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Review Article

Constant Warm Body Temperature Ensures High Response Reliability of Neurons in Endothermic Brains

Yuguo Yu[1]*

[1]Centre for Computational Systems Biology, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Fudan University, Shanghai, 200433, China

***Corresponding author:** Yuguo Yu, Centre for Computational Systems Biology, State Key Laboratory of Medical Neurobiology, Institutes of Brain Science, Fudan University, Shanghai, 200433, China, Email: yuyuguo@fudan.edu.cn

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Abstract

Mammals and birds have developed remarkably larger brains as well as a constant and warm body temperature, in contrast to other vertebrates and invertebrates. What is the benefit of a constant and warm temperature on brain signaling and large size brain development? Our previous experimental and computational studies [1] demonstrated that cortical action potentials are remarkably more energy efficient in a warm temperature rather than in a cold temperature. This study revealed that a constant temperature is critical in ensuring the reliable and accurate neural coding to sensory signals based on computational studies of the classical Hodgkin-Huxley neuronal model. An increase of temperature variance during neural responses to a repeated signal is correlated with a gradual degeneration of neural response reliability. In addition, computer simulations also suggested that temperature around 36-40°C may be a special range for cortical neurons to firing spikes more reliably than other temperature conditions. These results suggest that a warm and constant temperature have been critical for the accurate neural coding and reliable intra-neuronal communication that may be necessary for development of large brain circuit for endothermic animals.

Introduction

Evolution develops larger brains in Mammals and birds than do fish, reptiles and amphibians [2]. Living mammals and birds are also distinguished as endotherms by their maintenance of a high body temperature around 36 -40°C, while fish, reptiles and amphibians are ectotherms whose body temperature generally varies with that of environment [3]. An enlarged brain and endothermia are thus two unique features of mammals and birds. Is this a coincidence, or is there some causal link between them? Energy required for the large brain increases greatly as the size of the brain circuit, the computational power and duties increase largely. The major part of brain energy is consumed for generating action potentials for coding signals of sensory world and synapse signals for communication among neurons. In a previous study, we found that the increase in body temperature associated with the evolution of warm-blooded animals had an energetic benefit [1]. The metabolic cost of generating action potentials is 4 to 10 fold lower in warm body temperature than in colder temperatures [1]. These results indicate that mammalian brains, although requiring a great deal of energy to operate, are actually more efficient than expected due to a warm body temperature.

If a warm temperature facilitates energy efficient cortical spikings in saving energy, what is the benefit to have a constant body temperature for mammalian and bird's brains? Is it necessary for development of a large complex brain circuit with multi-layers? In cold-blood animals, their body temperature fluctuates with natural environments, by several to tens of degrees per day. How is this temperature condition variance correlated to the accuracy of neural coding and neural signal propagation. Surprisingly there is almost no study in this topic till now. Hence, to address the above issues, I have carried out a set of computational studies to examine how temperature fluctuations affect neural code based on Hodgkin-Huxley types of cortical neuronal models that were developed in my previous experimental studies on cortical neurons [1,4].

Results

An aperiodic signal s(t) was presented repeatedly to the neuronal model for a hundred times (for each trial there was an additional Gaussian colored which mimicked synaptic noise added to the neuron was repeated without change for all trials). The temperature value of the model neuron for each trial had a fluctuation (quantified by standard variance σ_T) around an average value (e.g., 35°C in Figure 1A). Computer simulations revealed that temperature variance may heavily degrade the reliable neural response to an input signal. Figure 1A shows that with a trial to trial variance in temperature (mean 35°C, standard deviation σ_T = 5°C), the spiking responses of the model neuron to the repeated signal were much less reliable with larger spike timing jitters than those in the responses of the neuron nearly constant temperature ((35°C) with a very small temperature variance σ_T = 0.1°C cross the trials (Figure 1B)). The raster plot (see Figure 1C) shows clearly the degeneration effect of temperature variance on the response reliability of the sensory neuron for the one hundred repeated trials of same input signal. Although at the beginning of the stimulus onset, the spiking responses were reliable for both situations, the spiking timings for case of σ_T = 5°C started to lose its timing precision after a hundred millisecond period of signal presentation. The post-stimulus time histogram (PSTH) ((yellow in Fig. 1C)) indicates that the neural coding responses lost their precise timings for each stimulus event in the situation of large temperature variance across stimulus trials. On the contrary, for the situation σ_T = 0.1°C, the spike timings for each stimulus event can be reproduced reliably with very small spike jitters (Figure 1D), and the PSTH displayed highly repeatable neural responses for all the stimulus features.

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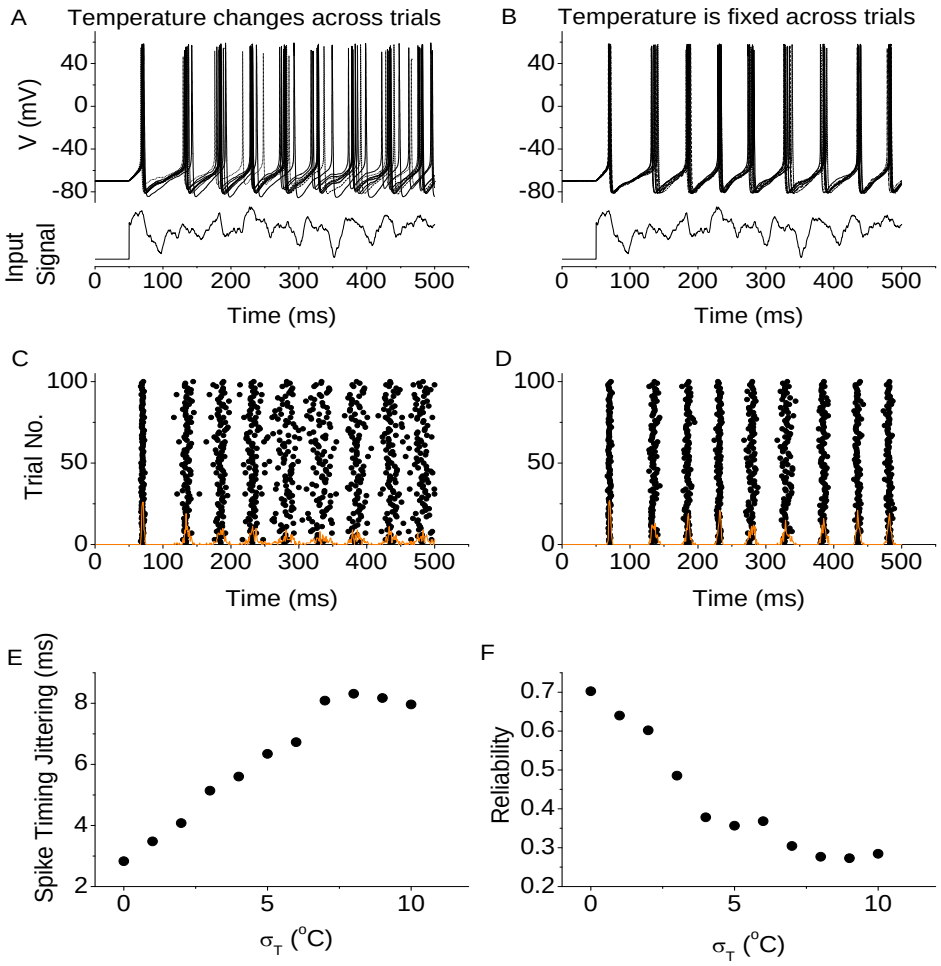

Figure 1: The importance of keeping a constant temperature for reliable neural coding. A. Top panel: the first 10 trials (of total 100 trials) of raw traces of action potentials produced from the cortical neuronal model in response to an aperiodic input signal. The temperature is same within one trial, but changes randomly from trial to trial with a mean value of 35°C, and standard deviation σ_T = 5°C. Bottom panel: an aperiodic signal obtained by convolution of a gaussian white noise with a low pass filter with time constant τ= 5 ms. B. Raw traces of the first 10 trials (of total 100 trials) of action potentials produced from the cortical neuronal model (top panel) in response to an aperiodic input signal (bottom panel, signal is same as in Figure 1A). The temperature is kept almost invariant across trials with a value of 35°C with σ_T = 0.1°C. C. Raster plot of spike timings from the total 100 trials and the post-stimulus time histogram (PSTH) (in orange color) show that the reliability of spike response and the spike timing precision are gradually lost as a function of time for temperature condition in Figure 1A. D. Raster plot of spike timing and the PSTH (in orange color) show that the reliability of spike response and the spike timing precision are well kept as a function of time (Notice, an independent Gaussian white noise (zero mean, standard deviation 0.2) has been added to the input signal to mimic intrinsic synaptic noise sources for both Figure 1A and B). E. Spike timing jittering increases as a function of temperature variance σ_T. F. Spike timing reliability decreases as a function of temperature variance σ_T.

To give a quantitative measurement on the spike timing precision, spike timing jittering and response reliability were calculated for different values of temperature variance σ_T. Figure 1E shows that the averaged spike timing jittering increases from a small value of 2 ms to over 8 ms as a function of increase σ_T. The spike response reliability decrease from above 0.7 (value 1 is corresponding to the highest reliability) to a low value of below 0.3 when the temperature variance σ_T increases (see Figure 1F).

The HH cortical model used here is based on previous references where model parameters were all derived directly from experimental studies, and the spiking properties of the model matched experimental observations of cortical spikings well experimental observations of cortical spikings [1,4-7]. In the previous paper, this model shows a quantitatively similar relationship between temperature and spiking properties as in experimental studies on cortical neurons[1]. Since cortical neurons of mammals or birds are living in a body temperature condition around 36-40°C (generally body temperature is around 36-37°C for mammals while 39-40 for birds), so it will be interesting to see whether this cortical neuronal model shows some particular preference for the 36-40°C temperature condition range.

Figure 2 shows the spiking timing reliability of a cortical model neuron in response to an aperiodic signal (as in Figure 1) measured in three temperature conditions, i.e., 16+-2°C, 37+-2°C, and 44+-2°C, respectively. Interestingly, for the same temperature variance, the neuronal model showed a much lower spike timing jittering and higher spike timing reliability for T=37+- 2°C (Figure 2B) than in the other temperature conditions (Figure 2A and C). The same tests were done for all the other temperature conditions from T=5 to 45°C in order to see whether temperature around 37°C is particularly special and preferable for cortical neuronal model. Figure 2D shows that the spike timing jittering actually went through a global minimum

when the mean temperature was around 34-37°C. correspondingly, the spike timing reliability also went through a global maximum when the mean temperature was around 34-37°C (see Figure 2E). For either a high temperature larger than 40°C or a temperature lower than 30°C, the neural spiking response lost its reliability for the same temperature variance across the repeated trials.

The trial to trial response variance in the above study is an outcome of the changes in neuronal excitability as a function of temperature. Figure 2F shows that the firing rate for the same signal increased linearly as the temperature was increased from 5 to 32°C. When the temperature was further increased from 32 to 40°C, the firing rate increased slowly, and then increased much more rapidly for temperature above 40°C. This temperature dependent increase in neuronal excitability has been reported in many experimental studies [1,8-12], however, its temperature-tuning property is not well-known. The present study suggests that the experiment-based HH cortical model studied here has more stable dynamics for temperature around 36-40°C than other temperature conditions.

Based on previous study [1], the average sodium charge per action potential was decreased exponentially as temperature was increased (see Figure 2B in reference [1]), indicating a lower cost of spikes in the higher temperature compared to that of lower temperature. The total sodium charge of a neural response (product of sodium charge per spike and firing rate) versus temperature was first decreased and then increased, displaying a global minimum value for temperature around 36-40°C (see Figure 2G). This suggests that a body temperature within 36 to 40°C might be the optimal temperature condition for neurons to produce highly reliable and energy efficient electric signals within neurons to perform neural coding and communication.

Summary

Since maintenance of a constant warm body temperature is very energy demanding, what is the evolutionary benefit? This paper has studied for the first time the functional benefit of keeping a constant warm temperature in endothermic animals for reliable brain signaling. As it is well-known that during intra-neuronal communications, the small spike timing jittering is critical for reliable neural response propagation across multiple cortical layers [13,14]. Spike timing responses with larger spike timing jitters cannot propagate through a long-distance in feed forward networks with multiple-layers. Figure 1E and F suggest that neural response in the presence of large temperature variance has very unreliable spike timings, which may be hard to propagate reliably across multiple-layer cortical networks. A constant body temperature that enables highly reliable spiking timings may be critical for reliable brain signaling propagation and communication inside the brain. Therefore, the precise and repeatable neural response to the same object from neurons with a constant temperature should be crucial for the complex brain to carry out reliable computations, decision makings and rapid actions.

In summary, the constant and warm body temperature of homeothermic mammals and birds ensures highly efficient and reliable brain signaling. A body temperature that changes with the environment brings large uncertainty in neural code of input signals for ectothermic animal brains, thus may limit the development of complex brain architectures. Therefore, the constant body temperature may act as an effective firewall for protecting mammalian brain for precise and reliable signaling from being affected by the fluctuated temperature in the natural environment. Thus, to keep a constant and warm body temperature in endothermic animals may

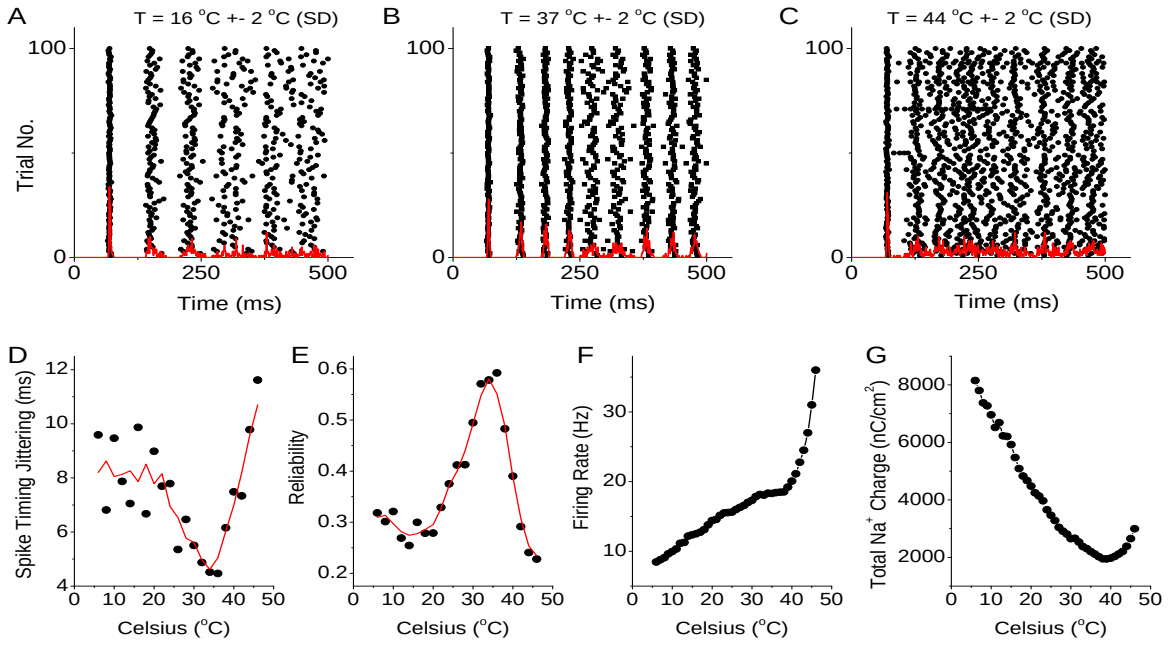

Figure 2: A. Raster plot of spike timings and PSTH of neuronal model response for temperature conditions 16+-2°C (A), 37+-2°C (B) and 44+-2°C (C) respectively. D. Spike timing jittering versus mean temperature. Temperature variance σ_T is fixed as 2 for all mean temperature conditions. E. Spike timing reliability versus mean temperature. Temperature variance σ_T is fixed as 2 for all mean temperature conditions. F. The firing rate of the model neuron versus temperature for a given DC=0.5 x10^{-2} pA/um2 in the presence of intrinsic Gaussian white noise (zero mean, standard deviation 0.2). G.The total Na^+ charge (product of Na+ charge per spike and firing rate) in response to a given signal as a function of temperature.

be crucial in promoting the development of complex neuronal circuit and multiple-layer structures of a large brain for high level cognitive functions.

Methods

Data analysis and statistics

The precision of the spike timing of neural response was evaluated by calculating the jitter in the timing of individual spikes produced by HH neuronal model in response to multiple presentations of the same aperiodic signal. In each trial, the neuron was stimulated with a signal that was repeated for at least 100 trials. For each trial, the temperature is fixed while changed across the trials with a variance described by standard deviation σ_T. The 100 trials of the spiking response were used to construct a peristimulus time histogram (PSTH) of the afferent spike trains. The PSTH was used to examine spike events that carry information about stimulus features in the signal. In other words, events corresponded to vertical columns of spikes in the spike time raster plots (see Figure 1C and D). For each of these events, the times of the associated spikes referenced to the start of a trial were extracted from the raw data file. The standard deviation (SD) of the individual spike times at each event was defined as the jitter of the event. The overall spike timing jittering for each PSTH was calculated as an averaged jitter over all the events. For each event, we defined its reliability as the fraction of the trials in which a spike was elicited. Hence, a small value of this fraction close to 0 suggests a low reliability while a high value close to 1 suggests a highly repeatable neural response.

Hodgkin-Huxley-Style Cortical Neuronal Model

To have a comparison with the results from the original HH model, and also to address the key factors contributing to energy efficient action potentials, only three major ionic voltage-dependent currents have been used in our cortical model: fast Na^+, I_{Na}, fast K^+, I_K, and a leak current, I_L. The equations describing the voltage and time dependence of the Na^+ and K^+ conductance's were based upon previous publications [15], whose channel kinetics are modified based on models of cortical neurons [4,16,17] and experimental studies [4,18-20]. The equations describing the cortical axon single compartment model:

$$C\frac{dV}{dt} = I_{stim} - g_{Na}^{\max}\cdot m^3\cdot h\cdot(V-V_{Na}) - g_{\kappa}^{\max}\cdot n\cdot(V-V_K) - g_L\cdot(V-V_L),$$

$$\tau_m\frac{dm}{dt} = -m + m_\infty \ , \tau_m = \frac{1}{\alpha_m+\beta_m}, m_\infty = \frac{\alpha_m}{\alpha_m+\beta_m}$$

$$\tau_h\frac{dh}{dt} = -h + h_\infty \ , \tau_h = \frac{1}{\alpha_h+\beta_h}, h_\infty = \frac{1}{1+e^{(V+60)/6.2}}$$

$$\tau_n\frac{dn}{dt} = -n + n_\infty \ , \tau_n = \frac{1}{\alpha_n+\beta_n}, n_\infty = \frac{\alpha_n}{\alpha_n+\beta_n}$$

$$\alpha_m(V) = \phi\cdot\frac{0.182\cdot(V+30)}{1-e^{-(V+30)/8}}$$

$$\beta_m(V) = -\phi\cdot\frac{0.124\cdot(V+30)}{1-e^{(V+30)/8}}$$

$$\alpha_h(V) = \phi\cdot\frac{0.028\cdot(V+45)}{1-e^{-(V+45)/6}}$$

$$\beta_h(V) = -\phi\cdot\frac{0.0091\cdot(V+70)}{1-e^{(V+70)/6}}$$

$$\alpha_n(V) = \phi\cdot\frac{0.01\cdot(V-30)}{1-e^{-(V-30)/9}}$$

$$\beta_n(V) = -\phi\cdot\frac{0.002\cdot(V-30)}{1-e^{(V-30)/9}}$$

$$\phi = Q_{10}^{(T-23)/10},$$

Where the Q_{10} effect, described by Φ regulating the temperature dependence of rate of biochemical reactions with Q_{10} =2.3 [21,22]. The relationship between temperature and I_{Na} and I_K activation and inactivation is not monotonic and varies in different species [23]. The reversal potential for Na^+ and K^+ currents was adjusted according to the Nernst equation with each change in temperature. Similar results were obtained with a variety of values for Q_{10}. Using a Q_{10} of 3, for example, yielded similar results in spike efficiency and changes in spike rate with temperature. In our cortical model, we slightly adjusted Na^+ kinetics to be faster than what we have used previously [4], owing to recent experimental observations by Schmidt-Hieber and Bischofberger [19]. The parameters used in our present cortical neuronal model are: membrane capacitance = 0.75 μF /cm^2, g_{Na} = 1500 pS/μm^2 (based on recent experimental results [18,19,24-26], density of g_K = 40 pS/μm^2 [20] and gleak = 0.33 pS/μm^2. The reversal potentials are V_L=-70 mV, V_{Na}=60 mV, and V_K =-90 mV for leak, sodium and potassium channels, respectively. The injected DC value is 0.5 x10^{-2} pA/μm^2 for Figure 1 and 2, respectively.

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