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Prospects for applied bioelectrochemistry

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Galvani, Volta, Davy and Faraday all recognized that life on earth and electrochemistry are intimately connected. The controlled transduction and flow of energy is at the heart of both.

Life exists along the grand solar energy vector that is made up of countless different living species' individual component vectors. Chloroplasts in photosynthetic cells and the mitochondria in all living cells function as the equivalent of a battery charging and discharging, and together form an electrochemical circuit that spans life's energy vector. An electrochemical circuit consists of two compartments with a chemical potential difference between them connected by two or more links that are selectively permeable to different chemical species. Link permselectivity determines whether the chemical energy is transduced to electrical or mechanical form: the two forms that predominantly control biological growth.

This review shows how a network of electrochemical circuits can have all the properties required to control chemistry and physics on space and timescales that are appropriate to the control of the biochemistry of creatures great and small: an amoeba or an elephant from its conception to its death. Evidence supporting this electrochemical circuit model is then discussed. A creature and its control network can grow together and when both are complete the fully balanced network appears as a distribution of electric potentials. Injury unbalances the network and so starts direct currents of injury flowing in it that may be the signal that intitiates and controls its repair. Many less highly evolved species, e.g. salamanders, can regenerate lost limbs, an ability that more highly evolved species have lost. Do they lack a sufficient current of injury? If so can the current of injury be provided artificially? It is now beyond reasonable doubt that recalcitrant bone fractures in humans can be stimulated to re-unite using electrical signals designed to generate a current of injury across the fracture. Orthopaedic surgeons now consider about 80% success as normal for non-unions that would probably be permanent if they remained unstimulated. There is now clinical evidence showing that stimulation is effective in promoting healing of peripheral nerves, varicose ulcers and burns. Most significantly, currents flowing into the ends of children's fingers that have been accidentally amputated are electrochemically very similar to those that control the regeneration of amphibian's lost limbs. Finger tips which are treated so as not to disturb these natural currents usually regenerate nearly perfectly. A great deal of evidence supporting the view that electrochemical circuit networks play a major part in controlling biological growth and healing processes is reviewed and it is suggested that it may soon be possible to manipulate their control functions to great humanitarian and probably ecomonic benefit.

1. Introduction

Michael Faraday is best known for his laws of electromagnetic induction because they are the foundation not only of the science of electricity and magnetism but have also led to the electrical engineering and technology that has so greatly transformed our everyday life. His laws of electrochemical equivalence are less well-known because, although they have had a great influence on the physical and chemical sciences, technologies based on them have a much smaller impact on everyday life.

Galvani and Volta, in founding electrochemistry, demonstrated the importance of electro-chemical phenomena in biology. In spite of having started so closely linked to biology, electrochemistry later developed as a purely physical science leaving such vital phenomena as biological energy transduction and nerve action to be studied

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within the life sciences. It is now clear that there is a great deal of electrochemistry involved in the way in which biological life on earth controls itself and its energy supplies, and this control is the kernel of life and the essence of survival for everthing that lives.

The recent revival of interest in bioelectrochemistry, and particularly in the role of electrochemistry in control, is not surprising therefore. It seems reasonable to predict that its study will quite soon, not only much broaden physical chemistry's horizons, but also lead to a bioelectrochemical technology that can transform life and health itself as radically as electrical technology has already transformed our society's everyday activities. This is the prospect for applied bioelectrochemistry.

The present review assesses these prospects first using many of the most fundamental premises of electrochemistry to show how electrochemical circuits can have the essential characteristics required for a biological control mechanism. A survey of a wide range of electrical phenomena in plant and animal life then brings out strong evidence for such circuits and their control functions. The survey suggests close analogies between electrical and electrochemical circuitry, and parallels between electrochemical circuitry and nervous systems in their control functions that reinforce the introductory message.

The survey is followed by a short review of some results of electrical interventions into the control mechanisms and some of the prospects for applied bioelectrochemistry are elaborated on.

2. Bioenergy flow control

Life on earth is effectively synonymous with the controlled flow of solar energy through the biosphere, an immerse diversity of organisms each drawing its energy and other nutrients from its own niche in the biosphere, and using that energy for synthesis, motility, reproduction and, in higher organisms, communication within the organism itself and with its environment. Plants and animals, fishes, birds, insects, every living thing, lives along its own peculiar energy flow vector which must always join with those of its neighbours if the species is to survive. Similarly, the vectors for a plant or animal's internal organs must match those of the rest of its body and so on down to the basic single living cell. Every different unit of life, be it an elephant or an amoeba, must be able to control fully the energy flow through itself from conception to death and match its energy requirements to those available in its own peculiar niche.

The total flow vector of life on earth starts with photosynthesis and ends with the final decomposition of organic matter into simple molecules and heat. The photosynthetic reaction

$$6CO_2 + 6H_2O + h\nu \rightarrow C_6H_{12}O_6 + 6O_2$$

summarizes how photosynthetic organisms absorb sunlight and use its energy to produce a storable form of hydrogen, carbohydrate and oxygen. In higher plants, this is carried in chloroplasts where the light, in effect, pumps electrons, donated by water, across a membrane to produce initially a reducing species (H) on one side, and an oxidizing agent (O) on the other. The solar energy is thus converted into an easily storable, safe chemical fuel and a universally-available oxidant. Energy is recovered in the reverse reaction in the mitochondrion, the power source in every living cell. The mitochondrion's essential element is again its membrane that first converts the chemical energy to a proton concentration difference across itself. The chloroplast and mitochondrion are thus a pair of electrolytic cells with membranes, selectively permeable to charged particles, as their electrolytes. Together they form a fuel cell, charged by sunlight and discharged as the power source of the living cell.

The interconversion of chemical and electrical energy is the common core of electrochemistry and life, and control of that conversion is the key to the survival of every form of life. The electrochemistry of the control of biological life must therefore be the most exciting and potentially rewarding growth point in electrochemistry and its offspring bioelectrochemistry. Recent advances in electrochemical techniques, coupled with new knowledge of the biochemistry of energy transduction, the importance of ions in biochemical processes and of ion selective channels and pumps in cell membranes, point the way towards understanding some of the characteristics of electrochemical mechanisms in biology.

They suggest that the applied bioelectrochemist may soon be able to manipulate those controls to great humanitarian and consequent economic benefit.

3. Electrochemical circuits

Galvani, in a classic experiment, connected an iron/copper/saline battery to a frog's leg muscle and showed that it produced strong muscular contraction. Galvani had made an electrochemical circuit with a chemical battery converting chemical energy to electrical energy connected to a biological electromechanical converter that converted the electrical energy into mechanical work. Galvani's electrochemical circuit also converted short-range saturated chemical forces into the longer range unsaturated coulombic and mechanical forces that are required to control chemistry and physics on spatial and temporal scales that are appropriate to the control of life.

The basic electro/mechano-chemical circuit, Fig. 1, consists of two compartments connected by at least two selectively permeable links. There is a difference of chemical potential between the two compartments and the two links are selectively permeable to different species. When the links conduct charged species, ions, the chemical potential difference is converted to an electrical potential difference that can drive a current round the circuit. Links that are neutral species conductive, convert the chemical potential to a hydrostatic osmotic pressure difference between the compartments that can drive a mechanical flow round the circuit. Link permselectivity thus decides between electrical or mechanical output.

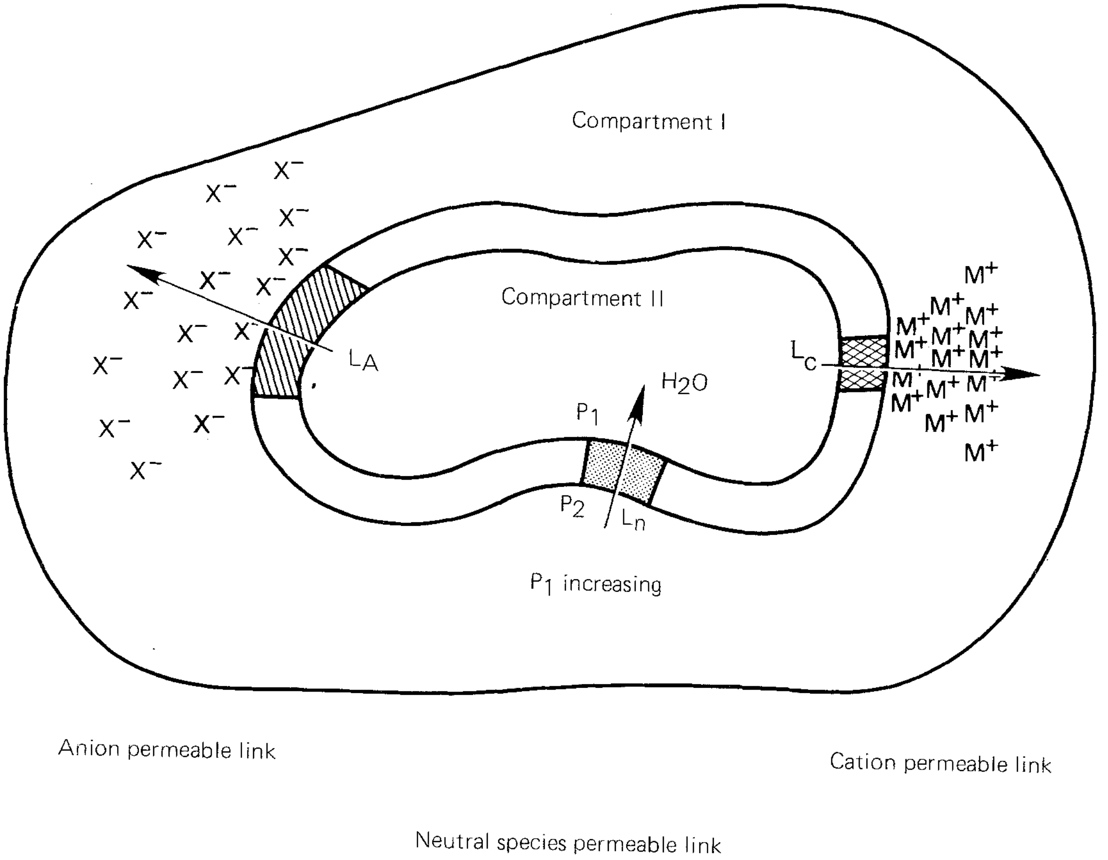

Fig. 1. The basic electro/mechano-chemical circuit. There is a difference in chemical potential between the two compartments. When these are joined by a link that is selectively permeable to an electrically charged species, the chemical potential difference is converted into an electromotive force. A link that is neutral-species selectively permeable converts it into a mechanical pressure. When there are two links, L_c and L_A, a motive force drives a current or a mass flow round the circuit, creating concentration gradients around the links.

The chemical potential difference determines the total electro/mechano-motive force in the circuit while the flows are determined by the impedance of the circuit as a whole. Ohm's and Kirchoff's laws and their mechanical equivalents will apply to such circuits.

Figure 2 idealizes Galvani's circuit. The chemical potential difference comes from the two dissimilar metals in saline. The metals form an electron-selective link and the saline solution an ion-selective (Na^+, Cl^-) link. The frog's leg muscle is the electric motor 'load'.

In any steady state, the flux of charges (current) or neutral species (mass flow) is constant throughout a circuit although the nature of the charge carrier or mobile neutral species will often change where a link joins a compartment. Such changes of carrier or mobile species create at the joints, concentration gradients whose magnitude increases with flow density (current density). The gradients are dissipated by convection and diffusion away from the joint, with concentration relaxation times for diffusion increasing with distance x from a plane joint according to the relation

$$t_R = \frac{x^2}{4D}$$

where D, the diffusion coefficient for small molecules is about 10^{-5} cm^2 s^{-1}. Table 1 shows a range of relaxation times for biologically significant distances. Electrical currents flowing in the electrochemical circuit thus create ion concentration gradients at the link/compartment junctions: gradients that can spread over distances comparable

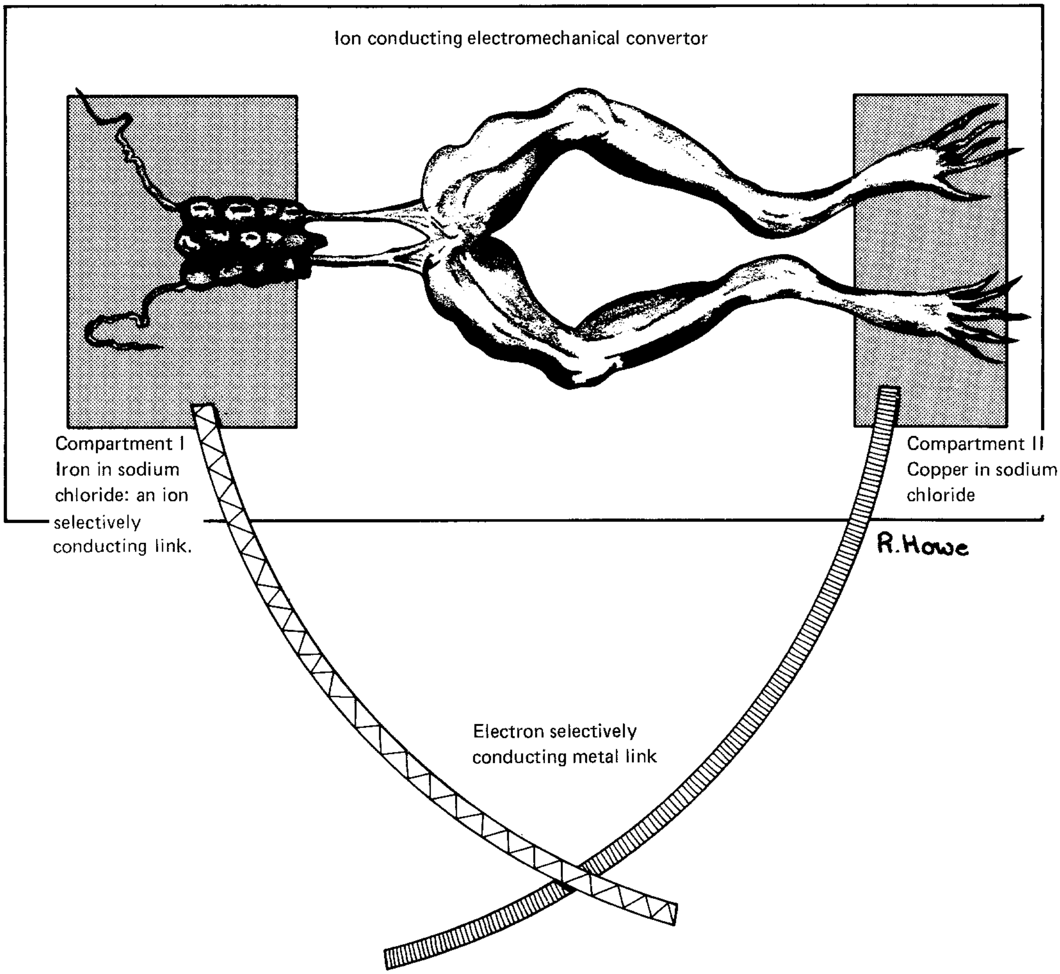

Fig. 2. Galvani's electrochemical circuit.

Table 1. Relaxation times and distances relevant to concentration differences that can be generated in biological cells. t_R = *relaxation time,* $C/C_0 = 1/e = X^2/4D$, $D = 10^{-5}$ cm^2 s^{-1}

Dimensions	X(μm)	t_R (S)
Length of haemoglobin molecule Thickness of membrane	7×10^{-3}	10^{-8}
Length of mitochondrion Length of *E. coli.* cell	2	10^{-3}
Length of chloroplast (spinach leaf)	8	10^{-2}
Length of liver cell	20	10^{-1}

with cellular dimensions. A gradient's composition is decided by link permselectivity while its magnitude is determined by local current density at that link. Furthermore, gradient location is decided by the location of the link/compartment joint. Current flowing in the circuit thus correlates ion concentration gradients separated spatially on a scale that can easily be comparable with a whole organism, yet with local dimensions and relaxation times typical of cellular and molecular dimensions and response times.

4. Control of growth and healing by electrochemical circuit networks

The metabolic rates of organisms are largely determined and controlled by enzymes whose catalytic activities are often in turn dependent on a simple ionic cofactor such as Ca^{2+} or Mg^{2+}. The pattern of ion concentration gradients set up by the current in an electrochemical circuit can therefore be translated into a congruent pattern of enzymic activities and hence of metabolic rates. Thus, an electrochemical circuit can correlate and exercise overall control at a molecular level over the metabolism of a macroscopic living organism. Any number of electrochemical circuits can be interconnected to form an electrical network that similarly can cover the whole of a much larger creature. Suppose that while the creature is growing its network is incomplete, so that the emf values in its component simple circuits are not balanced by those in adjacent circuits. Currents will flow in the partially formed network and its surroudings maintaining a pattern of ion concentration gradients and hence of metabolism. It is reasonable to hypothesize that this metabolic pattern is one that organizes and controls the creature's, and its associated network's, next stage of growth. The creature and its control system thus grow together, with the network progressing towards balancing all its emfs when the creature is fully-grown and complete. Then the control network will appear as a distribution of potentials covering the creature's whole body and will probably broadly reflect its morphology.

Injury or disease will disturb the balance and start currents flowing again. The idea of a 'current of injury' thus follows from the electrochemical circuit network model of the control of growth. The network is clearly electrically inductive while its selectivity permeable links are electrically insulating dielectrics shunted with ion conducting channels. When there are ion concentration differences across them, the links behave electrically as leaky condensers whose capacities are generally complicated functions of many variables.

When an organism moves in a magnetic field such as that of the earth, emf will be generated in its network's elementary circuits and these will, in principle, change the pattern of ion gradients and hence metabolism associated with the organism's motility. An organism's network and metabolism can thus respond sympathetically to changing magnetic fields in its environment. Furthermore, since the elementary circuits are inductively and capacitatively reactive, they have oscillatory modes albeit heavily damped by their high resistances. The complete network will thus have a set of oscillatory modes, each with its characteristic frequency.

The network model suggests a direct connection between motility and control of metabolism: an obviously very desirable, if not essential, faculty for the survival of species which rely on motility for their energy. The model equally easily accomodates a close coupling of biological rhythms and the controlled flow of energy within organisms.

The electrochemical network is also an electrical one which can interact with the electric and magnetic fields of species' environments. Evolutionary pressure will undoubtedly have adapted species to benefit from their interactions with the naturally occurring fields, for example, those associated with solar flares. Recently developed methods of electromagnetically stimulating the joining of recalcitrant bone fractures in humans show how man-made fields can be used to great benefit. However, in the last few decades, there has been a dramatic increase in both the frequency range and intensity of electromagnetic radiation in the biosphere associated with increases in communications, defence surveillance and microwave processes. What deleterious effects may these have? A question that makes all studies of electrically mediated biological control mechanisms the more urgent.

The next three sections review some of the more striking experimental evidence that supports the electrochemical network model of control already outlined and indicates some of its main characteristics in animals and plants. Much of the most direct evidence comes from the beautiful work of Jaffe and his colleagues [1, 2]. Jaffe has developed a vibrating microelectrode probe to measure ohmic potential gradients due to currents flowing around developing eggs and embryos. His probe is a 10–30 μm diameter black platinum sphere vibrating at several hundred hertz and with variable amplitude. Potential gradients are determined from the difference of potential between its extremes of amplitude measured using a lock-in detector tuned to the probe's vibration frequency. This lock-in technique improves the probe's signal-to-noise ratio by some three orders of magnitude compared with a similar sized static probe. Local current densities can then be calculated from potential gradients knowing the conductivity of the electrolyte solution (often essentially sea-water). Local current densities of 0.1 μA cm^{-2} can thus easily be measured with a spacial resolution of about 30 μm.

5. Currents controlling plant and animal embryo development

Measurements of currents associated with the earliest stages of the development of fertilized eggs of the brown seaweed, fucus, show very clearly that ion currents within the egg, and in the sea-water surrounding it, precede and predetermine the egg's development. The seaweed propagates by releasing unpolarized (spherical) fertilized eggs into the sea. Very soon after an egg settles on a solid support, there is a steady current flowing through it with positive ions flowing into the outer end of a diameter from the egg's point of attachment where chloride ions flow inwards. This transcellular current flow determines the egg's polarity and the axis along which it subsequently develops by first forming a protruberance on the outer end and then forming walls (membranes) that divide the egg along its axis. Similar current associated development has been found in the germination of other single plant cells, for example, green algae, with currents ranging from < 1 to 20 μA cm^{-2} near a growth point where an egg or cell's outer membrane is highly positive-ion leaky. Growth seems to be generally, and is perhaps universally, concentrated at points where positive ions, and in particular calcium ions, can most easily leak into the cell. Several simple marine plant cells and a wide variety of animal and insect embryos are now known to drive ion currents through themselves. These are currents that are closely associated with the insect or animal's subsequent development [3]. As an example, Jaffe and Stern [4] have plotted the current flow pattern around a chick embryo at its primitive streak stage, when sodium ions are being pumped into an intra-embryonic space, from which they leak out through the primitive streak. The whole primitive streak is a current source with its highest current density at about 25 mA cm^{-2}, close to an embryologically significant node. Stopping this current by blocking the sodium ion pump very seriously disrupts embryonic development. Furthermore, it is surely significant that, at this stage, every newly-created cell passes through the primitive streak into the intra-embryonic space where the main developmental activity occurs.

Developmentally determinative currents have also been found at later stages of embryonic development. Thus, Jaffe [3] reports Robinson's finding of strong (1–10 μA cm^{-2}) current leaks from a frog embryo at the point where its hind limb bud later appears and grows.

6. Electric potential distributions over fully-developed organisms

Highly amphipathic compounds, for example, long chain fatty acids, can spontaneously form vesicles and so separate a volume of sea-water

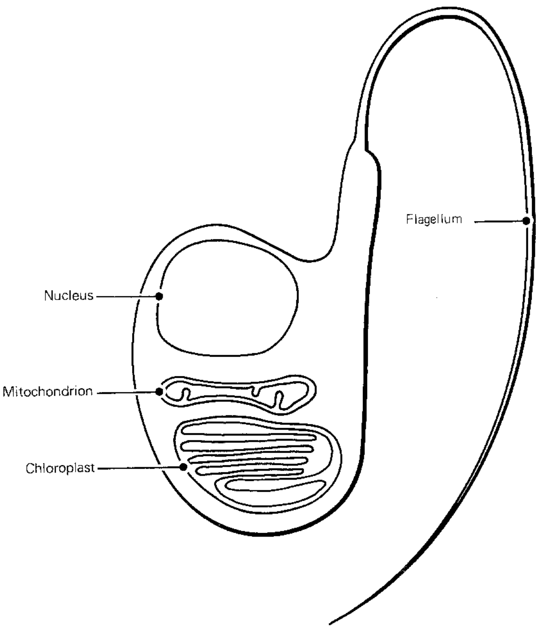

Fig. 3. Chloroplast and mitochrondrion in an early alga *Micromonas pusilla.*

from its surroundings. Some such forming of a cell and its enclosing membrane was probably almost the first organizational step in primordial life on earth because it allowed a difference in chemical potential to be created between the inside of a cell and its environment [5]. This simplest of cellular structures then developed into the first living organisms, photosynthetic bacteria, which developed their photosynthetic apparatus across invaginations of their containing membrane. Later organisms then separated off their photosynthetic and mitochondrial membrane segments forming enclosed volumes of solution, i.e. forming compartments within the cell's main volume. Figure 3 shows this schematically for *Micromonas pusilla,* one of the earliest marine algae. Light absorbed by chlorophyl in its lamellal membrane pumps electrons from water on one side into a receptor molecule on the opposite side of the membrane, thus creating a redox chemical potential difference between the inside and the outside of the alga's photosynthetic compartment. The lamellal membrane is effectively electron permselective and if it is also permeable to another ionic species, for example, protons, it can convert light into a purely chemical redox potential difference across itself. Indeed, some organisms can produce this as a simple hydrogen gradient. The mitochondrial membrane carries out the reverse reaction, transducing chemical energy into a proton gradient, an electrical potential across its membrane. Protons then spontaneously flow through special proton permselective channels where their energy is further transduced into adenosine triphosphate (ATP).

Electrochemically, biological membranes can be modelled as thin sheets of low dielectric constant insulating phospholipid with selectively permeable channels and ion selective pumps passing through them. Both are confined to the membrane but probably have lateral mobility within it. The channels are probably considerably smaller and more mobile than the pumps and so can be concentrated more quickly than the pumps. Figure 4 shows how any such concentration of channels or spatial separation of channels from pumps creates an electrochemical circuit around a membrane segment. Ion pumps (batteries), will then drive current round the circuit and

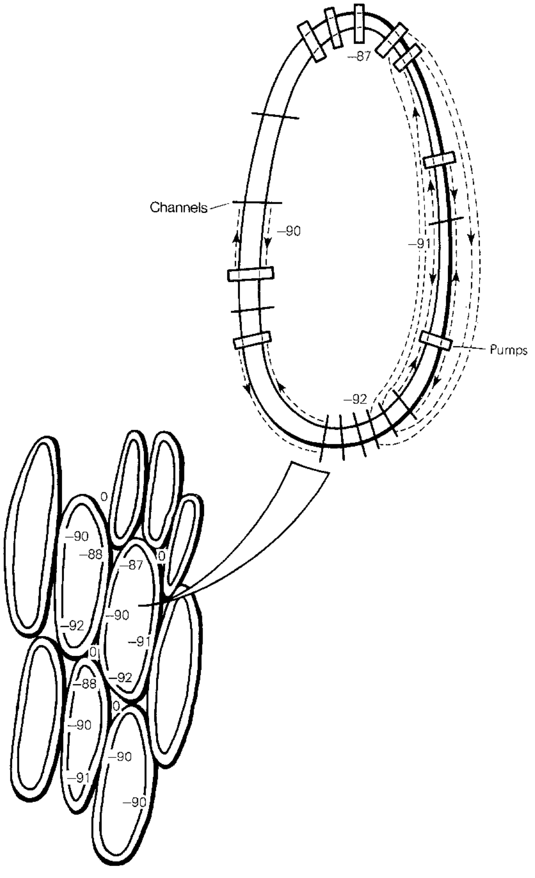

Fig. 4. Cellular polarization produced by the separation of membranal ion pumps and channels.

produce an ohmic potential difference between say a point where calcium selective channels are concentrated and those where chloride channels concentrate in fucus eggs attached to a rock. The *IR* drop will depend on the specific conductivity and geometry of the solution outside the membrane, that is, outside a cell's internal organelle, or outside a whole cell. The limiting case will be a cell with pumps concentrated at one pole and channels diametrically opposite it. There will therefore be two electrical potentials associated with the polarized cell. A large, about 100 mV transmembrane potential, and a much smaller about 10 mV potential difference across a cell diameter, 10^5 V cm^{-1} and 10^0 V cm^{-1}, respectively. Several types of cell respond to electric fields of 1 V cm^{-1} and Jaffe [2] has proposed that this response may be elicited through lateral electrophoresis of trans-membranal channels concentrating to form leaky regions of the membrane. Jaffe [6] has also shown that a local intracellular concentration of free calcium ions is intimately involved in spermal egg fertilization.

Potentials of the order of millivolts across distances commensurate with a complete organism may be very significant in controlling its development. Such potential gradients can be created by the ohmic resistance of biological electrolytes, e.g. sea-water, that are components of an organism's basic metabolic circuits, for example, its mitochondrion: a model that links control directly with basic energy production.

Many studies have been made of potential distributions over plants, plant seeds and animals. These usually show a pattern that reflects a plant's morphology or an animal's anatomy and nervous system. The measurements of Barker *et al.* [7] on guinea pigs and themselves are the most recent and striking examples of such measurements. Furthermore, they show that the potentials are due to batteries under the skin which, when it is intact has a very high resistance. The batteries drive current through any break in the skin. Barker *et al.* [7] believe that this current sets off the repair of injury. There are patterns of electric potential associated with fully grown plants and animals but their relevance to the control of development has not yet been demonstrated convinvingly. This is not surprising if the arguments presented here are valid. Potential measurements are intrinsically difficult and Fig. 4 makes it clear that potentials measured on living organisms will be extremely sensitive to where the electrode is placed in relation to membranes forming compartments, a parameter that is very difficult to decide practically, particularly when it is also important that the potential measuring probe does not alter or interfere with the current flow pattern around it. From a control point of view there may be a greater interest in the distribution of small differences of potential between quite widely separated parts of plants, insects and animals living under normal conditions. The development of sufficiently precise potential measurement techniques is one immediate challange to applied bioelectrochemistry.

7. Natural currents for repairs

Evidence for linking ionic currents and small potential gradients with the repair of injuries and, indeed, the regeneration of amputated parts of plants and animals is already considerably stronger than that which links static potentials with structural completeness. *Acetabularia mediterranea* is a giant unicellular alga that, full grown, has a stalk 2–3 cm long with a green photosynthetic cap several millimetres in diameter at one end. It is normal for a stalk to regenerate a cap that has been amputated. Prior to regeneration, potassium and chloride ion pumps in the stalk membrane re-establish a high transmembrane potential of about 170 mV (negative inside). The chloride ion pump also contributes to generating potential spikes that start at the cut-end and travel down the stalk as action potentials very similar in kind to, but much slower than, those transmitted along nerve fibres. There is also a small potential gradient of about 1 mV cm^{-1} along the stalk with the cut-end positive. Goodwin and Pateromichelakis [8] have shown a strong association between this lengthwise polarization, stalk elongation and cap regeneration. The latter is always associated with the positive end. Calcium ions are required for both the action potential and cap regeneration.

Many amphibians, for example, salamanders and newts, regenerate amputated limbs. Their skins contain sodium ion pumps which pump ions inwards. Borgens *et al.* [9] have shown currents up to 100 μA cm^{-2} flowing out of limb stumps shortly after amputation. These currents gradually fall as the limb regenerates. The crucial role of the sodium ion pump is shown by removing sodium ions from the creature's environment or blocking the pump entrance ports. Both treatments greatly reduce the outward current and seriously interefere with regeneration. It is widely accepted that there must be nerves in the stump for it to regenerate. Indeed, Rose [10] considers that the axis of regeneration is decided by contact between nerves and the epidermis, but the role of nerve cells in regeneration and its associated currents and potentials is not at all clear yet.

It is a great encouragement for applied bioelectrochemists that recently Illingworth and Barker [11] measured the currents coming out of accidentally amputated children's finger tips and have found them to be very similar to those coming out of amphibian stumps. Furthermore, clinical treatment that effectively left the currents alone resulted, in most cases, in nearly perfect regeneration.

8. Currents of injury

Biologists have wondered for a long time how it is that some less highly evolved creatures, specially amphibians, can regenerate completely lost limbs while more fully-evolved species, including man, can do no more that imperfectly repair comparatively minor injuries. There has also been much speculation about whether or not electricity is involved or could be used in injury repair. Speculation about electrical involvement eventually crystallized into the 'current of injury' concept which asserts that when injury occurs, a current starts to flow and is the signal to the injured creature that initiates its repair. This idea has now been taken further with the suggestion that there is a direct current component in more primitive nervous systems that controls their host's overall development and repair, and that in creatures higher in the evolutionary scale, this has progressively declined in favour of their nervous systems much more powerful information-handling pulsed-current modes of operation. This leads to the proposition that the latter, including man, have the genetic information and metabolic equipment to be able to regenerate lost parts but fail to do so because there is an inadequate current of injury to signal the need.

Many factors have contributed to a great revival of interest in currents of injury and two are specially relevant to the future prospects for applied bioelectrochemistry.

The first comes from the development of extremely sensitive magnetometers made possible by the discovery of the Josephson effect. The current in a ring of superconductive metal is quantized as is the associated magnetic flux that threads the ring. The current and magnetic flux are the macroscopic equivalents of the quantized angular momentum and magnetic moments associated with the more familar atomic and molecular orbitals. An imposed change in flux through a ring produces a corresponding change in the supercurrent flowing in it. When the ring contains a thin insulating link, a Josephson 'weak' link, a voltage appears across the link each time there is a quantum jump in the supercurrent. Very small changes in the magnetic fields through the ring can be measured using the device as a digital magnetometer quantized in units of about 2×10^{-7} gauss cm^2 [12]. These SQUID magnetometers are a most valuable tool for studying biologically generated currents. Thus, Cohen [13] measured the current of injury started by a controlled injury to a dog's heart muscle and found the expected direct current superimposed on the heart muscle's time-dependent currents. This result pointed to the cause of a hitherto unexplained feature on electrocardiographic traces for the same muscle injury.

A number of medical consultants, particularly orthopaedic surgeons, have argued that the ability to repair broken bones has evolutionarily always been vital for the survival of vertebrates including, of course, man. Human bone is piezoelectric and perhaps it is this that still normally provides a sufficient current of injury to start fracture repair. However, a considerable number of human bone fractures do not re-unite naturally, greatly disabling the patient and often, in the end, necessitating an amputation. In the last decade or so, orthopaedic surgeons have used various forms of electrical treatments on such recalcitrant fractures aimed at supplying a current of injury artificially. Several almost entirely empirically designed electrical regimes have already proved remarkably successful with success rates of about 80% now being expected. Successes are also now being registered with similar treatments on other injuries suggesting that it may be possible to provide artificial currents of injury to assist, or even eventually initiate, the healing of a wide range of injuries. The next section describes briefly some examples of electromagnetic interventions into healing to indicate the present state of the art and to suggest the scale of opportunities to apply further knowledge beneficially.

9. Electric and magnetic interventions

There are an immense variety of reports and studies on the effects of electric and magnetic fields on living organisms. Unfortunately, these very often provide only fragments of circumstantial evidence for responses because there was no adequate control of variables, the experimental conditions were very far from natural, or sometimes such large fields were used that the observed effects may well have been due to heating or some other gross indirect effect. Such results are not considered here where the examples have been selected using three criteria. First, that there is a reasonable measure of agreement between several different workers who have each attempted to control their experiments as far as present knowledge and ethics allow. Second, that the result illustrates a point of general importance for future attention. Third, that together the examples suggest the generality of electrochemical control mechanisms in biological growth and healing, and thus excite speculation on what may be achievable with a better understanding of electromagnetic interventions.

Experiments on amputated amphibian limbs show that the current of injury can be provided artificially. While a salamander is naturally regenerating an amputated limb, the stump end is negatively polarized relative to its base. If it is polarized positively using electrodes and a battery, no regeneration occurs [10]. However, a denervated stump is positively polarized and does not regenerate until it is artificially negatively polarized. The battery circuit thus appears to be effectively replacing the current naturally controlled or in some way provided by nerves, with the important difference that the former will also generate electrode reaction products whose nature and local concentration will depend on the battery voltage, the electrode materials and current density (electrode size). Many of the likely products, for example, chlorine and metal corrosion products at an anode or high pH at a cathode evolving hydrogen, severely damage tissues and kill cells. Adverse effects very probably due to electrode reaction products were observed in the salamander experiment and seemed very often to have been present in experiments and even clinical treatments that have used direct currents and implanted electrodes.

A very substantial number of human patients of all ages who have had bone fractures that have failed to unite naturally after sometimes a period of years, have now been treated successfully using implanted electrodes and direct current stimulation. It is widely but not universally agreed that a cathode stimulates bone formation. The direct current stimulation treatment involves putting one or more cathodes between the fracture ends and passing a total current of about 10 μA per cm^2 of fracture cross-section. Anodes are put well away from the fracture but so that the current flow will be from the fracture ends to the cathodes. Large anodes are used to keep down the anode current density and hence local concentrations of anodic electrode products which appear to be significantly more toxic than the cathodic products. Too little attention is often paid to current density control with the consequence that sometimes electrode product toxicities may more than cancel the stimulation effects and lead unnecessarily to a failure.

Electrical stimulation of bone healing has so far been restricted to non-unions which have failed to respond to normal orthopaedic treatments often including several bone grafts. Non-invasive inductive electrical treatments [14, 15] were developed originally to avoid the hazards of further surgery in such cases. They are based on the presumption that there are electrical circuits associated with the fracture that can be used as the secondary of a transformer whose primary approximates a Helmholtz pair of coils outside the fractured limb. Current pulses in the primary should then induce current in a secondary associated with the fracture. The coils are mounted on the standard immobilization plaster and positioned so that the induced current flows between the fracture ends. Several thousand patients have already had this inductive treatment with an overall success rate in the high seventies per cent on non-unions that otherwise would probably have been permanent. The treatment shows three special features. The first signs of union often appear after only 10 to 12 weeks of stimulation for 10 to 14 hours a day. After this, repair seems to continue without further treatment. Repair is not only completed more quickly but is generally better than a natural union. Interestingly, the treatment seems slightly less likely to succed when, for example, in the case of a highly oblique fracture, the coils have not been placed so that they induce a current across the fracture.

Although as yet there are but few examples, inductive treatments have been reported as effective in stimulating the healing of varicose ulcers and burns [16]. The burns again not only healed faster but were also, histologically, considerably more perfect.

There are several reports of inductive treatments that have substantially increased the rate of recovery of cut peripheral nerves [17]. These clinical effects are in line with experiments on animals and fish and some very carefully controlled measurements on the effects of an electric field on single neurons in cell culture [18]. The electric field increased the fraction of neurons that sprouted neurites and the neurites grew preferentially towards the cathode. Nerve cells seem generally to be more sensitive to, and respond more strongly to, electromagnetic stimulation than other types of cell.

10. The natural electrochemical control circuit network

All the higher forms of life and indeed some quite primitive forms have nervous systems that, together with chemical (endocrine) communications systems, largely control the life form's physiology. Nervous systems process and transmit information as electrical impulses that are carried in a network of neurons connected together by their axons which are ion conducting cables. The impulses are transient depolarizations of the axonal membrane fired by transmembrane potential changes of a few millivolts lasting about 10^{-3} to 10^{-4} s. The potential change opens sodium ion permeable channels which in turn open potassium selective channels, producing the well known 'action potential'. The axonal membrane is later reset to receive a following impulse by sodium and potassium ion pumps.

Nervous systems are therefore natural electrochemical control circuit networks. Nervous systems include terminal sense organs that are neurons specially developed for sensing an organism's environment. Some organisms have sense organs directly sensitive to an electric or magnetic field. Thus many fresh-water and salt-water fish detect electric potential gradients in the water through 'ampullae of Lorenzini' which have been described as ideal submarine cables open-circuited at their receiving ends [19]. With these, some sharks, for example, can detect a d.c. potential gradient as low as 1 μV m^{-1}. Very interestingly, fresh-water fishes' sensors are smaller and much less sensitive (50–100 μA m^{-1}) because, it has been suggested, of the lower conductivity of fresh-water compared with sea-water. At the other end of the scale certain aquatic bacteria swim along magnetic field lines, sensing them with a chain of magnetite particles [20]. The individual particles are the optimum for forming a single stable magnetic domain which thus gives the sensor its best possible specific sensitivity.

It is generally agreed that pigeons sense the earth's magnetic field in homing. Other birds and honeybees can also detect a magnetic field. Thus migrating birds [21] have been shown to respond to a low intensity (about 1% of the earth's field) low frequency (80 Hz) magnetic field surrounding a radar antenna, while bees comb-building and mobility in the dark [22] are both influenced by a steady magnetic field, and practically, beekeepers are reputed to have difficulties when their hives are too close to overhead power lines.

The action potentials in the alga *acetabularia*, already referred to show that even one of the simplest plants has a rudimentary nervous system, while Simons [23] makes a strong general case for electrical communication systems in plants and notes their close similarity to nervous systems in animals. Plants also have sense organs covering almost every variable in their environments including electric and magnetic fields [24]. Furthermore, there are clear indications of direct links between sensing these fields, insolation and the control of plant metabolism. Thus Athenstaedt [25] has found that many plant and animal tissues show pyroelectric properties* and believes this to be a basic characteristic of all living organisms. More recently, Lang and Athenstaedt [26] have found that the leaf surfaces of some cycads (plants about 350 million years old) show a unique pyroelectric effect where a small electric field enhances the pyroelectric response almost 50 times. Again, Morris [27] has shown how a 1.8 $\mathrm{V\,cm^{-1}}$ potential gradient applied to intact stems of pea seedlings completely inhibits the flow of auxin growth hormone.

11. Conclusions

It seems that almost every form of life has at least a rudimentary electrochemically based nervous control network and that many forms have specialized neurosensors that are highly sensitive to environmental electric and magnetic fields. These sensors are often most sensitive to fields varying at 'brain-wave' frequencies of 0 to 20 Hz. These brain waves can be detected externally. In principle, therefore, an externally applied field can excite neural responses and action potentials, as well as stimulating the growth and healing of neurons. The prospects for applied bioelectrochemistry thus extend beyond the physiological into neurological and psychological areas, with the possibility of contributing to understanding and so improving on such long established practices as acupuncture and its successor electroanaesthesia, and to the treatment of neurological and psychological disorders. Patterson's [28, 29] neuroelectrical therapy for drug addiction gives a foretaste of the enormous benefits that could come from a better understanding of the interaction of nervous systems with electric and magnetic fields. The same may well apply to so called 'alternative' medical treatments many of which may have an electrical basis [30].

Undoubtedly, cellular biochemistry, embryonic development, growth and healing processes can all be modified by both steady and time dependent electric and magnetic fields. Neurons seem to be more susceptible than many other types of cell. Several workers, for example, Mizell [31], and Siskin and Fowler [32], have shown that limb regeneration can be induced by implanting nerve tissue. An important task in applied bioelectrochemistry in the next few years will be to devise experiments to show the extent to which electromagnetic stimulation of growth and healing is direct or is mediated through the nervous system. An early answer on this should do much to increase confidence in all forms of electromagnetic therapy and so hasten and extend their use. At the same time it will provide a base for assessing and avoiding damage to life on earth from increases in the environmental level of electromagnetic radiations that result from increasing communications and uses of electrical equipment of all kinds. Finally, as plant life seems to be similarly responsive to electromagnetic fields, there should be many opportunities for profitable bioelectrochemical interventions in arable husbandry and horticulture as well as to human and veterinary health care.

These are some of the prospects for applied bioelectrochemistry.

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*Materials such as tourmaline that develop electric polarization spontaneously when heated.

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