RESPONSE CURVE OF AN ARTIFICIAL PACEMAKER NEURON

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Abstract:

An artificial pacemaker neuron is studied by plotting the response curves for different stimulus intensities and free-running periods. Emphasis is placed on phenomena of acceleration and deceleration of the pacemaker model by pulsatile stimulation, and on synchronization and frequency entrainment. The main features of the model are the possibility of spontaneous synchronization on a faster rhythm, and the appreciable range of frequency entrainment above and below the free-running frequency.

Synaptic input to a neuron gives rise to post-synaptic excitatory or inhibitory potentials (EPSP or IPSP) depending on the nature of the post-synaptic membrane and the type of chemical transmitter involved. The particular case of a pacemaker neuron (endowed with endogenous activity) subjected to excitatory stimulation is considered here by means of mathematical model which has been shown to have properties analogous to those of a pacemaker cell (1). The purpose is then to describe the various responses of the artificial pacemaker neuron to pulsatile stimulation and to draw inferences concerning the corresponding biological problem.

The artificial pacemaker neuron is given by the following equations:

$$\dot{x} = k[f(x) + by + z(t)]$$

$$\dot{y} = -\frac{1}{k}[ax + by - Zo]$$

where x may be identified with the transmembrane potential of the neuron and y is a variable corresponding to the excitability of the firing mechanism. The function $f(x)$ simulates the voltage-dependent nonlinear conductance of the neuron membrane and is chosen here as a third degree polynomial in x. In the model a, b and k are constants, and Zo is a parameter allowing to choose the desired frequency of spontaneous firing. The function $z(t)$ represents the pulsatile stimulation applied to the model.

In addition to properties of threshold, absolute and relative refractoriness, and spontaneous activity, this model has a property of paradoxical inhibition which allows an excitatory stimulus (simulating an EPSP) to have an inhibitory effect when the stimulus coincides with a particular portion of the pacemaker cycle. The behavior of the pacemaker model can be characterized further by computing the response curves for various stimulus intensities and free-running periods. The response curves described here have been obtained by plotting the phase advance (Ta) or phase delay (Tr) of the discharge produced by a single shock stimulus presented at given delays after a spontaneous discharge of the pacemaker model.

Fig. 1 shows four response curves of the model corresponding to three different free-running periods — $Vo = 750$, $Vo = 500$ and $Vo = 350$ msec — and to two stimulus intensities for $Vo = 500$ msec. The abscissa gives the delay, Δ in msec, between the spontaneous discharge and the onset of the stimulus. The ordinate is the time between two consecutive discharges encompassing one stimulus presentation. The case where $Vo = 750$ msec, uppermost curve in Fig. 1, is used here for the description.

For long delays, $500 < \Delta < 750$, the stimulus produces a premature discharge and shortens the period of the cycle. With $\Delta < 500$, the stimulus produces only a graded response (1) which decreases in amplitude as the delay is reduced further. Such a graded response is accompanied by a lengthening (Tr) of the period of oscillation. For $100 < \Delta < 400$, the graded response is small and the period of the cycle is not affected. Finally, there is a second portion of the cycle, corresponding to $50 < \Delta < 90$, where a slight increase in the period of the cycle is observed also. In the sequel these different portions of the response are referred to as early Tr ($\Delta < 100$) and late Tr ($\Delta > 250$) respectively.

Changes in the value of the free-running period do not modify the general shape of the response curve, Fig. 1. The magnitude of the early Tr remains the same, although the peak value is shifted towards the right; the latter effect being due to a broadening of the spike discharge with an increasing rate of spontaneous firing. The most remarkable changes are the decrease in the magnitudes of Ta and late Tr, and the corresponding decrease in the value of Δ at which the transition from maximum Ta to maximum Tr occurs. Changing the stimulus intensity, as illustrated by the middle pair of curves in Fig. 1, increases Ta and both the early and late Tr's. However, the magnitude of the late Tr is most affected. As can be expected also, the transition from maximum Ta to maximum Tr is displaced towards the left.

The response curve allows to specify the range of frequency entrainment by periodic stimulation, corresponding to a given free-running period and stimulus characteristics. The entrained period, Te , and the free-running period, Vo , are related as follows:

$$Te = Vo - Ta \quad \text{for} \quad Te < To$$

$$Te = Vo + Tr \quad \text{for} \quad Te > To$$

In Fig. 1, uppermost curve, the peak values are Ta = 150 msec and Tr = 150 msec so that the range of frequency entrainment is $600 < Te < 900$. The range of frequency entrainment increases with the stimulus intensity and decreases with the free-running frequency, Fig. 1.

The range of frequencies over which spontaneous synchronization (without frequency entrainment as defined above) occurs is smaller than the range of frequency entrainment. Its value cannot be determined from the response curve. Experimental observations with the present model indicates that spontaneous synchronization on a periodic stimulation of frequency higher than the free-running frequency is possible within about 15% of Vo . Spontaneous synchronization on a periodic stimulation of frequency lower than the free-running frequency is possible only when the stimulus intensity is very large, and yet the limit is only about 5% of Vo . This difficulty of synchronizing the pacemaker model on a slower rhythm is due to the narrowness of Tr .

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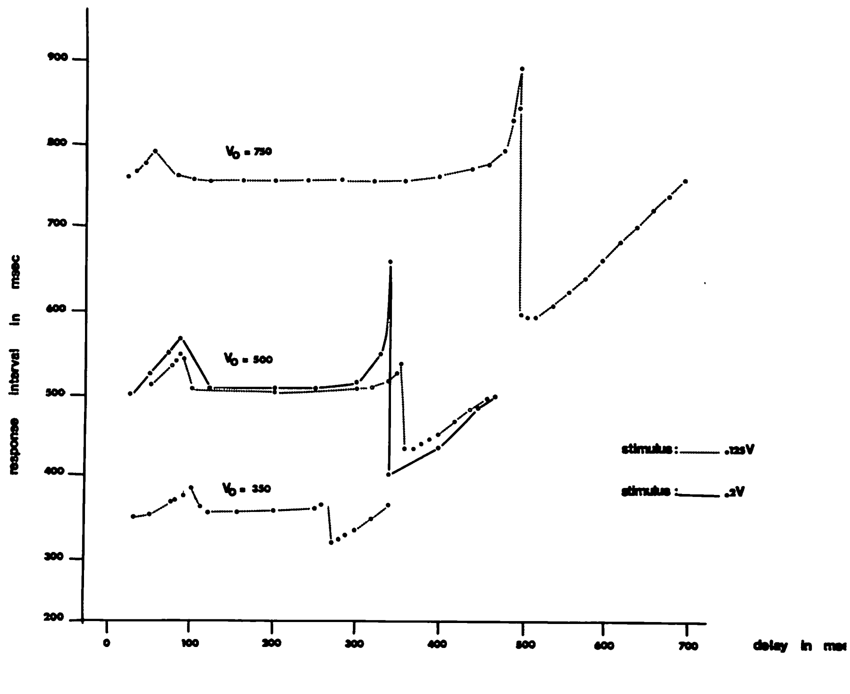

Figure 1