Abnormal frequency locking and the function of the cardiac pacemaker

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A heterogeneous reaction-diffusion medium consisting of two adjoining uniform regions is analyzed. The first region is a purely oscillatory one, while the second is bistable (oscillatory/excitable). We show that such a construction allows an abnormal domination of the low natural frequency of the oscillatory regime over the whole medium (abnormal frequency locking). Bifurcations leading to the appearance of the bistable regime are discussed as well as the specific dynamics of the bistable oscillations. The abnormal frequency-locking phenomenon could explain some dynamical properties of the cardiac pacemaker.

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I. INTRODUCTION

Synchronized motion of coupled oscillators is a common phenomenon in the exact and life sciences. A prominent example is the oscillations of electrical excitations in the human heart [1–3]. The excitations (action potentials) are periodically initiated by a specialized group of oscillating cells, the cardiac pacemaker, also called the sinus node (SN). Following initiation, the action potential travels throughout an excitable tissue (atria), reaching another small oscillating area called the atrioventricular node. Although the natural frequency of isolated atrioventricular node cells is lower than that of isolated SN cells, both nodes, as well as the atria, normally oscillate with an equal frequency, the higher of the two (frequency locking).

Similar high-frequency locking situations also appear both in a limit cycle (LC) region driven by an external fast oscillator, as well as in the case of two adjacent LC regions of different frequencies (see, e.g., Refs. [4–6], and references therein).

In the present work we demonstrate an *opposite* effect where the *lower* frequency becomes dominant over the whole composite medium.

Such "abnormal" frequency locking occurs in a simple system comprised of two uniform, spatially adjoining regions of different types: a pure LC region, and a bistable (LC/excitable) one. This type of bistability, also known as oscillators with "black holes," portrays the dynamics of real biological systems (see Ref. [7] and references therein). We demonstrate that the above formation indeed leads to the abnormal dominance of the lower frequency. We also examine the bistable mode creation, as well as the bifurcation mechanism leading to the frequency change of the bistable oscillations. The relevance of the obtained results to the function of the cardiac pacemaker is discussed.

II. PHENOMENON

We consider the one-dimensional (1D) FitzHugh-Nagumo (FHN) partial differential equations [8]:

$$\frac{\partial v}{\partial t} = \frac{\partial^2 v}{\partial x^2} + v(v-a)(1-v) - w, \tag{1}$$

$$\frac{\partial w}{\partial t} = \varepsilon(v - dw),$$

where $\varepsilon=\varepsilon_1$ if $x\leqslant x_0$, and $\varepsilon=\varepsilon_2$ if $x>x_0$. We set $\varepsilon_2>\varepsilon_1$. Here $v(x,t)$ stands for the *activator*, embodying, e.g., the *action potential* in the heart, while $w(x,t)$ is the *inhibitor*, or a *refractoriness* function. a is the *excitability* parameter [9]. Roughly speaking, $a<0$ produces an LC behavior, while $a>0$ yields an excitable case. In this work we set $a=-0.16$ in both regions. The parameter ε, usually small, specifies the ratio between the time constants of the activator and the inhibitor; d is a parameter. The time t is measured in units of the activator time constant. Neumann boundary conditions are imposed at both ends of the integration domain. The natural frequency of an FHN pure oscillatory medium is related to the magnitude of its ε: in the range of small values of ε, the larger is ε, the higher will be the frequency (e.g., Refs. [5,6]). We generally use increments of $\Delta t=1$ and $\Delta x=1$ for the numerical integration. Note that all parameters and variables are dimensionless. The value ε_2 will be selected in such a way that the right uniform region $x>x_0$ is in a bistable regime.

What happens in the $x>x_0$ region when the corresponding ε is varied? As long as ε remains sufficiently small, we have a pure LC, and an unstable focus $v=w=0$ inside. An increase in the value of ε leads to a bifurcation transition from this unstable focus into a stable one. This is accompanied by the creation of a closed *separatrix* curve, between two concentric basins of attraction: an internal stable focus, and an external stable LC. A further increase of ε pushes the separatrix curve towards the LC contour, which will eventually lose its stability via a subcritical Hopf bifurcation. Bifurcation values of the parameter ε specifying the borders of the bistable regime may thus be determined. By standard stability analysis, it follows in particular that in the vicinity of a stable focus, the eigenvalues of the linearized system (1) must be complex conjugate with negative real parts [10]:

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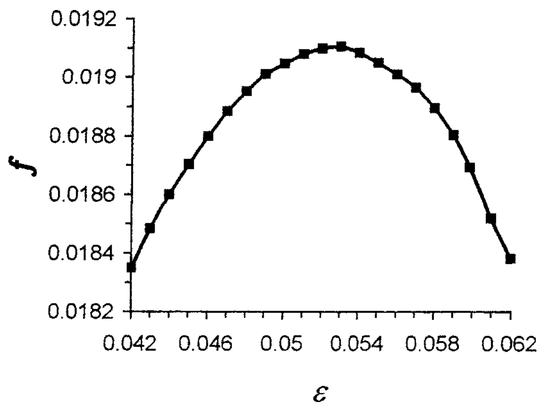

FIG. 1. The frequency f of a single oscillator as a function of the parameter $\varepsilon(a=-0.16, d=3, \Delta t=0.1)$. The maximum f value corresponds to the bifurcation transition from a pure LC behavior to a bistable one (see text).

$$4\varepsilon - (\varepsilon d + a)^2 > 0 \text{ and } (\varepsilon d + a) > 0. \quad (2)$$

The second condition yields

$$\varepsilon > -a/d, \quad (3)$$

giving $\varepsilon > 0.053$ for the selected values $a=-0.16$ and $d=3$.

It is interesting to note that the above-mentioned direct relation between ε and the frequency f of oscillations in a pure LC regime transforms into an inverse relation in the bistable regime. This frequency decrease (Fig. 1) can be explained by the size increase of internal basin of attraction. Our simulations reveal that the oscillations in the bistable regime exhibit slow motions in the vicinity of the separatrix, which increases with the size of the basin of attraction. Thus the maximum of the function $f(\varepsilon)$ presents an additional way of determining the lower ε limit of the bistable regime. Indeed the maximum in Fig. 1 occurs at $\varepsilon = 0.053$.

Before describing the main results of this work, let us mention that traveling waves and pulses in different spatially *uniform* bistable media have previously been investigated [11–14]. In particular a bistable FHN-like medium, where the bistability was obtained in a different way, was treated in Ref. [11]. It was shown that for an initially stable excitable regime [$a > 0$ in Eq. (1)] an increase of ε results in the appearance of a bistable (LC/excitable) regime via a subcritical Hopf bifurcation. The main disadvantage of this approach is that the generated activator pulses have small amplitude, while the inhibitor pulses exhibit abnormally large amplitude, and are therefore unsuitable for biological modeling. Nevertheless, an important distinctive feature of the medium in the bistable regime (which is also true in our case) was obtained in Ref. [11]: in spite of the fact that each medium point can oscillate with a fixed frequency, they display, when coupled, a sort of excitable dynamics. In other words, the application of a local, above threshold stimulation, results in the propagation of a *single* pulse.

We examine a system similar to the one previously used to study the effect of wave *pseudo reflections* for which usual frequency locking was responsible [6]. Here however, we show how the above-mentioned bistability feature in a *heterogeneous* medium leads to *abnormal* frequency locking. This comes about as follows: when the uniform bistable region operates in the excitable regime, it can only conduct a train of pulses generated by the adjoining pure LC region. This means that *any* frequency (even very low) of the LC region dominates the bistable one. Abnormal frequency locking takes place when the pure LC frequency is lower than the natural (uncoupled) frequency of the bistable region. This phenomenon is presented in Fig. 2, for $\varepsilon_2 = 0.058$. An initial local excitation is launched at point x_1 of the bistable region generating two oppositely propagating pulses [Fig. 2(a)]. The right traveling pulse vanishes after reaching the right Neumann boundary, because this boundary represents a reflection symmetry, and its action therefore is equivalent to the collision of two counterpropagating pulses; their combined effect, however, is not strong enough for this value of ε in order to allow the crossing of the separatrix contour into an LC regime. Meanwhile, the original left-going pulse, is *pseudoreflected* at the LC/bistable region interface, eventually causing a right-going train of pulses to propagate into the whole bistable region [Fig. 2(b)]. We used the term pseudoreflection in our previous work [6], where the dynamics of two different pure LC regions was analyzed. Here we consider a *limiting case* of pseudoreflection where a *single* pulse is replaced by an oppositely propagating sequence of pulses. The pure LC region in the present case operates as a "spatially extended driver," whose natural frequency determines the frequency of the pseudoreflected pulses; this effect, too, is similar to the one in Ref. [6].

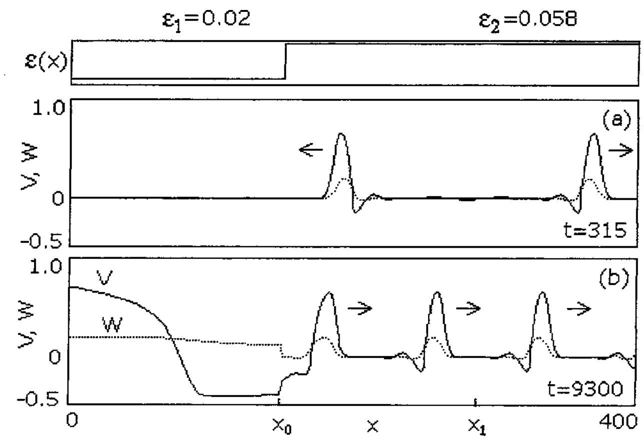

FIG. 2. The development of abnormal frequency locking in a medium with two uniform regions ($a=-0.16, d=3$ throughout). The LC region on the left ($\varepsilon_1 = 0.02$) has a lower natural frequency than that of the bistable region ($\varepsilon_2 = 0.058$) on the right. An exciting pulse is launched in the right region causing: (a) two pulses oppositely propagating in the bistable region; (b) a low-frequency train of pulses arising as a result of pseudoreflections at the interface occupies the whole bistable region. Wavelength increase is observed in the left region which operates as a spatially extended driver.

A slight decrease in ε_2 can result in a drastic change of the medium dynamics as illustrated in Fig. 3 for $\varepsilon_2 = 0.055$. Upon reaching the right Neumann boundary, the combined amplitude of the right-going activator pulse and its image now rises beyond the separatrix in the LC regime. A pseudoreflec-

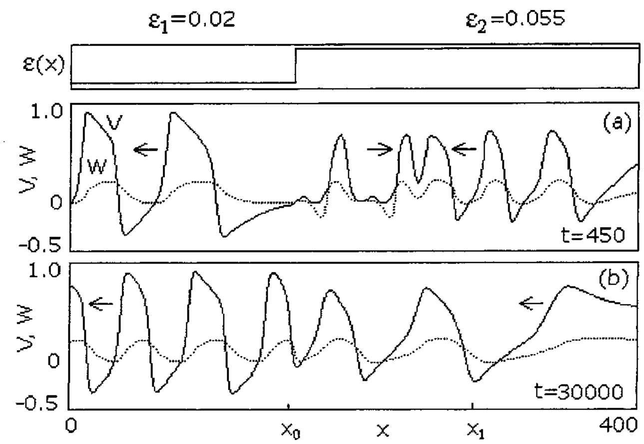

FIG. 3. A system similar to that of Fig. 2, except that $\varepsilon_2 = 0.055$. Here the usual frequency locking of the higher frequency takes place: (a) collision of the high-frequency waves from the right Neumann boundary with the lower-frequency train of pulses emerging from the interface; (b) the high-frequency waves occupy the whole medium. Wavelength increase is observed in the right region which now operates as the spatially extended driver.

tion thus takes place at the boundary, from which a left-going wave train begins to propagate [Fig. 3(a)]. The frequency of these waves is nearly the same as that of the natural oscillations in the bistable region, and is *higher* than that of the pure LC region. Thus, via the usual frequency locking process, this frequency will ultimately dominate the entire system. The bistable region on the right now operates as the spatially extended driver for the wave train in the left pure LC region [Fig. 3(b)].

Yet another situation is depicted in Fig. 4, where a third region, with $a \geqslant 0$ (excitable regime), is adjoined at the right edge of the system. As is generally known, no reflection occurs at the new boundary, except for a few specific cases [14,15] not considered here. Furthermore, no reflections occur at the interface between the bistable and excitable regions, for a wide range of ε values in the excitable region, $\varepsilon_3 \geqslant 0.01$. Note that this behavior differs from the pseudoreflections that do occur at the interface between pure LC and excitable regions (see Ref. [4]). Thus in such an extended medium (LC + bistable + excitable) only abnormal frequency locking is observed (Fig. 4) even for lower ε_2 values.

III. POSSIBLE APPLICATION

In addition to its obvious theoretical interest, we wish to discuss the possible importance of the abnormal frequency

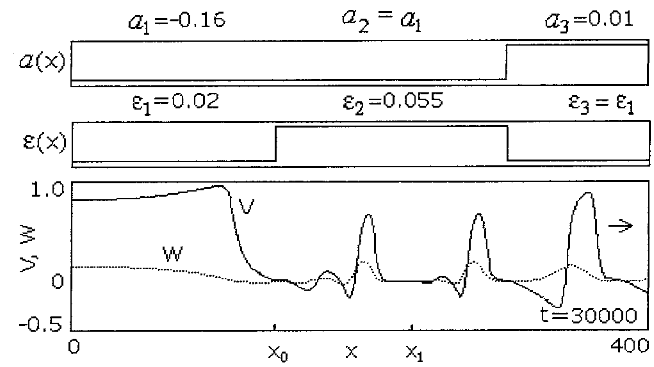

FIG. 4. The system of Fig. 3, with an additional excitable region ($\varepsilon_3 = 0.02, a_3 = 0.01, d = 3$).

locking obtained here for modeling the cardiac sinus node (SN). Despite the existence of a large number of experimental and theoretical works (see, e.g., Refs. [16–21]), the exact structure of this organ, as well as its intricate dynamics, are still far from being completely understood. The main problem is that the existing models of the cardiac SN which allow a good microscopic representation of the organ [16,17], typically include many equations and parameters, making them hardly tractable analytically. Simple models such as the FHN, or its modifications have also been developed (see references in Refs. [4–6]). However, they all suffer from the following problem: It is widely agreed that the SN is a strongly heterogeneous organ composed of at least two regions (see e.g., Ref. [16]): namely, a centralregion, and a peripheral zone or a perinode. Experimental results show that the intrinsic pacemaker activity of cells in the SN periphery is faster than that in its center [16,17]. Nevertheless, the overall frequency of the entire SN in the heart is smaller than that of the perinode alone. The simple models mentioned above are unable to portray this feature. An existing explanation used in the more complicated models (e.g., Refs. [16,20]) is that in a normally operating heart, the higher frequency of the perinode is decreased by the surrounding atrium. An alternative explanation in the context of the simple FHN model is offered here by way of the abnormal frequency-locking mechanism. Thus the SN center can be simulated by a low-frequency, pure LC region, while the perinode is *assumed* to be a bistable region. Due to the abnormal frequency locking, the low-frequency center operates as the driver of the entire heart. Furthermore, the bistable region can prevent pseudoreflections at the SN/atrium interface.

Some experimental results (see, e.g., Ref. [21]) show that part of the real SN cells actually operate in the bistable regime, as described in this work.

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