 2$ modulo terms of degree k or higher.The generators of $\Delta(\eta)$ are:

parameter	derivative of η
g_0	$v - V_0$
V_0	$-g_0$
g_j	$\psi_j(v)(v - V_j)$
V_j	$-g_j\psi_j(v)$

Since we are assuming $g_0 \neq 0$, all monomials of degree 0 or 1 are accounted for by $\partial\eta/\partial g_0$, $\partial\eta/\partial V_0$ and $\partial\eta/\partial I$. The problem is reduced to showing the monomials $(v - v_0)^j$ are in $\Delta(\eta)$, for $j = 2, \ldots, k - 2$.

We can rewrite the generators of $\Delta(\eta)$ modulo terms of degree k or higher and subtracting terms of degree 0 and 1 as:

$$\frac{\partial \eta}{\partial V_j}(v) - \frac{\partial \eta}{\partial V_j}(v_0) - (v - v_0)\frac{\partial^2 \eta}{\partial V_j \partial v}(v_0) = g_j \sum_{i=2}^{k-2}(v - v_0)^i \frac{\psi_j^i}{i!}$$

and

$$\frac{\partial \eta}{\partial g_j}(v) - \frac{\partial \eta}{\partial g_j}(v_0) - (v - v_0)\frac{\partial^2 \eta}{\partial g_j \partial v}(v_0) = \sum_{i=2}^{k-2}(v - v_0)^i \left(\frac{\psi_j^i}{i!}(V_j - v_0) - \frac{\psi_j^{i-1}}{(i-1)!}\right)$$

where we denote by ψ_j^i the derivative $\dfrac{d^i \psi_j}{dv^i}(v_0)$.

Let $\mathbf{D}_L^N(v_0)$ be the $2N \times L$ matrix with lines

$$\left(g_j \frac{\psi_j^2}{2!}, \ldots, g_j \frac{\psi_j^{L+1}}{(L+1)!}\right)$$

$$\left(\frac{\psi_j^2}{2!}(V_j - v_0) - \psi_j^1, \frac{\psi_j^3}{3!}(V_j - v_0) - \frac{\psi_j^2}{2!}, \ldots, \frac{\psi_j^{L+1}}{(L+1)!}(V_j - v_0) - \frac{\psi_j^L}{(L)!}\right)$$

with $j = 1, \ldots, N$. If $\mathbf{D}_L^N(v_0)$ has maximal rank L, with $1 \leq L \leq 2N$, then all monomials of degree up to $L+1$ are in $\Delta(\eta)$.

The Taylor polynomial of degree k of η at $v = v_0$ is called the k-jet of η at $v = v_0$ and denoted by $j^k\eta(v_0)$. More generally, given $\psi : \mathbf{R} \longrightarrow \mathbf{R}^N$, $\psi = (\psi_1, \ldots, \psi_N)$, its k-jet is $j^k(\psi(v_0)) = \left(j^k(\psi_1(v_0)), \ldots, j^k(\psi_N(v_0))\right)$. The set of all k-jets forms the vector space $J^k(\mathbf{R}, \mathbf{R}^N)$ of dimension $(k+1)N$, with a subspace $J^k(1, N)$ consisting of jets of maps sending v_0 into the origin.

Theorem 1 *For generic functions $\psi_j(v)$, if for some value of the parameters $\eta(v, g_0, g, V_0, V, I)$ is $\mathcal{K}$-equivalent to $(v - v_0)^k$ with $k \leq 2N + 2$, then η is a versal unfoding of η_0 and thus an arbitrarily small change of parameters splits the singularity into k simple zeros in an arbitrarily small neighbourhood of v_0.*

Proof: Let $M_L(\psi(v_0))$ be the $2N \times L$ matrix with lines

$$\left(\frac{\psi_i^{(2)}}{2!}, \frac{\psi_i^{(3)}}{3!}, \ldots, \frac{\psi_i^{(L+1)}}{(L+1)!}\right)$$

$$\left(\psi_i^{(1)}, \frac{\psi_i^{(2)}}{2!}, \ldots, \frac{\psi_i^{(L)}}{L!}\right),$$

with $i = 1, \ldots, N$. Assuming that the parameters g_i are non zero, it follows that $\text{rank}D_L^N = \text{rank}M_L$. Let $V_{L+1} \subset J^{L+1}(R, R^N)$ be the set of $L+1$-jets $j^{L+1}(\psi)$ of maps ψ such that $M_L(\psi(v))$ fails to have maximal rank. For $L \leq 2N$, V_{L+1} is the algebraic variety defined as the zero set of the $L \times L$-minors of $M_L(\psi(v))$. Now, it is a simple consequence of Thom's Transversality Theorem that for each L, $1 \leq L \leq 2N$, there exists a residual set $\mathcal{G}(L)$ of mappings

$$\psi : \mathbf{R} \longrightarrow \mathbf{R}^N \qquad \psi(v) = (\psi_1, \psi_2, \ldots, \psi_N),$$

such that $j^{L+1}\psi$ is transverse to V_{L+1}. Notice that when $L \neq 2N$,the codimension of V_{L+1} is greater than 1, hence transversality will imply that $j^{L+1}(\psi)$ does not intersect V_{L+1}, i.e. $\text{rank}M_L(\psi) = L$. Let $\mathcal{G}$ be the intersection of all $\mathcal{G}(L)$, $1 \leq L \leq 2N$. Then, given any function ψ in $\mathcal{G}$ with a singularity at v_0 and $\mathcal{K}$-equivalent to $(v - v_0)^k$, with $k \leq 2N + 2$, it follows that $\mathcal{E}(v - v_0) = T\mathcal{K}\eta + \Delta(\eta)$.

When $L = 2N$, V_{2N+1} is a codimension one subvariety of $J^{2N+1}(1, N)$. Thus, for any $\psi \in \mathcal{G}$, $\det M_{2N}(\psi)(v) = 0$ only at isolated points where $M_{2N-1}(\psi)(v)$ has rank $2N-1$. We shall see in Theorem 2 that for a generic set of ψ, $\eta^{(2N+2)}$ will be non-zero at these points and therefore $\eta \approx (v - v_0)^{2N+2}$. □

3 The recognition problem

Introducing new parameters $W_j = V_j g_j$, expression (2) takes the form:

$$\eta(v, g_0, g, W_0, W, I) = I + g_0 v - W_0 + \sum_{i=1}^{N} g_i v\psi_i(v) - W_i\psi_i(v)$$

For any fixed value of v we can solve $\eta(v, g_0, g, W, I) = 0$ for $W_0 - I$ and $\partial\eta/\partial v = \eta'(v, g_0, g, W_0, W, I) = 0$ for g_0. For $k \geq 2$ the derivatives $\eta^{(k)}(v) = \partial^k\eta/\partial v^k$ do not depend on the parameters g_0, W_0 and I and are given by:

$$\eta^{(k)}(v, g, W) = \sum_{i=1}^{N} g_i \left(v\psi_i^{(k)}(v) + k\psi_i^{(k-1)}(v)\right) - W_i\psi_i^{(k)}(v) \qquad (3)$$

Let $\mathbf{A}_L^N(v_0)$ be the $L \times 2N$ coefficient matrix for the v-dependent linear equations on (g, W) given by $\eta^{(k)}(v_0, g, W) = 0$ for $k = 2, \ldots, L+1$. In general we expect to be able to solve $2N-1$ of these equations. For a given value v_0 of v we want to describe the local singular sets $\Sigma_L \subset \mathbf{R}^{2N}$, the germs at v_0 of the closure of the sets:

$$\left\{(g, W) : \eta(v, g_0, g, W_0, W, I) \approx (v - v_0)^{L+2} \text{ for some } I, g_0, W_0\right\}$$

Notice that for $L = 1, \ldots, 2N$ we have

$$\begin{aligned}\Sigma_L &= \left\{p \in \mathbf{R}^{2N} : \mathbf{A}_L^N(v) \cdot p = 0 \text{ for } v \text{ near } v_0\right\} \\ &= \left\{(g, W) : \exists v \text{ near } v_0 \text{ such that for } k = 2, \ldots, L+1 \quad \eta^{(k)}(v, g, W) = 0\right\}\end{aligned}$$

and thus $\Sigma_{2N} \subset \cdots \Sigma_{L+1} \subset \Sigma_L \cdots \subset \Sigma_1$.

Theorem 2 *For generic functions $\psi_j(v)$ and for $L = 1, \ldots, 2N$ the local singular set Σ_L is a generalized ruled cone at the origin of codimension $L-1$ with singularities on Σ_{L+1}. For $L > 2N$, the sets Σ_L are empty.*

Proof: The coefficient matrix $\mathbf{A}_L^N(v)$ has the same rank as the matrix $M_L(\psi)(v)$ used in the proof of Theorem 1. The residual set $\mathcal{G}$ can be refined to contain only map germs ψ such that $M_{2N+1}(\psi)(v)$ also has rank $2N$ for all v, in the following way: consider the codimension $2N+1$ algebraic variety V_{2N+2} of $J^{2N+2}(R, R^N)$ given by the zeros of the $2N \times 2N$-minors of $M_{2N+1}(\psi(v))$;

then for ψ in the residual set $\mathcal{G} \cap \mathcal{G}(2N+1)$ the rank of $\mathbf{A}_L^N(v)$ is L for $L < 2N$. Moreover $\mathbf{A}_{2N}^N(v)$ has rank $2N$ for all values of v except at isolated values v_0 where $\text{rank}\mathbf{A}_{2N}^N(v_0) = \text{rank}\mathbf{A}_{2N-1}^N(v_0) = 2N-1$ and $\text{rank}\mathbf{A}_{2N+1}^N(v_0) = 2N$. Therefore, for generic ψ, for each $L < 2N$ and each $v \in \mathbf{R}$, the solutions of $\mathbf{A}_L^N(v)(g, W) = 0$ lie on a codimension L vector subspace of $\mathbf{R}^{2N}$. For isolated values of v_0 the solutions of $\mathbf{A}_{2N}^N(v_0)(g, W) = 0$ lie on a line through the origin, coinciding with the solutions of $\mathbf{A}_{2N-1}^N(v_0)(g, W) = 0$.

Let $f_L : \mathbf{R} \times S^{2N-1} \longrightarrow \mathbf{R}^L$ be given by $f_L(v, p) = \mathbf{A}_L^N(v) \cdot p$ for $L < 2N$. By the implicit function theorem, it follows that $f_L = 0$ defines locally a codimension L submanifold of $\mathbf{R} \times S^{2N-1}$. Moreover, $\partial f_L / \partial v(v, p) = P_1\left(\mathbf{A}_{L+1}^N(v) \cdot p\right)$, where P_1 is the projection from $\mathbf{R}^{2N}$ onto $\mathbf{R}^{2N-1}$ that 'forgets' the first coordinate. For $L < 2N$, the restriction to $f_L = 0$ of the map $(v, p) \mapsto p$ is singular when $\mathbf{A}_{L+1}^N(v) \cdot p = 0$, i.e. on $\Sigma_{L+1} \cap S^{2N-1}$.

When $L = 2N-1$ the same argument applies to all values of v where $\mathbf{A}_{2N}^N(v)$ has rank $2N$. Near those isolated values v_0 where both $\mathbf{A}_{2N-1}^N(v_0)$ and $\mathbf{A}_{2N}^N(v_0)$ have rank $2N-1$ the expression $f_{2N-1}(v, p) = \mathbf{A}_{2N-1}^N(v) \cdot p = 0$ defines a curve $(v, p(v))$ in $\mathbf{R} \times S^{2N-1}$ projecting into a curve in S^{2N-1} with a singularity at $p(v_0)$: at these points $p'(v_0) = 0$ and since $\mathbf{A}_{2N+1}^N(v_0)$ has rank $2N$ and $\partial^2 f_{2N-1} / \partial v^2(v_0, p(v_0)) = P_1(P_1(\mathbf{A}_{2N+1}^N(v_0) \cdot p(v_0)))$ it follows that $p''(v_0) \neq 0$. □

In the original parameters (g, V) the local singular sets are the germs at v_0 of the sets

$$\mathbf{S}_L = \text{closure}\left\{(g, V) : \eta(v, g_0, g, V_0, V, I) \approx (v - v_0)^{L+2} \text{ for some } I, g_0, V_0\right\}.$$

The local description of $\mathbf{S}_L$ is given in two ways. In the first we use the maps $b_j : (g_j, W_j) \mapsto (g_j, V_j) = (g_j, W_j / g_j)$ to send $\Sigma_L - \bigcup_j \{g_j = 0\}$ into a singular manifold contained in $\mathbf{S}_L$, non singular whenever Σ_L is smooth. The map $b : \mathbf{R}^{2N} - \bigcup_j \{g_j = 0\} \longrightarrow \mathbf{R}^{2N} - \bigcup_j \{g_j = 0\}$ given by

$$b(g_1, \ldots, g_N, W_1, \ldots, W_N) = (g_1, \ldots, g_N, W_1/g_1, \ldots, W_N/g_N)$$

is a diffeomorphism that blows-up the cone Σ_L at the origin. Its inverse b^{-1} can be extended to $\mathbf{R}^{2N}$, sending the subspace $\mathbf{S}_\infty = \bigcap_j \{g_j = 0\}$ into the origin of $\mathbf{R}^{2N}$.

At points of $\mathbf{S}_L$ not in the image of the blow-up, g_k must be zero for some k. In that case the expression for η is independent of both g_k and V_k, yelding

an equation with fewer channels. We relate the singular sets $\mathbf{S}_L$ for a generic system with $N > 1$ channels to the singular set $\mathbf{S}_L(k)$ of the Hodgkin-Huxley type equation with $N-1$ channels obtained omitting the k-th channel. By induction the picture is complete when the special case $N = 1$ is studied.

Theorem 3 *For an equation of Hodgkin-Huxley type with N channels and generic functions $\psi_j(v)$, the local singular set $\mathbf{S}_L$ for $L = 1, \ldots, 2N$ is a codimension $L-1$ singular submanifold of $\mathbf{R}^{2N}$ singular at $\mathbf{S}_{L+1}$. For $L > 2N$, $\mathbf{S}_L = \emptyset$ and for each $L \leq 2N$, $\mathbf{S}_L$ is a generalized ruled manifold, with rulings parallel to the subspace $\bigcap_j \{V_j = 0\} \subset \mathbf{R}^{2N}$. There are two local descriptions for $\mathbf{S}_L$:*

1. *All points $(g, V) \in \mathbf{S}_L$ with $g_j \neq 0 \ \forall j$ are in $b(\Sigma_L - \bigcup_j \{g_j = 0\})$.*
2. *For $L \leq 2N-2$ the singular set $\mathbf{S}_L$ meets each hyperspace $\{g_j = 0\}$ transverselly at $\mathbf{S}_L(j)$. For $N > 1$ and $L = 2N-1$ or $2N$, $\mathbf{S}_L \cap \{g_j = 0\} \subset \mathbf{S}_\infty$ for all j.*

Proof: The residual set of Theorem 2 can be refined again to yeld, for $N > 1$, a generic system with the same properties after removal of each channel. When one channel is omitted, $\mathrm{rank}\mathbf{A}_L^{N-1}(v)$ is still maximal for $L \leq 2N-2$, except for a discrete set of values v_0 such that $\mathrm{rank}\mathbf{A}_{2N-2}^{N-1}(v_0) = 2N-3$ and $\mathrm{rank}\mathbf{A}_{2N-1}^{N-1}(v_0) = 2N-2$.

The map $b : \Sigma_L - \bigcup_j \{g_j = 0\} \longrightarrow \mathbf{R}^{2N}$ takes each line $(\lambda g, \lambda V)$, $\lambda \neq 0$ through the origin in $\mathbf{R}^{2N} - \bigcup_j \{g_j = 0\}$ into the line $(\lambda g, V)$ with $V_j = W_j/g_j$ for all $j = 1, \ldots, N$. Since b is a diffeomorphism of $\mathbf{R}^{2N} - \bigcup_j \{g_j = 0\}$ this proves assertion 1.

For $N > 1$, let $f_L : \mathbf{R} \times \mathbf{R}^{2N} \longrightarrow \mathbf{R}^L$ be given by

$$f_L(v, g, V) = (\eta^{(2)}(v, g, V), \ldots, \eta^{(L+1)}(v, g, V)).$$

At a point (v, g, V) with $g_k = 0$ for some k and $g_j \neq 0$ for $j \neq k$, the derivative of f_L has the same rank as $\mathbf{A}_L^N(v)$ and f_L is a submersion for $L \leq 2N-2$. This shows that $\{f_L = 0\}$ is transverse to $\{g_k = 0\}$ in $\mathbf{R}^{2N+1}$. We may proceed as in the proof of Theorem 2, to show that the restriction to $\{f_L = 0\}$ of the map $(v, g, V) \mapsto (g, V)$ is thus non singular whenever $(g, V) \in \mathbf{S}_L - \mathbf{S}_{L+1}$.

In order to show that $\mathbf{S}_L = \emptyset$ for $L > 2N$, let

$$\sigma_L = \left\{ \begin{array}{l} (g,V) : \eta(v,g_0,g,V_0,V,I) \approx (v-v_0)^{L+2} \\ \text{for some } I, g_0, V_0 \text{ and } v \text{ near } v_0 \end{array} \right\}.$$

A necessary condition for (g,V) to be in σ_L is $\eta''(v,g_0,g,V_0,V,I) = \cdots = \eta^{(L+1)}(v,g_0,g,V_0,V,I) = 0$. For $N = 1$ and $L > 2$, genericity implies $\mathbf{A}_1^1(v)$ has rank 1 and a direct calculation shows that the necessary condition is satisfied if and only if either $\text{rank}\mathbf{A}_3^1(v) < 2$ or $g_1 = 0$. Genericity rules out the first possibility and if $g_1 = 0$, then $\eta(v,g_0,g_1,V_0,V_1,I) = g_0(v-V_0)+I$ is clearly not $\mathcal{K}$-equivalent to $(v-v_0)^{L+2}$ with $L > 2$. Thus $\sigma_L = \emptyset$ and $\mathbf{S}_L = \emptyset$.

For $N > 1$ and $L > 2N$, we already know $\Sigma_L = \emptyset$ and thus

$$b^{-1}\left(\sigma_L - \bigcup_j \{g_j = 0\}\right) \subset \Sigma_L$$

is also empty. By induction we have $\mathbf{S}_L(k) = \emptyset$ and therefore $\sigma_L \cap \{g_k = 0\} \subset \mathbf{S}_L(k)$ is also empty, showing $\mathbf{S}_L = \emptyset$.

In particular, we have also proved that $\sigma_{2N-1} \cap \{g_k = 0\} = \emptyset$. It remains to show that points in σ_{2N-1} cannot accumulate on the hyperspaces $\{g_k = 0\}$ anywhere outside $\mathbf{S}_\infty$. First we observe that the genericity of the ψ_j when the k-th channel is removed guarantees that $\text{rank}\mathbf{A}_{2N-1}^{N-1}(v) = 2N-2$ for all $v \in \mathbf{R}$. Thus $(g,W) \mapsto \mathbf{A}_{2N-1}^{N-1}(v)(g,W)$ is clearly an injective linear map from $\mathbf{R}^{2N-2}$ into $\mathbf{R}^{2N-1}$ for each V. Therefore any non trivial solution of $\mathbf{A}_{2N-1}^{N}(v)(g,g_k,W,W_k) = 0$ with $g_k = 0$ satisfies $W_k \neq 0$ i.e. $\Sigma_{2N-1} \cap \{g_k = 0\} \subset \{0\} \cup \{W_k \neq 0\}$ for each k, thus showing that $\mathbf{S}_{2N-1} \subset \mathbf{S}_\infty$. □

Notice that although η is linear in $\mathbf{S}_\infty$, this subspace is also a bifurcation set for the equations.

4 The original Hodgkin-Huxley equations

As an example, the original Hodgkin-Huxley equations are treated numerically in this section. This is a system with two channels, corresponding to Na and K ions. In the original notation the first equation in (1) is:

$$\frac{\partial v}{\partial t} = -\bar{g}_{Na} m^3 h (v - \overline{V}_{Na}) - \bar{g}_K n^4 (v - \overline{V}_K) - \bar{g}_0 (v - \overline{V}_0) + I$$

and thus in our notation,

$$u_1(y_{11}, y_{12}) = y_{11}^3 y_{12} = u_{Na}(m, h) = m^3 h \qquad u_2(y_{21}) = y_{21}^4 = u_K(n) = n^4$$

and

$$\psi_1(v) = \psi_{Na}(v) = \gamma_m^3(v)\gamma_h(v) \qquad \psi_2(v) = \psi_K(v) = \gamma_n^4(v).$$

In the Hodgkin and Huxley article [5] the functions γ_j are fitted to experimental data and are given in the form

$$\gamma_j(v) = \frac{\alpha_j(v)}{\alpha_j(v) + \beta_j(v)}$$

for $j = m$, n or h, where

$$\begin{array}{lllllll} \alpha_m(v) & = & \varphi((v+25)/10) & & \beta_m(v) & = & 4e^{v/18} \\ \alpha_n(v) & = & 0.1\varphi((v+10)/10) & & \beta_n(v) & = & 0.125e^{v/80} \\ \alpha_h(v) & = & 0.07e^{v/20} & & \beta_h(v) & = & \left(1 + e^{(v+30)/10}\right)^{-1} \end{array}$$

$$\text{with} \qquad \varphi(x) = \begin{cases} x/(e^x - 1) & \text{if } x \neq 0 \\ 1 & \text{if } x = 0 \end{cases}$$

Notice that $\alpha_j(v) + \beta_j(v) \neq 0$ for all v and j.

The functions $\gamma_j(v)$ of [5] were chosen to be almost constant outside an interval. They are monotonic, asymptotically 1 or 0 at $\pm\infty$. Their derivatives tend to zero very fast as v tends to $\pm\infty$ and the same is true *a fortiori* of derivatives of $\psi_i(v)$ (see figure1). We restrict our study to values of v where results may be significant both from a physiological and from a numerical point of view.

For single channel equations, both $\det M_2(\psi_K(v))$ and $\det M_2(\psi_{Na}(v))$ are never found to be zero (figure 2); note that $\det M_2(\psi_i(v))$ and the

Schwartzian derivative of ψ_i [4] always have opposite signs. The genericity conditions of Theorems 1–3 hold and the singular set $\mathbf{S}_2$ is empty.

When only the K channel is present, the singular set $\mathbf{S}_1$ is given by

$$\{(g_K, V_K) : V_K = v + 2\psi_K'(v)/\psi_K''(v), \qquad v \in \mathbf{R}\} \subset \mathbf{R}^2$$

forming a double (K) cover of $\mathbf{R}^2$ (figure 3). Thus, for each $(g_K, V_K) \in \mathbf{R}^2$, with $g_K \neq 0$, there are two values of the parameters g_0 and $g_0 V_0 - I$ such that $\eta_0(v) = \eta(v, g_0, 0, g_K, V_0, 0, V_K, I)$ has a triple zero. Similarly, there are three parameter values for g_0 and $g_0 V_0 - I$ where $\eta_0(v) = \eta(v, g_0, g_{Na}, 0, V_0, V_{Na}, 0, I)$ has three triple zeros.

The set $\mathbf{S}_0$ of fold points (double zeros) defines a curve in two dimensional slices of parameter space, with isolated singularities on $\mathbf{S}_1$ like those in figure 4. For the K channel the two cusp points appear on very different scales. In order to understand figure 4A and B, one must recall that $g_0 = 0$ may also be a bifurcation line. Only for very small positive values of g_0 can we find more than one zero of $\eta_0(v)$. The fold curve for the Na channel appears to be closed (figure 4C).

The genericity conditions of Theorems 1–3 also hold for the two channel Hodgkin and Huxley equations, since $\det M_4(\psi_{Na}(v), \psi_K(v))$ is also never zero for v in the interval $[-300, 100]$ (figure 5) and thus $\mathbf{S}_4$ is empty.

Recall that $\mathbf{S}_3$ is a ruled surface of the form $(V_{Na}(v), V_K(v), \lambda g_{Na}(v), \lambda g_K(v))$. Thus $\mathbf{S}_3$ is completely defined by its intersection with the affine subspace $g_K = 1$, a curve with many branches separated where either g_{Na} or g_K tends to zero (figure 6). Only on a small part of the curve can we find g_{Na} and g_K with the same sign. Assuming $g_j > 0$ for all j, the presence of a large number of zeros seems to be restricted to a narrow range of parameters. Figure 7 shows the intersection of $\mathbf{S}_0$ with several planes in parameter space, all parallel to the subspace $I \times g_0$ of $\mathbf{R}^6$.

5 Acknowledgements

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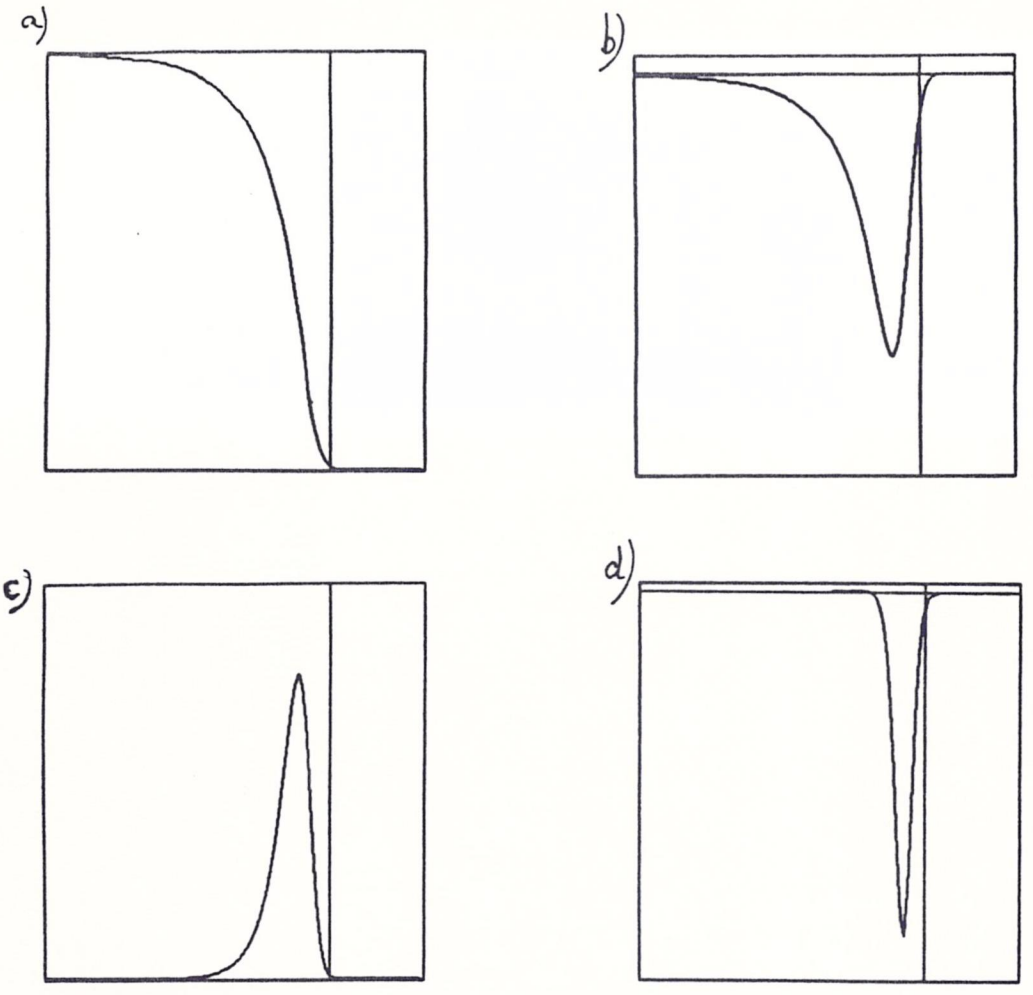


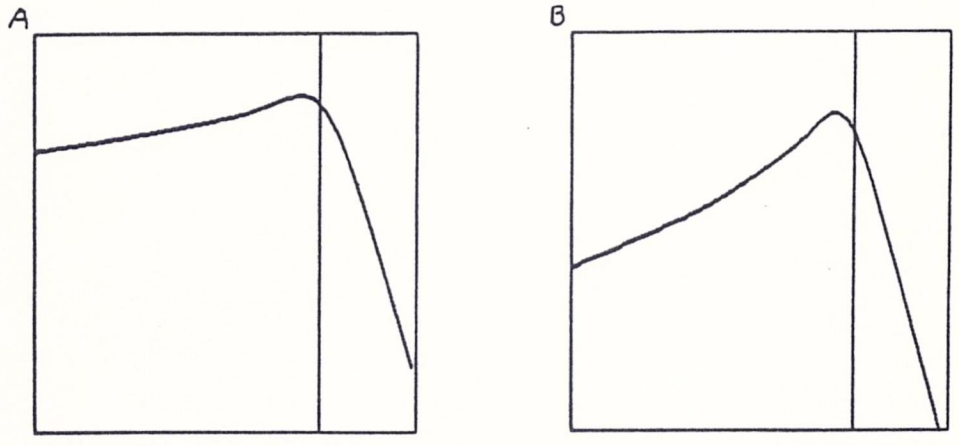
1. Graphs of $\psi_{Na}(v)$ and $\psi_K(v)$ and their derivatives for the original Hodgkin and Huxley equations. Scales:

   (a) $v \in [-300, 100]$, $\psi_K(v) \in [0, 1]$.

   (b) $v \in [-300, 100]$, $\psi'_K(v) \in [-0.2, 0.001]$.

   (c) $v \in [-300, 100]$, $\psi_{Na}(v) \in [0, 0.01]$.

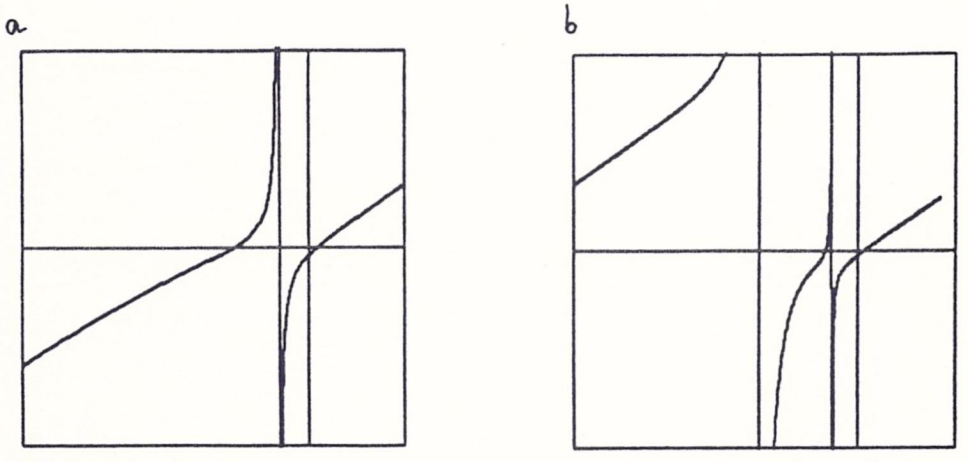
   (d) $v \in [-300, 100]$, $\psi'_{Na}(v) \in [-0.0007, 0.00002]$.



2. The genericity conditions of Theorems 1–3) are satisfied by single channel equations with the original Hodgkin and Huxley dynamics. For both Na and K ions, $\det M_2(\psi_{ion}(v)) > 0$:

   (a) $v \in [-300, 100]$, $\log \det M_2(\psi_K(v)) \in [-100, 0]$.

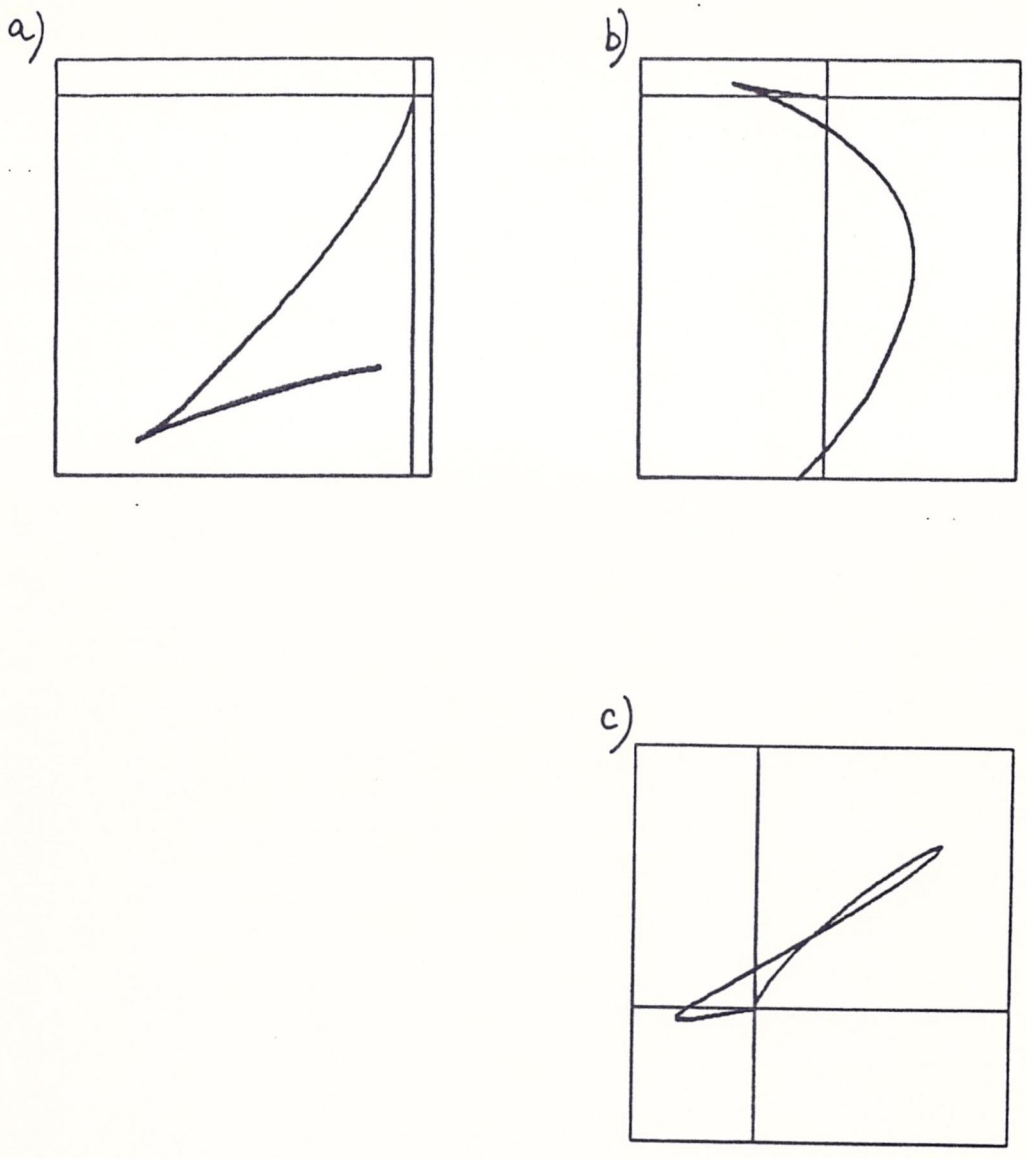
   (b) $v \in [-300, 100]$, $\log \det M_2(\psi_{Na}(v)) \in [-100, 0]$.



3. For single channel Hodgkin and Huxley equations, the singular set $\mathbf{S}_1$ of cusp points is a 'ruled surface' in $\mathbf{R}^2$ of horizontal lines of the form $(g_{ion}, V_{ion}(v))$ with $g_{ion} \in \mathbf{R}$ and $V_{ion}(v) = v + 2\psi'_{ion}(v)/\psi''_{ion}(v)$.

   (a) Graph of $V_K(v)$, $v \in [-300, 100]$, $V_K \in [-300, 300]$.

   (b) Graph of $V_{Na}(v)$, $v \in [-300, 100]$, $V_{Na} \in [-300, 300]$.

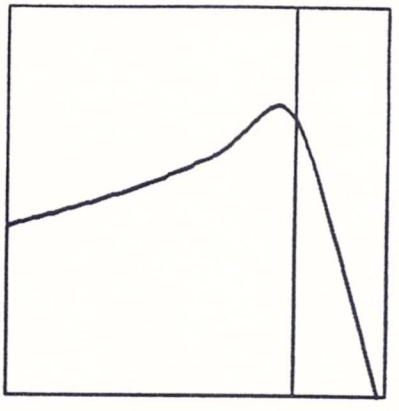


4. Curve of fold points in the $I \times g_0$ plane for single channel Hodgkin and Huxley equations, all other parameters (V_0, g_{ion}, V_{ion}) at original Hodgkin and Huxley values.

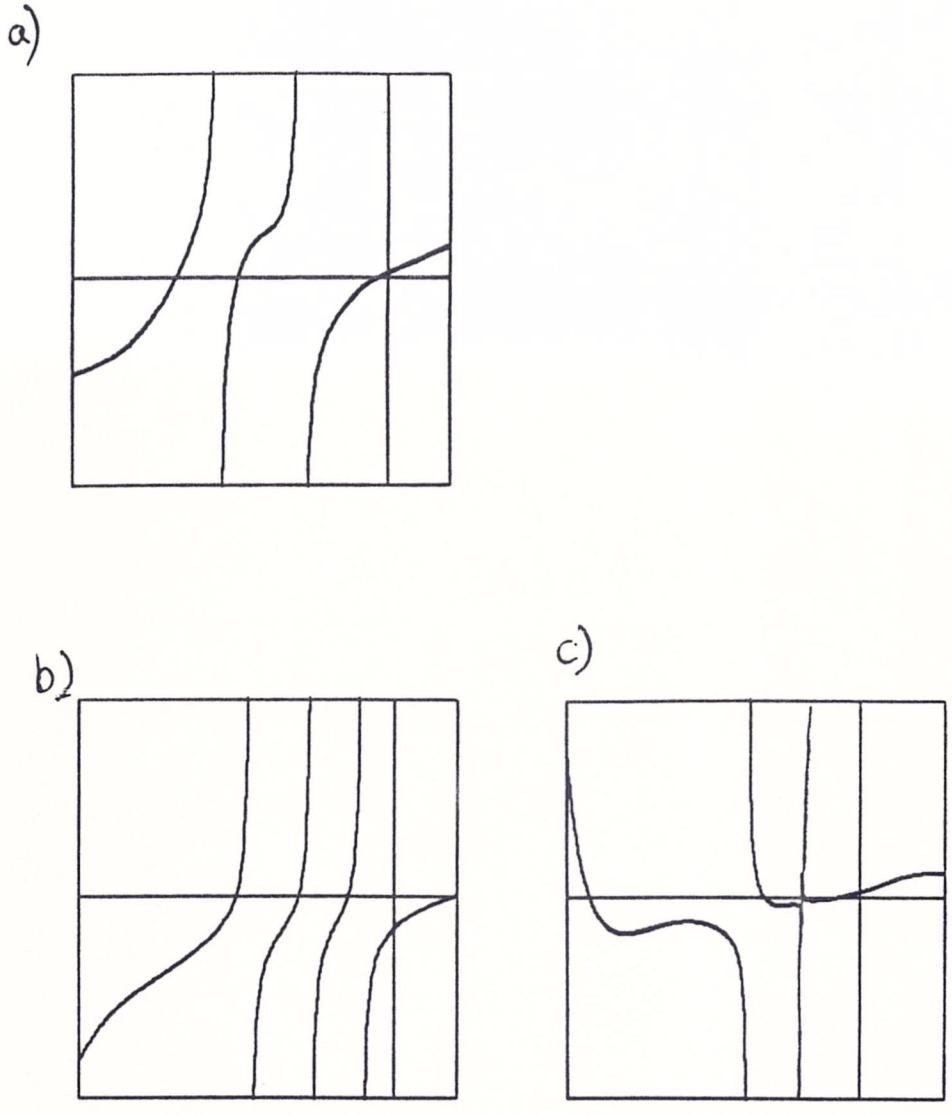
   (a) K channel, $v \in [-300, 100]$, $I \in [-2000, 100]$, $g_0 \in [-50, 5]$.

   (b) Detail of K channel, $v \in [0, 50]$, $I \in [-0.1, 0.1]$, $g_0 \in [-0.1, 0.01]$.

   (c) Na channel, $v \in [-300, 100]$, $I \in [-100, 200]$, $g_0 \in [-5, 10]$.



5. The genericity conditions of Theorems 1–2 are satisfied by the original Hodgkin and Huxley equations since $\det M_4(\psi_{Na}(v), \psi_K(v)) < 0$. Graph of $\log(-\det M_4) \in [-200, 0]$ for $v \in [-300, 100]$.



6. The singular set $\mathbf{S}_3$ for the original Hodgkin and Huxley equations: graphs of $(V_{Na}(v)$, $V_K(v)$ and $g_{Na}(v)/g_K(v))$. Scales:

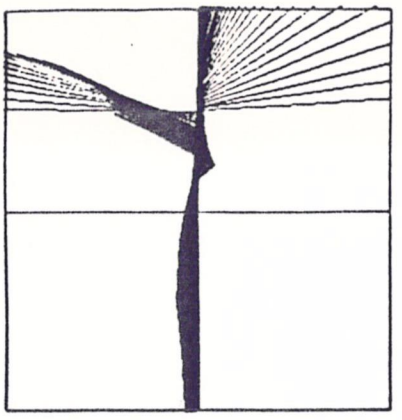
   (a) $v \in [-100, 20]$, $V_K \in [-150, 150]$;

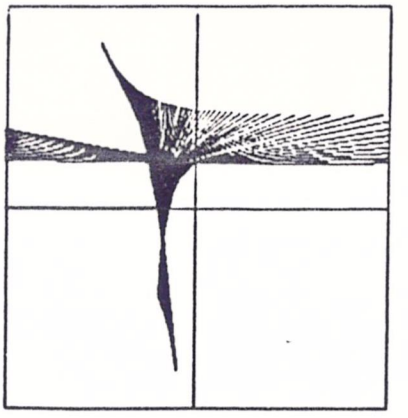
   (b) $v \in [-100, 20]$, $V_{Na} \in [-150, 150]$;

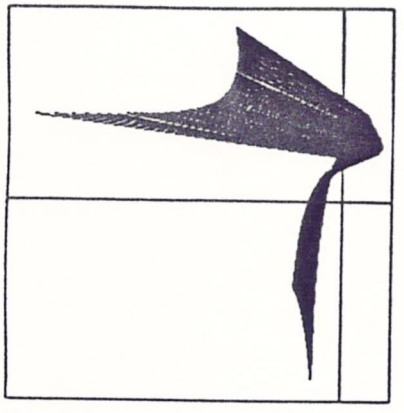
   (c) $v \in [-140, 40]$, $g_{Na}/g_K \in [-800, 800]$;

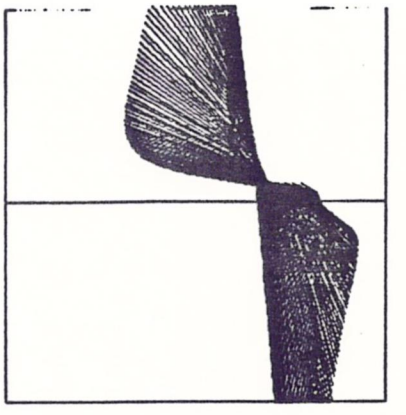
7. Curves of fold points in the $I \times g_0$ plane for the original Hodgkin and Huxley equations at different parameter values. In all cases, V_L has the original Hodgkin and Huxley value of 10.6, other values as in the table below. Figure A uses the original Hodgkin and Huxley values.

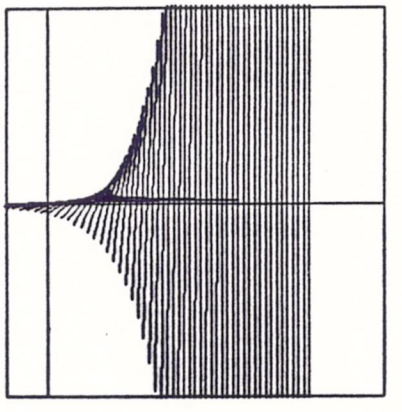
	v		I		g_0		g_{Na}	V_{Na}	g_K	V_K
A	-1000	100	-2000	200	-50	5	120	-115	36	12
B	-600	100	-2500	1000	-60	40	1000	-115	36	12
C	-1000	100	-2000	2000	-50	100	1200	-115	12	-100
D	-1300	40	-1500	150	-13	7	1200	-10	12	-100
E	-800	100	-2000	200	-50	5	120	100	36	12
F	-500	100	-700	100	-20	5	120	100	3.6	12
G	-500	100	-700	100	-20	5	120	100	12	0
H	-800	100	-2500	250	-100	10	1000	100	12	0











8. Projections of the singular set $\mathbf{S}_2$ into the plane $V_K \times g_{Na}/g_K$ for the original Hodgkin and Huxley equations.

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