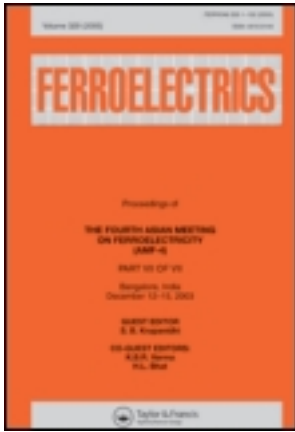


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BIOFERROELECTRICITY: MODELING THE TRANSITIONS  
OF THE SODIUM CHANNEL

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Abstract A thermodynamic model for a phase transition in sodium channels between a ferroelectric "closed" phase and an ion-conducting "open" phase is discussed. This model implies Curie-Weiss behavior in the dielectric properties of excitable membranes, and this is consistent with data from squid axon. The question as to whether a ferroelectric phase as small as a macromolecule of 270 kD can exist is analyzed. A molecular interpretation of the transitions is given in terms of helix-coil transitions.

"True relations may exist between ferroelectricity, the formation of liquid crystals, and the generation of electric impulses in nerves and muscles." --A. R. von Hippel, 1970<sup>1</sup>

INTRODUCTION

One of the mysteries of biophysics today is the mode of action of the macromolecules referred to as voltage-gated ion channels. These glycoprotein molecules, embedded in a lipid membrane, control the selective passage of specific ions according to the voltage across the membrane. The sodium channels of nerve and muscle are different from those of epithelial tissues, and there is a large array of different potassium channels. The channels also differ from species to species. Nevertheless, sodium channels from electric fish, insects and mammals have been found to be remarkably similar in their amino-acid sequence. This constancy over millions of years of evolution testifies to their functional perfection.<sup>2</sup>

ION CHANNELS IN EXCITABLE MEMBRANES

These ion channels are voltage-gated; that is, they switch from nonconducting to ion-conducting as the transmembrane

voltage decreases from the normal resting potential to a smaller threshold potential. The impulses that race along nerve and muscle fibers depend on two types of channels: the fast sodium channels and the much slower potassium channels. The membrane stores energy in two oppositely directed gradients: the internal ion concentration of  $\text{Na}^+$  is much lower, and that of  $\text{K}^+$  much higher, than the corresponding external concentrations.

The way an impulse is carried along a nerve fiber called an axon has been compared to the falling of a row of dominoes--but these dominoes quickly set themselves up again! The ion concentration gradients (primarily  $\text{K}^+$ ) cause the membrane to have a potential difference of about -70 mV (outside is ground). As the action potential (nerve impulse) nears, it draws current from the membrane capacitance, reducing the potential difference. This affects both channels: The  $\text{Na}^+$  channels open rapidly and transiently, allowing a current of  $\text{Na}^+$  to flow in, thus reversing the voltage to about +50 mV. The  $\text{K}^+$  channels open more slowly, allowing an outward current of  $\text{K}^+$  to restore the membrane's resting potential. Locally the process is completed in 3 ms, but it propagates along the axon at speeds up to some 200 cm/s.<sup>2,3</sup>

### THE SODIUM CHANNEL

What is the mode of action of an ion channel such as a sodium channel? This question has been addressed since about 1900.<sup>3,4</sup> The majority of biophysicists and electrophysiologists believe that the channel contains a water-filled pore through which ions flow; to close the channel, the pore is blocked by an obstruction; a selectivity filter assures that only ions of the proper type pass through the pore.<sup>2</sup> This view has been criticized on the basis that it leaves the mechanisms of voltage gating and ion selectivity unspecified.<sup>5</sup> Suggestions that ferroelectricity is involved go back as far as 1970 (see quotation by A. R. von Hippel<sup>1</sup> above).

We describe here our hypothesis that the sodium channel operates on condensed-state principles, and that the closed-open transition of the channel can be described as a transition from a ferroelectric state to a<sup>a</sup> paraelectric, superionically conducting state.<sup>6-13</sup>

Improvements in patch-clamp technique have made it possible to study the currents passing through a single channel. These are sharply defined stochastic fluctuations of a few pA, suggesting that the channels undergo first-order transitions. The conductance of  $\text{Na}^+$  channels from frog node is 7.9 pS at 13 °C; their density is 1900 channels per square micrometer of membrane.<sup>14</sup>

The sodium channel is a glycoprotein, 70% protein and 30% sugar. The protein has recently been cloned by techniques of molecular biology, and its primary structure has been determined.<sup>15</sup> Its 1820 amino-acid

residues were found to consist of four almost identical repeats, each with six transmembrane segments of  $\alpha$  helical structure. A particularly interesting feature occurs in the fourth of these segments, S4, which have positively charged residues (arginine or lysine) at every third position. Segment S4<sub>16</sub> has been experimentally identified as the voltage sensor.<sup>16</sup>

### EVIDENCE OF FERROELECTRICITY

Existing data suggest that current-voltage hysteresis, pyroelectricity and piezoelectricity have been observed in membranes containing ion channels. Optical experiments show voltage-dependent birefringence in excitable membranes. An upper temperature limit to membrane excitability exists; referred to as heat block, it has been identified as the transition temperature (Curie point) of the Na channel.<sup>6</sup> Data showing a sharp increase in membrane capacitance as the temperature rises to heat block<sup>17</sup> have been fitted to the Curie-Weiss law.<sup>18</sup>

A thermodynamic model for the operation of a sodium channel proposes that a phase transition propagates inward along the channel, converting the ferroelectric resting phase of the channel<sup>10</sup> into a paraelectric superionically conducting phase. In this model the voltage sensitivity is due to the electric-field dependence of the Curie point. (A potential difference of 70 mV across a 7-nm membrane represents a field of  $10^5$  V/cm.) As the field is reduced by depolarization of the membrane, the Curie point falls below the temperature of the channel, triggering the order-disorder phase transition. Shirane et al.<sup>19</sup> developed a catastrophe theory variant of the model and generated calculations of voltage vs time.

### A THERMODYNAMIC MODEL AND ITS IMPLICATIONS

The action of the sodium channel has been modeled thermodynamically<sup>7,9,10</sup>; this model has been extended by Bystrov et al.<sup>11-13</sup> The mathematical description of the ferroelectric channel unit is based on the theoretical work of Landau, Ginzburg and Devonshire.<sup>20,21</sup>

In a one-dimensional model, the equation of motion for the polarization distribution  $P$  may be written as a second-order partial differential equation. This model yields a nonlinear-wave solution, which may be a kink (domain wall) or a solitary wave. The kink solution may be interpreted as an inward propagation of the interphase boundary.<sup>13</sup> This solution is limited to a narrow temperature interval.

One of the implications of this model is that the dielectric constant of the Na channel must obey a

Curie-Weiss law,  $\epsilon = K/(T_0 - T)$ , just below the phase-transition temperature. This has been demonstrated by fitting data on membrane capacitance as a function of temperature<sup>17</sup> to the Curie-Weiss law.<sup>18</sup> Analysis of the fit yields a transition temperature for Na channels of the squid *Loligo pealei* of 49.8 °C and a Curie constant of about 6400 K, consistent with Group II order-disorder transitions.<sup>22</sup>

Other implications are changes in conductivity, piezoeffect, pyroeffect, and influences on the phase transition due to pressure, concentration and external fields. Effects of these types have been observed in excitable membranes containing ion channels.<sup>4,6</sup> The most important of these is the induction of a phase transition in the channel when the electric field is decreased from its resting value by a depolarization, since this initiates the opening of the channel.

### SIZE PROBLEM?

The Na channel is about 270 kD in molecular weight. It has been suggested that this may be too small to provide a ferroelectric domain (S. K. Kurtz, personal communication to HRL). When ferroelectric crystals are ground into fine powders, a ferroelectric state cannot be induced when the particles are below a critical size. Ishikawa et al.<sup>23</sup> studied the size effect on the ferroelectric phase transition in lead titanate ultrafine particles and found that 12.6 nm is a critical size below which the ferroelectricity becomes unstable. Yamakawa and Uchino<sup>24</sup> explained the particle size effect on the basis of surface tensional stress in ferroelectric materials.

So a claim that a sodium channel, with dimensions of some 4-6 nm, is ferroelectric naturally appears dubious. Can a sodium channel exhibit ferroelectricity when it is less than half the size of the smallest ferroelectric powder particle (other than relaxor ferroelectrics) ever observed? Let us, however, look at the differences between a sodium channel (SC) and a powder particle (PP):

--The SC is embedded in a phospholipid bilayer that divides two aqueous phases; thus it is in contact with both insulating and conducting media. The hydrophobic segments traverse the membrane while the hydrophilic stretches are in the aqueous phases. The PP has a free surface in air.

--The SC is held in a definite orientation within the bilayer; thus the electric dipole moments of two nearby SCs are parallel. The PP are in powder form, so their polarization axes are randomly oriented.

--The SCs are in a fluid medium, the phospholipid bilayer, and are well separated from each other. The PPs are in contact with each other, and have no freedom of rotational movement.

--Without a high biasing electric field between the aqueous phases, there would be no ferroelectricity in the SC. In

fact, it is the lowering of the resting field from its normal  $10^5$  V/cm that induces the ferroelectric-to-paraelectric transition. No biasing field is present in the PP.

These differences are so profound that the size limitations found in crystalline powder particles can not be considered to preclude<sup>25</sup> the existence of a ferroelectric phase in the Na channel.

#### A MOLECULAR MODEL

The structural information becoming available about the sodium channel, together with the interpretation provided by the ferroelectric-superionic transition hypothesis, has made it possible to extend the theory into the molecular realm.<sup>26</sup> Knowledge that the closed state of the channel is only metastable suggested looking for an instability in the channel. This instability is clearly present in the form of the electrostatic repulsions between the positively charged amino acids of the four S4 segments. At resting potential, these segments may be stabilized in an  $\alpha$ -helical configuration by electrostriction and other field-dependent forces. When the electric field is decreased in a depolarization of the membrane, the hydrogen bonds between the loops of the  $\alpha$  helices break. A helix-coil transition can nucleate at the external surface of the channel<sup>27</sup> and propagate inward. The dipole moments of the  $\alpha$  helices<sup>28</sup> are lost as they transform into random coils.

Oxygen atoms from the carbonyl groups may serve as binding sites for the Na ions. Translocation of the ions, stripped of their waters of hydration, along a continuous pathway of these sites across the membrane can take place by thermally activated hopping down the gradient of electrochemical potential.<sup>26</sup>

This molecular model is consistent with the thermodynamic model. It suggests new experiments, such as looking for a change in circular dichroism as channels gate.

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