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Response to sub-threshold stimulus is enhanced by spatially heterogeneous activity

S. SRIDHAR^(a) and SITABHRA SINHA^(b)

The Institute of Mathematical Sciences, CIT Campus - Taramani, Chennai 600113, India

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Abstract – Sub-threshold stimuli cannot initiate excitations in active media in the resting state, but surprisingly as we show in this paper, they can alter the time-evolution of spatially heterogeneous activity by modifying the recovery dynamics. This results in significant reduction of wave back velocity which may lead to spatial coherence, terminating all activity in the medium including spatiotemporal chaos. We analytically derive model-independent conditions for which such behavior can be observed. The phenomenon reported here may have possible implications for the termination of life-threatening cardiac arrhythmias (*e.g.*, fibrillation) by external electrical stimuli.

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Occurrence of spatiotemporal patterns is a generic feature of a wide variety of natural systems that are excitable [1]. Examples of such patterns include traveling waves in the Belousov-Zhabotinsky reaction [2] and propagating fronts of surface catalytic oxidation [3]. Excitability in these systems is characterised by a threshold. A stimulus that drives the system at rest above this excitation threshold leads to a transition from a quiescent to an active state, thereby generating an action potential (AP). Following this activation, the system slowly returns to rest. During this recovery period the system is either fully or partially insensitive to another identical stimulus. The dynamical consequences of these properties result in distinctive patterns, such as rotating spiral waves, that may in turn lead to spatiotemporal chaos [4–7]. While the threshold is a key parameter governing excitable systems, the demonstration of stochastic resonance (SR) [8] and coherence resonance (CR) [9] in such media suggest that weak sub-threshold signals could also have a significant effect on their dynamics [10,11]. SR-like response resulting from chaotic dynamics in simple systems [12,13] raises the intriguing possibility that spatially heterogeneous activity may enhance the response of an excitable medium to sub-threshold signals.

Understanding how weak signals affect spiral waves and other spatiotemporal activity in excitable media is

especially important because such patterns have critical functional consequences for vital biological systems. For example, rotating vortices in cardiac tissue that can lead to spiral chaos underlie many arrhythmias, *i.e.*, life-threatening disturbances in the natural rhythm of the heart [14,15]. Thus, controlling irregular activity in excitable media is not only a problem of fundamental interest in the physics of nonlinear dynamical systems but also has potential clinical significance [16–19]. Existing methods of spatiotemporal chaos control in excitable systems are almost exclusively dependent on using supra-threshold signals, either through a local high-frequency source [20,21] or using a spatially extended array [22–24]. Controlling spatial patterns with sub-threshold stimulation would not only utilize new physical principles, but also avoid many of the drawbacks in previously proposed schemes¹.

In this paper we show that sub-threshold stimulation, while having no significant effect on a quiescent medium, can induce a remarkable degree of coherence when applied on a system with spatially heterogeneous activity. Synchronizing the state of activation of all excited regions

¹Note that throughout the paper *sub-threshold* refers to stimuli that are insufficient to drive the resting tissue above the excitation threshold. In the context of cardiac control, occasionally threshold may also be used to refer to the minimum stimulus amplitude required for successful defibrillation. However, if such a stimulus causes an AP in resting tissue (*i.e.*, the medium crosses the excitation threshold), we refer to it as supra-threshold in this paper.

^(a)E-mail: ssridhar@imsc.res.in

^(b)E-mail: sitabhra@imsc.res.in

ensures that they return to rest almost simultaneously, in the process completely terminating activity in the medium. Thus, control of spatially extended chaos is achieved efficiently using a very low-amplitude signal. We explain the mechanism of this enhanced coherence in terms of the role played by sub-threshold stimulus in increasing the recovery period of the medium. It significantly reduces the propagation velocity of the recovery front, thereby increasing the extent of the inexcitable region in the medium. We present a semi-analytical derivation of the relation between strength and duration of the globally applied sub-threshold signal necessary for complete elimination of spatially heterogeneous activity in excitable media.

A generic model for describing the spatiotemporal dynamics of several biological excitable systems has the form

$$\frac{\partial V}{\partial t} = \frac{-I_{ion}(V, g_i) + I(t)}{C_m} + D\nabla^2 V, \quad (1)$$

where V (mV) is the potential difference across a cellular membrane, $C_m (= 1 \mu\text{F cm}^{-2})$ is the transmembrane capacitance, D is the diffusion constant ($= 0.001 \text{ cm}^2 \text{ s}^{-1}$ for the results reported in the paper), $I_{ion} (\mu\text{A cm}^{-2})$ is the total current density through ion channels on the cellular membrane, and g_i describe the dynamics of gating variables of different ion channels. The spatially uniform external signal, applied at all points of the simulation domain, is represented by the time-dependent current density, $I (\mu\text{A cm}^{-2})$. The specific functional form for I_{ion} varies for different biological systems. For the results reported here, we have used the Luo-Rudy I (LR1) model that describes the ionic currents in a ventricular cell [25]. For all our simulations, the maximum K^+ channel conductance G_K has been increased to 0.705 mS cm^{-2} to reduce the duration of the action potential (APD) [26]. To study the effect of sub-threshold stimulus on a stable spiral and on spatiotemporal chaos, we have used the maximum Ca^{2+} channel conductance $G_{si} = 0.04$ and 0.05 mS cm^{-2} , respectively. We have explicitly verified that our results are not sensitively model dependent by observing similar effects in other realistic channel-based descriptions of the ionic current, such as the TNNP model [27,28].

We consider in turn the response of a single cell, a 1-dimensional cable and a 2-dimensional sheet of excitable units to a sub-threshold current I . The spatially extended systems are discretized on a grid of size L (for 1D) and $L \times L$ (for 2D). For most results reported here $L = 400$, although we have used L upto 1200. The space step used for all simulations is $\delta x = 0.0225 \text{ cm}$, while the time-step $\delta t = 0.05 \text{ ms}$ (for 1D) or 0.01 ms (for 2D). The equations are solved using a forward Euler scheme with a standard 3-point (for 1D) or 5-point (for 2D) stencil for the Laplacian describing the spatial coupling between the units. No-flux boundary conditions are implemented at the edges. The external current is applied globally, *i.e.*, $I(t) = I$ in eq. (1) at all points in the system for the duration of stimulation, τ . A stimulus $\{I, \tau\}$ is sub-threshold

if it does not generate an action potential when applied on a quiescent medium. The initial spiral wave state is obtained by generating a broken wave front which then dynamically evolves into a curved rotating wave front. In the LR1 model simulations, an intact wave front is allowed to travel through the medium before creating the broken wave front in order to reduce the recovery period² so as to enable a spiral wave with at least one complete turn to exist within the simulation domain. Over a large range of parameter values, this spiral wave is a persistent dynamical state of the excitable medium. Under certain conditions (*e.g.*, for some parameter values or external perturbations), the spiral wave can become unstable, eventually breaking up into multiple wavelets leading to a spatiotemporally chaotic state. An alternative method for obtaining the spatiotemporally chaotic state is to randomly apply supra-threshold stimuli at different points in the medium over a small duration. In biological systems, spiral waves and chaos often appear spontaneously as a result of existing heterogeneities or stochastic fluctuations. In the cardiac medium, such dynamical phenomena can be initiated experimentally by applying cross-field stimulation [29]. The spatially extended chaotic state is a long-lived transient whose lifetime increases exponentially with the system size [22]. For biologically realistic simulation domain sizes, such as those used in this paper, the chaotic state persists longer than any reasonable duration of simulation.

Figure 1 shows that when sub-threshold stimulation is applied to an excitable medium with spatially heterogeneous activity, *viz.*, either a single spiral wave (a-c) or spatiotemporal chaos (d-f), there is a striking change in the subsequent dynamics of the system. Within a short duration (comparable to the APD) there is complete suppression of all activity in the medium, although in absence of this intervention, the existing dynamical state would continue to persist for an extremely long time. This result is surprising as the weak sub-threshold signal appears to be incapable of significantly altering the dynamics of an excitable system. For example, if we had applied sub-threshold stimulation on a large domain with a *single* wave propagating across it, there would have been no significant change in the time-evolution of the system with the wave continuing to move across the medium. This differentiates sub-threshold from other weak (*i.e.*, low-amplitude) but supra-threshold stimuli which, on being applied globally to the above system, would have excited almost the entire medium resulting in eventual cessation of all activity.

To understand the apparent paradox of sub-threshold stimuli terminating chaotic activity, we first note that such a stimulation rapidly decreases the number of cells that can be excited by existing activity in the medium (fig. 2(a)). Indeed, global suppression of activity results

²This is because of the restitution property of the medium, by which recovery is a function of the time interval between two successive propagating waves.

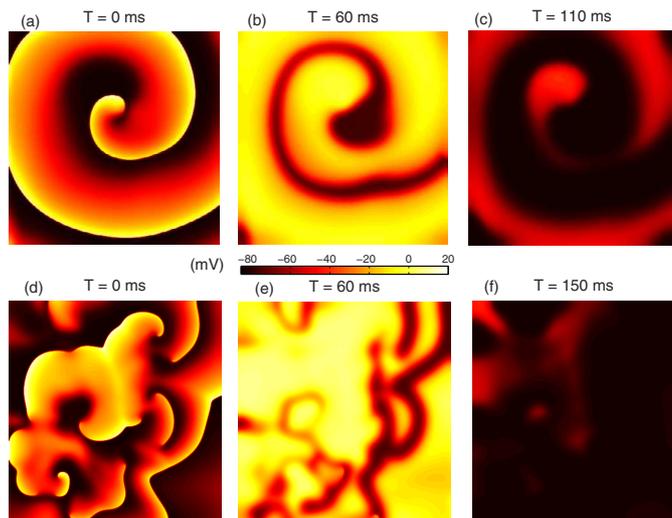


Fig. 1: (Colour on-line) Pseudocolor plots of transmembrane potential V for the two-dimensional LR1 model ($L=400$) showing the elimination of all activity on applying a sub-threshold current. The current I is switched on at $T=0$ for a duration $\tau=60$ ms on (a–c) a single spiral, with $I=1.6 \mu\text{A cm}^{-2}$, and (d–f) a spatiotemporally chaotic state, with $I=1.8 \mu\text{A cm}^{-2}$. By $T=150$ ms, excitation has been effectively terminated throughout the simulation domain.

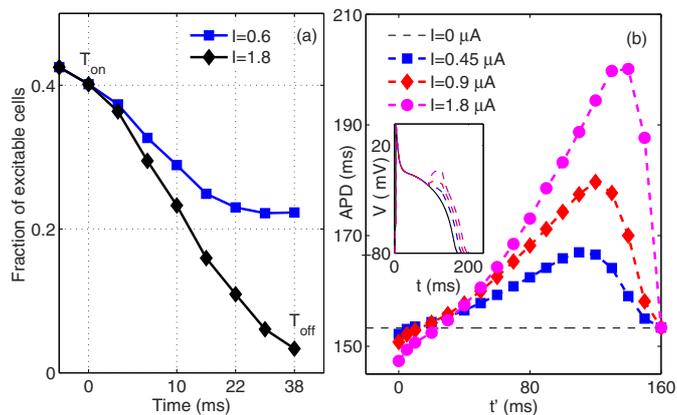


Fig. 2: (Colour on-line) (a) The fraction of cells that can be potentially excited (*i.e.*, with $V \leq -60$ mV) decreases with time during stimulation by sub-threshold current I in a two-dimensional system with spatiotemporal chaos. The total duration of the external signal is $\tau = T_{on} - T_{off} = 38$ ms. Results shown correspond to failed (squares) and successful termination (diamonds) of activity in the medium. (b) Effect of sub-threshold current on APD of a single cell. The current I is varied keeping the duration τ fixed ($= 38$ ms). In all cases, the APD is shown as a function of the time interval t' between the initiation of AP and T_{on} . The inset shows the corresponding effect on the AP profile.

when, by the end of the stimulation, the number of cells susceptible to excitation is insufficient to sustain the activity. This decrease in their number is because cells tend to remain in the recovering state for a longer period in the presence of a sub-threshold stimulus. We can see this

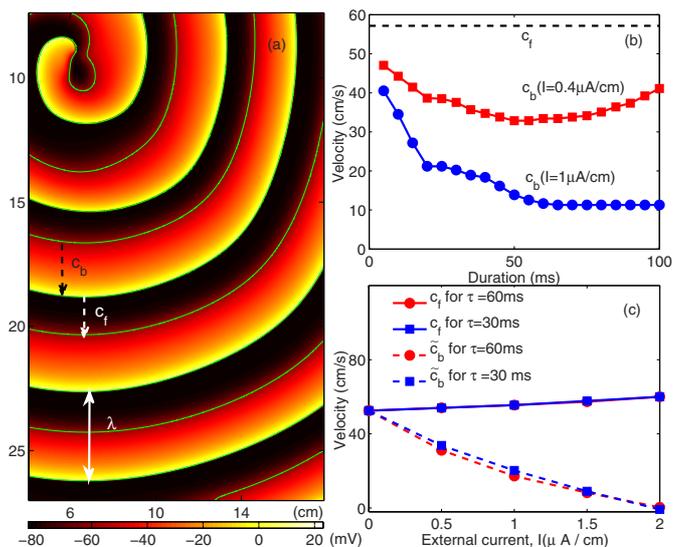


Fig. 3: (Colour on-line) (a) Pseudocolor plot of a spiral wave indicating the wavelenght λ , the wave front velocity c_f and the instantaneous wave back velocity $c_b (= c_f)$ in the absence of external stimulation. (b) Time-evolution of c_b during external stimulation of duration $\tau = 100$ ms using two different I corresponding to failed (squares) and successful termination (circles) of activity in the medium. During the course of stimulation, c_f is unchanged. (c) The average wave back velocity \bar{c}_b (broken lines) reduces with I in contrast to c_f (solid lines).

clearly in the response of a single *excited* cell to a subsequent sub-threshold current I applied for a fixed duration τ (fig. 2(b)). Increasing I significantly alters the recovery period resulting in a change in the APD. The time t' (measured from the initiation of the AP) at which the sub-threshold stimulation begins also affects the response of the cell to the signal. These results clearly indicate that the dominant effect of a sub-threshold stimulus is to increase the time period that a cell spends in recovering from prior excitation (or, in other words, increasing the APD).

In a spatially extended system, this enhanced recovery period of the cells results in altering the propagation characteristics of the traveling waves. Figure 3(a) shows a spiral wave propagating in a two-dimensional medium, where each turn of the wave is a region of excited cells, with the successive turns separated by recovering regions. As the state of the cells evolve with time, it is manifested in space as movement of excitation and recovery fronts. Their propagation speeds are referred to as wave front (c_f) and wave back (c_b) velocities, respectively. In the absence of any external stimulation, $c_f \simeq c_b$, ensuring that the width of the excited region remains approximately constant as the waves travel through the medium. However, on applying a sub-threshold stimulus, the wave back velocity becomes significantly lower than that of the wave front which is almost unchanged. Figure 3(b) shows that, once stimulation begins, c_b quickly decreases to a minimum value dependent on I . It then gradually rises to eventually become equal to c_f again. For a large sub-threshold

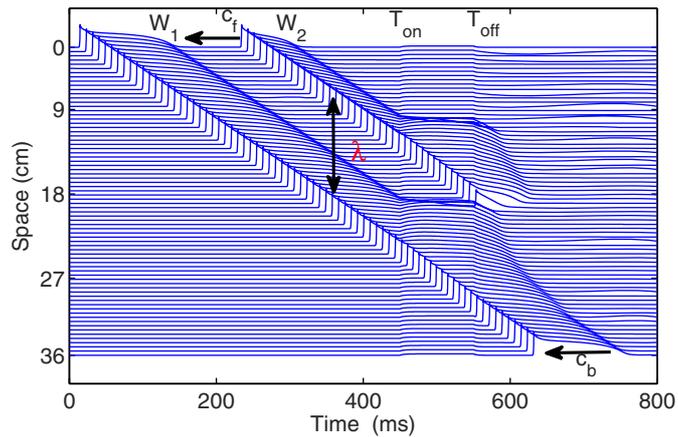


Fig. 4: (Colour on-line) Spatiotemporal evolution of two successive waves propagating along a 1-dimensional cable of excitable cells when a sub-threshold stimulus is applied over the time interval $[T_{on}, T_{off}]$. The propagation of the wave W_2 is blocked by the recovery front of W_1 due to reduction of its velocity, c_b . The wave front velocity c_f of both waves are almost unchanged. The spatial interval between the two successive waves at a time instant is indicated by λ .

stimulus I , the wave back velocity rapidly falls to its lowest value and changes very slowly thereafter. Under these conditions, we can ignore the time-variation of c_b for small τ and use the time-averaged value $\tilde{c}_b(I)$. Increasing I leads to an increased difference in the velocities of the excitation and recovery fronts, $c_f - \tilde{c}_b(I)$ (fig. 3(c)). For short stimulus durations, this difference is almost independent of τ . A significantly lower wave back velocity results in the inexcitable region between the excitation and recovery fronts of a wave becoming extended through the course of the stimulation (compare the profiles of APs in a 1D cable shown in fig. 4). This increases the overall area of the medium that cannot be excited, thereby making it progressively unlikely for the system to sustain recurrent activity.

This is explicitly shown for a 1-dimensional cable in fig. 4. When two successive waves propagate along the cable, globally applying the sub-threshold stimulus reduces the excitable gap between the recovery front of the leading wave (whose velocity c_b has decreased) and the excitation front of the following wave (whose velocity c_f is unchanged). For a high sub-threshold I applied for a long enough duration, the wave back of the first wave slows down sufficiently to collide with the succeeding wave front. This collision results in termination of the excitation front for the second wave which subsequently disappears from the medium.

The above physical picture is fundamentally unchanged for a rotating spiral wave with multiple turns as shown in fig. 3(a). We now use this to propose a simple semi-analytical theory for the mechanism by which the sub-threshold stimulus suppresses spatially heterogeneous activity. In the absence of any external stimulus, the

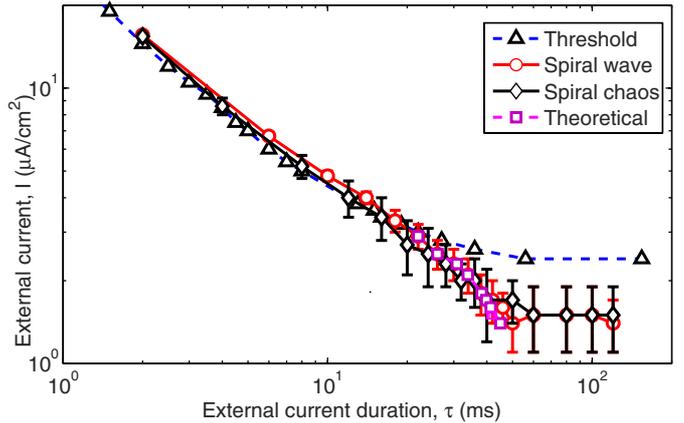


Fig. 5: (Colour on-line) Strength-duration curves for a two-dimensional medium with the external current applied at all points of a quiescent medium (triangles) or a medium with existing excitation activity, either a single spiral (circles) or spatiotemporal chaos (diamond). The theoretical prediction given in eq. (2) is also shown (square). Each (τ, I) point is averaged over 10 initial conditions.

width of the excited region of a wave lying between its excitation and recovery fronts is $l = c_f \tau_r$, where τ_r is the period for which the active cells remain excited. This time period is operationally measured as the duration for which the transmembrane potential of a cell (V) remains above its excitation threshold. On applying a sub-threshold external current I , c_f is almost unchanged but the resultant wave back velocity, $c_b(I, t)$, which varies with time over the duration of the stimulus τ , is seen to decrease with increasing I . If I is large or τ is small, the time-variation of c_b can be neglected and it is reasonably well approximated by the time-independent average value $\tilde{c}_b(I)$ over the stimulus duration. Thus, the width of the excited region of the wave increases to $l(I) = l + [c_f - \tilde{c}_b(I)]\tau$. If λ is the distance between excitation fronts of two successive waves in the medium, then collision between the recovery front of the leading wave and the excitation front of the following wave takes place when $l(I) \geq \lambda$. Thus, for a sub-threshold stimulus I , the shortest stimulus duration τ_{min} necessary to eliminate a source of recurrent activity such as a spiral wave is

$$\tau_{min} = \frac{\lambda - c_f \tau_r}{c_f - \tilde{c}_b(I)}. \quad (2)$$

Equation (2) provides us with an analytical relation between the stimulus magnitude and its minimum duration necessary for terminating activity in the medium in terms of measurable dynamical characteristics of the system. Figure 5 shows that this theoretical strength-duration curve for the external stimulation necessary to terminate activity matches very well with the empirical data obtained from numerical simulations for both single spiral wave as well as spatiotemporal chaos. In general, the weaker the sub-threshold current, the longer it has to

be applied in order to alter the dynamical behavior of the system. However, there is a lower bound for I below which there is no discernible effect of the sub-threshold stimulation regardless of its duration. Note that, for values of I just above this lower bound, the required τ_{min} is extremely long and the temporal variation of c_b over the duration of the stimulation can no longer be neglected. By explicitly considering the time-dependence of c_b in eq. (2), one can theoretically estimate the value of I where the strength-duration curve becomes independent of τ .

The mechanism of the sub-threshold response of excitable media proposed here depends only on the recovery dynamics of the system. In detailed ionic models of biological excitable cells, this dependence is manifested as a decrease in the ion channel conductance responsible for the slow, outward K^+ current during the sub-threshold stimulation³. Thus, simplistic models of excitable media which do not incorporate the effect of external current stimulation on the recovery dynamics are inadequate to reproduce the enhanced sub-threshold response reported here. Our results provide a framework for explaining earlier experimental observations that, in the human heart, sub-threshold stimulation can prevent subsequent activation [31]. In addition, applying such stimuli for a sufficiently long duration on biological tissue may result in an “accommodation phenomenon” that increases the threshold for activation and which can also significantly affect the dynamics of spatially heterogeneous activity [32].

The results reported here may have potential significance for understanding the spatiotemporal dynamics of excitable media in several practical situations such as, during clinical treatment of life-threatening arrhythmias. Current methods are primarily aimed towards synchronizing the activity of all regions by using supra-threshold stimuli having relatively larger amplitudes⁴. However, in such an approach, regions that have been rendered temporarily inexcitable due to prior activity remain unaffected. Thus, these regions can subsequently be re-activated by any remaining excitation after the stimulus is removed, leading to failure of control. By contrast, a sub-threshold stimulus slows the recovery of excited regions, thereby reducing the pool of cells available for excitation by existing activity in the medium. This suggests an alternative mechanism for the efficient termination of spatially extended chaos in excitable

³The decrease in wave back velocity compared to the wave front velocity under certain conditions has been associated with the existence of a steep slope in the APD restitution curve for the excitable medium, which relates the APD to the time interval between the recovery and subsequent re-excitation of a local region [30].

⁴Proposed methods for controlling spatiotemporal chaos in simple models of excitable media have occasionally applied stimuli to an aggregated *recovery* variable [33] which has no direct correspondence in biologically realistic models such as LRI. However, such methods rely on driving the medium to a bistable regime which requires the application of a supra-threshold external current in a realistic model of biological excitable media. Hence, such control schemes are also supra-threshold as per the definition used here.

systems. It may provide a key towards understanding how spatially irregular activity in biological systems (*e.g.*, fibrillation) are significantly affected by signals that have been strongly attenuated during passage through the intervening medium [34,35].

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