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Action Potentials

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Action Potentials and Electromechanical Coupling in the Macroscopic Chiral Phospholipid Bilayer

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Abstract

Action potentials are accompanied by mechanical displacement and forces (Iwasa and Tasaki 1980). The time dependence of the phenomenon can be explained by a coupling between the electrical polarisation and the mechanical force. It is shown from symmetry arguments that the action potential is a reversible hydrodynamic excitation of a liquid-crystalline fluid consisting of macroscopically ordered chiral molecules. We conclude that the electromechanical aspects of action potentials are a property of the lipid bilayer.

I. Introduction

Nerve action potentials (Hodgkin and Huxley 1952, Tasaki 1968) consist of a propagating pulse in the electric membrane potentials (Hodgkin 1938) coupled to the mechanical displacement of the membrane system (Hill et al. 1977;Iwasa, Tasaki and Gibbons 1980; Iwasa and Tasaki 1980, Tasaki and Iwasa 1982, Tasaki and Byrne 1982; Levin et al. 1984). Action potentials also consist of a pulse in the mechanical forces (Iwasa and Tasaki 1980, Tasaki and Iwasa 1982). Corresponding changes have been observed in the temperature (Abbott, Hill and Howarth 1958) and the optical birefringence of the cell surface (Tasaki et al. 1968; Cohen, Keynes and Landowne 1972). Last but not least,action potentials are coupled to a pulse in the electrical membrane current (Katz 1966).

This latter coupling has been investigated in great detail in the past due to its experimental accessibility in the squid giant axon (Hodgkin 1938; Cole and Curtis 1939; Hodgkin and Katz 1949; Katz 1966; Hodgkin 1976). The polarisation pulse depends on the applied electrostatic membrane potential (Hodgkin 1938), the chemical proton potential (Hille 1968), the sodium and potassium potentials

(Hodgkin and Huxley 1952), on calcium (Tasaki 1968) and other thermodynamic variables (Nachmansohn 1959; Katz 1966).

Coupling has been studied under voltage-clamp. In contrast to the action potential produced by the membrane, in voltage-clamp, the bulk aqueous compartments on either side of the membrane are clamped to fixed values of the electrostatic potential. Stepwise changes of this voltage are followed by relaxation of the ohmic membrane current. This relaxation is spatially homogeneous, in contrast to the propagating pulse. The currents observed under these conditions were quantitatively described by the assumption of ion-specific channels (Hodgkin and Huxley 1952) which depend on calcium (Lettvin 1964, Katz 1966). The mechanism of the action potential could not be resolved (Hodgkin 1976).

Ion channels of discrete conductivity and fluctuating open times (Haydon and Hladky 1972) have also been studied in the squid giant axon (Conti and Neher 1980). The relationship to the non-fluctuating, deterministic action potentials cannot be a simple superposition and is not known. One attempt to identify that relationship made use of tetrodotoxin (TTX) which alters action potentials with respect to the electrical and the mechanical pulse (Tasaki et al. 1980). Ion channels can be induced by the applied electrostatic membrane potential in a Na-dependent fashion when TTX-binding protein is present in a lipid bilayer (Hanke 1985).

Most authors in the field have assumed specific protein properties to describe the action potential. Whether by macromolecular approaches (Tasaki 1968) and decremental conduction (Lorente de No and Condouris 1959), or by local electrostatic equivalent circuits for ion-specific channels (Katz 1966; Hodgkin and Huxley 1952), the physical basis for the propagating action potential has not been identified in the protein molecules so far.

It has been proposed, however, that proteins serve to control the permeability of the lipid component of nerve membranes (Kaufmann 1977), and that the action potential represents a reversible excitation in the lipid bilayer rather than a dissipative flow through proteins. The deterministic thermodynamic forces in the bilayer explain the deterministic, propagating action potential; the thermodynamic fluctuations in the bilayer explain the statistical ion channel fluctuations (Kaufmann 1985a).

Specific protein activities thus serve to induce a thermodynamic response in the lipid bilayers. This response always consists of

1. the thermodynamic free energy
   or correctly the generalized thermodynamic
   potential (cf. Graham 1973),
2. the forces driving propagating excitations, and
3. the order fluctuations which open and close
   discrete ion channels (Kaufmann 1985b).

Experiments on pure synthetic lipid bilayers demonstrated corresponding electrical responses to protonic activities:

1. conformational changes of membrane capacitance (Kaufmann 1985a),
2. deterministic millisecond current pulses (Kaufmann and Silman 1980;1983), and
3. fluctuating opening and closing of ion channels (Kaufmann and Silman 1983).

The reversible nature of the current pulses was observed by the appearance of overshoot, i.e. of pulses directed against the electrochemical membrane potentials. Sometimes, the term adiabatic is used synonymously with the term reversible, since it describes processes which involve zero entropy production.

In this paper, we demonstrate using symmetry arguments that action potentials in the squid giant axon represent a reversible hydrodynamic excitation of the lipid bilayers. We take advantage of two recent developments:

1. The experimental observation of an electromechanical coupling during biological action potentials (Iwasa and Tasaki 1980) provides reliable and crucial information about the nature of the coupling processes. This will be shown from the order and the spatial symmetry required for the underlying, liquid-crystalline membrane.

2. The hydrodynamic theory of liquid crystals has recently been developed for chiral layered systems with tilt, i.e. smectics C*, including the role of electrical polarisation (Brand and Pleiner 1984) thus giving a complete macroscopic dynamics.

In the hydrodynamic regime one is focusing on long wavelength, low frequency excitations where low frequencies means that one is looking at frequencies small compared to any microscopic frequency (e.g. due to collisions). Correspondingly, one is looking at length scales large compared to the distance between two collisions. The hydrodynamic description of a system is known to be complete (Forster 1975) if all conserved variables (such as density, density of linear momentum, energy density etc.) and all variables characterising spontaneously broken continuous symmetries are taken into account. Broken continous symmetries appear, e.g., as superfluid velocity in ^{4}He, as staggered magnetisation in an antiferromagnet, or as director variations in a nematic liquid crystal.

In the limit of infinite wavelength, the frequencies of all truly hydrodynamic excitations go to zero.

In some cases, for example in the vicinity of a phase transition, one might have additional quantitites - e.g. the modulus of the order parameter close to the second order phase transition in ^{4}He - which relax in a large but finite

time. Nevertheless, this process might happen on the same frequency scale as the hydrodynamic excitation at finite wave length. Therefore, such variables which are not truly hydrodynamic but nevertheless very slow, are kept in the list of variables under consideration and they are called macroscopic.

The dynamics of the combination of both, the truly hydrodynamic and the macroscopic variables, is then frequently called macroscopic dynamics (cf. Brand 1986 for a recent discussion of such a description close to the uniaxial nematic to columnar phase transition in thermotropic liquid crystals).

It is generally accepted that biological membranes represent a liquid crystalline structure (Traeuble 1977, Helfrich 1981). The application of macroscopic dynamics is justified and important since the electrical, mechanical, thermal or optical observations on action potentials are macroscopic. The collective behaviour of the molecules is therefore essential to obtain any coupling between these variables. In contrast to the hydrodynamics of simple fluids, and liquid crystals in the nematic or smectic A, B and C phases (Martin, Parodi and Pershan 1972; Brand and Pleiner 1980), the possibility of reversible electromechanical coupling arises for the first time in chiral layered smectics C* (Brand and Pleiner 1984). This possibility is due to long-

range order of the orientation of the molecules and requires in addition chirality. Reversible electromechanical coupling therefore arises in a system showing m a c r o s c o p i c c h i r a l i t y .

The hydrodynamic limit of macroscopically long wavelengths and small frequencies is justified for action potentials. These are macroscopic in space and slow in time with respect to microscopic lattice constants (magnitude 1 nm), and plasma frequency (magnitude 10^{11} Hz). However, membranes are microscopic in thickness and no hydrodynamic excitation due to mere displacement of the bilayer is possible.

The chirality of the proteins and the lipid molecules is established. The influence of chirality on macroscopic order has been observed in lipid monolayers (Weis and McConnell 1984). No relation of chirality to electrical phenomena in biological membranes has so far been established. This effect has however been observed in chiral smectics C^* (Jakli et al. 1985; Brand and Pleiner 1985).

Smectics C^* resemble lipid bilayers since both are layered anisotropic ordered fluids of chiral molecules with tilt. Lipid bilayers differ, as mentioned, by the microscopic extension in the third dimension perpendicular to the layering of the membrane. In the following we will denote by parallel the direction in the plane of the layers and by perpendicular the direction parallel to the layer normal.

Myelin sheets of lipid multilayers more closely agree with the symmetries of smectics C* in three dimensions.

In this article we show that the electromechanical coupling during squid axon action potentials demonstrates an adiabatic, reversible excitation of a macroscopically ordered system of chiral molecules. This result will be obtained by symmetry arguments and does not require specific model assumptions.

The molecules in a lipid bilayer membrane represent the only system in biological membranes compatible with the macroscopic chiral order. Proteins could only contribute to the action potential if arranged in a continuous and fluid ordered layer. Single protein molecules cannot produce the action potentials, although proteins may induce the localised excitations in the lipid bilayer.

Our result implies that action potentials represent a propagating density pulse leading to a velocity gradient which produces the mechanical force observed. This force rotates the ordered molecules and the associated electrical dipoles. The rotation is geometrically equivalent to a displacement in phase or shifted by 180° with respect to the electrical polarisation pulse.

This result predicts that action potentials can be induced in pure lipid bilayers, but not in racemic mixtures, and consist of a pulse in all thermodynamic lipid variables, such as temperature, energy density; area, surface pressure; surface proton activity, electrochemical proton potential; calcium potential; and other ion potentials. Action potentials are propagative hydrodynamic excitations and therefore capable of overshoot against the electrochemical membrane potentials. Propagation proceeds with the velocity of sound and is much faster in multilayers than in bilayers.

II. Theory

Biological membranes consist of a lipid bimolecular layer (Danielli and Davson 1935) into which polypeptides and proteins can be incorporated (Singer and Nicolson 1972). Water is crucial for the constitution of the bilayer. The membrane state depends on the activity and the electrochemical potential of the aqueous ions, protons in particular (Eigen and deMaeyer 1958), sodium and potassium (Hodgkin and Huxley 1952), or calcium (Tasaki 1968). The local activity of membrane-bound enzyme reactions controls the proton potential (Silman and Karlin 1967). Myelination by multilayers surrounding the bilayer cell surface membrane must also be considered.

The macroscopic state of the membrane is characterised by the thermodynamic variables of the system. Among these variables are the mechanical and the electrical ones observed. It is not possible therefore to restrict the theory to the electrical variables only. Similarly, the electromechanical variables alone do not suffice to describe the other components of the excitation, e.g. excitation of the temperature or the proton potential. It is, however, possible to restrict the theory of excitations to those variables which break any one of the continuous symmetries

of the system. This procedure is completely general in the hydrodynamic limit (Martin, Parodi and Pershan 1972). The symmetry requirements must be obeyed even in nonequilibrium. The entropy production can however only be used if the generalised thermodynamic potential is known (Graham 1973; Haken 1977).

Due to presence of a spontaneously broken continuous symmetry, the system can be macroscopically excited. Microscopic excitations, on the other side, are too short-ranged and fast to account for action potentials. This procedure (Martin, Parodi and Pershan 1972) has been successfully applied to obtain the excitations in simple fluids (Landau and Lifshitz 1959), binary fluid mixtures (Landau and Lifshitz 1959), superfluids (Khalatnikov 1965; Graham 1974; Brand, Doerfle and Graham 1979), nematics (Forster 1975; Forster, Lubensky, Martin, Pershan and Swift 1971), cholesterics (Lubensky 1972), smectics A, C (Martin et al. 1972; Brand and Pleiner 1980), and smectics C* (Brand and Pleiner 1984) which resemble lipid bilayers when only two layers are considered.

In contrast to smectic multilayers, biological bilayer membranes give rise to a number of further degrees of freedom related to the various membrane constituents and the aqueous environment. On the other hand, the layer displacement variable disappears because it does not break

any macroscopic symmetry in a bilayer situation.

The asymmetry across the bilayer, i.e., the difference between the states of the two monolayers and the associated bulk aqeous volumes, has also to be considered. Without such asymmetry, no driving forces for transport across membranes arise. However, the membrane asymmetry corresponds to a discrete symmetry due to the microsopic bimolecular thickness of the membrane, and no additional macroscopic degree of freedom arises.

Moreover, the membrane potential couples to ion fluxes, a phenomenon crucial for biological functions but irrelevant for three-dimensional properties of smectics. For example, the electrochemical proton potential difference between the aqueous surfaces is crucial for biological free energy coupling. In addition, the usual sodium and potassium potentials as well as the calcium potential have also to be considered in the theory.

1. Variables

The macroscopic state of the biological membrane is defined by the extensive variables which follow from the conservation laws and the spontaneously broken continuous

symmetries. Only a few of these will turn out to be crucial for the discussion of the observed electromechanical coupling.

The conservation laws of mass, energy and momentum introduce the following variables:

ρ^{α} densities of the molecules and ions α in the membrane and at the membrane surface (water, protons, calcium, sodium, potassium, others).

ε internal energy density of the system. The entropy is conserved during reversible excitations. It is related by the Gibbs equation to the entropy density of the system and the other hydrodynamic variables. The two-dimensional density per membrane area is introduced, and the entropy of the membrane system including the aqueous environment is considered.

g_i density of linear momentum of the system with local cartesian components i = 1 normal to and i = 2,3 parallel to the membrane plane. Only the g_i at the level of the membrane allow for coupling to the membrane deformation. Conservation of angular momentum is guaranteed by a suitable

choice of the stress tensor (Martin, Parodi and Pershan 1972).

These conserved variables define the state of an isotropic fluid and cannot give rise to membrane polarisation and displacement. The complete set of hydrodynamic variables arises from the consideration of the spontaneously broken continuous symmetries (Martin, Parodi and Pershan 1972).

The mere displacement of the bilayer is not a hydrodynamic variable.

The tilt angle between the molecular axes and the layer planes stays constant as long as one stays away from a phase transition. This is well established for smectic C* liquid crystals and the transition to the A phase. Therefore, we will disregard in the following the tilt angle as a variable.

$\vec{P}_i$ A very important degree of freedom for membranes, especially during the action potential, is actually the polarisation, $\vec{P}_i$.

For the membrane itself (+) there is no reason for the magnitude of the polarisation to change just like in multilayer smectics.

As it is well established in bilayer smectics, i.e. in bulk smectic phases composed of bilayers (Brand, Cladis and Finn 1983), we will take the polarisation P_i to lie in the layer plane in the absence of a membrane potential, i.e., in the case of symmetry between both sides of the membrane. For constant magnitude of the polarisation, all that can happen during the action potential is a rotation and we arrive at the relation

$$\frac{\vec{P} \times \delta\vec{P}}{|\vec{P}|^2} = q_0 \vec{u} \qquad (1)$$

where $\delta\vec{P}$ denotes the change of the polarisation. $\vec{u}$ is the displacement vector perpendicular to $\vec{P}$ and $\delta\vec{P}$ and $\frac{2\pi}{q_0}$ is the pitch of the helical structure one would obtain if many bilayers were stacked on top of each other.

In contrast to bulk chiral smectic C*, the displacement along the helical axis is not necessarily parallel to the layer normal in the bilayer situation. A similar fact holds for $\delta\vec{P}$ which has both a component perpendicular to the

layers and (as in bulk smectic C*) a component within the layers. This is immediately clear upon inspection of Eq.(1).

The existence of q_0 reflects the fact that we are dealing with a system which has macroscopically ordered chirality, i.e. the handedness of the molecules is not only important on the molecular level, but also on a macroscopic scale involving many molecules.

A complete rotation of the polarisation by 360° corresponds to a displacement by the pitch $\frac{2\pi}{q_0}$. Eq. (1) provides us with a rigid relation between $\delta\vec{P}$, $\vec{P}$ and the displacement $\vec{u}$. In bulk smectic C* liquid crystals, the pitch is typically of order of a few μm (Brand, Cladis and Finn 1983).

The fact that our system lacks mirror symmetry is reflected by the existence of the pseudoscalar q_0 which transforms like a scalar under all transformations that do not include spatial inversion.

2. Analysis of symmetries

As a result of the following symmetry analysis, the observed electromechanical coupling is due to a coupling between polarisation and gradients of the velocity field $\vec{v}$. This is remarkable since, in principle, any variable couples to

any thermodynamic conjugated force. The result is also general since it follows from the symmetry properties under time reversal and spatial inversion, a requirement for any physical coupling. This result will enable us to draw unique conclusions about the origin of the electromechanical coupling during action potentials despite the complexity of the biological membrane system.

We proceed as follows.

First, macroscopic order of chiral molecules is concluded from the observed geometric coupling between mechanical displacement and electrical polarisation of the membrane (via Eq. 1).

Second, macroscopic chirality is shown to give rise to a reversible coupling between the mechanical force and the electrical polarisation in agreement with the observations.

Ordered, macroscopic chirality of the responsible molecular system is demonstrated by the time evolution and the type of coupling between the displacement and the mechanical force to the action potential (Hill et al. 1977; Iwasa and Tasaki 1980; Tasaki, Iwasa, and Gibbons 1980; Tasaki and Iwasa 1982; Tasaki and Byrne 1982; Levin et al. 1984).

3. Macroscopic chirality

The polarisation vector can either change in magnitude or in direction. A change in magnitude would be too rapid to explain millisecond action potentials (+). No physical mechanism in membranes is known to alter the magnitude of the macroscopic polarisation on that time scale. Therefore, the action potential cannot arise from dissociation or association of charges to the membrane, or from the length of molecular dipoles.

The direction, rather than the magnitude, of the polarisation vector changes during the action potential. Such a rotation is equivalent to a displacement along the helical axis. It requires therefore a system of macroscopically ordered chiral molecules.

(+) cf. section 10. for the discussion of the effect of protons in aqueous medium where we show that this holds for biologically relevant pH values.

Geometric coupling is represented by Eq. 1 and Fig.1. It is directly demonstrated experimentally in Fig.2 by the proportionality of displacement and polarisation. Thus, the macroscopic chirality in the membrane gives rise to a hydrodynamic excitation of the molecular electrical dipoles. This electrical excitation is equivalent to the observed spatial displacement along the helical axis of the ordered bilayer membrane.

4. Adiabatic excitation

Macroscopic chirality gives rise to adiabatic, reversible electromechanical coupling. The reason is as follows.

Any physical coupling is independent from the arbitrary choice of the spatial coordinate system, i.e., both sides of an equation between coupled variables must transform in the same way upon reversal of the spatial coordinates, ϵ^{P}. Reversible coupling is furthermore invariant under time reversal ϵ^{T}.

The observations shown in Fig. 3 demonstrate reversible dynamic coupling of the polarisation by the proportionality of $\frac{d\vec{P}}{dt}$ to the mechanical force. The mechanical force is known to be proportional to the gradients of the velocity

$\nabla_i v_j$. The polarisation current $\frac{dP_i}{dt}$ transforms like ϵ^P =-1, ϵ^T=-1, while $\nabla_i v_j$ transforms like ϵ^P=+1 (such as pressure) and ϵ^T=-1.

The momentum density g_i and its conjugate v_i are the only thermodynamic variables with ϵ^T=-1. Therefore, the velocity field v_i is responsible for the reversible dynamic coupling to the other variables including the polarisation.

Macroscopic chirality is the only physical property known which introduces a pseudoscalar quantity q_0 which transforms like ϵ^P = -1 and ϵ^T = +1. Macroscopic chirality includes as a special case helices as in cholesterics and chiral smectics (cf. Brand and Kaufmann 1986 for a detailed discussion).

It is crucial to note that the translational invariance does not allow for trivial coupling by translation of the membrane. Therefore, no coupling arises to the displacement itself, but only to the helical displacement u_i. The gradient expansion is well established in hydrodynamic theory (Martin, Parodi and Pershan 1972). This argument also excludes a static piezoelectric effect by membrane displacement of the layering.

The electrical polarisation is thus reversibly coupled to gradients of the velocity field for a mechanical force by a

macroscopic system of ordered chiral molecules, and the coupling equation reads

$$\frac{d P_i}{d t} = q_0 \xi_{ijk} \nabla_j v_k \qquad (2)$$

where ξ_{ijk} has 15 coefficients in a biaxial system.

In a forthcoming publication (Brand and Kaufmann 1986), we discuss in detail the structure of ξ_{ijk}. Since we have a biaxial system, it is richer in behaviour than the case of thick three-dimensional samples of smectic C* for which one has 5 independent coefficients (Brand and Pleiner 1984) contributing to the reversible coupling between the polarisation and gradients of the velocity field.

The conjugated reversible dynamic coupling between the electric field E_i and the density of linear momentum is expressed using the mechanical stress tensor σ_{ij}. It employs a coupling matrix $\tilde{\xi}_{ijk}$ equivalent to ξ_{ijk} and reads

$$\sigma_{ij} = q_0 \tilde{\xi}_{ijk} E_k \qquad (3a)$$

with $\tilde{\xi}_{ijk}$ the contributions of the electromechanical coupling to the mechanical stress tensor, which occurs in the conservation law for the density of linear momentum

$$\frac{dg_i}{dt} + \nabla_j \sigma_{ij} = 0 \qquad (3b)$$

These equations describe the reversible coupling between the hydrodynamic excitation of electrical polarisation and mechanical force during the action potential. Eq.2 is verified by inspection of the experimental force-polarisation coupling. Eq. 3 represents a prediction of the theory.

Dissipative couplings are also permitted, from symmetry arguments, to all other variables. Reversible dynamic couplings, however, only arise to the mechanical variables, i.e., to g_i, v_i .

It is obvious that reversible dynamic coupling immediately suggests a mechanism for propagation of action potentials. Depending on the value of the dissipative coupling coefficients, the reversible excitation can only propagate for a limited distance, estimated to at least cellular dimensions (Kaufmann 1985a). In this paper, we shall not write down all the dissipative coupling terms (Brand and Kaufmann 1986), since these are not crucial to the origin of the observed electromechanical coupling. Static coupling is also excluded by the observation (Fig.3) of dynamic coupling between polarisation and force.

The qualitative results obtained and the quantities estimated in the discussion do not depend on the values of the coupling coefficients. The coupling matrix $\mathcal{G}_{ijk}$ in Eq. 2 possesses 5 coefficients in chiral smectics C* (Brand and Pleiner 1984) and 15 coefficients in the present case and cannot be uniquely determined from the available data on lipid bilayers or axon membranes.

5. Limitations of the theory

The theory is restricted to the hydrodynamic limit of macroscopic wave lengths and long time scales. This raises the question on the origin of the time scale of milliseconds of action potentials, since much slower excitations should also be possible. Solitary wave solutions to the hydrodynamic equations have not been discussed here.

The theory is not restricted to linear hydrodynamic coupling. The linear coupling terms treated are present in the nonlinear regime, too. Higher order nonlinearities associated with new coefficients (Pleiner and Brand 1982) are unlikely to change the picture presented since they have not yet been observed experimentally in liquid crystals.

As mentioned already, bilayers are microscopic in the direction perpendicular to the membrane. No hydrodynamic excitation in the direction perpendicular to the membrane arises, in contrast to smectic liquid crystals.

The geometric derivation of macroscopic chirality is completely independent from any further variables in a biological membrane.

III. Discussion

We have for the first time provided a physical interpretation of the observation that nerve action potentials consist of a mechanical pulse coupled to an electrical excitation. By direct derivation from the detected shapes and phases of the mechanical membrane displacement, the mechanical force, and the electrical polarisation (Iwasa and Tasaki 1980), two main results appear:

The mechanical displacement and the polarisation are coupled geometrically (Figs. 1, 2). The geometric coupling results from a system that is macroscopically ordered and consists of chiral molecules. The mechanical displacement is therefore equivalent to the cooperative rotation of molecular electrical dipoles (Brand and Pleiner 1984). This ordered rotation is intrinsically coupled to the observed action potential.

The mechanical force is coupled dynamically to the

polarisation. The dynamic coupling results from the effect of the velocity gradient of the membrane fluid which induces the rotation of the molecular ordered dipoles. The coupling is reversible, not dissipative. Chemical reactions, viscous coupling, ohmic resistivity, and static piezoelectric effects cannot explain the dynamic phase relation between force and polarisation.

Macroscopic chirality and reversibility are confirmed in experiments at crayfish axons (Hill 1977), squid giant axons (Tasaki and Iwasa 1982), crab nerves (Tasaki and Iwasa 1980; Tasaki, Iwasa and Gibbons 1980; Tasaki and Byrne 1982).

The results are obtained by symmetry analysis and do not assume any model parameters. A reversible dynamic coupling is by definition not associated with entropy production. This result provides a mechanism for propagation. The mechanism of the action potential is adiabatic and represents a property of the lipid bilayer, in agreement with earlier prediction (Kaufmann 1985a).

We now discuss the molecular basis and the physical mechanism of electromechanical coupling, propagation and attenuation of action potentials. The threshold of the action potential (compare Hodgkin 1938), protonic control (compare Eigen and deMaeyer 1958), and the role of membrane proteins (compare Kaufmann and Silman 1980) are reobtained. Crucial predictions of the theory are derived which allow an experimental test.

The discussion proceeds as follows.

1. The molecular basis of the electromechanical coupling is identified in the lipid bilayer.
2. The reversible, non-dissipative nature of the coupling is derived.
3. The resulting mechanism of propagation is described.
4. The dissipative processes are shown to account for the duration, attenuation, and permeability during the action potential.
5. The microscopic events during the action potential are discussed.
6. Threshold and
7. subthreshold and "all-or-none" excitations are derived from lipid phase diagrams.
8. Voltage clamp,
9. capacitive currents and
10. ion channels are related to the action potential.

11. The control by protons is described in the framework of the macroscopic theory.

12. Proteins turn out to induce ion channels and action potentials by controlling the lipid state. Finally,

13. further crucial experimental predictions are derived, e.g., the presence of action potentials in non-racemic lipid monolayers.

1. Lipid bilayer

There is only one molecular system in squid axons which is of macroscopic chirality (Fig.1) such that the molecular orientation can give rise to coupled macroscopic polarisation and displacement (Fig. 2). This is the lipid bilayer which constitutes the biological membranes (Danielli and Davson 1935).

It is also the only continuous ordered system which therefore allows propagation of hydrodynamic excitations along the membrane (Kaufmann 1985a). The continuous aqueous

environment cannot explain the electromechanical coupling because it is lacking macroscopic chirality.

Proteins by themselves are not known to form liquid crystalline phases but crystallise as it is obvious from sharp Bragg peaks. Therefore, proteins without the matrix of the lipid bilayer cannot account for the action potential observed.

The gradients of the velocity of the membrane fluid cause the observed force. This force results from the stress tensor in the membrane. Due to mechanical stress and macroscopic chirality, the ordered molecules are both compressed and rotated (Brand and Pleiner 1984). Rotation is ordered macroscopically around a helical axis tilted with respect to the normal of the membrane. Therefore, the lipid bilayer represents a biaxial smectic with tilt.

The mechanical force and the polarisation pulse arise simultaneously. This ordered rotation is equivalent to the mechanical displacement.

2. Reversible coupling

The coupling between mechanical and electrical variables has reversible contributions. No dissipation is required to rotate the electrical dipoles by mechanical stress.

Adiabatic reversible coupling had been predicted on the thermodynamic level (Kaufmann 1985a). It explains propagation and the reversal of the action potential to the original value of the thermodynamic variables after the pulse. Such reversal has been observed for the electrical polarisation (Hodgkin 1938), the membrane current (Katz 1966), the mechanical displacement and force (Iwasa and Tasaki 1980, Tasaki and Iwasa 1982), and the temperature (Abbott et al. 1958), apart from their dissipative components.

The tensor coupling brings along several independent coefficients (5 in the case of smectics C*, Brand and Pleiner 1984) and can be estimated in order of magnitude from the relation Eq.2. From Fig.3, we take F = 1 dyne/cm^2 and $\partial P/\partial t$ = 100 mV/1 msec.

Using ρ_3 = 1 g/cm^3 and membrane thickness 10^{-6} cm, i.e. a two-dimensional density ρ = 10^{-6} g/cm^2, we get for c = 20 m/sec with $F = \rho c \nabla v$ and $\frac{\partial P}{\partial t} = q_0 \zeta \nabla v$ the magnitude

$$q_0 \zeta = 0.2 \text{ V}.$$

3. Adiabatic propagation

Adiabatic coupling at constant entropy immediately explains the propagation of the action potential (Fig.4). It also explains the appearance of overshoot.

Overshoot, i.e. flows against the thermodynamic forces, can only be explained by adiabatic coupling. Since the integral entropy production is zero, the excitation of the membrane is driven by the reversible forces in the membrane, and the coupled polarisation current may turn out to be opposite to forces or potential differences applied between the two aqueous bulk volumina.

The propagation velocity c is related to the adiabatic density derivative of the surface pressure $\tilde{\Pi}$ by

$$c^2 = \left.\frac{\partial \tilde{\Pi}}{\partial \rho}\right|_S \qquad (4)$$

From monolayer phase diagrams, this velocity has been estimated to 20 m/sec maximally (Kaufmann 1985a), with the possibility of slowing down in compressible states, even to 0 at phase transitions of second order (this has not yet been observed experimentally) and at the metastable point of first order transitions.

In multilayer smectics, on the other hand, the propagation velocity is in the order of km/sec (Miyano and Ketterson 1979). Therefore, the adiabatic pulse is propagated in a saltatory fashion if multilayer myelin sheets surround the nerve fibre.

4. Dissipation

The mechanical pulse cannot be arbitrarily short, since the frequency spectrum is broadened by dissipation. Dissipation will also attenuate the impulse.

The number of dissipative constants and eigenfrequencies follows from the analysis of all conservation laws and spontaneously broken continuous symmetries (Martin et al. 1972). The variable u is coupled to the propagating density of linear momentum. It also gives rise to a further

dissipative constant of rotational viscosity. Additional coefficients may also arise from non-lipid membrane components.

Furthermore, since the lipid bilayer is the origin of the action potential, dissipation in the lipid bilayer must attenuate the action potential.

a. Irreversible relaxation

Relaxation times of magnitude 10^{-3} sec and 10^{-1} sec have been reported by (Tsong 1974) in pure lipid bilayers near the phase transition. This relaxation is observed following a temperature-jump after (Eigen and deMaeyer 1963). Similar relaxation times were found earlier by (Hill 1936) in excitable nerve membranes.

In squid giant axon membranes, too, relaxation times of magnitude 1 millisecond have been observed electrically; this relaxation was observed following a voltage jump (Hodgkin and Huxley 1952). Millisecond electrical pulses also appear in pure lipid bilayers (Kaufmann 1985a).

The physical basis of that process is possibly the slow relaxation of the lipid state near a transition. The second relaxation time is even longer and has a very small activation energy (Tsong 1974). It seems compatible with the

lifetime of ion channel defects (cf. point 10 below).

b. Permeability

The membrane permeability is dissipative, too. We recall, however, that the transversal membrane dimension is microscopic and trans-membrane fluxes couple hydrodynamically only to the aqueous environment, but not directly to the quasi two-dimensional lipid state. It is interesting to show that a very similar msec time scale arises for attenuation experiments carried out on axons of length scale 1 cm.

The permeability in three-dimensional liquid crystals is at most of the order 10^{-9} cm^2/sec, the thickness of the bilayer is 10^{-6} cm. It follows that the time for dissipation of molecules through the bilayer is 10^{-3} sec. This coincidence with lipid bilayer relaxation times implies that molecules diffuse through the bilayer on the time scale of the duration of the action potential.

In fact, movement of ions through the membrane is increased due to action potential activity (Keynes 1951).

c. Shear viscosity

The width δx of the pulse increases due to dissipation D with time t according to the fluctuation-dissipation theorem, being the mean value of $(\delta x)^2$

$$\langle (\delta x)^2 \rangle = Dt \qquad (5)$$

The most important dissipative contribution is associated with the shear viscosity which is of order 5 cm^2/sec in smectic liquid crystals (Miyano and Ketterson 1979).

A passage of the impulse for distance x with velocity c is therefore accompanied by a broadening of $\sqrt{Dx/c}$ equivalent to the attenuation of the pulse. In the experiments of Huxley and Staempfli, for example, c = 10 m/sec and the length of axon investigated is x = 1 cm. Thus, we calculate a broadening of 0.07 cm. Since the original pulse was of duration 1 msec, it is attenuated after 1 cm by 7 %.

This is compatible with the small broadening and attenuation

observed by (Huxley and Staempfli 1946). Dissipation of monolayer pulses (Moebius 1984) is similarly weak, ca.30 % after 10 cm.

5. A possible microcopic interpretation

The theory of the electrical and mechanical aspects of action potentials presented above is completely macroscopic. No microscopic model assumptions have been made. Nevertheless, some microscopic conclusions can be drawn from the results and the following information:

a) The microscopic structure of lipid bilayers is known from X-ray analysis.

b) A longitudinal density pulse is part of the reversible excitation.

c) The shear viscosities of the lipid bilayer are the most important contribution to the dissipation of the action potential.

On this basis, we propose the following picture of the microscopic events during the action potential.

There is a longitudinal density pulse in the liquid-

crystalline membrane fluid which propagates with the velocity of sound. The density pulse is associated with ordered rotation and transversal displacement of the lipid molecules. The ordered rotation, and the surface polarisation density pulse, are also expressed by a polarisation pulse in phase with the displacement. Interestingly, the polarisation pulse will have components in all three spatial directions (Fig.5).

The microscopic picture which we propose thus gives rise to the relaxation time scale. It also correctly predicts the magnitude of the action potential and the capacitive membrane current and will be derived now.

6. Threshold of action potentials

The existence of a threshold for macroscopic excitations of the bilayer can be inferred from the existence of order transitions in lipid monolayers (Langmuir 1917; Traeuble 1977; Weis et al. 1984) and bilayers (Traeuble 1977; Janiak et al. 1979; Blume and Eibl 1979).

However, a phase transition of first order is not necessary for the existence of a threshold. A graded threshold arises whenever the susceptibilities are extremal. At any

susceptibility maximum, the response of the variables increases above a graded threshold of the applied thermodynamic force (Fig.6).

For example, the area response to a given step in surface pressure is very large at a maximum of the compressibility.

This "critical range" of highly susceptible states and the "all-or-none" transition across that range, can be induced by any thermodynamic force.

Correspondingly, various (if not all) susceptibilities become extremal simultaneously. For example, at a state of extremal compressibility of the phospholipids, the susceptibility to protonation becomes extremal, too. This effect gives rise to the apparent pK.

Quantitative magnitudes are derived for the model phospholipid dimyristoyl methyl phosphatidic acid which has an apparent pK of pH 4 to 5 that depends on surface pressure, temperature and pCa (Traeuble 1977).

The threshold force will be at most of a few pH units in case of neutral initial conditions pH 7. The threshold, (2) in Fig.6, required to induce the transition from the deprotonated state (1) will not be more than a few electrochemical units, ca. 60 mV per pH unit at room temperature. Therefore, voltage-induced action potentials in phospholipid bilayers should appear above a threshold of this magnitude. The voltage threshold depends on pH, pCa,

temperature, surface pressure.

7. Subthreshold and all-or-none potentials

Below threshold ((1) in Fig.6), the response of the phospholipids to perturbations is relatively small.

Most remarkably, the propagation velocity (Eq. 4) slows down at the threshold ((2) in Fig.6), since the adiabatic density derivative of the surface pressure is small. Truly critical slowing-down, i.e. $c = 0$, would occur if there were a second order phase transition. At first order phase transitions (dashed line in Fig.6), slowing-down takes place at the metastable state before onset of the transition.

The amplitude of the response increases dramatically when the threshold is exceeded ((3) in Fig.6). Further increase of the forces above threshold ((4) in Fig.6) does not significantly alter the response amplitude any more.

The amplitude of such "all-or-none" response depends on the extension of the transitional regime and therefore on all variables of the phospholipid bilayer.

An extension of the range of protonation, (2) to (3) in Fig.6, at the apparent pK by 1 to 2 pH units (Traeuble 1977) predicts electrochemical amplitudes of the action potential

of magnitude 1 to 2 units of 60 mV.

The amplitude of the mechanical displacement follows from the angle of rotation during transition. Complete rotation by 360 degrees corresponds to the pitch, ca. 1 μm in smectic liquid crystals (Brand, Cladis and Finn 1983). Rotation by 1 or a few degrees is possible at transitions due to the observed structural changes (Janiak 1979). Reversible displacement of magnitude 10 nm during the action potential is thus predicted.

Remarkable agreement is found with the magnitude of the threshold (Hodgkin 1938), the amplitude of subthreshold and of all-or-none action potentials (Hodgkin 1938; Katz 1966), and the mechanical displacement (Iwasa and Tasaki 1980).

We note that

a) lipid bilayers show many transitions, both continuous and first order; anyone could elicit action potentials with corresponding amplitude;

b) spontaneous oscillations can appear at first order transitions due to the unstable regime (positive slope of the dashed line in Fig.6);

c) biological phospholipid membranes do not show in general first order transitions, but at least one pK of extremal protonation susceptibility.

8. Voltage-clamp and action potentials

Two different experimental situations arise if

- the thermodynamic bilayer state is altered irreversibly, such as by temperature-jump in lipid bilayers (Tsong 1974) or by voltage-jump in squid axon membranes (Hodgkin and Huxley 1952);

- the thermodynamic bilayer state is altered reversibly, such as by a rapid voltage pulse which induces the action potential (Katz 1966).

Voltage-clamp relaxation experiments induce an irreversible transition (1) → (4), while propagating potentials arise after adiabatic excitation (1) → (4) → (1') with reversal of the transition (Fig.6).

The variables do not exactly return to the initial value (1) after the action potential due to dissipative effects.

9. Capacitive currents

The reversible component of the membrane currents during the action potential will be determined next. If Q is the effective charge and V is the observed electrostatic membrane potential across the bilayer, then the reversible capacitive current obeys

$$\frac{dQ}{dt} = C\frac{dV}{dt} + V\frac{dC}{dt} \quad (6)$$

The first term has been previously considered (Katz 1966) and represents the current when the capacity C is fixed. The second term, $V\frac{dC}{dt}$, is the current observed, e.g., when the voltage is fixed.

It is known that the membrane capacitance is that of the lipid bilayer, ca. 1 μF/cm at rest. Transitions in area and

bilayer thickness of magnitude 10 % or below (Janiak et al. 1979; Traeuble 1977) predict a change in membrane capacitance during the action potential of similar magnitude. By consequence, a dynamic capacitive current arises.

This dynamic capacitive current $V \frac{dC}{dt}$ is indistinguishable from an ohmic current. It is, however, capable of overshoot. An equivalent ohmic conductance of $\frac{dC}{dt}$ would produce the same current.

It is important to note that the dynamic capacitive current is out of phase by 90° with respect to the usual static capacitive current. The dynamic capacitive current is therefore in phase with an ohmic current but capable of overshoot against the applied voltage, in contrast to an ohmic resistor.

The magnitude of this capacitive, reversible conductance is determined as follows. A 1 millisecond pulse of 10% capacitance change corresponds to

$$\left(\frac{dC}{dt}\right)^{-1} \cong 10^4 \, \Omega \, cm^2$$

Cole and Curtis (1939) have observed a capacitance change of 5% and a resistance drop to 25 kohm cm^2 during the action potential in the squid giant axon.This observation was the basis to the interpretation of the action potential (Hodgkin 1976).

We conclude:

a) Clearly, the membrane current has a reversible component in agreement with our prediction. This reversible current is either in phase with dissipative ohmic currents, or out of phase by 180 degree. Overshoot of the action current has been observed in detail by Hodgkin and Katz (1949).

b) The current which is associated with the static capacitance, $C \frac{dV}{dt}$, has been previously considered in the situation of voltage-clamp, but not during the action potential (Hodgkin and Huxley 1952; Katz 1966). We have

$$C \frac{dV}{dt} \cong 10^{-4} \frac{A}{cm^2}$$

The static and dynamic capacitance therefore contribute to the reversible membrane polarisation current during an

action potential, $\frac{dP}{dt}$.

c) While, from the membrane point of view, the hydrodynamic excitation explains the appearance of the action current reversibly, from the electrode point of view, a major drop in apparent resistance accompanied by a small change in capacitance is expected and observed (Cole and Curtis 1939).

From the electrode view-point (Fig.5), the membrane current may be described, therefore, by a change in resistances in such a way that overshoot becomes possible (Hodgkin 1976).

10. Relation to ion channels

Action potentials, in contrast to ion channels, do not fluctuate. At squid giant axons (Conti and Neher 1980) and in pure lipid bilayers (Kaufmann and Silman 1983), both deterministic millisecond pulses and statistical opening and closing of ion channels were observed electrically.

On that basis, it has been concluded (Kaufmann 1985a) that action potentials are driven by the deterministic thermodynamic forces, while ion channels open and close due to the thermodynamic fluctuations in the lipid bilayer lattice. Defect structures in lipid bilayers have already

been proposed earlier (Helfrich 1981).

In contrast to action potentials, ion channels fluctuate even in thermodynamic equilibrium. Close to thermodynamic transitions with extremal susceptibility, the equilibrium fluctuations are extremal, too.

Thus, at the same transition, ion channels appear with increased probability in equilibrium, while nonequilibrium adiabatic excitations appear as all-or-none action potentials.

Nevertheless, action potentials can appear in the absence of ion channel defects, and should even be observable in monolayers. Action potentials are not composed of ion channels, although ion channel probability may be high during the action potential transition.

Ion channel defects in bilayers may vary in conductivity over many orders of magnitude, and diffuse only slowly, in contrast to the rapid propagation of solitary action potentials in monolayers, bilayers, and multilayer lipid membranes.

11. Protonic control

It has been earlier predicted that biological membranes represent favourable conditions for protonic control systems (Eigen and deMaeyer 1958).

Indeed, protons play a crucial role in the electrical effects during phase transitions in H_2O (Onsager et al. 1978), which have to be expected at the structured aqueous phospholipid surface. Proton pulses across lipid bilayers (Traeuble 1977) and propagating proton pulses along bilayers during actions potentials (Kaufmann 1985a) have been theoretically described.

Protonable phospholipids represent the majority of the membrane molecules. The densely packed phospholipid state is inseparable from the activity and electrochemical proton potential of the surface protons. Protons quickly relax to local equilibrium due to their semi-conductor like mobilities in water and ice (Eigen and deMaeyer 1958). Therefore, the local surface proton activity is in equilibrium with the phospholipid state and "slaved" to the slow macroscopic variables (Haken 1977).

It is remarkable to see that the high mobility of the protons, in the presence of sufficient proton activity, resolves at once the following problems:

A. Surface charge density

Protons rapidly move parallel to the phospholipid surface. Thereby, no longitudinal electric field can be built up parallel to the surface. Any density pulse in the membrane is electrostatically compensated by a surface proton pulse such that the effective surface charge density is constant on the slow, hydrodynamic time scale.

B. Local storage of electrochemical proton potential

Protons, surprisingly, diffuse very slowly away from the phospholipid surface into the bulk aqueous volume. In contrast to the semi-conductor like mobility along the surface which does not change but only propagates the excited lipid state, any diffusion away from the surface is equivalent to a change in the macroscopic phospholipid state. This transverse proton mobility is essentially that of the transition in the lipid bilayer chains and rather slow.

C. Propagating proton pulse.

In this way, a proton nonequilibrium surface potential is conserved for long (millisecond) relaxation times and propagated together with the phospholipid action potential.

One action potential of 1 cm extension of an axon of 10 μm circumference and 1 proton per phospholipid of density 1/50 $(A)^2$ would propagate up to 10^{11} protons.

The nonequilibrium pulse of the protons is coupled to a pulse of the water structure at the surface, similar to the electrical effects due to hydrated protons at phase transitions of H_2O (Onsager et al. 1978).

D. Constant magnitude of polarisation density.

The effective surface charge density is however constant within the pulse, due to the vanishing longitudinal electrical field (point A). Correspondingly, the magnitude of the polarisation density due to surface charge density and counterions is also constant during the action potential, and no ions except protons must move along the membrane.

Therefore, the assumption of constant magnitude of the polarisation made in section II is valid.

E. Absence of space charge effects.

Only if the proton activity is too small, at alkaline pH, the polarisation density is not constant, and space charge effects arise.

It is extremely important to realise that at neutral and

acid pH, the mobility of protons in water and ice (Eigen and deMaeyer 1958) thus provides for the localisation of the electrical phenomena to the membrane surface. This guarantees that the electrical action potentials are only due to rotation of the ordered polarisation density, and no space charge effects have to be considered at normal biological conditions.

Thus, the protons are "slaved" to the slow macroscopic variables (Haken 1977), the phospholipid state is inseparable from the local proton state, and the surface proton activity represents a slow l i p i d variable. In this sense, membranes represent most favourable conditions for protonic control systems as predicted (Eigen and deMaeyer 1958).

12. Role of proteins

The proteins of biological membranes have been considered in our theory by their activities ϱ^{α} and by their effect on the variables of the macroscopic lipid state. The symmetry arguments identified the lipid bilayer to carry the action potential. Thermodynamic principles rule out any independent origin of the phenomenon. For example, amplitude dependencies on specific ion activities, e.g. on

Na, K, Ca, cannot influence the qualitative result of the symmetry arguments.

Nevertheless, a crucial role is played by the proteins. Protein activities control the state of the lipid bilayer locally and specifically. It has to be expected that certain protein activities control the lipid responses in an ion-specific manner. E.g., the TTX-binding protein, and the specific Na,K-activated ATPase at the inner squid axon surface, may induce specifically action potentials, ion channels, and transport across and along the phospholipid bilayer. Protein activities are thus sufficient, but not necessary, to control the lipid mechanism of membrane excitation.

13. Predictions

The theory presented above predicts crucial experiments free of adjustable parameters. It can therefore be further tested directly. Among these predictions are:

- the absence of action potentials in racemic lipid mixtures;

- the absence of millisecond action potentials in the crystalline lipid state (only a motion of ferroelectric domains seems conceivable);

- the presence of action potentials in fluid lipid bilayers and monolayers;

- the propagation of action potentials in all non-racemic phospholipid bilayers;

- the presence of the polarisation pulse in all three spatial directions, across, along, and around the fibres;

- the presence of a capacitance change simultaneously with the density pulse;

- coupling during action potentials of electrical polarisation, membrane current; mechanical displacement, force; temperature, entropy; proton potential, proton activity; calcium potential, calcium activity; other ion potentials, ion activities; other thermodynamic surface variables and forces;

- the induction of action potentials by any of these thermodynamic variables above a certain threshold;

- reversible propagation of energy along the membrane in the action potential;

- propagation velocities of action potentials between 0 and a few 10 m/sec;

- saltatory propagation velocities of km/sec
  in three-dimensional smectic lipid multilayers.

The action potential represents a thermodynamic excitation and not a merely electrical phenomenon. Electrical action potentials are inseparable from force, displacement, temperature, entropy, and the other membrane variables. These variables are the property of an ordered fluid with macroscopic chirality, i.e., of the lipid bilayer.

Microscopic variables are excluded from the origin of action potentials. Single proteins may induce, and trans-membrane flows across the bimolecular layer may accompany the hydrodynamic excitation, the mechanism resides however in the macroscopic aspects of the lipid membrane.

Our results justify to approach a macroscopic description of action potentials (Tasaki 1968). The thermodynamic lipid bilayer mechanism of membrane function (Kaufmann 1977, 1985a,b) is generalized to hydrodynamics. It is worth noting that reversible electromechanical coupling has only recently been described in chiral smectics C* (Brand and Pleiner 1984) and was not available previously for the interpretation of action potentials in squid giant axons. The theory of liquid crystals therefore appears to provide a physical vehicle for the various aspects of the action potential.

Conclusion

We have shown that the temporal and spatial symmetry of the observed electromechanical coupling can only be obeyed if the origin of the action potential is a system with macroscopic chirality. We conclude that the action potential is a property of the lipid bilayers. A detailed mechanism for propagation and attenuation of action potentials has been proposed.

No fit parameters are introduced. The action potential by consequence is an ordered rotation of the molecular dipoles, brought about and propagated by the longitudinal density pulse in the membrane; dissipation is mainly due to shear viscosity. Subthreshold potentials, graded and all-or-none action potentials and the relationship to ion channels have been discussed.

We predict the presence of action potentials in lipid monolayers and bilayers, the participation of all hydrodynamic lipid variables, the control by protons, calcium, and protein activities, the propagation velocity, and saltatory conduction as well as the absence of the

electromechanical coupling in racemic lipid mixtures.

The macroscopic chirality is crucial and testable by the resulting polarisation pulse across, along, and around the squid giant axon in phase with the displacement. The concluded origin in the lipid bilayer and the electrical aspects of the action potential can be experimentally investigated in planar bilayer membranes.

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Fig.1.Geometrical coupling between polarisation and displacement.

We sketch the rigid geometric relationship between the polarisation $\vec{P}$, its deviation $\vec{\delta P}$ during the action potential and the displacement $\vec{u}$ along the helical axis which is due to the macroscopic chirality of the lipid bilayer system.

Fig.2. Mechanical displacement and electrical pulse during action potentials.
From Iwasa and Tasaki 1980 with permission.

The displacement perpendicular to the membrane (upper trace) is proportional to the electrical action potential (lower trace). This plot demonstrates the rigid relationship (Fig.1) between $\vec{\delta P}$ and the displacement $\vec{u}$ along the helical axis.

Fig. 3. Mechanical force and electrical pulse during action potentials. From Iwasa and Tasaki 1980

with permission.

The mechanical force measured perpendicular to the membrane (upper trace) is proportional to the time derivative of the polarisation (lower trace) during the action potential. The force results from the gradient of the velocity of the responsible anisotropic membrane fluid. The excitation is propagative. The opposite spatial inversion symmetry of velocity gradient and temporal derivative of the polarisation demonstrates that the force-polarisation coupling, too, originates from molecules of macroscopically ordered chirality.

Fig. 4. Origin of the electromechanical coupling during the action potential.

As already sketched in Fig.1, variations $\vec{\delta P}$ of the polarisation and the displacement $\vec{u}$ (which is, in general, not perpendicular to the planes of the layers) are rigidly coupled. We have plotted in Fig.4 qualitatively the spatial variation of the velocity field which couples to $\vec{\delta P}$ due to macroscopic chirality. Thus, Fig.4 symbolizes in an abbreviated fashion all main features of the action potential.

Fig. 5. Electrode view-point of the action potential.

The macroscopically ordered chiral molecules rotate during the propagating density pulse. The polarisation change has components in all three spatial directions. Shear also occurs during the ordered rotation and accounts for the dissipation of the action potential.

Fig.6. Threshold of the phospholipid action potential

Phase diagrams of phospholipid bilayers and monolayers demonstrate the appearance of a threshold for the onset of a transition. A thermodynamic force K as a function of an arbitrary variable n (e.g. surface pressure in dependence on area per lipid molecule) predicts the following lipid responses:

1. Resting state in the fluid lipid phase.
2. Non-propagative subthreshold excitation.
3. Transitional all-or-none excitation in the lipid state.
4. Small increase in amplitude above threshold of the stimulation.

Two experimental situations have to be distinguished:

a) Stepwise change in any force, e.g., temperature-jump or voltage-jump. The irreversible relaxation of the bilayer, e.g. (4) → (4) has relaxation times in the order of milliseconds.

b) Rapid applied pulse in the stimulating force. The adiabatic all-or-none lipid excitation (1) → (4) → (1') is propagative. The final state (1') is different from (1) due to the effect of dissipation.

Fig.1.

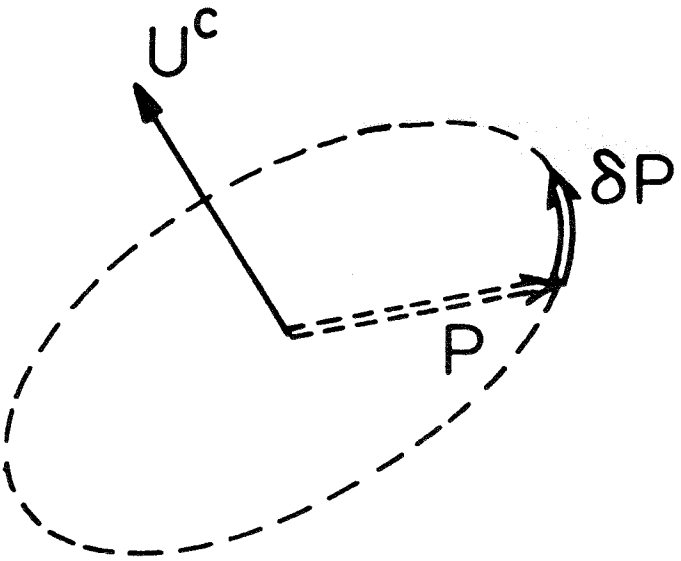

Fig.2.

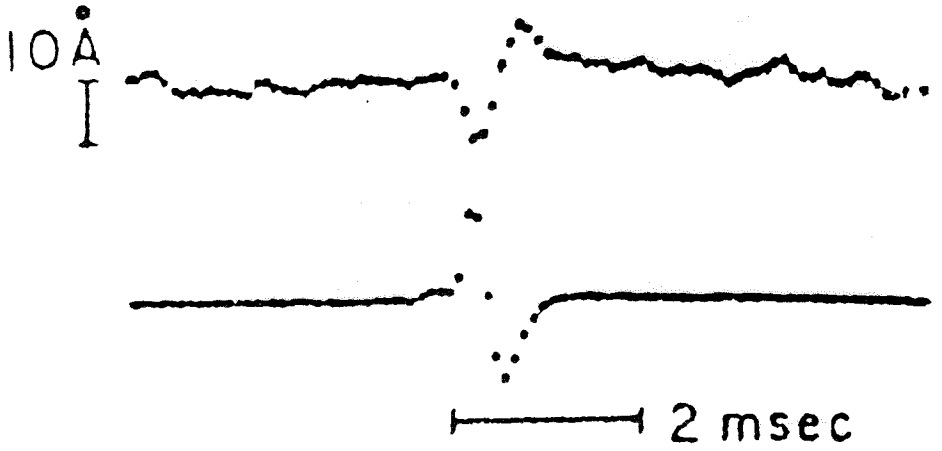

Fig.3.

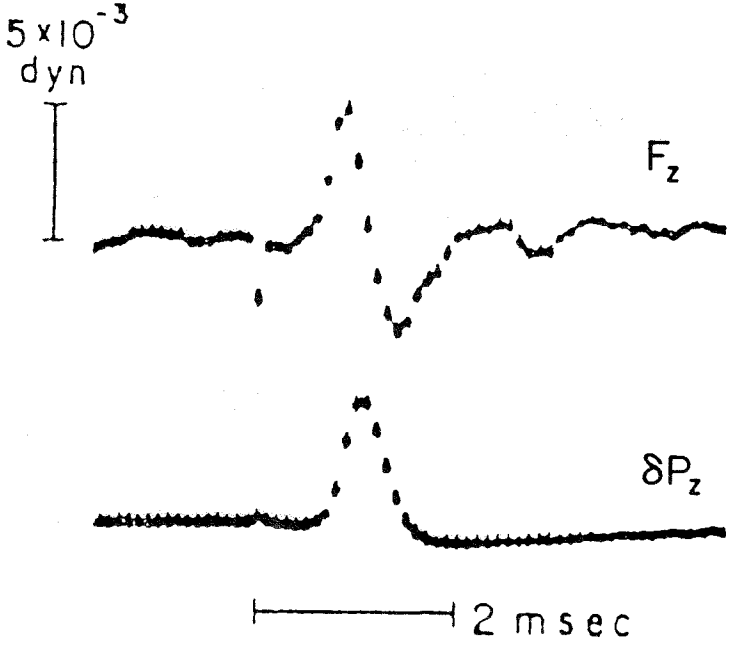

Fig.4.

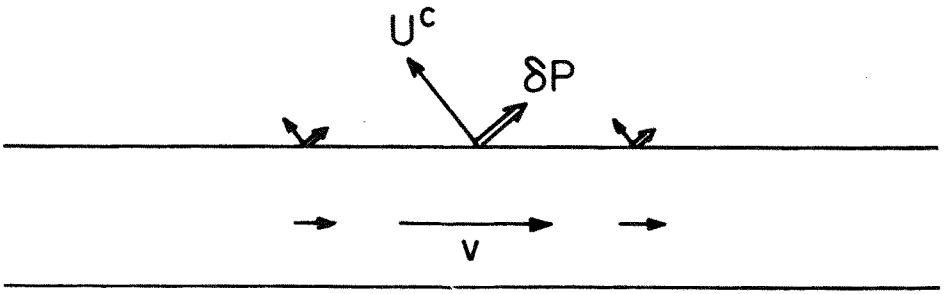

Fig.5.

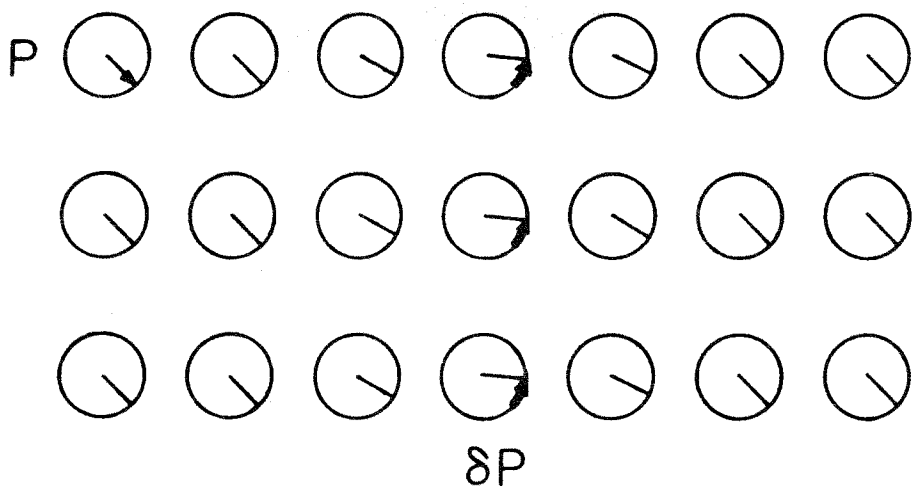

Fig.6.