Controlling spatiotemporal chaos in excitable media by local biphasic stimulation

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Controlling spatiotemporal chaos in excitable media by applying low-amplitude perturbations locally is of immediate applicability, e.g., in treating ventricular fibrillation, a fatal disturbance in the normal rhythmic functioning of the heart. We look at a mechanism of control by the local application of a series of biphasic pulses, i.e., involving both positive and negative stimulation. This results in faster recovery of the medium, making it possible to overdrive the chaos by generating waves with frequency higher than that possible with only positive pulses. This provides the simplest and most general understanding of the effectiveness of biphasic stimulation in controlling fibrillation and allows designing optimal waveshapes for controlling spatiotemporal chaos.

A characteristic feature of excitable media is the formation of spiral waves and their subsequent breakup into spatiotemporal chaos. Examples include catalysis of CO on Pt(110) surface [1], cAMP waves during slime mold aggregation [2], etc. Another example of obvious importance is the propagation of waves of electrical excitation along the heart wall, initiating the muscular contractions that enable the heart to pump blood. In fact, spiral turbulence has been identified by several investigators as the underlying cause of certain arrhythmias, i.e., abnormal cardiac rhythms, including ventricular fibrillation (VF) [3], a potentially fatal condition in which different regions of the heart are no longer activated coherently. Current methods of defibrillatory treatment involve applying small perturbations from a few local sources. To achieve control of spatiotemporal chaos, we locally apply a periodic perturbation, e.g., a series of pulses having a fixed amplitude and duration, applied at periodic intervals defined by the stimulation frequency $f$. The control mechanism can be understood as a process of overdriving the chaos by a small perturbation from a few local sources.

For most of the simulations reported in this paper we have used the modified Fitzhugh-Nagumo equations proposed by Pauflav as a model for ventricular activation [8]. For simplicity we assume an isotropic medium; in this case the model is defined by the two equations governing the excitability $e$ and recovery $g$ variables,

$$\frac{\partial e}{\partial t} = \nabla^2 e - f(e) - g,$$
$$\frac{\partial g}{\partial t} = \epsilon(e,g)(ke - g).$$

(1)

The function $f(e)$, which specifies fast processes (e.g., the initiation of excitation) is piecewise linear: $f(e) = C_1 e$, for $e < e_1$, $f(e) = -C_2 e + a$, for $e_1 \leq e \leq e_2$, and $f(e) = C_3 (e - 1)$, for $e > e_2$. The function $\epsilon(e,g)$, which determines the dynamics of the recovery variable, is $\epsilon(e,g) = \epsilon_1$ for $e < e_2$, $\epsilon(e,g) = \epsilon_2$ for $e > e_2$, and $\epsilon(e,g) = \epsilon_3$ for $e < e_1$ and $g < g_1$. We use the physically appropriate parameter values given in Ref. [6].

We solve model (1) by using a forward-Euler integration scheme. The system is discretized on a two-dimensional grid of points with spacing $\delta x = 0.5$ dimensionless units. The standard five-point difference stencil is used for the 2-D Laplacian. The spatial grid consists of $L \times L$ points; in our studies we have used values of $L$ up to 500. For the 1-D simulations we use a 3-point difference stencil for the Laplacian, with the spatial lattice consisting of $L$ points. The time step is $\delta t = 0.01$ dimensionless units. We did not observe any qualitative change in the results on decreasing the space and time steps by a factor of 2. On the edges of the simulation region we use no-flux (Neumann) boundary conditions.

To achieve control of spatiotemporal chaos, we locally apply a periodic perturbation, $AF(2\pi ft)$, of amplitude $A$ and frequency $f$. $F$ can represent any periodic function, e.g., a series of pulses having a fixed amplitude and duration, applied at periodic intervals defined by the stimulation frequency $f$. The control mechanism can be understood as a process of overdriving the chaos by a source of periodic excitation having a significantly higher...
frequency. As noted in Refs. [9,10], in a competition between two sources of high frequency stimulation, the outcome is independent of the nature of the wave generation at either source, and is decided solely on the basis of their relative frequencies. This follows from the property of an excitable medium that waves annihilate when they collide with each other [11]. The lower frequency source is eventually entrained by the other source and will no longer generate waves when the higher frequency source is withdrawn. Although we cannot speak of a single frequency source in the case of chaos, the relevant timescale is that of spiral waves which is limited by the refractory period of the medium, \( \tau_{\text{ref}} \), the time interval during which an excited cell cannot be stimulated until it has recovered its resting state properties. To achieve control, one must use a periodic source with frequency \( f > \tau_{\text{ref}}^{-1} \). This is almost impossible with purely excitatory stimuli as reported in Ref. [6]; the effect of locally applying such perturbations is essentially limited by refractoriness to the immediate neighborhood of the stimulation point.

A simple argument shows why a negative rectangular pulse decreases the refractory period for the Panfilov model in the absence of the diffusion term. The stimulation vertically displaces the model in the absence of the diffusion term. The stimulus pulse decreases the refractory period for the Panfilov neighborhood of the stimulation point.

Now, the time required by the system to enter this refractory state. To illustrate this, let us assume that the stimulation is applied when \( e > e_2 \). Then, the dynamics reduces to \( \dot{e} = -C_3(e-1) - g, \dot{g} = \epsilon_2(ke - g) \). In this region of the \((e,g)\) plane, for sufficiently high \( g \), the trajectory will be along the \( e \)-nullcline, i.e., \( \dot{e} \simeq 0 \). If a pulse stimulation of amplitude \( A \) is initiated at \( t = 0 \) (say), when \( e = e(0), g = g(0) \), at a subsequent time \( t \),

\[
e(t) = 1 + \frac{\epsilon_2 g(0)}{C_3}, \quad g(t) = \frac{\epsilon}{2} - \frac{g(0)}{2} e^{-\sigma t},
\]

where, \( \sigma = \epsilon_2 k(1 + \frac{A}{C_3}), b = \epsilon_2 [1 + (k/C_3)] \). The negative stimulation has to be kept on till the system crosses into the region where \( \dot{e} < 0 \), after which no further increase of \( g \) can occur, as dictated by the dynamics of Eq. (1). Now, the time required by the system to enter this region is

\[
\frac{\ln\left(\frac{\epsilon}{2} - \frac{g(0)}{2} e^{-\sigma t}\right)}{\epsilon_2 k(1 + \frac{A}{C_3})},
\]

\( \phi = C_3(1 - e_2) + A \). Therefore, this time is reduced when \( A < 0 \) and contributes to the decrease of the refractory period. Note that, the above discussion also indicates that a rectangular pulse will be more effective than a gradually increasing waveform, e.g., a sinusoidal wave (as used in [12]), provided the energy of stimulation is same in both cases, as the former allows a much smaller maximum value of \( g \). Therefore, phase plane analysis of the response to negative stimulation allows us to design waveshapes for maximum efficiency in controlling spiral turbulence.

To understand how negative stimulation affects the response behavior of the spatially extended system, we first look at a one-dimensional system. Fig. 1 shows the relation between the stimulation frequency \( f \) and effective frequency \( f_{\text{eff}} \), measured by applying a series of pulses at one site and then recording the number of pulses that reach another site located at a distance without being blocked by any refractory region. Depending on the relative value of \( f \) and \( \tau_{\text{ref}} \), we observe instances of \( n : m \) response, i.e., \( m \) responses evoked by \( n \) stimuli. From the resulting effective frequencies \( f_{\text{eff}} \), we can see that for purely excitatory stimulation, the relative refractory period can be reduced by increasing the amplitude \( A \). However, this reduction is far more pronounced when a negative stimulation is applied between every pair of positive pulses. The inset in Fig. 1 shows that there is an optimal time interval between applying the positive and negative pulses that decreases the refractory period by as much as 50%. The highest effective frequencies correspond to a stimulation frequency in the range 0.1 - 0.25, agreeing with the optimal time period of 2-5 time units between positive and negative stimulation.

A response diagram similar to the one-dimensional case is also seen for stimulation in a two-dimensional medium (Fig. 2). A small region consisting of \( n \times n \) points at the center of the simulation domain is chosen as the stimulation point. For the simulations reported here \( n = 6 \); for a smaller \( n \), one requires a perturbation of larger amplitude to achieve a similar response. To understand control in two dimensions, we find out the characteristic timescale of spatiotemporal chaotic activity by obtaining its power spectral density (Fig. 2, inset). We observe a peak at a frequency \( f_c \approx 0.0427 \). As seen in Fig. 2, there are ranges of stimulation frequencies that give rise to effective frequencies higher than this value. As a result, the periodic waves emerging from the stimulation point will gradually impose control over the regions exhibiting chaos. If \( f \) is only slightly higher than \( f_c \), control takes very long; if it is too high the waves suffer conduction block at inhomogeneities produced by chaotic activity that reduces the effective frequency, and control fails. Note that, at lower frequencies the range of stimulation frequencies for which \( f_{\text{eff}} > f_c \), is smaller than at higher frequencies. We also compare the performance of sinusoidal waves with rectangular pulses, adjusting the amplitudes so that they have the same energy. The former is much less effective than the latter at lower stimulation frequencies, which is the preferred operating region for the control method.

The effectiveness of overdrive control is limited by the size of the system sought to be controlled. As shown in Fig. 3, away from the control site, the generated waves are blocked by refractory regions, with the probability of block increasing as a function of distance from the site of stimulation [13]. To see whether the control method is effective in reasonably large systems, we used it to terminate chaos in the two-dimensional Panfilov model, with \( L = 500 \) [14]. Fig. 4 shows a sequence of images illustrating the evolution of chaos control when a sequence of biphasic rectangular pulses are applied at the center. The time necessary to achieve the controlled state, when
the waves from the stimulation point pervade the entire system, depends slightly on the initial state of the system when the control is switched on. Not surprisingly, we find that the stimulation frequency used to impose control in Fig. 4 belongs to a range for which \( f_{\text{eff}} > f_c \).

Although most of the simulations were performed with the Panfilov model, the arguments involving phase plane analysis apply in general to excitable media having a cubic-type nonlinearity. To ensure that our explanation is not sensitively model dependent we obtained similar stimulation response diagrams for the Karma model [15].

Some local control schemes envisage stimulating at special locations, e.g., close to the tip of the spiral wave, thereby driving the spiral wave towards the edges of the system where they are absorbed [16]. However, aside from the fact that spatiotemporal chaos involves a large number of coexisting spirals, in a practical situation it may not be possible to have a choice regarding the location of the stimulation point. We should therefore look for a robust control method which is not critically sensitive to the position of the control point in the medium. There have been some proposals to use periodic stimulation for controlling spatiotemporal chaos. For example, recently Zhang et al [12] have controlled some excitable media models by applying sinusoidal stimulation at the center of the simulation domain. Looking in detail into the mechanism of this type of control, we have come to the conclusion that the key feature is the alternation between positive and negative stimulation, i.e., biphasic pacing, and it is, therefore, a special case of the general scheme presented here.

Previous explanations of why biphasic stimulation is better than purely excitatory stimulation (that use only positive pulses), have concentrated on the response to very large amplitude electrical shocks typically used in conventional defibrillation [17,18] and have involved details of cardiac cell ion channels [19]. To the best of our knowledge the present paper gives the simplest and most general picture for understanding the efficacy of the biphasic scheme using very low amplitude perturbation, as it does not depend on the details of ion channels responsible for cellular excitation.

There are some limitations to achieving control over a large spatial domain in an excitable medium by pacing at a particular point. Under some parameter regimes, the circular waves propagating from this point may themselves become unstable and undergo conduction block at a distance from the origin (similar to the process outlined in Ref. [20]). In addition, the control requires a slightly higher amplitude and has to be kept on for periods much longer than spatially extended control methods [6]. However, these drawbacks may be overcome if we use multiple stimulation points arranged so that their regions of influence cover the entire simulation domain.

In conclusion, we have proposed a simple explanation of the efficacy of low-amplitude biphasic stimulation in controlling spatiotemporal chaos in excitable media (e.g., VF). It is based on the competition between the frequency of the applied stimulation, and the effective frequency (obtained from the dominant timescale) of chaos. The former can be increased relative to the latter only by decreasing the refractory period which is achieved by a negative stimulus prior to applying the excitatory positive stimulation. Our analysis makes it possible to design pacing waveforms for maximum efficiency in controlling chaos.

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FIG. 1. Stimulation response diagram for one-dimensional Panfilov model \((L = 40)\) for different stimulation frequencies \(f\). The dotted and broken curves represent purely excitatory pulses of amplitude \(A = 5\), pulse duration \(\tau = 0.05f^{-1}\), and \(A = 10\), \(\tau = 0.1f^{-1}\), respectively, while the solid curve represents biphasic pulses of amplitude \(A = 10\) and pulse duration \(\tau = 0.1f^{-1}\) (as shown in the bottom left corner). Note that, the highest effective frequencies \(f_{\text{eff}}\) for the three cases are very different. The ratio \(f : f_{\text{eff}}\) is shown for the first four peaks. The inset shows the decrease in refractory period in absence of the diffusion term when a negative stimulation is applied at different times \(t_{\text{neg}}\) after the initial excitation.

FIG. 2. Stimulation response diagram for two-dimensional Panfilov model \((L = 26)\) showing relative performance of different waveforms. The dash-dotted line represents a sinus wave \((A = 6)\) and the solid curve represents a wave of biphasic rectangular pulses \((A = 18.9)\), as shown in the bottom left corner, such that they have the same total energy. The inset shows the power spectra of spatiotemporal chaos in the 2-D Panfilov model \((L = 500)\). The \(\epsilon\) variable was recorded for 3300 time units and the resulting power spectral density was averaged over 32 points. The peak occurs at the characteristic frequency \(f_c \simeq 0.0427\) which is indicated in the main figure by the broken line.

FIG. 3. Distance dependence of stimulus response for different stimulation frequencies \(f\) in the two-dimensional Panfilov model. Biphasic rectangular pulses \((A = 18.9)\) having duration \(\tau = 0.1f^{-1}\) are applied, which elicit a response having an effective frequency \(f_{\text{eff}}\) at a particular location. The first three cells \((x = 1, 2, 3)\) are within the region subject to direct stimulation. The shaded regions represent different response ratios \(f : f_{\text{eff}}\). Integral multiples of the characteristic frequency \(f_c\) are indicated on the \(f\)-axis.

FIG. 4. Control of spatiotemporal chaos in the two-dimensional Panfilov model \((L = 500)\) by applying biphasic pulses with amplitude \(A = 18.9\) and frequency \(f = 0.13\) at the center of the simulation domain. The pulse shape is rectangular, having a duration of \(\sim 0.77\) time units. Snapshots are shown for (top left) \(t = 0\), (top right) \(t = 1000\), (bottom left) \(t = 2700\) and (bottom right) \(t = 3800\) time units. The excitation wavefronts are shown in white, black marks the recovered regions ready to be excited, while the shaded regions indicate different stages of refractoriness.