A Review of the Applications of Solid State Physics Concepts to Biological Systems*†

Freeman W. Cope

Biochemistry Laboratory
U. S. Naval Air Development Center
Warminster, Pa. 18974 USA

ABSTRACT. The evidence for solid state physical processes in diverse biological systems is reviewed. Semiconduction of electrons across the enzyme particles as the rate-limiting process in cytochrome oxidase is evidenced by the peculiar kinetic patterns of this enzyme and by microwave Hall effect measurements. PN junction conduction of electrons is suggested by kinetics of photobiological free radicals in eye and photosynthesis. Superconduction at physiological temperatures may be involved in growth and nerve. Phonons and polarons seem likely to be involved in mitochondrial phosphorylation. Piezoelectricity and pyroelectricity may be involved in growth and nerve. Infrared electromagnetic waves may transmit energy in lipid bilayers of nerve and mitochondria. Complexed sodium and potassium ions in structured cell water may be analogous to valence band electrons in a semiconductor, and the free cations may be considered analogous to conduction band electrons. Ionic processes in cell water therefore resemble electronic conduction processes in solid semiconductors, which leads to kinetic predictions in agreement with experiment. The future of solid state biology depends on the development of new experimental methods able to measure solid state physical properties in biological materials which are non-crystalline, impure, particulate, and wet.

*Dedicated to Felix Gutmann, who stimulated me to write this, and whose book on organic solid state physics provides a foundation for biological solid state physics.

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I. Introduction

The physics and chemistry of the *liquid* state has been widely applied to biological systems. However in addition to liquids, cells contain *solids* (particles and membranes), so that it is reasonable to expect that events of biological importance might occur in the solid parts of cells, and that these events should be governed by the physics of solids. Only recently, and only in a few laboratories, has serious attention been given to this possibility.

Szent-Györgyi[1] in 1941 suggested a role for semiconduction in biology, but the high activation energies of semiconduction in many biological solids measured during subsequent years made this suggestion seem unlikely. However, a particular protein (cytochrome oxidase), which gives kinetic evidence of semiconduction, was measured to have a much lower semiconduction activation energy, approximately equal to the activation energy of the enzymatic reaction catalyzed by this protein, which supports the concept of a semiconductive mechanism. Evidence for other sorts of solid state physical processes in cells (P-N junction conduction, superconduction, piezoelectricity, infrared electromagnetic wave transmission) has also been developed in recent years.

The only previous comprehensive reviews of solid state biology were those of Rosenberg and Postow[2] in 1969 and Cope[3] in 1970. Much has been done since then. The present review will update the 1970 review of Cope.[3] We shall describe in considerable detail work appearing since 1970, but earlier work will be described less completely, and the previous review[3] should be consulted if more details are needed regarding earlier studies. For general background in theory and experiment of organic semiconduction, the books by Gutman and Lyons[4] and Boguslavskii and Vannekov[5] may be consulted.

Solid state biology has been approached in two different ways from two opposite ends of the problem. The two approaches are described in partial separation in the next two sections of this review.

First, purified organic solids, extracted from living animals or plants, have been tested for various solid state physical properties such as semiconduction, superconduction and piezoelectricity. These and other solid state physical phenomena have indeed been observed in purified biological solids. One does not immediately know, however, whether the solid state physical properties of isolated, purified biological solids necessarily play any role in the function of living systems. They might not.

Second, solid state biology has been approached from the other end. Some observed properties of *organized living systems* are not easy to explain in terms of chemical processes in aqueous solutions, but may be derived readily from hypotheses of solid state physical processes in cells. One may then use the observed characteristics of organized living systems to deduce the quantitative properties of solid state physical phenomena which may cause them. One may then compare these deductions with the observed solid state physical properties of purified components of these complex organized living systems.

II. Solid State Physical Phenomena in Components of Living Cells

A. Semiconduction. In 1941, Szent-Györgyi[1] hypothesized that semiconduction of electrons in solid proteins or DNA might play a role in biological function. This idea led many investigators to measure the temperature dependence of electron conductivity for dried, compressed pellets of many components and extracts of biological systems, such as proteins or cell fragments. In general, the data did indeed conform to the semiconduction equation

$$\sigma = \sigma_0 \exp(-E_a/kT) \tag{1}$$

where σ = measured conductivity, E_a is activation energy of semiconduction, k is Boltzmann constant, T is absolute temperature and σ_0 is a constant. However, the value of E_a was usually in the region of 1.0 ev, so that conductivity at physiological temperature was very low, perhaps too low to

serve any useful biological function, and the 1.0 ev was much higher than the observed activation energies of most biological processes.[6] For these reasons, by the middle 1950's, most investigators concluded that semiconduction probably played no role in biology.

Several important points had however been overlooked.

First, the possible influence of water was overlooked. Measurements of semiconduction had been made only in *dried* systems. Living systems function only when wet (80 percent water). Water as an impurity at the surface of tiny biological particles or membranes might change electron conductivity by many orders of magnitude, as impurities adsorbed on thin film inorganic semiconductors are often observed to do. This effect of water adsorbed on a thin film semiconductor is used for humidity measurement in a commercially available humidity meter. The experiments of Rosenberg[7,8] suggest that the presence of water may indeed cause significant changes in conductivity and activation energy of semiconduction of proteins. A pulsed electron beam method with wet protein films in Russia seems to show the same result.[5,9]

Second, it was overlooked that a few proteins might exist which had unusual structures, specially adapted for high electron conductivities and low semiconduction activation energies. Cope[10] showed that the enzyme cytochrome oxidase had kinetic properties which suggested that it was rate-limited by solid state conduction in this particular protein (which has a specific and complicated structure quite different from most proteins). Then Straub[11,12] measured semiconduction activation energy in this particular protein, cytochrome oxidase, and found it to be approximately 0.3 ev (3 times lower than with most proteins, the high values of which were confirmed by Straub). It therefore seems that although most proteins do indeed have very high values of semiconduction activation energy which make them poorly suited to perform biological functions by semiconduction, there is at least one specialized protein with a low activation energy well suited to the biochemical role which it seems to play.

Third, it was overlooked that electron conduction *within* individual solid particles might be quite different from conduction across interfaces from particle to particle, which may be what one measures when one puts electrodes across a compressed mass of thousands of microscopic particles. To measure electron conductivity *within* individual tiny biological particles, a microwave Hall effect technique was developed by Trukhan[13,14] in Russia, and applied to various biological particles by various investigators.[14-22] The results seem to show that electron conductivities within individual biological particles may be much higher than previously deduced from conductivities of compressed masses of particles, and that cytochrome oxidase activity is positively correlated with microwave Hall effect mobility of electrons.[19,20]

It therefore seems likely that semiconduction within solid biological particles may indeed play a role in biological function in at least a few important biological systems, especially in the enzyme cytochrome oxidase. For more details and references to the earlier work, the previous review[3] may be consulted.*

B. PN Junction or Activation Energy Barrier Conduction. Conduction across an activation energy barrier, such as at a PN solid-state junction or liquid-solid junction of an electrode in an aqueous solution commonly shows a exponential or logarithmic voltage-current equation.

In exponential form

$$I = I_0 \exp(V/kT) \tag{2}$$

is known as the diode equation. In logarithmic form

$$V = a + b \log(I) \tag{3}$$

is known as the Tafel equation of electrodes, where V is voltage, I is current, k is the Boltzmann constant, T is absolute temperature and a and b are constants.

Liquid-solid, and solid-solid interfaces are common in biological systems. Therefore, this type of conduction might be expected in biological systems. Its existence has been deduced from behavior of organized systems as described in Section III of this review.

C. Phonons and Polarons. It has been proposed by Straub[11,23,24] that phonons (packets of lattice vibrational energy) may be involved in transmission of energy from oxidative reactions to phosphorylative reactions in solid protein systems such as membranes of mitochondria. Destruction of the phonons in the solid protein by thermalization may be prevented by the hydrophobic bonding of a layer of lipid separating the protein from the surrounding water.[24] The mitochondrial processes of respiratory control, reversed electron flow, uncoupling, and utilization of two electron transfer to accomplish one bond formation seem to be compatable with the phonon hypothesis.[11,23-26]

Phonon coupling between a pair of electrons to form a superconductive Cooper pair may also occur in biological systems at physiological temperatures. Biological superconduction will be discussed in the next section of this review.

A problem with the concept of phonons in mitochondria is probable lack of mobility, because these phonons would need to have an energy of approximately 0.39 ev (9.0 kcal/mole) which is the energy required for phosphorylation of ADP (the chief phosphorylation reaction carried out by mitochondria). Phonons of this energy are *optical* phonons (wavelength

*Good experimental evidence for electronic conduction in lipid membranes[167-169] and across the shells of crabs[170-172] is also available.

3.24 microns in the infrared band). Optical phonons are generally immobile, so that transport of energy by phonons from sites of oxidation to sites of phosphorylation might be expected to be slow.[25] However, the structure and geometry of the lipid bilayer of mitochondria seems well adapted to carry infrared electromagnetic waves (photons), which could serve as a rapid and efficient method to carry the energy of the phonons throughout the mitochondrion.[25] This mechanism is discussed in Section IIIC of this review.

That polarons rather than phonons may be the vibrational packets in mitochondria is suggested by the reversal at low temperatures of the enzyme activity vs (1/T) curve of cytochrome oxidase measured by DeVault and Chance[27] as analyzed by Cope and Straub.[12] Such a reversal is predicted from the concept that the charge carriers in solid cytochrome oxidase are polarons, according to the theory of Holstein.[28,29] A polaron is an electron or hole tied to a phonon. The probability of polaron conduction in organic semiconductors has been discussed by Siebrand[30] and by Gutman and Lyons.[4]

It has been suggested by Kemeny and Rosenberg[159] that polarons may be the charge carriers in proteins and other organic semiconductors, and may be responsible for the observed compensation law in these substances.

Volkenstein[160] has proposed a state in a protein which he calls a conformon, which he claims should be different from a polaron because of the non-regularity of the atomic lattice, resulting in lack of mobility and short lifetime. This has been studied further by others.[165-166]

It has been proposed on theoretical grounds that melanin (the black pigment found in skin, eye, and in parts of the brain and ear) may be a particularly efficient converter of photons to phonons and of the reverse process.[161-162] Evidence suggesting the phonon to photon conversion by melanin was the observation that ultrasound (10^4 Hz) was more damaging to cells containing melanin than to similar cells without melanin, correlated with previous observations that photons of high intensity light are more damaging to cells if melanin is present.[163-164] At lower intensities, however, melanin protects cells against damage by light.[162]

D. Superconduction. Superconduction is the conduction of electrons without the generation of heat, and hence with an electrical resistance equal to zero. Until recently, superconduction had been observed only in certain metals and only at a temperature colder than approximately 20° Kelvin. Theorists have long predicted that superconduction might occur at room temperature in organic solids. The development of new techniques of very high sensitivity has now led to the experimental detection of superconductive transitions in organic solids (various cholates) at temperatures as high as

277°K. Indirect evidence suggests that superconduction plays a controlling role in various functions of living systems at physiological temperatures.

A comprehensive mathematical theory (the BCS theory) of superconduction has been developed which explains and predicts many (but not all) of the experimentally observed electrical and magnetic properties of superconductors[31] and properties of electron tunneling across junctions between superconductors.[32,33] An extension of the BCS theory by Little[34,35] predicted that superconduction should occur in certain types of organic polymers *at room temperatures and above.* There is much controversy among theoretical physicists regarding the validity of this prediction.[36] All attempts to synthesize Little's superconductive polymers have so far failed, which may be due to inadequacies of the attempts.

Pauling[37] and London[38] claim that electron currents around benzene rings in aromatic compounds are analogous to superconductive currents in metals. This claim is disputed by Musher.[39,40] However, much quantitive data on magnitudes of chemical shifts of observed nuclear magnetic resonance spectra of compounds containing benzene rings is explainable in terms of superconductive ring currents.[41-45]

High temperature superconduction has also been predicted in a thin metal film adjacent to a dielectric layer, where the interaction between the two electrons of the pair occurs through the dielectric instead of within the conductor.[36,46-48] All attempts to manufacture such superconductive bilayers or sandwiches have failed, perhaps because the correct method was not tried.

Experimental evidence of superconduction in organic solids at high temperatures has been obtained very recently by Halpern and Wolf.[49-51] These findings required the use of new instrumental methods for the measurement of extremely small changes in magnetic susceptibility.[49-51,177] Transitions (abrupt changes) in susceptibility as a function of temperature and of applied magnetic field were observed in various cholates (4 rings with various side chains).[49-51] The rise of susceptibility is predicated on the concept that transition from normal to superconducting regions would initiate the Meissner effect which would cause internal magnetic field changes to be less than those imposed externally. X-ray diffraction patterns were observed to be unchanged at temperatures across the transition temperature, which showed that no change occured in the in the structure of the atomic lattice.[52] Therefore, the transition must be due to *electronic* rearrangements. A change between superconducting and normal conducting state was the most obvious possibility, and was consistent with the experimental data.[49-51,177] Transition temperatures observed for the cholates were as high as 277°K. Other types of organic compounds studied did not show evidence of superconductivity.[50,51] Cholates showed superconductive phenomena only when crystallized in

certain ways.[50-51,177] The heights of the observed transitions were small, which indicated that only a small fraction of cholate molecules were in the superconducting state at any given time.

Extrapolation[52] of the experimental data on cholates[49-51,177] suggests that cholesterol (a major constituent of nerve and of other tissues) may superconduct at physiological temperatures and above, so that cholesterol might be a site of superconduction in living systems.

Another experimental observation of probable high temperature organic superconduction is the recent data of Antonowicz.[54] He observed fluctuations in current through thin carbon films at room temperature as a function of magnetic field at very low fields (0.5 to 2.0 Gauss), with a pattern like that seen with the Josephson effect for two-electron tunneling at superconducting junctions. No other known physical phenomenon seems adequate to explain this experimental finding.

There is evidence suggesting that high electric fields may promote superconduction in organic fields at high temperatures, and that this might play a role in nerve conduction.[53] The room temperature Josephson effect of Antonowicz[54] in carbon films required a 2 volt electric potential across a carbon film that was presumably only a few molecules thick, so that the electric field would be very high. Magnetic fields of 2000-3000 Gauss cause changes in photocurrent in organic solids (anthracene and tetracene) at room temperature but only if the voltage is sufficiently high to be above the ohmic conduction region and into the square law conduction region.[55] This probably implies charge injection into the organic crystal.[53,55] The magnetic effects in both the above sets of experiments, as well as the square law conduction, may be understood from the hypothesis that high voltage electron injection into organic solids may produce superconductive Cooper pair charge carriers.[53] It is reasonable to consider that this superconductive process might occur in the thin lipid layers of nerve in response to the high electric fields which occur there,[53] especially since extrapolation of the data on cholates suggests that cholesterol (which occurs in large quantities in nerve) should superconduct at physiological temperatures.[52]

The evidence for high temperature superconduction in organic solids raises the possibility that superconduction in solid portions of cells might play a role in living systems. Three lines of indirect evidence suggest that this is so.

First, that bulk superconduction may play a biological role is suggested by the abrupt changes in rates of metabolism of growing tissues induced by magnetic fields of 50 to 150 Gauss,[56-58] although lower fields produced no effect, the higher fields produced no additional effect. A superconductive transition is the most obvious possible cause of a discontinuous effect produced by a magnetic field.[56]

Second, a role in biology for *two*-electron superconductive tunneling (Josephson effect) is suggested by the demonstration tnat numorous living systems (birds, insects, snails, and possibly man) can detect very low magnetic fields (0.5 to 1.0 Gauss).[59,60] No physical phenomenon other than the Josephson effect seems to have sufficiently high magnetic sensitivity to provide the physical basis for this observed biological magneto-detection.[59,60] In addition, the rates of some biological processes are observed to show *negative* temperature coefficients, which cannot be explained by ordinary chemical and physical rate processes, which all show *positive* temperature coefficients. However, Josephson superconductive tunneling has a *negative* temperature coefficient and hence could provide a physical basis for these observed biological phenomena.[56]

Third, a controlling role for *single*-electron superconductive tunneling in living systems is suggested by the temperature dependences of the rates of certain nerve and growth processes.[56] For the rates of most biological processes, like most chemical processes, the temperature dependence is given by linear plots of log of rate vs 1/T (a linear Arrhenius plot). However, a few biological processes show curved Arrhenius plots, and some of these are described by the equation

$$E_a^2 = aT + b \tag{4}$$

where E_a is the activation energy, measured from the slope of the Arrhenius plot, T is temperature in degrees Kelvin and a and b are constants. This type of temperature dependence is predicted for and observed in *single*-electron superconductive tunneling.[56] Therefore, one may surmise that these biological processes (all involving either nerve or growth) are rate-limited by single-electron superconductive tunneling.[56]

E. **Piezoelectricity and Pyroelectricity.** A piezoelectric solid is usually defined as one which generates a voltage proportional to an applied mechanical force, due to mechanical distortion or displacement of electric dipoles in the lattice.[61] Piezoelectricity has been observed directly in bone[62,63] and wood[64] by measuring electrical potentials induced by bending or compression.

Biological materials which are available only in powdered form cannot be tested for piezoelectricity by the *direct* method used for bone and wood. However, an *indirect* method capable of measuring weak piezoelectricity in powders is available and has been applied to dry biological powders. This method was developed by Giebe and Sheibe[65] and has been improved by others.[66-70] It uses the principle of the vacuum tube crystal oscillator, which has for many years been used as a source of frequency-stable radio-frequency voltage. In this circuit, a piezoelectric quartz crystal, cut to a size and shape to allow mechanical vibration resonance at the desired radiofrequency, is placed between metal electrodes, which are connected

to a vacuum tube feedback circuit. The entire electro-mechanical system then goes into oscillation, which generates a sinusoidal voltage whose frequency is determined by the mechanical properties of the piezoelectric crystal.

Because electrical oscillation in this type of circuit depends on the piezoelectricity of the crystal, the electrical oscillations can be used to detect piezoelectricity in the crystal. The same may be done if a compacted powder is used instead of a single crystal.

To obtain highest sensitivity of detection of weak piezoelectricity in powdered materials, special superregenerative oscillator circuits have been developed in which the amplitude of oscillation is decreased at frequencies at which piezoelectric resonance occurs in the powder.[65-70] These circuits have been used to measure the piezoelectric spectrum of biological materials as a function of frequency and temperature by Duchesne and Monfils[69,71-73] and others.[70,74-77]

Duchesne and Monfils[69,71-73] observed that the positions of the peaks in the piezoelectric spectrum showed a temperature dependence which could be described by the equation

$$\Delta = \frac{-1}{f}\frac{df}{dT} \tag{4A}$$

where df/dT is the observed change in the frequency (f) of the piezoelectric absorption peak per unit change in temperature (T), f is the approximate frequency of the peak, and the calculated constant (Δ) turns out to have approximately the same value for all peaks at all frequencies for any particular type of powdered sample. Δ is therefore a measurable piezoelectric constant characteristic of each organic or biological powder. Duchesne *et al*[69,71-73] believe that the constant Δ is related to other physical parameters of the solid by equation

$$\Delta = \alpha\gamma \tag{4B}$$

where α is the thermal expansion coefficient of the solid sample, and γ is the Grüneisen constant,[78,79] which is a dimensionless measure of the change in entropy with volume of the crystal.

Measured values of Δ for various biological and non-biological powders are given in Table 1.

We should like to know whether the observed piezoelectric properties of these biological materials play any role in function of living systems. They might or might not.

The characteristics of several biological processes suggest that piezoelectric phenomena do indeed perform biological functions.

First, it is observed that the architecture of bone continuously adapts itself to the mechanical loads placed upon it.[80] Growth of bone is

TABLE 1

Piezoelectric Temperature Coefficient of Various Substances

Sample	Δ ($\times 10^{-6}$) $(°C)^{-1}$	Reference
Quartz	6	77
Zinc sulfide	46	77
Potassium sodium tartrate	400	77
1-Chloramphenicol	100	71
DNA (thymus)	50	73
DNA (sperm)	56	73
DNA (yeast)	18	77
RNA (yeast)	6	77
Myosin	85	73
Actomyosin	100	73
Collagen	47	73

The constant Δ is characteristic of the material and is calculated by equation 4A from measurements of the frequency shifts of piezoelectric resonance absorption peaks as a function of temperature, which are measured as described in the text.

experimentally observed to be controllable by applied electric potentials.[81,83-88] Piezoelectric potentials of bone, generated in response to mechanical stress on the bone, may then serve to control the growth of bone to adapt it to the stresses placed upon it.[82]

Second, growth of tissue is stimulated by implantation of piezoelectric dusts.[89-91]

Third, the temperature dependence of the resting potential of nerve is observed to conform to the temperature dependence of piezoelectric resonance.[92] Petrov[93] has theorized that a membrane potential may be dependent on piezoelectric (flexoelectric) properties of liquid crystalline lipids. Piezoelectric properties of liquid crystals have been studied theoretically[94-97] and experimentally.[98,99] Therefore, piezoelectricity may be involved in nerve function.

Fourth, some of the observed properties of muscle stretch receptors may be derived from the hypothesis that piezoelectric elastic polymers are involved in detection of muscle stretch.[100]

Piezoelectric materials are usually also pyroelectric, which means that an electric potential is generated by the application of heat or cold. Pyroelectricity has been measured directly in tendon and bone,[149-155] meninges,[156] spinal cord,[149] and nerves.[156] Also, it is observed that the electrical responses of temperature sense organs of living systems show behavior which is typical of pyroelectric materials.[100] Application of a square pulse of increased temperature causes transient nerve responses of opposite sign at the two ends of the temperature pulse[100] (Fig. 1). This suggests that pyroelectricity does indeed play a role in biological temperature detection.

F. Amorphous Semiconductor Switching. McGinness *et al*[157] have shown that melanins (from melanoma tumors or synthetic melanins) switch from low current to high current when voltage is increased past a certain threshold voltage, which resembles the switching behavior of inorganic amorphous semiconductors (Ovshinsky effect). The increase from low to high current is 10 to 1000 times.

The mechanism of this effect in inorganic materials is in dispute, so that extrapolations of mechanism from inorganics to melanin have not been made. Some information regarding the mechanism of switching in melanin has been deduced from the experiments of McGinness *et al.*[157]

First, the current in the on-state is mostly electronic rather than ionic, because weight loss of sample which would occur if water were lost by electrolysis is negligible.[157]

Second, even though conduction is electronic, water is necessary for switching, because thoroughly dried melanin does not switch, but switching ability is recovered when the melanin is slightly hydrated.[157] Perhaps, water alters electronic conductivity of the melanin by lowering the activation energy for conduction of electrons between sites, analogous to the mechanism proposed by Rosenberg[8] for proteins. This requirement for water for switching to the high conductivity state may be related to the requirement for water for reversibility of electron transfer measured by generation and decay of photogenerated free radicals in eye melanin.[158]

The voltage threshold for switching for hydrated melanin is approximately 500 volts/cm which is much lower than the 5×10^5 volts/cm observed for cytochrome C, which is comparable to the values of voltage threshold observed for inorganics.[157] Various other organic materials of biological origin were tested and found not to show switching behavior.[157]

It would be interesting to know whether switching behavior in melanin plays any role in biological switching processes in regions where melanin occurs, such as skin, retina, brain, or ear.

III. Solid State Processes in Integrated Biological Systems

A. Growth. It is experimentally observable that a living bone grows continuously in a way that adapts it to withstand the stresses to which it is subjected.[80] The boney struts on the inside of a long bone (e.g. the leg bone) are located along the lines of stress. During life, a bone may change its structure to increase or decrease its strength to adapt to the loads habitually placed upon it. For example, a longshoreman's bones

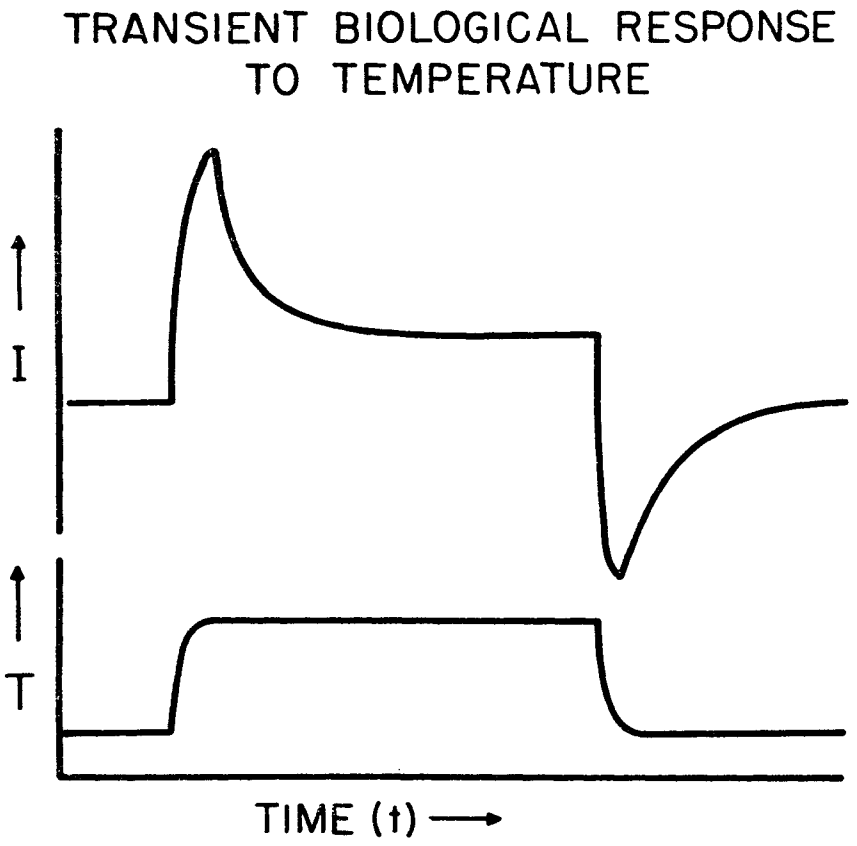

Fig. 1. Transient Biological Response to Temperature Pulse. Lower curve shows a pulse of temperature (T) applied to biological system during the passage of time (t). Upper curve sketches the form of a typical pattern of biological response (I), with transients of opposite sign at the start and end of the temperature pulse, and a steady state response after the initial transient has faded away.[100]

will become much stronger than average, while a person who remains in bed for some months will develop lighter bones. There must therefore exist some sort of system which controls the growth of bones in response to applied stress. It has been observed that application of a D.C. electric potential to the end of a broken bone causes growth.[81,83-88] It has also been observed that bones are piezoelectric, i.e. bending a bone generates an electrical potential.[62,63] It was therefore suggested by Becker, Bassett and Bachman[82] that these two phenomena working together might serve as a closed-loop feedback system by which the body controls the growth of bones in response to the applied stresses.

An additional indication of a relation of piezoelectricity to growth is the observation that implantation of peisoelectric dusts stimulates tissue growth.[89-91]

That superconductivity participates in cell growth is suggested by two lines of evidence. First, various growth processes show a temperature dependence described by a linear relationship between temperature and the square of the activation energy.[56] Such behavior is predicted and observed for single electron superconductive tunneling.[56] Second, the incidence of cancer throughout the world is a periodic function of earth's magnetic field for very low fields.[101] Such behavior is characteristic of two electron Josephson superconductive tunneling.[101]

B. Photobiological Systems (Eye and Photosynthesis). When light falls on a biological system, it may kick an electron up out of its resting position into some other state. One may know that this has happened by the observation by electron spin resonance spectroscopy of generation of free radicals (unpaired electrons) when the biological system is illuminated. This can be observed with illuminated particles (melanin granules) from the eye[102] and with photosynthetic particles (chromatophores) from bacteria.[103] Because decay of the free radical concentration after the end of illumination is slow (several seconds), there must be a barrier of some kind between the illuminated and resting positions of electrons.

Because these biological systems are solid particles floating in watery solution, it is reasonable to suppose that the laws of solid state physics apply within the particle, and that the particle surface acts as a solid-liquid interface, to which electrode physics should apply.

A simple hypothesis for such a system as to why return of illuminated electrons to equilibrium might be slow is that light has kicked the electrons across an activation energy barrier at the particle surface. Activation energy barriers at liquid-solid interfaces are commonly observed[105-107] in electrode physics, and give rise to a voltage-current relation across the interface of the form

$$V = b - \frac{RT}{Fa} \log_e(-i) \tag{5}$$

where V is voltage across the interface, i is current across the interface, T is absolute temperature, R is the gas constant, and a and b are constants. In electrode physics, this relationship is known as the Tafel equation,[104,105] but the same relation (written in exponential form) is seen in solid state physics at solid-solid interfaces, at which it is known as the diode equation. The use of equation 5 for electron conduction across interfaces is well justified on the basis of experimental observation. It also has a theoretical

basis, because it may be derived from the concept of electron conduction across an activation energy barrier at an interface by charge carriers having a Boltzmann distribution of energies and constant charge carrier concentration.[3,105]

We might like to test the hypothesis of an interfacial activation energy barrier in a particulate photobiological system by testing for conformity to equation 5. Unfortunately, a *direct* test is impossible because the eye melanin particles and photosynthetic particle are so small that one cannot make electrical contacts to the two sides of the interface in order to measure the voltage-current curve. An indirect test however, is possible because equation 5 leads to a prediction regarding the shape of the decay of concentration of unpaired electrons vs time after the end of illumination, which can be measured by electron spin resonance.

We may derive the concentration vs time curve as follows:

Let us consider a liquid-solid interface at a particle surface, across which electron current flow is described by equation 5. In the solution outside the particle, let there be an ion (a small molecular weight substance) which can exist in either the oxidized or reduced state, depending on whether it has gained or lost an electron from the nearby solid surface. This reaction may be written

$$x_{ox} + \epsilon^- \rightleftharpoons x_r$$

where x_{ox} and x_r are the oxidized and reduced forms of substrate molecule X respectively, and ϵ^- represents an electron, which may be rapidly and reversibly exchanged between the molecule X and the solid surface of the biological particle. According to theory and experiment of electrode physics, the particle surface then experiences an electrical potential *(V)* given by the familiar electrode equation

$$V = V_0 + (RT/F) \log_e (x_{ox}/x_r) \tag{6}$$

where x_{ox} and x_r are concentrations of oxidized and reduced forms respectively of substate molecule X, V_0 is a constant, and the other symbols are constants as previously defined. Because the sum of oxidized plus reduced forms of X-substrate is always constant $(= C_x)$, we may write

$$x_{ox} + x_r = C_x \tag{7}$$

Combining equations 6 and 7, we obtain

$$V = V_0 - (RT/F) \log_e \left[x_r/(C_x - x_r) \right] \tag{8}$$

If as assumed, light kicks electrons across the particle surface, it disturbs the equilibrium between the two sides of the surface and sets up an electrical potential difference across the surface. Decay of photogenerated unpaired electrons then consists of conduction of electrons back across the

surface in accord with the conduction equation (equation 5), driven by the potential difference of equation 8 for the potential on the liquid side of the surface minus a constant potential which we shall assume for simplicity on the solid side of the surface (this merely assumes an electron concentration in the solid that is large compared to the number of electrons transferred). *The surface reaction described above is equivalent to an electric circuit consisting of a diode connected across a battery.*

We may then equate the driving potential across the interface (given by equation 8 minus a constant) to the voltage drop across the interface given by equation 5 to yield

$$-\frac{RT}{F}\log\left[x_r/(C_x - x_r)\right] = \frac{RT}{Fa}\log(-i) + B \tag{9}$$

where B is a new constant. Because the conduction of one mole of electrons across the particle surface reduces (or oxidized) one mole of substrate molecules, we may write

$$i = F\,dx_r/dt \tag{10}$$

where t is time. Substituting equation 10 in equation 9, we obtain

$$-\frac{RT}{F}\log\left[x_r/(C_x - x_r)\right] = \frac{RT}{Fa}\log\left[-F\frac{dx_r}{dt}\right] + B \tag{11}$$

which is easily converted to

$$-\frac{dx}{dt} = \frac{1}{Fg}\left[\frac{x}{C_x - x_r}\right]^a \tag{12}$$

where g is a new constant. If a = 1, as is theoretically the case for an ideal electrode surface,[108] and if reaction velocity (v) is defined as $v = dx/dt$, then equation 12 may be written in the form

$$\frac{1}{v} = \frac{Fg}{1}\left[\frac{C_x}{x_r} - 1\right] \tag{13}$$

which may be compared with the classical rate equation of Michaelis-Menten for enzyme kinetics

$$\frac{1}{v} = \frac{1}{V}\left[\frac{K_s}{s} + 1\right] \tag{14}$$

where s is substrate concentration and V and K_s are constants.

The rate equation of classical enzyme kinetics (equation 14) is derived from the hypothesis of reactants in free solution obeying the mass action principle, while equation 13 was derived from solid state and electrode physics concepts. Equation 13 and 14 both predict linearity of a double

reciprocal plot of reaction velocity vs substrate concentration, but differ in that they predict opposite signs for the intercepts on the 1/v − axis.

The relevance of the solid state activation energy barrier equation (equation 13) to biology is supported by the fact that decay of photo-generated free radicals in eye melanin particles (Fig. 2) conforms to equation 13 and so does the decay of photoconductivity (Fig. 3) in invertebrate nerve.

Equation 12 for activation barrier kinetics may be put into another form, which is sometimes more convenient for application to experimental data, and which shows an important correlation with experimental solid state physics. This is true because the function log $[x_r/(C_x - x_r)]$ may be adequately approximated by a linear function of x_r which may be shown in the following way: Let us define a new variable λ equal to that fraction of total substrate concentration which is present in the reduced form. Hence, λ is defined by

$$\lambda = x_r/C_x \tag{15}$$

A graph of (Fig. 4) of the function $log_{10}[\lambda/(1-\lambda)]$ *vs* λ shows that $log_{10}[\lambda/(1-\lambda)]$ can be expressed fairly accurately as a linear function of λ for values of λ between approximately 0.15 and 0.85. By measuring the slope and intercept of the straight line approximation, we may write the approximate equation

$$log_{10}\left[\frac{\lambda}{1-\lambda}\right] = 2\lambda - 1 \tag{16}$$

The right hand side of equation 16 is actually the first two terms of the Taylor series expansion of the left hand side. Substitution of equation 15 in equation 16 and conversion to *log* to the base *e* gives

$$log_e\left[\frac{x_r}{C_x - x_r}\right] = \frac{4.6x_r}{C_x} - 2.3 \tag{17}$$

Equation 17 may be written in the form

$$\left[\frac{x_r}{C_x - x_r}\right] = exp\left[2.3\left(\frac{2x_r}{C_x} - 1\right)\right] \tag{18}$$

Equation 18 may be substituted in equation 12 to give

$$-\frac{dx_r}{dt} = me^{nx_r} \tag{19}$$

where m and n are new constants defined by

$$m = \frac{A'}{Fg}\ exp(2.3a) \tag{20}$$

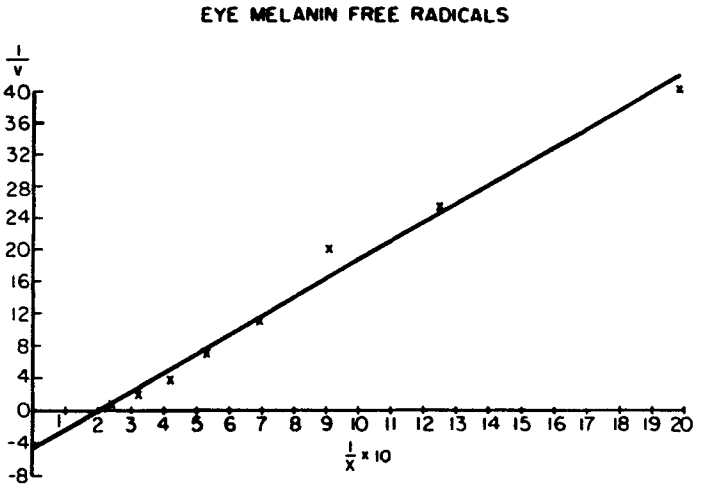

Fig. 2. Double Reciprocal Plot for Decay of Eye Melanin Free Radicals. x = substrate (free radical) concentration. v = reaction velocity = $-dx/dt$. This graph shows a *negative* intercept on the 1/v-axis, which may be contrasted with the *positive* intercept seen in the usual Lineweaver-Burk plot of data from an enzyme reaction conforming to Michaelis-Menten kinetics. Experimental data was obtained from electron spin resonance analysis of eye melanin particles in aqueous suspension at end of illumination with visible light.[109]

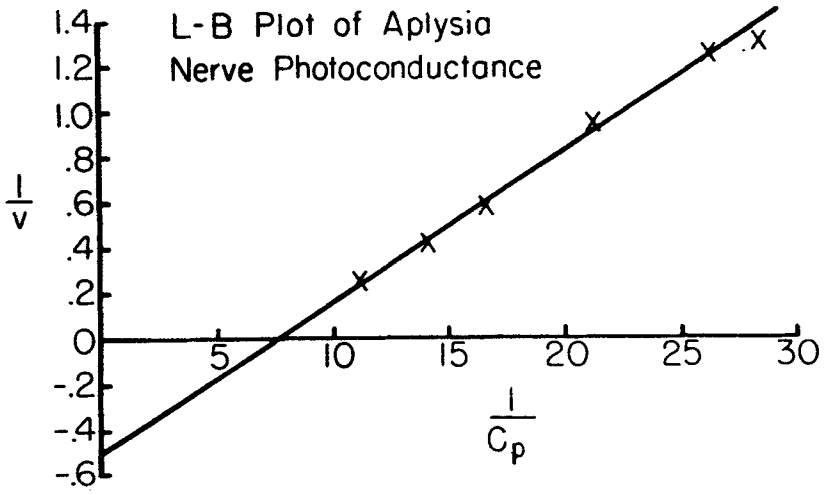

Fig. 3. Double Reciprocal Plot for Decay of Photoconductivity in Nerve. C_p = photoconductance in $(M\ \Omega)^{-1}$ of membrane of *Aplysia* neuron; $v = dC_p/dt$, where t is time. Experimental data were taken from figure 9 of Chalazonitis,[118] in which the data points represent microelectrode measurements of electrical resistance across the membrane of the photo-active neuron of *Aplysia* at various times after the end of exposure to 18 seconds of light with a wavelength of 470-510 $m\mu$. Calculations are taken from Cope.[119]

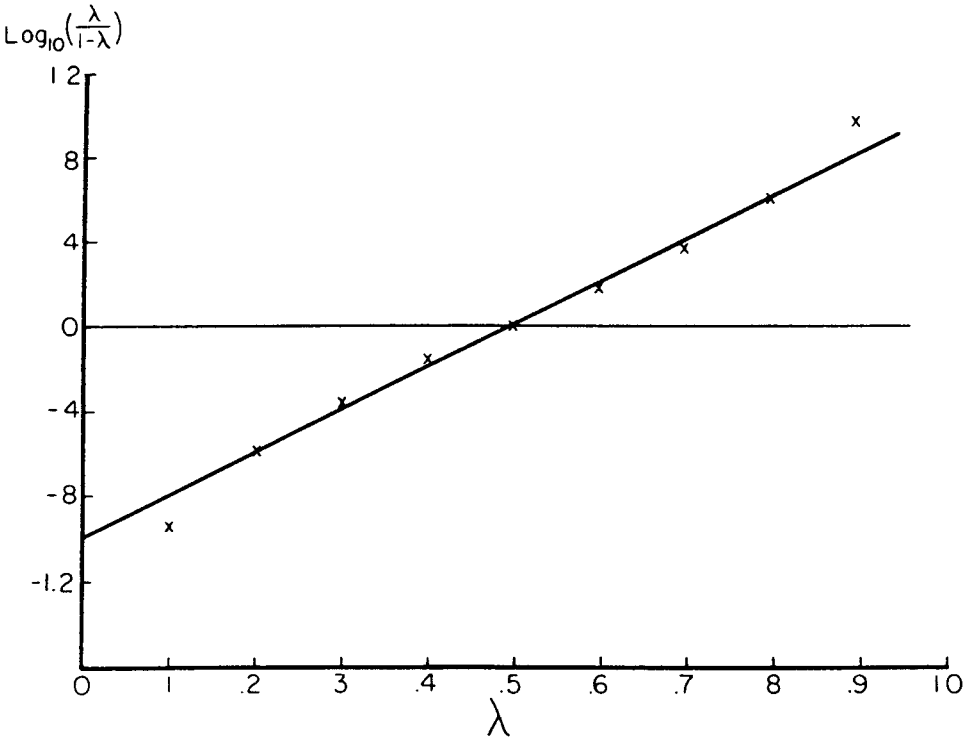

Fig. 4. Plot λ vs. the log function. The accuracy of this linear approximation is studied in the appendix of Reference 3.

and

$$n = \frac{4.6a}{C_x} \tag{21}$$

Equation 19 is called the Roginsky-Zeldovich equation or the Elovich equation.[109] It is named after its discoverers who observed that it described data on oxygen absorption and charge decay at surfaces of inorganic semiconductors. The applicability of the Elovich equation to experimental data of surface physics of semiconductors, such as Ge and Si, has been confirmed repeatedly.[109] The frequency of experimental observation of this equation suggested that it was a manifestation of fundamental physico-chemical principles of surfaces, probably connected with electron transport processes. A variety of derivations of the Elovich equation have been

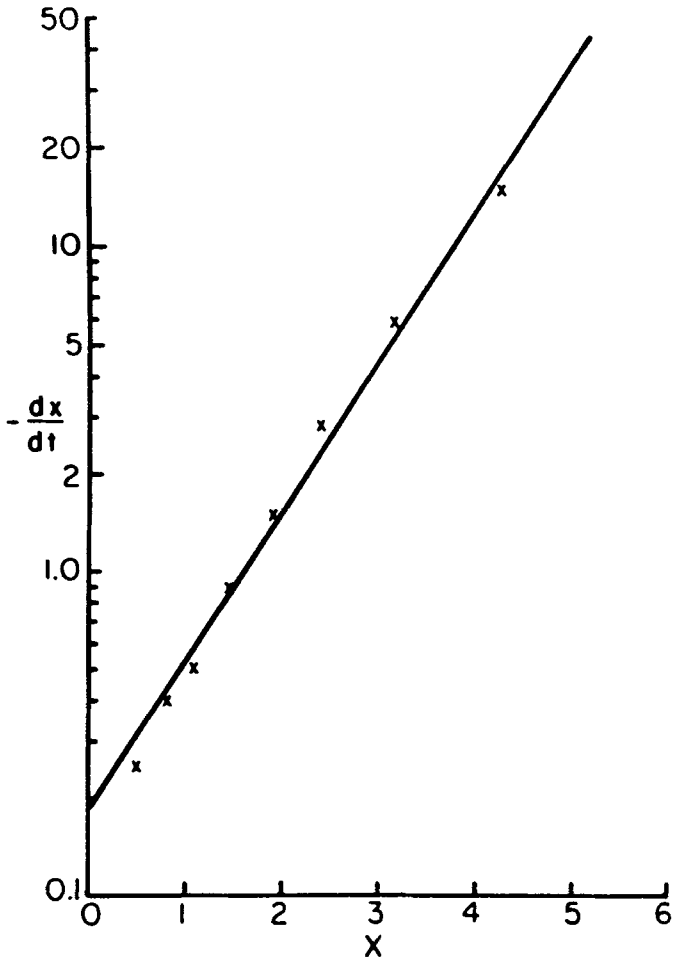

Fig. 5. Test of Eye Melanin Free Radical Decay Data for Conformity to Elovich Equation. Graph of log of reaction rate (−dx/dt) vs free radical concentration (x) for the experimental data of Fig. 2. Linearity of this graph indicates conformity of this data to the Elovich equation (equation 19).

proposed, but all seem to be based on postulates of doubtful validity.[109] The derivation presented here represents a new approach, which is based on postulates that have a good basis in experiment and theory.[109]

After the Elovich equation had been derived by Cope[109] from solid state activation barrier theory, its relevance to biology was confirmed by showing that it described considerable biological data. The Elovich equation describes well the decay of free radicals in eye melanin particles (Fig. 5) and the decay of photoconductivity in nerve (Fig. 6). It also described the decay of free radicals in photosynthetic particles,[110] and the decay of molecules responsible for delayed emission of light from green leaves.[111] All of these biological systems contain particles or membranes

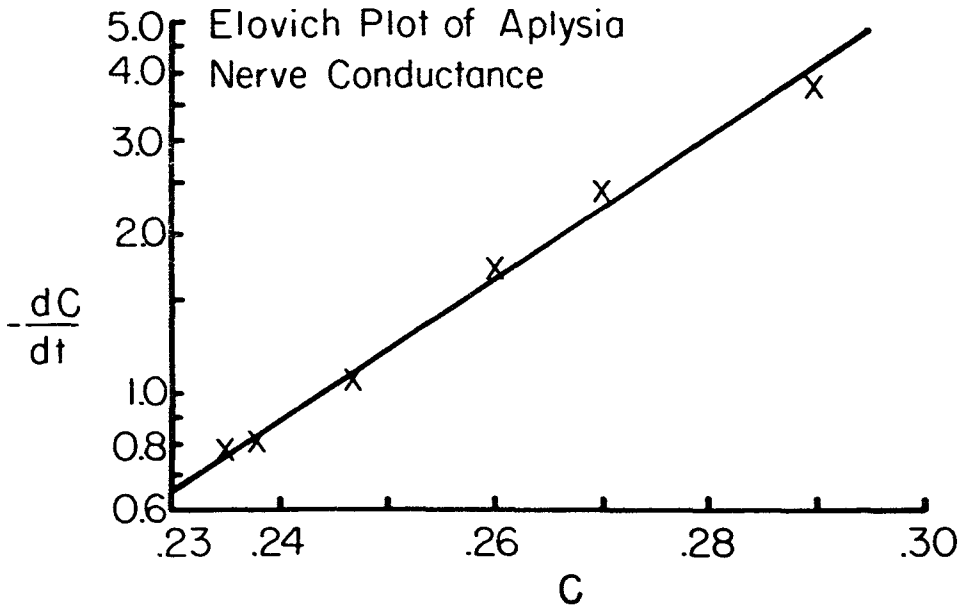

Fig. 6. Test of Nerve Photoconductivitv Decay Data for Conformity to the Elovich Equation. Graph of log of rate of change of nerve membrane conductivity (−dC/dt) vs conductivity (C) for the experimental data of Fig. 3 on *Aplysia* nerve membrane, using the data of Chalazonitis[118] as calculated by Cope.[119] Linearity of this graph indicates conformity of this data to the Elovich equation (equation 19).

as required by the activation overvoltage derivation of the Elovich equation. Support for the concept that solid state electron conduction may be involved in the eye melanin reaction derives from the measurement of relatively high electron mobilities in eye melanin by the new experimental technique of microwave Hall effect.[15]

In addition, the temperature dependence of the Elovich equation has been derived from activation overvoltage theory, and has been found to agree well with experiment, both for inorganic solid systems and for biological systems.[112]

C. Enzymes (Cytochrome Oxidase). Enzymes are the catalysts in cells with cause the chemical reactions necessary for life to procede at rapid rates. Without enzymes these chemical reactions would occur too slowly to support life. Because of their importance to life, the structure of enzymes, and the kinetics and mechanisms of chemical reactions catalyzed by enzymes, have been studied extensively by biochemists and physical chemists for many years.

The classical approach to chemical kinetics is the mass action theory. This is based on the hypothesis that all reacting molecules float free in solution, which implies that the rate of reaction is proportional to the rate of collision between reactants, which is proportional to concentrations of reactants. Most kinetic theories of enzyme action are merely elaborations of this simple idea. The Michaelis-Menten theory of enzyme kinetics is a well known form of the mass action treatment of enzyme kinetics, which has been found to describe much experimental data on many enzymes. For many of these cases, the enzymes and their substrates probably do float free in solution in cell water, so that the basic hypothesis of the mass action theory is in accord with reality.

Some enzymes are bound in or on particles or membranes in the cell. Despite this violation of the mass action hypothesis, biochemists have nevertheless attempted to use mass action theory to analyze such enzymes. One such enzyme is cytochrome oxidase, which in the cell exists as a part of the mitochondrial membrane, which can by appropriate treatment be cracked up into fragments of molecular weight 500,000 or more which retain the ability to catalyze the reduction of O_2 by the reduced form of the protein cytochrome c. The membrane fragment called cytochrome oxidase contains protein, unsaturated lipids, at least two types of haeme-iron groups, and copper. Purifications which remove any of these substances cause loss of catalytic activity of the enzyme.

Despite the fact that cytochrome oxidase is part of a membrane and hence violates the free solution hypothesis of mass action theory, biochemists have nevertheless tried to analyze its kinetics on the basis of mass action theory. The results have been poor. Cytochrome oxidase does *not* conform to the Michaelis-Menten pattern. Instead, it shows first order kinetics, with the peculiar feature that larger initial amounts of reduced cytochrome c substrate decrease the first order rate constant in a hyperbolic pattern. Such a result is difficult to derive from mass action theory. It can be done by assuming a four step reaction, *if the rate constants of the first and last step are assumed to be equal.*[113] The latter is possible, but seems rather unlikely.

Persistence by biochemists in attempts to apply mass action theory to membrane-bound enzymes which violate its postulates is psychologically understandable because of the great success of mass action theory in dealing with soluble enzymes. Reason dictates, however, that when reality conflicts with the postulates of theory and when predictions of theory are difficult to reconcile with experiment, then a different theoretical approach should be sought. This has been done by Cope[10,12,114] in order to deal with the kinetics of redox reactions in biological particles and membranes using realistic postulates. No longer does one impose the restrictive hypothesis of mass action theory that all processes must occur

in free solution. One concedes that the catalytic system contains solid particles and membranes, and that therefore catalysis may involve electron conduction through these solids in accord with the laws of solid state physics, and may involve electron conduction across the liquid-solid interfaces in accord with the behavior of electrodes. This approach leads in a direct manner to kinetic predictions that describe accurately and in considerable detail the kinetic experimental behavior of various particulate and membranous biological processes, including that of cytochrome oxidase.

The purpose of a kinetic theory of enzymes is to predict correctly the substrate concentration vs time curve for the chemical reaction when catalyzed by the enzyme (concentration vs time is the most easily measured characteristic of an enzymatic process). The derivation should be based on physical and chemical principles appropriate to the enzyme structure and conditions.

We shall now derive the substrate concentration vs time curve for a redox reaction catalyzed by an enzyme which is assumed to be a solid particle across which electrons can be conducted in response to a potential difference generated by electrode redox potentials of substrates on the opposite ends of the conductive particle (Fig. 7).* An equivalent electrical circuit would be a resistor connected across a battery. This model seems appropriate for an enzyme such as cytochrome oxidase which when studied in the test tube is a high-molecular weight fragment of a membrane. In life, cytochrome oxidase exists as part of the membrane of the mitochondrion. When in this larger and more complex solid system, some additional solid state processes may influence the cytochrome oxidase reaction, as will be discussed later in this section. The derivation, which will now be presented in simplified form, can be found in complete detail elsewhere.[10,12,114]

Let us postulate an enzymatic particle (or membrane fragment) as shown in Fig. 7. Let there be two sites on the particle at which small molecular weight substrate molecules can exchange electrons with the particle. The two substrates (X and Y) can each exist in an oxidased or reduced form. We assume enzymatic specificity of site for substrate: in other words, the X-site on the particle can exchange electrons only with X-substrate, and the Y-site can exchange electrons only with the Y-site.

Let us now consider the system shown in Fig. 7 from the point of view of solid state theory. The X-site and Y-site may be considered as two electrodes immersed in two solutions with different equilibrium electrode potentials. When the two electrode sites are connected by a wire, or by the internal resistance of the enzyme particle, a current of electrons will flow, which will be limited by the electrical resistance across the particle. This solid state model of an enzyme is electrically equivalent to a resistor

*Digby[170] independently proposed that this same mechanism operates across the shells of crabs and shrimps. The same mechanism had been proposed earlier by Lund[173-175] and by Jahn.[176]

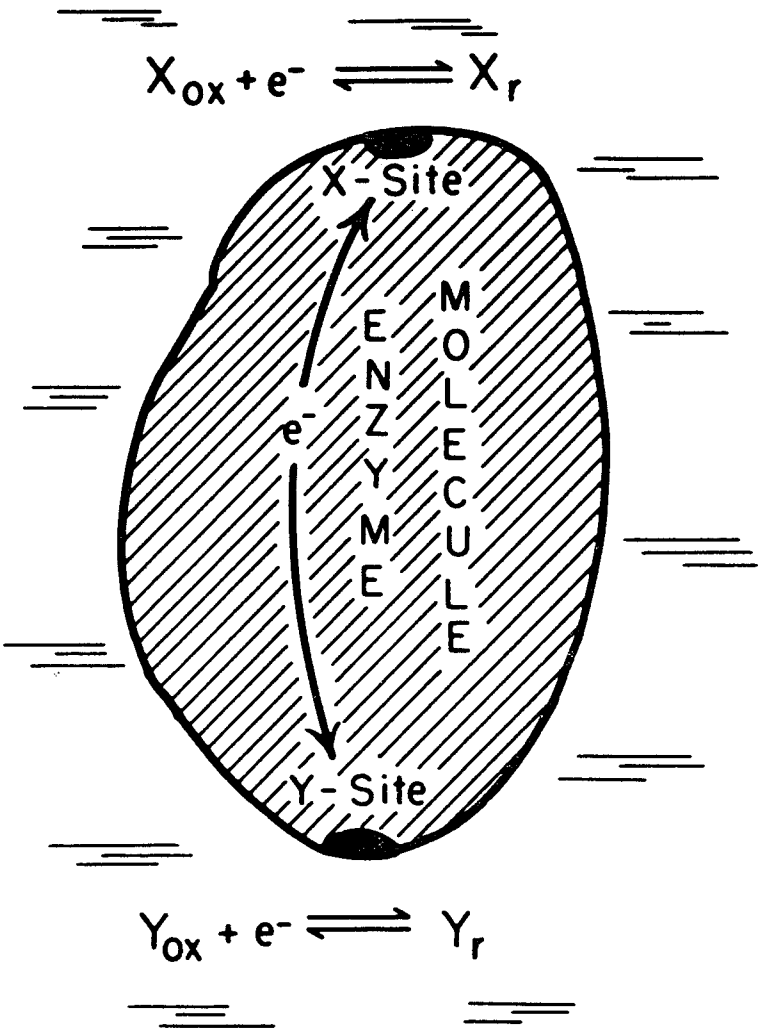

Fig. 7. Solid State and Electrode Model of the Cytochrome Oxidase Enzyme Particle. X-site on the particle acts like an electrode immersed in a solution of redox substrate X, so that the X-site develops on equilibrium electrode potential governed by the percent reduction of substrate X. The X-site is assumed to have enzymatic specificity for reaction with X-substrate. In other words, X-site can exchange electrons freely with X-substrate but will not react with Y-substrate. The Y-site, at the other end of the enzyme particle acts like a second electrode immersed in a solution of a second redox substrate Y, and develops an equilibrium electrode potential governed by percent reduction of Y. The direct reaction of X- and Y-substrates in solution is assumed to be insignificantly slow. The difference in electrode potentials at the X- and Y-sites causes a current of electrons to flow through the conductive solid enzyme particle. The rate of current flow, and hence the rate of oxidation of X-substrate by Y-substrate, is governed by the over-voltage phenomena at the X- and Y-sites, and by the electrical resistance across the solid enzyme particle.

connected across a tiny battery. To develop the theory of this behavior, we shall express the site (or electrode) potentials and the voltage-current equation in terms of substrate concentrations and time.

First, let us calculate the potential difference across the particle (Fig. 7), which we shall call the cell potential (V_{cell}). This is merely the difference in equilibrium electrode potentials experienced by the two sites at the two ends of the particle. Hence:

$$V_{cell} = V_x - V_y \tag{22}$$

where V_x and V_y are the electrode potentials at the X- and Y-sites respectively. Equation 22 may be put in terms of substrate concentration by the use of the familiar electrode equation

$$V_x = V_x^0 + (RT/F) \log_e (x_{ox}/x_r) \tag{23}$$

where x_{ox} and x_r are the concentrations of the oxidized and reduced forms of X-substrate, R is the gas constant, T is absolute temperature, F is the Faraday and V_x is a constant. Because the sum of oxidized plus reduced forms of X-substrate is always constant $(= C_x)$, we may write

$$x_{ox} + x_r = C_x \tag{24}$$

We shall assume for simplicity that Y-substrate is present in excess, so that the redox potential at the Y-site on the particle is constant $(= Y)$. We may then combine equations 22, 23, and 24 to obtain the potential difference across the particle (V_{cell}) (Fig. 7) in terms of concentration of reduced substrate as follows:

$$V_{cell} = V_0 - (RT/F) \log \left[x_r/(C_x - x_r) \right] \tag{25}$$

where V_0 is a new constant $(= V_x^0 - Y)$.

The potential difference across the enzyme particle causes a flow of electron current across the particle, like that which would occur through a resistor connected across a pair of electrodes in a battery. If we assume that current flow *(i)* across the enzyme particle is governed by Ohm's law, as is true for most organic semiconductors, we may write

$$V_{cell} = ir \tag{26}$$

where r is the electrical resistance across the enzyme particle.

Because the conduction of one mole of electrons across the enzyme particle reduces (or oxidizes) one mole of substrate, we may write

$$i = F\, dx_r/dt \tag{27}$$

We may now derive the differential equation for substrate reduction by substituting equations 25 and 27 in equation 26 to obtain an equation of the form

$$-\frac{dx_r}{dt} = A \log \left[\frac{x_r}{C_x - x_r}\right] - B \tag{28}$$

where x_r is concentration of the reduced form of X-substrate, t is time, C_x is total concentration of oxidized plus reduced forms of X-substrate, and A and B are constants.

Equation 28 is the basic differential rate equation describing the kinetics of a particulate enzyme that is rate-limited by ohmic conduction of electrons across the particle. Unfortunately, because of the log term, equation 28 cannot be integrated by any exact method. We may, however, test experimental data for ohmic conduction kinetics by plotting a graph of (dx_r/dt) vs log $[x_r/(C_x - x_r)]$, although this is rather inconvenient. Linearity of such a plot would indicate conformity of the data to equation 28.

Fortunately, equation 28 may be converted to an approximate form of reasonable accuracy, which is easy to integrate and easy to use for the analysis of experimental data. We may substitute the approximate equation 17 in equation 28 to give a new differential rate equation for a particulate electron conduction equation having the simple form

$$-\frac{dx_r}{dt} = \left[\frac{\alpha}{C_x}\right] x_r + \delta \tag{29}$$

where α and δ are constants. This approximation[10] is moderately accurate from 15 percent to 85 percent reduction of substrate (Fig. 4).

Equation 29 was derived on the assumption that ir is the only voltage drop in the equivalent circuit of Fig. 7. If we make our picture more realistic by assuming that a diffusion overvoltage at the X-site also exists due to slow diffusion of large substrate molecules and that Y-substrate is also significantly reduced during the course of the reaction, then the differential equation of reaction kinetics remains of the same general form as equation 29, but with some extra constants and becomes

$$-\frac{dx_r}{dt} = \left[\frac{\alpha}{C_x + \beta} + \gamma\right] x_r + \epsilon \tag{30}$$

where β is a positive constant that is a function of the diffusion constant of substrate x_r, γ is a positive constant and ϵ is a constant. Hence, like equation 29 for the simpler model, the improved theory predicts a hyperbolic relationship between the first order rate constant (k') and C_x, but of a more complicated form as follows:

$$k' = \frac{\alpha}{C_x + \beta} + \gamma \tag{31}$$

or

$$(k' - \gamma)\cdot(C_x + \beta) = \alpha \qquad (32)$$

Equations 29 and 30 predict the kinetics of substrate reduction to be expected from an enzyme particle which is rate limited by ohmic conduction of electrons across the solid particle without or with a diffusion overvoltage at the particle surface. The kinetics are predicted to be of first order with respect to the concentration of reduced substrate (x_r). The important and unusual special feature of the prediction is that the first order rate constant (k′) should decrease if larger *total* (oxidized plus reduced) concentrations (C_x) of substrate are used, and the relationship is predicted to be hyperbolic of the form given by equation 32.

A kinetic pattern of exactly this form has been observed experimentally with the enzyme cytochrome oxidase when catalyzing the oxidation of reduced cytochrome c by O_2 and has also been observed for the enzymes cytochrome peroxidase[10] and pyruvate carboxylase.[114] To account for this unusual behavior in terms of classical mass action mechanisms, one would have to postulate some sort of substrate inhibition, or a complicated sequence of reactions.[113]

In addition to predicting the kinetic pattern of the cytochrome oxidase reaction, the solid state theory predicts the experimentally observed temperature dependence of this enzyme.[12] The theory given here predicts that the activation energy of the functioning cytochrome oxidase enzyme should equal the semiconduction activation energy for the solid protein of the enzyme particle.[12] Solid state physical measurements made recently on purified dried cytochrome oxidase do indeed agree with this prediction, and show that cytochrome oxidase is unique among proteins thus far studied, in that it has a semiconduction activation energy three times lower than other proteins.[11,12] Additional support for the concept that cytochrome oxidase activity involves solid state electron conduction is provided by measurements of relatively high electron mobilities in mitochondria by two new experimental techniques (pulsed electron beam[5,9] and microwave Hall effect[13-22]).

When the cytochrome oxidase reaction is studied at low oxygen concentrations, the rate equation of the reaction is observed to change from first to second order, the oxygen concentration shows an inhibitory effect on the second order rate constant of hyperbolic form.[115] These experimental findings are quantitatively understandable from the same concept of a solid state electron conduction enzyme, with the additional features of space change injection of electrons (yielding square law instead of ohmic conduction) and trapping.[116]

According to intuition, and also according to detailed theory,[12] if cytochrome oxidase functions by a solid state mechanism, then the

activation energy of the cytochrome oxidase reaction should approximately equal the activation energy for semiconduction in dried cytochrome oxidase, as measured by solid state physical techniques. For various simple proteins, semiconduction activation energies as measured by numerous investigators had always been found to be in the region of 1.0 eV. Since the cytochrome oxidase enzymatic reaction had been observed to have an activation energy of 0.3 eV or lower, a semiconductive mechanism for enzyme action had been thought unlikely. The possibility was overlooked that cytochrome oxidase protein might have a different activation energy of semiconduction from most other proteins. When at long last it was measured,[11,12] the semiconduction activation energy of dried cytochrome oxidase was found to be approximately 0.3 eV, which supports the solid state physical concept of the cytochrome oxidase mechanism.

Direct experimental measurements of electron conductivity under physiological conditions in cytochrome oxidase and in other systems that show solid state kinetics would be desirable to test theoretical deductions. Such measurements present great technical difficulties. The conductivity and electron mobility techniques generally used in inorganic solid state physics require samples that are single crystals yet are big enough to allow the attachment of electrodes, purity to parts per million, absence of water, and ohmic contacts between electrode and sample. Biological samples usually satisfy none of these criteria. Therefore, conventional solid state physical techniques have proved useful only to a limited extent. New techniques to avoid the problems inherent in biological samples are under development and have yielded some interesting preliminary data.

The only study by conventional solid-state techniques that has proved illuminating is the measurement by Straub[11,12] of the activation energy of semiconduction of purified, dried cytochrome oxidase. This showed that cytochrome oxidase was unique among the proteins thus far studied in having an activation energy threefold lower than others, in agreement with the predictions of solid state kinetic theory. With regard to new techniques, preliminary results are available from a pulsed electron beam method developed in Russia,[5,9] which showed relatively high electron mobilities in mitochondria. This result, which agrees with theoretical expectations, has been confirmed in preliminary measurements with a new microwave Hall-effect technique by Eley and Pethig.[18] The method was invented in Russia by Trukhan[13,14] and improved in England by Eley and Pethig.[16,22] More recently, Eley *et al*[19,20] showed that cytochrome oxidase activity is positively correlated with microwave Hall mobility of electrons, which strongly supports the concept that cytochrome oxidase enzyme activity is rate-limited by solid state electron conduction.

In conclusion, the evidence in support of a solid state mechanism for cytochrome oxidase now seems fairly strong.

The theory just presented describes well the experimental behavior of cytochrome oxidase in reactions in the test tube. In life, however, cytochrome oxidase exists as a part of a much larger solid membrane system, which performs at least one important biochemical function in addition to what is done by purified cytochrome oxidase in the test tube. In life, cytochrome oxidase exists as part of the membrane of mitochondria (small granules present in every cell which are barely visible under the light microscope). Cytochrome oxidase participates in the oxidative or electron transport process of the mitochondria. In mitochondria which are undamaged, the energy from oxidation is converted into high energy phosphate bond energy by phosphorylation of adenosine dephosphate (ADP) to adenosine triphosphate (ATP) which is the immediate source of energy for most body functions (muscle contraction, nerve firing, secretion of acid in the stomach, etc.).

The mechanism of coupling between oxidation and phosphorylation in mitochondria is not understood by biochemists. Various biochemists present various explanations with an air of confidence, but the various explanations are different, so that at least some of them must be wrong.

If one concedes that the *oxidative* part of the oxidative phosphorylation of cytochrome oxidase might occur in a solid, then one may ask whether *phosphorylation* and the coupling process might also occur by solid state mechanisms. Preliminary theoretical considerations suggest that this is indeed possible. No experimental tests of this hypothesis have yet been made.

It was suggested by Straub[11,23,24] that phonons (packets of lattice vibrational energy) might be the immediate source of energy for the phosphorylation in the mitochondrial solid. It was then suggested by Cope and Straub[12] that the coupling process was a polaron (a combination of a phonon and an electron), which could be conducted across the mitochondrial solid and would give up its phonon for a phosphorylation. The evidence that suggested polaron conduction was derived from an analysis in terms of solid state kinetic theory of the temperature dependence of the cytochrome oxidase reaction as measured by deVault and Chance.[27]

If the carrier of the energy for phosphorylation is the phonon, we may inquire about the mobility of this carrier for transport of the energy through the mitochondrial solid. We must first note that the free energy of hydrolysis of adenosine triphosphate is 9.0 kcal/M or 0.39 eV, which must be the energy of phosphorylation of ADP. Hence, the phosphorylation phonon must carry at least this much energy, which is equivalent to a photon of light of 3.24μ wavelength, which is in the infrared (IR) range. Phonons of this energy range are localized vibrations (optical phonons) and do not significantly propagate through the solid, in contrast to lower energy

phonons (acoustic phonons) which move freely. It therefore seems unlikely that phonon movement can play a significant role in dissemination of energy through the lattice of the solid mitochondrial membrane. If the solid state carrier of energy should be an exciton, this might be either free or localized.[25]

A different method of dissemination of an energy packet of this size is suggested by the dimensions of the mitochondrion (3.3μ long by 0.5μ radius for rat liver). Because the length of the mitochondrion is approximately one wavelength of this phonon energy packet, Cope[25] considered the possibility that the mitochondrion might act as a resonant cavity for IR electromagnetic waves, which could serve as a rapid and efficient method for dissemination of IR energy throughout the mitochondrion from generation sites to utilization sites. The mitochondrion would then be a small scale analog of a microwave cavity made from a shorted section of waveguide, as used in radar systems.

A serious objection to this idea is the fact that water, which is the principle constituent of the mitochondrial sap, absorbs IR energy strongly, so that IR radiation within the mitochondrion would be mostly absorbed by water and wasted, instead of being transmitted.

A variation of the above mechanism would allow the mitochondrion to avoid the IR absorption by water.[25] Suppose that the IR radiation does not pass into the aqueous sap but is contained within the lipid bilayer of the mitochondrial membrane. Suppose that IR electromagnetic waves are generated at the surface of the lipid bilayer and kept within the lipid bilayer by internal reflections from the adjacent layers of protein. The mitochondrion would then be analogous to a coaxial transmission line where the lipid bilayer is the dielectric and the adjacent protein layers are analogous to the metal surfaces of the central wire and of the outer metal sheath.[25] This coaxial transmission line, when shorted at both ends, forms a coaxial cavity which is resonant for any integral multiple of a half wavelength (the multiple is 2 for the mitochondrion for 3.24μ wavelength energy packet). The composition and geometrical structure of the mitochondrial lipid bilayer minimize absorption of IR waves by the lipid dielectric, so that this could be a highly efficient method for energy propagation throughout the mitochondrial membrane.

The first reason for expecting low absorption, and hence low wastage of IR energy within the lipid bilayer of the mitochondrial membrane results from its chemical composition.[25] Analysis of mitochondrial lipids reveals that they consist mostly of compounds with very low IR absorption, including 33 percent saturated straight-chains (16-18 carbons), and 52 percent straight chain (18-20 carbons) with 2 or 3 double bonds. Indeed, the IR absorption of saturated straight-chain hydrocarbons is so low that such compounds (Nujol) are commonly used to make slurries of crystals for IR spectroscopy. The only significant IR absorption in saturated

straight chains is the C—H stretching frequency, which is located near 3.3μ. In unsaturated carbon chains, there is also an IR absorption band due to the C=C stretching frequency, which is very weak, although it becomes more intense when conjugation occurs with multiple double bonds.

Even though IR absorption in the mitochondrial lipid bilayer must already be low because of the chemical composition of the lipid, it must be reduced lower by the particular geometrical arrangement of lipid molecules relative to the geometrical pattern of the electric vector, which is produced in a coaxial cavity of this type.[25]

The electric field configuration to be expected in the IR coaxial cavity consisting of the mitochondrial membrane may be deduced easily from the theory of coaxial transmission lines. For a coaxial transmission line, at a wavelength (λ) longer than the cutoff wavelength (λ_c), only the principle transverse electromagnetic (TEM) mode can be propagated, where λ_c is given approximately by

$$\lambda_c = \sqrt{\epsilon}\,\pi\,(r_1 + r_2) \tag{33}$$

where r_1 and r_2 are the inner and outer radii of the coaxial transmission line, and ϵ is the dielectric constant.[25] For the rat liver mitochondrion, radius $\cong 0.5\mu$ and the thickness of the lipid bilayer dielectric is relatively small (60 Å = $6\times10^{-3}\mu$), so that $r_1 \cong 0.5\mu$. If we take the dielectric constant (ϵ) of the lipid bilayer as one, then we may substitute the numbers in equation 33 to obtain the cutoff wavelength for the mitochondrion $\lambda_c = 3.0\mu$. Because the wavelength of the energy packet for phosphorylation is 3.24μ which is longer than λ_c, only the principle TEM mode can be propagated in the mitochondrial membrane.[25] Higher order modes with other field configurations cannot exist.

The field configuration for the principle TEM mode in a coaxial transmission line has the electric vector (E) directed radially and the magnetic (H) directed circumferentially, which must therefore be the situation the mitochondrial membrane. According to the Danielli model of the lipid bilayer membrane, the carbon chains of the lipid molecules are directed perpendicular to the membrane surface, so that in the mitochondrial membrane, the carbon chains of the lipids are directed radially, which is parallel to the direction of the E vector. The C—H bonds are perpendicular to the chains and are therefore perpendicular to the E vector. As mentioned before, the principle IR absorption of straight carbon chain hydrocarbon molecules is the C—H stretching frequency. It has been shown by both theory and experiment that IR absorption by a molecular group is a minimum (which may be zero) when the E vector is perpendicular to the direction of the molecular vibration. It is therefore to be expected that the absorption of IR energy by the lipid bilayer of the mitochondrial membrane which already must be low because of the chemical composition, must be even lower because the C—H bonds are perpendicular to E. This expected

low IR absorption implies that dissemination of IR phosphorylating photons by the coaxial resonant cavity mechanism may be extremely efficient, because of very low losses expected from absorption in the lipid dielectric.[25]

In summary, it seems likely that the mitochondrial enzyme system, which operates in an organized solid membrane, functions by an integrated set of solid state processes. Oxidation by cytochrome oxidase occurs by solid state conduction of polarons, which yield phonons which perform phosphorylation of ADP to ATP. The phonon energy is disseminated rapidly and with low loss throughout the entire mitochondria membrane by infrared electromagnetic waves in the lipid bilayer of the mitochondrial membrane, so that the mitochondrian as a whole acts as an infrared resonant coaxial cavity.

D. Nerve. Nerve fibers consist of a solid matrix of protein and lipid with intersitial water containing various small ions, such as sodium (Na), potassium (K), and chloride (Cl). When a nerve fires, a complicated set of movements of these ions occurs through the water in the nerve. Extensive measurements of these ion movements have been made, and much of the experimental data has been put together (i.e. the experimental data has been curve fitted) by a complicated set of equations called the Hodgkin-Huxley theory.[117]

The Hodgkin-Huxley theory is not an explanation of nerve conduction in terms of the principles of physical chemistry. Rather, it is merely an ingenious curve fit of much experimental data on ion flows in nerve water. It ignores completely the possibility of solid state events within the solid protein-lipid matrix of the nerve.

Evidence is now available for several different solid state physical processes in the solid matrix of nerve. These include electron conduction over activation energy barriers, superconduction, piezoelectric phenomena, and transmission of infrared electromagnetic waves in the lipid bilayer. It seems reasonable to suppose that these solid state processes take part in transmission of the nervous impulse down the nerve fiber, and are integrated with the ionic events which take place in the nerve water.

Electron conduction across activation energy barriers in nerve is evidenced by the experimental observation of Chalazonitis[118] as analyzed by Cope[119] that decay of photoconductivity in pigmented invertebrate nerve conforms to the Elovich equation, the derivation and significance of which was discussed in Section IIIB of this review.

A role for superconduction in nerve function is suggested by several types of evidence. These include (a) the temperature dependence of certain neural processes is characteristic of single electron superconductive tunneling,[56] (b) certain other neural processes show *negative* temperature dependences, which are difficult to explain except from the hypothesis of two electron superconductive tunneling,[56] (c) numerous behavioral effects

on organisms are caused by magnetic fields smaller than 2 Gauss, for which no physical mechanism of adequate sensitivity is known, except the superconductive Josephson effect,[59,60] (d) dilute superconductivity has been observed experimentally[49-51] in various bile acids at temperatures as high as 277°K, and extrapolation of this data leads to the prediction[52] the cholesterol should superconduct as physiological temperatures and above. Cholesterol is a major constituent of the solid matrix of nerve. In addition, solid state magnetic phenomena suggestive of superconduction have been observed experimentally in the presence of high electric fields.[53] Nerve possesses thin lipid layers (containing cholesterol) in which high electric fields exist. The superconductivity predicted for cholesterol at zero electric field might be enhanced by these high fields,[53] so that superconduction could become of significant magnitude and play a role in nerve function.

Piezoelectricity and pyroelectricity in nerve are suggested by the following evidence. The temperature dependence of the resting membrane potential of an invertebrate nerve cell shows a temperature dependence for which log of the activation energy is a linear function of temperature, which conforms to theory of peizoelectric resonance.[92] A square pulse of increased temperature often produces in nerve systems two response transients of opposite sign at the start and end of the temperature pulse (Fig. 1). This is characteristic of a pyroelectric process.[100] It is seen in the fish thermoreceptor, which also shows proportionality between the time derivative of response and temperature, which is predicted from pyroelectric theory.[100] The muscle stretch receptor shows linearity of neural response with the logarithm of applied mechanical force. This is predicted from the concept that the neural response is governed by a piezoelectric effect in an elastic polymer macromolecule.[100] In addition, nerve is observed to be pyroelectric.[156]

Infrared (IR) transmission of electromagnetic energy by a coaxial transmission line mechanism in nerve fibers (axons) seems possible.[25] Like in mitochondria, the probable immobility of IR phonons will limit the transfer of energy along the axon, where high mobility would be useful to move energy along the great distances of axon length. Like in mitochondria, the cylindrical lipid bilayer of the axon membrane seems well constructed to serve as a coaxial transmission line for rapid and efficient transfer of IR electromagnetic waves along the axon within the lipid dielectric.[25] A bundle of axons in the nerve could then be regarded as a coaxial IR fiber optic system. Supporting this concept is experimental observation of emission of IR radiation from nerve during excitation.[120]

Some nerve fibers are larger in diameter than mitochondria, and consequently will have longer cutoff wavelengths and lower impedances than mitochondria. For an A-nerve fiber, such as commonly found in a mammalian motor nerve, a radius of 10μ might be typical, from which

one may calculate using equation 33 that the cutoff wavelength (λ_c) will be 60μ. Hence, in a typical motor nerve axon for wavelengths over most of the IR range, higher order modes will carry a significant fraction of the total IR energy, so that longitudinal transmission of IR energy will be less efficient than in mitochondria or in smaller nerve fibers, and dielectric losses may be somewhat higher because E is not always perpendicular to the C—H bonds of the lipid chains. In a C-nerve fiber, such as one might find in the sympathetic system, a radius of 0.25μ might be found, which substituted in equation 33 leads to a cutoff wavelength (λ_c) of 1.5μ, which makes for efficient longitudinal IR transmission and low dielectric losses.[25]

Impedance of a coaxial transmission line is given by (if resistive losses are small)[25]

$$Z = 138 \sqrt{\mu_r/\epsilon}\, \log_{10} (r_2/r_1) \tag{34}$$

where Z is impedance in ohms, r_1 and r_2 are inner and outer radii of the coaxial line, μ_r is permeability (= 1 except for ferroelectrics), and ϵ is dielectric constant of the lipid bilayer. The impedance (Z) for IR transmission will be different for different nerve fibers because of differences in radius, although the thickness of the dielectric lipid layer is probably much the same in all nerves and in mitochondria, and will here be considered a constant (= 0.006μ) as for mitochondria.[25] For a C-nerve fiber, with an inner radius (r_1) of 0.25μ, using equation 34, we may calculate impedance (Z) of 1.4Ω. However, for a A-nerve fiber with a radius of 10μ, we calculate[25] impedance (Z) of 0.036 Ω.

Because for different nerve fibers, radius varies markedly but thickness of the dielectric lipid bilayer remains approximately constant, it is instructive to show the simple approximate relationship between the radius of a nerve and its impedance for transmission of IR waves.[25] We use the approximate equation (derived by Clark[121] and Cope[122])

$$\log_e \left[\frac{\chi + \Delta}{\chi} \right] \cong \left[\frac{\Delta}{\chi + \Delta} \right] \cong \left[\frac{\Delta}{\chi} \right] \tag{35}$$

where $\chi > 0$ and $\Delta \ll \chi$. If we let χ = r (inner radius) $\cong$ r (mean radius of nerve fiber) and Δ = thickness of dielectric lipid bilayer, using 0.434 for the ratio of $\log_{10} x$ over $\log_e x$, we may substitute equation 35 in equation 34 and obtain

$$Z \cong 60 \sqrt{\mu_r/\epsilon} \left[\frac{\Delta}{r} \right] \tag{36}$$

where Z is axon impedance for IR transmission in ohms and the other symbols are as previously defined. This shows that, approximately, the axon impedance is inversely proportional to its radius.

The impedances for coaxial IR transmission for nerve fibers (1.4 Ω for C-fibers and 0.036 Ω for A-fibers) are much lower than the 75 Ω which is usual in man-made coaxial transmission lines for radio frequency waves. Most efficient energy transfer between generator, line and load occurs when impedance of the line equals that of generator and load. One may speculate that therefore the generators and absorbing systems for IR energy in nerve should have low load impedances to match the nerve transmission line, and might be of fundamentally different character than the relatively high impedance devices ordinarily used in man-made systems. Pertinent to the possible nature of the low impedance nerve generator and loads is the evidence for superconductive phenomena in nerve at physiological temperatures as discussed in previous paragraphs of this section. Superconductive junctions (Josephson junctions) have been fabricated which will generate and detect electromagnetic energy in the microwave and IR range of wavelengths.[123,124] These superconductive generating and absorbing systems have been observed[32,125] to have impedances in the range of 1 Ω. The expected low impedance of a superconductive IR generator or load in nerve might therefore be a reasonably good match to the calculated low impedance of an IR coaxial nerve transmission line.

Larger nerve fibers have lower impedances, with impedances inversely proportional to radius (see equation 36). Therefore, for efficient IR energy transfer, impedances of generators and loads should be correspondingly lower in larger nerve fibers. One might speculate[25] that if the generators and loads were uniformly distributed as sites over the circumferential area of the nerve with the same density in all nerve fibers, the number of sites per unit length of nerve would be proportional to radius, and the reciprocal of the total impedance of the unit length would be proportional to the sum of reciprocals of impedances of individual sites, whose number is proportional to circumferential area. Therefore, total impedance of generator or load sites per unit length of nerve would be inversely proportional to nerve radius, so that an equally good match of generator or load to transmission impedance could be obtained for nerves of all diameters using the same type and density of generator and load sites for all nerves. The hypothesis just expressed that sites of IR generation and absorption might be continuously distributed along the surface of the nerve lipid bilayer implies the possibility of repeated absorption and re-emission of the energy by the conductive walls (protein) as the IR energy is transmitted along the length of the nerve fiber within the dielectric lipid bilayer.[25]

IV. Application of Solid State Physical Concepts to Ionic Phenomena in Cell Water

We may consider the cell to resemble a sponge, consisting of a solid skeleton of membranes and particles constructed of lipids and proteins, in

which electron currents may flow, governed by the laws of solid state physics.[92] The interstices of the sponge are filled with water, in which reside dissolved proteins and small ions. NMR evidence[126-128] indicates clearly that cell water possesses more structure than liquid water, and that much of the Na^+ and K^+ in the cell is not free in aqueous solution, but is associated with charged sites on macromolecules.[129-133] The quantity of Na^+ and K^+ dissolved in tissue water is low, because of the structuring of the water. One may then make an analogy between the aqueous portion of the cell and a solid semiconductor. One may regard complexed Na^+ and K^+ as analogous to valence band electrons in a semiconductor, and free cations as analogous to conduction band electrons.[134,135] The complexed ions exchange rapidly with, but are only slightly soluble in, the structured water. Conduction, diffusion, and potential equations for ionic processes in cell water therefore resemble those for electronic conduction in a semiconductor solid. Experimentally useful predictions regarding ion transport have been obtained from this approach.[134,135]

An ionic form of solid state activation energy barrier kinetics has been developed by Cope[135,135] which predicts that Na^+ and K^+ leakage from cells should obey the Elovich equation, which agrees with experimental observation. This theory requires that there be an activation barrier to ion conduction at the cell surface. The cell surface must resemble a liquid-solid interface like an electrode surface. Since the extracellular space is presumably liquid, the intracellular phase must have solid-like properties if the theory is correct. Specifically, it is necessary to assume that cell water has more structure than liquid water and consequently a low solubility for Na^+ and K^+, and that Na^+ and K^+ exist in cells mostly associated with macromolecules rather than in free solutions. During the last few years, excellent evidence for cell water structuring from nuclear magnetic resonance (NMR)[126-128] and from water absorption studies[136,137] has become available and this has become the basis for an NMR method of cancer diagnosis.[138,139] It has been shown that the metabolism of the cell produces much less energy than is required to operate the Na^+ and K^+ pumps that are required to maintain ionic concentrations in the cell for the liquid state model of the cell.[140-143] Therefore, the liquid-state-free-cation model of the cell is thermodynamically impossible, but the solid state, or ion exchange resin, or structured water and associated cation model of the cell is compatible with all the evidence and with thermodynamics. An entire issue of the Annals of the N.Y. Academy of Sciences[144] was recently devoted to this problem.

Therefore, the weight of the experimental evidence supports strongly the analogy of the cell surface to a liquid-solid interface. Therefore, the application of solid state physical theory to the kinetics of ion transport

across the cell surface seems appropriate. Cope's solid state theory of cell water and ions is probably equivalent to a simplified form of the association-induction hypothesis of Ling[141,145] and the ion exchange theory of Damadian.[146,147]

V. The Future

New and better experimental techniques are needed for solid state biology. Biological processes function only when the system is complex, impure, noncrystalline and wet. The conventional experimental techniques of solid state physics are not usable under these conditions.

New experimental techniques suitable for solid state biology are beginning to be developed. Measurements of electron mobilities within wet protein particles by Hall effect at microwave frequencies have begun.[13-22,148] A pulsed electron beam method for measurement of electron mobilities in wet proteins has been developed in Russia.[5,9] Methods for measurement of dilute superconductivity, applicable to organic solids[49-51,177] and perhaps to biological systems have been developed.

When the experimental techniques of solid state physical biology become as well developed as those of liquid state biology, the author expects that solid state processes will be found to be equally as important for biological functions as liquid state processes.

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