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Fit of the dielectric anomaly of squid axon membrane near heat-block temperature to the ferroelectric Curie–Weiss law

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Abstract

In a 1969 experiment, Palti and Adelman reported that the capacitance of squid axon membrane rises sharply with temperature between 40 and 50°C. This phenomenon is here explained by the ferroelectric–superionic transition hypothesis, which also explains channel gating and other phenomena observed in excitable membranes. According to this hypothesis, gating in the Na channel is due to a first-order phase transition from a ferroelectric (closed) state to a superionic (open) state. From it, the dielectric permittivity of the Na channel, and hence the temperature-dependent component of membrane capacitance, is predicted to obey the ferroelectric Curie–Weiss law near the transition (heat-block) temperature. The Palti–Adelman data are fitted accurately by the predicted relationship. The parameters obtained permit an estimate to be made of the Curie constant of the channel, ~ 6400 K, consistent with an order–disorder ferroelectric. The Na channel appears to be a ferroelectric polymer component of a lyotropic lamellar liquid crystal.

Keywords: Sodium channel; Ferroelectric Curie–Weiss law; Order–disorder transition; Dielectric permittivity; Ferroelectric liquid crystals; Channel gating

1. Introduction

Excitability in nerve and muscle fibers depends on the electrical isolation of the interior of the cell from the exterior by the phospholipid bilayer of the plasma membrane, dual energy sources in the form of opposed Na^+ and K^+ concentration gradients across the membrane, and specialized macromolecules, the Na and K channels, which respond to voltage changes by switching their selective ion conductances on and off. Starting from a polarized membrane at resting potential, the Na channel initiates the action potential by sharply increasing the Na^+ conductance when the transmembrane field is decreased in a depolarization; the K channel, acting more slowly, restores the resting potential [1].

A number of mechanisms have been proposed to explain the gating action of the Na channel, but they generally do not provide an explicit physical link between membrane depolarization and the opening of the channel (reviewed in Refs. [2,3]).

However, one proposed model mechanism, the ferroelectric–superionic transition hypothesis [4–8] provides such a link. Its basic concept is that a transmembrane portion of the channel molecule, the ferroelectric channel unit, exists in an ordered state at low temperature and in a less ordered state at

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higher temperatures. In this model the ordered state exhibits spontaneous polarization reversible by an externally applied electric field, and so is ferroelectric [9,10]. In the high-temperature phase the permeant ions become itinerant and move through the channel as in a superionic conductor [11]. Further analyses and modifications of the ferroelectric–superionic transition hypothesis have appeared recently [12–14].

If the hypothesis is true, the dielectric permittivity of the Na channel would necessarily have to obey the Curie–Weiss law of ferroelectrics in the vicinity of a phase transition [15,16]. In a unique study, Palti and Adelman [17] measured the capacitance of squid-axon membrane as a function of temperature, finding an unexpected sharp rise in the 40–49°C range. It is the purpose of this paper to test the prediction of Curie–Weiss behavior against the data of Palti and Adelman [17]. A preliminary report has been presented [18].

2. Ferroelectricity in channels

Since ferroelectrics by definition exhibit spontaneous polarization reversible by an external field, they are characterized by polarization–field hysteresis [15,16]. The observation of conductance–voltage hysteresis in Na channels [19,20], thermal hysteresis in squid axon membrane [21], and hysteresis in Na activation and inactivation time constants [22] therefore suggests that the Na channel is ferroelectric [9,10].

Because an increase in temperature opposes the order required for maintenance of a ferroelectric phase, ferroelectrics generally exhibit a transition temperature, or Curie point, above which spontaneous polarization and hysteresis disappears. The phase above the transition temperature is less ordered and referred to as paraelectric [15,16]. Excitable cells exhibit an upper temperature limit, the heat-block temperature, above which no action potential is conducted [23,24]. Since the heat block can not be due to a failure of isolation in the bilayer or alteration in the ion concentrations of the electrolytes, it must be ascribed to one of the channels. Whether it is the Na channel or the K channel that fails at heat block has not been determined experimentally. However, since the action potential decreases to zero as the heat-block temperature is approached while the resting potential is little affected by temperature [23], it is most likely that heat block is due to a temperature-dependent change in the Na channel. If then the failure of excitability at heat block is due to a transition in the Na channel caused by elevation of the temperature to the heat-block temperature, and if a ferroelectric phase is necessary for the operation of the Na channel, it follows that the heat-block temperature and the ferroelectric transition temperature must be identical. This implies that the behavior of the Na channel near heat block should be similar to that of a ferroelectric near the Curie point.

The measured Na^+ currents through a population of voltage-clamped Na channels exhibit a rapid activation as the channels open in response to a suprathreshold step depolarization of the membrane and a slower inactivation on return to holding potential. These macroscopic currents are composed of unit currents through individual channels that open and close stochastically. According to the ferroelectric–superionic transition hypothesis, closed channels are in a ferroelectric state and open channels are in a paraelectric state [6].

A transition is said to be of the same order as the derivative of the Gibbs free energy that shows an abrupt change at the transition [25]. In single-channel transitions the electric field changes abruptly. Since the electric field is the first derivative of the Gibbs function with respect to electric polarization [15], the channel appears to be undergoing first-order transitions. This is also supported by the finding of thermal hysteresis [21], which only occurs in first-order transitions [16].

3. Channel gating

The thermodynamic theory of ferroelectrics shows that the Curie point rises with increasing electric fields [15,16]. This effect is sufficient to explain the stochastic opening of the Na channels when the membrane is depolarized [6]. The ferroelectric–superionic transition hypothesis explains the function of the resting potential: It provides an electric field sufficiently high to place the Na channels into a ferroelectric state. From this state the channel can be driven into a phase transition to a paraelectric state simply by lowering the electric field until the Curie point is below the actual temperature, i.e. by a threshold depolarization. The nonlinear equations arising from this model and their solutions have been explored [4–6,10,12–14].

In the new phase the Na channel is not only paraelectric but also permits fast conduction of Na^+, Li^+ and other metal and nitrogenous ions [2]. Materials with ion conductivities as high as 1 S/m and negligibly small electronic conductivity are called superionic conductors. Among these are crystalline Na^+ conductors such as β-alumina and Nasicon [26], as well as polymers, such as poly(ethylene oxide), which can form helical structures [11].

The determination of the primary sequence of the Na channel [27] has suggested that the membrane-spanning segments of the channel are α helices. Because their positive charges make the S4 segments the most likely candidates for the role of 'voltage sensors', they have been proposed as being involved in a phase transition [28]. Because of the large dipole moment of the helix [29], it has been proposed that the S4 segments undergo a helix–coil transition as a result of a channel depolarization, reducing the channel dipole moment and opening a transmembrane pathway of binding sites for permeant ions [30,31].

4. Curie–Weiss law

The transition from a ferroelectric to a paraelectric phase and the reverse transition are accompanied by a sharp increase in the dielectric permittivity ϵ, which varies with temperature, below T_C, according to

$$\epsilon = K/(T_0 - T), \quad T < T_C \tag{1}$$

and above T_C, according to

$$\epsilon = K'/(T - T_0'), \quad T > T_C, \tag{2}$$

where T_0 and T_0' are extrapolated Curie points lying above and below T_C respectively [16]. According to the thermodynamic theory of first-order ferroelectric transitions, the ratio of the slope $\partial(1/\epsilon)/\partial T$ just below T_C, $-K$, to that just above T_C, K', is -8 [16]. One of the implications of the ferroelectric–superionic transition hypothesis of the Na channel therefore is that its dielectric permittivity must obey Eqs. (1) and (2), referred to as the Curie–Weiss law of ferroelectrics. According to these equations, the predicted reciprocal dielectric permittivity $1/\epsilon$ in the vicinity of T_C is a discontinuous function of temperature (Ref. [16], p. 77, Fig. 3.4c). Below T_C it is a straight line with a negative slope, $-1/K$, and above T_C it has a positive slope, $1/K'$. The downward sloping line, if extended above T_C, intersects the T axis at T_0, above T_C, and the upward slope, if extended back, cuts the T axis at T_0'. Below T_C the material exhibits two stable polar states and hysteresis, while above T_C it exhibits a single nonpolar stable state and no hysteresis. Although no measurements have been published above heat block, this prediction can be tested below heat block, i.e. for $T < T_C$.

If the dielectric constant of the Na channels shows such a drastic increase with temperature near heat block, the membrane capacitance should reflect this behavior, although modified to account for the other components of the membrane, primarily the bilayer. A fluid mosaic membrane containing sodium channels can be considered to be a parallel array, so that the membrane capacitance per unit area C is

$$C = C_0 + C_{SC}, \tag{3}$$

where C_{SC} represents the capacitance per unit membrane area of the sodium channels, and C_0 that of the bilayer, K channels, pumps and other components. If a is defined as the area fraction occupied by the Na channels, L the membrane thickness and $\epsilon_0 = 8.854$ pF m^{-1}, then by Eq. (1)

$$C = C_0 + k/(T_0 - T), \tag{4}$$

where

$$k = \epsilon_0 aK/L. \tag{5}$$

From Eq. (4) it follows that $(C - C_0)^{-1}$ should be a linear function of temperature in a region below the transition temperature. This is a testable prediction of the ferroelectric–superionic transition hypothesis.

5. Data of Palti and Adelman

Measurements of membrane capacitance below the heat-block temperature were carried out in *Loligo* *pealei* by Palti and Adelman [17]. Palti and Adelman voltage clamped a squid axon to a repeated triangular ramp signal to obtain an approximately rectangular series of current steps, I_C. They evaluated the membrane capacitance per unit area C from the equation $I_C = C\ \mathrm{d}V/\mathrm{d}t$.

In their measurements of the effect of temperature on membrane capacitance from 3 to 49°C, Palti and Adelman [17] reported a large temperature coefficient of capacitance in the range 40–49°C. The data showed an increase in membrane capacitance, reaching values of 3 μF/cm^2 and with slopes as high as 23%/°C near 50°C. Palti and Adelman fitted their data with three continuous straight line segments. Their analysis of membrane polarization vs temperature suggests that the dielectric constant first increases with temperature and then reaches a plateau. They ascribe the break of the curve above 40°C to a phase transition of some component of the membrane, as in the present model. Unlike this model, however, is their belief that this transition is probably in the lipid bilayer. Such unusual dielectric behavior is not expected from the phospholipid bilayer; although lipids also exhibit phase transitions, a study by Raudino and Mauzerall [32] predicts only a weak dependence of lipid dielectric constant on temperature. Therefore the anomalous dielectric behavior of squid axon is probably a manifestation of one of the ion channels. Since the phenomenon occurs at the heat-block temperature it appears, by the argument used above to show that heat block is probably due to the Na channel, that the anomalous capacitance increase is also a manifestation of the Na channel. The question therefore arises as to whether the Palti–Adelman data on membrane capacitance versus temperature are consistent with that predicted from the application of the Curie–Weiss law to the Na channel.

6. Data fitting

The Palti and Adelman [17] data were digitized manually from the published graph. A statistical package, Minitab (Release 7.2, Minitab, Inc., State College, PA), was run on a Vax computer to fit the data to the Curie–Weiss law and an alternative hypothesis. Weighted linear regression was used to fit the 40 data points from 10 to 50°C to the expression, from Eq. (4),

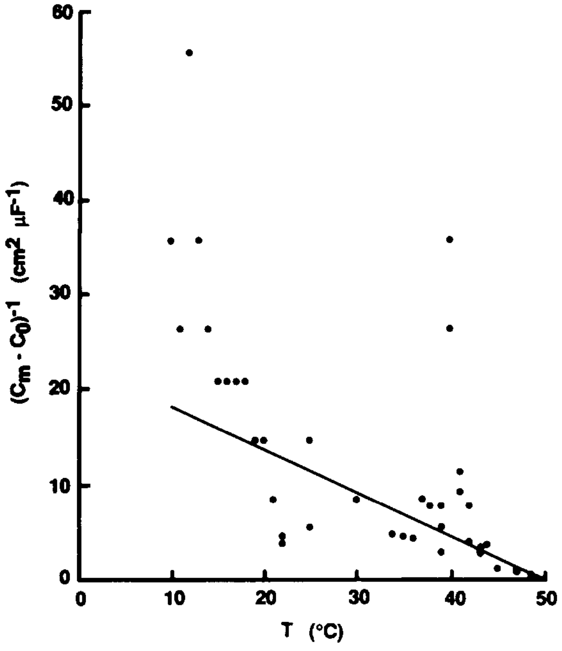

Fig. 1. Least-squares linear regression fit of $(C - C_0)^{-1}$ versus temperature as a test of Eq. (6) (line), derived from the ferroelectric Curie–Weiss law. The points are from membrane capacitance versus temperature data of Palti and Adelman [17]. The parameters evaluated are given in Eq. (7).

$$(C - C_0)^{-1} = (T_0 - T)/k = A + BT. \qquad (6)$$

The five points between 3 and 10°C were not used to avoid possible confusion due to separate effects in the vicinity of the cold-block temperature (see discussion below). Because $C - C_0$ is extremely small at low temperatures, leading to great magnification of minor fluctuations in the reciprocal, the regression was weighted by $C - C_0$ to reduce fitting errors. To obtain an accurate value of T_0, the baseline parameter C_0 was adjusted for best fit through the high-temperature points. Despite four standard residuals greater than 2.0 in magnitude, no outliers were dropped, all 40 points from 10°C upwards being used in the fit. The resulting regression equation was

$$(C - C_0)^{-1} = 22.60 - 0.454\ T. \qquad (7)$$

Fig. 1 shows the data for $(C - C_0)^{-1}$ versus temperature and the least-squares fit.

The regression fit was evaluated by an analysis of variance calculation, which gave MS (error) = 4.35, $s = 2.09$, $F = 42.77$ and $p < 0.001$. The parameters obtained were $A = 22.60\ \text{cm}^2/\mu\text{F}$, with standard deviation of the mean $\sigma_A = 2.79\ \text{cm}^2/\mu\text{F}$ ($p < 0.001$), and $B = -0.454\ \text{cm}^2/(\text{K}\ \mu\text{F})$, with $\sigma_B = 0.069\ \text{cm}^2/(\text{K}\ \mu\text{F})$ ($p < 0.001$).

The parameters obtained in the fit were

$$C_0 = 1.182\ \mu\text{F/cm}^2 \tag{8}$$

for the baseline capacitance per unit area,

$$T_0 = -A/B = (49.80 \pm 14.11)^\circ\text{C} \tag{9}$$

for the extrapolated Curie point, and

$$k = -1/B = (2.20 \pm 0.33)\text{K}\ \mu\text{F/cm}^2 \tag{10}$$

for the constant of Eq. (4). It should be pointed out that a lower heat-block temperature has been reported in *Loligo forbesi* by Hodgkin and Katz [23]; interspecies uniformity is not to be expected in this property.

Solving Eq. (7) for C allows the fit equation

$$C = 1.182\ \mu\text{F/cm2} + 2.20\ \text{K}\ \mu\text{F/cm}^2/(49.80^\circ\text{C} - T) \tag{11}$$

to be compared to the original data, as shown in Fig. 2. An alternative hypothesis, in which $(C - C_0)^{-1}$ varies as $(T_0 - T)^2$, was tested, but did not give acceptable fits.

7. Estimate of the Curie constant

From the value of k obtained, a value of K can be estimated from Eq. (5). The volume of the Na channel is estimated [33] as 0.26×10^6 Å^3. Assuming it is a cylinder 50 Å high, its cross-sectional area is $5.2 \times 10^{-17}\ \text{m}^2$. The density of Na channels, measured by toxin binding or gating charge, is about 300 channels/μm^2, or $3 \times 10^{14}\ \text{m}^{-2}$ [2]; a somewhat smaller but roughly consistent value was found in cut-open squid axon preparations [34]. Therefore a, the fractional area of Na channels in the squid-axon membrane, is roughly 1.56×10^{-2}. From Eq. (5) this makes the constant below T_C

$$K = kL/\epsilon_0 a = 8.0 \times 10^2\ \text{K}. \tag{12}$$

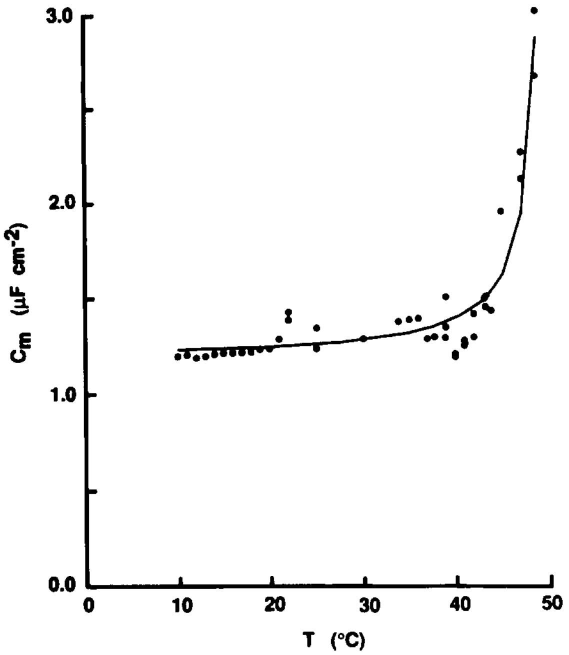

Fig. 2. Membrane capacitance versus temperature. The points are from Palti and Adelman [17]. The line is given by Eq. (4) and (11).

For a first-order transition, thermodynamic analysis (see below Eq. (2)) indicates the Curie constant *above* T should be 8 times as great, or 6.4×10^3 K. Comparison of this value to a distribution of ferroelectric Curie constants [35] indicates that the Na-channel transition falls within Group II of order–disorder transitions. The phase transitions in this group are explained by a model of reversible or rotatable permanent dipoles, which in a parallel orientation give rise to spontaneous polarization below the Curie point, but which lose that polarization when the order is lost above the Curie point. A crystalline ferroelectric, sodium nitrite, $NaNO_2$, has a comparable Curie constant of 5130 K, with a Curie point of 164°C [15].

8. Extension to other channels

Although this discussion has been restricted to the Na channel, the physiological and evolutionary similarities of the Na channel to Ca, K and other channels suggests that the present conclusions may be generalizable to these other ion channels. It is therefore significant that the capacitance of K channels has been determined to be highly voltage-dependent, with a sharp peak at about -70 mV, a very sharp drop-off in the direction of depolarization and a more gradual decrease in the direction of hyperpolarization [36]. Assuming a linear relation between voltage and transition temperature, the relationship shown appears to be compatible with the Curie–Weiss relations of Eqs. (1) and (2).

9. Discussion

The data from which the above analysis is made, although unquestionably reliable, appear to have been taken from a single fiber, possibly in a unidirectional sweep. A repetition of the experiment with modern techniques, exploring the variability of the parameters, would be highly desirable. The assumption, here justified by a plausibility argument, that the dielectric anomaly near-heat block is due to a transition in the Na channel can be checked by the use of tetrodotoxin (TTX) or one of its analogues. The explanation of TTX block of the Na channel by the ferroelectric–superionic transition hypothesis is that, in binding to the channel, TTX stabilizes (or freezes in) the ferroelectric phase [6]. A testable prediction that follows from this is that extremely low concentrations of TTX will elevate the transition temperature. Such an experiment should also explore the cold-block region (near 0°C in *Loligo*), where the sharp drop of the action potential conduction velocity with decreasing temperature [37] suggests the existence of another phase transition. This should help clarify the behavior in the low temperature region of the Palti and Adelman [17] data, which were omitted in the above analysis.

It is generally accepted that voltage-gated ionic channels must have charged structures that can move within the membrane and thus sense the membrane electric field [38]. Although it is frequently assumed that these charged structures move as rigid bodies within the channel, the assumption of rigid motion is not used here. Instead it is assumed that dipolar structures in a membrane-spanning part of the channel participate in the response to the field, migrating only small distances from their equilibrium positions in a cooperative movement. It is further assumed that this movement is, under channel gating conditions, governed by a nonlinearity that forms the basis of a phase transition.

The model that emerges from these assumptions is that the low-temperature, high-field phase of the ferroelectric channel unit is ferroelectric and ordered, while the high-temperature, depolarized phase is paraelectric and less ordered. The abruptness of the transition and the existence of thermal hysteresis classify the transition as first order. The assumption that cations become itinerant in the paraelectric state, which thus becomes a superionic conductor, completes the ferroelectric–superionic transition hypothesis. These simple physical assumptions explain gating and other aspects of channel behavior [5,6]. A microscopic model [39] proposes that the molecular basis of this transition is a transition of the four S4 segments of the Na channel from α helices to extended coils coordinated by unhydrated permeant ions, which move by thermally activated hopping. The question as to whether the small size of the Na channel may preclude its ability to support a ferroelectric state has been discussed recently [40].

It may be asked, can the evidence presented here be explained in terms of a polarized state, such as an electret, that is not a true ferroelectric? If it can not, what type of existing ferroelectric material would show similar characteristics? A number of investigators have explored the possibility that excitable membranes are electrets, materials that exhibit a polarized state [41,42]. The term ‘electret’ includes ferroelectrics, but is a broader term. Electrets are materials in which persistent metastable polarization is observed after the application of an electric field. The distinguishing characteristic of ferroelectrics is that their polarization below the Curie temperature does not relax, but is thermodynamically stable due to the cooperative interaction between the dipoles (Ref. [16], p. 546f). While most Na channels exhibit inactivation, so that their open state is metastable, persisting only for a few ms, the inactivation can be removed chemically, and is considered an independent property [1,2]. Thus it can be said that a noninactivating Na channel can be switched between two stable states by an external electric field. The claim of ferroelectricity in excitable membranes is based not only on the present demonstration of Curie–

Weiss behavior, but on the existence of hysteresis, piezoelectric and pyroelectric effects, and voltage-dependent birefringence, as discussed elsewhere [4–6,9]. Moreover, a microscopic mechanism for ion gating consistent with a ferroelectric channel phase has been proposed [39].

That leaves the second question: To what type of ferroelectric does the excitable membrane belong? Excitable membranes are complex, unique products of evolution, and materials science has as yet not been able to produce an exact analogue to them. However, a number of partial analogues exist, which illustrate aspects of membrane behavior.

Excitable membranes are thin sheets of lipid and protein, so one may be tempted to compare them to ferroelectric thin films. These are films of 0.1–1 μm deposited by vacuum evaporation or sputtering onto a metal substrate [16]. Since biological membranes are only ~ 5 nm thick, they might be referred to as ferroelectric ultrathin films. However, this categorization leaves aside the ordering of the membrane and the structure of its constituent molecules. For this we turn to ferroelectric polymers, molecular organic ferroelectrics and ferroelectric liquid crystals. Ferroelectricity has been demonstrated in polymers, such as polyvinylidene fluoride [43,44]. Seven molecular organic ferroelectrics are known, and others are presently suspected on symmetry grounds [45].

A liquid crystal is a material in a mesomorphic state, having more structure than a liquid but less than a solid. Both the amphiphilic lipid and protein components of a biomembrane are organized with respect to the aqueous phases they separate; therefore the membrane is a lyotropic liquid crystal, one in which a second component (water) plays an organizing role [46–48]. Lyotropic liquid crystals are generally anisotropic. The membrane phospholipids form a lamellar structure, the bilayer, and the intrinsic proteins including the channels are oriented asymmetrically within the bilayer, forming a polymer dispersed lamellar liquid crystal [49].

The two types of thermotropic liquid crystals most closely analogous to biological membranes are smectic A and smectic C, which have two-dimensional anisotropic order. Smectic A materials exhibit parallel monomolecular layers of rodlike molecules whose axes are perpendicular to the planes. Smectic C phases are similar but their axes are tilted. For chiral molecules, the designations become SmA* and SmC* [49,50]. Since the complex lipids and proteins of biomembranes are chiral and nonracemic, they are strongly analogous to these smectics. Ferroelectric liquid crystals were discovered in 1975; many of these materials are now known and in use. As expected, they also exhibit a pyroelectric effect [50]. They include the SmC* phase but not the SmA* phase. Thus a transition from a SmA* to a SmC* phase is a paraelectric–ferroelectric transition [51]. One may therefore tentatively characterize an excitable membrane as a mixed lyotropic, lamellar ferroelectric liquid crystal of polymer units. The relevance of ferroelectric liquid crystals to biomembranes has been discussed previously [52,53]. The fact that ferroelectric liquid crystals are fluid ferroelectric phases removes the basis for an objection to the hypothesis of ferroelectric units in excitable membranes by critics who claim that ferroelectrics are rigid and therefore cannot exist in a fluid membrane.

10. Conclusions

According to the ferroelectric–superionic transition hypothesis, the Na channel in an excitable membrane at resting potential is in a ferroelectric state. Threshold depolarization lowers the Curie point to the channel temperature, inducing a phase transition to a paraelectric state. Experimental data allow the channel phase transition to be classified as of order–disorder type and first order. The highest temperature at which such a phase transition can occur, the ferroelectric Curie point of the Na channel, is also the highest temperature at which an action potential can be generated, the heat-block temperature.

The assumption of nonlinear dielectric behavior near a ferroelectric phase transition leads to the prediction that the temperature dependence of the dielectric constant is given by the Curie–Weiss law in the ferroelectric phase, $\epsilon = K/(T_0 - T)$. As a result, the membrane capacitance (assuming other components to have temperature-independent dielectric constants) is $C = C_0 + k/(T_0 - T)$. That prediction was here tested on the basis of data obtained by

Palti and Adelman [17] on squid-axon membrane capacitance versus temperature. The curve fit for the 40 points between 10 and 50°C agreed with the data to a significance probability of $p < 0.001$, while an alternative hypothesis did not give reasonable fits.

The fit provides parameters that yield new information about the *Loligo pealei* Na channel: the extrapolated Curie point, 49.8°C; the temperature-independent capacitance, 1.18 $\mu F/cm^2$, and a coefficient of 2.2 K $\mu F/cm^2$. On the basis of estimated geometric factors and a theoretical factor of 8 between the coefficients above and below the Curie point, the Curie constant was estimated to be about 6400 K, placing the Na channel in the category of Group II order–disorder ferroelectrics. A study of the literature on ferroelectric liquid crystals suggests that the Na channel is a ferroelectric polymer within a lyotropic lamellar liquid crystal, with some similarities to the smectic C* phase.

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