J. Math. Biology (1984) 19: 211–225

Journal of
Mathematical
Biology

The dynamics of recurrent inhibition

M. C. Mackey[1] and U. an der Heiden[2]

[1] Department of Physiology, McGill University, 3655 Drummond Street, Montreal, Quebec, Canada, H3G 1Y6

[2] Universität Bremen NW2, Forschungsschwerpunkt "Biosystems Research", D-2800 Bremen 33, Federal Republic of Germany

Abstract. A heuristic model for the dynamics of recurrent inhibition, emphasizing non-linearities arising from the stoichiometry of transmitter–receptor interactions and time delays due to finite feedback pathway transmission times, is developed and analyzed. It is demonstrated that variation in model parameters may lead to the existence of multiple steady states, and the local stability of these are analyzed as well as the occurrence of switching behaviour between them. As an example of the applicability of this model, parameters are estimated for the hippocampal mossy fibre-CA3 pyramidal cell-basket cell complex. Numerically simulated responses of this system to alterations in presynaptic drive and titration of inhibitory transmitter receptors by penicillin are presented. Numerical simulations indicate the existence of multiple bifurcations between periodic solutions, as well as the existence of bifurcations to chaotic solutions, as presynaptic drive and receptor density are varied. It is hypothesized that the model offers insight into the sequences of events recorded in single CA3 pyramidal cells following the application of penicillin, a specific inhibitory receptor blocking agent.

Key words: lateral inhibition — recurrent inhibition — delayed feedback — multiple steady states — chaos — epilepsy — hippocampus — receptor physiology — difference-differential equations

I. Introduction

Recurrent inhibition, in which activity in a population of neurons excites a second population that in turn inhibits the activity of the first, is ubiquitous throughout the nervous system. The widespread occurrence of recurrent inhibition has intrigued many investigators, and generated considerable speculation concerning its functional significance.

In this paper, a simple mathematical model for a recurrent inhibitory neural feedback system is developed and investigated analytically and numerically. The model, framed in terms of a nonlinear functional (time delay) differential equation,

is a particular member of a large class of models which are known to display a rich spectrum of dynamical behaviour.

The organization of the paper is as follows. In the next section, based on known and presumably important neurophysiological aspects of recurrent inhibition, the model is developed. Particular attention is paid to nonlinearities introduced by the stoichiometry of inhibitory transmitter–receptor interactions, and the role of feedback pathway delays. It is demonstrated that the dynamic behaviour of the model is dependent on four internal parameters plus the level of presynaptic activity. Section III analytically examines the steady states of the model and their local stability as a function of model parameters. It is possible to show that under certain circumstances multiple steady states exist, and that alteration of model parameters will lead to switching between these steady states. This switching behaviour may display hysteresis. Furthermore, these steady states may be stable, corresponding to sustained activity, or unstable and thus give rise to periodic or aperiodic firing patterns. In the fourth section an attempt is made to estimate the model parameters from data obtained in studies of recurrent inhibition in the hippocampus. The response of the model to an experimentally accessible procedure, titration of inhibitory transmitter receptors by penicillin is examined. In the fifth and final section, some extensions of the model to more physiologically realistic situations are discussed.

II. Formulation of the model

The model considered here for recurrent inhibition considers three populations of neurons. These populations are the *presynaptic fibres*, which are excitatory to the *postsynaptic cells*, and the *inhibitory interneurons*. The interneuronal population is activated by axon collaterals from the postsynaptic cells and, in turn, returns an inhibitory input to the postsynaptic cells. Rather than dealing with populations of cells, it is assumed that, in the first approximation, each population may be replaced by a single "average" cell.

The postsynaptic cell has an input given by

$$E(t)-I(t),$$

where $E(t)$ is the excitatory postsynaptic potential (EPSP) due to activity in the presynaptic cell, and $I(t)$ is the inhibitory postsynaptic potential (IPSP) arising from activity in the inhibitory interneuron. Both $E(t)$ and $I(t)$ are measured in millivolts (mV) relative to the resting potential of the postsynaptic cell.

The output of the postsynaptic neuron is in the form of action potentials occurring at an instantaneous frequency $F(t)$, measured in Hertz (Hz). Here it is assumed that this postsynaptic cell output is given simply by

$$F(t)=\varkappa\cdot\vartheta(E(t)-I(t)-\theta), \tag{1}$$

where

$$\vartheta(x)=\begin{cases}0 & \text{if } x\leqslant 0\\ x & \text{if } x\geqslant 0\end{cases}.$$

In Eq. (1), the constant $\varkappa$ (Hz/mV) is the slope of the firing frequency versus postsynaptic cell input relationship and θ, measured in mV relative to the postsynaptic cell resting potential, is the threshold.

Activity in the postsynaptic cells activates the inhibitory interneurons, causing action potentials to be conducted along their axons which arrive at the synaptic terminals at a frequency $\tilde{F}(t)$. The arrival of an action potential at the inhibitory interneuron synaptic terminals leads to the release of inhibitory transmitter. This, in turn, diffuses across the synaptic cleft to combine with a receptor on the postsynaptic cell. The effect of this transmitter–receptor complex is to generate the IPSP, $I(t)$. However, due to the resistive–capacitive properties of the postsynaptic cell membrane this inhibitory potential will decay at a characteristic rate γ (msec^{-1}).

Combining the above sequence of events, the dynamics of the IPSP will be determined by

$$\frac{dI}{dt} = -\gamma I + \eta \tilde{F}. \tag{2}$$

η(mV) is a time-dependent inhibitory interaction coefficient given by

$$\eta(t) = TV_m G(\tilde{F}(t)). \tag{3}$$

In Eq. (3), T is the average number of inhibitory postsynaptic receptors per cell and V_m (mV) is the inhibitory potential resulting from activation of one receptor. The fraction of inhibitory receptors available for activation by transmitter is given by $G(\tilde{F})$.

To determine $G(\tilde{F})$ is is necessary to consider the stoichiometry of the transmitter–receptor interaction. Of the total receptor population T, L are active (combined with transmitter), and M are inactive. Here it is assumed that the receptor–transmitter interaction is governed by

$$M + nC \rightleftharpoons L,$$

where n is the number of molecules of transmitter (C) required to activate one receptor. If this reaction is sufficiently rapid to be at equilibrium, and conservation of receptors is assumed (i.e. $T = M + L$), then it is straightforward to show that the fraction of receptors available for activation is

$$\frac{K}{K + [C]^n},$$

where K is the equilibrium constant for the transmitter–receptor reaction, and $[C]$ is the concentration of transmitter.

If it is assumed that the pool of inhibitory transmitter is sufficiently large not to be depleted by interneuronal activity, then the relation between released transmitter levels and interneuron firing frequency will be $[C] = m\tilde{F}$, where m is a constant. Thus, the function $G(\tilde{F})$ is given by

$$G(\tilde{F}) = \frac{K}{K + (m\tilde{F})^n}. \tag{4}$$

Our final task is to relate the frequency of arrival of action potentials at the interneuron synaptic terminals ($\tilde{F}$) to the frequency of generation of action potentials in the postsynaptic cell (F). Here it is assumed that activity in the postsynaptic cell at a frequency $F(t)$ requires a finite time τ to be translated into activity at the synaptic terminals of the inhibitory interneuron. Thus we take

$$\tilde{F}(t) = \alpha F(t-\tau), \tag{5}$$

where α is to be interpreted as the reciprocal of the number of action potentials in the postsynaptic cell required to elicit one interneuronal action potential.

Equations (1) through (5) may be combined to give

$$\frac{dI(t)}{dt} = -\gamma I(t) + \alpha T V_m F(t-\tau) \frac{K}{K + (m\alpha F(t-\tau))^n} \tag{6}$$

and

$$F(t) = \varkappa \vartheta(E(t) - I(t) - \theta). \tag{7}$$

Equations (6) and (7), in conjunction with an initial condition $I(t) = I_0(t)$, $-\tau \leqslant t \leqslant 0$, and a specification of $E(t)$, form a complete description of the simplified recurrent inhibitory feedback neuronal network.

Equations (6) and (7) contain a number of parameters. This number can be reduced by rescaling the system.

Moreover it will facilitate later analysis and computation if (6) and (7) are rewritten in dimensionless form. Thus, the following notation is introduced:

$$\begin{aligned} \bar{t} &= t/\tau & \psi^n &= K(\tau/m\alpha)^n \\ e(\bar{t}) &= E(t)/\theta & \Gamma &= \gamma\tau \\ i(\bar{t}) &= I(t)/\theta & \beta &= \alpha T \psi V_m/\theta \\ f(\bar{t}) &= \tau F(t)/\psi & H &= \tau\varkappa\theta/\psi. \end{aligned} \tag{8}$$

Using (8), Eqs. (6) and (7) may be written as

$$\frac{di(\bar{t})}{d\bar{t}} = -\Gamma i(\bar{t}) + \beta g(f(\bar{t}-1)) \tag{9}$$

and

$$f(\bar{t}) = H\vartheta(e(\bar{t}) - i(\bar{t}) - 1) \tag{10}$$

where

$$g(f) = \frac{f}{1+f^n}. \tag{11}$$

Thus the dynamics of the recurrent inhibitory neuronal feedback model are dependent on the four parameters β, Γ, H, and n, and the normalized EPSP, $e(\bar{t})$.

III. Steady states and local stability

Henceforth it is assumed that the EPSP is constant in time, $e(\bar{t}) = e$. In a steady state, all quantities appearing in (9) through (11) are independent of $\bar{t}$ and the

steady state values of the IPSP and postsynaptic cell firing frequency, denoted by i^* and f^*, are given by the solutions of

$$f^* = H\vartheta(e - i^* - 1) \tag{12}$$

and

$$\frac{\Gamma}{\beta} i^* = g(f^*). \tag{13}$$

As shown below, the pair of Eqs. (12), (13) may have one, two, or three solutions depending on the values of the parameters Γ, β, H, n, and e.

Steady states. The situation is especially simple if $e \leqslant 1$, and is summarized in:

Proposition 1. (a) *If* $e \leqslant 1$ *then* $i^* = f^* = 0$ *is the unique steady state*; *and* (b) *If* $f^* = 0$ *then* $i^* = 0$ *and* $e \leqslant 1$.

Proof: (a) From (13) $i^* \geqslant 0$ so $e - i^* \leqslant 1$ and Eq. (12) gives $f^* = 0$. Hence we conclude $i^* = 0$ from (13). (b) If $f^* = 0$ then $i^* = 0$ by (13) and, because of (12), $e - i^* \leqslant 1$. Hence $e \leqslant 1$.

Now we examine the situation when $e > 1$. In this case, by Proposition 1(b) any steady state f^* is positive and given by $f^* = H(e - i^* - 1)$. Thus $i^* = -f^*/H + e - 1$. Substituting this expression for i^* into Eq. (13), the steady state is determined by

$$e = \frac{f^*}{H} + \frac{\beta}{\Gamma} g(f^*) + 1. \tag{14}$$

The right-hand side of (14) is a function

$$\rho(f^*) = \frac{f^*}{H} + \frac{\beta}{\Gamma} g(f^*) + 1, \tag{15}$$

depending on the parameters β, Γ, H, and n, but not on e. Any steady state f^* satisfies $e = \rho(f^*)$.

If ρ is a strictly monotone function of f^*, then f^* is uniquely given by

$$f^* = \rho^{-1}(e), \tag{16}$$

where ρ^{-1} denotes the inverse function of ρ. An examination of $d\rho/df^*$ and $d^2\rho/df^{*2}$ shows that ρ is strictly monotone increasing (and, thus, so is ρ^{-1}) if

$$\frac{\Gamma}{\beta H} > \frac{(n-1)^2}{4n}. \tag{17}$$

Conversely, if

$$\frac{\Gamma}{\beta H} < \frac{(n-1)^2}{4n} \tag{18}$$

then ρ has two local extrema $\tilde{f}, \tilde{\tilde{f}}$, $\tilde{f} < \tilde{\tilde{f}}$, as shown in Fig. 1. In this case there is a unique steady state f^* only if $e < e_1 \equiv \rho(\tilde{\tilde{f}})$ or $e > e_2 \equiv \rho(\tilde{f})$. For all values of e satisfying $e_1 < e < e_2$ there are three steady states $f_1^* < f_2^* < f_3^*$ since there are three values of f^* satisfying $e = \rho(f^*)$.

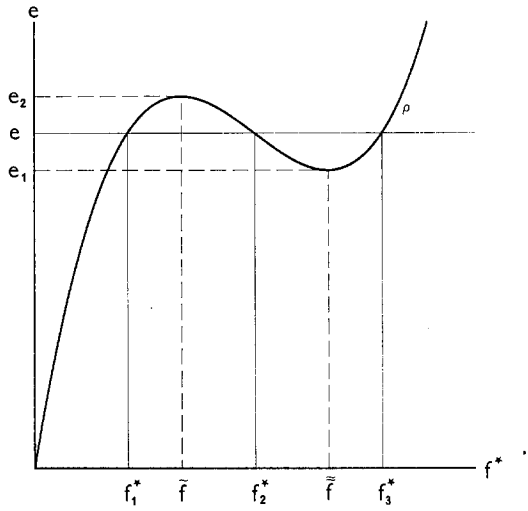

Fig. 1. The graph of $\rho(f^*)$ versus f^* when inequality (18) is satisfied and multiple steady state solutions to the system of Eqs. (9)–(11) may exist. Steady states are determined by solutions of $e = \rho(f^*)$. See the text for further details

In summary we have proved:

Theorem 1. (a) *If inequality* (17) *holds, then for every* e *(constant) the system* (9)–(11) *has a unique steady state* (i^*, f^*). *For fixed* β, Γ, H, *and* n, f^* *is a monotone increasing function of* e; *and* (b) *If inequality* (18) *holds, then there are values of presynaptic input* $e_1 = e_1(\beta, \Gamma, H, n)$ *and* $e_2 = e_2(\beta, \Gamma, H, n)$ *such that the system* (9)–(11) *has exactly*

(i) 3 *different steady states if* $e_1 < e < e_2$,
(ii) 2 *different steady states if* $e = e_1$ *or* $e = e_2$,
(iii) 1 *unique steady state if* $e < e_1$ *or* $e > e_2$.

As illustrated in Fig. 1, when inequality (18) is satisfied variation of the constant presynaptic input e may lead to abrupt switching between steady states. Further, this switching behaviour will display hysteresis. Thus, an increase in e will lead to an abrupt shift from a low to high postsynaptic cell steady state firing frequency $(f_1^* \to f_3^*)$ at $e = e_2$. Conversely, a decrease in e to $e = e_1$ will result in a sudden drop in output cell activity $(f_3^* \to f_1^*)$.

Local stability. Having enumerated the possible steady states for this model we now turn to an examination of their stability. First note that if $e < 1$ then the steady state $(i^*, f^*) = (0, 0)$ is asymptotically stable since $y = i - i^*$ obeys

$$\frac{dy}{dt} = -\Gamma y$$

in a neighbourhood of zero (writing t instead of $\bar{t}$ throughout).

Now consider $e > 1$. Then $i^* > 0$, $f^* > 0$, and there is neighbourhood U of f^* such that $f(t) = H[e - i(t) - 1]$ whenever $f(t) \in U$ and

$$\frac{df(t)}{dt} = -H\frac{di(t)}{dt} = \Gamma H i(t) - \beta H g(f(t-1)).$$

Eliminating $i(t)$ by using $i(t)=e-1-f(t)/H$ this equation becomes

$$\frac{df(t)}{dt}=\Gamma H(e-1)-\Gamma f(t)-\beta H g(f(t-1)). \tag{19}$$

The characteristic equation [8] for the eigenvalues λ of (19) near the steady state f^* is given by

$$\lambda+\Gamma+\beta H g' e^{-\lambda}=0 \tag{20}$$

where

$$g'=\left.\frac{dg}{df}\right|_{f=f^*}. \tag{21}$$

It is well known [8, 14] that all of the eigenvalues λ will have negative real parts if and only if

$$-\Gamma<\beta H g'<[\xi_1^2+\Gamma^2]^{1/2} \tag{22}$$

where ξ_1 is uniquely determined by

$$\xi_1=-\Gamma\tan\xi_1, \qquad 0<\xi_1<\pi. \tag{23}$$

If this criterion is satisfied then f^* is asymptotically stable, while if (22) is violated then f^* is unstable.

We first consider the case when inequality (17) holds (and, hence, Theorem 1(a)). In this case our stability results are summarized in:

Theorem 2. *Let β, Γ, H and n be fixed, let inequality* (17) *be satisfied and ξ_1 given by* (23). *Then*

(a) *if $\beta H<[\xi_1^2+\Gamma^2]^{1/2}$ then, for each e, the steady state of equation* (9) *is asymptotically stable*;

(b) *if $\beta H>[\xi_1^2+\Gamma^2]^{1/2}$ then there is a value $\tilde{e}=\tilde{e}(\beta, \Gamma, H, n)>1$ of e such that the steady state of equation* (9) *is unstable whenever $1<e<\tilde{e}$ and is asymptotically stable whenever $e>\tilde{e}$.*

Proof: Since

$$\frac{dg(f)}{df}\geqslant -\frac{(n-1)^2}{4n}$$

for all $f\geqslant 0$, it follows that the first inequality of (22) is always satisfied. Further

$$\frac{dg(f)}{df}\leqslant 1$$

for all $f\geqslant 0$. Thus the second inequality of (22) is satisfied if $\beta H<[\xi_1^2+\Gamma^2]^{1/2}$, proving (a).

To prove (b), assume $\beta H>[\xi_1^2+\Gamma^2]^{1/2}$. If $e-1$ increases from 0 to ∞, then f^* increases from 0 to ∞ by Eq. (16). If f^* increases from 0 to $\sqrt[n]{1/(n-1)}$, then g' decreases from 1 to 0, and $g'<0$ for all $f^*>\sqrt[n]{1/(n-1)}$. Thus there is a unique $\tilde{e}>1$ such that the second inequality of (22) does not hold for e between 1 and $\tilde{e}$, but holds for all $e>\tilde{e}$. The proof of the theorem is complete.

We finish with a consideration of the stability when a set of parameters β, Γ, H, n satisfies inequality (18). Then Theorem 1(b) is applicable, and we introduce the following notation. Let the single steady state existing for $e < e_1$ be denoted by f_1^*, the single steady state for $e > e_2$ be called f_3^*, and the three steady states existing for $e_1 < e < e_2$ be called $f_1^* < f_2^* < f_3^*$. Then we have:

Theorem 3. *Let β, Γ, H, n satisfy inequality* (18).
Then: (a) *f_3^* is asymptotically stable*; (b) *f_2^* is unstable*; *and* (c) *if $\beta H < [\xi_1^2 + \Gamma^2]^{1/2}$ then f_1^* is asymptotically stable*; *or* (d) *if $\beta H > [\xi_1^2 + \Gamma^2]^{1/2}$ then there is a value $\tilde{e} = \tilde{e}(\Gamma, \beta, H, n)$, $1 < \tilde{e} < e_2$, such that f_1^* is unstable whenever $1 < e < \tilde{e}$ and f_1^* is asymptotically stable whenever $\tilde{e} < e < e_2$.*

Proof: Part (a) follows from

$$-\frac{\Gamma}{\beta H} < \left.\frac{dg}{df}\right|_{f=f_3^*} < 0,$$

which implies inequality (22).

At the steady state f_2^* we have

$$\left.\frac{dg}{df}\right|_{f=f_2^*} < -\frac{\Gamma}{\beta H}$$

so inequality (22) is violated, and part (b) is proved.

Finally the proof of (c) and (d) follows entirely analogously to the proof of Theorem 2 with f_1^* replacing f^* everywhere.

Remark: Though local instability of a steady state implies it is globally unstable, local stability of a steady state offers no insight into its global stability properties. However in either case a result of an der Heiden [1] can be used to show that for a non-negative initial condition $i_0(\bar{t})$, $-1 \leq \bar{t} \leq 0$, to the system of Eqs. (9)–(11) the solution $i(\bar{t})$ is bounded below by zero [$i(\bar{t}) > 0$ for all $\bar{t} > 0$] and for some finite $t_+ > 0$,

$$\sup i(t) \leq \frac{\beta}{\Gamma} \sup_{\bar{t} \geq 0} g(\bar{t}) \quad \text{for all } t > t_+.$$

Thus we know that any non-constant solution $i(\bar{t})$ is bounded above and below, as is $f(\bar{t})$.

The system of Eqs. (9)–(11) describing recurrent inhibition is of the form

$$\frac{dx(t)}{dt} = -\gamma x(t) + h(x(t-\tau)) \tag{24}$$

where $h(x)$ is a non-monotone "humped" function of x. Analytic and numerical studies of time-delay differential equations of this type by a number of authors [1, 3–5, 12, 18, 21, 24, 26, 27] have revealed a rich structure of bifurcating periodic solutions as well as the existence of apparently aperiodic ("chaotic") solutions.

Rather than examine the possible behaviours of the numerical solutions to the system (9) through (11) for variations in all of the parameters β, Γ, H, n, and e, in the following section we examine a specific example.

IV. A specific example

In this section, we apply this model to a well studied recurrent inhibitory circuit in the hippocampus, the mossy fibre-CA3 pyramidal cell-basket cell complex.

The CA3 pyramidal cells (the postsynaptic cells) receive excitatory presynaptic input from the mossy fibres, and recurrent inhibitory input from the basket cells via what is generally considered to be a monosynaptic pathway. The inhibitory transmitter is γ-aminobutyric acid (GABA) [7, 17].

From data [16, 25] it is estimated that $\theta = 4$ mV, $\gamma^{-1} = 10$ msec, and $\varkappa = 2.25$ Hz/mV. Other work [6] yields an estimate for τ of 100 msec, $V_m = 24$ mV, and $\alpha = 0.1$. Finally the half maximal GABA response is 5 μM [20], so $\sqrt[n]{K} = 5$ μM; and $n = 2$ or 3 [20], or $n = 3$ or 4 [28], so we take $n = 3$.

Two parameters we have been unable to estimate are T (the average number of GABA receptors per CA3 pyramidal cell) and m. With these uncertainties in mind, the above data give $\Gamma = 10$, $n = 3$, $H = 0.18$ m, and $\beta = 3T/m$, where m is in units of μM-sec.

Penicillin competitively binds to the GABA receptor, and indeed the topical application of penicillin is a common experimental tool for the generation of epileptic-like behaviour in cortical cells. Viewed within the context of this model, the application of penicillin is equivalent to the titration of the number, T, of GABA receptors on the CA3 cell. Thus, to investigate the response of this model to variations in T, in Fig. 2 we show the steady state deviation of the dimensionless membrane potential from the resting potential, $e - i^*$, as a function of receptor density for presynaptic inputs, e, ranging from 1.1 to 2 times threshold. In constructing Fig. 2 the estimated hippocampal parameters data were used under the assumption that $m = 50$ μM-sec. The local stability or instability of $e - i^*$, as determined by Theorems 2 and 3 of the previous section, is indicated by a solid or dotted line respectively. Once e exceeds approximately 1.3 times threshold, there is a range of receptor densities for which multiple steady states may exist. For this set of parameter values the intermediate steady state $e - i^*$, corresponding to f_2^*, is always locally unstable while the largest steady state (f_3^*) is predicted to be locally stable. f_1^* may be stable or unstable depending on the value of T.

Using an integration step size of 0.01 (corresponding to 1 msec integration steps, since $\tau = 100$ msec) and an initial condition of $i_0(\bar{t}) = 0.1$, $-1 \leqslant \bar{t} \leqslant 0$, the full set of dynamical Eqs. (9) through (11) were integrated with parameters determined by the estimates from the hippocampal data, $m = 50$ μM-sec, and a variety of receptor densities T and presynaptic input levels e.

Our simulations seem to indicate that, whenever there is a single steady state for the system (9)–(11), and the conditions of Theorem 2(a) are fulfilled then this steady state is globally attracting. The same is true when the conditions of Theorem 2(b) apply and the steady state is stable ($e > \tilde{e}$). However, in the situation that it is unstable ($1 < e < \tilde{e}$) all numerical solutions are attracted to an apparently globally stable limit cycle whose complexity may vary.

The situation is even more interesting when the possibility of three steady states exist. In this case, when $1 < e < \tilde{e}$ (compare Theorem 3(d)) then the steady state f_1^* appears to be replaced with either limit cycle or aperiodic behaviour.

To illustrate this, in Fig. 3, using a variety of receptor densities T and a presynaptic input level of $e = 1.6$, the resultant dynamical variation in $e - i(\bar{t})$ is

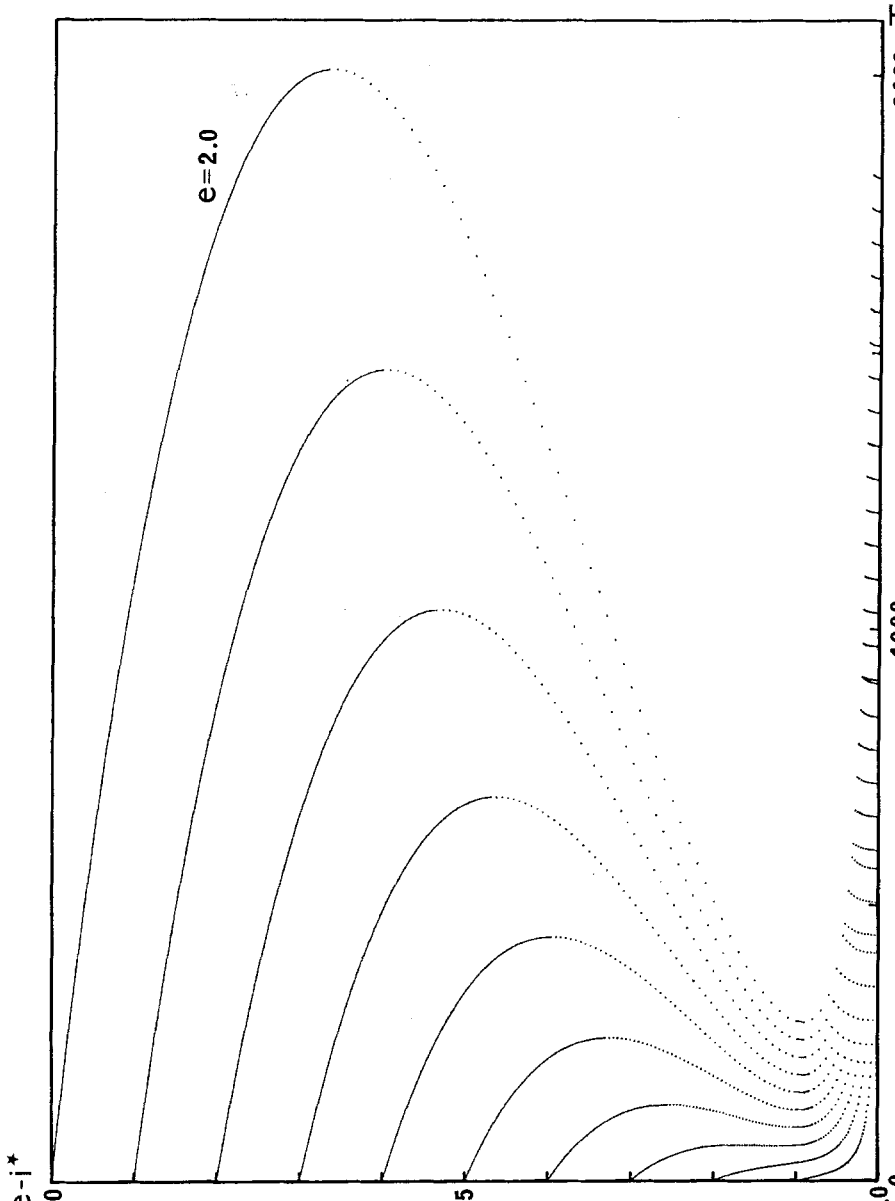

Fig. 2. The variation in the steady state membrane potential $[e - i^*]$ is shown as a function of receptor density T for parameter values appropriate to the hippocampus, $m = 50$ μM-sec, and a range of constant EPSP levels from $e = 1.1$ to $e = 2.0$ in steps of 0.1. The curves are presented as solid (dotted) lines if the steady state is locally stable (unstable)

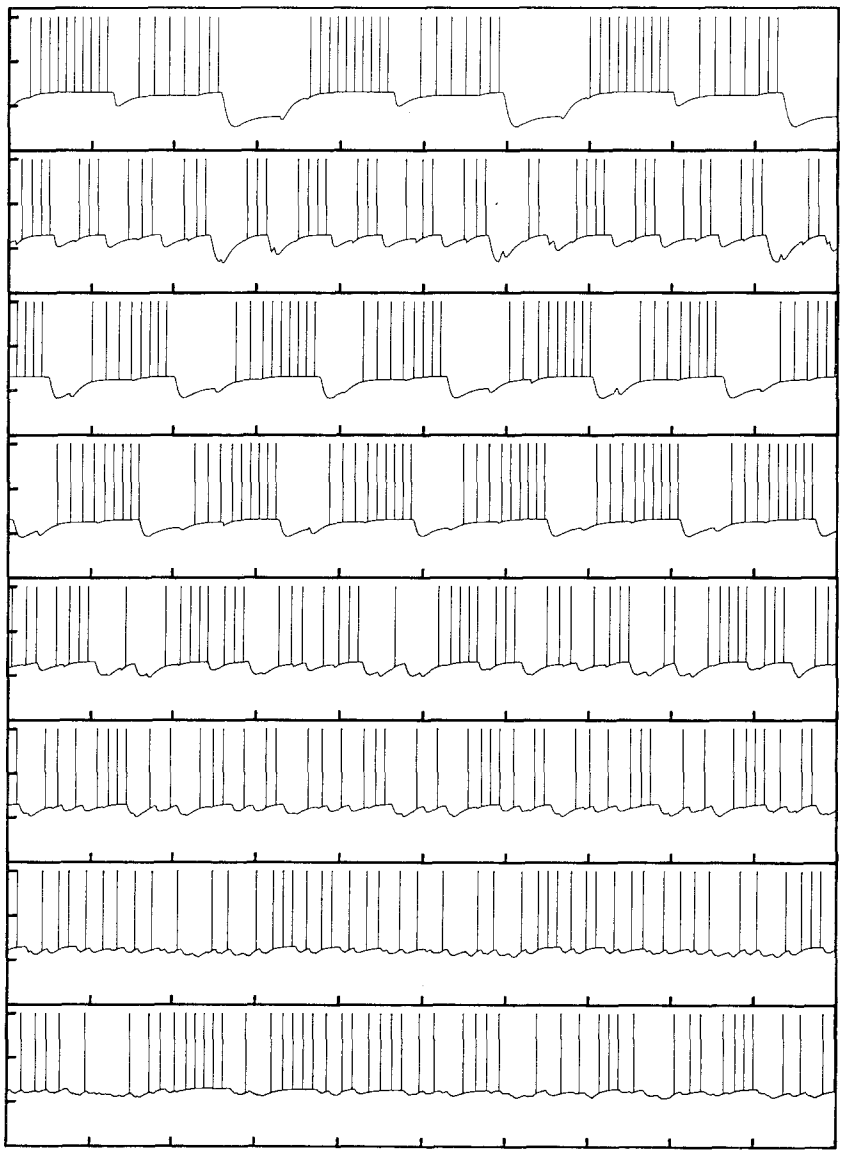

Fig. 3. Model predicted behaviour as a function of GABA receptor density (decreasing, top to bottom) for the same parameters used in Fig. 2. Each panel represents one second of simulated CA3 pyramidal cell activity after a three second period to allow transients to die out. In each panel the ordinate (membrane potential) runs from −5 to +10 in threshold units, or from −20 to +40 mV, relative to the resting potential. Going from top to bottom the receptor density falls from $T = 1900$ to $T = 500$ in steps of 200

shown for $\bar{t} = 30$ to 40 (corresponding to 1 second of activity in the CA3 fibres since $\tau = 100$ msec). As an aid to understanding, superimposed vertical lines corresponding to the occurrence of action potentials are included.

At high receptor densities ($T = 1900$) the membrane potential $e - i(\bar{t})$ is periodic and the output cell displays bursting behaviour. Decreasing T from this value brings about a surprising sequence of behaviours in which bursting in various patterns is interspersed with patterns of irregular continuous activity. Prior to the transition to sustained regular firing (f_3^*, not shown) the model for recurrent inhibition predicts the occurrence of irregular fluctuations in membrane potential (e.g. $T = 700$ and 500) and an attendent irregularity in CA3 firing patterns. These sequences of changes in the underlying dynamics of this model for recurrent inhibition are exactly analogous to the patterns of multiple period doubling bifurcations and the onset of "chaotic" dynamics noted by others for time delay differential equations like (24) with non-monotone h.

The sequence of dynamical behaviours exhibited in Fig. 3 as T is decreased, at constant e, is remarkably similar to that seen following the application of penicillin wherein bursting behaviour is gradually transformed into irregular firing patterns to finally be superseded by sustained high level firing [22]. Just as decreases in T may result in a transition to this high level of sustained activity at constant levels of presynaptic drive e, increases in e at constant GABA receptor numbers may result in the same phenomenon. As with decreases in T, increasing the presynaptic drive results in a number of different activity patterns before the transition to sustained high level activity occurs. It is tempting to speculate that experimentally observed irregular variations in membrane potential and action potential generation may, on some occasions, not be due to stochastic fluctuations. Rather, they may reflect the fact that a recurrent inhibitory mechanism is operating in a region of parameter space characterized by chaotic dynamics.

V. Discussion

The occurrence of hysteresis phenomena in neural network models has been considered previously [13, 29]. Wilson and Cowan [29] considered mutually excitatory–inhibitory networks, while Hadeler [13] examined the Hartline–Ratliff equations with pure mutual inhibition and external excitation. In this case, however, the multiple steady states which may occur are not homogenous, and it has been shown [2] quite generally that neural networks containing only monotone nonlinearities and inhibitory couplings cannot have several homogenous steady states.

Other models like (24) have been proposed for lateral inhibition in the retina of *Limulus* but with monotone non-linearities [9, 10]. The periodic solutions in these models are much simpler than those discussed here, and there is experimental evidence for the existence of periodic activity in this preparation [23].

From a neurophysiological perspective there are at least two assumptions in this model for recurrent inhibition to which objections may be raised.

The first is related to the assumption, contained in Eq. (1), that the output cell firing frequency is a linearly increasing function of the cell input, $E-I$, once the threshold has been exceeded. This assumption neglects, for example, the

attainment of a maximal firing rate equal to the reciprocal of the output cell absolute refractory period. Thus in the more general case (1) might be replaced by

$$F = \begin{cases} 0 & E - I < \theta \\ \xi(E - I - \theta) & E - I \geqslant \theta \end{cases}$$

where $\xi(x) \geqslant 0$, $x \geqslant 0$; $[d\xi/dx] > 0$ at $x = 0$; and $\lim_{x \to \infty} \xi(x) < F_m < \infty$. A simple graphical consideration of the steady state behaviour of the recurrent inhibition model with this more general relation between membrane potential and output cell firing frequency reveals that if F_m is sufficiently small then it is possible for multiple steady states [Theorem 1(b)] to disappear. However, for the specific example considered here of hippocampal recurrent inhibition, the introduction of a more general saturating relation ξ between $E - I$ and F will not affect the qualitative behaviour described in the previous section, though quantitative details will change.

The second objectionable assumption involves the supposition that the recurrent inhibitiory pathways all operate with an identical delay of τ. In the more realistic case, a distribution of axonal diameters, conduction pathway lengths, and synaptic transmission times would lead to a relation of the form

$$\tilde{F}(t) = \alpha \int_{-\infty}^{t} F(u) k(t - u)\, du$$

replacing (5), where α is a constant and $k(x)$ is the distribution of transmission times. On general neurophysiological grounds, one would expect $k(x)$ to have the following properties:

(1) $k(x) = 0$ for $0 \leqslant x \leqslant \tau^*$, $\tau^* > 0$ (i.e. there is a minimum non-zero transmission time τ^*);
(2) $k(x) \geqslant 0$ for $\tau^* < x$;
(3) $\lim_{x \to \infty} k(x) = 0$; and
(4) $\int_0^\infty k(x)\, dx = 1$.

Thus the mean transmission time around the recurrent inhibitory feedback pathway is

$$\bar{\tau} = \int_0^\infty x k(x)\, dx$$

Numerical simulations of systems like (24) replacing a single time delay with a distribution of delays indicate that the qualitative behaviour of solutions is largely unaffected by the addition of a distribution of delays [1]. Numerical studies of recurrent inhibition models with distributions of time delays have been published previously [15, 19].

A third objection, specifically related to the application of this model to the dynamics of the CA3 pyramidal cell-mossy fibre-basket cell complex, involves the neglect of any recurrent excitatory pathway. In their study of penicillin induced hippocampal seizured activity, Dichter and Spencer [11] postulated the existence of not only recurrent inhibition but also recurrent excitatory circuits. They speculated that the paroxysmal depolarizing shift noted after the application

of penicillin was due to the occurrence of large synchronous EPSP's generated by recurrent excitation.

Though, as the present study indicates, a sudden depolarizing shift with accompanying sustained activity is not dependent on the presence of recurrent excitation, the existence of a recurrent excitatory circuit would certainly augment such a response. The inclusion of recurrent excitation within the context of this model is straightforward, and will result in the more complicated dynamical scheme

$$\frac{dI}{dt} = -\alpha I + \alpha_I T_I V_{mI} F(t-\tau_I) \frac{K_I}{K_I + (m_I \alpha_I F(t-\tau_I))^n I}$$

and

$$\frac{dE}{dt} = -\alpha E + \alpha_E T_E V_{mE} F(t-\tau_E) \frac{K_E}{K_E + (m_E \alpha_E F(t-\tau_I))^n E}$$

in conjunction with (7), where the quantities have their previous meaning and the subscripts E and I refer to the recurrent excitatory and inhibitory pathways respectively. Such a situation is of obvious interest, as self generated oscillatory behaviour is now possible in the absence of presynaptic excitatory drive, but will not be dealt with further.

References

1. an der Heiden, U.: Delays in physiological systems. J. Math. Biol. **8**, 345–364 (1979).
2. an der Heiden, U.: Analysis of neutral networks. Lecture Notes in Biomathematics, Vol. 35. Berlin–Heidelberg–New York: Springer, 1980
3. an der Heiden, U., Mackey, M. C.: The dynamics of production and destruction: Analytic insight into complex behaviour. J. Math. Biol. **16**, 75–101 (1982)
4. an der Heiden, U., Walther, H. O.: Existence of chaos in control systems with delayed feedback. J. Diff. Eqns. **47**, 273–295 (1983)
5. an der Heiden, U., Mackey, M. C., Walther, H. O.: Complex oscillations in a simple deterministic neuronal network. Lectures in Applied Mathematics, Hoppensteadt, F. (ed.), pp. 355–360. American Mathematical Society, Providence, 1981
6. Anderson, P., Eccles, J. C., Loyning, Y.: Location of postsynaptic inhibitory synapses on hippocampal pyramids. J. Neurophysiol. **27**, 592–607 (1964)
7. Anderson, P.: Organization of hippocampal neurons and their interconnections. In: The Hippocampus, Isaacson, R. L., Pribram, K. H. (eds.), Vol. 1. New York: Plenum Press, 1975
8. Bellman, R., Cooke, R. L.: Differential-Difference Equations. New York–San Francisco–London: Academic Press 1963
9. Coleman, B. D., Renninger, G. H.: On the integral equations of the linear theory of recurrent lateral interactions in vision. Math. Biosci. **20**, 155–170 (1974)
10. Coleman, B. D., Renninger, G. H.: Theory of the response of the *Limulus* retina to periodic excitation. J. Math. Biol. **3**, 103–119 (1976)
11. Dichter, M., Spencer, W. A.: Penicillin-induced interictal discharges from the cat hippocampus. II. Mechanisms underlying origin and restriction. J. Neurophysiol **32**, 663–687 (1969)
12. Glass, L., Mackey, M. C.: Pathological conditions resulting from instabilities in physiological control systems. Ann. N.Y. Acad. Sci. **316**, 214–235 (1979).
13. Hadeler, K. P.: On the theory of lateral inhibition. Kybernetik **14**, 161–165 (1974)
14. Hayes, N. D.: Roots of the transcedental equation associated with a certain difference-differential equation. J. Lond. Math. Soc. **25**, 226–232 (1950)
15. Horowitz, J. M., Freeman, W. J., Stoll, P. J.: A neural network with a background level of excitation in the cat hippocampus. Intern. J. Neuroscience **5**, 113–123 (1973)

16. Kandel, E. R., Spencer, W. A.: Electrophysiology of hippocampal neurons. II. After-potentials and repetitive firing. J. Neurophysiol. **24**, 243–259 (1961)
17. Lopes da Silva, F. H., Arnolds, D. E. A. T.: Physiology of the hippocampus and related structures. Ann. Rev. Physiol. **40**, 185–216 (1978)
18. Mackey, M. C., Glass, L.: Oscillation and chaos in physiological control systems. Science **197**, 287–289 (1977)
19. Mates, J. W. B., Horowitz, J. M.: Instability in a hippocampal neural network. Comp. Prog. Biomed. **6**, 74–84 (1976)
20. Nowak, L. M., Young, A. B., Macdonald, R. L.: GABA and bicuculline actions on mouse spinal cord and cortical neurons in cell culture. Brain Research **244**, 155–164 (1982)
21. Peters, H.: Globales Lösungsverhalten zeitverzögerter Differentialgleichungen am Beispiel von Modellfunktionen. Dissertation, University of Bremen, F.R.G., 1980
22. Prince, D. A.: Microelectrode studies of penicillin foci. In: Basic Mechanisms of the Epilepsies, Jasper, H. H., Ward, A. A., Pope, A. (eds.), pp. 320–328. Boston: Little, Brown and Company, 1969
23. Ratliff, F.: (ed.): Studies on Excitation and Inhibition in the Retina. London: Chapman and Hall 1974
24. Saupe, D.: Beschleunigte PL-Kontinuitätsmethoden und periodische Lösungen parametrisierter Differentialgleichungen mit Zeitverzögerung. Dissertation, University of Bremen, F.R.G., 1982
25. Spencer, W. A., Kandel, E. R.: Electrophysiology of hippocampal neurons. III. Firing level and time constant. J. Neurophysiol. **24**, 260–271 (1961)
26. Walther, H. O.: Homoclinic solution and chaos in $\dot{x}(t)=f(x(t-1))$. Nonlinear Anal. **5**, 775–788 (1981)
27. Wazewska-Czysewska, M., Lasota, A.: Roczniki Polskiego Towarzystwa Mathematycznego, Seria III: Matematyka Stosowana VI, 23–39 (1976)
28. Werman, R.: Stoichiometry of GABA-receptor interactions: GABA modulates the glycine-receptor interaction allosterically in a vertebrate neuron. In: Advances in Experimental Medicine and Biology, vol. 123, pp. 287–301, Mandel, P., De Feudis, F. V. (eds.). New York: Plenum Press, 1979
29. Wilson, H. R., Cowan, J. D.: Excitatory and inhibitory interactions in localized populations of model neurons. Biophys. J. **12**, 1–24 (1972)

Received May 30/Revised December 29, 1983