Conduction Velocity Costs Energy

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Abbreviated title: Conduction Velocity Costs Energy

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Abstract

Hodgkin's 1975 hypothesis that the squid axon is optimized for maximum conduction velocity is flawed by its approximate value and the prohibitive energetic expense of his prediction. By considering the importance of metabolic demands placed on neurophysiological function, we investigate the metabolic cost of conduction velocity. In two separate parameterizations involving the manipulation of ion channel density and the Nernst battery strength, we find that the metabolic cost for velocity is significant and must be considered as energy expenditure in brain.

Keywords: Squid; Optimization; Metabolic cost; Conduction velocity

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_2 supply: loss of consciousness can occur in as little as seven seconds after stopping blood flow to the brain [9].

Compared to vegetative metabolism, the metabolic requirements of neurophysiological function are quite large. In rabbit retina 50% of the energy generated is used for Na^+ transport and glycolytic metabolism in a flash-stimulated environment could increase by a factor as high as 2.3 [5]. Even though the retina uses about 50% more energy than grey matter on a per gram basis [2], function-related increases in glucose utilization in brain indicate that metabolic requirements are large during activity compared to rest [6,10]. In brain, as in retina, the margin of safety in the balance between energetic supply 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 found significant error in Hodgkin's proposal [3,8] that the squid has evolved its giant axon to maximize conduction velocity of its action potential. Conduction velocity increases monotonically with the fast Na^+ channel density; however, the extra capacitance associated with increasing the channel density begins to limit the velocity, suggesting an optimum channel density for maximum conduction velocity. The disagreement between the shape and speed of the Hodgkin and Huxley action potential and the experimental trace (see figure 1) motivated us to make the necessary corrections to the velocity dependent 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. 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.

Citing this difference as an unacceptable error, we propose that the substantial cost of velocity explains why velocity alone cannot be used as an optimizing function. Indeed, the energetic cost of the wave front increases approximately in proportion to the channel density. Equivalently, as we increase the velocity beyond the biological value of 21.3 m/s (at 18.5 ^{o}C), the energetic cost becomes prohibitive.

Methods

All simulations were performed at 18.5 ^{o}C using the simulation environment NEURON [7]. 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 μm. The passive electrical characteristics were chosen so that the resting conductivity was 0.036 S/cm^2 and the resting capacitance was 1.01 $\mu F/cm^2$. The membrane capacitance was composed of a voltage independent contribution of 0.88 $\mu F/cm^2$ from the lipid bi-layer by itself, and a voltage dependent contribution of the channel gating capacitance that varied from 0.13 $\mu F/cm^2$ at rest to 0 $\mu F/cm^2$ at large depolarization. Unless otherwise stated, the Nernst potentials for Na^+ and K^+ were 50 mV 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 cm and 8 cm along the axon. The requisite computational accuracy was achieved by resolving the axon into 3000 conjoined segments and using time steps of less than 25 μs. Using the Crank-Nicholson scheme, higher resolution simulations have shown that the results are insensitive to the longest time step used (25 μs).

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.

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 [3,4]. Thus we associate the cost of conduction velocity with the cost of the velocity dependent rising phase. We measure this cost by measuring the net influx of Na^+ ions that traverse the membrane between the time at which the membrane is depolarized to a nominal level (0.01 mV) until the peak of the action potential. We can then relate the influx of Na^+ ions to the quantity of ATP production required to drive the Na^+ / K^+ pump that maintains proper intracellular Na^+ / K^+ ion concentrations.

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:

$$i_{Na} + i_K + i_L = g_{Na}(V_R - E_{Na}) + g_K(V_R - E_K) + g_L(V_R - E_L) = 0 \qquad (1)$$

The resting membrane conductance is fixed at the biological value of $0.036\ S/cm^2$:

$$g_{Na} + g_K + g^L{}_{Na} + g^L{}_K = 0.036\ S/cm^2 \qquad (2)$$

where g^{L}_{Na} and g^{L}_{K} are the passive leak conductance values and we have tacitly assumed leak current to be composed of Na^{+} and K^{+} currents. The values for g^{L}_{Na} and g^{L}_{K} can be derived from equations 1 and 2 and the leak current may be written as:

$$i_L = g^L_{Na}(V_R - E_{Na}) + g^L_K(V_R - E_K) \tag{3}$$

with

$$g^L_{Na} = \frac{g_K(V_R - E_K) + g_{Na}(V_R - E_{Na}) + (0.036 - g_K - g_{Na})(V_R - E_K)}{E_{Na} - E_K} \tag{4}$$

$$g^L_K = 0.036 - g_K - g_{Na} - g^L_{Na} \tag{5}$$

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, Na^{+}, K^{+}, and leak channel densities were varied in concert by multiplying $\bar{g}_{Na}$, $\bar{g}_K$, and g_L by a dimensionless number *c* called the relative channel density. 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. As an example, the Nernst battery strengths E^*_i are chosen to satisfy: $b(V_R - E_i) = V_R - E^*_i$, where the E_i are the biological values of the Nernst batteries for each ion. In each case, the procedures were chosen because they ensured a resting potential of -65 mV.

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 – 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 figure 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 figure 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 Na^+ flux is a monotonic increasing function of velocity. The curve parameterized by channel density rises steeply and becomes double-valued at about 23 m/s indicating that a maximum achievable velocity is obtained. The last point shown on this curve in figure 3 corresponds to the peak of the curve parameterized by channel density in figure 2.

It may be argued that the broadness of the peak in figure 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 figure 3 precludes this claim. When either channel density or Nernst battery strength are the selective parameters, the metabolic demand placed upon velocity more than doubles throughout the biological range of velocities. These cases emphasize the importance of considering metabolic constraints when conjecturing a function which evolution has optimized.

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. We have also demonstrated the probable reason for the inadequacy of velocity considerations alone: the benefit of an increased velocity incurs a substantial metabolic penalty, i.e., velocity costs energy. In the most simplified approach, we suggest an optimization function ξ whose general form satisfies the following constraints: i) ξ is a monotonic increasing function of velocity, ii) ξ 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.

In our treatment, the evolutionary biology of the squid axon has focused entirely upon the electrophysiological properties of the action potential's wave front. Our approach has been justified on the basis that the benefit of conduction velocity and its corresponding metabolic penalties can be considered independent of other more complex considerations such as the refractory period and spiking dynamics. Indeed, the squid axon mediates an escape response, and the transmission speed of a single spike may be of primary importance to the organism. The importance of metabolic efficiency is considered as an example in the case of the squid axon; however, the delicate balance of energy supply and demand in the CNS suggests that metabolic efficiency is important for all unmyelinated axons.

Acknowledgments

This work was supported by NIH MH63855 and RR15205 to WBL, the Meade Munster Foundation, and the Department of Neurosurgery.

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Figure Legends

Figure 1: The reparameterized model previously described [11] has provided an action potential that matches the shape, height and propagation speed of the biological action potential. The improvement from the original HH model (shown for comparison) was essential for the analysis of the cost and benefits associated with conduction velocity in the squid axon.

Figure 2: The choice of conduction velocity as an optimization function fails to optimize at the biological value of either channel density or electrochemical potential (i.e. Nernst battery strength). In dimensionless units, the biological value of relative channel density and relative battery strength is unity and is marked by the vertical dashed line.

Figure 3: The energetic cost of velocity is a monotonic increasing function that more than doubles over the biological range of conduction velocities. The prohibitive constraint of metabolic costs for velocity makes its inclusion necessary in any future choice of an optimization function.

FIG 1

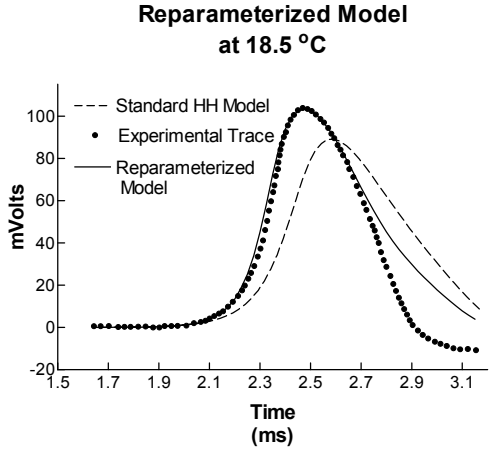

FIG 2

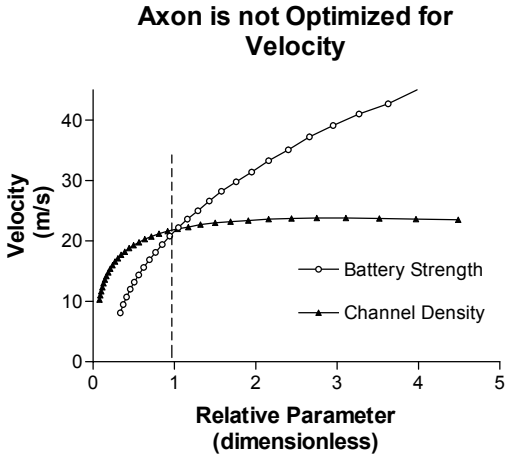

FIG 3