Influence of Temperature on Neuronal Excitability in Cochlear Nucleus

Ting Zeng¹, Jiafu Wang¹,² and Shenbing Kuang¹
1 School of Sciences, Wuhan University of Technology, Wuhan 430070, China
2 State Key Laboratory of Advanced Technology for Materials Synthesis and Processing, Wuhan 430070, China

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The influence of temperature on neuronal excitability is studied by numerical simulations on the spiking threshold characteristics of bushy cells in cochlear nucleus periodically stimulated by synaptic currents. The results reveal that there is a cut-off frequency for the spiking of bushy cell in a specific temperature environment, corresponding to the existence of a critical temperature for the neuron to respond with real spikes to the synaptic stimulus of a given frequency, due to the finiteness of spike width. An optimal temperature range for neuronal spiking is also found for a specific stimulus frequency, and the temperature range span decreases with increasing stimulus frequency. These findings imply that there is a physiological temperature range which is beneficial for the information processing in auditory system.

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Electric excitability has been attracting much attention for decades, for it is the basis of information processing and is essential to coding in neural systems. The excitability of a neuron originates from integrated effect of the kinetics [1], as well as the spatial distribution [2], of ion channels on the cellular membrane in proper environment, and determines the functional properties when responding to external stimulus, such as the frequency sensitivity [3, 4] or selectivity [2], interaural time difference (ITD) sensitivity in auditory system [6], etc. Excitability and response properties of a neuron may vary in different environmental conditions of, say, temperature and pH values [7]. Recently, the influence of temperature on the excitability of rat suprachiasmatic nucleus neurons has been investigated experimentally, and the results reveal that there is a temperature-sensitive range for the neuronal activities; this may provide cues to the circadian synchronized rhythmicity [8, 9]. Biophysically, temperature may influence the functioning of a neuron through the temperature dependence of various ion channel conductances and time constants of channel activation/inactivation variables [10]; hence changing temperature alters the basic properties of excitable neuron, such as the membrane potential, the input resistance, the shape and amplitude of action potentials, and the propagation of spikes [11, 12, 13, 14]. Up to date, however, there has been little theoretical investigations of the influence of temperature on neuronal excitability in literature.

Neuronal excitability can be described by the firing properties, like the spiking threshold of the neuron responding to periodic stimulus [5]. Characteristics of the spiking threshold of excitable neurons have been discussed in several studies [3, 3, 15, 16, 17], where the stimuli applied are mostly sinusoidal. More realistically, in fact, the stimulus to a post-synaptic neuron is often described by a current with alpha-function channel conductance [18], which is used in the present study. Comparable with Ref. [5], this work focuses on the effect of temperature on the spiking threshold of an auditory neuron periodically stimulated by excitatory post-synaptic current (EPSC). The frequency dependence of the spiking threshold varies in different temperatures. Our results on the temperature dependence of the spiking threshold reveal that, for the EPSC stimulus with a given frequency, there is a temperature sensitive range for the neuron, and that this range reduces as the stimulus frequency increases. These imply that there is a physiological temperature range which is beneficial to the information processing in auditory system.

The model used in this work is presented by Rothman and Manis (RM) [10] for bushy cells in ventral cochlear nucleus of auditory midbrain based on electrophysiological experiments [19]. It consists of a single electrical compartment with a membrane capacitance (C) connected in parallel with a fast-activating slow-inactivating low-threshold K⁺ current \( I_{LT} \), a high-threshold K⁺ current \( I_{HT} \), a fast-inactivating TTX-sensitive Na⁺ current \( I_{Na} \), a hyperpolarization-activated cation current \( I_h \), a leakage current \( I_{lk} \), and an excitatory synaptic current \( I_E \). The membrane potential \( V \) is described by the following first-order differential equation:

\[
\frac{dV}{dt} = G_{Na}m^3h(V_{Na} - V) + G_{LT}w^4z(V_K - V) + G_{HT}[\varphi n^2 + (1 - \varphi)p](V_K - V) + G_h(V_h - V) + G_{lk}(V_{lk} - V) + I_E,
\]

where \( G \)‘s denote the maximum channel conductances, and \( V_{Na}, V_K, V_h, \) and \( V_{lk} \) are the reversal potentials for potassium, sodium, cation, and leakage channel currents, respectively. The channel currents are governed by some

*Correspondence: jasper@whut.edu.cn*
activation/inactivation variables \( x = (w, z, n, p, m, h, r) \) satisfying the differential equation \( dx/dt = [x_\infty(V) - x]/\tau_x(V) \), where \( \tau_x \) and \( x_\infty \) are the voltage-dependent time constant and the steady-state value of \( x \), respectively. All the model parameters used here are the same as in Ref. \[10\]. In the present study, the EPSC is modeled by \( I_E = g_E(t)(V_E - V) \), where \( V_E \) being the reversal potential of the EPSC (usually chosen as \( V_E = 0 \) mV for excitatory synapse) and \( g_E(t) \) being the time-dependent post-synaptic conductance in response to a sequence of synaptic stimuli turn on at different time \( t_i \). \( g_E(t) = \sum_i G_{syn}(t - t_i) \), \( G_{syn} \) determines the peak of synaptic conductance and \( t(t/\tau_E) \exp[1 - (t/\tau_E)], t > 0 \), with \( \tau_E \) determining the time to reach the stimulus peak (chosen as \( \tau_E = 0.2 \) ms in this study). Standard fourth-order Runge-Kutta algorithm is applied to solve the differential equations. Noticeably, in comparison to the definition in Ref. \[3\], the spiking threshold here is characterized as the critical value of \( G_{syn} \) for a neuron to fire. The implementation of calculating the spiking threshold is based, still as usual \[3, 5, 15, 16\], on estimating whether the membrane potential \( V \) of the stimulated neuron can exceed a voltage threshold \( V_{th} \) (chosen as \( V_{th} = -25 \) mV here).

The parameters given in the RM model \[10\] are obtained from the experiments in vitro \[19\] operated at room temperature \( T = 22^\circ\text{C} \). In order to include the influence of temperature on the excitability of bushy cells, we will take the suggestion in Ref. \[10\] that all the model time constants \( \tau_x \) are divided by a Q10 factor of 3 while all the maximum channel conductances (except for \( G_{syn} \)) are multiplied a Q10 factor of 2. These Q10 values are approximations to those reported for Na\(^+\) currents \[20\] and K\(^+\) currents \[11, 21\].

Our investigation begins with the frequency characteristics of the spiking threshold of the RM model neuron stimulated by periodic EPSCs (with frequency \( f_s \)) at \( T = 22^\circ\text{C} \), the temperature at which most of the experimental data in vitro was recorded in the model construction \[10, 19\]. The frequency dependence of the spiking threshold is illustrated in Fig. 1. Different from the case of sinusoidal stimuli (see the results in Ref. \[3\]), the spiking threshold in the case of more realistic synaptic stimulus here depends slightly on the stimulus frequency in low frequency range. This may result from the effect of the refractory period of the neuron; when the stimulus frequency period is long enough for the membrane potential to return to the resting value, the spiking threshold will change little with respect to the stimulus frequency. The existence of a minimum spiking threshold at the frequency about 40Hz (see inset (a) in Fig.1) is consistent with the previously reported frequency sensitivity phenomenon in bushy cells \[3\], as well as in Hodgkin-Huxley (HH) \[4, 16\] and Hindmarsh-Rose \[4, 15, 16\] neurons, likely due to the intrinsic oscillation in the excitable neuronal system \[8, 16\].

Furthermore, the frequency dependence of spiking threshold implies an abrupt jump in the high frequency range. As a matter of fact, when the stimulus frequency is higher than the frequency range of the abrupt jump, the neuron does not really fire any spike no matter how large the stimulus amplitude is, though the membrane potential may exceed \( V_{th} \) (see an example in the inset (b) in Fig. 1, where one may find that the neuron does not experience any refractory period, nor even hyperpolarization). If one uses three-compartment model in simulation, one will find that such kind of non-spiking response can not propagate to the end of a long axon. Therefore, we would refer to the frequency of the abrupt jump as the cut-off frequency for the neuron to fire spike. The existence of this cut-off frequency may come from that the neuron needs a time width to complete a spike; if the stimulus period is shorter than a complete spike width, the neuron will not fire any real spike.

The frequency characteristic of the spiking threshold may vary at different temperatures, for temperature changes the maximum channel conductances and the time constants of the channel activation/inactivation variables. Some examples for bushy cell at \( T = 10^\circ\text{C}, 30^\circ\text{C}, \) and \( 38^\circ\text{C} \) are illustrated in Fig. 2, where one can see that, at different temperatures, the frequency characteristics of spiking threshold are very similar, but the values of the cut-off frequencies are distinct; the higher is the temperature, the higher is the cut-off frequency. For each temperature the cut-off frequency is close to the reciprocal of the corresponding spike width, confirming that the existence of cut-off frequency for bushy cell is due to the finiteness of spike width of the neuron. Since increasing temperature shortens the time constants of channel variables and makes the neuron respond faster to external stimulus, the spike width decreases and correspondingly the cut-off frequency increases (see Fig. 2 and inset therein).

Figs. 1 and 2 show that at a given environmental temperature there is a reliable frequency range of stimuli for a bushy cell to respond to fire real spikes (propagable along axon). This will be very important to neuronal communication and/or coding. If the frequency of an external stimulus (such as sound signal) is too high, the neuron will not respond properly, nor will process the information carrying by high frequency signals. Seeing that a bushy cell can not work properly for very high frequency stimuli at room or body temperature, one may draw the conclusion that the bushy cells in auditory midbrain will not be responsible for perceptual task of frequency discrimination/coding in auditory information processing. This conclusion is consistent with the results in Ref. \[5\].

For a neuron stimulated by EPSCs of a given frequency, on the other hand, how does the neuron’s excitability depend on the environmental temperature? The temperature dependence of spiking threshold of a bushy cell stimulated by periodic EPSCs of \( f_s = 100Hz \), as an example, is illustrated in Fig. 3. One can see that the spiking threshold exhibits a global minimum in an environmental temperature range where the bushy cell needs weakest synaptic stimulus to initiate spikes, indicating the occurrence of optimal use of synaptic transmission. This result implies that there is a
sensitive temperature range for neuronal activities/communication of bushy cells. To further explore the mechanism underlying the emergence of sensitive temperature range, we examine the effects of temperature regulation through the maximum ion conductances (inset (a) in Fig.3) and through the time constants of channel gating variables (inset (b) in Fig.3), respectively. If only the influence of temperature on the maximum ion channel conductances is considered, the spiking threshold has a monotonous temperature dependence; in contrast, the sole temperature effect via channel activation/inactivation rates yields a temperature dependence of spiking threshold similar to the control result (Fig.3).

Thus we conclude that the emergence of the temperature sensitive range results mainly from the effect of temperature upon ion channel kinetics. Theoretically, a U-shaped dependence of a physical quantity characteristic may results from the competition of the impacts of (at least) two dominant factors/aspects. The temperature dependence of spiking threshold (as shown in Figs.3 and 4) comes likely from the competition of the effects of temperature regulation on channel kinetic rates of activation and of inactivation variables (cf. Ref. [22] for HH model). Detailed study will appear elsewhere.

In Fig. 3 one may also find a sudden swerve (at about 6°C) on the temperature-dependent spiking threshold curve. Actually when temperature is lower than the temperature at the swerve, the bushy cell does not fire any real spike; this is consistent with the existence of cut-off frequency described above (cf. Fig. 2). Such kind of critical temperature for the synaptic stimulus of a given frequency, below which the neuron does not work well, also exists in the temperature dependence of spiking threshold subject to periodic EPSCs of other frequencies (see examples in Fig. 4). Fig. 4 also shows that there exists a specific temperature-sensitive range for each stimulus frequency, while the temperature range span decreases with increasing stimulus frequency.

In summary, the influence of temperature on neuronal excitability has been investigated by numerically simulating the characteristics of spiking threshold of bushy cell stimulated by periodic EPSCs of different frequencies in various environmental temperatures. We find that, at a given environmental temperature, there is a cut-off frequency for the spiking of bushy cell, leading to an open question how the signal of high frequency is processed in auditory system. On the other hand, for the synaptic stimulus of a given frequency, there exists an optimal temperature range for the excitable neuron to respond most sensitively to external input; the essence of this temperature dependence for neuronal excitability may account for the temperature-sensitive properties found in other kind of neurons [8]. Furthermore, the existence of a critical temperature for neuronal spiking found in this study may relate to the mechanism of hibernator activities in winter.

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FIG. 1: The frequency dependence of spiking threshold of a bushy cell stimulated by periodic EPSCs at $T = 22$ °C. Inserts: (a) Details for the frequency range around the spiking threshold minimum. (b) The response of the bushy cell to periodic EPSCs with $G_{syn} = 500$ nS (larger than the spiking threshold) at $f_s = 800$ Hz (higher than the cut-off frequency).

FIG. 2: Frequency dependence of spiking threshold of bushy cell stimulated by periodic EPSCs at different temperatures. (For each temperature only the reliable frequency range is shown.) Inset: The responses of a bushy cell to a synaptic stimulus (with $G_{syn} = 100$ nS), showing spike widths, at different temperatures.
FIG. 3: The temperature dependence of spiking threshold of a bushy cell stimulated by periodic EPSCs of $f_s = 100$ Hz. Main: Both the channel conductances and the time constants of channel variables are regulated by the Q10 factors of temperature proposed in Ref. [10]. Insets: (a) Only the temperature regulation on the channel conductances is considered. (b) Only the temperature regulation on the time constants of channel variables is considered.

FIG. 4: The temperature characteristics of spiking threshold of bushy cell for the stimuli of different frequencies. (For each stimulus frequency only the reliable temperature range is shown.)