Predicting Unpinning Success Rates for a Pinned Spiral in an Excitable Medium

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Abstract

Today, the only robust technique for terminating ventricular fibrillation is an electrical shock of up to 400 joules. A reliable more gentle alternative to this procedure is desirable, as the strong currents of the shock may result in cardiac lesions and therefore may increase the risk of further abnormal heart rhythms. Reentrant arrhythmias are associated with the existence of spiral waves in the tissue. Their termination by local control is substantially limited by anchoring of these waves at natural heterogeneities. Far-field pacing (FFP) is a control strategy that has been shown to be capable of unpinning waves from obstacles. The success of unpinning is both frequency-dependent and sensitive to the initial position of the spiral. Therefore, in this article, we systematically analyze the response of a single pinned wave to FFP. By quantifying the response of the wave for a single pulse in a generic model of excitable media and incorporating the results into an iterative map, we predict the response of the wave to multiple pulses.

1. Introduction

Generic activation patterns such as plane waves, spiral waves and spiral defect chaos which are known from many different excitable media also occur in cardiac tissue. Normal activity is associated with plane waves. During tachycardias, reentrant waves (spiral or scroll waves) produce increased heart rate. Effects such as spiral wave breakup can ultimately lead to a state composed of many (possibly unstable) spirals which represents lethal ventricular fibrillation [1]. In this article we examine a control method known as far-field pacing (FFP), which exploits natural heterogeneities in the tissue and has been discussed in a number of studies (e.g. [2]). Experimentally, the tissue is subjected to a weak pulsed electric field. FFP has been shown to be capable of unpinning a spiral wave which is pinned to a heterogeneity (called "obstacle" in the following). Although the method is very promising in providing an alternative approach to even terminate fast arrhythmias and fibrillation [3], the mechanisms are still not well understood. Therefore this numerical study tries to systematically develop an understanding of the response of pinned spiral waves to periodic FFP. This is done by quantitatively analyzing the response to a single stimulus and extrapolating the obtained information to multiple stimuli. Thus, the aim is to get a picture of the essential effects which influence the reaction of a pinned wave to a stimulus train and to provide an alternative to the trial-and-error approach for finding optimal pacing frequencies.

2. Methods

2.1. Computational model

All simulations in this article are carried out using the Barkley model [4] with the reaction-diffusion equations

$$\frac{\partial u}{\partial t} = \frac{1}{\epsilon}u(1-u)\left(u - \frac{v+b}{a}\right) + \nabla^2 u, \quad \frac{\partial v}{\partial t} = u - v,$$

consisting of a fast variable u, a slow inhibitory variable v and three parameters $\epsilon = 0.02$ (determining the time scale of the fast variable), $a = 0.8$ and $b = 0.09$. All simulations were carried out with a constant spatial resolution of $\Delta x = 1/6$ and a simple Euler time step of $\Delta t = 1/500$. More details on the boundary conditions for modeling the obstacle can be found in reference [5]. All plots in the result section in this paper refer exemplariliy to simulations with an obstacle of radius R=3. At this obstacle size, the spiral wave's undisturbed rotation period is roughly 7.5 time units. FFP in all simulations was applied with a field strength of E=3 and a pulseduration of 0.1 time units. For other obstacle sizes and field strengths we obtain similar results.

2.2. Unpinning and success rate

The success of the unpinning mechanism critically depends on the position of the spiral at the time of the pulse. In the following, we will refer to this position as the "phase" $\varphi \in [0, 1[$ of the spiral, $\varphi = 0$ conveniently chosen as the place of FFP wave nucleation. There is only

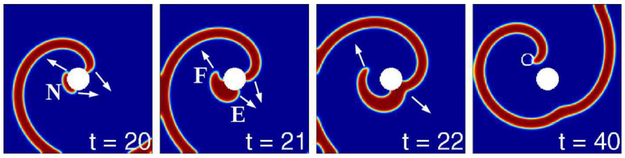

Figure 1. Successfull unpinning by FFP in a generic model of excitable media. N: wave nucleated by electric pulse. F: End of the new free spiral wave. E: End of the wave annihilating with the initial spiral wave. The new spiral core is indicated by a circular white line. Figure reproduced from [6].

a finite so-called unpinning window (i.e., a limited range of phases), in which unpinning is possible in the way depicted in figure 1. For an experimental situation, in which the phase of the spiral is not known (e.g., during cardiac fibrillation), the fraction of the phase interval $[0, 1[$, in which unpinning is possible, can be viewed as a success rate for a single pulse to unpin the spiral wave from the obstacle. Similarly, a success rate can be defined for multiple pulses by determining the fraction of initial phases for which, after a sequence of pulses, the spiral wave has been unpinned from the obstacle.

2.3. Phase response

The qualitative structure of the unpinning window for single pulses has already been the subject of previous studies [6, 7].

A single pulse can (i) unpin the spiral wave from the obstacle (unpinning window), (ii) have no effect at all (within the refractory tail) or (iii) produce a new wave (within the excitable gap).

To quantitatively characterize the response of a spiral to a single FFP stimulus, we calculate phase response curves. This is a map of the phase immediately before the pulse to the "apparent phase" after the pulse. The phase change is computed from the difference between the perturbed and the unperturbed spiral period and is assumed to happen instantaneously with the pulse (followed by rigid rotation with the unperturbed velocity). Obviously, these assumptions are not true. Thus, the resulting phase is called the "apparent phase". It is an auxiliary construct that allows for easy calculation of the phase at arbitrary times after the pulse, only by knowing the unperturbed propagation velocity of the spiral. However, one should bear in mind that the result is only meaningful for times when the real spiral has truly resumed rigid rotation with constant velocity.

In section 3.2, we will use the obtained phase response curve to predict the response of the spiral for multiple pulses.

3. Results

3.1. Unpinning success

To quantify the ability of a stimulus train to unpin waves, we carry out simulations with different initial phases at the beginning of pacing. We then determine the success rate described in section 2.2 as the fraction of initial phases resulting in successful unpinning. Figure 2 shows the results for $f_{\text{pacing}}/f_{\text{spiral}} \in [0.1, 2]$.

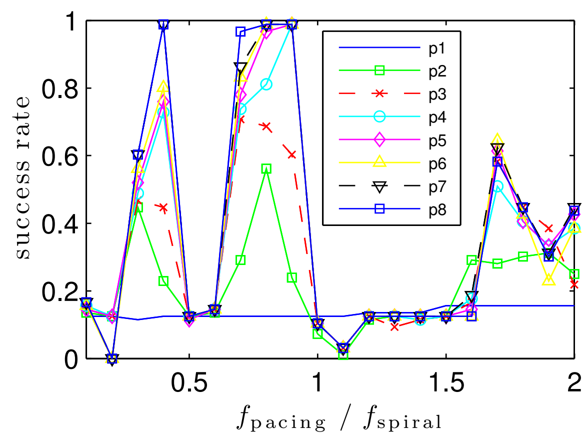

Figure 2. Unpinning success rates for up to 8 periodic pulses (p1 to p8). $f_{\text{pacing}}/f_{\text{spiral}} \in [0.1, 2]$; number of simulations for each frequency = 96; medium parameters and FFP specifications as listed in section 2.1.

From figure 2, we see that there are certain frequency regimes in which multiple pulses are very successful and others where multiple pulses lead to the same or even lower success rates than that of a single pulse. We will learn more about the underlying mechanisms in section 3.2.

Cases in which the success rate for multiple pulses is even lower than for a single pulse are due to so-called repinning, i.e. reattachment of the free unpinned wave to the obstacle. This can happen as a result of meandering or due to interaction of the free spiral with subsequent pulses.

3.2. Phase response and iterative map

The phase response curve (labeled $g(\varphi)$) for a single spiral is shown in figure 2. Interestingly, except for the unpinning window, no abrupt changes in the apparent phase are visible, which one would have expected thinking of the regimes (i), (ii) and (iii) mentioned in section 2.3.

Qualitatively, the characteristics of the phase response curves measured in [8] in the FitzHugh-Nagumo Model are consistent with our results. Quantitatively, the shape of the curve differs slightly due to model-dependent dynamics.

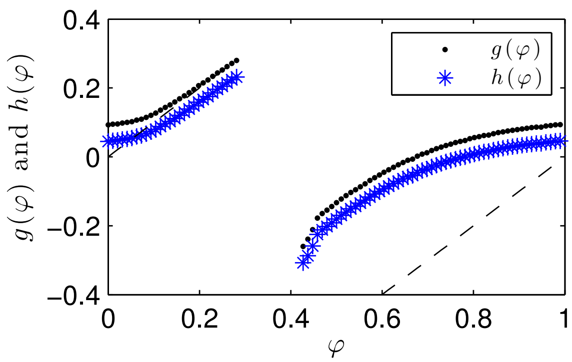

Figure 3. The functions $g(\varphi)$ and $h(\varphi) = g(\varphi) + f_{\text{spiral}}/f_{\text{pacing}}$ are plotted against the phase at which the pulse is given. The resulting phase is mapped to the interval [-0.4,0.4[. The intervall, for which no data points exist, corresponds to the unpinning window. The identity is plotted as a dashed line, corresponding to an unchanged phase. $f_{\text{pacing}}/f_{\text{spiral}}$ = 1.05; medium parameters and FFP specifications as listed in section 2.1.

With the help of the phase response curve, we now construct an iterative map to predict the response of the spiral to multiple stimuli: Let $g(\varphi)$ be the phase response function. Because of the way the phase response curve was constructed in section 2.3, we can assume that, between two pulses, the spiral advances uniformly by $f_{\text{spiral}}/f_{\text{pacing}}$ (in phase units). Thus, the map that transforms the phase of a spiral before one pulse into the phase before the next pulse is $h(\varphi) = g(\varphi) + f_{\text{spiral}}/f_{\text{pacing}}$ (followed by a modulo operation that takes the phase back to the unit interval). Of course, this function is undefined where $g(\varphi)$ is undefined (corresponding to successful unpinning). We can interpret $h(\varphi)$ as an iterative map $\varphi_{n+1} = h(\varphi_n)$. For a specific pacing frequency, the success rate corresponds to the fraction of initial phases $\varphi_0 \in [0, 1[$ for which (during N_{pulses} iterative applications of $h(\varphi)$) the result becomes undefined. For the rest of initial phases, $\varphi_{N_{\text{pulses}}}$ corresponds to the phase of the spiral one pacing period after the last pulse.

The intersection of $h(\varphi)$ with the identity function indicates the existence of fixed points in the iterative map. It is the existence of these fixed points that leads to the phase resetting mechanism described in [7]. At certain frequencies this mechanism avoids an increase of the success rate by multiple pulses compared to that of a single pulse.

By plotting the phase φ_n of the spiral at the moment of the nth pulse, we get an idea of a mechanism that we call phase scanning. Figure 4 illustrates how the spiral's phase is shifted by each pulse until it reaches the unpinning window. Due to this mechanism, the success rate at certain frequencies is very high. The ideal combination of number of pulses and pacing frequency depends on the spiral's rotation period and hence on the obstacle size and the choice of model parameters.

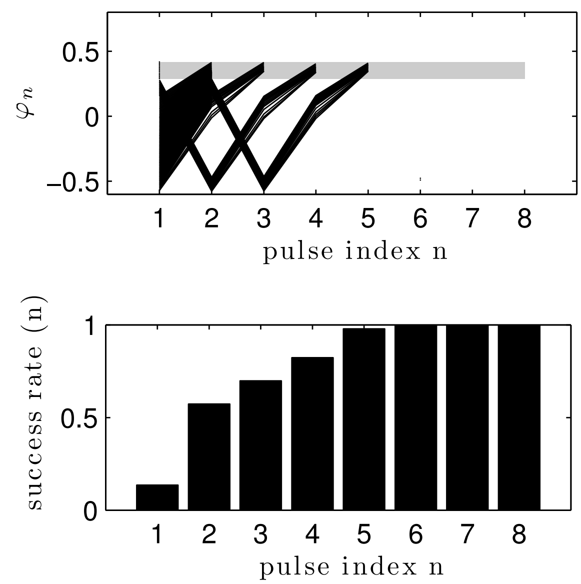

Figure 4. Phase scanning mechanism at $f_{\text{pacing}}/f_{\text{spiral}} = 0.8$. Top: Apparent phase φ_n at the moment of nth pulse. The light grey bar indicates the unpinning window. Bottom: Success rate after nth pulse. Medium parameters and FFP specifications as listed in section 2.1.

3.3. Predictions by the iterated map

Figure 6 shows the success rate predicted by the iterative map $h(\varphi)$ in comparison to the results obtained by numerical simulations. As a result of the high computational effort, the resolution of the numerically computed success rate is 0.1 whereas the map was computed for frequency intervals of 0.0001. For pacing frequencies slower than the spiral frequency, the map is largely able to accurately predict the unpinning success rate for further pulses. For high pacing frequencies, the interaction of consecutive pulses with each other leads to deviations of the predicted phase response from the response obtained by direct numerical simulation.
The success rate prediction shows a repetitive structure which results from the fact, that (for $f_{pacing} \leq f_{spiral}$) the ratio $f_{spiral}/f_{pacing} \mod 1$ is decisive for the unpinning result. To make sure that the fine structure of the predicted success rate is actually due to physical mechanisms of the model and not just a numerical artifact, the success rate for the frequency range $f_{pacing}/f_{spiral} \in [0.5, 1]$ was again computed from full simulations with a resolution of 0.01.

From figure 5 we can see that the predicted and the numerical results fit nicely except for some local deviations.

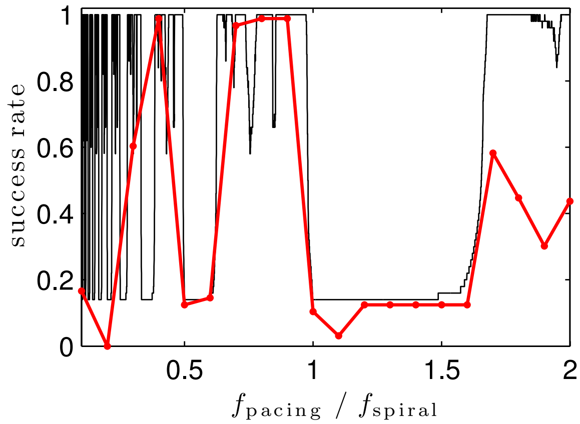

Figure 5. Success rate after 8 pulses. Red: Success rate obtained from numerical simulations (frequencies in steps of 0.1). Black: Success rate computed with iterative map (frequencies in steps of 0.0001). Medium parameters and FFP specifications as listed in section 2.1.

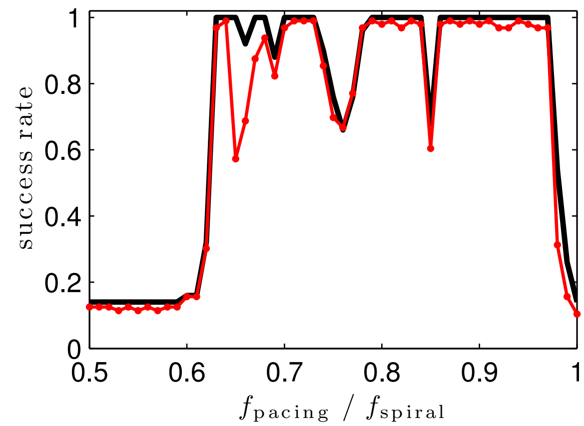

Figure 6. Success rate after 8 pulses. Red: Success rate obtained from numerical simulations (frequencies in steps of 0.01). Black: Success rate computed with iterative map (frequencies in steps of 0.01). Medium parameters and FFP specifications as listed in section 2.1.

4. Discussion and conclusions

We conclude that, for $f_{pacing} \lessapprox f_{spiral}$, the unpinning success of multiple FFP pulses can be predicted by the iteration of the phase response of a single pulse only. We have confirmed the mechanisms of "phase scanning" and "phase resetting" that lead to very high and very low unpinning success rates respectively.
In [8] González et al. compare the results of numerical single pulse phase response measurements to experimental data gained from cell culture experiments. Further investigations will be necessary to study the significance of numerically predicted success rates for experimental situations.

Acknowledgements

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