Standing waves in the FitzHugh-Nagumo model of cardiac electrical activity

P. C. Dauby,* Th. Desaive, and H. Croisier
Institut de Physique B5a, Université de Liège, Allée du 6 Août 17, B-4000 Liège 1, Belgium

Ph. Kolh
Hemodynamic Research Center (HemoLiège), Université de Liège, Tour de Pathologie B23, avenue de l'Hôpital 13, B-4000 Liège 1, Belgium

(Received 22 June 2005; revised manuscript received 4 November 2005; published 16 February 2006)

When excitable media are submitted to appropriate time dependent boundary conditions, a standing wave-like pattern can be observed in the system, as shown in recent experiments. In the present analysis, the physical mechanism explaining the occurrence of such space-time patterns is shown to be a competition between Ohmic diffusion and an action potential propagation across the system, coupled with the existence of refractory states for excitable media.

DOI: 10.1103/PhysRevE.73.021908 PACS number(s): 87.19.Hh, 05.45.−a

I. INTRODUCTION

Excitable systems have become standard models to describe the heart electrical activity and it is well known that a large variety of structured and ordered dynamical behaviors can be observed in such spatially extended excitable systems. It is the purpose of the present work to study one of these behaviors, namely the occurrence of a kind of standing wave when the system is periodically forced at its boundaries.

Usually standing waves appear in linear systems as a result of the superposition of two counter propagating waves. An important characteristic of these patterns is the occurrence of spatial nodes, where the amplitude of the time oscillations vanishes. Moreover, for such linear standing waves, the oscillations of the different spatial points are always in phase. Excitable systems are instead described by highly nonlinear equations with no superposition principle. Moreover, the interaction of nonlinear waves is such that two colliding pulses usually annihilate, even if crossing is also possible in some cases [3]. For these reasons, a completely different concept of "standing wave" must be introduced in excitable media. In the following, we will consider that "standing waves" in excitable systems are defined by the occurrence of "nodes" at which the amplitude of the time oscillations has a local spatial minimum which can be different from zero. We will also see that such standing waves usually do not give rise to in-phase oscillations of the system.

Standing waves in excitable systems were recently discovered in experiments carried out on an isolated rabbit heart [1]. Two ring shaped electrodes were fixed at the top and bottom of the heart and it was observed that when an alternative electric field of sufficient strength is applied between these electrodes, a dynamical behavior looking like a standing wave can appear in the myocardium. The experiments also suggested that these standing waves can be in close relation with fibrillation in the heart. Indeed, when the amplitude of the forcing is too weak to induce standing waves, fibrillation was usually observed when the electrical forcing is terminated, while no such behavior is displayed when the electrical field was high enough to generate the standing waves. For this reason, a detailed analysis of standing waves in excitable media is of primary importance in order to better understand the mechanism of cardiac defibrillation.

In Ref. [1], the authors also show that numerical simulations of the so-called "tridomain" model can provide dynamical solutions similar to the experimentally observed standing waves. In particular, the numerical study shows that the standing waves have a unique node in a one-dimensional (1D) geometry while a two-node solution can be displayed when a spatially nonhomogeneous two-dimensional system is considered, in agreement with their observations.

Recently, a first theoretical analysis of standing waves in cardiac muscle was proposed in Ref. [2]. Numerical simulations with the FitzHugh-Nagumo and the Luo-Rudy models are reported which show that standing waves in excitable media are completely general phenomena whose study do not require the tridomain model. It is also claimed in that work that the nodes of the standing waves are similar to the points in the core of a rotating vortex where the amplitude goes to zero. However, no proof of this suggestion is provided in the text and the authors concede in the conclusion section that further analysis is still needed to decide whether their approach can explain the observations. Finally, the authors emphasize interesting analogies with solutions of general Ginzburg-Landau equations and with different physical phenomena described by these equations.

In the present work, we concentrate on the physical origin of standing waves in excitable media, which are a truly surprising nonlinear behavior. We propose a detailed analysis of the physical mechanism explaining the occurrence of standing waves in excitable media. The principle of this mechanism rests on an interplay between Ohmic diffusion, the propagation of action potentials (pulse propagation), and the existence of refractory states.

The study of the mechanism is presented in the next section. Then, a comparison with previous works and the conclusion are given in Sec. III.

*Electronic address: PC.Dauby@ulg.ac.be

II. MECHANISM OF STANDING WAVES

Since all the different mathematical models considered in Refs. [1,2] show the occurrence of standing waves, the phenomenon can be considered as generic. For this reason, only the simplest qualitative FitzHugh-Nagumo model will be used in this paper to illustrate our point. Moreover, only a 1D approach will be considered since the mechanism we will underscore is one dimensional in essence. To describe the heart as an excitable medium, we thus use the following equations corresponding to the well-known FitzHugh-Nagumo model [4] in a one-dimensional situation:

$$\partial_t u = D\partial_x^2 u + A^2(u - U_m)(u - U_s)(U_M - u) - v, \qquad (1)$$

$$\partial_t v = \epsilon(u - gv), \qquad (2)$$

where u is the membrane potential, v is a (slow) gating variable, D is the diffusion coefficient, and A, U_m, U_s, U_M, g, and ϵ are constants. The external stimulation of the system is introduced thanks to the boundary conditions. In this work, a sinusoidal variation of the potential is imposed at the "left" ($x=0$) and "right" ($x=L$) boundaries of the 1D domain of length L, with a phase lag equal to π: $u(x=0,t)=U\sin\omega t$ and $u(x=L,t)=U\sin(\omega t+\pi)$, where U and $f=P^{-1}=\omega/2\pi$ are the amplitude and frequency of the forcing (P is the period). The numerical resolution of these equations was carried out using the Crank-Nicholson method. Except otherwise stated, the values of the parameters used in the calculations are the following: $D=1$, $A=1$, $U_m=0$, $U_s=0.1$, $U_M=1$, $g=2.5$, and $\epsilon=0.01$ (due to the qualitative nature of the FitzHugh-Nagumo model, the units remain arbitrary). The rest state of the system $u=0$, $v=0$ is then stable and will be used as an initial condition for all calculations. Note also that the transient behavior of the system (a few periods of the excitation) is never represented in the results described below.

We have already mentioned that only strong enough alternating electric fields were able to generate standing waves in experiments [1]. As preliminary numerical simulations, we have checked that the mathematical FitzHugh-Nagumo model also displays this property and we have even shown more generally that in a semi-infinite 1D system, the amplitude of a sinusoidal forcing at the boundary must be larger than some critical value in order to generate an action potential which actually propagates across the domain. If the amplitude is smaller than this threshold, a perturbation is generated close to the border but no propagation is initiated. The solid curve in Fig. 1 is a plot of this critical value U_c of the forcing potential as a function of the frequency f. To obtain these results numerically, L was fixed to a large value ($L=50$), a sinusoidal potential was used on the left boundary while a no-flux condition was introduced at $x=L$. It is worth noting that the curve $U_c(f)$ displays a minimum for some frequency. Moreover, it is interesting to note that the period P corresponding to this minimum is more or less equal to the duration of an excitation, i.e., the time needed for an excited cell to return to its rest state. We can also see that for large values of f, no propagation can be initiated, whatever the value of U: indeed, if too fast transitions from negative to

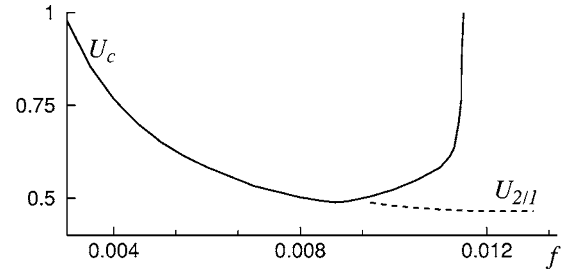

FIG. 1. Critical value U_c of the boundary condition allowing propagation of a pulse against the frequency f of the forcing (solid line). The dashed line corresponds to the threshold $U_{2/1}$ allowing the propagation of one pulse every two excitations.

positive values are imposed to the potential on the boundary, the medium close to the border, and whose potential has been brought to negative values has no time enough to recover and is still in a refractory state when positive values of u could induce the propagation of a new pulse. For those large values of f, however, it is possible to determine a critical $U_{2/1}$ above which a pulse can be initiated one time out of two. In Fig. 1, this critical $U_{2/1}$ is plotted with dashed lines. In the following, the amplitude of the forcing U will always be fixed at 1, since for this value propagation is possible for a large range of frequencies. Moreover, due to the steepness of the right part of the solid curve in Fig. 1, a further increase of U would not enlarge much the frequency range allowing propagation.

Consider now the mechanism giving rise to standing waves in excitable media and let us describe how the competition between the propagation of action potentials, or pulse propagation, and Ohmic diffusion within the medium can lead to the occurrence of nodes. Imagine first that a negative electrical potential is imposed at a boundary. This forcing can be considered as a perturbation of the system with respect to its rest state. Due to Ohmic diffusion, the cells adjacent to the boundary will also be brought to a negative potential but no excitation will be induced in the neighborhood of the border of the domain. For this reason, the perturbation imposed at the boundary will propagate towards the opposite side by Ohmic diffusion only. The velocity of such a diffusive process is known to be a decreasing function of time and can be estimated by $v_\Omega \approx \sqrt{(D/t)}$. Consider now that a positive potential is imposed on a boundary. The Ohmic diffusion just described is, of course, still active but a propagating pulse can also be generated, whose motion is a combined effect of diffusion and excitability. For fixed values of the parameters of the model, the velocity v_P of the pulse in an infinite domain is a constant. This velocity can be estimated by analytical formulas in the case of the FitzHugh-Nagumo model [4] but can also be determined more precisely by numerically integrating Eqs. (1) and (2). In finite domains, the pulse velocity v_P is a bit smaller, due to the presence of the boundaries. The order of magnitude of this velocity was estimated by tracking the motion of a pulse along the x axis in a domain with $L=25$ and for $f=0.008$. For the values of the parameters given above, we found the value $v_P=0.3957$ (12% smaller than in an infinite domain) which is used in the rest of the paper. It is then interesting to notice

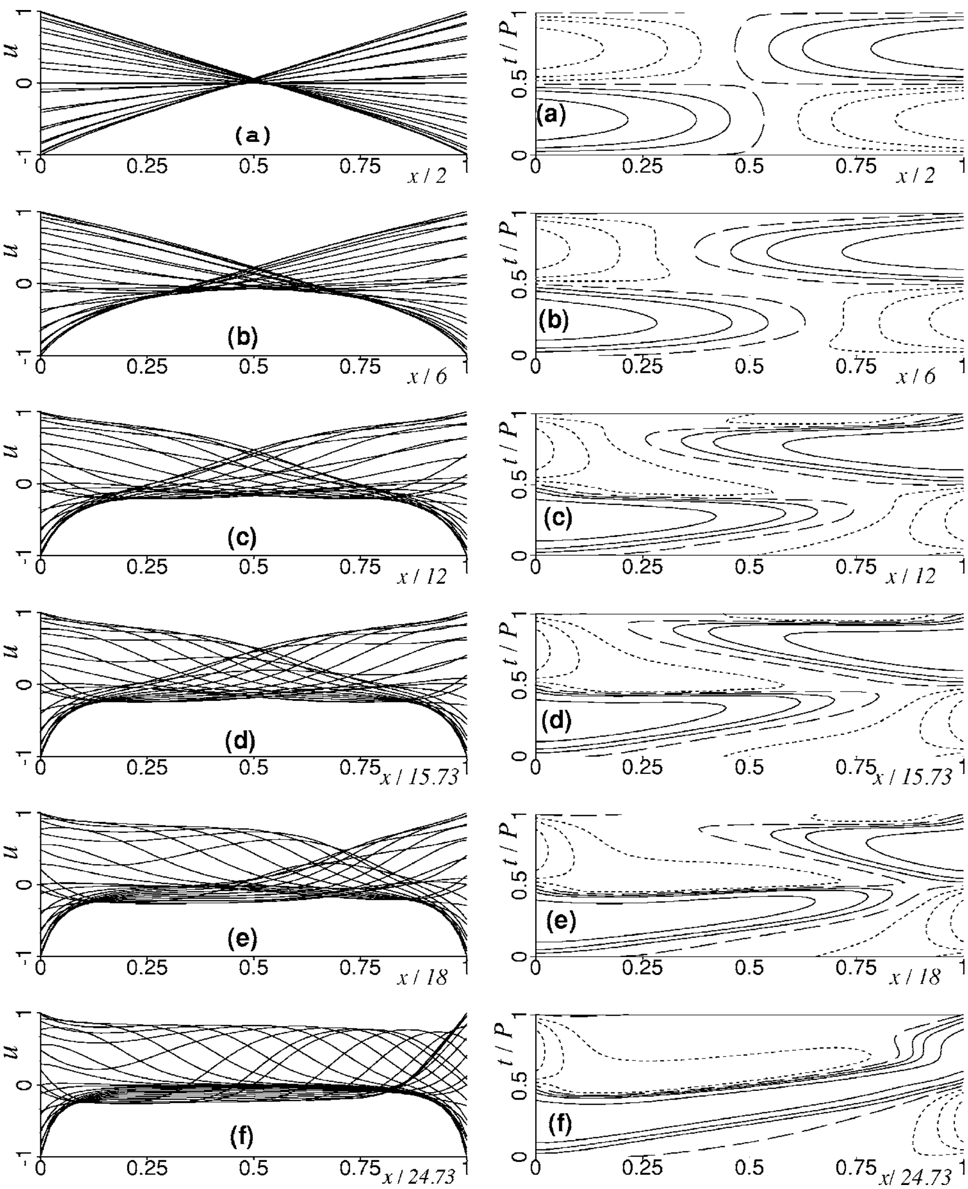

FIG. 2. Snapshots (left column) and corresponding space-time contour plots (right column) describing the evolution of the potential u for $f=0.008$. In the contour plots, the isolines with $u=0,\pm 0.15,\pm 0.3,\pm 0.6$ are represented, dotted lines are used for negative values, and long dashes for $u=0$ ("front"). From top downwards, the different pictures correspond, respectively, to $L=2$ (a), 6 (b), 12 (c), $L_{cn}=15.73$ (d), and 18 (e) and $L_{nn}=24.73$ (f).

that because of the dependence of v_Ω with respect to time, the diffusion velocity on short time and length scales is larger than the velocity v_P of the pulse. For this reason, the propagation of a positive perturbation of u is mainly diffusive over small distances. On the other hand, excitability and pulse propagation with constant velocity become dominant for larger time intervals or distances.

The formation of nodes in small domains can then be understood as follows. In the first half period of the external forcing, a positive potential is imposed on the left, while u is negative on the right. The perturbations imposed on the two boundaries propagate in the medium and collide somewhere in the domain. Since L is small, the time scale is too short for a pulse to propagate from the left and both perturbations are transported by diffusion, with the same velocity $v_\Omega \approx \sqrt{(D/t)}$. The collision thus occurs in the middle of the domain, where u keeps its rest value 0. Of course, the conclusion is the same for the second half period of the forcing and a minimum appears at the center of the domain in the envelope curve of Fig. 2(a) (left). This node is characterized by an amplitude of oscillations which remains equal to zero. It is possible to estimate the maximum length L_Ω for which such a node exists. This length can be defined by the fact that the time $\tau_P=(L_\Omega/2)/v_P$ needed by a pulse to arrive at the center is equal to the time $\tau_d=(L_\Omega^2/4)/D$ which is necessary for a perturbation to be transported by diffusion to the center of the domain. One thus gets $L_\Omega=2D/v_P\sim 4.4$. It is worth noting that this result is independent of the frequency f of the forcing and numerical integrations of the equations confirm these results, by displaying a node of vanishing amplitude for L smaller than the value given above, whatever the frequency of the forcing.

If the length of the domain gets larger than L_Ω, the positive perturbations move towards the opposite side using pulse propagation, which is in this case faster than diffusion. Consider then the motion of the "front," which we define as the place x in the domain where $u=0$ [long dashes in Fig. 2 (right)]. During the first half period, the position of the front goes through a maximum, that will be denoted f_L, which is larger than $L/2$. Similarly, during the second half period, the maximum penetration of the front from the right has coordinate $f_R < L/2$. Consequently, the node, which is the minimum of the envelope curves in Fig. 2 (left), is always located in the center of the domain and has intrinsically a nonzero amplitude: indeed, it is only in the limiting case of $L < L_\Omega$ that this amplitude vanishes, as we have seen it above. The occurrence of nodes with a nonzero amplitude thus makes our point of view quite different from that presented in Ref. [2], where the nodes are related to a zero amplitude for the oscillations. Another consequence of the true propagation of pulses as soon as $L > L_\Omega$ is the fact that the different spatial points of the domain do not oscillate in phase [Fig. 2 (left)], which makes standing waves in excitable media quite different from the usual linear standing waves.

It is also useful to introduce the following interpretation of the appearance of nodes. We can, in fact, consider that nodes are displayed because the propagation of each pulse is stopped when the front encounters a refractory region. This refractory region can be induced by diffusion of the negative potentials imposed on the opposite side [Figs. 2(a) and 2(b)], or it can also consist in the refractory tail of the previous pulse coming from the other boundary [Figs. 2(c) and 2(d)].

Another important phenomenon appears when the width of the domain is progressively increased. For L larger than some critical value L_{cn} (index "cn" stands for "central node") the node begins to move off the center (either to the right or to the left, depending on the initial conditions). The appearance of such a noncentral node is due to the interaction of a pulse arriving at a boundary with the next pulse generated at that boundary. When L (larger than L_Ω) remains rather small, all pulses are stopped by the refractory zone generated by the negative diffusing potential at the opposite boundary [Fig. 2(b)]. If L is increased, a pulse can also meet the refractory tail of the previous wave and stop anyway [Figs. 2(c) and 2(d)]. In both cases, however, it is interesting to note that the amplitude of the pulse arriving close to a refractory zone will decrease, due to the interaction with the negative u in front of it. It is also important to understand that if L is rather small, a pulse coming from the left, for instance, will have completely disappeared before the next pulse starts to propagate from the right. For this reason, the pulse from the left has no influence on the departure of the next pulse from the right. The critical length L_{cn} associated with the occurrence of a noncentral node is defined by the fact that a vanishingly small positive perturbation arrives at the opposite boundary precisely when the potential imposed at that boundary goes from negative to positive values, which means that the excitation of the next pulse is just beginning at that time [Fig. 2(d)]. For larger L, a small collision will occur since a small pulse, with a nonzero amplitude, will perturb the birth of the next wave and slightly delay its departure. Moreover, the new pulse will have to face the refractory tail of the previous one and will stop prematurely. The symmetry between the pulses coming from the two sides of the domain is then broken and a noncentral node appears [Fig. 2(e)]. In Fig. 3, the critical length L_{cn} is plotted as a function of the frequency of the forcing. The curve was numerically obtained by determining for each f the largest L giving rise to a central node. However, for not too large frequencies, the variations of L_{cn} can be theoretically explained as follows. Assuming that the

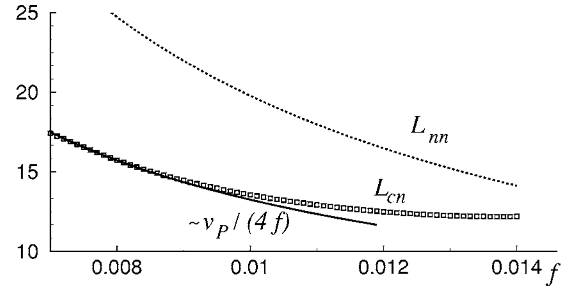

FIG. 3. Critical lengths L_{cn} and L_{nn} in terms of the frequency f of the forcing. The curve $L_{cn} \sim v_P/(4f)$ is also given (and is such that the theoretical value for $f=0.008$ is equal to the result obtained numerically).

origin of the vanishingly small pulse arriving at the right border is the maximum of the potential imposed on the left border, the time needed by this pulse to cross the domain is of order $P/4$. If the period of the forcing is increased by ΔP, then the change in the critical length allowing a noncentral node will be of order $\Delta L_{cn} = v_P \Delta P/4$ and one can thus write $L_{cn} \sim v_P P/4 = v_P/(4f)$. This theoretical determination of the critical length is also represented in Fig. 3 and it is seen that the agreement with the numerical results is very good for small f. For large frequencies, the period of the forcing becomes smaller than the duration of an excitation and, as already discussed in relation with Fig. 1, more complex interactions between successive pulses can occur and make our simple model nonvalid.

When the length of the domain is increased further from L_{cn}, the node progressively moves from the center towards one of the boundaries. Eventually, for L larger than some critical L_{nn} ("nn" stands for "no node"), the node completely disappears. Indeed, if the domain is large enough, the motion of a pulse is not affected by the negative potential imposed far in front of it. Its amplitude is thus constant during the motion and for an appropriate length L_{nn}, its arrival at the opposite boundary is exactly in phase with the condition imposed on that boundary for the potential u. This critical length L_{nn} can also be seen as the minimum length for a full collision between the arriving pulse and the next nascent one, which is, in fact, completely stopped before leaving the boundary. An estimate of this critical length is easily obtained by considering the distance covered by the pulse in half a period. One gets $L_{nn} = v_P P/2 = v_P/(2f)$. This curve is also represented in Fig. 3 and the space-time evolution of the potential u for this critical length is given in Fig. 2, f, where no node is displayed. Let us mention that when L is larger than L_{nn}, the collision between the pulses coming from the two boundaries occurs somewhere in the domain and the two action potentials annihilate each other, as expected.

III. DISCUSSION AND CONCLUSION

In the first theoretical analysis of standing waves mentioned above [2], the authors propose that the nodes of the standing waves are similar to the points in the core of a rotating vortex where the amplitude goes to zero. However, only analogies are proposed and no genuine mechanism is proposed to explain the phenomenon. In the present paper, the mechanism giving rise to standing waves in excitable media is clearly underscored, and is shown to be based on the competition between diffusion and propagation. We have also seen that the amplitude of the oscillations at a node is usually not zero, which makes the comparison with the rotating vortex referred to above not valid in most situations. Indeed, it is only in the limiting and very special case of a vanishingly small length L that the amplitude at a node tends to zero. From this point of view, the present work, in which domains of any length are studied, is also more general than the analysis presented in Ref. [2]. Moreover, it is interesting to note that the experimental results presented in Ref. [1] clearly show the occurrence of nodes with nonzero amplitudes. For this reason, a theoretical analysis may not be restricted to small L and the description of standing waves in larger domains is also essential to understand the experiments.

As a conclusion, let us briefly summarize our point. We have defined standing waves in excitable media by the occurrence of spatial "nodes" in the space-time behavior of the system, i.e., the occurrence of points where the amplitude of the time oscillations has a local spatial minimum (possibly different from zero). These standing waves were analyzed in detail and a mechanism was proposed to explain thoroughly the occurrence of such patterns. We have shown that a competition between the diffusive propagation of perturbations and pulse propagation, coupled with the existence of refractory states for excitable media, accounts for the standing waves that had been observed experimentally. It was also shown that the behavior of the excitable medium depends crucially on the dimension of the domain. Three new critical lengths were underscored in 1D domains and their physical interpretations were discussed. The first (L_Ω) is the limit for pure diffusive propagation of the electrical potential. The second (L_{cn}) is the maximum length allowing a central node while the last one (L_{nn}) is the absolute limit allowing a node in the system. Numerical simulations with the FitzHugh-Nagumo model were used as illustrations but the results are general since the physical phenomena on which they are based are not restricted to this model.

ACKNOWLEDGMENTS

We are pleased to thank the University of Liège for financial support (Crédit d'Impulsion I-03/21). Fruitful discussions with L. Piérard, P. Gérard, Th. Pochet, and E. Huvelle are also cordially acknowledged.

[1] R. A. Gray, O. A. Mornev, J. Jalife, O. V. Aslanidi, and A. M. Pertsov, Phys. Rev. Lett. **87**, 168104 (2001).

[2] S. Takagi, A. Pumir, L. Kramer, and V. Krinsky, Phys. Rev. Lett. **90**, 124101 (2003).

[3] M. Argentina, P. Coullet, and V. Krinsky, J. Theor. Biol. **205**, 47 (2000).

[4] J. Keener and J. Sneyd, *Mathematical Physiology* (Springer, New York, 1998).