Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

The Effects of Phase Resetting Technique in Cardiac Models

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***Abstract*—When a brief current pulse is incident on excitable cells in cardiac and other nervous tissue, a change in phase of the cell's response is usually observed. In cardiac tissue, the cells are bared to external stimulation of generally positive currents, which depolarize the cells. In this paper an overview of the application of the phase resetting technique (PRT) in several cardiac models is presented. We discuss the effects of external stimuli in several cardiac cell models and we provide the phase transition curves (PTCs) resulted from the application of PRT with the Zhang *et al.* [1] sinoatrial node model.**

I. Introduction

PHYSIOLOGICAL rhythms play an important role in life. Some of them are sustained throughout life but even a brief interruption leads to death. Variation of rhythms outside normal limits, or appearance of new rhythms, where none existed before indicates disease [2]. After a perturbation of the repetitive activity, the timing of subsequent repeats of the events is generally altered: the prior rhythm eventually reasserts itself, only with its phase reset relative to an unperturbed control. The amount of the resetting depends both on the magnitude and manner of the external stimulus and on the phase in the oscillation when the perturbation begins. The exponential growth of computer power, combined with refined experimental methods, make it possible to develop highly accurate models of the behavior of several cardiac cell models. The topological approach offers new insights into the analysis of the resetting of the cardiac cells. In this work, we summarize the most important studies were the authors applied the PRT in cardiac models and we provide a brief description of the results that they published. In addition, we present an extension of our work done in this field [3], where we investigate and characterize the effects of external stimulation on central and peripheral SAN cells using the Zhang *et al.* model [1].

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II. Phase Resetting Technique

A. The mathematical background

The response of biological oscillators to external perturbations has been extensively studied using both theoretical and experimental approaches (reviewed in [4]). Using topological arguments, Winfree [5] greatly contributed to the qualitative understanding of phase resetting responses in biological oscillators and pointed out that, in a spatially extended system like cardiac tissue, such responses play a crucial role in the initiation of arrhythmias. Stimuli of critical amplitude and phase might lead to annihilation of normal rhythmic activity and the initiation of complex spiral wave arrhythmias. It is possible to make predictions about the response of a biological oscillator to perturbation without knowing anything about the details of the biology.

Fig. 1 illustrates the general situation of a perturbation in a repetitive activity of an oscillator. It is common to associate the oscillation with a stable limit cycle in the phase space. Stable limit cycle is the periodic solution of a differential equation in the limit $t \to \infty$. The period of the physiological rhythm is T_0 and after the perturbation at $t_{stimulus}$ the new period is T. Also the new period T is defined as:

$$T = \delta + \mu, \tag{1}$$

where δ is the time period between the onset of the oscillator and the occurrence of the stimulus, and μ the time interval until the next onset of the oscillation (Fig. 1). Dividing Eq. (1) with the old period T_0, the normalized T denoted by τ becomes:

$$\tau = \phi + \theta, \tag{2}$$

where the old phase is ϕ and θ is the cophase of the oscillation. The stimulus application produces an advance or delay calculated as $\Delta T = T_0 - T \Rightarrow \quad \frac{\Delta T}{T_0} = 1 - \frac{T}{T_0}$ $\Rightarrow \Delta\phi = 1 - \tau$. Therefore the phase shift is given as:

$$\Delta\phi = 1 - \tau. \tag{3}$$

If $\Delta\phi > 0$, we have an advance (i.e. firing earlier) while if $\Delta\phi < 0$, we have a delay. The new phase ϕ' is:

$$\phi' = \phi + \Delta\phi = \phi + 1 - \tau \,. \quad (4)$$

Just before the stimulus the oscillator had reached a phase ϕ while just after it, it appears to resume from a new phase ϕ'.

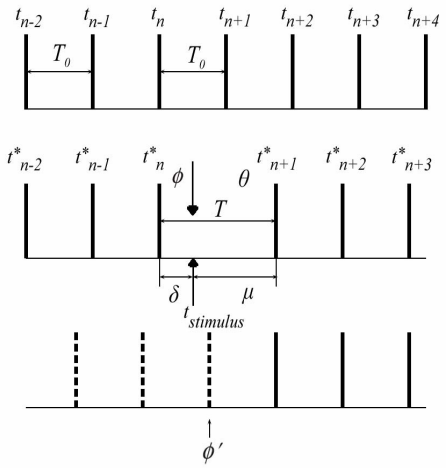

Fig. 1. Schematic representation of phase resetting technique. The application of a brief pulse at $t_{stimulus}$ of a repetitive activity leads to a reset of the phase of the oscillation, from the old phase ϕ to the new phase ϕ'.

More analytically the phase shift $\Delta\phi$ is calculated as:

$$\Delta\phi = \frac{T_0 - T}{T_0} = \frac{(t_{n+1} - t_n) - (t^*_{n+1} - t^*_n)}{T_0}, \quad (5)$$

where $t_{n+1}, t_n, t^*_{n+1}, t^*_n$ are the time points of the sequence shown in Fig. 1. Both old and new phase ranges between 0 and 1, equivalent to the full circle which ranges from 0-360^o.

B. Phase Transition Curves (PTC)

The effects of a stimulus to a biological oscillator are represented by the phase transition curves (PTC). The application of the stimulus perturbs, the state of the oscillator and his period transiently changes, but with the initial period becoming reestablished asymptotically in time. However, the trajectory will asymptotically approach a point at the limit cycle that has a different phase (ϕ') from that of the initial starting point of the limit cycle (ϕ). The perturbation in Fig. 1 shifts the oscillation from the old phase ϕ to the new phase $y(\phi)$. The function $y(\phi)$ is called the phase transition curve. In [6,7], all the important aspects of the effects of a stimulus on a limit cycle oscillators and the continuity theorem are summarized. The phase transition curve $y(\phi)$ is a circle map of function y. Circle maps can be continuous or discontinuous. A continuous circle map $x(\phi)$ can be characterized by its topological degree, which defines the number of times that $x(\phi)$ wraps around the unit circle as ϕ goes around the circle once [8-10].

III. PHASE RESETTING AND CARDIAC MODELS

A. Phase resetting in experimental studies

Electrophysiological studies have suggested that the activity of cardiac cells with automaticity (e.g SAN, Purkinje network, atrial and ventricular myocardium) can be modulated by stimulating with current pulses (subthreshold depolarizing or hyperpolarizing) applied extra cellularly [11-14]. The two basic research goals of the experimentalists who reset cardiac cells, is the phenomenon of annihilation (the permanent termination of the spontaneous cardiac pacemakers activity [15]) and the generation of spiral wave reentry in a disseminate medium [16]. Effects of external stimuli on the frequency of biological oscillators are observed in a wide range of species, and their overall experimentall characteristics can be well described by PTCs [11,12,17]. Systematic perturbation techniques, stimulating the pacemaker at various phases of its intrinsic cycle, have been applied to experimentally investigate and establish the shape of PRC [13,18].

B. Phase resetting in cardiac models

As the development of cardiac cell models from several sites of the heart grow, the investigation of the topology from the phase resetting application in cardiac cells becomes an interesting research field. One of the first studies is the phase resetting in a mathematical model of sinus node [17]. This was the first attempt of transition from clinical experiments to the investigation of the annihilation hypothesis in mathematical models. The model of purkinje fiber [20] with some modifications used in the study of Guevera *et al.* [21]. The authors applied phase resetting and the results closely correspond with published experimental data.

Almost all studies that investigate PRT in cardiac models provide the results with three basic diagrams: (i) the normalized perturbed interbeat interval T/T_0 plotted against the old phase ϕ (Fig. 2), (ii) PTCs, where the new phase ϕ' is plotted against the old phase ϕ (Fig. 3) and (iii) three-dimensional contour plots of the new phase ϕ' against old phase ϕ and the amplitude of the stimulus current (Fig. 4). The various parameters of the PRCs found in the analytical study of Abramovich *et al.* [22].

The stimulation protocol of the perturbation varies in the published studies, but the basic rules that have been considered are: (i) the external perturbation is applied in resting, active and refractory period, (ii) the effect of the external stimulus is only on the first following cycle, and it does not have any late influence on the next cycle lengths, (iii) when repetitive stimulus are applied, each stimulus has the same effect, (iv) if multiple stimulus fall within a single

cell cycle each of these stimuli affects the cell independently and sequentially [22].

Recently, PTCs were used as a tool to predict the reentrant cardiac waves and examine the conditions under which resetting data fail to predict the effects of periodic stimuli to reentrant excitation [23]. The findings of PTCs gave useful data to the efforts of scientists in order to terminate the reentry phenomenon [24].

IV. PHASE RESETTING IN SINOATRIAL NODE

The sinoatrial node (SAN) is the natural pacemaker of the heart. Spontaneously active cardiac cells, like other nonlinear oscillators, respond to discrete perturbations by a transient change in the cycle length. The response of the SAN to applied current perturbations has been studied in both isolated tissue [15] and in mathematical models [17,19]. PTCs and effects of PRT in several SAN cell models have been reviewed in [3,10].

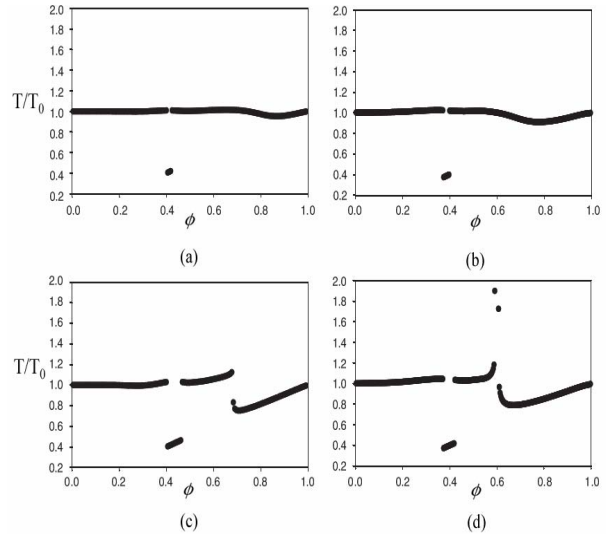

Fig. 2. Alteration of the timing of the first action potential after stimulation is plotted T/T_0 vs. ϕ for various stimulation amplitudes. (a,c) Peripheral cell at -0.5nA and at -2.5nA, respectively. (d,b) Central cell at -0.2nA and -0.4nA, respectively. ($T_{0,central} = 320ms$, $T_{0,Peripheral} = 160ms$).

A. Phase response characteristics of sinoatrial node cells

Below, the dynamic response of the SAN to short external stimuli using the Zhang *et al.* model [1] is described. The total membrane potential is given from the equation:

$$\frac{dV}{dt} = \frac{-1}{C} I_{tot}, \tag{6}$$

where V is the transmembrane potential, C is the capacitance and I_{tot} is the total ionic current. The model equations are solved twice for the central cell and for the peripheral cell using Runge-Kutta with time step $\Delta t = 0.1$ msec. A short current pulse is applied to reset the spontaneous rhythmic activity of the single sinoatrial node cell. Depending on the stimulus timing either a delay or an advance in the occurrence of next action potential is produced. This resetting behavior is quantified in terms of PTCs (Fig. 3) for short electrical current pulses of varying amplitude which span the whole period. For low stimulus amplitudes the transition from advance to delay is smooth, while at higher amplitudes abrupt changes and discontinuities are observed in PTCs. Such discontinuities reveal critical stimuli, the application of which can result in annihilation of activity in central SAN cells. The detailed analysis of the ionic mechanisms involved in its resetting behavior of SAN cell models provides new insight into the dynamics and physiology of excitation of the sinoatrial node of the heart.

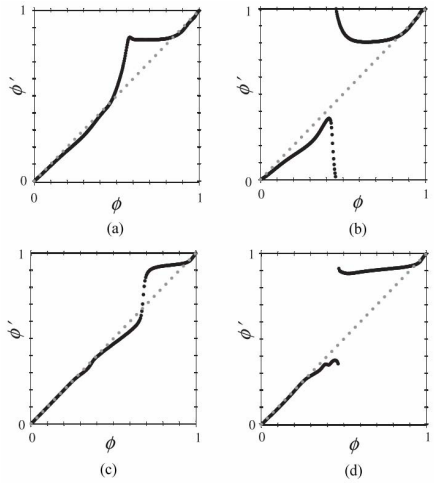

Fig. 3. Phase Transition curves for (a,b) central SAN cell and (c,d) peripheral SAN cell.

The advance or delay in the occurrence of the first action potential after perturbation for a set of experiments for which the stimulus phase varies from 0 to 1, can be visualized by plotting the ratio of the corresponding period T (during which the stimulus was applied) to the period T_0 of the unperturbed cycle over the stimulus phase ϕ. Such plots were obtained for the central and peripheral SAN (Fig. 2). The three-dimensional phase transition plots for the central, transitional and peripheral SAN cells are shown in Fig. 4 as 3D mesh plots. The difference in the stimulus amplitude for the corresponding plots is due to the difference in the amplitude of the corresponding total membrane current (a stronger stimulus is required to produce Type 1 phase resetting behavior). In the three-dimensional phase transition plots shown in Fig. 4a, there exist regions where the new phase ϕ' is very dense (e.g. for t=0.55 and $I_{stim} = 0.4$ nA). Such regions indicate the existence of a singularity and should be further investigated by fine-tuning of both interval Δ and amplitude I_{stim}.

V. CONCLUSIONS

Investigation of the dynamic behavior of biological

oscillators and their response to external perturbation is of great importance in biological research since biological oscillations are involved in many vital processes in living systems. Understanding the dynamic response of the SAN to external perturbations is important in elucidating its behavior under normal and pathological conditions.

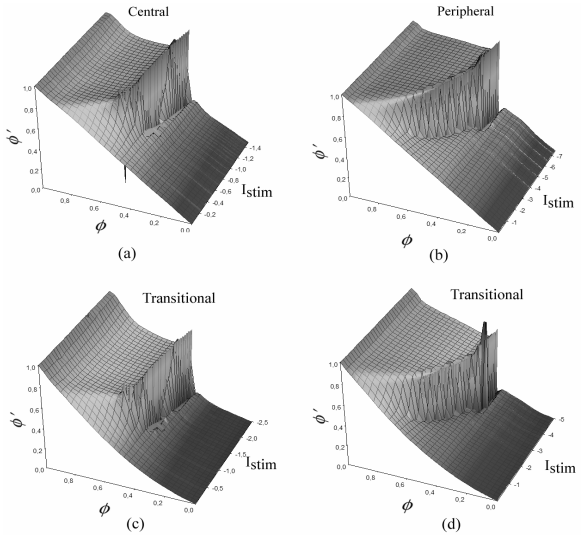

Fig. 4. Three dimensional plots of old phase ϕ against new phase ϕ' and stimulus current I_{stim}.

Studies in the past have concentrated on the elucidation of the phase resetting dynamics of the SAN using biophysical ionic models but did not address the issue of regional differences between central and peripheral node cells. Our work is going to be extended in the one dimensional model of SAN and we will focus on how a brief pulse at the central SAN may affect the peripheral SAN node in a strand of central, peripheral and atrial cells.

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