J. Theoret. Neurobiol. **4**, 61–71 (1985)
Printed in Australia

REPOLARIZING CURRENTS AND PERIODIC ACTIVITY IN NERVE MEMBRANE*

A. V. HOLDEN,[1] M. A. MUHAMAD[2] and A. K. SCHIERWAGEN[3]

(Received February 25, 1985)

Abstract

Equilibrium solutions of membrane excitation equations lose their stability, and give rise to periodic solutions, at Hopf bifurcation points. These occur in response to a depolarizing applied current, or a reduced repolarizing current, produced by either a reduction in the maximal potassium conductance $\bar{g}_K$, or a shift in the Nernst potential for K^+. In both the $V_K - I$ and the $g_K - I$ plane there is a region where there are 3 equilibrium solutions: this is the projection of a cusp catastrophe.

1. Introduction

The electrical activity of isopotential neuronal membrane may be represented by an excitation equation of the form

$$dV/dt = F(V,x,y) \tag{1}$$

with $x\varepsilon[0,1]^l$ and $y\varepsilon[0,1]^k$ the l-activation and k-inactivation gating variables controlling voltage dependent ionic conductances. The Hodgkin-Huxley system is an example of an excitation equation, with two activation variables (m and n) and an inactivation variable h; other excitable membranes have different number of gated conductances and gating variables. Mathematical and comparative aspects of excitation systems are reviewed in Holden (1982) and Holden and Winlow (1984).

The quasi-threshold behaviour of an excitable membrane is determined by the fast

*Address all correspondence to: A. V. Holden, Centre for Nonlinear Studies, The University, Leeds LS2 9NQ, England.

[1]Reader in General Physiology, Centre for Nonlinear Studies, The University, Leeds, LS2 9NQ, U.K.
[2]Jabatan Fisiologi, Fakulti Perubatan, Universiti Malaya, Lembah Pantai, Kuala Lumpur, West Malaysia.
[3]Carl-Ludwig-Institut fur Physiologie, 7010 Leipzig, Liebigstrasse 27, GDR.

processes that give rise to the upswing of the action potential: this is the basis of the two-dimensional reduced V-m system of FitzHugh (1960). However, with the exception of the giant axons of escape systems of invertebrates, an action potential in a neurone has little consequence on the behaviour of an animal. The normal operating mode of a neuron is an irregular, repetitive discharge. This repetitive activity may be idealized as periodic solutions of the membrane excitation system.

Periodic solutions are influenced by the ionic currents that produced repolarization and that flow during the interspike interval: these are K^+-selective currents. For a uniformly polarized membrane with some independent conductance systems g_j in parallel with a capacity C_m the membrane current I_m can be described by the equation

$$I_m = C_m \frac{dV}{dt} + \sum_j g_j(V - V_j) \tag{2}$$

where V is the membrane voltage and $g_j = g_j(V)$ are the voltage-controlled conductances for ion species $j = 1, 2, \ldots$. The corresponding electro-chemical equilibrium potential V_j is determined by the Nernst formula

$$V_j = \frac{RT}{zF} ln\left[\frac{C_o}{C_i}\right]$$

where z is the valence of the ion, C_i and C_o are the inside and outside ion concentrations, respectively, and $\frac{RT}{F}$ is the usual constant.

The number and kind of the conductances determine membrane behaviour of different complexity. If only a single species of ion is permeable through the membrane, i.e. for $i = 1$, inexcitability follows as the $I_m - V$ relation for a single conductance can have only a single root $I_m = 0$ that is necessarily stable. The minimal number of conductances required for excitation is two to generate the N-shaped $I_m - V$ relation that characterizes excitability. Thus the nodal membrane of rabbit myelinated nerve seems to be one of the simplest possible excitable membranes (Chiu *et al.*, 1979).

The standard H-H model involves three conductances g_{Na}, g_K and g_L, which is a constant. The time and voltage dependence of g_{Na} and g_K is given as

$$g_{Na} = \bar{g}_{Na} m^3 h; g_K = \bar{g}_K n^4 \tag{3}$$

where the bar denotes maximal conductances (mS/cm^2), and the activation and inactivation variables follow first order kinetics.

$$\frac{dx}{dt} = \alpha_x(1 - x) - \beta_x x \tag{4}$$

for $x = m, h, n$ and the rate coefficients α_x, β_x are voltage dependent.

Recent voltage clamp results show that the membranes of the soma and of the presynaptic terminal of molluscan nerves are more complex than that of the axon (Kandel, 1980). Thus it is now established that there are at least three independent

K^+ channels in the cell body membrane (Hagiwara *et al.*, 1961; Neher & Lux, 1971; Meech, 1974): an early or fast K^+ conductance g_A, a conventional slow H-H K^+ conductance g_K (both g_A and g_K are controlled by activation and inactivation processes), and a calcium activated K^+ conductance $g_{K(Ca)}$ that overlaps in time with the slow g_K. Each of these repolarization conductances is implicated in rhythmic activity, though in different ways: the fast g_A is considered to be instrumental in determining the repetitive discharge characteristics by changing the interspike interval, g_K contributes to the repolarization phase of the action potential, and $g_{K(Ca)}$ may be responsible for modulation of firing behaviour (Heyer & Lux, 1978).

All the major currents of the molluscan neuronal cell body can also be found in vertebrate neurons, including those of mammals, whose neuron somata can contain an even richer variety of conductances (Llinas, 1984). Some of these newly discovered conductance systems can be described by H-H like equations, as for example the early or fast K^+ conductance g_A of Connor and Stevens which is analogous to the transient outward current described by Gustaffson *et al.* (1982) in hippocampal CA3 neurons of the guinea pig.

In spite of the great number and staggering variety of conductances found in both vertebrate and invertebrate neuron somata, the original H-H model still provides a framework for the analysis of the functional role of the ionic currents in the electrical behaviour of neuronal excitable membranes.

2. Methods

The membrane current density and potential for an isopotential patch of membrane were given by the standard 6.3°C 1952 Hodgkin-Huxley equations, with a maintained applied current I, and the maximal potassium conductance $\bar{g}_K$ and the Nernst potential for potassium V_K treated as bifurcation parameters. Numerical solutions were obtained using the simple Euler method of integration, with an integration step of 0.02 ms, with specified initial conditions (V, m_0, h_0, n_0).

The Jacobian matrix for the Hodgkin-Huxley system, evaluated at a stationary point where $dV/dt = dm/dt = dh/dt = dn/dt = 0$, is

$$\begin{bmatrix} -\frac{\partial F}{\partial V} & -\frac{\partial F}{\partial m} & -\frac{\partial F}{\partial n} & -\frac{\partial F}{\partial h} \\ \gamma_m m'_\infty & -\gamma_m & 0 & 0 \\ \gamma_n n'_\infty & 0 & -\gamma_n & 0 \\ \gamma_h h'_\infty & 0 & 0 & -\gamma_h \end{bmatrix}$$

with $\gamma_x = \alpha_x + \beta_x$, for $x = m, n, h$, and $F(V, m, n, h)$ given by the Hodgkin-Huxley membrane equations.

The eigenvalues of this Jacobian were calculated using algebraic methods, and the characteristics were evaluated according to the methods of Marsden and McCracken (1976). Calculations were performed in BASIC on a microcomputer (Zilog MCZ 1/20), and in FORTRAN 77 on the University of Leeds mainframe Amdahl V/470. Further details are given in Holden and Schierwagen (1985).

3. Results

The Hodgkin-Huxley equations may be driven into repetitive activity by a maintained depolarizing current density, a decrease in the maximal K^+ conductance, or by moving the Nernst potential for K^+ in the depolarizing direction. In all these cases large amplitude period solutions are obtained, as illustrated in Fig. 1, which shows a family of solutions arising from a standard initial condition as V_K is moved towards the standard resting potential.

Although such large amplitude periodic solutions correspond to a repetitive dis-

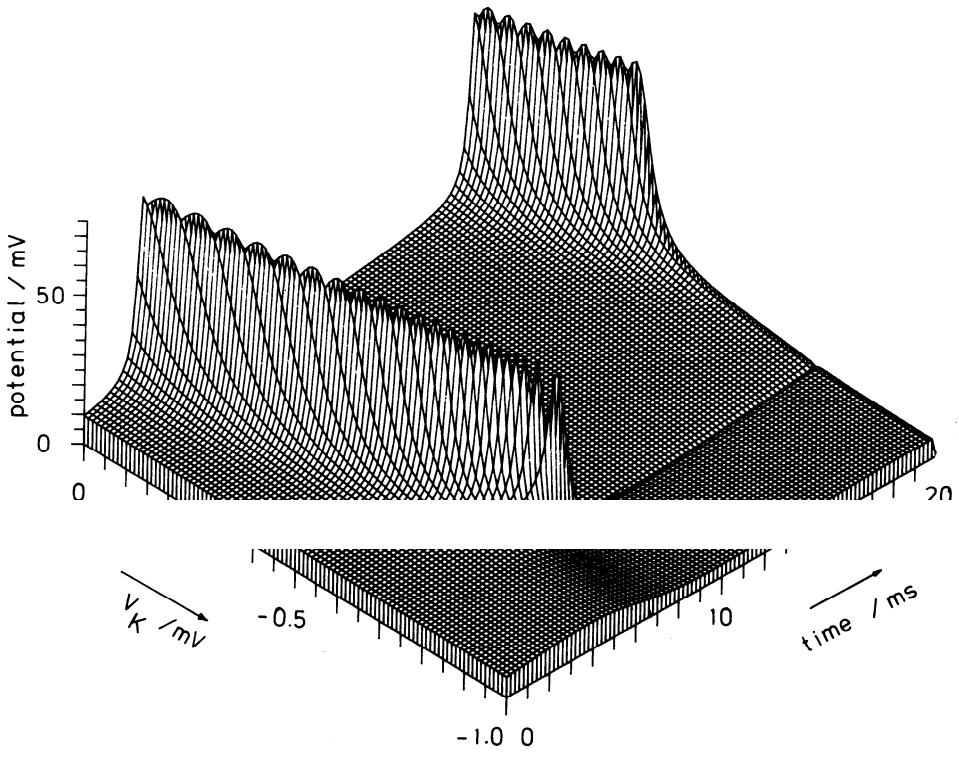

Fig. 1. Numerical solutions of the standard Hodgkin-Huxley membrane equations as the Nernst potential for K^+, V_K, is moved in the depolarizing direction from -5 mV towards the standard resting potential of 0 mV. The standard V_K is -12 mV.

charge of action potentials, one would expect small amplitude periodic solutions to emerge as the equilibrium solution loses its stability. The equilibrium solution is unstable if any of its eigenvalues have positive real parts: at a Hopf bifurcation a single complex conjugate pair of eigenvalues crosses the imaginary axis. Numerical evaluation of the eigenvalues show, that as a depolarizing current I is increased, or the maximal K^+ conductance is decreased, or as V_K moves in the depolarizing direction, a single complex conjugate pair of eigenvalues crosses the imaginary axis (Hassard, 1978; Holden and Yoda, 1981). Thus Hopf bifurcations into small amplitude periodic solutions occur. For the standard Hodgkin-Huxley equations at 6.3°C, these Hopf bifurcations occur at I close to 9.8 μA cm^{-2}, and g_K close to 19.7 mS cm^{-2}, and V_K close to -1.9 mV. In all these three cases the small amplitude periodic solutions that emerge are unstable: they are subcritical Hopf bifurcations. The unstable periodic solutions that emerge at such a subcritical Hopf bifurcation will not be seen in experiments, or in numerical integrations: they will provide the transient

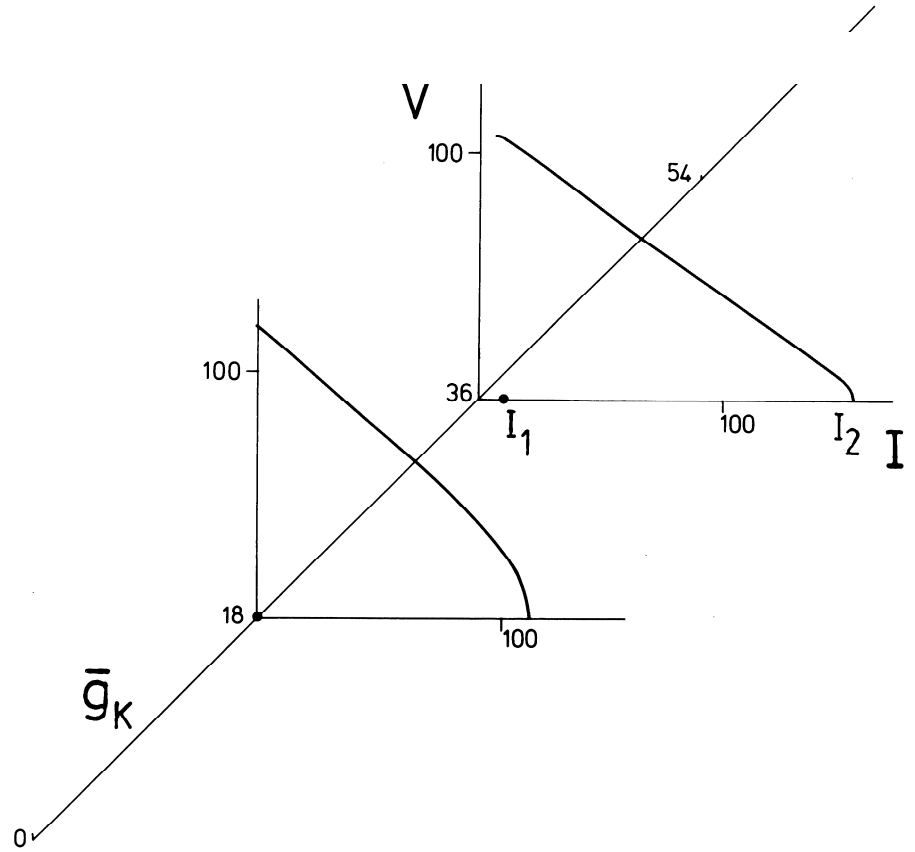

Fig. 2. Peak-to-peak amplitude v of periodic solutions of the standard Hodgkin-Huxley equations as the depolarizing current density is increased, for $\bar{g}_K$ of 18 and 36 mS cm^{-2}. Filled circles mark subcritical Hopf bifurcations; I_1 and I_2 are the sub- and the supercritical Hopf bifurcation points for the standard, unmodified H-H membrane equations driven by a depolarizing current density.

pathway to the stable, large amplitude periodic solutions that correspond to action potentials.

Just below such a subcritical Hopf bifurcation, there is a narrow range of the bifurcation parameter within which there is a stable, large amplitude, periodic solution, an unstable, small amplitude periodic solution, and a stable equilibrium solution. Thus there is the possibility of the annihilation of a repetitive discharge of action potentials within this parameter range, by an appropriate perturbation (Best, 1979); this has been seen experimentally (Guttman *et al.*, 1980).

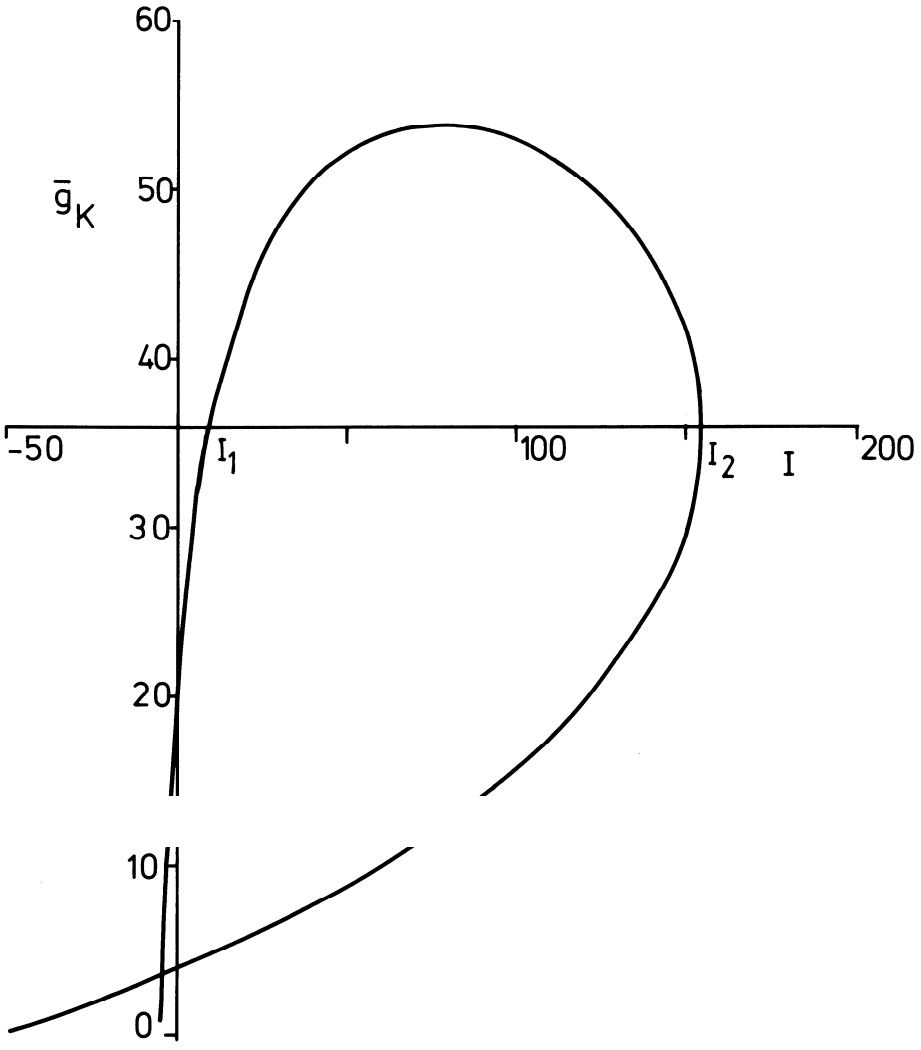

Fig. 3. Hopf bifurcation curve in the $\bar{g}_K - I$ plane. Where the curve crosses over itself there is a region of multiple equilibria.

The peak-to-peak amplitude of the periodic solutions produced by a maintained depolarizing current density decreases as the current density increases, until the periodic solutions vanish in a stable, depolarized, equilibrium solution. This depolarized equilibrium solution emerges at a supercritical Hopf bifurcation. This is shown for two values of maximal potassium conductance in Fig. 2: the small amplitude, stable periodic solutions found close to the bifurcation into the stable, depolarized equilibrium will be seen in experiments and numerical integrations.

The Hopf bifurcation points when two parameters are changed form curves in the plane of those parameters. For the parameters $\bar{g}_K$ and I all the bifurcation points fall on a single curve in the plane $\bar{g}_K - I$ as shown in Fig. 3. The curve crosses over itself at low $\bar{g}_K$ and hyperpolarizing current densities, as under such conditions there is a cusp-shaped region where there are three equilibrium solutions, and the two Hopf bifurcations are from different equilibrium solutions (Holden *et al.*, 1983).

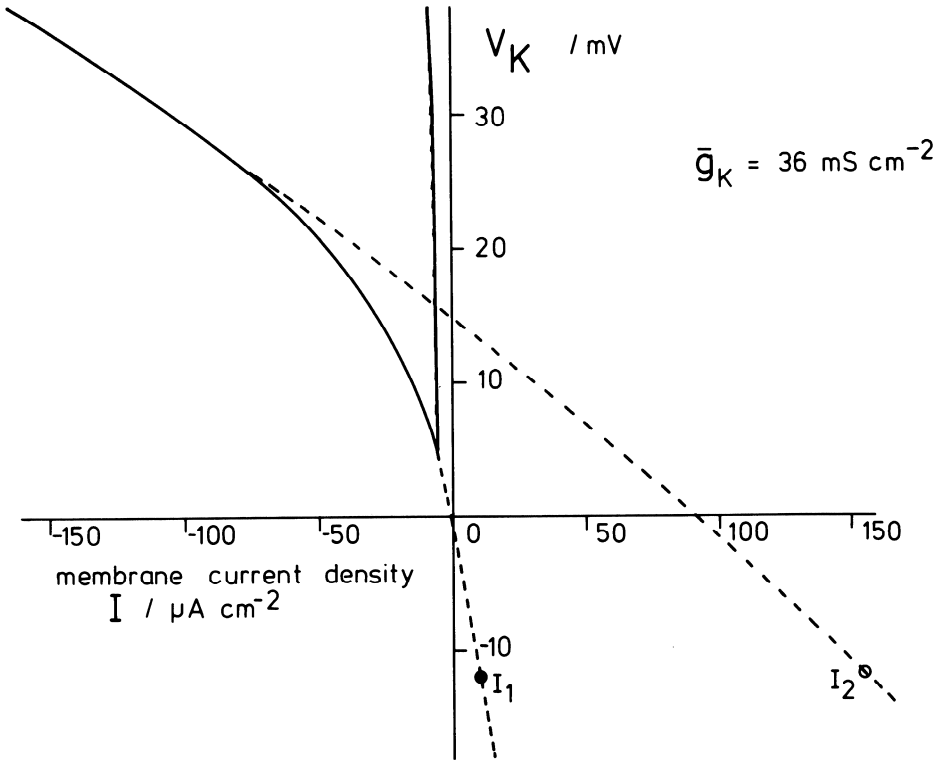

Fig. 4. Bifurcation curves in the $V_K - I$ plane. I_1 and I_2 are the same Hopf bifurcation points as in Fig. 3; the dashed lines are the Hopf bifurcation curves and the solid curves enclose a region where there are three equilibrium solutions.

Such a region of multiple equilibria is also found with hyperpolarizing current densities as V_K is moved in the depolarizing direction. These three equilibrium solutions occur in the interior of the solid curves in Fig. 4 and 5, where the dashed curves represent the Hopf bifurcation curves. The region of multiple equilibria in the plane $V_K - I$ is the projection of a cusp.

The extent of this region of multiple equilibria increases in the $V_K - I$ plane as $\bar{g}_K$ is lowered: Fig. 5.

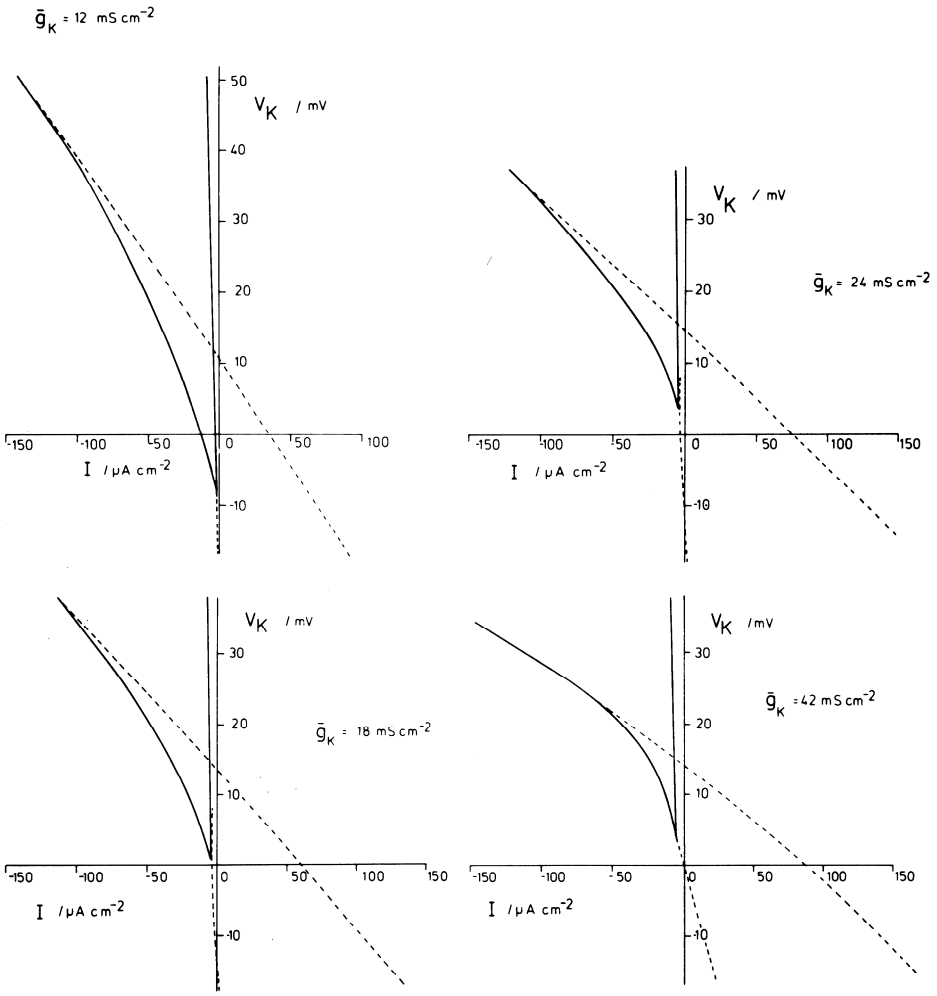

Fig. 5. Bifurcation curves in the V_K plane at different values of $\bar{g}_K$. Solid curves enclose the region of multiple equilibria, the dashed lines are the Hopf bifurcation curves.

4. Discussion

Repolarization currents, with reversal potentials close to, or more negative than the resting membrane potential, are usually thought of as contributing to the repolarization of the action potential. However, Na^+-inactivation, in the presence of a voltage-independent leakage conductance, is sufficient for repolarization, and provides the mechanism of repolarization in the nodal membrane of mammalian myelinated fibres.

The numerical studies described here emphasize the role of repolarizing currents in the control of endogenous, periodic activity. Whether or not a membrane is resting or autorhythmic is determined by the stability of the equilibrim solution of its excitation equation (2): for the modifications of the Hodgkin-Huxley membrane equations considered here, the equilibrium loses its stability at a Hopf bifurcation.

The repolarizing current is the product of a conductance and a driving potential for a conductance pathway with a linear instantaneous current-voltage relation. A Hopf bifurcation occurs when the K^+-current is reduced by a reduction in either the maximal K^+-conductance (or potassium channel density) or in the driving potential. $(V-V_K)$. In both these cases there is a subcritical bifurcation into small amplitude periodic solutions that are unstable, and so large amplitude periodic solutions that correspond to a repetitive discharge of action potentials are seen in numerical integrations. Thus, as the repolarizing current is being reduced, there is a narrow region where a stable equilibrium or stable large-amplitude periodic solutions are possible, before the equilibrium loses its stability at the Hopf bifurcation point. Within this region small, appropriately timed perturbations could initiate or annihilate the repetitive activity. If a membrane becomes autorhythmic by a gradual reduction in $\bar{g}_K$ or a gradual accumulation of $[K^+]_o$ the onset of repetitive activity will be marked by irregular bursts, as the membrane is switched between the two stable states of silence and repetitive activity.

Multiple equilibria are found in the presence of a hyperpolarizing current when the repolarizing current is reduced by a reduction in either $\bar{g}_K$ or by a shift of V_K in the depolarizing direction. At one of these equilibrium solutions the sum of the Na^+ and K^+ currents is equal and opposite to the sum of the leakage current and the applied hyperpolarizing current, and so the applied hyperpolarizing current is equivalent to an increased leakage conductance.

A membrane with a low $\bar{g}_K$ and a restricted extracellular space, within which the accumulation of K^+ can occur, will be liable to develop behaviour associated with multiple equilibria: the low $\bar{g}_k$ leads to autorhythmicity, which gives an increase in $[K^+]_o$, and a shift in V_K in the depolarizing direction. Membrane potential trajectories would show repetitive activity, bursting, and complicated, paroxysmal depolarizing shifts, similar to those seen in central neurones during epileptic discharges. This behaviour would be prone to develop when the leakage conductance was high, or when the cell was damaged. Although an increase in $[K^+]_o$ from 3 to 10 to 12 mM is seen during experimental epileptogenesis (see review by Prince and

Schwartzkroin, 1978), this appears to be a consequence, rather than a cause, of the convulsant activity.

In the region of multiple equilibria, a plot of the equilibrium value of the potential V against the applied current density I is a section through a cusp, and so the current-voltage relation is "N"-shaped, or has the characteristics of a cubic.

References

Best, E. N. (1979). Null space in the Hodgkin-Huxley equations: a critical test. *Biophys. J.* **27**, 87–104.

Chiu, S. Y., Ritchie, J. M., Rogart, R. B. and Stagg, D. (1979). A quantitative description of membrane currents in rabbit myelinated nerve. *J. Physiol. (Lond.)* **292**, 149–166.

Connor, J. A. and Stevens, C. F. (1971). Prediction of repetitive firing behaviour from voltage clamp data on an isolated neurone soma. *J. Physiol. (Lond.)* **213**, 31–59.

FitzHugh, R. (1969). Mathematical models of excitation and propagation in nerve. In, *Biological Engineering.* H. P. Schwann (ed.), pp. 1–85. McGraw-Hill: New York.

Gustafsson, B., Galvan, M., Grafe, P. and Wigstrom, H. (1982). A transient outward current in a mammalian central neurone blocked by 4-aminopyridine. *Nature (Lond.)* **299**, 252–254.

Guttman, R., Lewis, S. and Rinzel, J. (1980). Control of repetitive firing in squid axon membrane as a model for a neuroneoscillator. *J. Physiol. (Lond.)* **305**, 377–395.

Hagiwara, S., Kusano, K. and Saito, N. (1961). Membrane changes of *Onchidium* nerve cells in potassium-rich media. *J. Physiol. (Lond.)* **155**, 470–489.

Hassard, B. D. (1978). Bifurcation of periodic solutions of the Hodgkin-Huxley model for the squid giant axon. *J. Theoret. Biol.* **71**, 401–420.

Heyer, C. B. and Lux, H. D. (1978). Unusual properties of the Ca-K system responsible for prolonged action potentials in neurones from the snail *Helix Pomatia.* In, Chalazonitis, N. and Boisson, M. (eds) *Abnormal neuronal discharges.* Raven: New York.

Hodgkin, A. L. and Huxley, H. E. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)* **117**, 500–544.

Holden, A. V. (1982). The mathematics of excitation. In, *Biomathematics in 1980.* L. M. Ricciardi and A. C. Scott, eds, pp. 15–48. North-Holland: Amsterdam.

Holden, A. V., Haydon, P. G. and Winlow, W. (1983). Multiple equilibria and exotic behaviour in excitable membranes. *Biol. Cybernetics* **46**, 167–172.

Holden, A. V. and Schierwagen, A. K. (1985). Numerical methods for locating and identifying bifurcation points in excitation systems. (In preparation.)

Holden, A. V. and Winlow, W. (1984). Comparative neurobiology of excitation. In, *The Neurobiology of Pain.* A. V. Holden and W. Winlow (eds), pp. 3–28. Manchester Univ. Press, Manchester, U.K. and Dover, New Hampshire, USA.

Holden, A. V. and Yoda, M. (1981). Ionic channel density of an excitable membrane can act as a bifurcation parameter. *Biol. Cybernetics* **42**, 29–38.

Kandel, E. R. (1980). The multichannel model of the nerve cell membrane: a perspective. In, *Molluscan Nerve Cells — from Biophysics to Behaviour.* J. Koestler and J. H. Byrne (eds), pp. 1–10. Cold Spring Harbor Laboratory.

Llinas, R. (1984). Comparative electrobiology of mammalian central neurons. In, *Brain slices.* R. Dingledine (ed.), pp. 7–24. Plenum: New York.

Marsden, J. E. and McCracken, M. (1976). *The Hopf Bifurcation and its Applications.* 408 p. Springer-Verlag: Berlin, Heidelberg and New York.

Meech, R. W. (1974). The sensitivity of *Helix aspersa* neurones to injected calcium ions. *J. Physiol. (Lond.)* **237**, 259–277.

Neher, E. and Lux, M. D. (1971). Properties of somatic membrane patches of snail neurons under voltage clamp. *Pflug. Arch. ges. Physiol.* **322**, 35–38.

Prince, D. A. and Schwartzkroin, P. A. (1978). Nonsynaptic mechanisms in epileptogenesis. In, *Abnormal neuronal discharges.* N. Chalazonitis and M. Boisson (eds), pp. 1–12.