Optimum ion channel properties in the squid giant axon

Robert K. Adair
Department of Physics, Yale University, New Haven, Connecticut 06520-8121, USA
(Received 10 July 2003; published 30 April 2004)

Evolutionary pressures are presumed to act so as to maximize the efficiency of biological systems. However, the utility of that premise is marred by the difficulties in defining and evaluating both the efficiency of systems and the character of the available variation space. Following Hodgkin and Adrian, we examine the character of voltage gated ion channels in the nonmyelinated giant axons of the squid and find that both the channel densities and channel transition rates have values that nearly optimize signal sensitivity as well as signal velocity.

DOI: 10.1103/PhysRevE.69.042902 PACS number(s): 87.16.Uv, 87.17.Nn, 87.16.Ac

Perhaps the quintessential question in science is "Why are things as they are?". In biology, it seems likely that evolutionary pressures drive biological mechanisms towards local maximum efficiencies. Thus many systems are supposedly as they are because they are maximally efficient in ensuring the survival and reproduction of the organism.

In 1975 Hodgkin [1] and Adrian [2] concluded that the density of voltage-gated Na^+ ion channels in the nonmyelinated giant squid axon is such as to maximize signal velocity in those axons. That axon carries the signal which activates the tail flip action that sends the squid out of danger. Thus the importance of that velocity to the survival of the animal can be considered to contribute to an evolutionary drive that sets the channel densities to maximize that signal velocity.

Here I extend their analyses, using the Hodgkin and Huxley (HH) [3] model of ion channel dynamics to show that the channel densities that are observed are such that also maximize the sensitivity of the axon system to signal pulses. Since the generation of an action pulse by a lower trigger voltage requires a smaller metabolic expenditure for signal transmission, evolution may drive the system to greater efficiency through minimizing that trigger voltage. Then I consider the domain transition rates that minimize that trigger voltage and, again, find that the known rates are those that lead to maximum sensitivity.

The parallel conductance diagram of Fig. 1 suggests the basic structure of the axon electrical system. According to the HH description the ion conductances derive from voltage dependent Markov transitions between states of the four independent domain elements that make up each ion channel. Thus, the channel conductance is voltage dependent and dependent on the voltage history and thus time.

I review briefly the basic Hodgkin-Adrian argument relating axon signal velocity to channel density.

From elementary cable theory, the velocity of transmission θ of a wave front down an axon varies as [4]

$$\theta \approx \left(\frac{G_m a}{2 R_i C_m^2} \right)^{1/2}, \tag{1}$$

where a is the axon radius, G_m is the specific membrane conductance in m^2/Ω, R_i is the specific cytoplasm resistivity in $\Omega\ m$, and C_m is the membrane capacitance per unit area.

[Hodgkin [1] states that he prefers a formulation, his Eq. (8), that mixes densities and transition rates. That recipe leads to a density for maximum velocity that is somewhat closer to the observed values. However, I choose to treat transition rates separately.]

The membrane conductivity is almost wholly due to the conductivity of the membrane Na and K ion channels, where I write, g_{Na} and g_K for individual channel conductivities. The channels contribute to the effective capacitance C_m through the translation of gating charge, across the membrane upon a transmembrane voltage change ΔV_m. Thus for each channel, $C_{Na}=q_{Na}/\Delta V_m$ and $C_K=q_K/\Delta V_m$, where q_{Na} and q_K are the gating charge transfers upon a change in membrane potential ΔV_m.

Assuming, plausibly, that most of the conductance of the membrane at the voltage rise from the leading edge of an action pulse is due to the Na channel conductivities, and that the capacitance at that time is generated by a base capacitance plus a contribution from the Na channels, we write, $C_m=C_0+NC_{Na}$ and $G_m=Ng_{Na}$ where N is the number of Na channels per unit area (m^2). Thus,

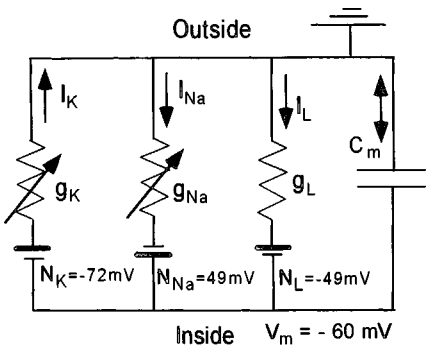

FIG. 1. Parallel conductance model for the HH description of the squid axon. The sodium and potassium conductances, g_{Na} and g_K, proportional to the channel densities, are voltage dependent and time dependent. The leakage conductance is constant. Ion pumps which keep the inside resting potential at approximately $V_m=-60$ mV are not shown; C_m is the membrane capacitance. The Nernst potential for Na is taken as 49 mV, the K potential as −72 mV, and the leakage potential as −49 mV.

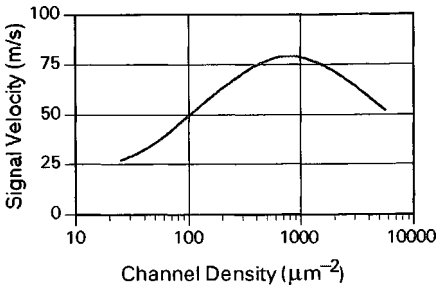

FIG. 2. The variation of axon pulse velocity with Na channel density according to Hodgkin Ref. [1], where the density is stated in channels per μm^2.

$$\theta = \left(\frac{aNg_{\mathrm{Na}}}{2R_i(C_0 + NC_{\mathrm{Na}})^2} \right)^{1/2}. \tag{2}$$

Then when N is small ($N \ll C_0/C_{\mathrm{Na}}$), the velocity will increase with N varying as $\sqrt{N}$. But when N is large ($N \gg C_0/C_{\mathrm{Na}}$), the velocity will fall off with increasing N, varying as $1/\sqrt{N}$.

Figure 2 shows the variation of velocity with channel density in an axon of radius $a=0.35$ mm, calculated using Eq. (2) from Hodgkin where I take $C_0=0.008$ F/m^2, $g_{\mathrm{Na}}=4$ pS Na [5,6] $C_{\mathrm{Na}}=10^{-17}$ F, $R_i=0.35$ Ω m [1], and the density N is the number of Na channels per μm^2. The peak velocity of 79 m/s occurs when $NC_{\mathrm{Na}}=C_0$ or $N=800$ channels per μm^2. However, the velocity varies slowly with channel density near that maximum and is still high for $125<N<330$, values that cover estimates made in different ways (see, Ref. [7] Tables 12.2 and 12.3). Hence, the channel densities are near that which generates maximum signal velocity.

From Eqs. (1) and (2), the velocity also varies as the square root of the axon radius; thus the giant axon. That size incurs development costs which are minimized by the proper choice of channel densities.

The impulse that generates the signals that are transmitted by axons must require some kind of energy expenditure. Hence, in many circumstances an organism is best served if the axon is sensitive to small signals, thus minimizing that expenditure. However, if that sensitivity is too great, the transmitted information may be degraded by signals generated by system noise. For large nonmyelinated axons noise is probably not a serious problem and the systems are best served if the threshold for signal generation is low. We consider characteristics of the axon system that will then minimize the threshold for the generation of a signal presuming that evolutionary forces may push systems towards a minimal threshold.

In particular, I examine the threshold for the generation of an action pulse in the nonmyelinated giant squid axon as a function of ion channel density from numerical calculations using the HH formulations to describe the pulse generation. Taking the channel conductivities from Conti *et al.* [5,6] as 4 pS per Na channel and 12 pS per K channel and the membrane conductivies from HH, the Na channel density is then 300 channels per μm^2 and the K channel density is 36 per μm^2. For the capacitance per unit area, I take C_0

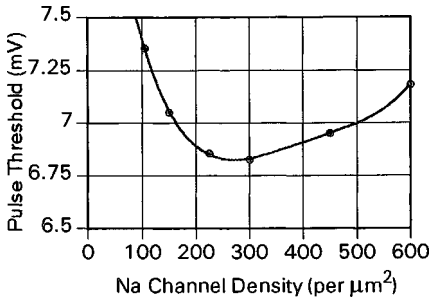

FIG. 3. The variation of signal threshold as a function of Na channel density where the density is stated in channels per μm^2.

$=0.01$ F/m^2. (The transfer of gating charge does not contribute to this capacitance.) Since the generation of the whole pulse, depolarization and repolarization, requires both Na and K channel activity, I keep the ratio of Na and K channel densities constant (at a value of 300/36) while I vary the overall density and vary the leakage conductivity likewise, thus keeping the resting potential at −60 mV.

Figure 3 shows the variation of the threshold for the generation of an action pulse as a function of the density of the Na channels. The minimum threshold value is near 300 Na channels per μm^2, in good agreement with estimates of that density.

The pulse shapes for signals just above the threshold values vary with channel densities. At extremely high, or low, densities, the generation of the action pulse will be compromised. Pulse shapes for moderate variations of the densities are shown by the solid line curves in Fig. 4.

At Na channel densities less than 100 per μm^2, the repolarization of the system after the pulse calculated from the HH equations was protracted and the system was correspondingly unstable.

While the overall densities of the voltage-gated ion channel systems in large unmyelinated axons are consistent with

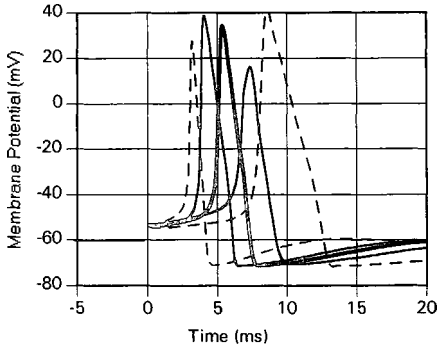

FIG. 4. Pulse shapes generated by signals just above threshold at time zero for different channel densities and different reaction rates. The heavy solid curve shows the pulse shape where the Na channel density is taken as 300 per μm^2 and the transition rates are those taken from HH. The solid curve to the right shows the pulse shape with the channel density at 600 per μm^2 and to the left for a channel density of 105 ppm. The dashed curve to the left shows the pulse shape at the standard channel density of 300 per μm^2 but with transition rates increased by a factor of 2; the dashed curve to the left show the shape at the standard channel density but the transition rates reduced by a factor of 0.5.

the view that they are generated by evolutionary optimization, the observed ratio of Na^+ channels and K^+ channels does not seem to derive from that source. The sensitivity to signals (or decrease in signal generating threshold) calculated using the HH equations seems to increase monotonically as the Na/K channel density ratio increases if that ratio is a free parameter. However, I suggest that this ratio is likely to be determined by the Na/K ion pumping ratio of 3:2 characteristic of the metabolically driven ion pumps [7] that establish the resting potential.

At that resting potential there is a certain amount of "leakage" ion flow. A small outward K^+ ion current passes through the small fraction of *K* channels open at that potential while a small Na^+ ion current passes into the axon through the fraction of open Na channels. Presumable, a balance is obtained through the pumps each of which removes about 300 Na^+ ions from the axon and inserts about 200 K^+ ions per second where the 3:2 ratio is set by the characteristics of the molecular pump process.

By direct calculation using the HH equations, at the nominal resting potential of −60 mV a current of about 275 000 K^+ ions per second pass out of each square micron of the axon and about 73 000 Na^+ ions per second pass in. While other currents (the HH "leakage" current) are presumed to balance the charge exchange, if axon Na^+ and K^+ ion concentration equilibria are to be established, the leakage fluxes of these ions must be countered by pumps. But the pumping ratio of 3:2 differs from theleakage ratio of about 1:4. However, the HH system relations may not be quite correct for polarized systems where the probability of the channel being open and conducting is very small. Also, there may be other small competing Na^+ and K^+ ion conductances that set the total ion current leakage ratio to match that of the pumps.

The complexity of the protein channel structures suggests the likelihood that there is a dense set of possible protein channel configurations and thus nature has a near continuum of transition rate choices to choose from. With this position in mind, I examined the variation of signal threshold as the transition rates were varied. In this exercise, I held again the ratio of the Na and K channel open-close rates to the HH values and used the channel densities derived from their membrane conductivities and the channel conductivities previously stated.

Figure 5 shows the variation of the signal threshold with respect to the channel transition rates relative to that stated by HH. Here, the signal threshold was determined while every HH transition rate [$\alpha_k(V_m)$ and $\beta_k(V_m)$ for the different HH domain types, $k=m,h$, and n] was increased, or decreased, together. For transition rates less than about one third of the canonical HH rates, the flow of current was not sufficient to generate pulses. The minimum threshold—and the maximum energy efficiency—is seen to occur at rates that are nearly equal to those derived by HH to fit their extensive data. Thus the system is maximally sensitive when driven at the rates that nature has provided.

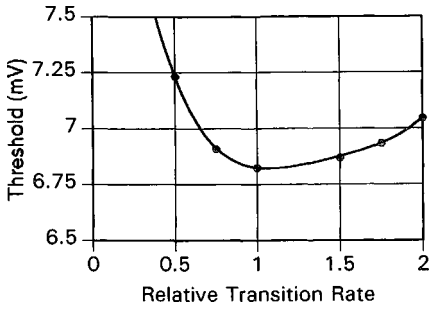

FIG. 5. The variation of signal threshold as a function of Na and K channel open-close transition rates described in terms of the ratio of the rates to the regular HH rates.

Of course, the pulse shapes vary with the transition rates. The dashed lines in Fig. 4 show pulse shapes for signals just greater than the threshold values for transition rates twice that of the HH rates and one-half of the HH rates.

We ask, "In the case of the giant squid axon, why are the channel densities as they are?". Assuming that the ratio of Na and K channel densities is determined otherwise, my direct calculations using the HH equations lead to two answers; the known densities lead to maximum signal velocities and the known densities lead to the greatest trigger signal sensitivity.

Then I ask a third question that does not seem to be closely related to the first two: "Why are the channel transition rates as they are?" and find that they have values that maximize trigger signal sensitivity.

In these inquiries, the channel densities and transition rates have been treated as orthogonal variables—there may be better optima that follow from combinations of different densities and transition rates. Also, the ratio of the Na and K channel densities was assumed to be set by the discrete ion pump ratio which is determined by structural factors and is not sensitive to modification by evolutionary pressures. However, there is no quantitative fit to that hypothesis.

I thank Professor F. J. Sigworth for his suggestion that I look into such optimizations.

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