ROBUSTNESS OF LOCAL FORCING IN INHIBITION OF REENTRY

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Abstract

It was systematically analyzed and has been shown that the low-voltage "point" forcing is not a robust method to terminate reentrant arrhythmias. Even in homogeneous isotropic tissue simulated by a simplified ionic model it was found that success/failure of local pacing strongly depends on the type of reentry, location of the electrode, phase of stimuli during the rotation period, stimulation frequency and waveform and the size of tissue. Along with elimination of spiral waves, shift of spiral cores closer to unexcitable boundaries or no effect, the local forcing may also cause spiral-wave turbulence (fibrillation) and prolong existence of an otherwise self-terminating single spiral wave (reentrant tachycardia).

Key words

Pacing, spiral waves, cardiac tissue, suppression.

1 Introduction

Despite extensive work and achieved progress on a frontier between cardiology, electrophysiology, physics and engineering, the problem of abnormalities in the electrical activity of the heart (cardiac arrhythmias) still attracts a considerable interest. One of the most important open questions here is termination of arrhythmias occurring in ventricles, i.e. ventricular tachyarrhythmias [Jordan and Christini, 2005; Zipes and Jalife, 1995]. Ventricular tachyarrhythmias including ventricular tachycardia (VT) and ventricular fibrillation (VF) can lead to extremely rapid and uncoordinated contractions, resulting in dysfunction of the blood pumping by the heart. As is known, VT, which is induced by a rotation of a single reentrant wave (spiral wave in 2D and scroll wave in 3D) may lead to VF due to the breakup of the rotating wave. VF is the prevalent mode of death among patients with cardiovascular diseases occurring because of abnormal contraction of ventricles associated with multiple reentrant waves (see, e.g., [Zipes and Jalife, 1995; Winfree, 1987]).

For terminating VT and VF devices surgically implanted in the bodies of high-risk cardiac patients are used. Modern implantable cardioverter defibrillators (ICDs) possess pacing, cardioversion and defibrillation capabilities, and may try to pace the heart faster than its intrinsic rate in the case of VT in order to break it before the latter proceeds to VF (see, e.g., [Jordan and Christini, 2005; Stevenson et al., 2004]). This local forcing is known as overdrive pacing, fast-pacing, or anti-tachycardia pacing (ATP). It locally applies one or more series of low-power suprathreshold stimuli to return a racing heart to its normal rhythm.

ATP would be a desirable therapy for both types of ventricular tachyarrhythmias as in comparison to high-energy defibrillating shocks it implies low-energy stimulation to one or several (multi-electrode ATP [Pak et al., 2003]) sites and prevents destruction of the cardiac and surrounding tissues and adverse side effects. However, the success rate of ATP is around 70-90 % (see, e.g., [Takagi et al., 2004; Ripplinger et al., 2006] and references therein) for slow tachycardias (cycle length $>$ 300-320 ms, or frequency $<$ 188-200 beats/min) and even less for fast tachycardias (cycle length 240-300 ms, frequency 200-250 beats/min). The latter as well as VF are often treated by shock because of safety concerns. If ATP fails or if VT has higher frequency than programmed for pacing, ICD proceeds with delivering high-energy defibrillating shocks.

Although, ATP does not always terminate even a single reentry, a number of experiments were conducted to check whether low-amplitude local rapid forcing defibrillates real atrial and ventricular tissue (see [Allessie et al., 1991; Kirchhof et al., 1993] and references in [Stamp et al., 2002]). Instead of suppression of reentry only regional entrainment resulting in small areas of organized electrical activity was observed. Furthermore, many attempts to terminate fibrillative activity in numerical simulations were carried out [Stamp et al., 2002; Zhang et al., 2003; Breuer and Sinha, 2004; Vysotsky et al., 2005; Yuan et al., 2005; Zhang et al., 2005; Cao et al., 2006; Loskutov and Vysotsky, 2006;

Zhuchkova et al., 2009; Cao et al., 2007; Sinha and Sridhar, 2007]. In all these papers the authors tried to suppress two-dimensional or even three-dimensional [Zhang et al., 2005; Cao et al., 2007] complex reentrant activity in generic models of excitable media or models of cardiac tissue by low-amplitude local forcing. With proper parameters to be chosen, chaotic activity could be always suppressed or some additional methods like calcium channel blockers in [Stamp et al., 2002] and gradient field in [Cao et al., 2006; Cao et al., 2007] were needed. Pacing was realized by a single small square or long stripe electrode located in the center or at the medium boundary. In all the cases the stimulation frequency seemed to have a great importance and the input-output frequency dependencies were constructed to obtain the maximal output frequency of a medium. Forms of pacing signals were different but biphasic rectangular shapes were proved to be the most effective giving larger output frequencies [Stamp et al., 2002; Breuer and Sinha, 2004].

In general, to eliminate reentrant activity, local forcing must be able to generate pacing stimuli, which in turn must be stable and able to propagate regularly in tissue and to compete with the reentrant wave. The main factors responsible for the successful termination include (1) the phase of the stimulus during the rotation period of reentry (it depends on the type of reentry, when the reentry cycle length decreases, the "vulnerable window" is reduced, and only a short range of phases may induce the reentry inhibition), (2) the pacing protocol, (3) the waveform of the stimulation, (4) the frequency of the stimulation, (5) the stimulation amplitude, (6) the pacing area, (7) the location of the stimulating site (electrode) with respect to the rotating wave, (8) the number of electrodes, (9) the system size, (10) obstacles (functional or anatomical), around which the reentry rotates [Sweeney, 2004; Cao et al., 2007]. Sometimes even a single stimulus applied at a correct phase may terminate reentrant VT but the efficacy is low [Davidenko et al., 1995]. Multiple stimuli delivered in the form of pacing drive trains increase the likelihood of termination.

In this paper we apply periodic local forcing to terminate two types of simulated VT. For this purpose we use a three variable simplified Fenton-Karma ionic model of cardiac excitation [Fenton and Karma, 1998; Fenton et al., 2002] and two types of suggested in the literature biphasic waveforms [Stamp et al., 2002; Vysotsky et al., 2005; Loskutov and Vysotsky, 2006; Zhuchkova et al., 2009]. Fixing the stimulation protocol (we continue to stimulate the medium uninterruptedly during the observation time without any changes in the stimulation frequency), the stimulation amplitude (we restrict ourselves to low-amplitude impact), size and number of pacemakers (we consider a single point electrode), we check an ability of low-amplitude local forcing to terminate a single reentry in homogeneous isotropic tissue by varying other parameters. Namely, we investigate the influence of the choice of the pacing frequency

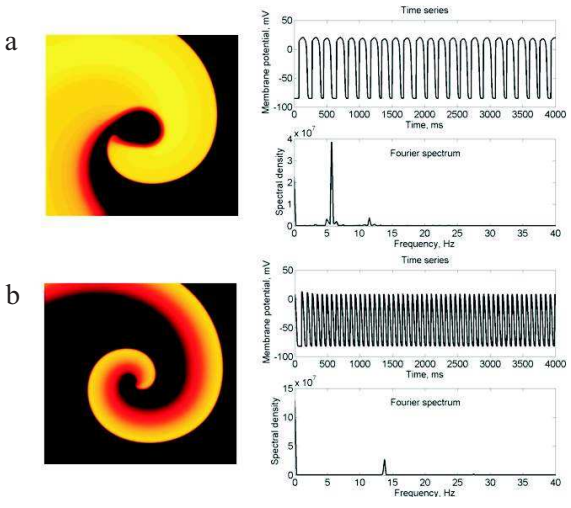

Figure 1. Types of spiral waves in the simplified ionic model. a, A self-terminating at 4930 ms spiral wave obtained at $k = 10$, the frequency of rotation $\omega \approx 5.75\ Hz$. b, A stable spiral wave obtained at $k = 1$, the frequency of rotation $\omega = 13.75\ Hz$.

in detail, we apply also single stimuli at various phases during the rotation period, and we locate an electrode at different positions in relation to the reentry core. Furthermore, we compare results of the stimulation for a smaller piece of tissue.

2 Fenton-Karma model with external forcing

The simplified ionic model (SIM), or Fenton–Karma equations, has the following form [Fenton and Karma, 1998; Fenton et al., 2002]:

$$\begin{aligned}
\partial_t u &= \nabla(D\nabla u) - (J_{fi}(u,v) + J_{si}(u,w) + J_{so}(u))\,,\\
\partial_t v &= \Theta(u_c - u)(1-v)/\tau_v^-(u) - \Theta(u-u_c)v/\tau_v^+,\\
\partial_t w &= \Theta(u_c - u)(1-w)/\tau_w^- - \Theta(u-u_c)w/\tau_w^+,
\end{aligned} \tag{1}$$

where u is a dimensionless membrane potential; v, w are fast and slow ionic gates, respectively; D is a diffusion tensor that in our case is a diagonal matrix with equal diagonal elements ($0.001\ \mathrm{cm}^2/\mathrm{ms}$), which corresponds to an isotropic medium; $\Theta(x)$ is a standard Heaviside step function; $\tau_v^-(u) = \Theta(u-u_v)\tau_{v1}^- + \Theta(u_v-u)\tau_{v2}^-$; J_{fi}, J_{so}, J_{si} are scaled ionic currents describing the Na^+, K^+, Ca^{2+} currents, respectively:

$$\begin{aligned}
J_{fi} &= -v\Theta(u-u_c)[(1-u)(u-u_c)]/\tau_d,\\
J_{si} &= -w(1+tanh(k(u-u_c^{si})))/2\tau_{si},\\
J_{so} &= u\Theta(u_c-u)/\tau_0 + \Theta(u-u_c)/\tau_r.
\end{aligned} \tag{2}$$

The parameters correspond to the set 1 in [Fenton et al., 2002] with an increased depolarization time τ_d equal to 0.41. The parameter k (so-called activation

width) in some cases was changed to 1. If it is not specially noted, the numerical simulations were performed in a 2D grid of 500×500 elements corresponding to the tissue size of $12.5 \times 12.5\ cm$. We used Neumann (no-flux) boundary conditions.

The SIM supports many different mechanisms of spiral wave breakup into a complex reentrant activity [Fenton et al., 2002]. However, here our aim is to ensure conditions under which ATP is usually applied and thus we choose such a parameter set to have a single rotating wave. Decreasing the parameter k from 10 to 1, we simulated two different types of spiral waves. The left side of Fig.1 shows distribution of the membrane potential and the right side corresponds to time series and Fourier spectra of the membrane potential at an arbitrary point. Fig.1a corresponds to reentry rotating at approximately 5.75 Hz. Colliding with the refractory tail the wave front was not able to propagate due to a conduction block. This led to wave break close to the tip of the spiral and the further displacement of the core. Eventually reentry terminated itself at 4930 ms. On the contrary a spiral wave with $k = 1$ was stable, meandering and rotated at a much higher frequency $\omega = 13.75\ Hz$ (Fig.1b).

To terminate reentry we added an external current $J_{ext} S^{\Omega_i}$ to the right part of the cable equation. Here S^{Ω_i} is equal to unity inside the area Ω_i (external electrode) and zero outside. Electrodes were chosen to be *point* pacemakers, their size 2×2 nodes corresponds to $0.5 \times 0.5\ mm$.

Newer ICDs typically use a biphasic shape of external stimulation, which was also suggested in many papers as one of the most effective pacing shapes to suppress fibrillative activity in mathematical models (see, e.g., [Stamp et al., 2002; Breuer and Sinha, 2004]). Therefore, we applied external forcing of the same biphasic waveform of two different types with varied [Vysotsky et al., 2005; Loskutov and Vysotsky, 2006; Zhuchkova et al., 2009] and fixed [Stamp et al., 2002] to 10 ms duration of stimuli (Fig.2) with the amplitude $A = 100\ \mu A/cm^2$ corresponding to the fourfold excitation threshold. We took $\tau = 0.3$ so that for the second type of the waveform (Fig.2b) and for single stimuli duration of the negative part is equal to 3 ms whereas the total duration of the biphasic signal is 10 ms, which agrees with experiments.

3 Results

In this section we present results of pacing with single and periodic stimuli.

3.1 Single stimuli

First, we used single stimuli to understand which effects on both spiral waves they cause. Stimuli were applied at three different phases during rotation periods of both spiral waves: during refractory time, vulnerable period and rest state. We have observed that a single stimulus could quickly terminate reentry only if the latter was unstable (Fig.1a), the electrode was located close to the core and a stimulus was applied during the rest state. A stimulus applied far from the spiral core during a vulnerable window could lead to the so-called figure-of-eight reentry, which was self-terminated. Application of single stimuli at other phases either did not result in significant influence on the rotation of both spiral waves or even could prolong the existence of the unstable spiral wave.

3.2 Periodic stimulation

As is mentioned in many sources (see, e.g., [Stamp et al., 2002]), the wave train with the highest frequency will eventually entrain all other waves. However, their suppression is not guaranteed and the time to suppression depends inversely on the frequency difference between the waves, and the velocity of the wave with the highest frequency. The pacing frequency that is a slightly higher than tachycardia frequency is used in ATP algorithms [Sweeney, 2004]. We are interested in how high should be the frequency for the effective termination of reentry and which effects on spiral wave rotation are resulted from pacing with arbitrary period. To solve this problem, we first investigated the response of the medium to local forcing, i.e. measured the period of target waves emitted by an external electrode as a function of its own period and then tried to terminate reentrant pattern with frequencies corresponding to this data.

For this aim we generated a pacemaker in the center of the medium and determined the frequency ω_{out} of the target waves at some distance from the pacemaker as a function of the internal pacemaker frequency ω_{in}. As the stimulation onset we took 50 ms (applied at this moment of time single stimuli could not terminate reentry). Figures 3 and 4a show the frequency dependencies during biphasic stimulation with varied duration for the tissue having unstable reentry and the stable spiral wave correspondingly. Fig.4b represents the frequency response of the medium with stable reentry to external pacing with fixed duration of the signal. The frequency dependencies consist of several $N : 1$ (where N is a number of stimulation events) synchronization branches due to the existence of a refractory period [Stamp et al., 2002]. In Fig.3 one can also note a remarkable $5 : 2$ synchronization between $2 : 1$ and $3 : 1$ branches appeared according to Farey rule. The maximal output frequency corresponds to the left $(1 : 1)$ local maximum in Fig.4 and left $(1 : 1)$ and middle $(2 : 1)$ maxima in Fig.3. Note that the maximal frequency is not just a reciprocal of the refractory period, since it depends on the forcing type of the system having a stable reentry.

Fig.3a represents effects of pacing by the central electrode. Circles of red, blue and green colours correspond to the failed, successful and very quick reentry termination respectively. We considered elimination of the unstable spiral wave as a failed one if it was terminated at $t \geq 4930\ ms$ (the moment of the self-

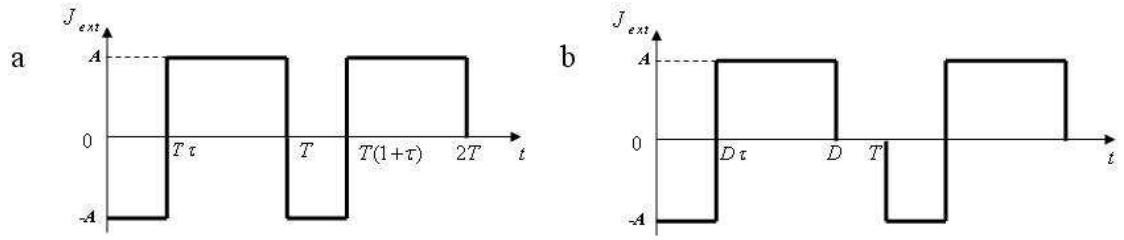

Figure 2. Biphasic periodic stimulation, $0 < \tau < 1$, here $\tau = 0.3$. a, Duration of the biphasic signal is a function of its period. b, Duration of the negative part is fixed to 3 ms (total duration D of the signal is equal to 10 ms).

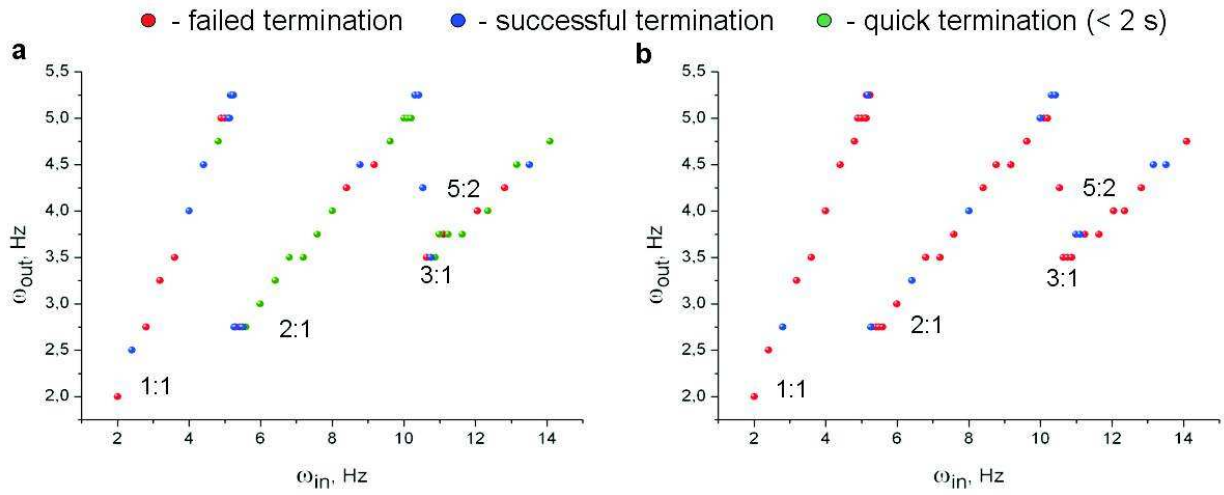

Figure 3. Dependencies of the frequency ω_{out} of target waves on the pacemaker frequency ω_{in} at $k = 10$. a, Stimulation at the central electrode. b, Stimulation at the remote electrode. Stimulation onset is 50 ms. Further explanation is in the text.

termination). Termination was successful if the termination time $2000\ ms < t < 4930\ ms$ and it was very quick if $t \leq 2000\ ms$. One can see that it is easier to inhibit reentry if the stimulation frequency corresponds to the $2:1$ synchronization branch where the stimulation frequency is higher than the frequency of the spiral wave but it is not too high. In comparison to pacing by the central electrode, stimulation at the remote electrode was rarely successful and never very fast (Fig.3b) because of the necessity to overcome a bulk of excited and refractory tissue to approach the spiral tip.

Another situation has been observed at pacing the stable spiral wave during 10 seconds with the same biphasic waveform (Fig.4a). One can see that the maximal output frequency here is less than the frequency of the spiral wave denoted by the dotted horizontal line. As was expected, in all cases termination was unsuccessful and reentry continued to rotate with minor changes (black circles), it was displaced (blue and green circles or was multiplied (orange circles). The blue circle represents the case of simultaneous existence of target waves and the spiral tip. Tripling the observation time in this case leads to displacement of the spiral core close to the boundary and entrainment by the external forcing. If the stimulation frequency is slightly higher than that corresponding to the target-spiral pattern (blue circle), a single rotating wave degenerates into multiple spiral waves (orange circles).

Fig.4b shows the frequency response of the same system as in Fig.4a to another type of the biphasic pacing with fixed duration of 10 ms (Fig.2b). In contrast to [Gray, 2002] here this kind of forcing with short duration of stimuli is more effective than pacing by long stimuli since it provides the maximal output frequency higher than the frequency of the spiral wave denoted by the dotted line. Red circles here correspond to forcing with the maximal output frequency resulting in the "almost" suppression phenomenon and spiral replacement. Note that continuation of pacing with this frequency and tripling the observation time does not lead to the total elimination of the spiral wave, the latter continues rotation at the boundary. In this case reentry is only entrained and after switching off the forcing it will remain. Increasing the observation time for pacing with $\omega_{in} = 13.89\ Hz$ resulted in degeneration of the spiral-target pattern (blue circle) into the entrained

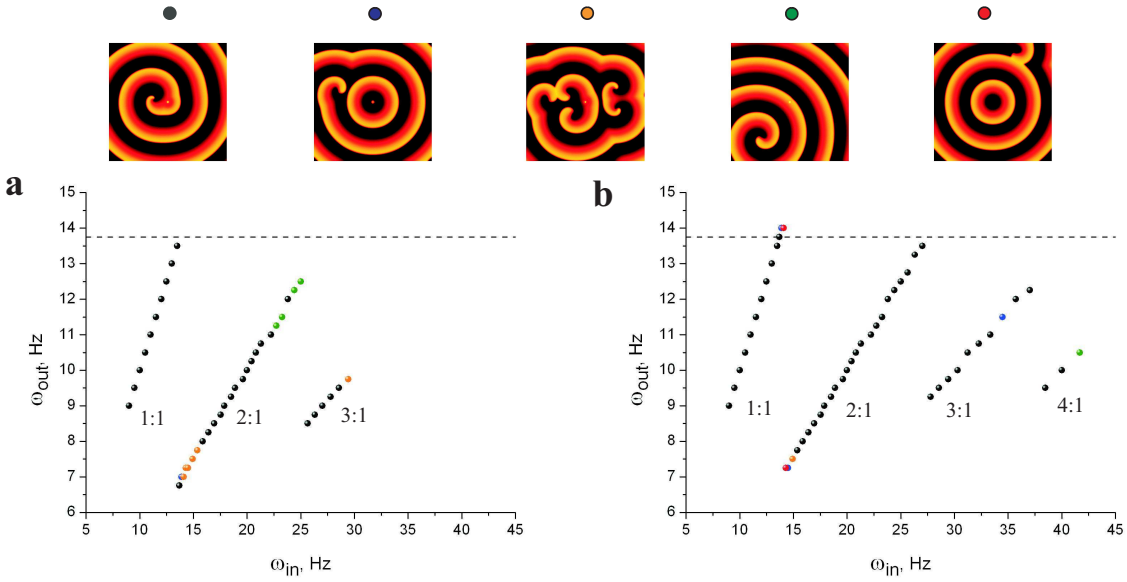

Figure 4. Dependencies of the frequency ω_{out} of target waves on the pacemaker frequency ω_{in} at $k = 1$. a, Stimulation waveform corresponds to Fig.2a. b, Stimulation waveform corresponds to Fig.2b. Stimulation onset is 50 ms. Further details are in the text.

reentry (red circles) whereas continuation to force with $\omega_{in} = 14.49\ Hz$ (blue circle) during 30 seconds led to multiplication of the spiral (orange circles). This shows that the target-spiral pattern is not stable and serves as a transient regime between the entrained reentry and turbulent activity.

We have mainly considered the tissue of the large size in order to avoid strong influence of boundaries. If the tissue size is smaller (we have twice reduced the tissue size: $6.25 \times 6.25\ cm$), it means that the spiral tip is located closer to the electrode and the boundaries. In this case the probability of the suppression event is higher but it almost does not depend on the stimulation frequency (or this dependence is distorted by the proximity of tissue boundaries).

4 Conclusion

In this manuscript we have investigated effects of low-amplitude local forcing on rotation of two different spiral waves. We have observed that elimination of unstable reentry was much easier than the termination of the stable spiral wave and it could occur even at application of a single stimulus and at stimulating with different frequencies (no regularity was seen). This could be connected with its eventual self-termination or with the fact that the more complex activity is more susceptible to external forcing.

We have found that the farther an electrode from the spiral core, the harder the inhibition of spiral waves was to achieve. This can be explained by longer time needed to approach the spiral core. In the case of the unstable reentrant pattern local pacing by a distant electrode mainly led to prolongation of its existence.

During the observation time the stable reentry in large tissue was not terminated. So, even a single reentrant wave can not be always suppressed in homogeneous tissue by local forcing (even when the maximal output frequency is higher than the spiral wave frequency). Tripling the time also failed in observation of elimination events. However, at increased stimulation time the spiral-target pattern transformed to the entrained pattern or to multiple rotating waves. The entrainment phenomenon could occur faster if the difference between the stimulation frequency and the reentry frequency was larger.

We have found the proximity in input frequency of the entrained pattern to the spiral turbulence pattern. This means that one must be very careful at application of ATP to patients. These two regimes degenerate into each other at a slight change of the pacing frequency, which is little higher than the reentry frequency and is actually used in ATP protocols [Jordan and Christini, 2005; Sweeney, 2004].

At increasing the stimulation frequency, the remarkable sequence of events can be observed: the rotating spiral wave gives rise to the spiral-target pattern, which modifies to the entrained spiral rotating at the tissue border, then the spiral-wave turbulence emerges later degenerating into the rotating spiral wave (the spiral core could be slightly replaced from the center). It is interesting that the multiplication of the spiral was observed only at the bottom of the $2:1$ synchronization branch (at $k = 1$). If one increases observation time up to 30 seconds, the similar sequence of events excluding transient target-spiral pattern is observed.

The current work has several limitations, the main ones of them are the following. (1) The used model is simplified and it was not designed for a human cardiac tissue. Therefore the frequency of the stable reentry does not correspond to reality (it is too high in compari-

son to real human heart). (2) Increasing the observation time does not have much sense. In relation to real patients this is not adequate, since VT and especially VF require immediate termination. (3) The maximal output frequency in real inhomogeneous heart is not the same everywhere in the tissue. However, these limitations do not influence on the main conclusion of the paper that the success/failure of the local forcing strongly depends on many parameters and it is not robust. One may try other methods, e.g. feedback-mediated control [Schlesner et al., 2008], to inhibit reentry in the heart.

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