



Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Neurocomputing 65–66 (2005) 907–913

NEUROCOMPUTING

www.elsevier.com/locate/neucom

Conduction velocity costs energy

Thomas Sangrey, William B Levy*

Department of Neurosurgery, University of Virginia Health System, P.O. Box 800420, Charlottesville, VA 22908-0420, USA

Available online 15 December 2004

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.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Squid; Optimization; Metabolic cost; Conduction velocity

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 O₂ 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

*Corresponding author. Tel.: +1 434 924 9996; fax: +1 434 982 3829.

E-mail address: wbl@virginia.edu (W. B Levy).

for 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 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].

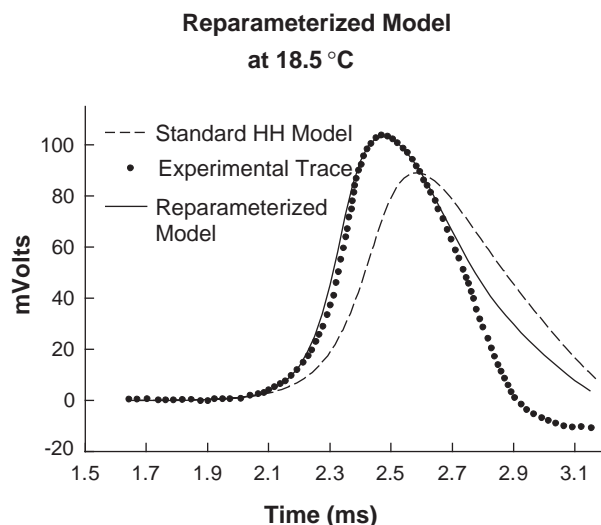


Fig. 1. The reparameterized model previously described [10] provides an action potential that matches the shape, height and propagation speed of the rising phase of biological action potential. The improvement from the original HH model (shown) was essential for the analysis of the cost and benefits 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 μm . The passive electrical characteristics were chosen so that the resting conductivity was 0.036 S/cm² 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⁺ and K⁺ 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 μs achieved the requisite computational accuracy 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.

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⁺ 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⁺/K⁺ ATPase pump, this value (integrated flux up to peak) is proportional to the ATP required to maintain proper intracellular Na⁺/K⁺ 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 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_{Na}^{L} and g_{K}^{L} 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_{Na}^{L} and g_{K}^{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, 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. Na^+ and 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 Na^+ reversal potential changes from 50 to 165 mV, and for 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—

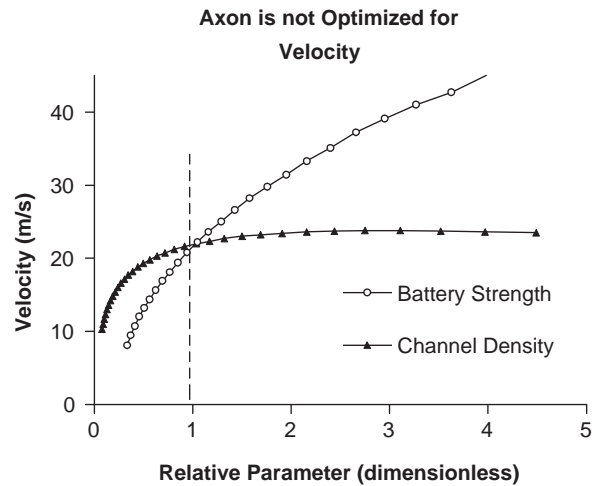


Fig. 2. The choice of conduction velocity as an optimization function fails to optimize at the biological value of either channel density or electrochemical potentials (i.e. Nernst battery voltages). The units of the abscissa are relative, i.e., dimensionless; the observed, biological value of channel 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 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

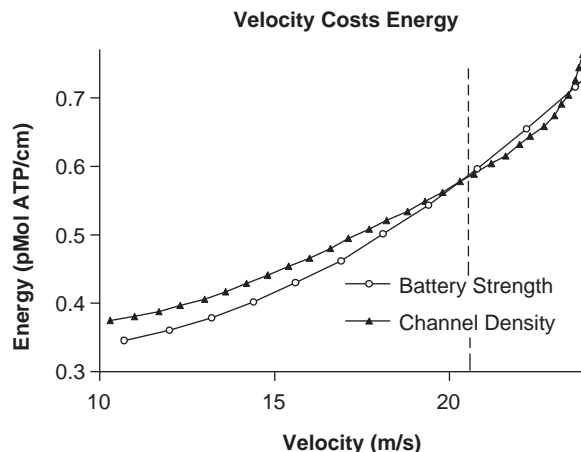


Fig. 3. The energetic cost of velocity is a monotonic increasing function that more than doubles over the biological range of conduction velocities. The significant metabolic costs for velocity suggests that energy consumption be included in any future choice of an optimization function.

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 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.

Acknowledgements

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

References

- [1] R.H. Adrian, Conduction velocity and gating current in the squid giant axon, *Proc. R. Soc. Lond. B* 189 (1975) 81–86.
- [2] R.H. Adrian, W.K. Chandler, A.L. Hodgkin, Voltage clamp experiments in striated muscle fibers, *J. Physiol.* 208 (1970) 607–644.
- [3] A. Ames, Energy requirements of CNS cells as related to their function and to their vulnerability to ischemia: a commentary based on studies on retina, *Can. J. Physiol. Pharmacol.* 70 (1991) S158–S164.
- [4] D. Attwell, S.B. Laughlin, An energy budget for signaling in the grey matter of the brain, *J. Cereb. Blood Flow Metab.* 21 (2001) 1133–1145.
- [5] L.J. Gentet, G.J. Stuart, J.D. Clements, Direct measurements of specific membrane capacitance in neurons, *Biophys. J.* 79 (2000) 314–320.
- [6] M.L. Hines, N.T. Carnevale, The NEURON simulation environment, *Neural Comput.* 9 (1997) 1179–1209.
- [7] A.L. Hodgkin, The optimum density of sodium channels in an unmyelinated nerve, *Phil. Trans. R. Soc. Lond. B* 270 (1975) 297–300.
- [8] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, *J. Physiol.* 117 (1952) 500–544.
- [9] W.B. Levy, R.A. Baxter, Energy efficient neural codes, *Neural Comput.* 8 (1996) 531–543.
- [10] R. Rossen, H. Kabat, J.P. Anderson, Acute arrest of cerebral circulation in man, *Arch. Neurol. Psychiatry* 50 (1943) 510–528.
- [11] T.D. Sangrey, W.O. Friesen, W.B. Levy, Analysis of the optimal channel density of the squid giant axon using a re-parameterized Hodgkin–Huxley model, *J. Neurophysiol.* 91 (2004) 2541–2550.

Thomas Sangrey studied physics at Temple University and received a Ph.D. in condensed matter physics from Wesleyan University in 2003. He is currently a research associate in William B. Levy's Laboratory at the University of Virginia where he uses a computational biophysics approach to study the evolution of the brain.

William B. Levy earned a B.A. in Psychology from Princeton University and a Ph.D. in Psychobiology from the University of California, Irvine. He served as Assistant Professor of Psychology at the University of California, Riverside from 1974 until 1979. In 1979 he joined the faculty at the University of Virginia where he is currently a professor in the departments of Neurological Surgery and of Psychology.