



# Conduction velocity costs energy

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## Abstract

Hodgkin and Adrian's 1975 hypothesis that the squid axon is optimized for maximum conduction velocity is flawed by (i) the inaccurate value of its prediction for channel density, and (ii) the prohibitive energetic expense entailed by their prediction. Here we investigate the metabolic cost of conduction velocity. By manipulating ion channel density or by manipulating the Nernst battery voltages, we demonstrate that action potential velocity has a significant metabolic cost. Thus, in addition to the cost of information transmission (Neural Comput. 8(1996) 531 [9]), there is a cost associated with the timely arrival of such transmitted information.

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## 1. Introduction

It is well known that metabolic requirements in the CNS are large in comparison to other organs. The human brain accounts for 20% of resting oxygen consumption even though it comprises only 2% of the body's weight. In addition, vulnerability to ischemia in mammals underscores the tight constraint on O<sub>2</sub> supply: loss of consciousness can occur in as little as 7 s after stopping blood flow to the brain [10].

Compared to vegetative metabolism, the metabolic requirements of neurophysiological function are quite large. In rabbit retina 50% of the energy generated is used

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for  $\text{Na}^+$ -transport and glycolytic metabolism in a flash-stimulated environment could increase by a factor as high as 2.3 [3]. In brain, as in retina, the margin of safety in the balance between energy supplies and demand is quite small implying that the two are closely matched. This places a premium on energetic efficiency.

In previous work [11] the authors demonstrated the unsatisfactory nature of Hodgkin and Adrian's proposal [1,7] that the squid has evolved its giant axon to maximize conduction velocity of its action potential. Conduction velocity can be increased by increasing fast  $\text{Na}^+$ -channel density up to a point; eventually however, the extra capacitance associated with increasing the channel density begins to limit the velocity, suggesting an optimal channel density for maximum conduction velocity. To evaluate this proposal, the shape and speed of the Hodgkin and Huxley action potential versus the experimentally recorded trace (see Fig. 1) had to be improved in the rising phase. Our aim was to bring the modeled action potential into agreement with the experimental action potential in order to produce a more credible analysis of Hodgkin's velocity optimization hypothesis. Unfortunately, even with significant improvements to the accuracy of the shape and speed of the rising phase, Hodgkin's maximum velocity hypothesis still predicts an ion channel density that is nearly three-fold higher than the biological value.

Motivated by this prediction error, we proposed that the substantial cost of velocity explains why velocity alone cannot be used as an optimizing function. Thus, we hope to explain, in part, the Attwell and Laughlin estimate that action potential production comprises 47% of total energy usage in grey matter [4].

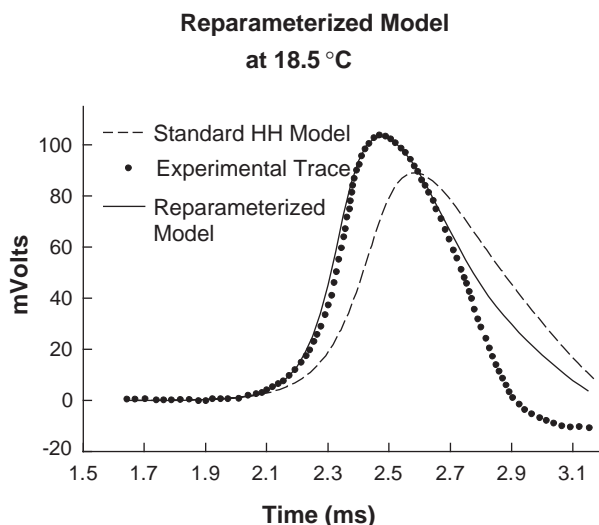


Fig. 1. The reparameterized model previously described [10] provides an action potential that matches the shape, height and propagation speed of the rising phase of biological action potential. The improvement from the original HH model (shown) was essential for the analysis of the cost and benefits associated with conduction velocity in the squid axon.

## 2. Methods

All simulations were performed at 18.5°C using the simulation environment NEURON [6]. The axon geometry was chosen to reflect the anatomy of the squid giant axon with a fiber length of 10 cm and a fiber diameter of 476  $\mu\text{m}$ . The passive electrical characteristics were chosen so that the resting conductivity was 0.036 S/cm<sup>2</sup> and the resting capacitance was 1.01  $\mu\text{F}/\text{cm}^2$  [8]. The membrane capacitance was composed of a voltage independent contribution of 0.88  $\mu\text{F}/\text{cm}^2$  from the lipid bilayer by itself [5], and a voltage-dependent contribution of the channel gating capacitance that varied from 0.13  $\mu\text{F}/\text{cm}^2$  at rest to 0  $\mu\text{F}/\text{cm}^2$  at large depolarization [11]. Unless otherwise stated, the Nernst potentials for Na<sup>+</sup> and K<sup>+</sup> were 50 and –77 mV, respectively, while the leak potential was adjusted to maintain a net rest current of zero.

Measurements of the propagation velocity were achieved by noting the times at which an arbitrary point on the wave front passed two positions located at 6 and 8 cm along the axon. Resolving the axon into 3000 conjoined segments and using time steps of less than 25  $\mu\text{s}$  achieved the requisite computational accuracy  $\mu\text{s}$ . Using the Crank–Nicholson scheme, higher resolution simulations have shown that the results are insensitive to the longest time step used (25  $\mu\text{s}$ ).

The active electrical characteristics of the membrane such as the ion channel conductance and the voltage-dependent gating capacitance were implemented in the manner previously described [11]. We turn now to a discussion of energetic calculations of action potential production and the relation of metabolic cost to velocity.

### 2.1. Calculation of metabolic cost

Although it may seem difficult to ascribe a definite cost to conduction velocity, it is intuitively clear that the velocity of an action potential is well established over the rising phase and depends very little on the events that occur beyond the peak. This dependence would seem to be exactly true once the steady-state conditions of a traveling wave have been established. Indeed, conduction velocity can be approximately calculated based on the time constant of the exponentially rising wave front at the foot of the action potential [1,2]. Thus we associate the metabolic cost of velocity with the cost of the rising phase. Specifically, the Na<sup>+</sup> current was integrated over the course of the rising phase from a nominal level of 0.01 mV above rest to the peak of the action potential. Based on the Na<sup>+</sup>/K<sup>+</sup> ATPase pump, this value (integrated flux up to peak) is proportional to the ATP required to maintain proper intracellular Na<sup>+</sup>/K<sup>+</sup> ion concentrations.

### 2.2. Current through the leak conductance

In each simulation, we have taken care that the alteration of the selective parameters such as channel density and Nernst battery strength did not alter either the resting membrane potential or the resting membrane conductance. At rest, the

net ion current must be zero:

$$i_{\text{Na}} + i_{\text{K}} + i_{\text{L}} = g_{\text{Na}}(V_{\text{R}} - E_{\text{Na}}) + g_{\text{K}}(V_{\text{R}} - E_{\text{K}}) + g_{\text{L}}(V_{\text{R}} - E_{\text{L}}) = 0. \quad (1)$$

The resting membrane conductance is fixed at the biological value of  $0.036 \text{ S/cm}^2$  [8]:

$$g_{\text{Na}} + g_{\text{K}} + g_{\text{Na}}^{\text{L}} + g_{\text{K}}^{\text{L}} = 0.036 \text{ S/cm}^2, \quad (2)$$

where  $g_{\text{Na}}^{\text{L}}$  and  $g_{\text{K}}^{\text{L}}$  are the passive leak conductance values and we have tacitly assumed leak current to be composed of  $\text{Na}^+$  and  $\text{K}^+$  currents. The values for  $g_{\text{Na}}^{\text{L}}$  and  $g_{\text{K}}^{\text{L}}$  can be derived from Eqs. (1) and (2) and the leak current may be written as

$$i_{\text{L}} = g_{\text{Na}}^{\text{L}}(V_{\text{R}} - E_{\text{Na}}) + g_{\text{K}}^{\text{L}}(V_{\text{R}} - E_{\text{K}}) \quad (3)$$

with

$$g_{\text{Na}}^{\text{L}} = \frac{g_{\text{K}}(V_{\text{R}} - E_{\text{K}}) + g_{\text{Na}}(V_{\text{R}} - E_{\text{Na}}) + (0.036 - g_{\text{K}} - g_{\text{Na}})(V_{\text{R}} - E_{\text{K}})}{E_{\text{Na}} - E_{\text{K}}}, \quad (4)$$

$$g_{\text{K}}^{\text{L}} = 0.036 - g_{\text{K}} - g_{\text{Na}} - g_{\text{Na}}^{\text{L}}. \quad (5)$$

### 2.3. Variation of the selective parameters

Throughout the course of our simulations we have varied either channel density or the Nernst battery strengths to simulate the selective pressures that will stabilize at the optimum biological values. In the former case,  $\text{Na}^+$ ,  $\text{K}^+$ , and leak channel densities were varied in concert by multiplying  $\bar{g}_{\text{Na}}$ ,  $\bar{g}_{\text{K}}$ , and  $g_{\text{L}}$  by a dimensionless number  $c$  called the relative channel density.  $\text{Na}^+$  and  $\text{K}^+$  channel densities were not changed individually while keeping the other fixed because this led to unrealistic passive leak conductance values for each ion channel. In the latter case, the individual Nernst batteries were changed in concert by scaling the electrochemical potential differences calculated at rest by a dimensionless number  $b$  called the relative battery strength. Based on the Nernst equation, realistic values of  $b$  cannot be expected to stray very far from unity; however, we have included a large range of  $b$  values for the purposes of establishing trends and comparisons. As an example, the Nernst battery strengths  $E_i^*$  are chosen to satisfy:  $b(V_{\text{R}} - E_i) = V_{\text{R}} - E_i^*$ , where the  $E_i$  are the biological values of the Nernst batteries for each ion. For instance, if  $b = 2$ , then the  $\text{Na}^+$  reversal potential changes from 50 to 165 mV, and for  $\text{K}^+$  the change is from  $-77$  to  $-89$  mV. In each case, the procedures were chosen because they ensured a resting potential of  $-65$  mV.

## 3. Simulation results

Out of the many possible parameters that we could have used in our simulations, we have chosen to focus on just two: channel density and the Nernst battery strength. The premise of our program is that a specified optimization function—

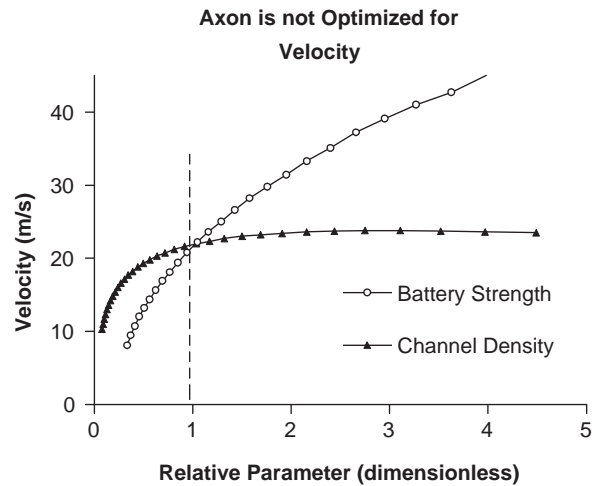


Fig. 2. The choice of conduction velocity as an optimization function fails to optimize at the biological value of either channel density or electrochemical potentials (i.e. Nernst battery voltages). The units of the abscissa are relative, i.e., dimensionless; the observed, biological value of channel density and Nernst batteries are therefore unity, and this value is indicated by the vertical dashed line.

velocity in this case—will be maximized at the biological values of the chosen parameters if it is indeed the evolved optimization function, or an approximation thereof.

In Fig. 2, we show the dependence of conduction velocity upon both the relative channel density and the relative Nernst battery strength. These relative parameters are adjusted in the manner described in Methods. It is clear that the squid axon is not optimized for velocity alone. In the case of channel density, velocity rises rapidly at first before it reaches a broad peak at a relative channel density of 2.6. The curve parameterized by relative battery strength never optimizes and continues to rise well outside the biological range of battery strength. The biological values are represented by unity for each relative parameter and are marked by the vertical dashed line.

A clear demonstration of why velocity alone does not approximate a workable optimization function can be seen in Fig. 3. Here, our primary assertion—that velocity costs energy—can readily be seen. In two separate parameterizations the metabolic cost integrated over the wave front in terms of  $\text{Na}^+$ -flux is a monotonic increasing function of velocity. Increasing channel density eventually leads to the steepest increases at about 23 m/s which is in the vicinity of the maximum achievable velocity. Large battery voltages produce a nearly linear variation in velocity and energy use at this point. Similar results, i.e., a monotonically positive relationship, are produced by increasing axon diameter.

It may be argued that the broadness of the peak in Fig. 2 is indicative of a soft selective pressure that permits a range of conductances around the true optimum. However, the steep dependence of energetic cost upon velocity that we see in Fig. 3 precludes this claim. When either channel density or Nernst battery strength are the

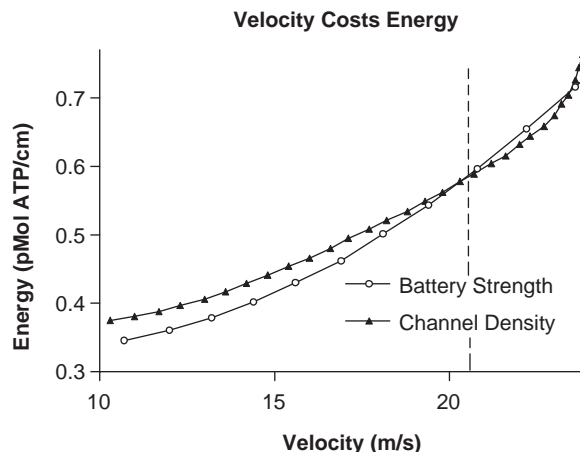


Fig. 3. The energetic cost of velocity is a monotonic increasing function that more than doubles over the biological range of conduction velocities. The significant metabolic costs for velocity suggests that energy consumption be included in any future choice of an optimization function.

selective parameters, the metabolic demand placed upon velocity more than doubles throughout the biological range of velocities. These cases emphasize the importance of metabolic constraints when conjecturing a function which evolution has optimized.

#### 4. Conclusion

Using two parameters, the results of our simulations have shown that velocity alone is not a viable optimization function for the squid axon: neither channel density nor Nernst battery strength optimizes velocity at the biological values. Furthermore, we demonstrate the inadequacy of velocity considerations alone: any benefits of an increased velocity is mitigated by a substantial metabolic penalty; i.e., velocity costs energy. In the most simplified approach, we suggest an optimization function  $\xi$  whose general form satisfies the following constraints: (i)  $\xi$  is a monotonic increasing function of velocity, (ii)  $\xi$  is a monotonic decreasing function of energy. An obvious example is the quotient of velocity and energy; however, other constraints may also and probably will, play a role in future analysis.

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