Impact of Frequency on the Energetic Efficiency of Action Potentials

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Abstract. Sodium entry during the decaying phase of the action potential determines the metabolic efficiency of a neuron's spiking mechanism. Recent studies have reported that mammalian action potentials are close to metabolic optimality but that fast-spiking inhibitory neurons are less efficient than their pyramidal counterparts. It is postulated that this represents nature's tradeoff between metabolic efficiency and the ability to discharge at high rates. Using eight different published Hodgkin-Huxley models of mammalian neurons to cover a wide range of action potential metabolic efficiencies, we show that the cost of operating a neuron is heavily dependent on its output frequency. We observe that this cost is significantly smaller than the frequency-dependent cost naively estimated from an isolated action potential, the gap increasing with increasing frequencies. Our results demonstrate that metabolic efficiency cannot be considered only in terms of isolated action potentials but must be studied over a range of meaningful frequencies.

Keywords: Hodgkin-Huxley-type models, action potential, energetic efficiency, energy metabolism, frequency dependence.

1 Introduction

The brain is one of the most energy-demanding organ, representing $\sim$ 2% of the body weight but accounting for $\sim$ 20% of the total body glucose and oxygen utilisation. Of the metabolic energy generated from glucose, about 20% is expended on action potentials and up to 60% on subsequent postsynaptic potentials [1, 2, 3].

The metabolic cost of an action potential is approximately one-third of the total sodium entry into the neuron during its generation [4]. A metabolically efficient neuron should then have sodium entry restricted to the rising phase of the action potential as sodium entry during the falling phase leads to an overlap of the opposing sodium and potassium currents, augmenting the metabolic cost

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for no immediate apparent benefits. This can be encapsulated into an efficiency measure, defined as the integral of the sodium current during the action potential divided by the theoretical minimal charge transfer required to achieve the observed depolarisation [3, 5]. A metabolically optimal action potential has an efficiency of 100%.

Analyzing the action potential in the squid giant axon, Hodgkin and Huxley established that its efficiency is low ($\sim 25\%$), owing to the fact that the sodium channels remain open during the falling phase of the action potential [6]. This has led to the idea that action potentials are metabolically inefficient and this value was used as key input in a number of studies aiming at establishing an energy budget for brain tissue (see e.g. [4]). However, two recent studies have overturned this idea. Mammalian neurons, having fundamentally similar action potentials as the squid giant axon, are significantly more efficient owing to lesser sodium entry during the falling phase of the action potential [3, 5]. Of particular interest, it has been reported that different central neurons exhibit significantly different sodium current dynamics and associated metabolic efficiencies during the action potential [5]. More specifically, cortical and hippocampal CA1 pyramidal neurons are very efficient with efficiencies up to about 85% while inhibitory neurons have less efficient action potentials with both cerebellar Purkinje neurons and cortical basket cell interneurons having efficiencies around 50%. It is postulated that metabolic efficiency of fast-spiking neurons is traded against the ability to spike faster and that this is permitted by shorter action potentials and incomplete inactivation of sodium channels [5, 7].

In the present work, we use eight published single compartment Hodgkin-Huxley models for central mammalian neurons, reproducing a range of action potentials and underlying currents relevant to this debate. The models we use are of a mouse fast-spiking neocortical interneuron (Erisir model) [8], a mouse fast-spiking neuron (MFS) [9], a rat hippocampal interneuron (RHI) [10], a regular spiking rat cortical neuron (PoRS), a fast-spiking rat cortical neuron (PoFS), a cat visual cortex bursting neuron (PoBurst), a cat rebound bursting cell (PoLTS) [11] and a rodent hippocampal interneuron (Wang model) [12]. We then use this framework to investigate the functional advantages of metabolically inefficient action potentials and how the discharge frequency affects their efficiency.

2 Methods

Eight Hodgkin-Huxley-type models were taken from the literature and simulated as originally published. They are: (i) the Erisir model [8], (ii) the MFS model [9], (iii) the RHI model [10], (iv) the PoRS model, (v) the PoFS model, (vi) the PoBurst model, (vii) the PoLTS model [11] and (viii) the Wang model [12]. In all eight models, the membrane voltage V follows the Hodgkin-Huxley formalism and is given by

$$C_m \frac{dV}{dt} = -\sum_k \mathrm{i}_k - \mathrm{iExt} \tag{1}$$

with C_m the membrane capacitance, i_k the currents associated to the different ion channels and iExt an externally applied current. We refer interested readers to the references cited above for the exact definition of i_k for each individual model.

All simulations were performed using MATLAB (The Mathworks, Natick MA, USA). Equations were integrated using the function ode15s(.) with a time step of 20 μs. Action potentials in Figure 1 were triggered by a 1 ms square pulse just above threshold. For Figures 2 and 3, the models were driven by either a constant current, a random current or random conductances. For constant current input, multiple simulations were run while progressively increasing the current amplitude. The random current consisted of a Gaussian white noise and both its mean and standard deviation were independently modified in multiple simulations. Random conductances g_{exc} and g_{inh} were simulated using an Ornstein-Uhlenbeck process with $\tau_{\text{exc}} = 2.5$ ms and $\tau_{\text{inh}} = 6.1$ ms as characteristic time constants for the excitatory and inhibitory components respectively [13, 14]. The synaptic current is given by

$$\text{iExt} = g_{\text{exc}}(V - E_{\text{exc}}) + g_{\text{inh}}(V - E_{\text{inh}}) \tag{2}$$

where g_{exc} (g_{inh}) is the total excitatory (inhibitory) conductance and $E_{\text{exc}} = 0$ mV ($E_{\text{inh}} = -80$ mV) is the corresponding reversal potential [13]. The mean and standard deviation of the excitatory and inhibitory conductances were varied in independent simulations.

3 Results

3.1 Different Neurons Have Action Potentials of Different Metabolic Efficiencies

In this report, we use eight different single compartment Hodgkin-Huxley models from the literature, exhibiting action potentials (AP) with different metabolic characteristics. AP waveforms for these models are shown in Figure 1a and were generated by application of a 1 ms minimum amplitude suprathreshold current pulse. While all eight APs follow a relatively similar time course, their metabolic cost (calculated as the total sodium charge transfer) and their metabolic efficiency vary significantly (Fig. 1b). The metabolic efficiency is defined as the ratio between the capacitive minimum and the total sodium load, the capacitive minimum being defined as the smallest charge transfer needed to achieve the observed depolarization. As all APs peak in the same positive voltage range, the efficiency and the metabolic cost are linearly anti-correlated (not shown; $R^2 = 0.92$, $p = 2 \cdot 10^{-4}$). The metabolic cost of APs is also correlated with their height ($R^2 = 0.61$, $p = 0.02$) but not with their width ($p = 0.21$).

3.2 The Metabolic Efficiency of Neurons Is Dependent on Their Firing Frequency

Next, in order to test how the firing frequency affects the energetic efficiency of these models, we stimulated them using three different input scenarios. All

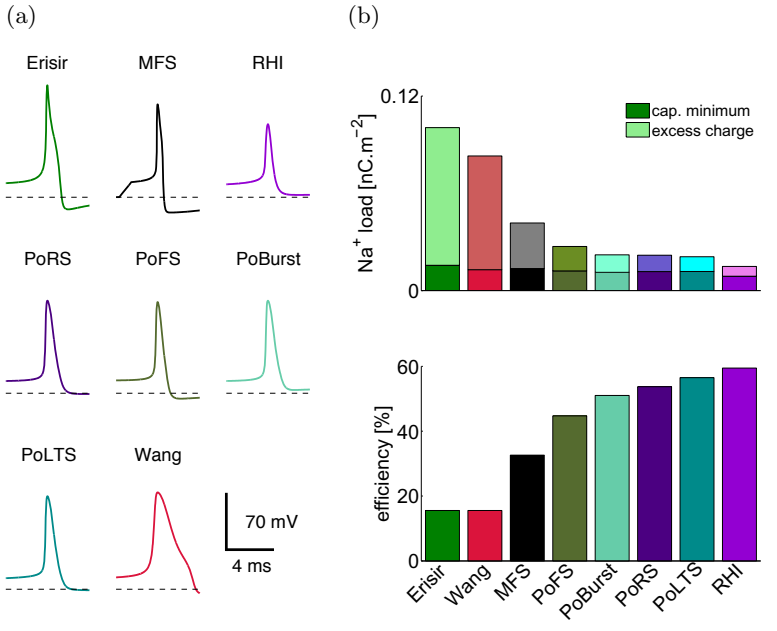

Fig. 1. Different neurons have action potentials of different metabolic efficiencies. **(a)** Action potential waveforms elicited by a single depolarising current pulse for eight different neuron models (see text). The dotted line marks −70 mV. **(b)** Metabolic cost (top) and metabolic efficiency (bottom) associated with the eight action potentials in (a). The capacitive minimum is defined as the smallest charge transfer needed to achieve the observed depolarisation. The efficiency is calculated as the ratio between the capacitive minimum and the total sodium load.

models were driven by: (i) a constant current input, (ii) a random current input and (iii) random excitatory and inhibitory conductances. For each scenario, the amplitude of the stimulation was increased in consecutive simulations. Figure 2 shows the metabolic cost per second plotted versus the frequency for three typical models. In each case, the total sodium load was calculated in two different ways, first adding the cost of triggering the APs (2/3 of the input current or 2/3 of the excitatory conductance, see [4]) to the cost of generating the APs (total ionic charge flowing through sodium channels) and second, including only the cost of generating the APs. While for some models the metabolic cost follows almost exactly the cost one can estimate by multiplying the cost of an individual AP by the frequency (Figs. 1b and 2c), other models deviate significantly from this naive estimate as their effective cost only marginally increases beyond a certain level at high frequencies (Fig. 2a). For each model, this behavior is consistent across all three stimulation paradigms.

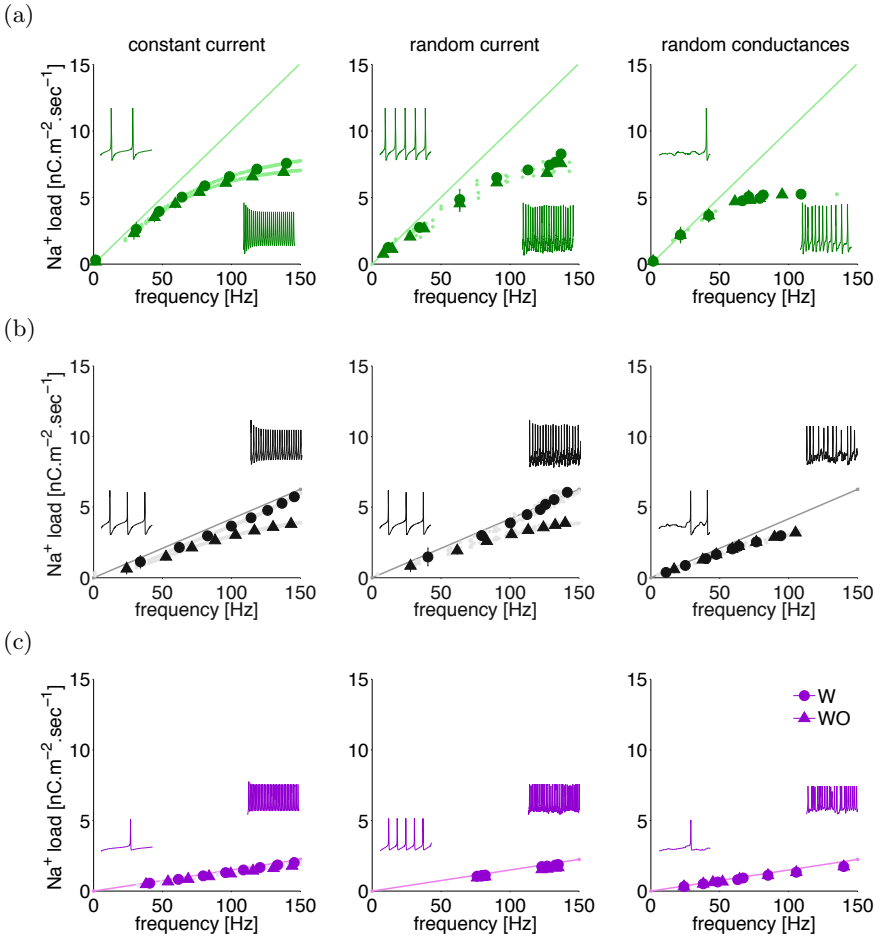

Fig. 2. The metabolic load per second is reported versus the achieved frequency for different input scenarios for the Erisir model (a), the MFS model (b) and for the RHI model (c). From left to right: constant current input, random current input and random conductances input. In each case, the metabolic cost is calculated using the sodium current(s) only (WO; triangles) or including the cost of the input (W; circles; 2/3 of the input current or 2/3 of the excitatory input conductance). The smaller dots represent individual simulations. The symbols were obtained by averaging neighbouring points using k-mean clustering. In each case, the expected cost obtained by multiplying the cost of an individual action potential as in Figure 1 by the frequency is plotted as a solid line. In each panel, two 400 ms sample spike trains are plotted (100 ms for constant current), one obtained at low frequency and one obtained at high frequency.

3.3 Inefficient Action Potentials Save More Energy with Increasing Firing Frequencies

In order to assess if deviations from the naive metabolic cost relate to the basic characteristics of action potentials, we defined a savings measure S. For each

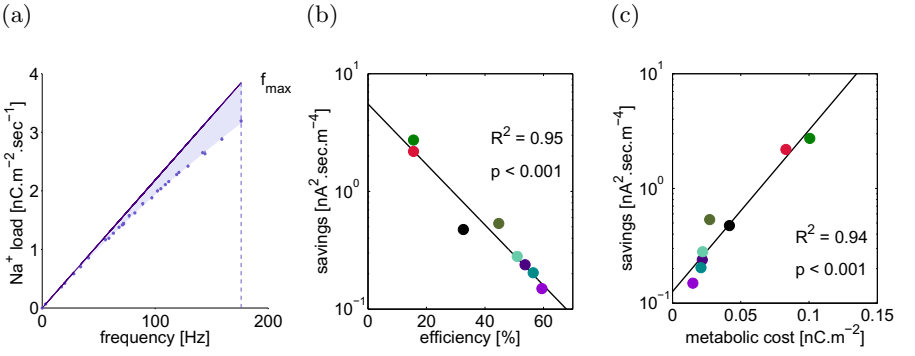

Fig. 3. Models with metabolically inefficient action potentials save more energy with increasing frequencies. **(a)** The savings measure S for the PoRS model (shaded area). S is calculated by integrating the difference between (i) the cost expected by multiplying the cost of an individual action potential by the frequency (dark solid line) and (ii) the actual cost obtained in the random conductance input scenario (symbols). The whole is then normalised by the observed peak frequency for that model ($f_{\max}$). For the purpose of integration, the actual cost is fitted by a polynomial function. **(b)** S is plotted versus the efficiency as measured in Figure 1 for all the models considered. A linear regression was performed on $\log(S)$ (solid line, R^2 and p values). **(c)** Same as in (b) with S plotted versus the metabolic cost as measured in Figure 1.

model, S is calculated by integrating the area comprised between the naive sodium load estimated from the cost of isolated APs and the effective sodium load as obtained when the model is driven by random conductances. As not all models reach the same maximal frequency, this area is integrated between 0 Hz and the peak frequency ($f_{\max}$) and then normalized by $f_{\max}$ (Fig. 3a). Figure 3b and c show that the savings measure S is exponentially related to the APs metabolic cost and efficiency. In other words, the more costly and less efficient an action potential, the more the model deviates from a naive estimate based on the cost of an isolated action potential. $\log(S)$ is also weakly linearly correlated to the height of APs (not shown; $R^2 = 0.59$, $p = 0.03$) but not to their width ($p = 0.18$).

4 Discussion

The high energy consumption of the brain is a constraint on information processing [15]. That consideration has motivated numerous studies addressing the energetics of the brain from the perspective of coding and network design [4, 15, 16] or from the perspective of channel kinetics [2, 3, 5]. The present study follows this tradition but specifically addresses questions related to channel kinetics with consequences for coding efficiency. Based on the original findings of Hodgkin and Huxley [6], it was assumed until recently that neurons are relatively metabolically inefficient at generating action potentials. This concept was recently invalidated

by two experimental studies showing that mammalian neurons are at least twice as efficient as initially thought and sometimes nearing metabolic optimality [3, 5]. Unfortunately, inefficient action potentials have entered most calculations about brain energy metabolism [4, 17], which now need to be revised accordingly. More recent energy budgets [1, 3, 2] suggest that the largest position in the brains energy budget is dedicated to synaptic transmission, i.e. reversing ion movements occurring at postsynaptic terminals and in dendrites, immediately followed by action potentials.

Intriguingly, the work by Carter and Bean suggests that pyramidal neurons tend to generate more efficient APs than fast-spiking inhibitory neurons [5]. It is usually postulated that metabolic efficiency of fast-spiking neurons is traded against the ability to spike faster and that this is permitted by shorter action potentials and incomplete inactivation of sodium channels [5, 7]. In this paper, we have used eight different published Hodgkin-Huxley models that cover the range of metabolic efficiencies observed in the brain (Fig. 1b). Applying three different stimulation paradigms, we observe that the overall metabolic cost is heavily dependent on the firing frequency (Fig. 2) and tends to saturate at values lower than the cost estimated from isolated action potentials. Furthermore, we show that the logarithm of the energy savings of a model are inversely proportional to the efficiency and directly proportional to the metabolic cost of eliciting an isolated AP (Fig. 3). Taken together, these results suggest an evolutionary mechanism by which inefficient action potentials are tuned to operate at higher frequencies than efficient ones. Our results demonstrate that metabolic efficiency cannot be considered only in terms of isolated action potentials but must be studied over a range of meaningful frequencies. They also suggest that metabolically inefficient action potentials do not represent a trade-off but instead specifically take advantage of their ion channels dynamics when firing action potentials in rapid sequences. As a consequence, networks of fast-spiking inhibitory neurons might constitute a very cost-effective method for the brain to compute [18]. A systematic study of if and how these findings transfer into an action potential-dependent optimal information capacity per second and per energetic load is currently under way.

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