Phase Resetting in Central and Peripheral Sinoatrial Node Cell Models

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Abstract

We characterize the effects of external stimulation on central and peripheral sinoatrial node (SAN) cells using the Zhang et al. model [1]. Phase transition curves (PTCs) for brief (0.5ms) depolarizing and hyperpolarising electrical current pulses of varying amplitude and of timing spanning the whole period are obtained. The application of a critical depolarizing stimulus (about 0.4 nA) during the late repolarization phase of the action potential resulted in annihilation of activity in central SAN cells, revealing the existence of a stable singularity in the corresponding model configuration. The peripheral SAN cell does not exhibit a similar singularity and annihilation of the normal activity.

1. Introduction

Sinoatrial node (SAN), the natural pacemaker of the heart, is subjected to external stimuli under both clinical interventions (defibrillation) and physiological autonomic control. Results from extensive experimental and theoretical studies [2] on the response of biological oscillators to external perturbations indicate that, in the cardiac tissue, such responses play an important role in the generation of arrhythmias [3]. Stimuli of critical amplitude and phase can lead to annihilation of normal rhythmic activity.

The analysis of phase response characteristics provides new insight into the dynamics of the models, as well as an experimentally verifiable test for the accurate reconstruction of SAN tissue dynamics. Simulation of the spatial variation in the electrical properties of SAN cells and their phase response profiles is an important step for the reconstruction of the complex dynamics of the sinoatrial node tissue.

In this work, we characterize the effects of external stimulation on central and peripheral SAN cells using the Zhang et al. SAN-model [1]. A Runge-Kutta method is used for the numerical solution of the differential equations describing the model. Brief (0.5ms) depolarising and hyperpolarising electrical current pulses of varying amplitude and of timing spanning the whole period are applied and phase transition curves (PTC) are obtained [4]. Three dimensional PTCs [5], relating old phase and stimulus amplitude to the new phase after stimulation, are generated in order to locate critical stimuli and singularities in the models. Numerical simulations for transitional cells lying between the center and periphery of the SAN [1], as well as under modulation of specific ionic currents are also conducted.

2. Methods

The electrical activity of central and peripheral sinoatrial node cells is simulated using the Zhang *et al.* model [1]. The total ionic current I_{tot} appearing in the differential equation which models the membrane potential V:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{I_{\mathrm{tot}}}{C_{\mathrm{m}}} \tag{1}$$

comprises of the currents: I_{Na}, $I_{\mathrm{Ca,L}}$, $I_{\mathrm{Ca,T}}$, I_{to}, I_{sus}, $I_{\mathrm{K,r}}$, $I_{\mathrm{K,s}}$, I_{f}, $I_{\mathrm{b,Na}}$, $I_{\mathrm{b,Ca}}$, $I_{\mathrm{b,K}}$, I_{NaCa} and I_{p}. The transition from central to peripheral SAN activity was modelled as in [1], using a scaling factor which depend on the distance of each cell from the center of the sinoatrial node.

Equation (1) and the differential equations for the gating variables are solved using a fourth order Runge-Kutta method using time step 0.1 ms.

The model equations for central, peripheral and transitional cell configurations were integrated until a stable limit cycle is obtained. The minimum diastolic potential is determined on the stable limit cycle and the vector of dynamic variables at this point are recorded and used as the initial condition in subsequent simulations.

For each of the configurations examined, a single 0.5 ms depolarizing or hyperpolarizing current stimulus of a given amplitude is applied at several time steps during the whole period. The starting reference point is selected at the membrane potential level of -10 mV during the depolarization

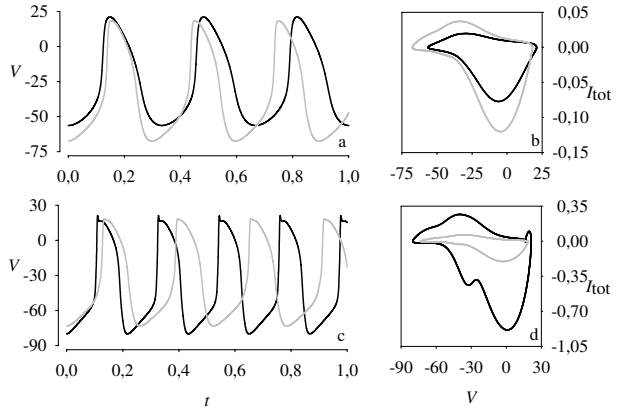

Figure 1. Normal electrical activity in central (a,b), peripheral (c,d) and transitional sinoatrial node cells (grey solid lines in a-d). In b and d the total ionic current $I_{\rm tot}$ is plotted versus the membrane potential V for each of the corresponding simulations in a and c.

phase of the action potential and at each subsequent run the stimulus timing increases by 1 ms. Stimulation current amplitude is varied from 0 to -7.5 nA.

For a given stimulus amplitude the corresponding phase transition curve is constructed [4], while for the whole range of stimulus amplitudes three-dimensional phase transition plots are obtained [5].

The simulation of a 1 min interval of central SAN cell activity takes approximately 19 sec on a Pentium IV 2.4 GHz and 512Mb RAM.

3. Results

The normal electrical activity of central, peripheral and transitional sinoatrial node cells is shown in Fig. 1. The membrane potential V of central (dark solid line - plot 1.a) and peripheral (dark solid line - plot 1.c) sinoatrial node cells is plotted versus time (simulation duration 1s). The grey lines show the electrical activity of the transitional cells. In the model proposed by Zhang the transition between central and peripheral activity is modelled using a scaling factor (ranging from 0 to 1) which depends on the distance of the cell from the center of the sinoatrial node (see equations 80 and 81 in [1] and ref. [6]). The scaling factor is used in order to calculate the capacitance as well as the ionic conductances of transitional cells given their corresponding values at the center and the periphery of the sinoatrial node.

For the transitional cell activity shown in Fig. 1 the scaling factor values (0.04 in plot 1.a and 0.13 in plot 1.c) were selected so that they mark the point where a sharp change in action potential configuration is evident. Thus, in plot 1.c the transitional cell shows the characteristic spike-and-dome configuration of peripheral cells.

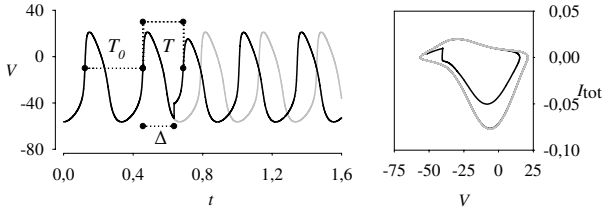

Figure 2. Single pulse perturbation protocol for the central sinoatrial node cell. A depolarizing stimulus of 0.45nA was applied with a time delay Δ after the detection (at V=-10mV during the depolarization phase) of the second action potential. The solid grey trace corresponds to the unperturbed activity.

In plots b and d of Fig. 1 the total ionic current $I_{\rm tot}$ is plotted versus membrane potential V for each of the corresponding simulations. The difference in $I_{\rm tot}$ amplitude between central and peripheral cells is mainly due to the contribution of $I_{\rm Na}$ which is absent in central cells. The $I_{\rm tot}$-V plots provide a means to visualize the effects of external perturbation on the sinoatrial node cell activity (see Fig. 2) and could be considered as a representation of the complete multi-dimensional phase space of the model.

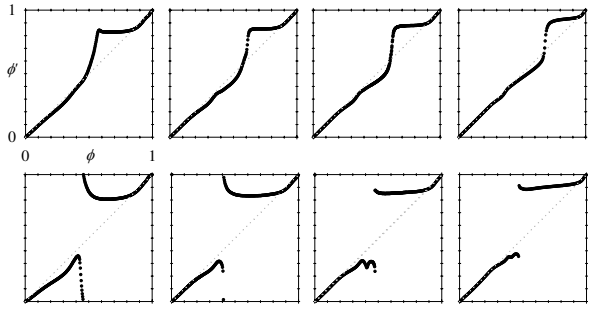

Figure 3. Phase transition curves for central, peripheral and transitional cells.

The single pulse perturbation protocol used is shown in Fig. 2. The grey solid line represents the normal unperturbed electrical activity of central sinoatrial node cell with a period T_0 of 334ms. The onset of the action potential is marked at V=-10mV (depolarization phase). At a time interval Δ after the onset of the action potential a brief (0.5ms) depolarizing current pulse is applied resulting in early depolarization of the cell membrane (dark solid line). The phase ϕ of the stimulus is Δ/T_0 while the new phase of the perturbed oscillator is $\phi' = \phi + 1 - \frac{T}{T_0}$ where T is the period of the perturbed cycle (see [4]). The electrical activity resumes immediately after the first perturbed cycle as it is evident from the $I_{\rm tot}$-V plot (right plot of figure 2) in which both simulations are shown (grey line: unperturbed limit cycle oscillation of the central sinoatrial node

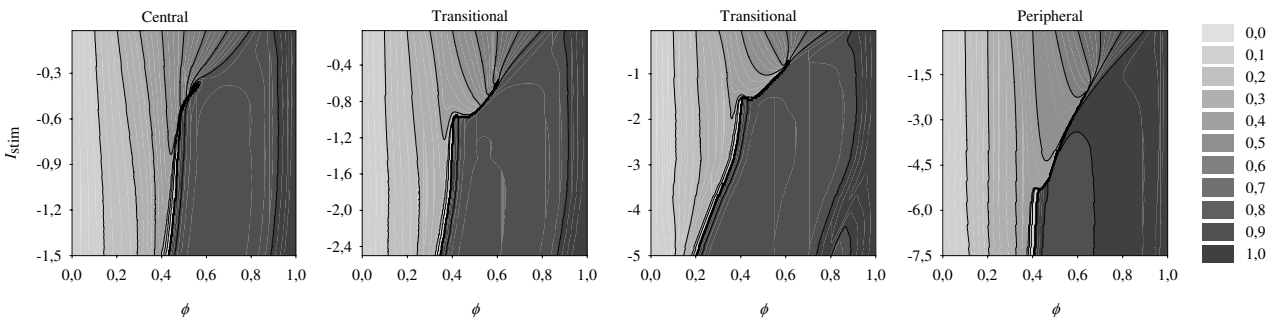

Figure 4. Contour plot of new phase versus old phase and amplitude for central and peripheral SAN cell.

cell).

The experiment shown in Fig. 2 is repeated for each one of the cell configurations shown in Fig. 1 with Δ ranging from 0 - T_0 (ϕ from 0 to 1) and current stimulus amplitudes from 0 to -7.5nA. The results are summarized in Fig. 3 where representative phase transition curves are shown. Top traces correspond to low amplitude stimuli (-0.3nA) while bottom traces correspond to high amplitude stimuli (from left to right: -1.2, -2.0, -4 and -6.0nA). The far left and the right plots correspond to central and peripheral cells while the inner left and inner right plots correspond to the transitional cell configurations shown in Fig. 1 (grey lines in plots 1.a and 1.c respectively).

The phase transition curves shown in Fig. 3 indicate that in central, peripheral and transitional sinoatrial node cells both Type 0 (top traces) and Type 1 (bottom traces) phase resetting is obtained. Low amplitude stimuli produce continuous phase transition curves since the effect of the external perturbation on the phase of the limit cycle oscillator is less pronounced. The discontinuities of the phase transition curves for stronger stimuli (Type 1 phase resetting) are indicative of the existence of a singularity in the limit cycle.

Each of the phase transition curves in Fig. 3 represent a set of experiments like the one shown in Fig. 2 where the stimulus amplitude is kept constant while only the interval Δ varies. A set of such curves for various stimulus amplitudes produces a three dimensional phase transition surface [5] relating both ϕ and stimulus amplitude to the new phase ϕ' of the perturbed oscillator. Such three dimensional phase transition plots allow further investigation of the phase resetting behavior of an oscillator. Moreover such phase transition curves can help in finding the exact stimulus phase and amplitude combination that bring the oscillator close to the singularity.

The three dimensional phase transition plots for the central, transitional and peripheral sinoatrial node cells are shown in Fig. 4 as contour plots with the new phase ϕ' color-coded on a grey scale from 0 to 1. The ordering of the plots is similar to that of Fig. 3 and the corresponding phase transition curves of Fig. 3 can be considered as horizontal "slices" of the data at the corresponding current stimulus amplitude ($I_{\rm stim}$). 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 - cf. Fig. 1).

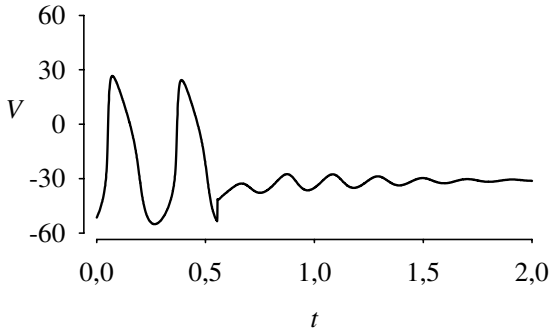

Figure 5. Annihilation of sinoatrial node repetitive activity by a single critical current stimulus.

In the three-dimensional phase transition plots of Fig. 4 there are regions where the new phase ϕ' is very dense and come very close together (e.g. first plot - central sinoatrial node - at ϕ=0.55 and $I_{\rm stim}$=-0.4). Such regions indicate the existence of the singularity and should be further investigated by fine-tuning both the Δ and $I_{\rm stim}$ steps.

Further experiments with finer values for Δ and $I_{\rm stim}$ within those regions revealed the existence of a stable singularity for the central sinoatrial node cell. In the simulation shown in Fig. 5 a critical stimulus of -0.4 nA was applied at t=0.53s resulting in the permanent annihilation of the normal repetitive activity. Transitional cells as well as the peripheral cell do not show similar behavior.

Instead the application of stimuli of appropriate amplitude and phase (e.g. ϕ=0.4 and $I_{\rm stim}$=-5.4) results in a series of low amplitude oscillations of the membrane po-

tential with normal limit cycle behavior resuming after 2-3 cycles.

4. Discussion

The investigation of the dynamical 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 [2, 3]. Understanding the dynamical response of the sinoatrial node to external perturbations is important in elucidating its behavior under normal and pathological conditions [3]. Studies in the past have concentrated on the elucidation of the phase resetting dynamics of the sinoatrial node using biophysical ionic models [7, 8, 9] but did not address the issue of regional differences between central and peripheral node cells (the corresponding ionic models described central cell behavior).

The sinoatrial node is a complex structure and regional differences in the electrical activity of regional cells seem to be important in the behavior of the natural pacemaker of the heart [6, 10, 11]. The Zhang *et al.* model [1] used in this study accounts for regional differences and can be used to model the electrical activity of central, peripheral as well as transitional cells.

The analysis of phase resetting characteristics of each type of sinoatrial node cells by means of three-dimensional phase transition plots, revealed important differences in their response to external electrical stimuli (see Fig. 4). Although all types of cells display both Type 0 and Type 1 phase resetting behavior, the stimulus amplitude at which Type 1 phase resetting behavior first appears varies. This is a result of the regional differences in I_{tot} amplitude (see Fig. 1): I_{tot} is higher in in the periphery of sinoatrial node (mainly due to the dominance of I_{Na}) and thus a higher amplitude of external stimulus is required in order to significantly affect the normal limit cycle behavior. Moreover, the existence of a critical stimulus amplitude - phase combination which is capable of annihilating the electrical activity of the central sinoatrial node cells was demonstrated. It is believed that such critical stimuli are involved in the generation of certain cardiac arrhythmias [3]. In a complex structure like the sinoatrial node, regional differences and spatiotemporal interactions could play an important role in its pathophysiological response to external perturbations and should be further investigated.

Acknowledgements

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