Influence of spatially modified tissue on atrial fibrillation patterns:
Insight from solutions of the FitzHugh-Nagumo equations

Claudia Lenk\textsuperscript{1}, Mario Einax\textsuperscript{1}, and Philipp Maass\textsuperscript{2}\textsuperscript{†}

\textsuperscript{1}Institut für Physik, Technische Universität Ilmenau, 98684 Ilmenau, Germany
\textsuperscript{2}Fachbereich Physik, Universität Osnabrück, Barbarastraße 7, 49069 Osnabrück, Germany

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Abstract

We study the interplay between traveling action potentials and spatial inhomogeneities in the FitzHugh-Nagumo model to investigate possible mechanisms for the occurrence of fibrillatory states in the atria of the heart. Different dynamical patterns such as ectopic foci, localized and meandering spiral waves are found depending on the characteristics of the inhomogeneities. Their appearance in dependence of the size and strength of the inhomogeneities is quantified by phase diagrams. Furthermore it is shown that regularly paced waves in a region R, that is connected by a small bridge connection to another region L with perturbing waves emanating from an additional pacemaker, can be strongly disturbed, so that a fibrillatory state emerges in region R after a transient time interval. This finding supports conjectures that fibrillatory states in the right atrium can be induced by self-excitatory pacemakers in the left atrium.

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\textsuperscript{*}Electronic address: claudia.lenk@tu-ilmenau.de
\textsuperscript{†}Electronic address: pmaass@uos.de; URL: \texttt{http://www.statphys.uni-osnabruck.de}
I. INTRODUCTION

Atrial fibrillation (AF) is the most frequently appearing heart arrhythmia since it accounts for one third of all hospitalizations caused by heart arrhythmia in the industrialized countries [1]. During AF the electric conduction system of the heart is disturbed and an increased rate of activation by a factor of 3-12 compared to normal sinus rhythm occurs. Special spatio-temporal patterns of the electric potential like spiral waves, mother waves or ectopic foci are thought to be underlying generating mechanisms of AF [2–5]. These patterns are often located near physiologically modified regions of the heart tissue in the left atrium [5–8]. The question hence arises, how these physiologically modified regions can be responsible for the generation of spiral waves or ectopic foci and how they influence the properties of these patterns.

To tackle these questions, we study generating mechanism for AF on the basis of the FitzHugh-Nagumo model [9], which is a simple model for action potential generation and propagation. By modeling physiologically modified regions using a spatial variation of the parameters characterizing cell properties like excitability or resting state stability, we calculate phase diagrams, which specify the type of spatio-temporal excitation pattern in dependence of the extent of the modified region and the strength of the modification. Thereupon we investigate how self-excitatory sources as spiral waves or ectopic foci with rather regular dynamics in one region can induce irregular, fibrillatory excitation patterns in some other region. Irregular, fibrillatory states are often observed in the right atrium [7, 8, 10] and it was conjectured that these are caused by the perturbation of regular waves generated by the sinus node by waves emanating from an additional pacemaker like a spiral wave or ectopic foci in the left atrium.

II. MODEL

The FitzHugh-Nagumo (FHN) equations [9] are a set of two coupled nonlinear ordinary differential equations, which describe excitable media via an inhibitor-activator mechanism. They were originally developed by searching for a simplified version of the Hodgkin-Huxley equations for electric pulse propagation along nerves [11]. When combined with a spatial
diffusion term, the equations are

\[
\begin{align*}
\frac{\partial u}{\partial t} &= D \left( \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + c(v + u - \frac{u^3}{3} + z) \\
\frac{\partial v}{\partial t} &= -\frac{1}{c}(u - a + bv) .
\end{align*}
\]

(1)

This set of partial differential equations serves as a prototype for a large variety of reaction-diffusion systems, which occur, for example, in chemical reactions such as the Belousov-Zhabotinsky reaction \[12, 13\] or the catalysis of carbon monoxide \[14, 15\], in population dynamics \[16\], in biology in connection with aggregation processes \[17\] or plancton dynamics \[19\], as well as in the spreading of forest fires \[20\].

Here we will use Eqs. (1) in their original context as a model to investigate the spatio-temporal evolution of electric excitations in the heart. In this approach the variable \(u\) is roughly associated with the membrane potential and the variable \(v\) with the ion currents through the cell membrane. The resting state is given by the pair of values \(u = u_0 = 1.2\) and \(v = v_0 = -0.6\). The diffusion coefficient \(D\) describes the coupling between the cells, and \(z\) is an applied external current (stimulus). The influence of the parameters \(a\), \(b\) and \(c\) can be inferred by numerical solutions of Eqs. (1) without the diffusive term. The parameter values have to be limited to some range in order to generate excitability, and their detailed effect on the pulses is complicated due to mutual interdependencies originating from the nonlinearity in Eq. (1). Roughly speaking, \(a\) affects the length of the refractory period, \(b\) influences the stability of the resting state, and \(c\) controls the excitability and strength of the cells’ response to a stimulus. To capture the propagation and form of a typical action potential, the following set of parameters can be used: \(D = D_0 = 0.1\), \(a = a_0 = 0.7\), \(b = b_0 = 0.6\), and \(c = c_0 = 5.5\). These values will be associated with a “healthy tissue” in the following. Figure 1 shows the time development of \(u\) and \(v\) during an excitation after a stimulus with these parameters. Note that the variable \(-u\) mirrors the form of a pulse in an usual representation of an ECG recording.

Ectopic foci and spiral waves are thought to be caused and influenced by physiologically modified regions of the tissue, which in the modeling correspond to spatial variations of the parameters. To simplify the analysis, we fix \(a = a_0\) and \(D = D_0\), and consider variations of
the parameters \( b \) and \( c \) according to

\[
\begin{align*}
\frac{\partial u}{\partial t} &= \nabla (\nabla u - F(u,v)) + I - u,
\end{align*}
\]

(1)

\[
\begin{align*}
\frac{\partial v}{\partial t} &= g(u) - v,
\end{align*}
\]

(2)

where the amplitudes \( \Delta b, \Delta c \) characterize the strength, and the correlation lengths \( \xi_b \) and \( \xi_c \) characterize the spatial range of modification.

The calculations are carried out on a two-dimensional simulation area of size 20 × 20, which represents an isolated section of atrial heart tissue, as it is used often in experiments [21–23]. The boundary conditions of the simulation area are of von Neumann type, i.e. \( \partial u/\partial n = 0 \), where \( \partial/\partial n \) denotes the normal derivative.

To solve the two nonlinear coupled partial differential equations (1) we use the finite element method (FEM) with a triangulation consisting of 4225 nodes and 8192 triangles, and a constant integration time step \( \Delta t = 0.01 \). A simulation time of 1 corresponds to a time of roughly 5 to 5.5 ms. The nonlinearity \( u^3(\vec{x}, t) \) in Eq. (1) is treated as an inhomogeneity, which means that for \( u(\vec{x}, t_i) \) the value \( u(\vec{x}, t_{i-1}) \) of the preceding time step is used.

### III. Generating Mechanisms

#### A. Ectopic activity

Ectopic foci are regions in the atria, which generate activation waves emanating from self-excitatory hyperactive cells. In these cells the transmembrane potential raises without external stimulation until the threshold value is reached and an action potential results. In optical mapping studies and spatially resolved ECG recordings, ectopic foci are often localized in the regions of the pulmonary veins [7, 8].

To model a tissue with physiologically modified properties that result in ectopic activity, we fix \( c = c_0 \) (\( \Delta c = 0 \)) and vary the resting state stability \( b \) around the center of the simulation area \( (x_0 = y_0 = 10) \) according to Eq. (2). Initially the system is in the excitable resting state \( (u = u_0 \) and \( v = v_0) \). Figure 2b shows the resulting activation pattern for \( \Delta b = 0.4 \) and \( \xi_b = 0.8 \). The modified tissue is self-excitatory and acts as a pacemaker for activation waves, which propagate radially. In the time evolution shown in Fig. 3, \( u \) decreases until the threshold value \( u_{th} \approx 0.6 \) for activation is reached and an action potential with a
steep fall in $u$ occurs. In response to this activation, the inhibitor variable $v$ increases and pulls $u$ back to a value even larger than its initial value (overshoot) before $u$ returns to it, and the self-excitatory process starts anew.

In order to systematically characterize the occurrence of ectopic activity, we calculate a phase diagram, where in dependence of $\xi_b$ and $\Delta b$ regions of ectopic activity can be distinguished from that without self-excitatory behavior. The results in Fig. 2b show that there exists a minimal $\Delta b_{\text{min}} \simeq 0.25$, below which no ectopic activity occurs. The corresponding value $(b_0 - \Delta b_{\text{min}}) \simeq 0.5$ is the critical value of resting state stability in the FHN equations (1) in the absence of the diffusion term. For fixed $\Delta b > \Delta b_{\text{min}}$ the ectopic activity vanishes, when $\xi_b$ falls below the dashed transition line in Fig. 2b. In this region the diffusive current from the modified tissue to the surrounding causes the initial decrease of $u$ to become so slow, that the counter-regulation by $v$ eventually hinders $u$ to reach its activation threshold, cf. Fig. 3. Only small oscillation of $u$ around a reduced resting state value can be seen in Fig. 3, which become weaker with growing time.

The temporal-spatial pattern of the activation in the phase of ectopic activity is characterized by the frequency of the ectopic focus. We calculate this frequency as the inverse mean time interval between consecutive action potentials. As shown in Fig. 4 the frequency becomes larger with increasing $\Delta b$ (at fixed $\xi_b$) and $\xi_b$ (at fixed $\Delta b$), and it tends to saturate for large $\xi_b$. With increasing $\xi_b$, the diffusive current of the inner cells of the modified tissue decreases and thus a larger frequency is obtained. In the saturation limit the frequency is nearly the same as in the absence of diffusion and thus is mainly determined by the refractory period.

B. Spiral waves

In this section we study the influence of physiologically modified regions, called “obstacles” henceforth, on spiral wave behavior. It was observed that spiral waves in the atria can be generated by a perturbation of the propagation of planar excitation waves by anatomic obstacles as, for example, the pulmonary veins, the venae cavae, the pectinate muscle bundles or some localized region of modified tissue [6, 21, 24, 25]. These regions are considered as not fully excitable and are thus modeled as regions with a reduced parameter $c$ according to Eq. (3).
In an experiment by Ikeda and coworkers [21] a nearly rectangular area of atrial tissue was placed on an electrode plaque in a tissue bath. Holes with different diameters were created and a reentrant wave was initiated by cross-field stimulation. The resulting behavior of the wavefront was, amongst others, classified according to whether the spiral is anchored by the obstacle, and by the relationship between hole size and cycle length of the reentry. It was observed that for large obstacle sizes (6, 8 and 10 mm), the reentrant wave attaches to the obstacle, leading to a linear increase of the cycle length with the hole diameter. For small obstacle diameters below about 4 mm, by contrast, meandering spirals with a tip getting variably closer to or further away from the hole were found. In this case the cycle length becomes independent of the hole diameter. Similar results were observed by Lim and coworkers [24]. They analyzed the behavior of spiral waves near holes with diameters ranging from 0.6 to 2.6 mm and obtained a higher attachment rate for larger obstacle diameters as well as a positive linear correlation of the reentry conduction velocity and wave length with the obstacle diameter in the case of attached spirals. For smaller obstacle diameters the spiral waves were found to attach to and detach from the obstacle.

The missing anchoring for small hole sizes was explained in [21] by invoking a “source-sink relationship”. The “source” is the activation wavefront and provides a diffusive current to the surrounding tissue in the resting state, which constitutes the “sink”. The sink becomes larger for smaller obstacles, where more cells become depolarized by the activation wavefront. If the source-to-sink ratio is decreased below a certain critical value, the wavefront detaches from the obstacle.

To elucidate these experimental findings, we perform numerical calculations for a geometry corresponding to the experiments with the following initial state and parameters settings: the modified region, is, as in the previous Sec. [IIIA] placed in the center of the simulation area at \( x_0 = y_0 = 10 \). Initially a “planar” (linear) wave is generated by inducing a current \( z \) in the stripe \( 9.5 \leq x \leq 10, 0 \leq y \leq 10 \), and by setting the area \( 0 \leq x \leq 9.5, 0 \leq y \leq 10 \) into a refractory state with \( u = 1.6 \) and \( v = 0 \), while the rest of the simulation area is in the resting state (\( u = u_0, v = v_0 \)). This initial state resembles the activation pattern directly after application of a cross-field or paired-pulse stimulation (two rectangular pulses). At the “upper part” of the initial planar wavefront (\( 9.5 \leq x \leq 10, y = 10 \)), diffusive currents flow “radially” in all forward directions (\( y > 10 \)), while at the “right boundary” (\( x = 10, 0 \leq y \leq 9.5 \)) the diffusive currents can flow only in positive \( x \) direction (due to
the refractory state in the area $0 \leq x \leq 9.5, 0 \leq y \leq 10$). This higher loss by diffusion leads to a smaller propagation speed of the initial wavefront at its upper boundary compared to its right boundary. As a consequence, the wavefront becomes curved, and a reentrant spiral wave develops for all reductions $\Delta c$ in excitability and obstacle sizes $\xi_c$, in accordance with the experimental observations. Figure 5 shows activation patterns for $\xi_c = 2$ and a) $\Delta c = 4.5$, and b) $\Delta c = 1.5$. The stronger reduction of excitability in Fig. 5a leads to an anchoring of the spiral wave, while in Fig. 5b the spiral is meandering.

To analyze the parameter regimes of the occurrence of anchored or meandering spiral waves, we perform a frequency analysis for different values of $\Delta c$ and $\xi_c$. Therefore, we determine the peak positions in the time series of $u$ at 8 positions far away from the center of the spiral and calculate the peak-to-peak intervals. The frequency of one point is one over the mean of the peak-to-peak intervals and the mean cycle length is one over the average of all these local frequencies. The results in Fig. 6 show that, as in the experiments, attached spiral waves occur for large $\Delta c \gtrsim 3$ and for sufficiently large $\xi_c > \xi_c^*$, where $\xi_c^*$ decreases with increasing $\Delta c$. For these anchored spirals, the frequency is proportional to $f = \eta/2\pi \xi_c$, where $\eta \simeq 0.82$ is the conduction velocity in the FHN model. Accordingly, $1/f$ increases linearly with $\xi_c$ for $\xi_c > \xi_c^*$ in Fig. 6. For small $\Delta c \lesssim 3$, only meandering spirals are observed. The transition from large to small $\Delta c$ reflects the transition from anatomical to functional reentry \cite{26}, as it has been reported in medical studies \cite{24}. The fact that for small $\xi_c$ always meandering spirals occur, can be interpreted by the small source-sink ratio \cite{21}. The same mechanism can also lead to meandering spirals for large $\xi_c$ if $\Delta c$ becomes small. Note, that nevertheless the spiral wave is not anchored to the obstacle, its movement is still influenced by the obstacle.

IV. INDUCED FIBRILLATORY STATES IN THE RIGHT ATRIUM

In previous studies on interactions of paced waves with self-excitatory waves, the influence of the pacing on a spiral wave was studied \cite{27,28} with the aim to suggest a possible therapy to suppress fibrillation or tachycardia. The pacing was applied to the region, where the spiral wave was located. It was found that the pacing leads to an annihilation of the reentrant activity or to a shift of the spiral core \cite{28,31}.

Here we investigate the perturbation of regular paced waves from a source representing
the sinus node by waves emanating from an additional pacemaker located in a distant region. Electrocardiogram recordings and their frequency analyses show that regular excitation patterns are often observed in the left atrium, where additional pacemakers like spiral waves or ectopic foci are located \[5, 8\], and that at the same time irregular, fibrillatory-like states in the right atrium occur \[7\]. This led to the conjecture that fibrillatory states can be induced in the right atrium by self-excitatory pacemakers in the left atrium. In this connection it is important to better understand how a fibrillatory state can occur, if regular paced waves, as generated by the sinus node, are disturbed by additional pacemaker waves. To this end, we consider the waves to be located in spatially separated regions that are connected by a small region. To be specific, we choose a simulation area of size \(21 \times 10\), which is divided into three regions (see Fig. 7). The rectangular area \(L\) with \(0 \leq x \leq 10\), \(0 \leq y \leq 10\) representing the left atrium, the rectangular area \(R\) with \(11 \leq x \leq 21\), \(0 \leq y \leq 10\) representing the right atrium, and the small bridge \(B\) with \(10 < x < 11\), \(4 < y < 6\) representing the connection between the atria. The grid used in the finite element calculations consists of in total 8871 nodes and 17350 triangles.

We focus on situations where the pacemaker in the region \(L\) is located far outside the left part of the simulation area, so that the resulting wavefronts become “planar” (linear). In the simulation they are generated by application of a stimulating current \(z = -1\) with duration \(t_z = 1 = 100\Delta t\) and a period \(1/f_{pert}\) in the region \(x \leq 0.5\) and \(0 \leq y \leq 10\). The activation waves representing the pacemaker in region \(R\) are generated by the application of a current \(z = -1\) with duration \(t_z = 1\) and period \(1/f_{pace}\) in the region \(11 \leq x \leq 21\) and \(y \leq 0.5\).

The irregularity of the resulting patterns in region \(R\) is quantified by calculating the Shannon entropy of the distribution of local activation frequencies for every grid point in \(R\). To this end we divide the frequency range into \(N_b\) bins of size \(\Delta = \min \{\exp [0.626 + 0.4 \ln(N_g - 1)]^{-1}, 0.01\}\) \[32, 33\] and calculate the probabilities

\[
p_l = \frac{n(f_l \leq f \leq f_l + \Delta)}{N_g},
\]

of finding frequency \(f\) in bin \(l\), where \(N_g\) is the total number of grid points. The normalized entropy then is given by

\[
s = \frac{S}{S_{max}} = -\frac{\sum_{l=1}^{N_b} p_l \ln p_l}{\ln N_b},
\]
For a single frequency \( p_l = \delta_{l,0} \), \( s = 0 \), while for a chaotic activation pattern with a uniform distribution \( p_l = 1/N_b \), \( s = 1 \).

For small perturbation frequencies \( f_{\text{pert}} \leq 0.1 \) the influence of the activation wavefronts from the additional pacemaker onto the sinus node waves is almost negligible. Small deformations of the linear wavefronts are observed, but the measured frequencies are close to the pacing frequency, and the overall spatiotemporal pattern in R is regular.

With increasing perturbation frequency the spatiotemporal pattern in region R becomes more irregular and a breakup of the regularly paced waves can occur. Figure 8 shows the time evolution of the excitation patterns for a perturbation frequency \( f_{\text{pert}} = 0.105 \) and a pacing frequency \( f_{\text{pace}} = 0.091 \). For small times, the waves are only slightly perturbed and the pattern remains regular, as can be seen from the four consecutive snapshots in Fig. 8a. At a later time, however, the perturbation by the waves from region L results in a breakup of the waves close to the bridge B in region R, as can be seen from the four consecutive snapshots in Fig. 8b. The onset of this breakup was found to occur at a time \( t \approx 160 \).

In order to investigate how the spatial irregularity is reflected in the time evolution, we consider three different points \( P_1 = (11.49, 5.34) \), \( P_2 = (11.33, 6.34) \) and \( P_3 = (11.94, 6.15) \) in region R. The time evolution of \( u \) for these three points is shown for two different perturbation frequencies \( f_{\text{pert}}^{(1)} = 0.1 \) and \( f_{\text{pert}}^{(2)} = 0.105 \) in Fig. 9 (\( P_1 \): black solid curve, \( P_2 \): red dashed curve, \( P_3 \): blue dash-dotted curve). For the lower frequency \( f_{\text{pert}}^{(1)} \) the evolution at all three points is regular, see Fig. 9a. For the higher frequency \( f_{\text{pert}}^{(2)} \), by contrast, the break ups of the waves seen in Fig. 8b yield unsuccessful activations during refractory periods, as can be seen, for example, at time \( t \approx 175 \) in point \( P_2 \) (red dashed curve) and at time \( t = 179 \) in point \( P_1 \) (black solid curve). These unsuccessful activations are caused by a rapid pacing of the region by the curled wave. Another feature is that the shape of the action potential varies. This can be seen, for example, at point \( P_1 \) (black solid line) when comparing the pulses at \( t \approx 160 \) and \( t \approx 194 \). It is important to note that these irregularities are hardly observed at point \( P_3 \) (blue dash-dotted curve), showing that they exhibit a spatial heterogeneity.

The total irregularity in region R quantified by the normalized Shannon entropy \( s \) of the local frequency distribution is shown in Fig. 10 as a function of the frequency \( f_{\text{pert}} \) of the perturbing waves from region L. For small perturbation frequencies \( f_{\text{pert}} \lesssim 0.1 \) the entropy \( s \) equals the unperturbed case, while for \( f_{\text{pert}} \gtrsim 0.1 \), \( s \) sharply increases until it reaches a maximum at \( f_{\text{pert}} \approx 0.1075 \). For higher \( f_{\text{pert}} \) a return to more regular activation pattern is
found, indicating that the disturbance is most pronounced if $f_{pert}$ is close to $f_{pace}$.

To conclude, the disturbance of the wavefronts in region R by waves emanating from an additional source in region L and propagating through the bridge region B can lead to irregular, fibrillatory-like activation patterns in region R. On the other hand, the waves in region L are almost unaffected by the waves in R with primary wavefront orthogonal to the cross section of the bridge. The irregularities in region R are most pronounced at a certain perturbation frequency $f_{pert}$. How this value is influenced by the geometry of the bridge and the parameters characterizing the cell properties remains further investigation.

V. SUMMARY

The influence of physiologically modified regions on the generation and properties of spatio-temporal activation patterns was investigated on the basis of the FitzHugh-Nagumo equations with von Neumann boundary conditions, in particular the occurrence of ectopic foci and spiral waves under spatial inhomogeneities of the parameters characterizing the cell properties. It was shown that the reduction $\Delta b$ of the resting state stability in circular regions of the tissue can lead to ectopic activity. A minimal size of hyperactive tissue is necessary for ectopic activity to occur, as well as a minimal strength of the reduction of resting state stability with respect to the “healthy” reference value. With increasing size $\xi_b$ of the hyperactive tissue, the frequency of the ectopic focus first increases and eventually saturates. The saturation frequency depends on the strength of the modification $\Delta b$.

For spiral wave patterns it was found that an anchoring of the wave to the obstacle can occur. To uncover this mechanism, an obstacle was modeled as a patch of modified tissue with reduced excitability by a reduction of the parameter $c$ in the FHN equations. The obstacle was placed in the middle of a two-dimensional square simulation area and a planar excitation wave was generated aside of the obstacle in front of a refractory region, which represents an activation pattern observed after cross-field stimulation in experiments. As in the experiments, reentrant waves are observed. These exhibit either functional or anatomical reentry in dependence of the obstacle size and reduction strength $\Delta c$ of excitability. An analysis of the spiral wave frequency in dependence of the obstacle size yields results in accordance with the experimental observations.

Finally we studied the question, if and how fibrillatory-like states can arise in the right
atrium due to the presence of self-excitatory spiral waves or ectopic foci in the left atrium. To this end the simulation area was separated into two rectangular regions L and R connected by a small bridge B. Planar excitation waves were generated with different frequencies in the left region L to model a pacemaker far outside the left part of the simulation area. Planar excitation waves resembling stimulation by the sinus node were generated by periodic application of a stimulating current at one boundary in the right part R of the simulation area. For small perturbation frequencies in L, the disturbance of the waves in R turned out to be small. For higher perturbation frequencies, the waves in R become significantly disturbed and the spatio-temporal activation pattern eventually becomes irregular. The time evolution of the activation variable $u$, representing the electric potential in the FHN equations, shows features in close resemblance to the ones found in intra-atrial electrocardiogram recordings during fibrillation in the right atrium. The spatial variation of the excitation frequency was quantified in terms of an entropy, which showed, for a given pacing frequency, a maximum as a function of the perturbation frequency. Further investigations will focus on the influence of the geometry of the bridge and the wavefronts as well as analyse the behavior for different pacing frequencies. The reliability of the measure of irregularity $s$ should be analysed and if necessary other methods to characterise the system behavior should be searched.

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[1] V. Fuster, L. E. Ryden, D. S. Cannom, H. J. Crijns, A. B. Curtis, K. A. Ellenbogen, J. L. Halperin, J.-Y. Le Heuzey, G. N. Kay, J. E. Lowe, S. B. Olsson, E. N. Prystowsky, J. L. Tamargo, S. Wann, S. C. Smith, A. K. Jacobs, C. D. Adams, J. L. Anderson, E. M. Antman, S. A. Hunt, R. Nishimura, J. P. Ornato, R. L. Page, B. Riegel, S. G. Priori, J.-J. Blanc, A. Budaj, A. J. Camm, V. Dean, J. W. Deckers, C. Despres, K. Dickstein, J. Lekakis, K. McGregor, M. Metra, J. Morais, A. Osterspey, J. L. Zamorano, Europace 8, 651 (2006).

[2] S. Nattel, Nature 415, 219 (2002).

[3] S. Nattel, D. Li, L. Yue, Annu. Rev. Physiol. 62, 51 (2000).

[4] S. Nattel, L. H. Opie, Lancet 367, 262 (2006).

[5] R. Mandapati, A. Skanes, Y. Chen, O. Berenfeld, J. Jalife, Circulation 101, 194 (2000).

[6] T.-J. Wu, M. Yashima, F. Xie, C. A. Athill, Y.-H. Kim, M. C. Fishbein, Z. Qu, A. Garfinkel, J. N. Weiss, H. S. Karagueuzian, P.-S. Chen, Circ. Res. 83, 448 (1998).

[7] J. Sahadevan, K. Ryu, L. Peltz, C. M. Khrestian, R. W. Stewart, A. H. Markowitz, A. L. Waldo, Circulation 110, 3293 (2004).

[8] P. Sanders, O. Berenfeld, M. Hocini, P. Jais, R. Vaidyanathan, L.-F. Hsu, S. Garrigue, Y. Takahashi, M. Rotter, F. Sacher, C. Scavee, R. Ploutz-Snyder, J. Jalife, M. Haisaguerre, Circulation 112, 789 (2005).

[9] R. FitzHugh, Biophys. J. 1, 445 (1959).

[10] S. Lazar, S. Dixit, F. E. Marchlinski, D. J. Callans, E. P. Gerstenfeld, Circulation 110, 3181 (2004).

[11] A. L. Hodgkin, A. F. Huxley, J. Physiol. 117, 500 (1952).

[12] S. M. Tobias, E. Knobloch, Phys. Rev. Lett. 80, 4811 (1998).

[13] M. Bär, M. Eiswirth, Phys. Rev. E 48, R1635 (1993).

[14] S. Jakubith, H. H. Rotermund, W. Engel, A. von Oertzen, G. Ertl, Phys. Rev. Lett. 65, 3013 (1990).

[15] G. Ertl, Science 254, 1750 (1991).

[16] M. G. Clerc, D. Escaff, V. M. Kenkre, Phys. Rev. E 72, 056217 (2005).

[17] K. J. Lee, E. C. Cox, R. E. Goldstein, Phys. Rev. Lett. 76, 1174 (1996).

[18] J. D. Murray, Mathematical Biology, Springer (1988).
[19] L. S. Schulman, P. E. Seiden, Science 233, 425 (1986).
[20] V. Mendez, J. E. Llebot, Phys. Rev. E 56, 6557 (1997).
[21] T. Ikeda, M. Yashima, T. Uchida, D. Hough, M. C. Fishbein, Circ. Res. 81, 753 (1997).
[22] S. Iravanian, Y. Nabutovsky, C.-R. Kong, S. Saha, N. Bursac, L. Tung, Am. J. Physiol. Heart Circ. Physiol. 285, H449 (2003).
[23] T. Ikeda, L. Czer, A. Trento, C. Hwang, J. J. C. Ong, D. Hough, M. C. Fishbein, W. J. Mandel, H. S. Karaguezian, P.-S. Chen, Circulation 96, 3013 (1997).
[24] Z. Y. Lim, B. Maskara, F. Aguel, R. Emokpae, Jr., L. Tung, Circulation 114, 2113 (2006).
[25] A. M. Pertsov, J. M. Davidenko, R. Salomonsz, W. T. Baxter, J. Jalife, Circ. Res. 72, 631 (1993).
[26] L. Boersma, J. Brugada, C. Kirchhof, M. Allessie, Circulation 89, 852 (1994).
[27] G. V. Obisov, A. T. Stamp, J. J. Collins, Control of Oscillations and Chaos (Proc.) 3, 453 (2000).
[28] J. M. Davidenko, R. Salomonsz, A. M. Pertsov, W. T. Baxter, J. Jalife, Circ. Res. 77, 1166 (1995).
[29] K. Agladze, M. W. Kay, V. Krinsky, N. Savazyan, Am. J. Physiol. Heart Circ. Physiol. 293, H503 (2007).
[30] Y.-Q. Fu, H. Zhang, Z. Cao, B. Zheng, G. Hu, Phys. Rev. E 72, 046206 (2005).
[31] G. Gottwald, A. Pumir, V. Krinsky, Chaos 11, 487 (2001).
[32] R. Otnes, L. Enochson, Digital Time Series Analysis, John Wiley & Sons (1972).
[33] M. Rosenblum, A. Pikovsky, J. Kurths, C. Schäfer, P. A. Tass, Handbook of Biological Physics 4, 279 (2001).
[34] D. Cysarz, H. Bettermann, P. Van Leeuwen, Am. J. Physiol. Heart Circ. Physiol. 278, H2163 (2000).
FIG. 1: Time evolution of a) $u$ and b) $v$ calculated with the FHN equations and the parameters representing a healthy tissue.
FIG. 2: (color online) a) Activation pattern of the ectopic focus at $\Delta b = 0.4$ and $\xi_b = 0.8$. The lines represent isolines for $u = -0.8$ and four times $t = 5$ (black solid line), 7 (red dotted line), 9 (blue dashed line), and 13 (green dash-dotted line). Initially ($t = 0$) the system is in the resting state ($u = u_0$, $v = v_0$). b) Phase diagram of ectopic activity for modifications according to Eq. (2). Red diamonds and black circles refer to the occurrence and absence of ectopic activity, respectively. The dotted line is drawn as a guide to the eye and marks the transition between the regions of ectopic activity and absence of self-excitatory behavior.
FIG. 3: (color online) Time evolution of $u$ and $v$ for $\Delta b = 0.4$, and two values $\xi_b = 0.8$ (black solid line) and $\xi_b = 0.5$ (red dashed line). For $\xi_b = 0.8$, $u$ decreases below the threshold value $u_{th} \simeq 0.6$ and an action potential is generated. For $\xi_b = 0.5$ the decrease of $u$ is slower and less steep due to the stronger diffusive current compared to $\xi_b = 0.8$. As a consequence the response of $u$ is more susceptible to the initial decrease of $v$, which is not distinguishable for $\xi_b = 0.5$ and $\xi_b = 0.8$. Thus, $u$ does not reach the threshold value and relaxes with small oscillations to a value $u \simeq 0.9$. 
FIG. 4: (color online) Frequency of ectopic activity in dependence of the size $\xi_b$ of the modified tissue for various modification strength $\Delta b$ of the resting state stability. A frequency of 0.053 in the simulation corresponds to a frequency of roughly 10 Hz.
FIG. 5: a) Isolines for $u = -0.8$ at four different times $t = 82$ (black solid line), $87$ (red dotted line), $92$ (blue dashed line) and $t = 97$ (dash-dotted line) for an obstacle with $\xi_c = 2$ and $\Delta c = 4.5$ (marked by the black circle). The spiral wave is pinned and rotates around the obstacle (anatomical reentry). b) Isolines for $u = -0.8$ at four different times $t = 82$ (black solid line), $84.5$ (red dotted line), $87$ (blue dashed line) and $t = 89.5$ (dash-dotted line) for an obstacle with $\xi_c = 2$ and $\Delta c = 1.5$. The spiral wave rotates around a moving center not corresponding to but influenced by the obstacle and is not attached to the obstacle (functional reentry).
FIG. 6: (color online) Mean cycle length $1/f$ as a function of obstacle size $\xi_c$ for four different strength of the modification of excitability $\Delta c$. A cycle length of 15 corresponds to a frequency of roughly 12 Hz. For the two smaller values $\Delta c = 1.5$ and $\Delta c = 2.5$ the cycle length is independent of $\xi_c$ (functional reentry). For the two larger values $\Delta c = 3.5$ and $\Delta c = 4.5$ a transition from functional to anatomical reentry occurs, when $\xi_c$ exceeds a threshold value $\xi_c^*$ that increases with decreasing $\Delta c$. The dashed lines are fits to the data for mean cycle lengths independent of $\xi_c$ (functional reentry) and mean cycle lengths proportional to $\xi_c$ (anatomical reentry).
FIG. 7: Illustration of the simulation area. The red dotted line describes a regular paced wavefront of the sinus node. The blue dashed line is a wavefront of the perturbing pacemaker. P<sub>1</sub>, P<sub>2</sub> and P<sub>3</sub> mark the "observation points", for which the time evolution of u is shown in Figure 9.
FIG. 8: Time evolution of excitation pattern observed by perturbation of a regular pacemaker with frequency $f_{\text{pace}} = 0.091$ in the right part R of the simulation area by an additional pacemaker with frequency $f_{\text{pert}} = 0.105$ in the left part L through a bridge region B. The blue solid lines are isolines for $u = -0.8$. The shaded regions represent the boundaries of the bridge between the two parts L and R. a) For small times the excitation in R is regular. b) At later times breakups of waves in region R occur close to the bridge region B, resulting in irregular excitation patterns.

FIG. 9: (color online) Time evolution of the activation variable $u$ at three different points of the simulation area: $P_1 = (11.49, 5.34)$ (black solid line), $P_2 = (11.33, 6.34)$ (red dashed line) and $P_3 = (11.94, 6.15)$ (blue dash-dotted line) for a pacing frequency $f_{\text{pace}} = 0.091$ and two different perturbation frequencies a) $f_{\text{pert}} = 0.1$, and b) $f_{\text{pert}} = 0.105$. We have checked that this behaviour remains qualitatively the same even at a three times longer simulation time which suggests that this time evolution corresponds to a stationary state.
FIG. 10: (color online) Normalized entropy of the local frequency distribution in region R as a function of the frequency $f_{\text{pert}}$ of the perturbing waves in region L. The pacing frequency in region R is $f_{\text{pace}} = 0.091$. The dotted (black) line through the data points is a guide to the eye and the dashed line marks the value of $s$ for the regularly paced system without perturbation by an additional pacemaker.