Interaction of Pacemakers as Generating Mechanism of Atrial Fibrillation

Claudia Lenk[1], Mario Einax[2], Gunnar Seemann[3], Philipp Maass[2]

[1] FG Theoretische Physik 2, Technische Universität Ilmenau, Ilmenau, Germany
[2] Fachbereich Physik, Universität Osnabrück, Osnabrück, Germany
[3] Institut für Biomedizinische Technik, Karlsruher Institut für Technologie, Karlsruhe, Germany

Abstract

We study, if mechanisms for the generation of fibrillation patterns observed recently in studies of the FitzHugh–Nagumo (FHN) model can be seen also in the model of Bueno-Orovio, Cherry and Fenton (BOCF), that has been adapted specifically to the atrial electrophysiology. The mechanisms are associated with the interference of two spatially separated pacemakers that are connected by a small bridge of the conducting tissue. One of the two pacemakers represents the sinus node, while the second one represents a self-excitatory source in the left atrium, as an ectopic focus or microreentrant circuit. In the FHN model, three different types of irregular patterns are observed and which type occurs depends on the frequency ratio of the two pacemakers. However, only one of these types is observed in the BOCF model. Particularly interesting is the fact that the strength of the irregularity is determined by the sinus node frequency. This may be an explanation why AF is typically intermittent at its beginning.

1. Introduction

Atrial fibrillation (AF) is a not life-threatening arrhythmia of the heart but accounts for one third of all hospitalizations caused by heart arrhythmia in the industrialized countries [1]. It has strong side effects like a strongly increased risk for stroke or other heart diseases. Particular spatio-temporal patterns of the electric potential, like spiral waves or ectopic foci, often located in the left atrium [2], are thought to be underlying generating mechanisms of AF [3]. The irregular excitation states, which are characteristic of AF, are often observed in the right atrium [2]. we could show in [4] we could show that the perturbation of waves, generated by a primary pacemaker representing the sinus node in the right atrium, by waves emanating a secondary pacemaker, comparable to the self-excitatory sources in the left atrium, can cause irregular excitation patterns in the FitzHugh–Nagumo (FHN) model [5]. The FHN model is a simple model of action potential propagation, based on an activator-inhibitor mechanism, and does not reflect the atrial electrophysiology. To test if this perturbation of one pacemaker by another one can be a possible generating mechanism of AF, we perform calculations of the model of Bueno-Orovio, Cherry and Fenton (BOCF) [6] with parameters adapted to the atrial electrophysiology [1], and compare these with the results obtained for the FHN model.

2. Methods

Both, the FHN model and the BOCF model, describe excitable media via an inhibitor-activator mechanism and allows one to investigate the spatio-temporal evolution of electric excitations in the heart. When combined with a spatial diffusion term, the FHN equations are

$$\begin{aligned}\frac{\partial u}{\partial t} &= D\left(\frac{\partial^2 u}{\partial x^2}+\frac{\partial^2 u}{\partial y^2}\right)+c(v+u-\frac{u^3}{3}+z)\\ \frac{\partial v}{\partial t} &= -\frac{1}{c}(u-a+bv)\,.\end{aligned} \tag{1}$$

The variable u is roughly associated with the membrane potential and the variable v with the ion currents through the cell membrane. The values $u = u_0 = 1.2$ and $v = v_0 = -0.6$ denote the resting state. Parameter 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. The set of parameters $D = D_0 = 0.1$, $a = a_0 = 0.7$, $b = b_0 = 0.6$, and $c = c_0 = 5.5$ is considered as the normal, physiological state in the following.

The BOCF model is more complex by involving four state variables, whose time evolution is given by:

$$\begin{aligned}\frac{\partial u}{\partial t} &= \nabla\cdot D\nabla u-(I_{fi}+I_{so}+I_{si})\\ \frac{\partial v}{\partial t} &= -\frac{v}{\tau_v^+}H(u-\theta_v)+\frac{(v_\infty-v)}{\tau_v^-}\left[1-H(u-\theta_v)\right]\\ \frac{\partial w}{\partial t} &= -\frac{w}{\tau_w^+}H(u-\theta_w)+\frac{(w_\infty-w)}{\tau_w^-}\left[1-H(u-\theta_w)\right]\\ \frac{\partial s}{\partial t} &= \frac{1}{\tau_s}\left[\frac{1}{2}\Big(1+\tanh[k_s(u-u_s)]\Big)-s\right]\,.\end{aligned} \tag{2}$$

with the currents

$$I_{fi} = -v\,(u-\theta_v)\,(u_u-u)\,H(u-\theta_v)/\tau_{fi}$$
$$I_{so} = (u-u_o)\,[1-H(u-\theta_w)]/\tau_o + H(u-\theta_w)/\tau_{so}$$
$$I_{si} = -w\,s\,H(u-\theta_w)/\tau_{si}\ . \qquad (3)$$

The variable u can be converted into the cellular transmembrane potential (in mV) by $V = 85.7u - 80.9$. The fast, inward current I_{fi} represents the sodium current, the slow, inward current I_{si} stands for the calcium current and the slow, outward current I_{so} represents the potassium current. $H(x)$ is the Heaviside-function. The gating variable v regulates I_{fi} and the gating variables w and s regulate I_{si}. Due to these three gating variables the model exhibits restitution properties of typical heart cells and the typical spike-and-dome shape of cardiac action potentials. The resting state is given by $u = u_0 = 0, v = v_0 = 1, w = w_0 = 1$ and $s = s_0 = 0$ and the parameters, representing physiological, atrial cell properties were taken from Weber [1].

The calculations are carried out on a two-dimensional simulation area. The simulation area is of size 21×10 and divided into three regions: the rectangular area with $0 \le x \le 10$, $0 \le y \le 10$ represents the left atrium, the rectangular area with $11 \le x \le 21, 0 \le y \le 10$ represents the right atrium, and the small bridge B with $10 < x < 11$, $4 < y < 6$, representing the fast conducting pathways between the electrically isolated atria as the Bachmanns Bundle or the cristae terminales. The boundaries, which confine the barrier between the left and the right region and of the simulation area, are of von-Neumann type.

The pacemaker in the right region, representing the sinus node, will be called the primary pacemaker in the following and the waves emanating it are called primary waves. The pacemaker in the left atrium is named secondary pacemaker and the waves generated by it are called secondary waves. We focus on situations where the secondary pacemaker in the left atrium 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 with the perturbation frequency f_{pert} in the region $x \le 0.5$ and $0 \le y \le 10$. The primary waves are generated by the application of a current with the pacing frequency f_{pace} in the region $11 \le x \le 21$ and $y \le 0.5$.

To solve the two nonlinear coupled partial differential equations (1) of the FHN model we use the finite element method (FEM) with a triangulation consisting of 66049 nodes and 131072 triangles, and a constant integration time step $\Delta t = 0.01$. 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. For the solution of the BOCF model we apply the cardiac simulation tool acCELLerate from the Institute of Biomedical Engineering of the KIT [7], which solves the four coupled nonlinear partial differential equations with a finite differences method (FDM) with constant integration time step $\Delta t = 10^{-5}$s and a space discretization length $\Delta x = 0.1$mm.

The irregularity of the excitation patterns is characterized by the order parameter R [8], which quantifies the phase coherence in the system. For each element j of the discretization grid we can associate to the potential $u_j(t)$ an unique imaginary part $\tilde{u}_j(t)$ by Hilbert transformation, see, e.g., for details [9], and accordingly a phase $\phi_j(t) = \arctan(\tilde{u_j}(t)/u_j(t))$. The order parameter is then given by:

$$R(t) = \left| \frac{1}{N} \sum_{j=1}^{N} \exp(i\phi_j(t)) \right| \ , \qquad (4)$$

where N is the number of grid points. If the difference $|(R(f_{\mathrm{pace}}, f_{\mathrm{pert}}) - R(f_{\mathrm{pace}}, 0))|/R(f_{\mathrm{pace}}, 0) \approx 0$, then no irregularity is observed. $R(f_{\mathrm{pace}}, 0)$ describes the undisturbed case with the primary pacemaker only. An increase in ΔR is a deviation from the undisturbed case and thus quantifies the irregular states.

3. Results

Both temporal and spatial irregularities were found for the FHN model for certein regimes of the pacemaker frequencies. Temporal irregularities are associated with unsuccessful activations during the refractory period and changes in the action potential shape. Spatial irregularities are associated with wave breaks and the possible evolution of reentries. With respect to the spatial irregularity, three different types could be distinguished in the FHN model.

Type I is caused by the detachment of the primary waves from the lower bridge at a point close to the bridge in the right atrium. This results in an open end of the primary waves, which evolve into reentrant patterns in the upper part of the right atrium. These reentrant waves always occur for sufficiently high pacing frequency f_{pace} independent of the perturbation frequency f_{pert}. We suppose, however, that the relevance of type I irregularity for the generation of AF is quite low, since f_{pace} has to higher than the typical frequencies of the sinus node.

Type II is induced by the detachment of the secondary waves from the upper part of the bridge and occurs in the FHN model, if the perturbation frequency becomes higher than a certain threshold f_c. Reentrant patterns are observed, which can evolve into stable or meandering spiral waves in dependence of f_{pert}, if both pacemaking activities are suspended. The relevance of the irregularity type II for the generation of AF might be high, since ectopic foci and microreentrant sources observed in the left atrium often have quite high frequencies of up to 11.7Hz [2].

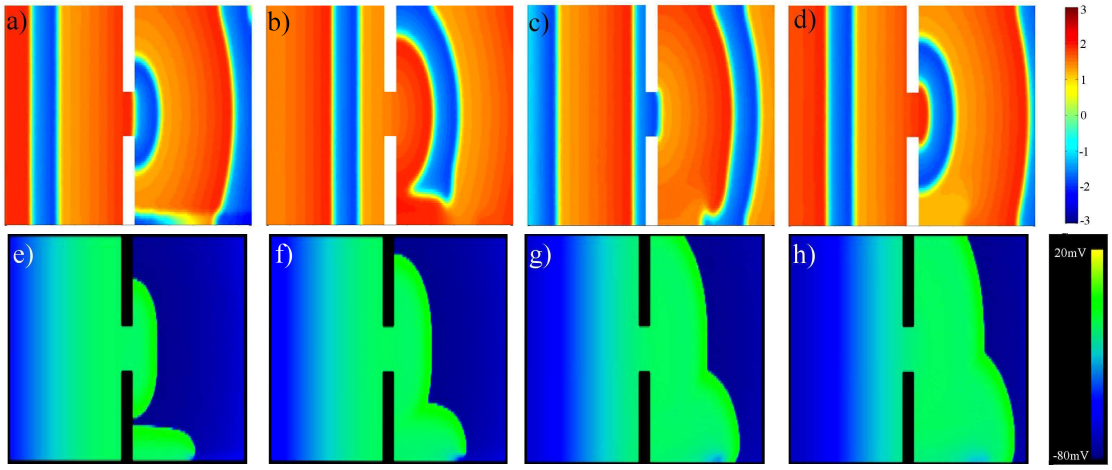

Figure 1. Time evolution of irregular excitation pattern type III in the FHN model (a-d) and in the modified BOCF model (e-h). Variable u is shown color coded with the excitable state red (a-d) and blue (e-h) and the excited state in blue (a-d) and green (e-h). Note that $-u_{\mathrm{FHN}}$ behaves like u_{BOCF}.

Type III occurs if the perturbation frequency is lower than the threshold f_c but still higher than f_{pace}. In this case the secondary waves 'repel' the primary waves and enter the right part of the simulation area as circular waves, due to the influence of the bridge. Thus lines along x for a constant y ($y \neq 5$) are activated successively with increasing x. This results in a phase shift along x for a constant y. The primary pacemaker, which activates simultaneously the lower boundary of the right atrium, can generate thus only wave fragments, or is suppressed totally, due to the distribution of activation states along x. These wave fragments partly evolve into reentrant patterns, which can be stable spiral waves, if both pacemakers are disabled. This type of irregularity evolves always, if $f_{\mathrm{pace}} < f_{\mathrm{pert}}$. The difference $f_{\mathrm{pert}} - f_{\mathrm{pace}}$ only influences the transition time, after which the irregularity is observed. The increase of the frequency measured in the right part of the simulation area compared to the pacing frequency is the highest for irregularity type III, up to 3.5 times the pacing frequency. Irregularity type III might be also a possible generating mechanism of AF as it is often observed that the frequency of the pacemaking sites in the left atrium show higher frequencies than the sinus node [2].

To test if these three types of irregular patterns are also observed in a model with more realistic atrial electrophysiology, calculations of the BOCF model with a specific adaption of parameters to the atrial electrophysiology [1] are performed. Irregularities of type I and type II are not observed in the BOCF model, since the detachment of waves from the bridge found in the FHN model is not occurring in the BOCF model. We believe that this is due to the different restitution properties of the two models, in particular with respect to the action potential shape, amplitude and refractory period. As described by Starobin *et al.* [10] the detachment of waves from sharp corners can occur if the safety factor S_F becomes zero. This safety factor S_F is the difference between the available charge to yield an excitation of the adjacent tissue in the resting state and the required charge of the adjacent medium. It tends to zero for high frequencies at the sharp corner, since the high pacing leads to a reduced excitability of the tissue. The reduction of excitability in dependence of the frequency thus determines a critical frequency, for which detachment occurs. The restitution properties of the tissue, in particular the reduction of the action potential amplitude, define the dependence of the reduction of excitability on the frequency.

Irregularity of type III is observed also in the BOCF model. In fig. 1 the time evolution of the excitation patterns for irregularity type III is shown for both models. In both models wave fragments are generated by the primary pacemaker due to the phase shift in x-direction at constant y. In contrast to the results of the FHN model, however, the BOCF model generates a curling of the wavefront only, but no reentrant patterns. This is caused by the much broader action potentials in the case of atrial electrophysiology compared to the action potentials in the FHN model. Thus the open end of the wave fragment starts to curl but collides with its refractory tail and is thus extinguished.

In the FHN model the strength of irregularity for type III, quantified by the order parameter ΔR, depends on the pacing frequency f_{pace} as shown in fig. 2 for different pacing frequencies. With increasing pacing frequency the order parameter ΔR decreases, indicating a reduced irregularity in the system. Thus the pacing frequency can have stabilizing effects, suppressing irregular patterns. If the pacing frequency is increased further, not shown, this

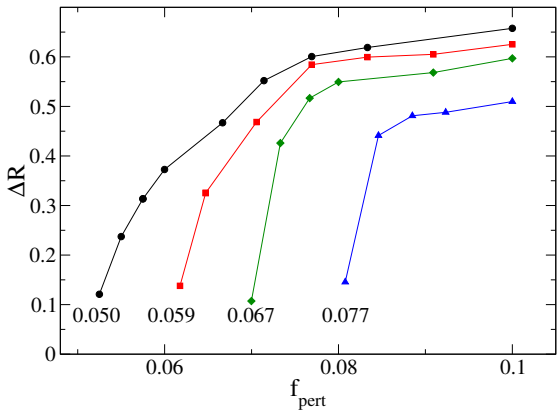

Figure 2. Dependence of ΔR on the perturbation frequency f_{pert} in the FHN model for different pacing frequencies. The numbers at the curves denote the value of f_{pace}.

effect vanishes and even more irregular patterns are observed.

4. Discussion and conclusions

In the BOCF model the detachment of waves from the bridge does not occur and thus irregular patterns of type I or II are not observed, possibly due to the different restitution properties compared to the FHN model. It has to be further explored in future studies, what exactly prevents the waves from detaching from the corners. If under some circumstances the electrophysiology of the atrial cells is changed in a way that their restitution properties become more similar to the FHN restitution properties, the detachment of waves from the sharp corners combined with the interaction of two pacemakers might become more relevant in generating irregular patterns. Thus calculations with, e.g., remodelled tissue, i.e. tissues with changed properties due to the ongoing AF, can yield quite different results.

The mechanism yielding type III irregularity can be relevant for the generation of AF. It yields a perturbation of the propagation of the sinus node waves, but no wave breaks or reentrant patterns occur, and the frequency is only slightly increased in the right part of the simulation area. The question, under which circumstances reentrant patterns occur also in the BOCF model, still needs to be clarified. A change in the pacing (sinus node) frequency can enhance or suppress the generation of irregular patterns for type III irregularity, which could give an explanation for the often intermittent occurrence of AF in its initial stadium.

Acknowledgments

C. L. thanks the Thuringian government and the Carl-Zeiss-Stiftung for financial support.

References

[1] Weber F. Personalizing Simulations of the Human Atria-Intracardiac Measurements, Tissue Conductivities, and Cellular Electrophysiology. In: Karlsruhe Institute of Technology, Institute of Biomedical Engineering. Karlsruhe Transactions on Biomedical Engineering Vol.12 2011.

[2] Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, Hsu L-F, Garrigue S, Takahashi Y, Rotter M, Sacher F, Scavee C, Ploutz-Snyder R, Jalife J, Haisaguerre M. Spectral analysis identifies sites of high-frequency activity maintaining AF in humans. Circulation 2005;112:789-797.

[3] Nattel S. New ideas about AF 50 years on. Nature 2002;415:219-226.

[4] Lenk C, Einax M, Maass P. Irregular excitation patterns in reaction diffusion systems described by the FHN equations caused by the interaction of excitation sources. arXiv:1004.0883; ibid. to be published.

[5] FitzHugh R. Impulses and physiological states in theoretical models of nerve membrane. Biophys. J. 1961;1:445-466.

[6] Bueno-Orovio A, Cherry EM, Fenton FH. Minimal model of human ventricular action potentials in tissue. J. theo. Biol. 2008;253:544-560.

[7] Seemann G, Sachse FB, Karl M, Weiss DL, Heuveline V, Dössel O. Framework for modular, flexible and efficient solving the cardiac bidomain equations using PETSc. In: Fitt AD, Progress in Industrial Mathematics at ECMI 2008. Mathematics in Industry 2010;15:363–9

[8] Taylor AF, Kapetanopoulos P, Whitaker BJ, Toth R, Bull L, Tinsley MR. Phase clustering in globally coupled photochemical oscillators. Eur. Phys. J. Special Topics 2008;165:137-149.

[9] Hamann C, Bartsch RP, Schumann AY, Penzel T, Havlin S, Kantelhardt J. Automated synchrogram analysis applied to heartbeat and reconstructed respiration. Chaos 2009;19:015106-1-8.

[10] Starobin JM, Zilberter YI, Rusnak EM, Starmer CF. Wavelet formation in excitable cardiac tissue: the role of wavefront-obstacle interactions in initiating high-frequency fibrillatory-like arrhythmias. Biophys. J. 1996;70:581-594.

Address for correspondence:

Claudia Lenk
FG Physikalische Chemie/Mikroreaktionstechnik (IfCB)
Technische Universität Ilmenau
Weimarer Strasse 25, 98693 Ilmenau,Germany
claudia.lenk@tu-ilmenau.de