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Numerical Experiments in a Modified Beeler–Reuter Cable Model: Initiating Fast (Na) and Slow (Ca) Waves

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Abstract—We have modified the Beeler–Reuter model of cardiac muscle cells to account for the action of catecholamines. This model reveals the ability for slowly propagating calcium waves to coexist with the normal rapidly propagating wavefront associated with sodium activation. Either slowly propagating calcium waves or rapidly propagating sodium waves may be selectively invoked by changing the slope of a 'ramp' stimulus pulse. Rapid changes in stimulus potential evoke fast sodium wavefronts while stimulation with a gradual ramp with a rate of change adequate to inactivate sodium channels will initiate a slowly propagating calcium wavefront. Possible mechanisms for transitions between fast- and slow-propagating wavefronts are considered. Transition between calcium and sodium wavefronts may result in chaotic medium dynamics.

INTRODUCTION

The fast inward current which is carried by Na-cations is responsible for the normal electrical activity of cardiac cells. A rapid change in stimulus amplitude above a threshold potential activates sodium channels and initiates a wavefront of high propagation velocity, and thus maintains synchronization among cardiac cells. In specialized conducting and working myocardial tissues, a rapid increase in membrane potential caused by Na-influx is followed by the development of a slow inward current which is carried mainly by Ca-ions. When fast Na-channels are blocked by drugs or inactivated by a depolarized resting membrane potential, the slow inward current, enhanced by specific agents like catecholamines, may initiate slowly propagating waves in myocardium. This is believed to play an important role in the initiation of certain cardiac arrhythmias associated with re-entry excitation and disturbances in heart excitation conduction [1–4].

The aim of this study is to explore the properties of a model describing the conduction of slow waves and to simulate initiation of rapidly and slowly propagating waves in a one-dimensional cable.

MATHEMATICAL MODEL

We modified the Beeler–Reuter (BR) model of a cardiac cell [5] for these studies. We enhanced the model to reflect the action of catecholamines—neurotransmitters that influence cellular membrane conductances.

Adrenaline and noradrenaline primarily increase the permeability of cardiac cell membranes to Ca- and K-ions [6–8]. The increase in slow (Ca) channel conduction enhances the action potential plateau height and tension of contractions in Purkinje fibers [6]. The duration of the action potential, which is significantly dependent on the slow inward and the delayed potassium currents, exhibits dose-dependent behavior [6, 9]. At low concentrations noradrenaline prolongs the action potential duration whereas at concentrations exceeding the value of the order of 0.5 μM shorten the action potential [6, 9]. Here we examine conditions corresponding to a noradrenaline concentration of approximately 0.5 μM.

As observed by different investigators, the time-constants of the slow calcium and of the delayed rectifier potassium channels in the presence of catecholamines change slightly [7, 8] in comparison with the dramatic rise in channel conductance. Thus, in our model we modified only the maximal ionic conductances which are represented by $\bar{g}_s$ for the slow inward and $\bar{g}_{x1}$ for the time-dependent outward currents, with other parameters being the same as in the original paper by Beeler and Reuter [5]. The maximal conductance of the fast inward current, $\bar{g}_{Na}$, is modified as well in several numerical simulations to reflect the action of Na-channel blockers.

Independent experimental measurements of the increase in ionic conductances of real membranes give more accurate results for the delayed potassium current which is readily separated from the net membrane current. In the presence of 0.5 μM noradrenaline, a 2.7- [6] to a 7- [8] fold increase in peak conductance was observed, while for the slow inward current the estimated scaling factor varied from 1.39 to 5.9 [7] (adrenaline concentration was not indicated). According to the plots presented in ref. [6], $\bar{g}_s$ increases in the presence of 0.5 μM noradrenaline by a factor of about 4.

In our model we selected the averaged scaling factor for the potassium conductance, $\bar{g}_{x1}$, which was taken to be equal to 5. We also increased $\bar{g}_s$ by 2.5 in order to obtain the small reduction in action potential duration observed in experiments. In numerical simulations, all the parameters of single excitable units except $\bar{g}_{Na}$, $\bar{g}_s$ and $\bar{g}_{x1}$ were those used by Beeler and Reuter [5], and the parameters for the cable model were those used in ref. [10].

An example of an action potential computed with our model is represented in Fig. 1(a) by a solid line, while the solution of original BR equations is depicted by a dashed line for comparison. The initial spike amplitudes, as seen, are equal in both cases and this should result in equivalent propagation velocities. The plateau enhancement, which is clearly seen in the plot from the modified model, along with the overall shape of this action potential reveals qualitative similarity to that recorded using the microelectrode technique in cardiac cells [4]. In this and further numerical experiments, the integration steps are 10 μs and 0.33 mm in time and space for a cable of 200 excitable units (6.6 cm). Non-flux von Neumann's boundary conditions are imposed at the cable ends.

RESULTS AND DISCUSSION

We first explored with our model slow propagation that is observed when Na-current is blocked in order to prevent fast response initiation and propagation. Figure 1(b) presents the time course of a slow response when $\bar{g}_{Na} = 0.1$ which is 40 times lower than its normal value of 4.0: membrane potential, E, is depicted by a solid line, the potential rate of change, dE/dt, is depicted by a dashed line, and zero time is arbitrary. The cable was stimulated at one end while the response was recorded at the midpoint.

In simulations, the propagation velocity of slow responses was 2.2 cm s^{-1} which is approximately 4% of that of the fast responses in the original and modified BR models when $\bar{g}_{Na} = 4.0$. The potential increase from foot to peak was 94.7 mV while the action

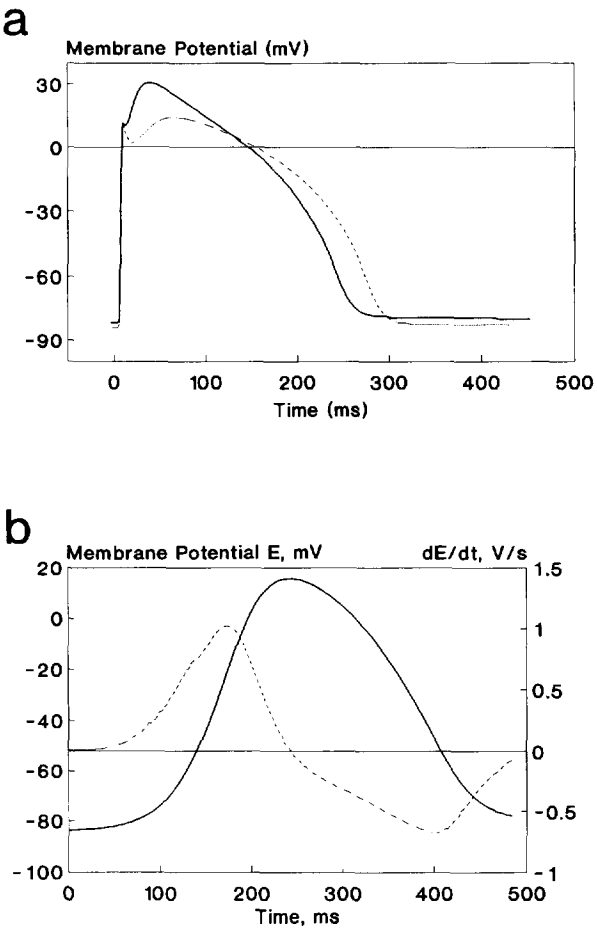

Fig. 1. Fast- and slow-propagating responses in the original and modified BR models. (a) Time course of fast-propagating responses, zero time is arbitrary and $\bar{g}_{Na} = 4.0$, in modified (solid line) and original (dashed line) BR models. Note that the plateau is enhanced and the action potential duration is decreased in the model modified to include the effects of cathecholamines. The initial spikes are of the same amplitudes. (b) Time course of a slowly propagating response in the modified model, when $\bar{g}_{Na} = 0.1$. The membrane potential, E, is depicted by a solid line while the rate, dE/dt, is represented by a dashed line. All the responses are recorded 3.3 cm away from the stimulated cable segment.

potential duration was 365.6 ms at the level of −70 mV. Some increase in action potential duration (APD) compared to that of the fast wave may be attributed to the long forefront of the slow response. The most striking feature is the reduction in wavelength, which is frequently considered a proarrhythmic factor, since it facilitates the development of spirals by reducing the spatial requirements for evolution and maintenance. Table 1 summarizes the parameters of different types of waves in the original and modified BR models.

The observed slow waves described by the modified model propagate stably with no decrease in amplitude throughout the cable. These wavefronts are quite different from responses observed in experiments with the original BR equations, when the Na-channel conductance is significantly reduced. Figure 2 demonstrates the response of the cable with $\bar{g}_{Na}(x) = 0.1$ and where the cable is stimulated at the middle section by the injection of an external current of 12 $\mu A\,cm^{-2}$ for 10 ms. In the original BR model, Fig. 2(a), the response appears to be nonpropagating when compared with our model, Fig. 2(b), where the response slowly travels along the fiber in both directions.

Table 1. The parameters of fast- and slow-propagating waves in the original and modified BR models

	BR	Modified BR (fast/slow)
Velocity, $cm\,s^{-1}$	50.0	51.2/2.2
Amplitude, mV	99.8	115.2/94.7
APD (−70 mV), ms	283.4	251.6/365.6
Wavelength, cm	14.2	12.9/0.8
$E_{resting}$, mV	−84.8	−82.4/−83.2

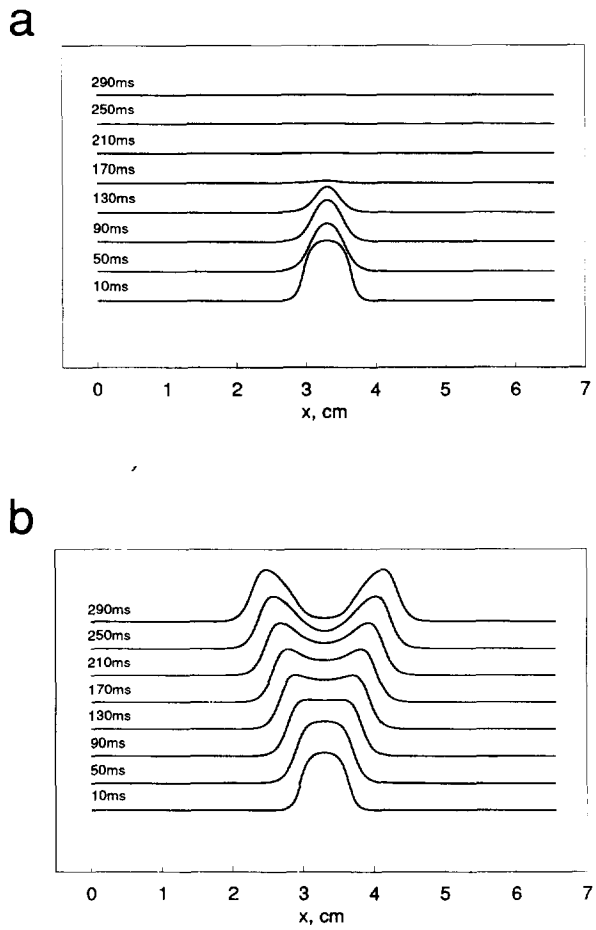

Fig. 2. The responses of the cables composed of the original BR excitable units and modified BR excitable units when Na-conductance is uniformly blocked ($\bar{g}_{Na} = 0.1$). The successive states of the cable, the distribution of potential, are presented. Horizontal axes denote the position along the cable. Cables were stimulated at the midpoint by injection of an external current of 12 $\mu A\,cm^{-2}$ for 10 ms. In the original BR model, (a), the response appears to be nonpropagating which is quite different from the response behavior in our model, (b), where it slowly travels in a stable manner along the fiber in both directions.

As previously shown in experiments, to initiate the propagation of slow waves, two essential conditions should be met [1–4]: (a) the cardiac membrane conductance of the slow inward current should be substantially increased, and (b) the fast Na-current should be blocked. The fast current may be reduced, e.g. either by specific drugs like tetrodo-

toxin, lidocaine etc. or Na-channels may be permanently rendered unavailable (inactivated) by increasing the resting potential due to high concentrations of extracellular potassium [1–4]. Here we show that under moderate adrenaline concentrations the second condition of slow conduction occurrence (b) is unnecessary, and may be replaced by constraints on the stimulus waveform.

To eliminate the rapid cellular (sodium) response in experiments with cat papillary muscles under normal conditions, the stimulation procedure used in ref. [11] consisted of the injection of a 'saw-toothed' stimulating current into the myocyte. After rapidly increasing the stimulus 'strength', normal, rapidly propagating wavefronts were observed, while for a slowly increasing stimulus amplitude, below a certain threshold, usually only slow responses were developed (slow response was nonpropagating, because of the low $\bar{g}_s$ conductance of normal membrane). This may be readily explained by inactivation of fast Na-channels while the membrane is slowly depolarized.

In our current study using the modified BR equations with $g_{Na} = 4.0$, we apply a similar linearly increasing stimulus (ramp) at one end of the cable. This stimulus waveform was simulated here by a linear increase of transmembrane potential, E, at the edge of the cable. The rate of E increase (ramp rate), was fixed for each particular numerical experiment procedure, and varied for successive numerical simulations in order to determine the critical value of dE/dt when fast responses at the stimulating site changed to a slow one. The results of these numerical experiments are presented in Table 2.

Unexpectedly, we observed that the responses to slow (dE/dt small) ramp stimulation waveforms propagated along the cable as slow waves (note that sodium conductance has its normal value). Because the same cable is able to conduct a fast response also (see Fig. 1(a)), it may be concluded that our cable model may reveal different responses—fast propagating and slow propagating—depending only on the stimulating conditions. The most interesting feature of cable behavior is that the slow wave remains slow even when Na-conductance is not reduced.

This fact may be qualitatively explained by the following observation. The rate of increase of membrane potential at the front of the slowly propagating wave (dE/dt maximal value is $1\ V s^{-1}$, see Fig. 1(b)) is less than the critical ramp rate ($1.3\ V s^{-1}$, see Table 2) required to initiate a fast response. For such low rates and delayed stimuli, fast Na-channels become inactivated. The low effective conductance to Na-ions makes the cellular membrane capable of only producing a slow response, since slow channels have a much longer time-constant of inactivation.

Since our model can produce such qualitatively different types of responses, hence two different kinds of wave solutions coexist simultaneously in the cable. By changing the stimulating voltage rate we can select which kind of response (wave) will be initiated. The two classes of nonlinear waves may be regarded as either two different coexisting waves or two branches of the same wave but, as was mentioned above, each type of excitation propagates stably, conserving its inherent characteristics (velocity, time periods, amplitudes of ionic currents etc.).

We hypothesize that it is possible to produce transitions between the two types of excitation waves, and if the waves are stable and this conversion cannot occur spontaneously, then such transitions may require certain conditions or, perhaps, medium

Table 2. The qualitatively different responses of the cable in the modified BR model to ramp stimulation: a linear increase in stimulus potential

dE/dt ($V s^{-1}$)	1.0	1.25	1.3	1.5	2.0	>2.0
Response	slow	slow	fast	fast	fast	fast

disturbances to be realized. If such conditions or disturbances are supplied by the medium or by the waves traveling within the medium, the concept of continuous, spontaneous and chaotic transitions of propagating waves appears to be a promising model of ventricular and atrial fibrillation. This hypothesis is supported to some extent by multiple experimental observations, revealing that electrical activity during fibrillation consists of slow potentials, and may be suppressed by the appropriate agents—blockers of slow inward current [12, 13].

Stimulating the cable at several sites simultaneously, or in the same site at sequential moments of time, can evoke multiple coexisting waves of different types—slow and fast—interacting with each other. As may be expected, wave interaction could possibly represent the required medium disturbance which will make possible the above-mentioned transition of waves from one type to the other. Here we examine two possibilities of transformation: (a) the conversion of a fast wave as a result of a medium inhomogeneity (inexcitable gap on the cable) and (b) the impact of two propagating waves in a homogeneous medium, where a slow wave is followed by a fast one.

Figure 3 represents examples of simulations of wave interaction and wave transformation in the presence of an obstacle in the modified BR cable model. The interaction of the wave with an inexcitable gap of 0.17 cm width, marked by a filled rectangle, is drawn in Fig. 3(a) as the successive states of potential distribution. The horizontal axes denote the position along the cable. Everywhere in the homogeneous cable $\bar{g}_{Na} = 4.0$, except the gap where $\bar{g}_{Na} = 0.1$. Since the medium with reduced excitability conducts only slowly propagating responses, a fast wave is transformed into slow waves within the gap, and travels further as a slow wave.

In Fig. 3(b) the collision of fast and slow waves is represented. First, a slow wave is initiated at the left end of a homogeneous cable by gradually increasing the stimulus amplitude. The following fast response was generated by a rapid jump of potential at the same site. The interaction of fast and slow waves, as it may be seen, results in annihilation of the fast wave, while the slow response continues to propagate. The mechanisms of backward transformations, slow wave to fast one, will be considered in further studies.

CONCLUSIONS

Modifying the well-known BR equations to incorporate effects of catecholamines, we developed a model describing the conduction of slow waves, which was not revealed with other cardiac models. Initiating fast and slow waves in a one-dimensional cable, we found the main properties of the solution to be similar to those observed in experimental preparations under the action of catecholamines. In addition to facts known from the experimental studies (for fast responses)—the enhanced plateau height, reduced APD, normal propagation velocity etc.—we found first that our modified model predicts the simultaneous coexistence of fast and slow propagating waves in myocardium.

This was not observed in earlier studies because, in many experiments, the fast inward current was usually blocked to prevent the development of fast response. We found that adjusting the rate of change of a ramp stimulation waveform, we may selectively evoke either of two types of waves which can propagate stably along a quiescent cable. The fast-response propagation behavior and the conditions of its stability are the same as for the original BR action potential. The mechanism of the stability of slow waves, which is less clear and thus more interesting, is the gradual inactivation of Na-channels during the slow depolarization of cell membranes at the slowly propagating wave forefront.

We considered the hypothesis that these two types of waves may convert from one to another due to disturbances of medium inhomogeneities. Media inhomogeneities, whether

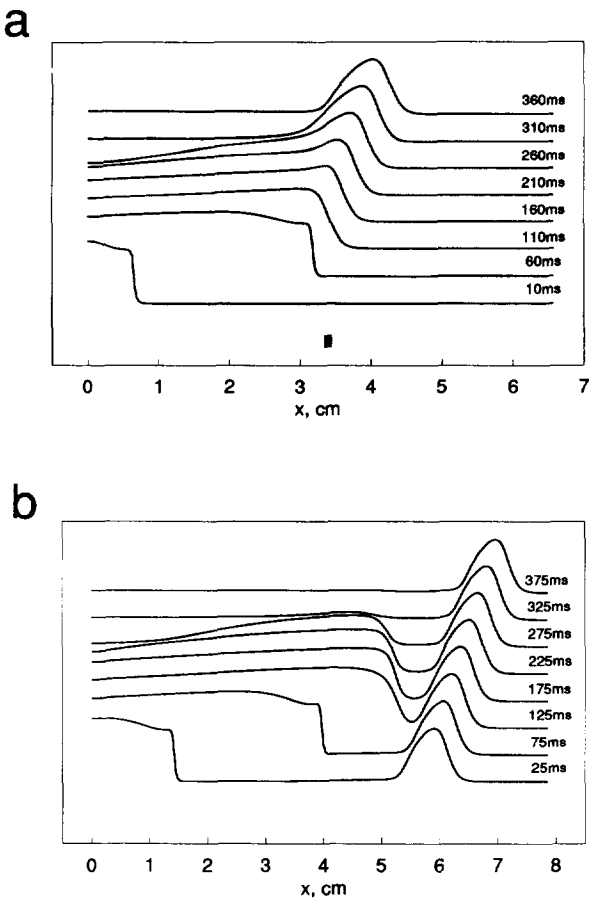

Fig. 3. The interaction of fast-propagating wave with an obstacle in modified BR cable model. As in Fig. 2, the sequential states of potential distribution are presented. (a) The interaction of a wave with an inexcitable gap of 0.17 cm width, marked by a filled rectangle. Everywhere $\bar{g}_{Na} = 4.0$, except the gap where $\bar{g}_{Na} = 0.1$. Since the medium with reduced excitability conducts only slowly propagating responses, fast waves transform into slow ones inside the gap and continue propagating as a slow wave. (b) The collision of fast and slow waves. First, a slow wave is initiated at the left end of a homogeneous cable by gradually increasing the stimulus amplitude. The following fast response was generated by rapid jump of potential at the same site. The interaction of fast and slow waves results in annihilation of fast wave while the slow response continues to propagate.

structural or functional, may initiate chaotic transformation of waves which can be regarded as a promising model of ventricular fibrillation. Two possible mechanisms of fast-to slow-wave transformations were studied here: the interactions of fast-propagating wave with an inexcitable gap and with the leading slow wave. The examples of transformation in the presence of an inexcitable gap as well as fast-wave annihilation which are impossible for known excitable media were demonstrated.

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