# ATTRACTORS AND PATHOLOGICAL ASPECTS IN EXCITABLE CELLS

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## ABSTRACT

In this article, physiological and pathological forms of excitability are studied in a two-dimensional electrical model of excitable cell endowed with a generic inward persistent conductance. Bifurcation analysis of the model is performed as a function of the maximal inward persistent conductance, the input current, or the voltage dependency of the activation function. Several discharge modes are exhibited, including: (1) a basic mode that corresponds to a resting potential and production of action potential; (2) bistability between resting potential and self-sustained spiking; (3) a pacemaker mode of discharge; and (4) bistability between resting potential and plateau potential. These behaviours can be compared to experimentally described physiological and pathological forms of excitability that depend upon inward persistent conductances. In the results obtained, attractors allow for a qualitative description of physiological and pathological states. However, it is not possible to obtain an unambiguous identification of particular 'physiological attractors' or 'pathological attractors'. In the perspective of the theory of dynamical systems, we suggest that pathological states can be modelled in two different ways, i.e. by bifurcation (as in the present model) or by perturbation. We also highlight some other theoretical concepts that may be relevant to a theoretical description of pathology.

## 1. INTRODUCTION

Physiological and pathological states are sometimes considered, from a theoretical point of view, as particular attractors of living organisms. While being seductive, this general assumption remains highly speculative and may possibly be irrelevant. Moreover, other theoretical concepts could be useful in describing these states. In well-delimited systems (e.g. cells, organs), it is possible to evaluate to which extent attractors allow for a satisfactory description of physiological and pathological states. In that perspective, the case of excitable cells represents a good working example. Indeed, excitable cells can display pathological forms of excitability that affect the physiological functioning of the organism they are part of. Moreover, they have been widely studied as dynamical systems, notably using the qualitative theory of differential equations. In this article, we therefore examine, in the case of excitable cells, the way physiological and pathological states can be described theoretically.

Excitable cells are endowed with numerous types of ionic conductances that determine their intrinsic firing properties (Llinàs, 1988), and quite naturally, the possible origin of abnormal excitability has been searched at that level. Indeed, accumulating evidences suggest that inappropriate regulation of ionic conductances can be responsible for dysfunctional forms of excitability related to various pathological states, especially inward persistent (IP) conductances carrying sodium or

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calcium ions. IP conductances have been suggested to be implicated in several human diseases, including myotonia and periodic paralysis (Cannon, 1996), a congenital form of long-QT syndrome (Bennet *et al.*, 1995), spasticity (Nielsen and Hultborn, 1993), epilepsy (Tunnicliff, 1996), and schizophrenia (Yang et Seamans, 1996; Goldman-Rakic and Selemon, 1997). This should not be surprising, as these conductances are ubiquitous in excitable cells, including muscular cells, cardiac cells and neurons. Moreover, as inward non-inactivating conductances, they provide long-lasting positive feedback to depolarisation and often dominate the electrical properties of excitable cells in which they are present (Bargas and Galaraga, 1995). Hence, they participate in numerous intrinsic properties, such as amplification of synaptic inputs (Lipowsky *et al.*, 1996), subthreshold oscillations (Klink and Alonso, 1993), spike threshold (Yang and Seamans, 1996), firing frequency (Lampl *et al.*, 1998), self-sustained spiking (Hounsgaard *et al.*, 1984) and plateau potential (Yuen *et al.*, 1995).

In this article, we build a two-dimensional model of an excitable cell endowed with a generic IP conductance. In line with previous works (FitzHugh, 1961; Nagumo *et al.*, 1962; Rinzel, 1985), we take advantage of geometrical representation in two-dimensional phase-space to characterise the bifurcation behaviour of the model as a function of the IP conductance. We then compare the different behaviour modes of the model to experimental physiological and pathological forms of excitability. Finally, we discuss the interest and limitations of the theoretical description of pathology obtained in the present model of excitable cells.

## 2. MATERIALS AND METHODS

The two-dimensional model studied in this paper was derived from an excitable cell model of the Hodgkin-Huxley type used to describe the electrical behaviour of neocortical pyramidal cells (Delord *et al.*, 1997). The original model was isopotential and endowed with four conductances: the fast sodium and potassium conductances, a persistent inward conductance and a leak conductance. The membrane potential followed:

$$C\frac{dV}{dt} = -(I_{Na} + I_k + I_{IP} + I_{leak}) + I \qquad (1)$$

where the membrane capacitance $C$ was $1\mu F.\text{cm}^{-2}$ and $I$ was an injected current ($\mu A.\text{cm}^{-2}$). The leakage, fast sodium and fast potassium currents were respectively given by $I_{leak} = \bar{g}_{leak}(V - E_{leak})$, $I_{Na} = \bar{g}_{Na}m^3h(V - E_{Na})$ and $I_K = \bar{g}_K n^4(V - E_K)$. The persistent inward current was described as $I_{IP} = \bar{g}_{IP}m_{IP}(V - E_{IP})$. The conductance comprised an activation gate ($m_{IP}$) but was non-inactivating. The gating particles $m$, $h$, $n$ and $m_{IP}$ obeyed Hodgkin-Huxley first-order kinetics, the details of which are given in Delord *et al.* (1997).

Following the method of Rinzel (1985), the original model was reduced to a two-dimensional system. The following approximations were made. Firstly, the fast sodium activation variable was substituted by its steady state activation function $m = m_\infty(V)$. This was reasonable because $m$ evolves much faster than all other gating variables. Fast sodium steady-state activation function was fitted from Delord *et al.* (1997) by a sigmoidal function: $m_\infty(V) = 1/(1 + \exp(-(V - V_m^{half})/k_m))$. Secondly, $h$ and $n$ were replaced by $1\text{-}W$ and $W/s$, with $W = (sn + s^2(1-h))/(1+s^2)$ being a linear

combination of 1-$h$ and $n$ (see Av-Ron *et al.* (1991) for a description of that point). This was made possible because simulations of the whole model showed that $h$ and $n$ varied almost linearly both during single action potentials and repetitive firing. In line with these 'reduction rules', further reduction of the model to two dimensions was achieved by substituting $m_{IP}$ by $W$. This choice was possible since: (1) $m_{IP}$ increased with $W = 1 - h$, and (2) it evolved with a time constant in the same order as those of $h$ and $n$. The reduced model was written as:

$$C\frac{dV}{dt} = \bar{g}_{Na}m_\infty^3(V)(1-W)(E_{Na}-V) + \bar{g}_K(W/s)^4(E_K-V)$$

$$+\bar{g}_{IP}W(E_{IP}-V) + \bar{g}_{leak}(E_{leak}-V) + I \qquad (2)$$

$$\frac{dW}{dt} = \frac{W_\infty(V)-W}{\tau_W} \qquad (3)$$

The steady-state function $W_\infty(V) = (sn_\infty(V) + s^2(1-h_\infty(V)))/(1+s^2)$ was approximated by a simple sigmoidal function $W_\infty(V) = 1/(1+\exp(-(V-V_W^{half})/k_W))$. The time constant of $W$ was voltage independent. Simulations ran with a voltage-dependent time constant, using classical Hodgkin-Huxley-like functions, did not change the results appreciably.

The qualitative behaviour of the reduced model was studied in order to characterise the role of IP conductances on the firing properties of excitable cells. $\bar{g}_{IP}$ was chosen as the bifurcation parameter, as maximal conductance represents density of ionic channels, a privileged target for physiological regulation (Turrigiano *et al.*, 1994). Moreover, in the present model, $\bar{g}_{IP}$ is the only conductance parameter that affects the IS current without affecting directly the fast Na and K currents. Note that $I$ was zero in most cases (Figures 1-5). However, in simulations, it was taken non-null for brief periods of time, to trigger transitions of one basin of attraction to another. In Figure 6, the behaviour of the model was studied with different constant values of $I$, i.e. in that case the system was different. Stationary solutions ($V_{sol}$, $W_{sol}$) of the system were found numerically (note that $W_{sol} = W_\infty(V_{sol})$). Nullcline curves, corresponding to $dV/dt = 0$ and $dW/dt = 0$, were obtained using equations (2) and (3), respectively giving $A(V)W^4 + B(V)W + C(V) = 0$ and $W = W_\infty(V)$. The jacobian matrix of the system was computed at stationary solutions and eigenvalues determined the stability. The existence and stability of limit cycles was studied numerically.

Reversal potentials were $E_{leak} = -71.5mV$, $E_{Na} = 45mV$, $E_K = -85mV$. We chose $E_{IP} = 45mV$, so that $I_{IP}$ represented a sodium current. Qualitatively similar results (not shown) were obtained using a low-threshold persistent calcium current, with $I_{IP} = \bar{g}_{IP}m_{IP}^2(V-E_{IP})$ and $E_{IP} = 115mV$. Maximal conductances were $\bar{g}_{leak} = 0.05mS.cm^{-2}$ (passive membrane time constant: 20 $ms$), $\bar{g}_{Na} = 20\ mS.cm^{-2}$, and $\bar{g}_K = 2mS.cm^{-2}$. Activation function parameters were $V_W^{half} = -33.5\ mV$, $k = 6.5$, $V_W^{half} = -44mV$, $k_W = 5.2$, $\tau_W = 1\ ms$. The value of $s$ was evaluated 1.32 by linear regression from the original model.

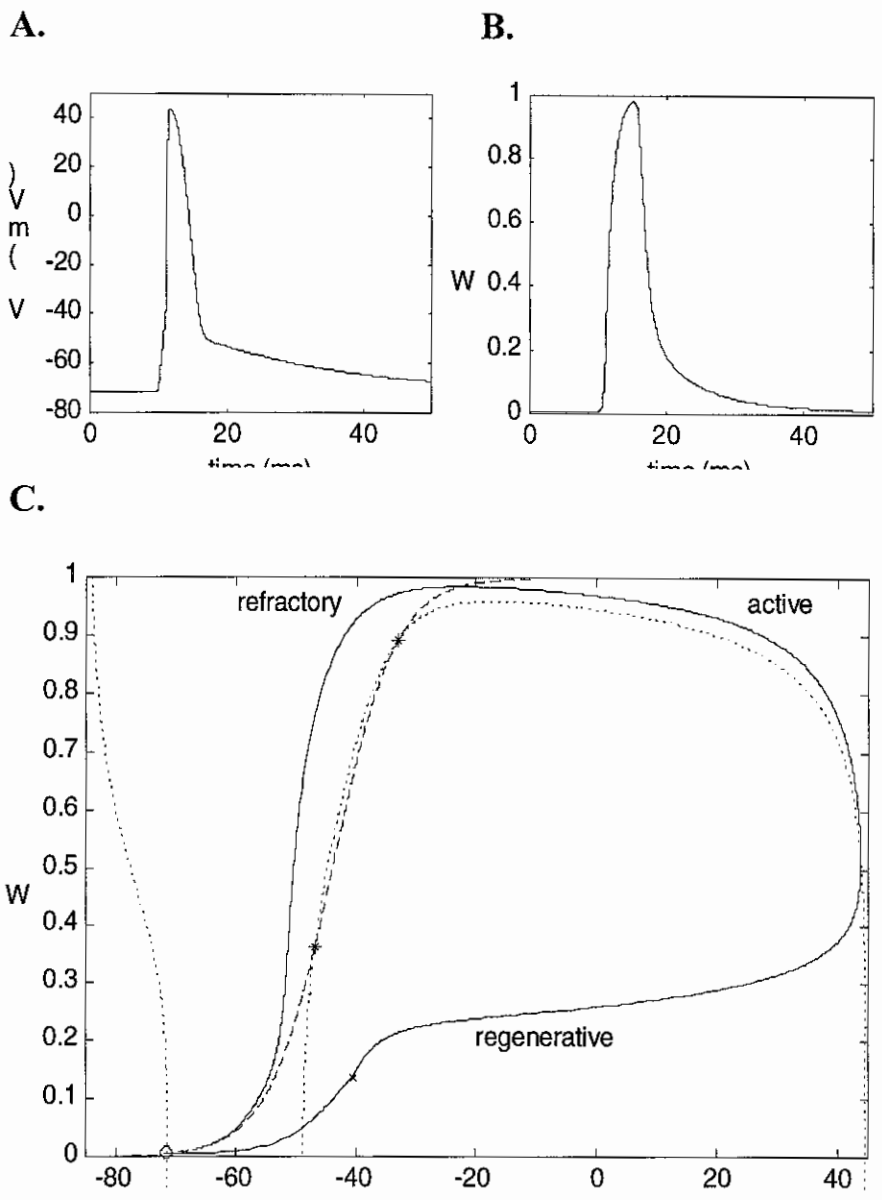


**Figure 1**. Basic mode of excitability for $\bar{g}_{IP}$ below $\bar{g}_1 = 0.0219\ mS.cm^{-2}$ ($\bar{g}_{IP} = 0$). A single action potential is triggered by a transient depolarising input. A. Time domain representation of membrane potential ($V$). B. Time domain representation of $W$. C. Phase-space representation of action potential trajectory. After the end of repolarising current (cross), the cell depolarises during the regenerative stage and repolarises to the resting solution during active and refractory stages. $V$ and $W$ nullclines (dotted and dashed lines) cross at the stable resting solution (open circle), the saddle and the unstable upper solution (stars).

# 3. RESULTS

## Bifurcation behaviour of the model

We first studied the reduced model without inward persistent conductance ($\bar{g}_{IP} = 0$). The cell displayed a single stable stationary solution corresponding to the resting potential (V ~ -71.5 *mV*). When depolarised beyond threshold ($V_\theta$ ~ -48m*V*) by a transient step of current ($I = 30\ \mu A.cm^{-2}$ for 1 ms), the cell fired a single action potential (Figure 1A), and membrane potential repolarised to the resting potential after the variable W had peaked (Figure 1B). This behaviour was observed at all $\bar{g}_{IP}$ below a critical value $\bar{g}_1$, and is referred to as the '*basic mode*' of discharge hereafter. The action potential trajectory is represented in the phase plane together with *V* and *W* nullclines (Figure 1C). Contrary to the *W* nullcline that was the classical sigmoidal (dashed line), the *V* nullcline had two distinct branches (dotted lines). The *V* and *W* nullclines cross at three stationary solutions, a stable solution (the *resting solution*), a saddle (the *middle solution*) and an unstable solution (the upper solution). The left, bottom part of the right branch of the *V* nullcline can be viewed as a threshold curve for action potential. The action potential could be divided, in a classical way, in three stages. In the *regenerative stage*, *V* depolarised fast and *W* increased. As the *V* nullcline was crossed, the *active stage* was entered, and *V* repolarised while *W* was still increasing. In the *refractory stage* (after the *W* nullcline was crossed) both *V* and *W* decreased back to the resting solution.

For values of $\bar{g}_{IP}$ comprised between $\bar{g}_1$ and $\bar{g}_2$, the cell displayed the stable resting solution, the saddle and the unstable upper solution. It also showed stable self-sustained firing, and it was possible to switch back and forth between the two stable states with transient injected currents. This region of $\bar{g}_{IP}$, therefore, displays a bistable behaviour since a stable stationary solution and a stable limit cycle coexisted (Figure 2). This behaviour is referred to as the *'spiking bistability'* mode. Oscillations arose at $\bar{g}_{IP} = \bar{g}_1$ as self-sustained spiking with non-zero amplitude (full spikes) and with apparent null frequency (although numerical resolution did not permit obtaining arbitrarily small frequencies). Note that with increasing values of $\bar{g}_{IP}$, left and right branches of the *V* nullcline approached until they fused, resulting into two top and bottom branches at $\bar{g}_{IP} \sim 0.032 mS.cm^{-2}$. From that point, the stable resting solution and the saddle were both situated on the bottom branch of the *V* nullcline.

At $\bar{g}_{IP} = \bar{g}_2$, the stable resting solution and the saddle merged and disappeared together. For values of $\bar{g}_{IP}$ comprised between $\bar{g}_2$ and $\bar{g}_3$, the cell only displayed the unstable upper solution around which oscillations occurred (Figure 3). This behaviour was termed the *'pacemaker'* mode. As $\bar{g}_{IP}$ was increased, oscillations frequency increased and amplitude diminished. At $\bar{g}_{IP} = \bar{g}_3$, oscillations disappeared with zero amplitude and non-null frequency (~300 *Hz*). For values of $\bar{g}_{IP}$ above $\bar{g}_3$ the upper solution was stable (the *plateau solution*) and was, therefore, the only attractor.

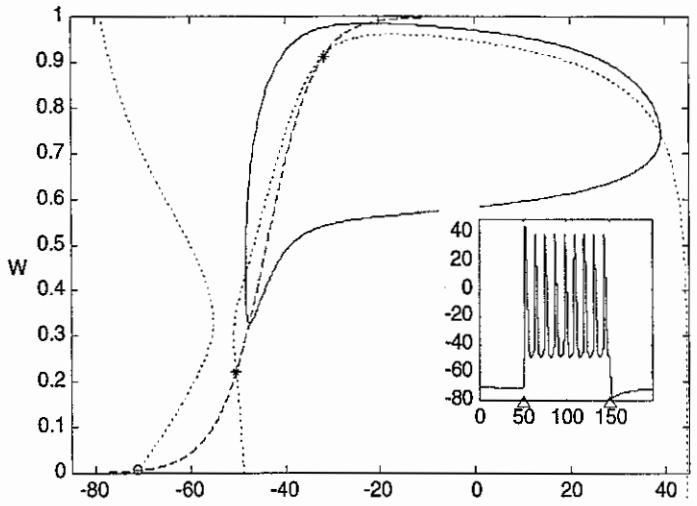


**Figure 2**. Spiking bistability mode of excitability for $\bar{g}_{IP}$ between $\bar{g}_1 = 0.0219\ mS.cm^{-2}$ and $\bar{g}_2 = 0.1724\ mS.cm^{-2}$. Transient depolarising inputs switch the cell between resting potential and self-sustained discharge (inset, $\bar{g}_{IP} = 0.03\ mS.cm^{-2}$). Inputs were $15\ \mu A.cm^{-2}$ and $-10\ \mu A.cm^{-2}$ for 3 ms each (triangles). Phase-space representation of $V$ and $W$ nullclines (dotted and dashed lines), the stable resting solution (open circle), the saddle and the unstable upper solution (stars), and the stable limit cycle (solid curve).

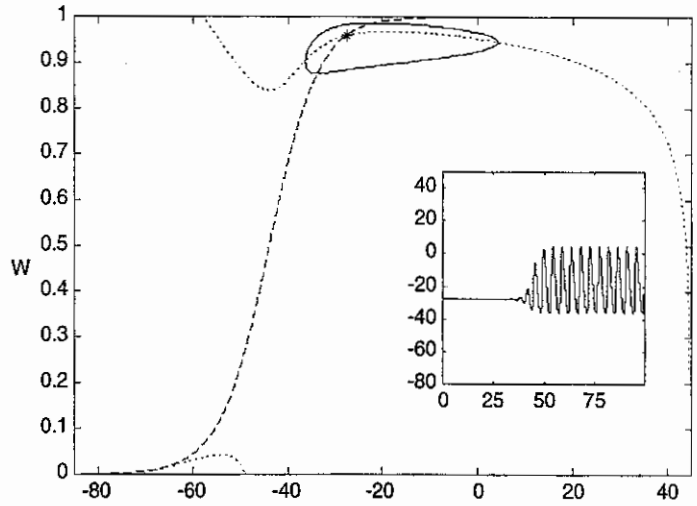


**Figure 3**. Pacemaker mode of excitability for $\bar{g}_{IP}$ between $\bar{g}_2 = 0.1724\ mS.cm^{-2}$ and $\bar{g}_3 = 0.252\ mS.cm^{-2}$. The cell only displays a self-sustained discharge (inset, $\bar{g}_{IP} = 0.18\ mS.cm^{-2}$). $V$ and $W$ nullclines (dotted and dashed lines) cross at the unstable upper solution (star) situated inside the stable limit cycle (solid curve).

Changing other conductance parameters than $\bar{g}_{IP}$ could produce additional interesting behaviour. For example, increasing the value of the half-activation potential $V_W^{half}$ of $W_\infty$ the steady-state function could give rise to a *'plateau bistability'* mode. In that case, a stable resting solution and a stable plateau solution coexisted, and it was possible to switch between them by transient injected currents (Figure 4).

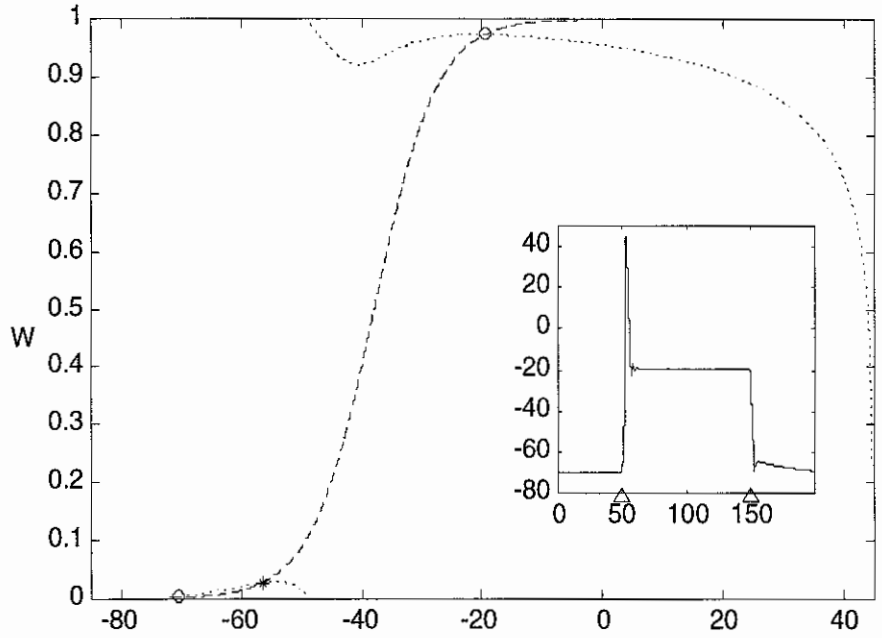


**Figure 4.** Plateau bistability mode of excitability. Transient depolarising inputs switch the cell between a resting potential and a plateau potential (inset, $\bar{g}_{IP} = 0.26\ mS.cm^{-2}$, $V_W^{half} = -38\ mV$). Inputs were $15\ \mu A.cm^{-2}$ and $-25\ \mu A.cm^{-2}$ for 3 ms each (triangles). Phase-space representation of $V$ and $W$ nullclines (dotted and dashed lines), the stable resting and plateau solutions (open circles) and the saddle (start).

The bifurcation diagram shown in Figure 5 summarises the behaviour modes obtained when varying $\bar{g}_{IP}$. Together, the results we obtained allowed identification of different bifurcations of the excitable cell model (Ioos and Joseph, 1990; Wang and Rinzel, 1995; Kuznetsov, 1995). The apparition of non-null amplitude, zero frequency stable oscillations from a saddle at $\bar{g}_{IP} = \bar{g}_1$ was classified as a homoclinic bifurcation at regular saddle. At $\bar{g}_{IP} = \bar{g}_2$, the stable resting solution and the saddle collapsed at a saddle-node bifurcation (of stationary solutions). Finally, at $\bar{g}_{IP} = \bar{g}_3$, the disappearance of zero amplitude, non-null frequency oscillations as the upper solution became stable corresponded to a supercritical Andronov-Hopf bifurcation.

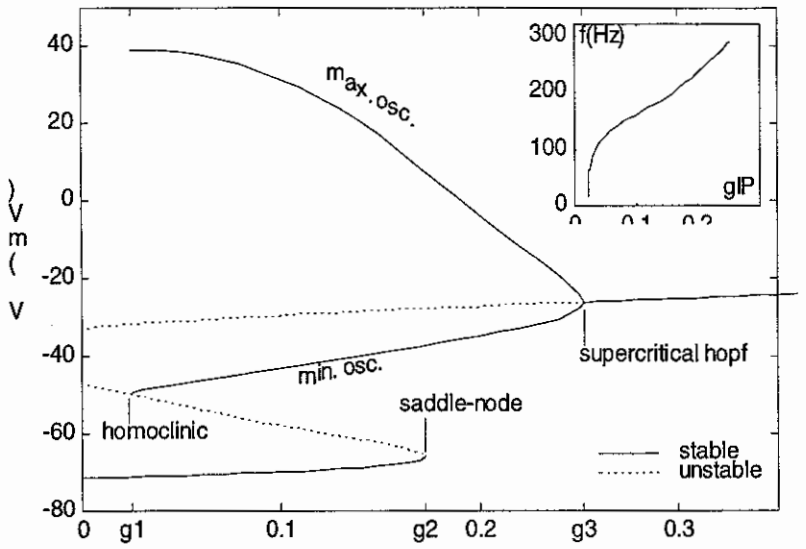


**Figure 5.** Bifurcation diagram of the excitable cell model as a function of $\bar{g}_{IP}$ (see text). Homoclinic at regular saddle, saddle-node, and supercritical Hopf bifurcations occur respectively at $\bar{g}_1$, $\bar{g}_2$ and $\bar{g}_3$ values of $\bar{g}_{IP}$. Insert: firing frequency of stable oscillations.

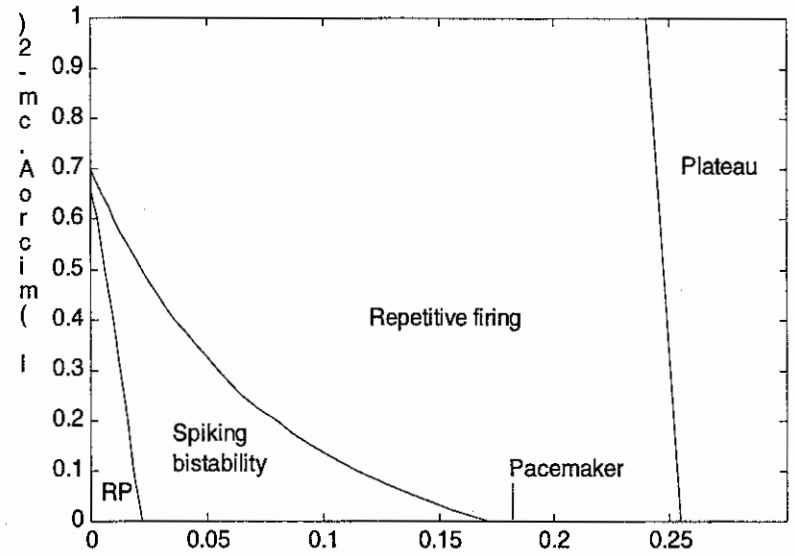


**Figure 6.** Domains of discharge of the excitable cell model in the ($\bar{g}_{IP}$, $I$) plane. RP: stable resting potential. Plateau: stable upper solution (no resting potential). Repetitive firing occurs due to the presence of a constant depolarising injected current and/or the IP conductance. In the domain of spiking bistability, it co-exists with resting potential. For $I = 0$, repetitive firing corresponds to a pacemaker mode of discharge.

Finally, we systematically studied the discharge mode of the model as a function of the injected current, because this parameter represents a major input control on excitable cells. Figure 6 represents domains of excitability in the ($\bar{g}_{IP}$, $I$) plane. Several behaviours are displayed: (1) the basic mode of discharge; (2) spiking bistability; (3) self-sustained spiking alone; and (4) plateau potential alone. The pacemaker mode of discharge described previously corresponded to self-sustained spiking for $I = 0$. As can be seen, it was possible to switch between different behaviours at a given value of $\bar{g}_{IP}$, depending on the constant current injected.

## Comparison with physiological and pathological forms of excitability

The different behavioural modes exhibited by our reduced model of excitable cell can be compared with functional and pathological forms of excitability that have been observed or hypothesised in normal and pathological states. The different examples reviewed in this section are summarised in Table 1.

**Table 1**. Comparison betwen model discharge modes and physiological and pathological states in several excitable cells endowed with IP conductances. See details in the text. References: (1) Cannon and Corey, 1993; (2) Cannon *et al.*, 1993; (3) Hounsgaard *et al.*, 1984; (4) Nielsen and Hultborn, 1993; (5) Connors *et al.*, 1982; (6) Tunnicliff, 1996; (7)Delord *et al.*, 1997; (8) Yang and Seamans, 1996; (9) Laven and Grace, 1998; (10) Cowan and Wilson, 1994.

| Discharge mode | Basic | Spiking bistability | Pacemaker | Plateau bistability |
|---|---|---|---|---|
| Attractors | Resting solution | Resting solution and limit cycle | Limit cycle | Resting and plateau solutions |
| Muscular cells | Normal (1) | Myotonia (2) | / | Periodic paralysis (2) |
| Motoneurons | / | Normal (3) | Spasticity (4) | / |
| Central mammal. neurons | Normal (5) | / | Epilepsy (6) | / |
| Frontal cortex neurons | Schizophrenia (7,8) | Normal (9, 10) | / | / |

*Myotonia and periodic paralysis*

Muscular cells normally display a resting potential from which action potentials can be fired by depolarisation (Cannon and Corey, 1993). However, an increased persistent sodium conductance seems to be responsible for abnormal excitability in myotonia and periodic paralysis (Cannon *et al.*, 1993). In myotonia, once excited above threshold, the cell enters a self-sustained spiking mode that is responsible for maintained muscular contractions that characterise this disease. In periodic paralysis, depolarisation switches the muscular cell from the resting potential to a plateau potential, which precludes spiking (through inactivation of the fast sodium

conductance) and muscular contraction (Cannon and Corey, 1993). In the present model, the 'basic' mode reproduces normal excitability of muscular cells while abnormal forms of excitability occurring in myotonia and periodic paralysis are well described by 'spiking bistability' and 'plateau bistability' modes, respectively.

*Spasticity*

In mammalian spinal motoneurons, excitability is governed by a low-threshold persistent calcium conductance. The functional firing behaviour is a bistability between resting potential and self-sustained spiking (Hounsgaard *et al.*, 1984). In spasticity, patients display stretch reflexes that probably derive from an increased excitability in motoneurons (Nielsen and Hultborn, 1993). During spasticity, the firing of neurones is supposed to last longer than under normal circumstances (i.e. when following bistable patterns). We suggest that during spasticity, an upward regulation of persistent calcium channels could switch motoneurons from 'spiking bistability' to the 'pacemaker' mode of discharge displayed in the present model.

*Epilepsy*

Cortical pyramidal neurones normally fire spikes or bursts of spikes by depolarisation from resting potential (Connors *et al.*, 1982). During epileptic crises, pyramidal neurones enter a state of high excitability and fire spontaneously at high frequency. In vitro, the non-inactivating sodium conductance of cortical neurones is a primary target of widely used antiepileptic drugs, such as phenytoin (Tunnicliff, 1996). Moreover, it can be responsible for pacemaker activity in entorhinal cortical neurones (Dickson *et al.*, 1997). According to our model, an up-regulated sodium conductance driving neurones from the 'basic' to the 'pacemaker' mode of firing could take part to the cortical paroxystic activity encountered during epileptic crises.

*Schizophrenia*

Negative symptoms and working memory deficits in schizophrenia have been related to a dysfunction of frontal cortex (Goldman-Rakic and Selemon, 1997) that is probably linked to decreased dopamine stimulation of this structure (Okubo *et al.*, 1997). In vivo, frontal neurones display bistability between resting potential and spiking (Lavin and Grace, 1998; Cowan and Wilson, 1994) which has been suggested and to participate to sustained activities related to working memory (Guigon *et al.*, 1995; Camperi and Wang, 1998). This bistability is probably subserved by a persistent sodium conductance (Yang *et al.*, 1996; Delord *et al.*, 1997) that is up regulated by dopamine (Yang and Seamans, 1996). Decreased dopamine stimulation in schizophrenia may thus diminish persistent sodium conductances in frontal neurones, resulting in a loss of spiking bistability. In turn, such a change in firing behaviour in some frontal neurones could induce disorganised temporal patterns of activity responsible for working memory deficits in schizophrenia. In the present model, the 'spiking bistability' and 'basic' modes would, therefore, represent the functional and dysfunctional forms of excitability of certain frontal neurones in the case of schizophrenia.

# 4. DISCUSSION

The model studied in this article illustrates distinct modes of excitability that can arise from the presence of a generic persistent inward conductance in an excitable cell. Although many factors are not taken into account (e.g. interacting conductances and spatial dimension), this simple model is capable of reproducing typical features of physiological and pathological cellular excitability. In this section, we first examine some specific aspects of bifurcation in the reduced model. We then discuss the way physiological and pathological states can be described theoretically, in the case of excitable cells, as well as more generally.

As already observed in a higher-dimensional model endowed with an IP conductance (Delord *et al.*, 1997), the present model of excitable cell can display a bistable mode of discharge between resting potential and self-sustained spiking (spiking bistability). The corresponding limit cycle appears at a homoclinic bifurcation at regular saddle, i.e. oscillations arise aside the resting potential, with zero frequency and non-null amplitude (full spikes). This behaviour can be classified as type I excitability according to experimental and theoretical criterions (Arvanitaki, 1939; Hodgkin, 1948; Wang and Rinzel, 1995). Spiking bistability of type I has been shown in the Morris-Lecar model, when the recovery variable time constant is decreased (Rinzel and Ermentrout, 1989), and in the FitzHugh-Nagumo model, with increased extracellular $K^+$ and injection of a constant hyperpolarising current (Rinzel, 1985). Spiking bistability was also observed in type II excitability, where oscillations appear through subcritical Andronov-Hopf bifurcations (Wang and Rinzel, 1995), as it is the case in the Hodgkin-Huxley model (Rinzel, 1990). In the present model, spiking bistability displays two interesting features: (1) it appears at physiological density (French *et al.*, 1990) of a widely distributed generic type of conductance for a large domain of the ($\bar{g}_{IP}$, $I$) plane, rather than from particular parameter tuning (as in homoclinic bifurcations cited above); (2) contrary to type II (Hopf bifurcation) spiking bistability, resting potential and self-sustained spiking lie in disjoined potential ranges. In principle, this should allow for a more robust segregation of the two regimes under physiological noisy inputs, which might be important in a functional perspective (Conway *et al.*, 1988; Wang and Ross, 1990).

As emphasised in Section 3, the qualitative behaviours displayed in the present model can be compared to experimentally described physiological and pathological forms of excitability in several excitable cells. Here, attractors allow for a qualitative description of these states. However, they are not necessarily described by single attractors, but can correspond to sets of attractors, as in the case of spiking and plateau bistabilities. Moreover, in different cells, the same attractors or sets of attractors can describe physiological or pathological states. Therefore, in this very simple model, the direct identification between some particular attractors and physiological and pathological states is not straightforward. Hence, in more complex systems (e.g. with multiple levels of organisation), the situation might well become definitely ambiguous.

In the present model, physiological and pathological states are separated by bifurcations (i.e. through changes in model parameters). Theoretically, apparition of pathology by bifurcation can be viewed as accounting for a trauma leading to some irreversible structural (parameter) changes in a system. However, many diseases are reversible and display stereotyped temporal patterns in the transitions between physiological and pathological states. In terms of dynamical systems, these evolutions

correspond to trajectories in the phase-space between co-existing physiological and pathological attractors (which is not the case in the present model). In such models, pathology appears by (a pathogenic) perturbation in the phase-space. These models present the advantage of possibly providing information on prophylactic and therapeutic strategies. However, they typically require additional information, for example constraints transforming previous bifurcation parameters into new dynamical variables.

Finally, we would like to emphasise the importance of other theoretical concepts of dynamic systems in the description of pathology. For example, the size of the basin of attraction of a physiological attractor is relevant to pathology because it sets the maximal size for perturbations that do not displace the system toward the pathological attractor(s). Sometimes, attractors are simply not needed to describe pathology. For example, long action potentials due to abnormal persistent sodium currents in cardiac cells (Bennet *et al.*, 1995) participate in a congenital form of cardiac arrhythmia that can lead to sudden-death. In that case, pathology comes from an abnormally slow transitory behaviour rather than a qualitative change of the system's stability. More generally, the time constant with which a perturbed system returns to its physiological state can be important, because spending too long away from homeostatic conditions may have pathological consequences.

In summary, the model studied in this article constitutes a good example because attractors allow for a qualitative description of pathological states in several excitable cells. However, a satisfactory description of pathology may require other concepts from the theory of dynamical systems, or additional constraints, in order to obtain a dynamic description of the relation between physiological and pathological states.

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