"QUANTUM WORLDS"

"My Discovery of the existence of Dr. Einstein's Unified Field Theory from Alpha to Omega".

"Quantum Molecules existing and evolving inside of Protein Molecules"

(E = M C\2 now M = E\2 over C).

CDI QUANTUM IMAGING TECHNOLOGY DISCOVERED, RESEARCHED AND DEVELOPED BY

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INTRODUCTION

We still need a strategic account of biological foundations at all levels, to be arrived at through dialogues between physical biologists and biological physicists
F. Eugene Yates

Matter, information and energy are inseparable entities. When aggregated in special assemblies that organize themselves in hierarchical structures of increasing complexity, all interconnected by a continuous bi-directional flow of energy, they can bring about another entity which possesses very unique properties and is known by the name of *life*. Since higher hierarchies come from lower hierarchies, life ultimately must have arisen from the physical world.

It took 3.8 billion years for present life to evolve. In the course of evolution, matter bonded to matter to make up structure and the information embodied in matter organized that structure. This organized structure provided both initial and boundary conditions for dynamics. The information selected in the process of constructing the cellular structure was somehow stored locally, in the form of symbols, in the genome of every cell. According to Pattee, there are two control models in present life, each complementing one another - the *genetic*, which controls the amino acid sequence (primary structure) of biopolymers and the *dynamic*, which controls, in a coherent way, the folding of biopolymers into proteins, their mutual interactions and interactions with all other components of the cell.
These two models of life have been brought together by the Unitary Theory of Whyte. Dynamics is no longer seen as an isolated series of interactions among molecules. Energy, information and dynamics cannot be separated from function and structure. They are all components of a single comprehensive process operating under the guidance and constraints of the laws of nature. This conceptual change of dynamics is the subject of this book.

We do not believe that biological systems are reducible to physical systems. Instead, they differ from them in several ways. Biological systems are more complex, much more interactive, more delayed in action, self-constructing, and work in a state far from thermodynamic equilibrium. They have functions, such as that of reproduction, and functional properties that physical systems do not have. Nevertheless, biological systems obey to physical laws as physical systems do. This work merely emphasizes the physical rather than the biochemical side of biology.

Like any other entity in the universe, life is ultimately derived from the fundamental forces of nature. Given its dynamic character and the characteristics of these forces, only the long-range electromagnetic force could possibly have led to the genesis of life. Life has an electromagnetic basis and the reason why water was chosen as the living medium should have been rooted in its special dielectric properties. Biomatter was then organized from the bottom up, from the microscopic to the macroscopic level, life being a macroscopic phenomenon. As a consequence, living systems must obey to the laws of quantum mechanics, a theory of the microworld that considers waves and particles to be different aspects of the same reality.

We live within space and interact with one another and with nature through space. Matter and energy-information are exchanged at the interface. Most of our metabolic energy is extracted from the C-H bond of carbohydrates and fats contained in the food we eat but some energy comes to us directly from space in the form of electromagnetic waves. This energy, not considered by classical thermodynamics, is of critical importance to the structuring of biomatter. Living structure and space structure are continuously trying to achieve a mutually consistent state. Current biology entirely disregards the dynamic relationship between life and the universe. Living systems, however, owe their structuring and functional capabilities to the subatomic processes of space.

The living system-space relation is mediated by waves and there are reasons to believe that the interactions between components within living systems is effected by waves as well. As pointed out by Reid, in terms of quantum theory, viewing living systems as interactions of wave forms is just as valid as viewing the same processes in terms of the biochemistry of their interacting units, be they molecules or macromolecules. These new concepts must somehow be introduced into a biochemically oriented biology and medicine, if these natural sciences are to keep the pace with the faster developing physical sciences. This was the motivating goal for this work.

In addition to quantum concepts, the book conveys a number of other physical theories, some with sound experimental basis, which challenge current views on the organization and function of living processes or throw light into biophenomena until now unexplained. In the process, I offered my own interpretations of these theories which may not be entirely accurate. In any case, they should be no substitute for the reading of the original works. Throughout the book, there was a constant preoccupation of avoiding deepening too much into physics. It was a slack rope walking from beginning to end, trying to maintain an equilibrium between a rather superficial but hopefully still clear understanding on one side and a fuller but necessarily more entangled description on the other.

The book is divided in 11 chapters aligned in a connecting sequence. The writing is concise and straight to the point. To enhance comprehension, diagrams illustrating specific structure, function or concepts were added. The first two chapters are introductions to the main text. The first chapter deals with basic concepts of quantum mechanics, which have an intrinsic weirdness and seem strange when first introduced. The second chapter gives an overall view of the electromagnetic nature of living processes. A description of the living structure and function at increasing levels of organization then follows. Being at the foundation of life, water and its chemical and electrical interactions with ions and proteins appears everywhere throughout the book. The main theme however is energy and information described from the physical point of view.

1

THE QUANTUM NATURE OF MATTER AND ENERGY

The world, at bottom, is quantum mechanical
H.C. von Baeyer

Biosystems are complex dynamical systems. At the macroscopic level they are governed by classical Newtonian mechanics but at the microscopic level they obey to the rules of quantum mechanics, a branch of mathematical physics based on quantum theory. A quantum in physics can be defined as the minimum amount by which certain properties of a system, such as energy, charge and spin, can change. These properties do not vary continuously but do so in integral multiples of the relevant quantum. Quantum mechanics deals with the motions of electrons, protons, neutrons, and other subatomic particles. It was introduced with the primary purpose of describing the behavior of atoms and molecules, but the theory has also led to the questioning of the relation between the microworld we seek to observe and the macroworld to which we belong.

The quantum description of matter posits that there is a *wave* associated with every particle. Particles propagate like waves and so can be described by a quantum-mechanical wave function. As a consequence of the wave character of matter, the possible energy states of the electrons in an atom or molecule can assume only a discrete set of values, there is, they are quantized. In effect, all phenomena in submicroscopic systems exhibit quantization.
Waves are central to the structure of matter and therefore to physical, chemical and biological phenomena. It is no longer possible to present a modern description of dynamics of living systems, even in a rather superficial way, without the framework of quantum mechanics. The most basic of quantum wave concepts are introduced below and other more elaborated ones will be dealt with in subsequent chapters.

1. The wave-particle duality

In quantum physics, things we normally think of as solid particles, such as soccer balls and atoms, behave under some circumstances like waves and things we normally describe as waves, such as sound and light, occasionally behave like particles (1). This duality was first recognized by Planck when studying the distribution in wavelengths of the radiation from a black body, an ideal solid that absorbs all the light falling on it and has zero reflectivity. In essence, the problem was that of quantitatively describing how hot bodies become redder and brighter as their temperature is increased.
To explain the observed wavelengths distribution Planck had to assume that emission and absorption of radiation occurs in quanta of energy, now called *photons*, each quantum having an energy (**E**) equal to the constant **h** (Planck's constant) times its frequency, or **E = h f.** Later, de Broglie suggested that the duality shown by light might be extended to particles other than photons. In particular, he postulated that the behavior of electrons is somehow governed by an accompanying wave motion (2).

Nowadays, physicists tend to regard all matter as being dually associated with waves (matter waves). In the case of the large bodies of classical mechanics, the wavelengths are just too small for their effects to be detectable. Furthermore, particulateness and waviness are now viewed as degrees of the same underlying property of a quantum. A quantum is not a wave or a particle, but both and neither. It has a quantum-mechanical property observed as waviness at one end of the spectrum, particulateness at the other. The quanta of the microworld need not be waves or particles; they can be a little bit of each, pe, 40 percent particle and 60 percent wave. Particle and wave are just extremes of a continuum (3).

1.2 The electronic structure and dynamics of atoms

Modern quantum theory considers the atom to be made up of a positively charged central nucleus surrounded by a halo of negatively charged electrons swarming in *"probability clouds"* of different shapes. The denser the halo is in a given small domain of a cloud, the more probable that electrons are occurring in that domain. Thus, the idea of electrons in fixed orbits has been replaced by that of a probability distribution around the nucleus – an atomic *orbital*. The orbitals, each of which can accommodate two electrons, are arranged in *shells* of increasing distance from the nucleus, each successive shell being composed of a larger number of orbitals (4).

An implication of wave-particle duality is that small systems such as atoms can exist only in discrete energy states. The atom has a fixed energy corresponding to the orbitals in which its electrons move around the nucleus. It can accept a quantum of energy (a photon or light quantum) to become an excited atom if that extra energy will raise an electron to a permitted orbital. Between the ground state, which is the lowest possible energy level, and the first excited state there are no permissible energy levels. According to the quantum theory, only certain energy levels are possible. An atom passes from one energy level to the next without passing through fractions of that energy transition (2).

In matter interactions, not all electrons behave similarly. The ones closer to the nucleus and more tightly bound to it are non-reactive. Dynamically, nucleus and non-reactive electrons form a single unit, the *core*; the outermost, least tightly bound electrons, the *valence* electrons, are the ones that interact to form chemical bonds with other atoms. Every property of a material (electromagnetic, chemical, thermic, mechanical) is rooted in the interactions of the valence electrons of its atoms. Core electrons occupy the filled inner orbitals of the atoms and their main effect is to screen the nuclear charges from the valence electrons (5,6).

1.3 The quantum property of superposition

Another consequence of the wave-particle duality is that quantum mechanical waves, like water waves, can be superposed, or added together. Taken individually, these waves offer a rough description of a given's particle position. When two or more such waves are combined, though, the particle's position becomes unclear. In some weird quantum sense, then, an electron can sometimes be both here and there at the same time. Such an electron's location will remain unknown until some interaction (such as a photon bouncing off the electron) reveals it to be either here or there but not both (1).

In calculating the probability distribution for a given electron in the cloud of an atom, the electron is considered to be a superposition of waves rather than a particle. The superposition principle is occasionally extended to other phenomena, such as that of spin or rotational motion. Anything that rotates or moves around a fixed point has angular momentum. The earth, for example, has orbital angular momentum from its yearly circuit around the sun and intrinsic angular momentum from its daily

rotation on its axis. The spin of a subatomic particle corresponds to intrinsic angular momentum. It is a quantized variable, that is, it has just two possible states, an up state and a down state. However, according to the rules of quantum mechanics, it is possible to have a qualitatively new state made up of a superposition of the two spin states: a combined, in-between condition that can be, say, 35 percent up and 65 per cent down (3).

1.4 The quantum property of coherence

When two or more superposed quantum waves behave like one wave, they are said to be coherent. *Coherent waves* have a constant phase relationship, with peaks and troughs always similarly placed. From all characteristics of a wave, it is the phase that bears more direct connection with the quantum nature of matter. As we will see later, coherence is a very important means of long-range communication in biology.

The process by which coherent waves regain their individual identities is called *decoherence*. For an electron in a superposition of two different energy states (or, roughly, two different positions within an atom), decoherence can take a long time. Days can pass before a photon, say, will collide with an object as small as an electron, exposing its true position (1).
In ordinary, so-called bulk matter, the time it takes for a photon to bounce off the material is too brief for the eye or any instrument to detect. Macroscopic matter is simply too bulky for its exact location to go undetected for any perceivable amount of time (1,7). Consequently, only bodies of subatomic, atomic and possibly molecular dimensions exhibit quantum properties. Quantum theory is thus a theory of the microworld.

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2

THE ELECTROMAGNETIC NATURE OF LIFE

The evolution of any species is equivalent to changes
in its characteristic electromagnetic field
A.R. Liboff

Current biology describes living processes in biochemical terms – chemical reactions between molecules and macromolecules. However, underlying these reactions and controlling them there are more fundamental mechanisms of an electromagnetic nature.
The basic components of life, water and proteins, possess intrinsic electromagnetic properties. Macromolecules organized in microfilaments inside the cytoplasm of cells – the cytoskeleton – are capable of conducting electricity on their surface. It is now known that most metabolic processes take place on the cytoskeleton and have an electrochemical character. Life runs on electricity.
The tiny electrical currents associated with living processes are difficult to measure but their electrical fields are manifested in the encephalogram, cardiogram and myogram, which are recordings of the electrical activity of brain, heart and muscle, respectively.
Quantum mechanics on attributing a waveform to every particle of matter makes the connection between living matter and the electromagnetic field more clearly apparent. In what follows, evidence is presented for an electromagnetic origin and functioning of life and examples are given of the new ways of thinking brought about by the electrical theory.

2.1 The elementary particles

All matter, inanimate and animate, is ultimately made of a few fundamental constituents called the *"elementary particles"*. According to the *Standard Model* of physics, there are two kinds of fundamental particles – particles of matter and particles that interact with matter. The latter are the mediators of the four fundamental forces (transmitted through fields) – strong nuclear, electromagnetic, weak nuclear and gravitational (Fig. 1).
Basically, all matter is composed of quarks, leptons and mediators. The quarks, held together by the strong force mediated by gluons, form protons and neutrons that combine to make atomic nuclei. Electrons, which are leptons, orbit nuclei to form atoms and molecules.
Electrons are special elementary particles, possessing some mass, a negative charge and even a bit of magnetism. Their quantum fields interact naturally with the electromagnetic field that attracts them to the nuclei. Electron-photon interactions are involved in all events that support the living state. Life, therefore, must be a manifestation of the electromagnetic force.

2.2 The electromagnetic force and life

All physical entities in the world are inevitable consequences of one or more of the four *fundamental forces.* The atom, for instance, is mostly a product of the electromagnetic and strong forces. The influence of gravity on the atomic level is negligible and the contribution of the weak force to the motion of electrons is small.

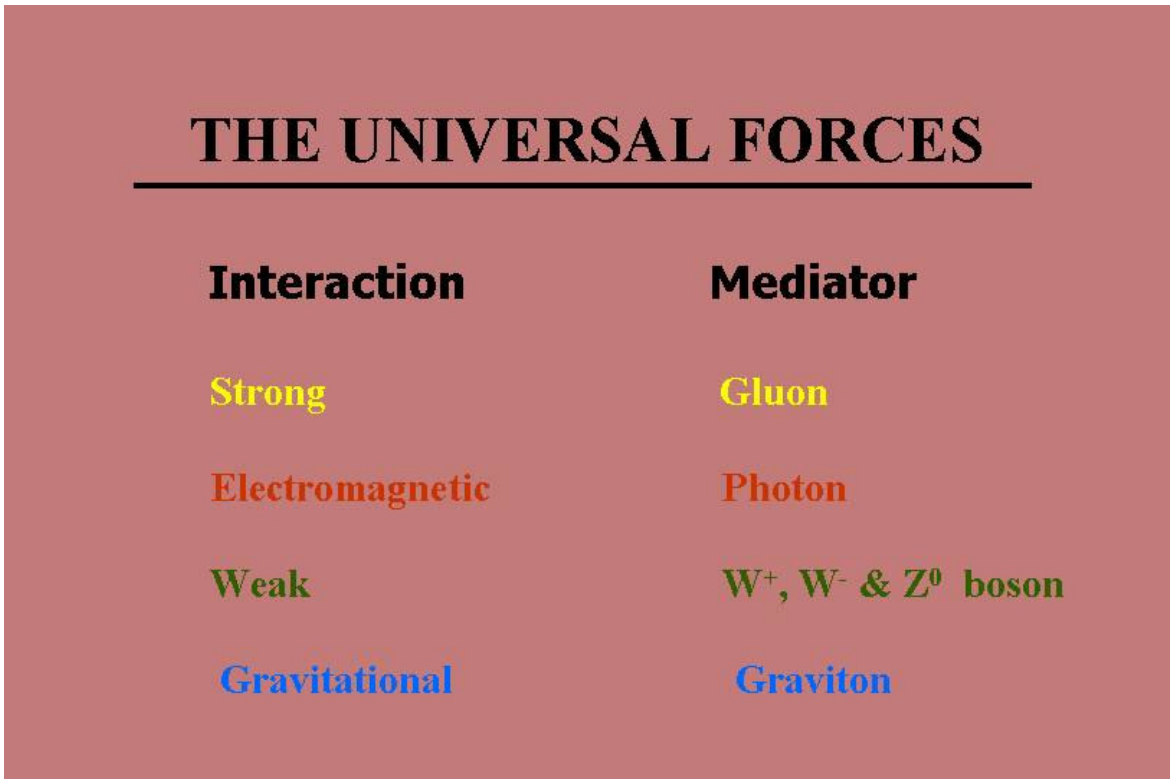

Fig. 1. The universal forces and their respective mediator particles. The concept of gravitons as presumed carriers of gravity is derived from String Theories. These particles have not been detected and have not been incorporated into the Standard Model of particle physics.

Although all the forces may have had a common source, they differ in their strength and range of action. The gravitational force, for instance, is extremely weak compared with the electromagnetic force. If it were as strong, a scale would read out our weight in a number some 40 digits long! The range of action of the weak and strong forces is exceedingly small, in effect intranuclear, whereas that of the electromagnetic and gravitational forces is virtually infinite.

Living organisms represent merely another physical entity, additional to atoms, stars and planets. From all the four forces, it is the *electromagnetic force* that must be primarily responsible for life, since the gravitational force is too feeble and the strong and weak interactions are of very short range.
The reason why the electromagnetic force is the one responsible for life is to be found in the atom itself. It is the attractive electromagnetic force between positively charged protons and negatively charged electrons that holds the atoms together and the atoms are the building blocks of molecules. We can therefore say that the atoms and molecules derive from the electromagnetic field. If we now extend the atom-molecule sequence to systems of increasing complexity – polymers, macromolecules, protein structures, cell organelles, cells, organs – we finally reach the level of living organisms. On this basis, it is likely that life is a natural and inevitable consequence of the mere existence of the electromagnetic force (1). This is not to say that the other forces are unimportant for life. The gravitational force, for

instance, is responsible for our weight and walking speed and, in a less direct way, for our conscious experiences. The weak force, in turn, is responsible, among other things, for sunlight which is the major energy source of life.

2.3 The flow of electric charge in the body

The electrolytic medium where living processes take place is a sea of electric interactions, so strong that the number of positive charges due to cations must always be equal to the number of negative charges due to anions in every compartment of the body. This physical requirement is known as the *principle of electroneutrality.*
Electricity cannot flow overtly in the body because the high reactivity of the electron does not allow ordered flow of electrical current in the solvent water. Electrons must flow in organized solid structures capable of conducting them, such as in membrane and protein matrices. They are known to flow in mitochondrial inner membranes, from carrier to carrier, until they finally reach oxygen, which they reduce to water in the process of oxidative phosphorylation. Less direct evidence for electron flow has been found in virtually all cell membranes, where electrons carriers, such as flavoproteins and cytochromes, have been found and redox reactions have been demonstrated to occur. Furthermore, semiconduction and even *superconduction* (conduction without resistance) are now accepted to occur in proteins at body temperature. A major difference between chemical and physical processes lies in their efficiency. Whereas in a chemical reaction only a discrete amount of electrons is exchanged, in a current there can be flows of electrons which can be used for the structuring and energizing of matter (2).

Besides the flow of electrons of classical electricity, life also uses the flow of ions to carry charge from one aqueous compartment to another through membrane pores. The large size and relatively poor mobility of ions (other than protons), however, make them unlikely candidates for conduction in the solid-state phase of the cell. Proton current is found in the mitochondrial inner membrane, where it takes place either within the membrane or along a surface channel or plane. It gives rise to a proton gradient across the membrane which drives the phosphorylation of ADP in the process of ATP synthesis. Proton conduction within proteins has been experimentally established and thought to occur in a vectorial manner through a series of hydrogen-bonded chains. The layers of structured water at the protein surface (hydration shell) are thought to provide those hydrogen-bonded chains (3).

In addition to charge flow, fixed negative charges (sulfate, carboxyl and hydroxyl groups) are also present in the gel structures of interstitium and vessel walls and ionic pumps are present in cell membranes. One of those pumps, the electrogenic Na^+/K^+ ATPase, generates a sodium gradient between the inside and outside of cells which, under the influence of the bulk electrostatic properties of body fluids (4), ultimately acts as controller of all cell functions. This brief general view of body electricity strongly supports the electrical basis of living processes.

2.4. The electric field and particle transport

Any system of electric charges produces an electric field at all points in space. The electric field is a vector quantity, which means that it is characterized by both a direction and a magnitude. The fundamental significance of the electric field is that any other electric charge in it will experience a force, which is proportional to the size of the charge and the magnitude of the electric field. The force on a positive charge (pe, sodium ion) is in the same direction as the field while the force on a negative charge

(pe, chloride ion) is in the opposite direction. The motion, along field lines, of a charged particle in an electric field is called *electrophoresis*.

But not only charged particles can be moved in an electric field. If the field is nonuniform, neutral particles can be moved too. Under these circumstances, the uncharged particle acquires a polarization – one positive charge and one negative charge. Although the charges are equal, the fields operating on them are not and this gives rise to a net force which impels the particle (translational motion) toward the region of stronger field. This less well known phenomenon is called *dielectrophoresis* (5). So, in contrast to metals that are highly conductive for electrons but not at all for ions, electrolytes allow the co-transport of ions and neutral substances but not electrons by endogenous or applied electric fields. Ultramicroscopic electro- and dielectrophoretic processes go on incessantly in every membrane and compartment of the body.

2.5 The electric field and fluid transport

Electrical fields are very difficult to measure in vitro, let alone in vivo. This is part of the reason why progress in this area has been slow. But calculation of these fields together with a deeper knowledge of structure and acceptance of the fixed charge concept have led Wolgast and coworkers (6) to challenge classical views of fluid transport across vessel walls. According to current concepts, fluid filtration across capillary membranes is believed to be driven by hydrostatic and osmotic forces. This requires the assumption of rigid porous membranes. Modern electrical theory views capillary membranes as hydrated gels whose integrity is preserved not by rigid elements but by negative charges fixed to the gel matrix. These negative charges attract mobile positive counter ions which, via their osmotic action, draw water into membranes, thus generating an intramembranous hydrostatic pressure which opposes external forces. The electric field created by the charges within membranes is the net driving force for fluid transport. The theory, which has been validated by experiment, was developed for the glomerular filtration membrane but applies equally well to other capillary membranes. It is likely that electric fields are involved in local functions in all membranes.

2.6 A proposed electrogenic systemic circulation

Charge flow is mainly related to metabolism but also occurs with tissue injury and in the growth process. When local tissue is damaged or bleeding occurs, an electrochemical potential is always generated between the degrading hypoxic and the normal, well-oxygenated tissue. Differential speeds of diffusion, convection and recombination of liberated ions, as well as redox potential differences account for this potential.
The electrochemical potential is comparable to a charged battery and the situation in tissue resembles that of an ordinary flashlight. To obtain the desired effect out of such systems, it is necessary to create a closed circuit between the two battery poles. In vivo, this closed circuit is created by the vascular-interstitial circuit. In a simplified way, blood vessel walls are the conducting cables and plasma-interstitium are the conducting electrolytic fluids. Ions are driven by electric fields in the open vessels and in the interstitial matrix. This multidirectional *electrogenic circulation* cooperates with the mechanical circulation of blood and lymph. Presumably, this electric network is also activated whenever a sudden increase in metabolism occurs. Under these circumstances, mechanical circulatory adjustments may not be enough to take care of the rapid bi-directional exchange of positive and negative ions along the same channels.

Structured flow of electricity in the form of closed circuits was first described by Nordenstrom (7). These systems are numerous and of varying size and construction but they are all dominated by the flow of ions in circulating fields. They produce structural and functional effects by electric and magnetic influences, far beyond what man can produce artificially.

2.7 The electromagnetic field

Tiny magnetic fields are generated whenever electric current is flowing in the body. Furthermore, changing magnetic fields create an electromotive force capable of moving electric charges, that is, of generating electric current. In this way, a temporarily changing electric field creates a magnetic field which itself produces another electric field. As the effects of this interaction spread out, they lead to processes known as *electromagnetic waves.*

Living cells exhibit electromagnetic activity which is connected with the biological processes inside them. Perhaps, even more fundamental, some molecules and macromolecules – water, proteins, nucleic acids, polysaccharides – have an intrinsic oscillatory electric behavior. They are capable of generating electromagnetic waves of various frequencies and of absorbing them as well. This electromagnetic interaction forms the basis for the communication of information in life. Furthermore, our communication with the outside world is also made mainly by electromagnetic waves. Two of our major senses, vision and hearing, are dependent on them. We live within the electromagnetic field, from where we derived and to where we must regress. In between, lies a highly organized circulation of energy which we call life (8).

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3

THE PHYSICS AND BIOLOGY OF WATER

So we may as well make a beginning
of science by studying water
T. H. Huxley

No other place in the whole universe has so much water as earth, and life could not exist without it. Its central role in life arises because water is a prime natural medium for chemical reactions. Its mobile molecules act to diminish the electromagnetic forces that link atoms together, freeing them to combine chemically with other free floating atoms. This peculiar property stems from the structure of the water molecule itself and the binding together of water molecules to form liquid water (1).

3.1 The water molecule

The water molecule (H_2O) is not linear. It is bent, so that the two atoms of hydrogen and one of oxygen form a blunt V whose angle happens to be about 104.5 degrees. That angle is a good approximation to the tetrahedral angle (109.5 degrees), the angle between two vertices of a regular tetrahedron, or triangular pyramid, as seen from its center (2). Although the molecule is electrically neutral, it has hidden charges. They arise from the way that the atomic structures of oxygen and hydrogen combine. In simplified terms, oxygen has eight negatively charged electrons circling its positively charged nucleus: two in an inner shell and six in an outer shell. The inner shell's maximum capacity is two electrons, so it is full, but the outer shell can hold as many as eight. Hydrogen has only one electron. When oxygen combines with two hydrogens, it attracts each hydrogen's electron in an attempt to fill its outer shell. Because oxygen has greater affinity for electrons than hydrogen, each hydrogen electron spends more time around the oxygen atom than around its own positively charged nucleus. This creates an asymmetric distribution of charge, an *electric dipole*: there are two clouds of slightly negative charge around the oxygen atom, and its two hydrogen atoms are left with slightly positive charges (3). (Fig. 2)

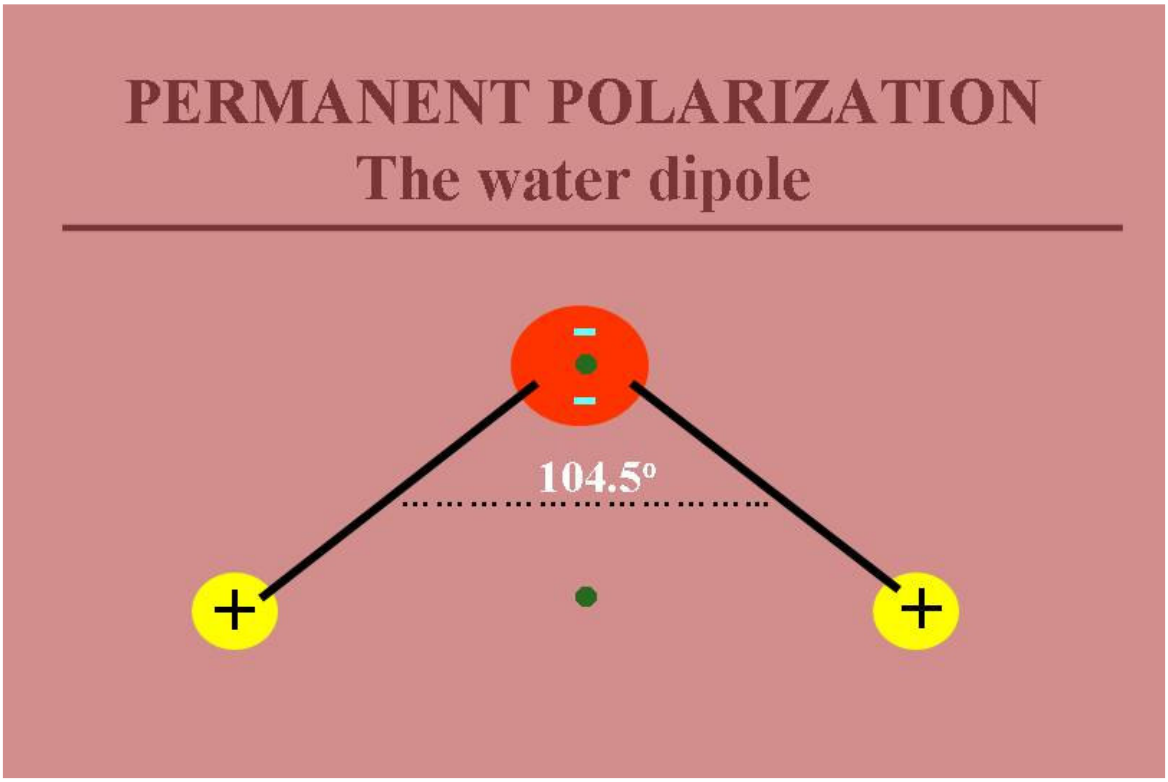

Fig. 2. Schematic representation of water molecule's permanent dipole. The poles were taken as the centers of gravity of charges. The center of negative charges (lone pair of electrons) was taken to be at the oxygen atom and the center of positive charges at a point midway along the line joining the hydrogen atoms.

3.2 The hydrogen bond

If two water molecules are close together and properly oriented, a positive hydrogen atom in one attracts the negative oxygen atom in the other. Thus, a hydrogen atom always intervenes between two oxygens, one in each molecule, and is covalently bonded (by a shared electron) to one and hydrogen bonded (by electrostatic forces) to the other (4). These two types of bonds are not entirely separate. The electron in the covalent bond spreads out its influence into the hydrogen bond by a purely quantum mechanical effect (5) (Fig 3). The covalent bonds are the ones that keep the water molecules themselves from flying apart (the H_2O molecule survives temperatures as high as 1,200 ^{o}C); the hydrogen bonds are vastly weaker although powerful (3-7 kcal/mol) when compared with the nonspecific van der Waals bonds (1 kcal/mol) that attract uncharged atoms to each other (6).

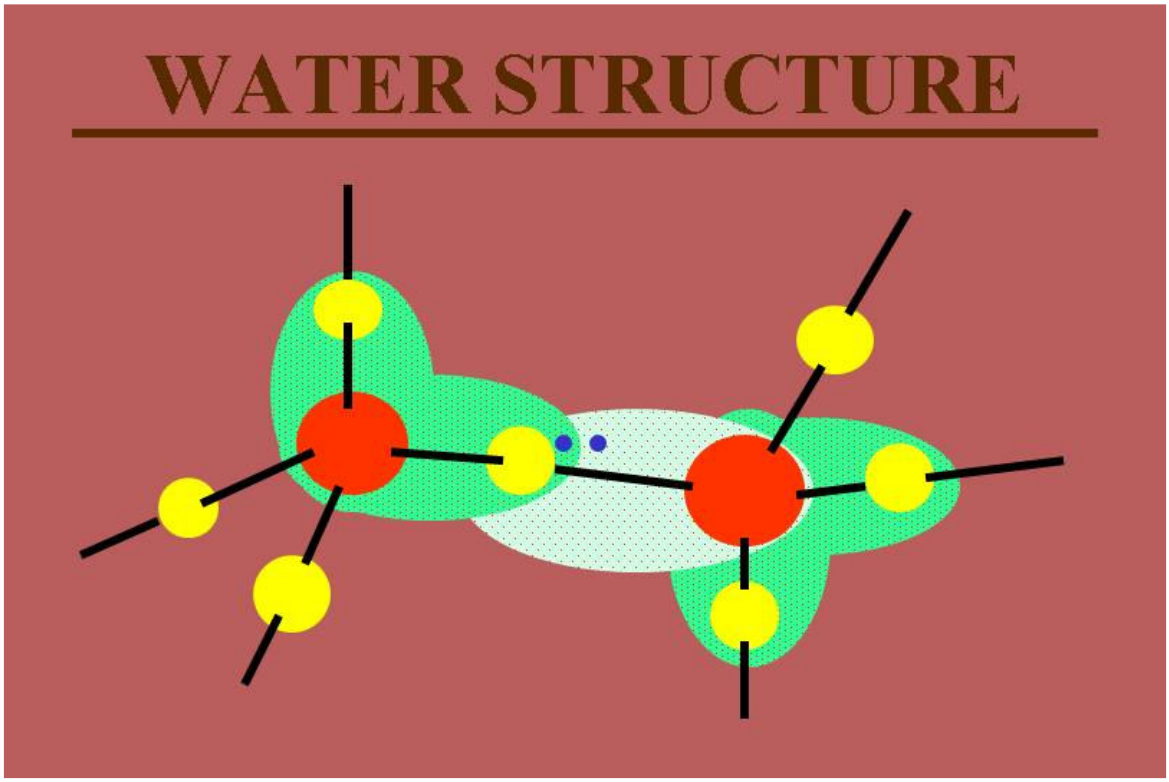

Fig. 3. Covalent bonds (darker green clouds) in water spread their influence into intermolecular hydrogen bonds (lighter blue cloud). Adapted from Isaacs ED, Shukla A, Platzman PM, Hamann DR, Barbiellini B, Tulk CA. Phys Rev Lett 82, 600-603, 1999. Copyright (2002) by American Physical Society.

3.3 The water network

Water is singular as a liquid because of its ability to form tri-dimensional networks of molecules, mutually hydrogen-bonded. Reflecting water's tetrahedral geometry, each molecule in liquid water often forms four hydrogen bonds: two between its hydrogens and the oxygen atoms of two other water molecules, and two between its oxygen atom and the hydrogens of other water molecules. But the detailed structure of liquid water – unlike ice, which is usually composed of a lattice of water molecules arranged in perfect tetrahedral geometry – can be quite random and irregular. The actual number of hydrogen bonds per liquid water molecule ranges from three to six, with an average of 4.5. This is possible because the oxygen atom of one molecule may make more than two hydrogen bonds with hydrogens of neighboring molecules. The necessity of maintaining a tetrahedral geometry gives water an "open", loosely packed structure. This explains its low density and, in part, its good solvent properties.

As a direct consequence of their permanent dipoles, water molecules are in constant rapid motion orienting themselves in the electric fields. This involves turning, twisting and vibrating of the molecules which puts constant strain on the hydrogen bonds. They have to bend, stretch and occasionally break and link again, all this occurring on a time scale of picoseconds. Ordered aggregates of water molecules (clusters) are also formed as a result of on-going polymerization and depolymerization, a process that involves cooperative making and breaking of hydrogen bonds (7).
Water appears to be a macroscopic space filling gel-like network, held together by relatively short-range microscopic hydrogen bonds between neighboring molecules (8). It is currently believed that the

hydrogen bonds range in strength from weak to strong and that they are continuous throughout liquid water.

If the structure of pure water is difficult to characterize, that of an aqueous solution in which chemicals have been dissolved is even more. When table salt (consisting of sodium and chloride in equal proportions) is dissolved in a glass of water, each positively charged sodium ion attracts the negatively charged oxygen atoms of several surrounding molecules, while each negatively charged chloride ion attracts the positively charged hydrogen sites. When the salt is fully dissolved, each sodium ion is likely to be surrounded by four or more water molecules, while each chloride ion attracts a smaller number of them. So, the mere addition of salt makes the structure of water more complex. In a living cell, which contains vast amounts of solute – not only sodium and chloride but potassium, magnesium and phosphate, as well as a variety of proteins, carbohydrates and fats – the complexity is even greater. Perturbed by the presence of solutes, the molecules of water lose some of their freedom (activity). In thermodynamic terms, the *chemical potential* of water is said to be lowered. Besides activity (concentration × activity coefficient), the chemical potential is also influenced by temperature, pressure and molar volume. The molar volume is inversely proportional to density (density = mass/volume), which means that when molar volume increases, density decreases and vice-versa. The water network is continuous throughout the body and, at equilibrium, its chemical potential is the same everywhere.

3.4 The solvent properties of water

The importance of water in living processes derives not only from its ability to form hydrogen bonds with other water molecules but also from its capacity to interact with other biological molecules. Because of its polar nature, water readily interacts with other polar and charged molecules, such as acids, salts, sugars and some regions of proteins and DNA. As a result of these interactions water can dissolve polar molecules, which are consequently described as hydrophilic (water-loving).

In a vacuum, the Coulomb force between two charges depends only on the magnitude of the charges and the square of the distance separating them. If some medium is introduced between the charges, the force per unit charge will decrease as a result of the permittivity of the medium. The medium permittivity (ε), corrected for the permittivity of the vacuum (ε_o) is called *dielectric constant* ($\varepsilon/\varepsilon_o$), which is simply a measure of the capacity of the medium to decrease the coulombic force (9). The higher the dielectric constant, the lower are the attraction forces between opposite charged particles.

The dielectric constant of water is among the highest for solvents. It is 80, at 20^o C, much greater than that of methanol (33), ethanol (24) and diethyl ether (4.3). This unusually high dielectric constant is due to the permanent polarization of water molecules and their capacity to form oriented solvent shells around ions. These oriented solvent shells produce electric fields of their own, which oppose the fields produced by the ions (6). Consequently, electrostatic attractions between ions are markedly weakened by the presence of water. It is by this mechanism that water promotes the ionization of salts.

The existence of life on earth depends critically on the capacity of water to dissolve a remarkable array of polar molecules that serve as fuels, building blocks, catalysts, and information carriers. High concentrations of these molecules can coexist in water, where they are free to diffuse and find each other.
But the excellence of water as a solvent poses a problem. It also weakens interactions between polar molecules or polar groups in a molecule by competing with their hydrogen bonds. Biological systems

have solved this problem by creating water-free microenvironments, such as specially constructed cavities in protein molecules, where polar interactions have maximal strength (6).
In contrast to polar molecules, water is reluctant to dissolve nonpolar molecules, such as lipids, hydrocarbons and aromatic compounds, giving rise to the observation that oil and water do not mix. Nonpolar molecules are therefore termed hydrophobic (water-fearing).

When several oil droplets are dispersed in a glass of water they tend to form a single large drop. An analogous process occurs at the molecular level - nonpolar molecules or groups tend to cluster together in water. They do so, not because they have high affinity for each other but because the water in between them is squeezed out. The force involved in this process is called the *hydrophobic force.* It is a major force in the folding of macromolecules, the binding of substrates to enzymes, and the formation of membranes that define the boundaries of cells and their internal compartments (6). The origin of this force is very controversial and will be described later (see chapters 4 and 5).

3.2 The gel state of matter

According to current theories, a *gel* is a semisolid system consisting of a high molecular weight compound, such as a macromolecule or a polymer, in very close association with a liquid. Proteins and proteoglycans (aggregates of polypeptides and polysaccharides) are the main macromolecular components of biological gels. According to current concepts, high enough concentrations of the solid phase are needed to form a gel. To illustrate this point, take the linear molecule of hyaluronate, a common component of the extracellular gel. For a molecule consisting of 10,000 repeating disaccharide units, the weight is 4,000, 000 daltons and the length is 10 m, approximately. When in solution, it assumes a random coil conformation. At a concentration of 1 mg/ml, the random coil molecules already come in contact with each other and at 5 mg/ml they are all entangled, forming a tri-dimensional flexible molecular network characteristic of a gel (10).

For a living gel to work properly, two more components are required, one mechanical and the other electroosmotic. The mechanical component is a fibrous network which offers support to the soluble macromolecules. That of the extracellular gels, it is made of collagen and elastin fibers but the intracellular network is of more delicate construct and will be described in the next chapter. The electroosmotic component is the one that gives life to the gel. It derives from the presence of high number of fixed negative charges in the macromolecular component. In proteoglycans, most of the charges are found in the sulfate groups of the polysaccharides (SO_4^{--}); in intracellular proteins, at physiologic pH, carboxyl groups ($HCOO^-$) are the predominant charge carriers.

In solution, these charged macro-ions attract small mobile counterions (cations) to neutralize their charge and they constitute most of the osmotic component of a gel. The electrostatic interaction of relatively small ions with poly-ions seems to depend primarily on the valence of the counterions and the charge density of the polyion. Solutions of proteins and proteoglycans behave as typical polyelectrolytes in that they undergo sensitive changes in conformation with changes in the concentration of their microion environment and the type of counterion. This interaction forms the basis for a variety of properties exhibited by these compounds.
When networks of crosslinked synthetic macromolecules are exposed to a solvent the networks swell until the tendency to “dilute” the macromolecules with solvent is exactly balanced by the mechanical restraining forces generated in the network strands. More precisely, the stresses generated in the network are balanced mechanically by an increase of hydrostatic pressure in the swelling medium. The increased pressure of the swelling medium compensates the osmotic contribution of the dissolution of the network

strands so that the *chemical potential* of the solvent in the network matches the chemical potential of pure solvent outside. The strands of the network here serve both as the osmotic and the mechanical elements which establish the swelling equilibrium. If the medium outside involves a solute which cannot enter the network the point of compensation of the solvent chemical potential is suitably altered. The same is true if the solute can enter, but exists at different concentrations inside and out. In this case, solute chemical potential will also have to be balanced (11).

Retention of water by a gel is one example of a natural tendency for components of a solution to mix, as thoroughly as they can. The hyaluronate gel, for instance, may contain as much as 99.9% water, by weight. Liquid water is restrained by the small amount of gel material by this powerful force of mixing, which operates on the whole assembly of water molecules. To separate water from the gel, work must be done against this force (4). A more powerful molecular theory of osmosis will be introduced later.

The layer of counterions in close proximity to the charged surfaces induces changes in the structure of local water with consequent changes in all its properties. These dynamic interactions are so important that they deserve to be described in some detail. In their discussion, we will concentrate our attention on interactions with proteins.

3.6 *The solvent properties of gel/water systems*

Water-ion-protein interactions have been under intensive study for over a century. As a result of a concerted effort from many investigators, the rules of assembly start unveiling but no unified theory was ever presented. Working with artificial porous membranes and gels, Philippa Wiggins did just that. Over the years, she painstakingly developed a coherent theory which ties up changes in water structure with changes in solvent and other properties. The theory seems equally applicable to the concentrated gel/water systems that support life. The theoretical framework is heavily based on thermodynamic concepts and so, for clarity, a simplified version is given here (4).

Proteins, the principal nonaqueous constituents of cells, present two different kinds of surfaces to water – charged (hydrophilic) and uncharged (hydrophobic). At cell pH, the charged surfaces are net electronegative and so they attract small mobile cations. As a result, the ionic (cationic) concentration in a limited region of solution around charged surfaces is always higher than in regions farther away. This remains true no matter how much solute is dissolved. The simple presence of an increased amount (concentration) of solute inevitably leads to a lowering of the chemical potential of the layers of water dissolving them. This local water must somehow increase its chemical potential to equalize that of surrounding water. If some water molecules can be moved out of that region, they will do so. If not, at constant pressure, temperature and activity, there is only one degree of freedom left for water to equilibrate – to change its molar volume. Water molecules, therefore, decrease their molar volume by bending and breaking some or all their hydrogen bonds and, in the process, they become freer and more active, but also closer to each other – *the density of water increases.* High density water is more reactive than normal water because the breaking of bonds exposes lone pairs of electrons and frees OH groups, which are the reactive centers of water molecules.

The hydrophobic surfaces present a different challenge to water. Water molecules make only weak hydrogen bonds or no bonds at all with these surfaces and they cannot increase the number of bonds with their neighbors. These molecules are in a state of higher energy and higher chemical potential than those of more distant molecules which are making strong bonds with one another. Since hydrogen bonding is cooperative, weak bonding is propagated through several layers of molecules. The preferable

response of the system to its high energy state is to squeeze some of the high energy water out. This is the origin of the attractive hydrophobic force between nonpolar surfaces separated by water. If this is not feasible, high energy molecules must increase their molar volume to lower their chemical potential and so they expand. Their excess energy is used to do the work of expansion. Collectively, they move apart each other and stretch their bonds – *the density of water decreases.* Low density water is inert because it exhibits a paucity of reaction centers and its viscosity is high.

Changes in the structure of water are associated with changes in all its properties. For biology, the most important consequence of changes in water density are changes in its ability to dissolve solute. Given the opposition to change of the tri-dimensional structure of water, relatively minor changes in chemical potential require quite large changes in molar volume. The secondary changes in the properties of water are correspondingly greater.

Energetically, it would be very costly to accommodate small but highly hydrated cations (Mg^{2+}, Ca^{2+}, H^{+}, Na^{+}) and multivalent anions (HPO_4^{2+}) in low density water, since it would require the breaking of too many hydrogen bonds. Consequently, these ions are relatively excluded from this water population and accumulate, together with hydrophobic molecules, in high density water. Large but lesser hydrated cations (NH_4^{+}, K^{+}) and univalent anions (Cl^{-}, $H_2PO_4^{-}$, HCO_3^{-}), together with a variety of small hydrophilic solute, selectively accumulate in low density water (Fig. 4).

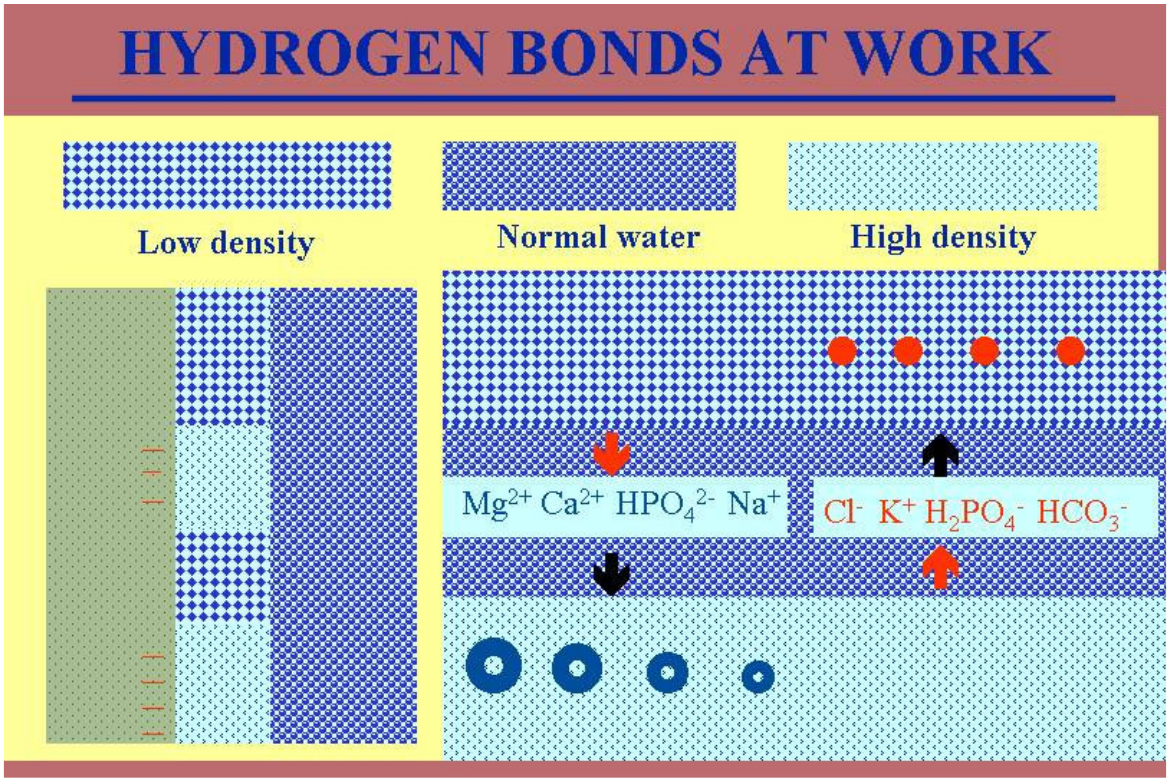

Fig. 4. Schematic representation of water structures near charged and hydrophobic surfaces and their selective solvent properties. Low density water excludes highly hydrated cations and multivalent anions and preferentially accumulates lesser hydrated cations and univalent anions. Explanation in text.

This movement of ions from one water population to another, as a result of changes in solvent properties, will, in turn, influence the chemical potential of resident water which may require further restructuring, possibly followed by more ion movement. Depending on the velocity of these processes and on the activity state of the cell, water equilibrium may never be reached. Since intracellular and extracellular compartments consist of mixtures of polymers presenting to water charged and hydrophobic surfaces, it is highly probable that they contain a continuous spectrum of water populations, ranging in structure from dense and reactive to stretched and inert.

In regards to medical physiology, there are important consequences of these new concepts. Firstly, there is considerable amount of water inside gels that is not available to solute, even small solute. So, it is wrong to assume that solutes, including drugs, are distributed in total body water. Secondly, with populations of water of differing solvent properties and reactivities coexisting in the interior of cells, the assumption that intracellular osmolality equals extracellular osmolality is no longer valid. It is the chemical potential of water inside and outside cells that equilibrates. Thirdly, the classic Donnan membrane equilibrium is not directly applicable to the distribution of ions and water in charged gels. Water must finally equilibrate not by pressure (osmotic pressure), but by changing its density (12). Finally, the intracellular K^+ concentration is not maintained by the action of the Na^+-K^+ pump alone. The high affinity of K^+ for the less dense, more strongly bonded water, also contributes.

3.7 The microosmotic force

The partition of solute between two adjacent water populations of differing density creates micro-gradients of ions and water with complex local effects, collectively known as *microosmosis.* It is a new force in biology with a wide range of predicted actions and profound implications to living processes. The microosmotic force is vectorial, non-linear, self-limiting or oscillating, and capable of performing work or creating highly ordered spatial distribution of solute. These are all attributes required by enzymes, which perform work of transport or of chemical synthesis. Microosmosis is thought to be involved in ATP synthesis and hydrolysis, in the operation of proton pumps and in the opening and closing of ion channels, to name just a few processes (13).

Under the thermodynamic conditions that characterize living systems, water-ion-polymer interactions, through microosmosis, become self-organizing entities capable of generating higher degrees of order. These interactions reveal water to be not a passive element in the background of things but an active and changeable participant in the structure and function of life.

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4

THE STRUCTURAL ORGANIZATION AND REGULATION OF CELLS

A universal set of building rules seems to guide the design of organic structures – from simple carbon compounds to complex cells and tissues
D.E. Ingber

Natural structures are characterized by many attributes but three of those are fundamental: *geometric form, electric charge and physical mass.* Electric charge and physical mass are conserved properties of matter. Conservation, however, constrains the compositions of higher structural objects from lesser ones by selecting objects that are stable over the time scale of operation. But constraints do not apply to form, which is not conserved. The absence of conservation rules for geometric form has been a source of biological diversity (1). Cells, for instance, exist in a huge variety of shapes and sizes, from the almost spherical lymphocyte, to amoeboid cells such as macrophages, to flattened spindle-shaped fibroblasts or polygonal epithelial cells, to neuronal cells with their dendrites and axons. We know today that cell form is stabilized by a very dynamic internal filamentous framework known as *cytoskeleton.*

4.1 The cytoskeleton discrete network

Living cells are anchored to insoluble extracellular matrix scaffolds (basement membrane, interstitial matrix) and to neighboring cells. The anchorage is not continuous but takes place through discrete contact points known as *focal adhesion complexes* and *junctional complexes,* respectively. The cytoskeleton connects mechanically these contacts points on the cell surface to discrete contacts on the nucleus in the center of the cell. A structurally unified system is thus established, which provides mechanical stability to tissues and, at the same time, serves as path for direct communication between cells and the extracellular world (2).

The basic building blocks of the cytoskeleton include actin microfilaments (about 7 nm in diameter), tubulin microtubules (24 nm in diameter), and a variety of intermediate filaments (about 10 nm in diameter). Each filament type is composed of linear polymers of globular protein subunits, which are assembled and disassembled by the cell in a carefully regulated fashion, sometimes at astonishing rates. Although the cytoskeleton is surrounded by membranes and penetrated by viscous cytosol, it is this discrete filamentous network that provides most of the mechanical strength of cytoplasm.

4.2 The cytoskeleton as tensegrity structure

Living cells and most biological tissues exhibit a stiffening (strain-hardening) response to stress and there is sound evidence showing that shape and stiffening response of cells are closely interrelated, as they participate in processes such as growth, division and differentiation (3). To explain the stress-hardening response of cells, Ingber et coworkers have sought support for the concept of cellular

"tensegrity" (from tensional integrity). Tensegrity architecture (towers, bridges, domes) is a known building system in which tension and compression forces are held in balance. Some tensegrity structures, even before they are subject to an external force, have their structural members already in tension or compression – that is, they are *prestressed.* Within these structures, the rigid compression-bearing members stretch, or tense, the flexible tension-bearing members, which, in turn, compress their compressive counterparts. It is these counteracting forces, equilibrated throughout the structures, that enable them to stabilize (4).

Like those tensegrity structures, the cytoskeleton includes compressive elements (microtubules associated with intermediate filaments) in equilibrium with tensive elements (actin microfilaments). An increase in tension in one of the tensive (contractile) elements results in increased tension in all elements throughout the structure. This global increase in tension is balanced by an increase in compression within the compressive elements, spaced throughout the structure. In other words, the contractile microfilaments pull the membrane and internal cellular contents towards the nucleus and the microtubules, together with the extracellular matrix, oppose this inward pulling (4). The intermediate filaments connect microtubules and microfilaments to one another, as well as to the surface membrane and to the nucleus. Essentially, all these interconnected structural elements rearrange themselves in response to a local stress. The cell stiffening response occurs because these structural elements reorient themselves to lie more in the direction of applied stress.

The mechanical stability of tensegrity structures is determined by both, prestress and architecture. Prestress determines the initial stiffness of the structure and assures that the system will respond immediately when externally stressed. It also determines the characteristic frequency of vibration (harmonic oscillation) that the structure will exhibit. In contrast, architecture determines how the interconnected structural elements rearrange themselves and thus how the entire structural assembly stiffens in response to stress. Tensional forces transmit themselves over the shortest distance between two points, so the members of a tensegrity structure are precisely positioned to best withstand stress. For this reason, tensegrity structures offer a maximum amount of strength for a given amount of building material (2).

Evidence available so far has shown that cells can and do use the architecture of tensegrity to shape their cytoskeleton. This building system, by minimizing energy and mass, appears to be preferred by nature. It is thought to be present not only at cellular level but at all levels below and above, from atoms to black holes. In tensegrity theory, our body, for instance, is composed of 206 compression-resistant bones that are pulled up against the force of gravity and stabilized through interconnections with a continuous series of tensile muscles, tendons, and ligaments. Its mechanical stiffness is determined by the level of tone or prestress in our muscles and not by osmotic forces. This is true for all types of animals, independent of size or species (2).

4.3 The cytoskeleton and the microtrabecular lattice

Recent morphologic investigations have demonstrated that, in addition to the cytoskeleton and intimately connected to it, a highly cross-linked *"microtrabecular lattice"* is also found in the cytogel which envelopes all subcellular organelles. The average "pore size" of the lattice seems to be less than 50 nm, a size sufficiently small to constrain to a significant extent the diffusion of proteins through it (5). Together with the cytoskeleton, it forms the protein component of the intracellular gel (see 5.3).

It has been suggested that all catalytic activity may be carried out by enzymes adsorbed to the cytoskeleton and microtrabecular lattice. The living cell is pictured as a two- phase system: *a solid-state phase* within and adjacent to which enzyme-catalyzed reactions of intermediate metabolism take place and a *bulk aqueous phase* containing low molecular weight organic solutes and ions. This design is highly appropriate for an *electrochemical system* – the solid phase representing a multi-electrode array and the aqueous phase representing the electrolyte (5). Modifications of this design and implications of an electrochemical system for metabolism will be discussed later.

4.4 Tensegrity and mechanochemical transduction

The role of the cytoskeleton and of tensegrity is not confined to the stabilization of cellular and nuclear form. The microtubules, for instance, are also involved in intracellular protein transport. They serve as rail tracks on which motor proteins, such as kinesins and dyneins, convey their cargoes around cells. They are also involved in the movement of chromosomes along the mitotic spindle during mitosis. Actin filaments and their architecture, on the other hand, participate in the signal tranduction circuitry of the cell, in response to extracellular an intercellular signals. Furthermore, if indeed much of the cell's machinery functions in a solid state, the force balance of tensegrity could provide a means to integrate mechanics and biochemistry at the molecular level (6). This implies that enzymes are somehow *mechanosensitive.*

The steps leading to chemical reactions in this new enzymology have not been elucidated but something is known about the mechanisms of mechanotransduction. Experimental evidence suggests that the localized adhesion sites of junctional and focal adhesion complexes are clustered with specific mechanoreceptors. The most studied ones have been the integrin receptors of the cell membrane facing the extracellular matrix. They appear to be centers of integration of mechanical signals (changes in gravitational acceleration, arterial pressure, osmotic pressure, and movement) and chemical signals emanating from the extracellular matrix (changes in the level of hormones, growth factors, cytokines). The integrated signal is then transmitted to the cell via the microfilament system. In this line of reasoning, cell shape *per se* appears to govern how individual cells will respond to chemical signals in their local microenvironment (2).

Connecting the cytoplasmic tail of integrins with actin filaments, there exists a set of actin-binding proteins, all of which appear to bind to a common site on these filaments. They are believed to act as *chemomechanical* coupling agents in the processes of receptor-linked signal transduction (7).
Less is known about the intermediate filaments, mainly because of a lack of tools with which to study their assembly and disassembly.

Tensegrity provides a mechanism to mechanically and harmonically couple interconnected structures at different size scales and in different locations throughout living cells and tissues. Thus, cell and tissue tone may be tuned by altering the prestress in the system. Increasing the stiffness of the network will alter vibration frequencies and associated molecular mechanics of all the constituent support elements. This may, in part, explain how the part (molecule, cell) and whole (cell, organ, organism) can function as a single mechanically integrated system (2).

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5

THE QUANTUM OF WATER AND PROTEIN AND THE STRUCTURE OF THE CELL

I believe that it is this fact, that the cell functions as an entity and not as a jumble of its interval events, that gives it the holistic quality we recognize as "alive"
John G. Watterson

This book would fail its purpose if new, more fundamental theories, no matter how disturbing they might be to generally accepted ones, were left unexposed. We do not know how the living cell ultimately works but we do know that the cell is structurally a water-protein system. So, any new concepts integrating the active participation and cooperation of the solvent in the functioning biosystem warrant full consideration. One such theory is that engineered by John Watterson which brings a new order to the biological world and explains a variety of biological phenomena previously thought to be unrelated. It is known as the *"wave-cluster-domain model"* (1). The theory literally quantizes cell water and protein. These quanta, which are of macroscopic proportions, are considered to be the building blocks of the living fabric. The water quantum, based on physical principles operating at the molecular level, introduces the concept of cluster tension as the physical force of osmotic flow and gelation. The theory has far reaching implications in regards to signaling and metabolism which will be discussed in later chapters.

5.1 Cluster waves, pressure and tension

Waves can be viewed as organized propagating oscillations. What makes the oscillations propagate is an imbalance between potential and kinetic energies (2). In water, the intermolecular making and breaking of hydrogen bonds creates oscillations and potential energy. The kinetic energy required for propagation comes from a special property of hydrogen bond interactions – they are *cooperative,* that is, their effects are transmitted. Bonded molecules make even stronger bonds with other neighbors and, reciprocally, newly formed bonds strengthen existing ones. These interactions have definite velocity and direction and therefore set up a wave pattern. Since these processes are continuous, the structure forming process, over time, travels like a wave through the liquid medium. The wave units or clusters, though constantly changing, are at any instant held together internally by an unbroken linkage of intermolecular bonds. This means that the molecules in a cluster exert *tension* (negative pressure) on one another.

The theory assumes that it is clusters, rather than single solvent molecules, that act as individual entities. In other words, a cluster is viewed in some respects as a particle, because the molecules that comprise it are, at any given moment, bonded together (1). Furthermore, liquids are thought to exert both pressure and tension simultaneously, since they lie between solids and gases and should, therefore, possess properties of both of those phases. Following this line of reasoning, at room temperature and pressure, and under equilibrium conditions, the volume occupied by one molecule of gas should be identical to that of one cluster. This volume is about 40 cubic nm which corresponds to a cube with an edge 3.5 nm

long. This unit of space contains some 1,400 water molecules and has a molecular weight of around 25,000 daltons. Watterson calls this space unit the *"pressure pixel"* (3).

The "pressure pixel" concept is very important for the model because it represents a critical level in the size hierarchy of physical phenomena. In information science, a pixel is that region of size where information becomes fuzzy and then lost. Similarly, the pressure pixel is that size volume beyond which pressure has no meaning. In other words, we cannot speak meaningful of pressure in volumes smaller than this basic unit. And as a consequence, over spatial dimensions larger than a cluster size, pressure and not tension operates throughout the liquid. These opposing forces coexist with equal force in liquid water and do not cancel each other out.

5.2 *The molecular mechanism of osmosis*

Hammel has compared the story of osmosis to a tapestry because there are so many strands (ideas) in it (4). Over the last century, many physicists, chemists, biologists and physiologists have studied it, indeed. Yet, there is no agreement as to the nature of the osmotic force and flow. Watterson, however, has proposed a molecular mechanism of osmosis that may help to reconcile some longstanding differences of opinion. The subject of osmosis is of paramount importance to medicine since it governs to a large extent the transport of water and solutes through biological membranes.

Osmosis is the passage of a solvent (water) through a semipermeable membrane separating two solutions of different concentrations. A semipermeable membrane is one through which the molecules of the solvent can pass but the molecules of most solutes cannot. Under these circumstances, there is a tendency for the solutions to become equal in concentration, the water flowing from the weaker to the stronger solution. Osmosis will stop when the two solutions reach equal concentration, and can also be stopped by applying a pressure to the liquid on the stronger-solution side of the membrane. The pressure required to stop the flow from pure water into a solution is a characteristic of the solution, and is called the *osmotic pressure*. For simplicity, our discussion will be limited to an ideal semipermeable membrane, one freely permeable to water and impermeant to solute.

Probably the most prevalent theory of osmosis in medicine today is that of Guyton which attributes osmosis to a primary action of solute. The nondiffusible solute on side 2 of the membrane simply lowers the concentration of water in the solution, as compared to pure water on side 1 (solute simply dilutes the solvent). As a result, the chemical activity of water molecules on side 2 is less than on side 1 and so fewer molecules strike each pore of the membrane each second on the solute side of the pore than on the pure water side. This results in net diffusion of water molecules, down an activity gradient, from side 1 to side 2, which increases the pressure in the solution. The flow against ever-increasing pressure continues until the osmotic pressure is reached (4).

The water dilution idea has proven to be false. First of all, not all solutes lower the molal concentration of water and some may even increase it. Yet in these cases water never diffuses from solutions to pure water where its concentration is lower (4). Secondly, the flow of solvent *against* pressure violates the physical laws of motion. The solvent should flow with pressure and not against it. This thought leads us into admitting that the force underlying osmosis may not be pushing the solvent into the solution but may be pulling it instead. For these reasons and others, diffusion-based thermodynamic theories are untenable (5).

In the osmotic theory of Watterson, the osmotic force is generated within the solution. Osmosis is viewed as a direct result of the wave structure of water or, more specifically, of the structural aggregates of solvent molecules known as wave units or clusters. It is the structure wave itself, and not the solutes, that governs the molecular motions underlying osmosis. Since solvent can move through the semipermeable membrane, it can be considered as a single continuous medium pervading both phases. This means that the structure wave can pass unhindered from one phase to the other transferring structural energy in the process. Addition of solute breaks down the extent of solvent-solvent cooperative interactions because the molecules in contact with the solute can no longer rotate as freely as before. As a consequence, the wavelength is shortened in the solution resulting in clusters smaller in size and energy but increased in number (concentration). In other words, the solute causes a decrease in the size of the pressure pixel. The increase in concentration of clusters in the solution phase is equal to the concentration of solute molecules (3).

At the membrane, there is a net energy flow from the energy-rich clusters of solvent into the smaller clusters of solution. This increases the tensile strength of the intermolecular bonds, so that the smaller clusters can pull solvent across the membrane increasing the pressure on the solute side. At equilibrium, the pressure in the solution has become high enough to counteract the pull of the smaller clusters and flow equalizes. At this point, the energy of the smaller clusters equals that of the pure solvent clusters (5), (Fig 5).

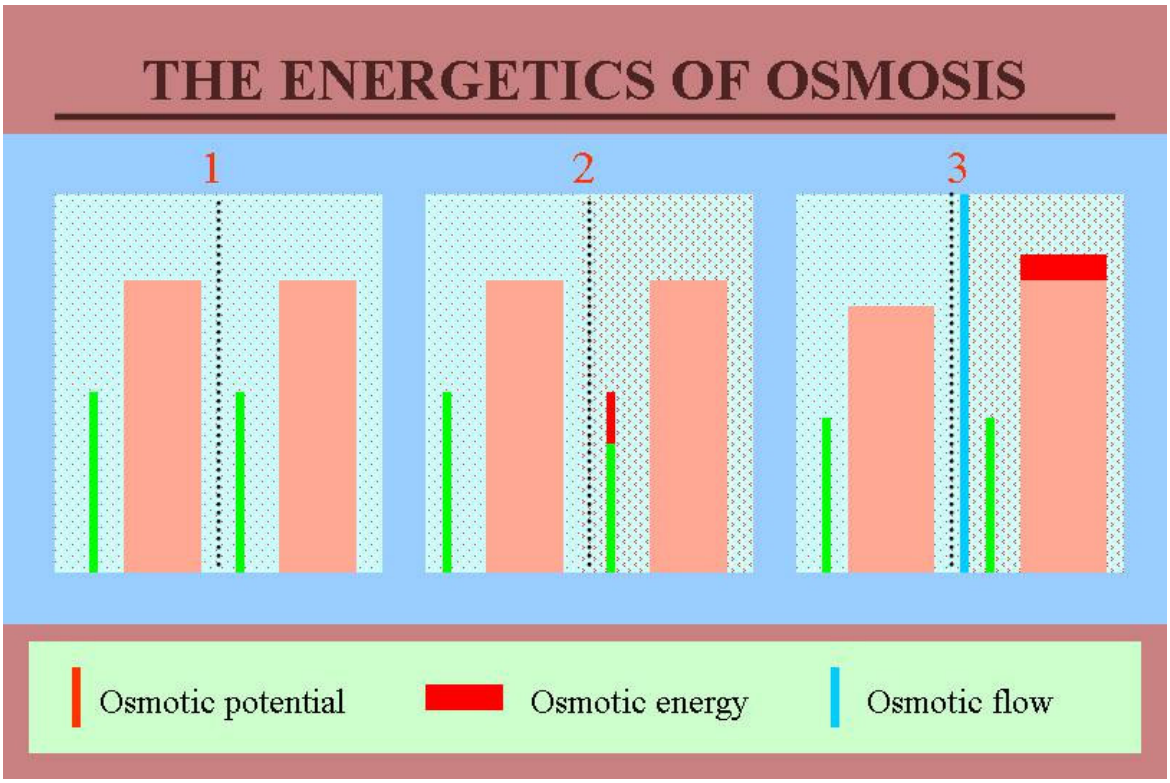

Fig. 5. Schematic representation of the osmotic process. The blocks are meant to represent a solvent (left)-solute (right) system in three stages: 1, before addition of solute; 2, immediately after addition of solute, and 3, at equilibrium. The narrow bars represent the energy level of each cluster and the wide bars the total available structural energy in each phase. The osmotic potential and the total osmotic energy and flow exchanged are indicated. In the estimation of solvent volume in stage 3, only the solvent exchanged was taken into consideration and all other factors were ignored. Further explanation in text.

The idea of solution water attracting solvent water is not new. As early as 1903, Hullett deduced it from a simple thought experiment and attributed it to increased solvent tension in the solution. Where and how solvent tension develops or is enhanced by addition of solute has been the subject of much discussion. In modern kinetic theories, the osmotic force is not a tension but a solute-mediated pressure difference between solvent molecules at pore exit, the pressure being lower on the solution side (6). These theories, therefore, are only valid for membranes with wide, water-filled pores. By taking the osmotic force away from solute motion, and so making it pore-irrelevant, and transferring it into water wave motion and by introducing the concept of pressure pixel, Watterson has developed a more general kinetic theory, whose validity appears solid but, of course, must withstand the test of time.

5.3 The intracellular gel

In the currently accepted theory of *gelation* exposed in subchapter 3.5, the macrosolute occupies the central role and there is no active role for the solvent. It requires the macrosolute to be present in high enough concentrations in order to achieve an infinite degree of random cross-linking. Although this picture can explain why macromolecules stop flowing relative to one another, it cannot explain why solvent molecules do not flow. Indeed, it is precisely the cessation of flow of solvent and not solute that is so surprising when a gel sets. Furthermore, it has been experimentally found that gels of tubulin (the dymer of microtubules) can be produced even at protein contents below 1%, without the need for filament cross-linking. Therefore, to explain the protein gel of cytoplasm, a theory where solvent plays a predominant role is required (1).

In bulk water and in the absence of boundaries, there are no given directions to guide the wave propagation and reflection and so the motion does not become stationary. However, the introduction of a solid surface into the liquid medium imposes restrictions on the rotations of adjacent water molecules, thereby forming a boundary in the wave motion. The surface induces clusters to take up position and to organize themselves into a packed layer. So, a stationary boundary forms stationary waves which result in stationary clusters. And stationary clusters mean no bulk flow. Thus, in regions where stationary clusters are aligned and linked by hydrogen bonding the medium forms a gel. There is no *macroscopic flow* of solvent because the clusters are fixed in space by being anchored onto the surfaces of fixed solutes. This does not mean that the individual water molecules are not moving. They move about just as in bulk water, thus maintaining the wave motion. It is only the monolayer of water molecules adsorbed directly onto the solute surface that is restricted in its movement (1).

In the Watterson's model, the shapes and sizes of globular proteins are spatially compatible with water clusters. The majority of proteins whose tri-dimensional structure is known are composed of two or more discrete domains of about 150-250 amino acid residues. In its functional state, this chain length is folded back and forth in a predetermined way into a compact, water-free shape, which occupies roughly the same volume, about 40 cubic nm. This volume size corresponds to that of a water cluster and fits the size of the pressure pixel. Therefore, within the domain, tension and not pressure prevails. Because the amino acids are linked together by covalent bonds, proteins behave like "permanent clusters".
With compatible size and internal dynamics, clusters of water and domains can pack mutually together and build the large scale integrated assembly of protein and solvent we know as *cytoplasmic gel.* The gel is not infinitely cross-linked. On the contrary, the separate building blocks, water clusters and protein domains, fit together as replaceable parts. The assembly is flexible, but fragile.

For this assembly to function as a unit, the opposed surfaces of the clusters need to be compatible, in the sense that their individual networks of hydrogen bonding need to be joined, so that overall cooperativity

remains ensured and the structure wave can pass smoothly across the interface. Under these circumstances and with the clusters aligned in a regular array, it is possible for the wave motion to achieve an harmonic transition (widening of the wavelength) that converts many small clusters into a single large one. That is to say, the wavelength (which defines the size of a cluster) can become large enough to encompass the whole assembly of clusters holding it together as a single coherent entity. The transition occurs without the need of any special energetic mechanism, because the tensile force is now extended throughout the entire assembly. This tensile force is the same as that responsible for osmosis and so we can say that water is maintained in the gel by osmotic forces (1,3).

The role of surface charge or the lack of it is not apparent in this model of gelation. Solvent clusters are the active components and an hydration layer will always form adjacent to any hydrophobic or hydrophilic surface whether biological, organic or mineral. Presumably, tensional forces outweigh all other forces, although in the presence of divalent cations this may not always be so. The model, therefore, is not inconsistent with that of Wiggins which concerns the structural water level below, ie, the individual water molecules and the hydrogen bond network at large. Obviously, nothing is changed in regards to ionic interactions.

5.4 The cellular architecture

Water clusters adjust their shape to that of the biological surface. Around each filament of the cytoskeletal structures, an hydration layer of clusters highly extended in one dimension is formed. In those regions of the cell containing arrays of parallel protein filaments, the medium is constrained to form parallel elongated solvent clusters packed in columns together with the filaments, building an overall integrated structure. This is a cooperative process, so that the larger the superstructure, the more stable are its components. It has been estimated that as much as 50% of total cell water may be associated with the cytoskeleton, if the hydration layer is of the order of 3 nm. This 3 nm dimension repeats itself at the cell membrane where the hydrocarbon region of each lipid bilayer has been found to be about 3 nm across. As with the arrays of parallel protein filaments, there is always a layer of water clusters between lipid bilayers. So, the cytoplasmic gel is continuous with that of the cell membrane and with the extracellular gel beyond (7).

One of the strength of this model is that it presents a uniformity of cellular architecture built upon small molecular structures of similar size and dynamics, clusters of water and domains. Functionally, these small structures behave like particles that can be exchanged without loss of anatomic integrity of the architecture. For instance, we can imagine protein-protein contact between a soluble protein and a structural protein to take place by displacement of one or more water clusters of the hydration layer by one or more domains of the protein. Obviously, for specific interaction to occur other functional requirements must somehow be met.

5.5 The cell as an integrated unit

Starting at molecular level and going upwards in the dimensional scale, it is costumary to divide the cell into three somewhat distinct hierarchical levels. The bottom level is called microscopic and is the domain of single water molecules, in constant random agitation in the thermal bath. The uppermost level is called macroscopic and it is the domain of organized structures, superstructures and hyperstructures where movement is highly ordered. In between, extending somewhere from 1 – 5 nm in the dimensional scale, lies the mesoscopic level, a world where disorder predominates and order is latent.

Water clusters and protein domain are mesoscopic entities that emerged from the chaos of thermal motion as a result of cooperative order-disorder interactions between molecules. Because of the dynamic nature of these opposing interactions, these basic elements appear as a wave, and are best understood as *structural quanta.* If favorable spatial and temporal conditions exist among many such quanta, their wave form can resonate and fuse to produce a high-level quantum. Then, many small pixels become one macroscopic pixel, disruptive molecular pressure becomes unifying tension, and the multicomponent assembly becomes one entity. When such a transition spreads through the whole cytoplasm, the cell acts as one. This macroscopic quantum gives the protein gel its alive quality. Since the lipid gel within the membrane is a natural extension of the protein gel inside, the wave motion can extend beyond the cell, to the level of tissue (7).

The Watterson's model rests upon the wave structure of liquid water. By quantizing cell water and protein, it raises the foundation of life from the thermal chaos of single molecules to the ordered structure of the protein gel, from a thermal bath to a tension bath. In so doing, the model allows for organized, vectorial (sequential) metabolism and for cell signaling mechanisms in line with modern quantum field theory.

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6

THE ELECTROMAGNETIC FLOW OF INFORMATION

The electromagnetic field is contiguous from structure to structure and is coupled through coherent charged states and cooperative processes
Jerry I. Jacobson

There can be no life without a constant flow of energy and information. One of the characteristics of living systems is their self-organization. For that to take place energy and information are both required. Energy alone can do work but for the performance of organized work information is also needed.

Information and energy are intimately related and they flow together mostly in the form of electromagnetic waves. During the course of evolution, the electromagnetic waves have organized into a coherent endogenous electromagnetic field, which is no more than an extension of the universal electromagnetic field. Most of the information generated in life processes is transmitted through this biological field.

Little is known about information. Not all mediators have been identified and the secrets of transmission, transduction and processing only now start unveiling. Interactions between the endogenous and external, man-made electromagnetic fields occur and by interference with normal information pathways they can affect cellular functions. For the purpose of this discussion only the physics of information will be emphasized, particularly those mechanisms not considered by information theory. The special *photonic transmission system* of microtubules will be described later.

6.1 The electromagnetic spectrum

Electromagnetic radiation is energy resulting from the acceleration of electric charge and the associated electric and magnetic fields. The energy can be regarded as waves propagated through space. The different types of radiation are distinguished by their wavelength, which is the distance between successive crests or troughs. The electromagnetic spectrum is the range of wavelengths over which electromagnetic radiation extends. The longest waves are radio waves and the next longest are microwaves and infrared waves. Then comes the narrow band of visible light, followed by ultraviolet waves, x-rays and gamma rays. Typical wavelengths extend from the size of mountains for radio waves to the dimensions of atomic nuclei for gamma rays (Fig. 6).

The radiation that reaches the earth's surface in significant amounts is that of radio waves with wavelengths between 100 m - 1 cm and visible light. All other radiation is either, blocked or transmitted with extreme attenuation by the earth's atmosphere. This variation of transmission depends largely on the type of gases that comprise our atmosphere (1).

The number of cycles of a wave per second is called frequency and is expressed in *hertz* (cycles per second). Within the body, most of the electromagnetic radiation is produced by molecular vibrations and is thus confined to the wide spectral region of infrared, between 10^{11} to 10^{14} Hz.

6.2 Piezoelectricity of biopolymers

In certain materials, an externally applied mechanical stress gives rise to electrical polarization and, conversely, an externally applied electric field gives rise to a mechanical strain. The former is called the direct piezoelectric (piezo, from Greek "press") effect and the latter the inverse piezoelectric effect.

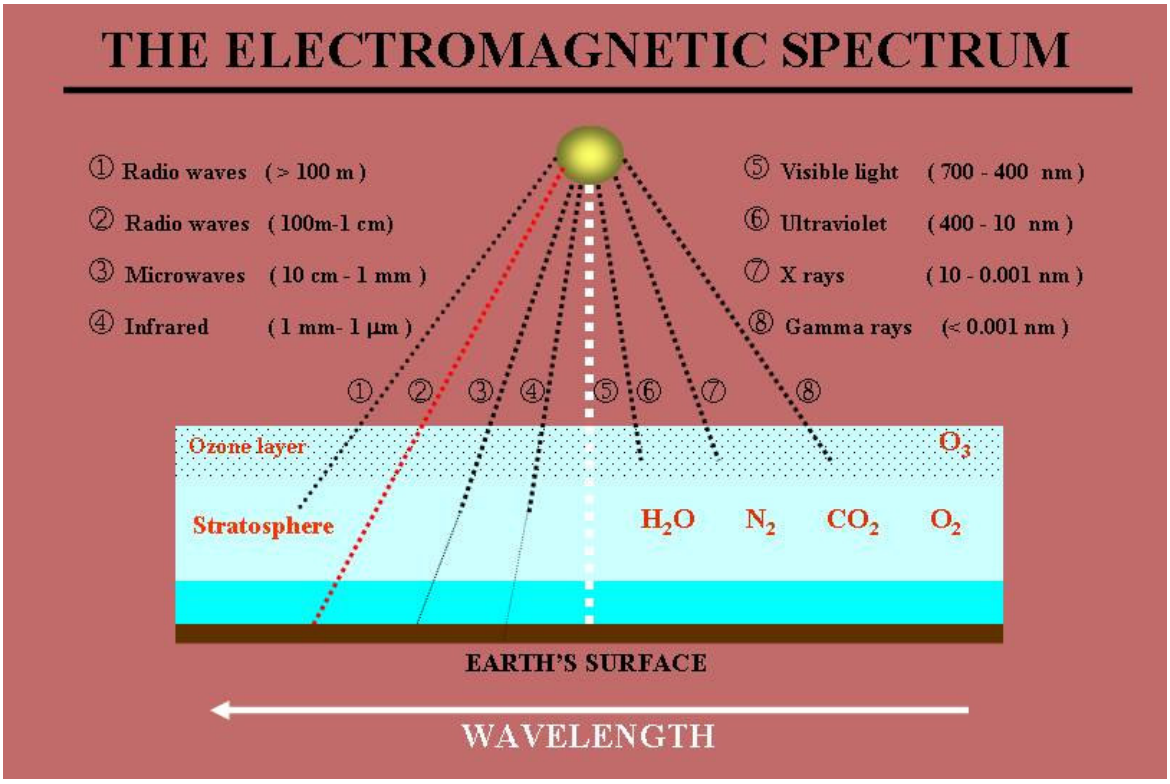

Fig. 6. Simplified view of the electromagnetic spectrum. The sun is the major source of the electromagnetic radiation received from space but all stars and a variety of other cosmic sources, within and outside our galaxy, emit the radiation. Our body and man-made devices also emit electromagnetic radiation.

Piezoelectricity is typically found in certain nonconducting crystals, such as quartz, but it is also found in biological materials. To exhibit piezoelectricity, a material must have a certain kind of symmetry, such as the uniaxial symmetry found in wood, bone and a large number of biopolymers belonging to the class of polysaccharides, proteins and nucleic acids.

The piezoelectric effect appears to originate from crystalline and highly oriented regions of biopolymers. Studies in synthetic polypeptides with either an α-helical or β-sheet conformation have shown that it is the CO-NH peptide bond that plays the important role. Each CO-NH peptide unit is attached to an asymmetric carbon atom of an amino acid residue and its asymmetric distribution of charge makes it a dipole (Fig 7). The CO-NH macrodipoles are oriented cooperatively in a given direction inside the molecule. When the helix is sheared, the direction of each dipole makes a slight rotation and the

summation of these rotations results in electric polarization in the direction perpendicular to the shearing plan (2). As a result of piezoelectric effects, when electromagnetic oscillations act on piezoelectric structures they are converted to mechanical vibrations in the structures themselves, and vice-versa.

The CO-NH peptide bonds are the strong, main chain-main chain, covalent bonds that hold the amino acids together along the backbone of a protein. But proteins in a folded conformation, that is, in their functional state, also possess a multitude of much weaker, non-covalent cross-connections in their side chains. These weak bonds lend flexibility to proteins and are responsible for their constant motion (3,4). Among these weak connections are hydrogen bonds, which are special cases of dipole-dipole and charge interaction. As their counterparts in water, they are essentially electrostatic in nature. A positively charged particle, a proton, is mutually attracted to two electronegative atoms (usually oxygen-nitrogen or nitrogen-nitrogen), separated by a distance of less than one nanometer. This atomic arrangement gives this bond a very high oscillating frequency, of the order of 10^{11}-10^{12} Hz. The maximal stability of the bond is reached when the four atoms CO-NH lie on the same axis (Fig. 7) but the bond can also bend, stretch and compress. The potential flexibility of these special piezoelectric bonds makes them very responsive to physical energies of various types – mechanical compression and tension, ultrasound, electromagnetic fields. They are considered to be energy transduction piezoelectric centers that play a central role in protein stabilization and function.

Piezoelectric structures can be defined physically as aggregates of atoms with an integrated vector. They vibrate in space and the vibrations are regulated by the endogenous coherent electromagnetic field and other elements essential to the root of life itself.

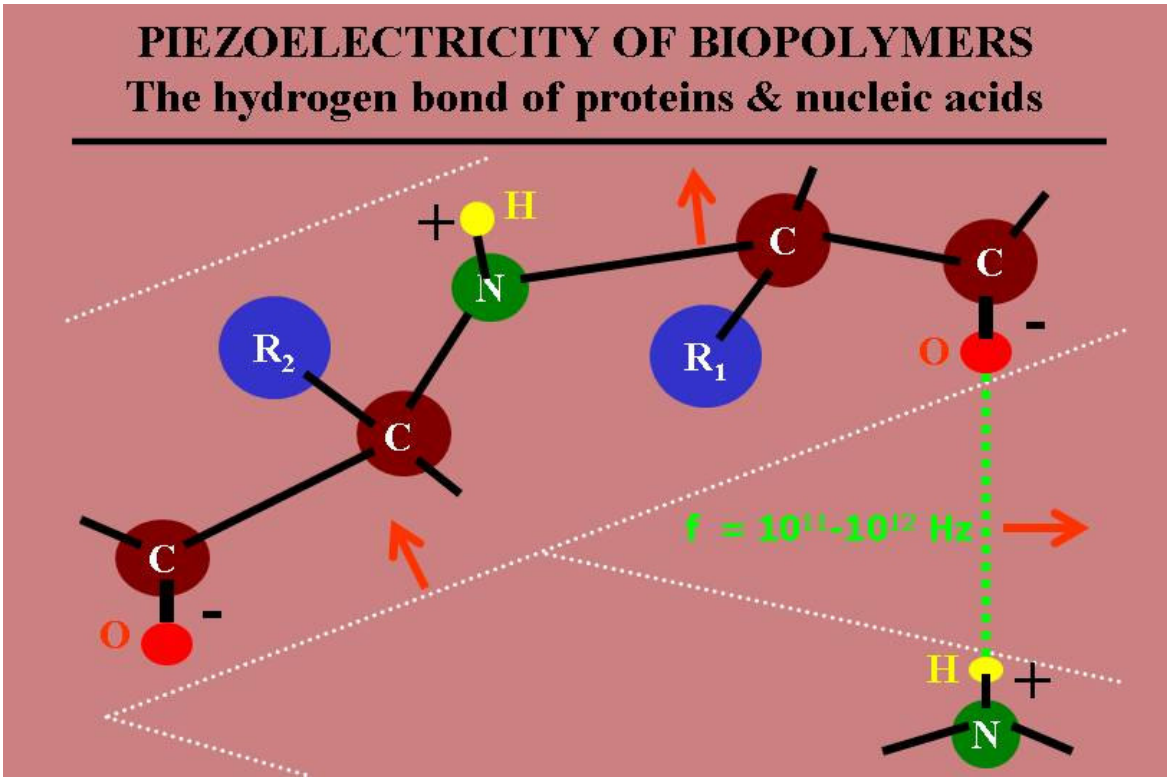

Fig. 7. Diagrammatic view of two of many CO-NH peptide dipoles that form the structure of the α-helix of a protein. Each CO-NH bond is attached to an asymmetric carbon atom (a carbon atom to which four different groups of atoms are attached) of an amino acid residue, R1 or R2. The direction of the respective dipole vectors is

indicated by the arrows. The origin of piezoelectricity lies in the internal rotation of the dipole vectors. Also shown is a hydrogen bond, itself an oscillating CO-NH dipole, connecting two neighboring helical regions.

6.3 The endogenous electromagnetic field

Living systems have a large number of internal degrees of freedom. In systems with similar characteristics, quantum field theory predicts that a macroscopic order must derive from the collective properties of the microscopic components. In the case of life, these microscopic components are the many species of molecular *electric dipoles,* the basic components of biomatter. The water dipoles and the dipoles found in biopolymers whose induced polarizability is the source of piezoelectricity are among them.

In the dawn of life and under a constant inflow of metabolic energy, dipole-dipole interactions in the protocells grew in number and organization. When a given density of dipoles was reached, the polarization oscillations became coherent. Over time, the nascent *coherent electromagnetic field,* now well organized, developed mutual interactions with the molecular stuff of the polar structures. It is from these long-range electromagnetic-molecular correlations, between microscopic and macroscopic levels, that the self-organization of matter arises (5). The proposed chemical self-organization of matter of current biology, based on short-range molecular-molecular interactions, is obviously inadequate and can no longer be invoked as a major component of biological order.

In the present electromagnetic field, the field-matter interactions are allowed to be neither too strong nor too weak and so contemporary life exists on the border between order and disorder or, in quantum language, between coherence and decoherence (5).
On a deeper physical level, the endogenous electromagnetic field is coupled to the fundamental electromagnetic field. It is therefore not surprising that, in addition to special characteristics of its own, the endogenous field also manifests the stability inherent to the field of nature. To put it another way, the apparently distinguishing characteristics of organisms are extreme expressions of the true underlying physics of the universe (6).

6.4 The electrical properties of matter

The electrical properties of matter are defined by the capacitance to store electricity and the ability to conduct it. The capacitance per volume unit is termed the dielectric constant or, more modernly, *relative permittivity* and the conductance per volume unit is the *conductivity*. Relative permittivity reflects the ease with which localized electronic charge in the material can be polarized by the application of an electric field; conductivity reflects the ease with which free electric charges can migrate through the material under the influence of the electric field. Normally, the conductivity is dominated by the movement of inorganic ions and is a function of their concentrations, valencies and mobilities. In biomatter, relative permittivity and conductivity generally change as a function of field frequency, typically in an irregular fashion. As the frequency is increased, permittivity decreases and conductivity rises (3,7).

The atomic electrons of some materials are strongly bound to their parent nuclei. When they are placed in an electric field, practically no current flows in them because, unlike metals, they have no loosely bound, or free, electrons that may drift through the material. Instead, *polarization* occurs. The positive charges within the material are displaced minutely in the direction of the electric field, and the negative

charges are displaced minutely in the direction opposite to the electric field. Materials that behave in this way are called *dielectrics.*

Some dielectrics, such as water and proteins, already possess one or more permanent dipoles in their structures. These molecules are called *"polar".* If the dipole consists of single elementary charges *(q^+, q^-)* of opposite sign separated by a distance *s,* the molecular dipole moment, μ, is given by $\mu = qs$, and is usually expressed in Debye units ($1\ D = 1 \times 10^{-18}$ esu). Polar dielectrics have two dipole moments, one electronic or permanent and the other orientational or induced by the external field. In general, the total dipole moment is the sum of the induced (usually the larger) and the permanent dipole moments. Neutral dielectrics have only an induced dipole. The water molecule has a single permanent dipole with a substantial dipole moment ($\mu = 1.85$ D) but protein macromolecules typically have dipole moments of a few hundred Debye, equivalent to some 3-5 elementary charges separated by the macromolecular diameter (7).

When molecules with permanent dipoles are placed in an electric field, the field forces try to orient the dipoles and it is this dipole-field interaction that accounts for the changes of relative permittivity and conductivity with frequency. In a slowly oscillating electric field, individual water molecules can rotate and align their dipoles with the outer field so that the field exerts only a small effect. But, in a high frequency oscillating field, the molecules are unable to reorient fast enough to align with the field and, as a consequence, permittivity drops and ionic conductivity is greatly enhanced. At 20^o C, the dielectric constant of water, a reflection of its orientational polarizability, is 80 in a field with $f < 2 \times 10^9$ Hz but it is only 4 in a field with $f = 2 \times 10^{11}$ Hz (8).

In their folded conformations, proteins are very heterogenous from the point of view of dielectrics. Their peptide backbone has a large permanent dipole in the peptide plane (a summation of numerous cooperatively aligned CO-NH dipoles) and several of their constituent amino acids have side chains with either charges (positive or negative) or permanent dipoles in them. These charges and electric dipoles are distributed in an asymmetric but specific way which is controlled by the genomic information.

Charges and dipoles interact with each other and with other electrostatic structures within the molecule to generate an electric field in the overall matrix. This internal field, specific for each protein, plays an essential role in molecular recognition, which characterizes individual proteins in the mediation of many biological phenomena. On the protein surface of guest ligands and host proteins there are electrostatic complementarities that are intuitively recognized (3). These electrostatic complementarities may guide the geometric (shape) complementarities of current biology, the lock-and-key molecular interactions, in the recognition process. Molecular recognition underlies genetic regulation, protein assembly, information processing, enzyme activation, antigen-antibody recognition and many other biological functions.

There is an intimate and very dynamic interaction between the internal electric field and the molecular conformation in a protein. The molecule is constantly undergoing fluctuations on a pico- or millisecond time scale. Its backbone and particularly its side chains are in constant motion, their non-covalent interactions being constantly modified. Presumably, this motion is being controlled by the genetic information stored in the protein. Since molecular dynamics has a determining influence on biomolecular activity, the information regarding the state of the molecule or of its active site must be communicated to the protein environment where the biological reactions occur.

6.5 Dynamics of intermolecular communication

According to recent views, proteins are not the last stores of genetic information. The ultimate forms of gene expression are concentration gradients, particularly of ions, located intracellularly and across cell membranes, and mechanical stress gradients, located in biopolymers such as those that constitute the cytoskeletal structures. These dynamic, *dissipative structures* determine the internal state of the cell and act as direct causes for all cell functions. Ionic gradients (Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}) are required to couple events between proteins and their environment, on one hand, and between the inside and outside of the cell, on the other (9).

When a charged protein is dissolved in a polar liquid such as water, there is a reordering of the high density solvent molecules around the protein. They rotate their dipoles in an attempt to decrease the free energy of the system, and in so doing the electrostatic force produced by the solute protein is shielded. In addition to this dielectric shielding of water molecules, the density distribution of small ions (counterions) in the solvent also changes to shield the electric field originating from the protein. Positive metal ions tend to be located near the negative charges, and negative ions, such as chloride and phosphate, near the positive charges (3). Under these circumstances, the electric field of a protein, a domain or an active site cannot be communicated and the proteic conformation can not be recognized at a distance. Even if this was possible, the information could be altered by the polarization dynamics of the electrolytic environment.

For a protein to communicate with its environment or other neighboring proteins a dynamic cooperation of the protein with surrounding water and ions is required. Richard McCorkle has developed a theoretical formulation of this communication process, based on well established dielectric theory (10). According to his view, summarized below, ion fluxes act as triggers and regulators, water molecules as intermediate agents and protein conformations as emitters and modulators.

In an inactive state, ion densities are of low amplitude and frequency. Since salt-ions are strongly hydrated, water coordination is able to follow the ionic oscillations and damping is strong. However, during an ion enhancement (signal), as may be triggered by membrane gating, the frequency of the ionic oscillations is shifted to a region ($f \sim 3 \times 10^{11} - 10^{12}$ Hz) where the rotational response of the water molecules is no longer able to follow the collective ion motion. The ions are now free to vibrate at their natural frequency of vibration, there is, ion resonance emerges. It happens that the frequency of these ionic oscillations matches the frequency of the major internal motions of macromolecules, with which they resonate. With the dielectric shielding effect of water molecules removed by the frequency-induced drop in permittivity, the dipoles of a template macromolecule can now send resonant *polarization waves* to the ambient dielectric, communicating thereby conformational information to distances of hundreds of angstroms. The internal structured motions of the macromolecule are displayed in the solvent by the special characteristics of the wave pattern, in a way that has some resemblance to what occurs in a photographic plate.

The energy density of the oscillations (excitation energy) is large enough to exert a controlling influence on the coordination chemistry in the region of the template molecule. Fundamentally, a complete chemical reaction consists of a change from solvated reactants (reactants with strongly coordinated solvent molecules) to a solvated product. It is a collective activated event involving the coordinated motion of many particles. By impressing its conformational message in the solvent, a locally dominant macromolecule is able to select a particular conformation of reactants, organize the ionic environment and, through effects on water structure, control the energetics required for the reaction to occur. The agents at work in this action at a distance are resonant polarization oscillations. They are the ones that drive the fundamental process by which chemical reactions occur (10).

6.6 The organism wide web

Among the ionic gradients involved in intracellular communication those of calcium play a predominant role, in part because these multiply charged ions are capable of generating strong oscillations. Calcium signaling controls diverse cellular processes by changing the electric characteristics of the signal. Calcium gradients can emit single, puff-like transients of different concentration (amplitude modulation) or can emit repetitive, wave-like oscillations of different frequency (frequency modulation). These signals can be very localized for control of specific functions or can spread as far away as to adjacent cells, through gap junctions, to coordinate intercellular responses (11,12).

Our present physical and biological knowledge of the communication system of the whole organism, the organism wide web, is sketchy and can only be outlined in a general way. Each level of organization has its own characteristics but they are all interconnected, in numerous cooperative ways, forming a vast bidirectional network crossing different physical scales, from the micro, to the meso, to the macro. The endogenous electromagnetic field must play a central role in this process. The interface with the macroscopic environment is the external membrane of cells. The arriving input signals – physical, chemical, mechanical - are integrated at the membrane and transduced, through calcium gradients and other second-messenger mechanisms, to intracellular chemical and molecular events. Integrin receptors and cytoskeletal structures are emerging as fast integrating pathways connecting the extracellular matrix to the cell interior. The information is finally processed inside the cell and an output response is generated and amplified to a macroscopic output action (13).

6.7 Interactions with man-made electromagnetic fields

At the dawn of civilization, only the natural fields surrounded us – the universal electromagnetic field, the terrestrial magnetic field and the atmospheric electric field. The contribution of man-made electromagnetic fields was insignificant until the advent of electricity and its use as a power source. Then, the telephone and radio were invented, the cathode-ray tube and lasers were discovered and with them all related technologies. Man-made electromagnetic fields have been on the rise since.

In regards to interactions with biomatter, the *electromagnetic spectrum* is divided by visible light, into two major types of radiation. The most energetic waves, such as gamma-rays and x-rays, which propagate at frequencies greater than 10^{16} Hz, can dislodge electrons when they hit matter and are therefore called *ionizing radiation.* Lower frequency waves, such as radiowaves and microwaves, which are not energetic enough to break chemical bonds, are called *nonionizing radiation.*

This discussion is limited to nonionizing radiation generated by man and to which the general population is exposed. It extends from extremely low frequency (ELF, up to 10^3 Hz) to ultra-high frequency fields (UHF ~ 2.5×10^9 Hz). Examples of sources of nonionizing radiation in the home, in ascending order of frequency, include: power-lines, telephone, AM radio, cordless phone, FM radio, TV, cellular phone and microwave oven.

Electric fields exist whenever electric charges are present, regardless of whether current is flowing; their units in the SI system are volts/meter (V/m). Magnetic fields are produced by moving charges, such as an electric current flowing through a wire; their units in the SI system are tesla (T). Actual electric fields depend on the design, configuration and voltage of the line, and because the voltage of a line is closely

regulated, the resulting electric fields are essentially constant. By contrast, the magnetic fields depend on the current load, and they can be very variable from day to day, and even within a day (14). Both of these fields decrease with the distance to the observer. Average values for residential fields in the USA are: electric field, 0-10 V/m and magnetic field, 0-0.2 μT.

Power-frequency refers to the 50-60 Hz alternating current frequencies used in electric power systems. It produces both electric and magnetic fields. Since exposure to power-frequency occurs at distances shorter than the wavelength of 50-60 Hz radiation (~ 5000 Km), the associated electric and magnetic fields are considered independent entities. This is in contrast to electromagnetic radiation (pe, from radio-frequency sources), in which the electric and magnetic fields are inextricably linked. Because electric fields from power lines do not easily penetrate buildings, electric fields within residences are dominated by internal sources. Magnetic fields within residences, on the other hand, are influenced by nearby distribution and transmission lines as well as by internal sources (14).

There is a widespread public concern that exposure to electricity (ELF fields) is linked to cancer, particularly leukemia and brain tumors. This concern derives from epidemiological studies performed over the last twenty years. The trigger study, published in 1979, indicated an association between the current carrying potential (wire code) of the external wiring supplying the house and childhood leukemia and brain cancer. In this study, it was implicitly assumed that the high current capabilities of the higher wire codes equalled high magnetic field exposure. A number of subsequent studies where the magnetic field was estimated by other means or actually measured showed either no association with childhood or adult leukemia or a weak, not consistent, association (14,15).

The major difficulty with retrospective studies is the absence of accurate data on which to base exposure in the critical etiological period preceding the diagnosis. The exposure data should include not only magnetic fields, which are characteristically difficult to measure, but also electric fields and exposure to house appliances as well. Since prospective studies do not appear to be feasible, retrospective epidemiologic studies by themselves are not expected to shed further light on whether exposure to ELF fields in the home is the cause of leukemia or brain cancer.

On physical grounds, ELF electric fields are not energetic enough to cross spherically shaped membranes such as the nuclear membrane or the external membrane of cells. Consequently, they can not interact directly with DNA. The ELF magnetic fields are not shielded by cell membranes and they might act on the internal DNA but calculations show that the effects would be negligible compared to the energy of thermal agitation (16). However, it is still physically possible for ELF fields to interact with DNA by upsetting the endogenous signal transduction processes of the cell. External ELF oscillating electric fields can exert periodic forced vibrations (coherent motions) of all free ions around and fluxing through the cell membrane. The frequency of these vibrations is the same as that of the external field but their amplitude is inversely proportional to the frequency. Beyond a critical amplitude, the oscillating ions could give false signals for opening and closing channels that are voltage gated (17). Similarly, ELF magnetic fields can interact with the intracellular Ca^{2+} oscillator, thus interfering with Ca^{2+} signaling pathways (18). The disturbed information flow could then lead to abnormal metabolism and higher concentration of free radicals, possibly leading to higher rates of DNA damage.

Whether ELF fields can induce or facilitate mutations is not known for sure but they do influence cell proliferation, membrane transport, enzyme activity, biopolymer synthesis and other cell functions in vitro. Unfortunately, direct measurements of the electromagnetic field generated by living cells are still not possible (the electric power output is expected to be of the order of 10^{-15} watts or less (19)) and therefore only cell responses to applied ELF fields can be measured. At present time, these studies are

faced with the problem of lack of reproducibility of results. The reasons for that are not clear but it appears that all characteristics of the physical signal (frequency, amplitude, duration) and all environmental conditions must be controlled and standardized, if reproducible results are to be achieved, at least for frequencies < 100 Hz (20). Our knowledge on causality of ELF fields has just begun and it is to early to rule out possible adverse effects on health, including carcinogenesis.

The stand point on the issue by US regulatory authorities is that there is insufficient evidence to warrant aggressive regulatory action. Instead, reduction of public exposure is recommended (14). To achieve that, it is suggested that: (1) electric blankets, shavers and hair dryers be used with caution, because of their proximity to the body; (2) electric alarm clocks be moved away from the head, because they produce fields of 0.05-0.5 μT at 50 cm; (3) television be watched away from the screen and (4) children be kept out of the kitchen when microwave ovens, dishwashers, can openers or food processors are in use because these appliances produce fields greater than 0.2 μT at one meter.

In regards to exposure to UHF radiation (radiowaves, 300 Hz-1,000 megaHz; microwaves, 1,000-2,000 MHz), there has been a change in recent years. Radiofrequency exposure was typically very low until portable devices (cellular phones, two-way pagers) that transmit in close proximity to the body started proliferating. Worries about brain cancer have been renewed. At high power, UHF radiation can heat organic material – that is the way microwave ovens work – but cell phone emissions are much too weak to cook human tissues. The average power transmitter by a typical mobile phone is about a quarter of a watt. If the phone's antenna is placed next to someone's head for a few minutes, the waves will raise the temperature of the nearby brain cells by a maximum of about 0.1^{o} C. Because this heating is about one tenth of the normal fluctuations of the brain's temperature, it is unlikely to affect the organ (21). Neurons, however, are unique cells in regards to interaction with electric fields and non-thermal adverse effects can not be disregarded. Even ELF fields are not excluded from them. Specifically, field penetration is dictated by the geometry of the cell and its orientation with respect to the applied field. Due to its elongated shape, neurons permit an electric field to penetrate, providing that the field is directed along the cell's extended axis. The interesting result is that the relatively spherical form of the nuclear membrane shields the nucleus and protects its DNA contents but the extremities of the cell are exposed to the applied external fields. These fields interact strongly with the dipoles of microtubule and in this way can interfere with the biochemistry and function of the neuron (22). Furthermore, when self-synapsing neurons are exposed to magnetic fields, the induced electric fields in their nearly closed loops can be larger by a factor of 3,000 or so than the value in other synapses. It has therefore been suggested that the nervous system might possibly be affected in selected spots by radio and microwave radiation (23). Systemically, exposure of the right hemisphere to a cellular phone field for 35 minutes causes an increase in sympathetic efferent activity which raises resting blood pressure by 5-10 mm Hg, most likely due to more pronounced vasoconstriction (24).
Because cell phone energy penetrates more deeply into the brain of a child than of an adult and until more is known about biomater interactions with this relatively high energy radiation, the Bristish government has recommended that children should be discouraged of using mobile phones for nonessential calls (15).

But not all is wrong with electromagnetism. Nordenstrom has maintained that dynamic electromagnetic interactions occur widely within the human body and that electrodynamics plays a vital role in human physiology concomitant with its biochemistry. He drew attention to biologically closed electric circuits and vascular interstitial closed circuits, and believed that these electrical systems are produced intrinsically by the human body and could play a role in regulating the structural and functional integrity of tissues and cells (25). It is encouraging that some of the research experiments so far performed suggest the possibility of control over cell functions by electromagnetic radiation (22).

There is also evidence suggesting that an electromagnetic field is interpreted by the cell as a stress and the system responds via the stress-response mechanism. Stress proteins have been induced in vitro by the application of ELF fields. More recently, coherent non-thermal 60 Hz electromagnetic fields induced stress responses that protected chick embryo myocardia from anoxic damage (26).
Nonionizing electromagnetic radiation has been used therapeutically in the healing of bone fractures, wounds and inflammation, but still in a somewhat uncontrolled way. Much more needs to be known about the biomatter interaction but it does appear that electromagnetism can be beneficially used in clinical medicine. We are just in the early stages of the electromagnetic era.

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7

ENERGY, ORDER AND BIOLOGICAL ORGANIZATION

No matter how energy will be defined in the future, it will remain in some sense the lord and giver of life, a reality transcending our mathematical description. Its nature lies at the heart of the mystery of our existence as animate beings in an inanimate world
Freeman J. Dyson

Living systems exhibit a special kind of order. Their components seem to be correlated in a dynamic rather that in a static sense. It can be said that life constitutes a fourth state of matter. Gas is matter that fills its container; liquid is matter that conforms to the shape of the container; solid is matter that supports its own shape; life is matter that is organized and maintained in a self-ordering state of high energy. Only carbon, hydrogen, oxygen, nitrogen, phosphorus, and sulfur can possibly support life as we know it (1,2).

For living systems to be autonomous and persistent, they must exchange energy and matter with their environment. They must tap environmental potentials for free energy and then process the free energy internally, under the constraints of the laws of thermodynamics.

Modern biology has provided detailed information about the number, structure and biological function of the different components of the living system, but it has not accounted for the cooperation of these components into a working whole. Classical physics has also not presented a comprehensive, logically coherent, dynamic description of the biological world. One theory attempting to do so is that of *molecular complementarity*. It is based on reversible interactions among molecules and is therefore of great generality. This theory is described here as introduction to a more powerful theory, in effect universal, founded on non-classical physics, to be described in chapter 9.

7.1 The nature of energy and information

In physics today we have no knowledge of what *energy* is. It is an abstract, invisible, and ultimately unimaginable quantity. It is not a material thing and this prevents us from dealing with energy directly. Classic physics describes it as matter in motion, general relativity identifies it with mass ($E = mc^2$) and quantum mechanics considers it to be quantized. We can think of energy as a *capacity* to produce movement or change (3).

Being an immaterial quantity, energy, by itself, cannot and does not exist in the real world. It must somehow become part of a material process for us to be able to deal with it and to measure it (4). We must go down to the microscopic world where quantum effects take place to better understand how this process is accomplished. At microscopic level, matter is constantly interacting with matter, that is, material signals are constantly being exchanged and measured internally. These signals are no more than messages coded in the form of material aggregates, each one (quantum particle) carrying information of an experience (quantum information). For a measurement to be registered, the interaction within the

quantum system must involve an exchange of energy (quantum energy) (5). It is quantum mechanically possible for the quantum energy resulting from local, internal exchange interactions at microscopic level to become manifest at mesoscopic and macroscopic levels and be measurable by external observers. In the wave-particle duality sense, the detection of a particulate phenomenon is a consequence of the energy flux interacting with the measuring apparatus. In other words, it is the means of measurement that gives reality to energy. Energy exists only when it is measured by something else (4,5).

We cannot distinguish energy from matter or information. Energy cannot exist in isolation. Energy exists as, not the energy to be, an atom. Energy is matter and matter is condensed energy. Likewise, information is no more than a codified microstate of energy (4).
Energy is the basic force of our cosmos. It is the ultimate substrate and fabric of the world, the beginning and end of everything that exists. It is a constant quantity that cannot be created out of nothing nor destroyed. It can only be transformed.

7.2 Laws of thermodynamics and the concept of free energy

Thermodynamics is the study of the laws that govern the conversion of energy from one form to another, the direction in which heat will flow, and the availability of energy to do work. It is based on the concept that in an isolated system anywhere in the universe there is a quantity of energy, called the internal energy of the system. This is the total kinetic and potential energy of the atoms and molecules of the system that can be transferred directly as heat; it therefore excludes chemical and nuclear energy (6).
The value of the absolute internal energy of a system in any particular state cannot be measured. Instead, the value of the change in internal energy is taken as the significant quantity. A change in internal energy can occur only if the system ceases to be isolated. Under these circumstances, the internal energy can change by the transfer of mass to or from the system, the transfer of heat to or from the system, or by work done on or by the system.

The *first law of thermodynamics* states that “in a system of constant mass, when mechanical work is transformed into heat or heat into work, the amount of work is always equivalent to the quantity of heat”. In this way, the total energy of the system and its surroundings remains constant. This law is therefore known as the law of conservation of energy, or more precisely of mass-energy.
The first law has been experimentally proven and found to hold everywhere, from the subatomic to the cosmological level. It guarantees that energy can neither be created nor destroyed and in this sense it is the guardian of the balance of the universe (3). For biological systems, one important consequence of the conservation law is that the heat produced in the transformation of one substance to another is always the same, whatever the metabolic pathway taken.

All natural processes conform to the first law. Some of these processes are reversible but most of them are irreversible, that is to say, they only proceed in one direction. The direction that a natural process can take is the subject of the *second law of thermodynamics.* It can be stated in a variety of ways: “it is impossible by any continuous self-sustaining process for heat to flow from a colder to a hotter body” or “in any closed system (one that allows only exchange of energy) there must be either a conservation or an increase in entropy”. *Entropy* (heat transferred/absolute temperature) remains constant in reversible processes and increases in irreversible processes (for instance, when one form of higher grade energy is transformed into one of lower grade energy).
Strictly speaking, the second law applies not to changes in temperature but to changes in entropy. Both of these properties, however, determine the direction in which an irreversible process can go.

Temperature is a measure of the intensity of heat; entropy (from the Greek “trope” for transformation) is a measure of the unavailability of the energy of a system to do work.

Unlike energy, entropy is not conserved. It increases with time and this property provides a means to differentiate between the past and the future. The second law of thermodynamics was the first law of physics to impose on time a sense of direction (forward direction or time’s arrow) that is absent from the three directions of space. The vector property of entropy prevents the universe from reversing its course (3).

The second law of thermodynamics applies only to systems in thermodynamic equilibrium, where the conditions of mechanical, chemical and thermal equilibrium are satisfied and energy and entropy are in balance. Most biological systems, however, are in a state far from equilibrium. As a way of measuring the balance between energy and entropy in these nonequilibrium systems, a third variable is used, known as *free energy* (or Gibbs function). Free energy is a measure of a system’s ability to do work and is expressed as:

$$\text{Free energy (G)} = \text{enthalpy} - \text{temperature} \times \text{entropy}$$

In a chemical reaction, pressure remains constant but there may be slight changes in volume. The volume work (PV) is not available but must be accounted for. Its energy is added to that of internal energy and the resultant property is called *enthalpy* (Fig.8). For biological systems, enthalpy is roughly equal to internal energy.

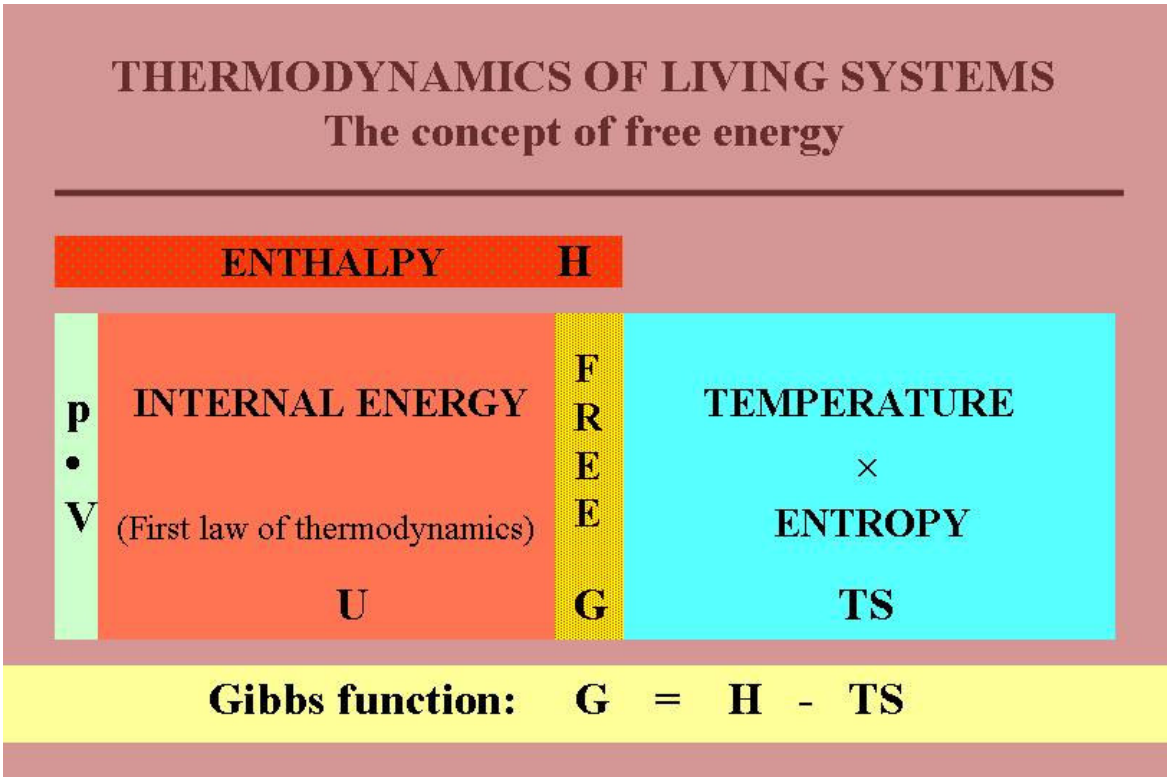

Fig. 8. An overview of the concept of free energy. The thermodynamic property enthalpy is equal to internal energy plus the pressure-volume work, which is not available. The part of the enthalpy that is freely available is called free energy.

A system always endeavors to keep free energy at a minimum. For many processes in aqueous solution, there is an approximately linear relationship between enthalpy and entropy changes. They increase or decrease together. A glance at the above equation shows that if a large change in entropy is accompanied by a large change in enthalpy the resulting change in free energy is relatively slight. Large entropy increases are accompanied by small decreases in free energy and vice-versa. There is, thus, a sort of a tug of war between entropy and free energy (8).

Free energy is the most useful thermodynamic concept in biochemistry. It enables one to ascertain whether a given chemical reaction is thermodynamically favorable. If $\Delta G < 0$, that is, if the Gibbs function for the products is less than the Gibbs function for the reactants, the reaction is exergonic and can run spontaneously; if $\Delta G > 0$, the reaction is endergonic and an additional input of free energy is required to run the reaction. Since at equilibrium $\Delta G = 0$, the ΔG of a reaction is a measure of how far away the reaction is from equilibrium.

The first and second laws of thermodynamics complement each other. The first deals with the quantity of energy, the second with the quality of energy; the first governs the conversion of energy from one state to another, the second refers to the direction of energy flow and the availability of that energy for work. These laws are also deeply interrelated. Energy conservation and energy dissipation are both required for energy to exist and, in living systems, to self-organize. There is also a *third law of thermodynamics* and a fourth one has been proposed. The third law states that the entropy of a crystalline substance is zero (or thereabouts) at absolute zero temperature. This law provides a means for measurement of entropy. It implies that the human system, maintained at the relatively high temperature of 310.5^{o} K (37.5^{o} C), must contain at all times some amount of entropy.
It can be deduced from the above laws of thermodynamics that, in an open system such as the organism, a flow of energy is absolutely necessary for the existence of life. Now, a tentative *fourth law* has been proposed which states that a flow of energy is also sufficient for the formation of an ordered structure (7). The tentative law is still awaiting general acceptance.

7.3 Structural order and the concept of negative entropy

Contrary to the first law of thermodynamics, the second law has not been experimentally proven but so far has weathered all the storms challenging it. One of those appears to be life itself. With most of the metabolic reactions running irreversibly, how is life sustained in a state of low entropy and constant temperature? According to the second law, entropy should constantly increase and this would make life impossible. The explanation is that the second law applies to closed systems and the organism is an open system, one that exchanges not only energy but also matter with the environment.

Life uses the universe as a source of energy and a sink of entropy and, in addition, minimizes the production of entropy. In the exchange of matter, the body takes up food and air and exports end products. The energy imported in food is made available during metabolism by a process described in the next chapter. It is used by the body to sustain irreversible reactions away from thermodynamic equilibrium and to produce chemical, osmotic, electric and mechanical work. According to the second law, entropy is produced from the energy dissipated in both of those operations (internal entropy) and it is always positive. This internal entropy, in the form of heat, then diffuses into the atmosphere. As a result, the entropy of the universe, if it is considered a closed system, is constantly increasing. This statement is one of the original definitions of the second law of thermodynamics.

Qualitatively, entropy refers to the amount of disorder in a material's atomic or molecular arrangement. When water heated to100^{o} C is transformed to steam at 100^{o} C, its entropy goes up from 1.31 in the liquid phase to 7.36 kilojoules per kilogram per degree Kelvin, in the vapor phase (8). The water molecules are clearly more disordered in steam than in liquid water. They move more randomly and are scattered widely apart. They assume this new arrangement to maintain thermodynamic equilibrium. In 1944, Erwin Schrodinger, an Austrian physicist and one of the fathers of thermodynamics, argued that entropy, taken with a negative sign, is itself a measure of order (9).

In open systems, the exchange of matter can be viewed as exchange of entropy (external entropy). Unlike the entropy of the second law that is always positive, external entropy is almost always negative. This is the basis of Schrodinger's famous sentence: "What an organism feeds upon is negative entropy". In other words, the device that the organism uses to maintain itself in a stationary state of high level of orderliness, that is, at a low entropy level, consists of continuously importing order (negative entropy) from the environment and exporting disorder (positive entropy) into it (10). Thus, whereas a closed system is characterized by maximum entropy, true reaction equilibrium (with reversible reactions) and by performing work only once, the body, as an open system, is capable of continuous work with the production of a minimum of entropy.

In biological life, the essence of the negative entropy or anti-entropy process is control of the internal state. Besides the import-export of entropy, there are many other counter-entropy strategies, directly or indirectly related to metabolism, that contribute to the same goal. They are based on the thermodynamic concept of *coupling* which, in qualitative terms, is an interaction between two or more energy processes. A thermodynamically unfavorable reaction, which decreases entropy, can be driven by a thermodynamically favorable one, which increases entropy, that is coupled to it by, for instance, a shared chemical intermediate (11,12). The Na^{+}-K^{+} ATPase or sodium pump, which requires free energy, is coupled, by the electrochemical Na^{+} gradient that it generates, to several other secondary Na^{+} pumps that transport other ions or substrates without further expenditure of energy. This coupling of sodium pumps resembles the situation of a locomotive pulling a connected line of railroad cars. Only the locomotive requires energy.

7.4 Irreversiblity and the concept of order through fluctuations

The states corresponding to thermodynamic equilibrium are automatically stable. This stability, however, cannot be extrapolated to systems farther from equilibrium. Under these circumstances, stability becomes threatened by the excess of entropy production. This is bound to occur in biological systems whose kinetic structure is based on cooperative catalytic loops or complex feedback mechanisms where nonlinear steps are involved. In systems with these characteristics, at a critical distance away from equilibrium, excess entropy production may become negative and the system unstable. Surprisingly, with the breakdown of stability a new molecular order appears that basically corresponds to a giant fluctuation, stabilized by the exchange of energy with the environment. The fluctuation invades the whole system and its coherence compels it to evolve to a higher level of order. Pushed too far from equilibrium, the molecules of these nonlinear chemical systems suddenly lose their independence and simultaneously organize into a uniform whole.

Structures that behave in this way are called "dissipative structures". The term was coined by Prigogine and co-workers, the physicists who first studied them theoretically (13,14). It was meant to emphasize the association, which at first appears paradoxical, between dissipation or waste on one hand and structure and order on the other.

In the inanimate world, the phenomenon is found in hydrodynamics when increases in flow rate spontaneously convert stable laminar flow to turbulent flow. Although turbulent flow may appear disordered, it is in reality highly ordered at microscopic level. Part of the energy of the system, which in laminar flow is in the thermal motion of the molecules, is transferred to organized motion in turbulent flow. Since turbulence corresponds to the coherent behavior of millions and millions of molecules, the transition from laminar flow to turbulence can be viewed as a process of self-organization (15). Although the mechanism of its genesis is similar, the occurrence of dissipative structures in living systems is obviously more complex. It is very sensitive to global features, such as size and form of the system and boundary conditions imposed on its surface. Generally, for dissipative structures to occur, the system's size must exceed some critical value and so the oscillations do involve long-range order (14). Their period depends on the type of dissipative structure but for chemical reactions it is of the order of one minute. Since the oscillations extend from the microscopic to the macroscopic levels of organization, dissipative structures are truly self-organizing in space and time.

On a broader scale, these dynamic states of matter reflect the interaction of the system with its surroundings. Therefore, the gravitational field and the electromagnetic field must play an essential role in the self-organization of living matter, in this case through the type of fluctuations that they allow to occur. This field-matter interaction, at molecular level, may be viewed as a prebiological adaptation in the evolution of life (15).

Oscillating systems abound in biology. Among the most significant are those related to enzyme activity in metabolism and those that occur as a consequence of regulatory processes at the cellular level. The best understood oscillatory system occurs in the feedback structured glycolytic cycle, where the degradation of one molecule of glucose leads to the overall production of two molecules of ATP by means of a linear sequence of enzyme-catalyzed reactions. Here all glycolytic intermediates oscillate with the same period but with different phases (13,14). Less impressive and less well known are the oscillating chemical systems that produce gradients of ionic concentrations, which are involved in signal transmission, as described in subchapter 6.5 for calcium ions.

7.5 Complementarity theory and the organization of the living state

A basic characteristic of a biological system is its *complexity.* It results from the very high number of its components and their mutual interactions. This kind of dynamics is required for coherent oscillations of large amplitude to be generated. In systems with small number of particles, strong oscillations are damped by the multiple small fluctuations always present in the outside world (14). Coherence is necessary for the achievement of long-range structural and functional order.

If a single complex system were to function independently, all its parts would respond probabilistically to an energy flux. In order to localize energy within a part of a system and achieve order by coherence, systems must interact with one another, that is to say, they must be *"coupled"* (16). In this context, living beings are gigantic networks of dynamic, incessantly interacting coupled systems.
To accommodate requirements of the first and second laws of thermodynamics, the underlying dynamics of coupled systems must be *nonlinear* (2). Contrary to linear systems where magnitude of responses are proportional to strength of stimuli, proportionality does not hold for nonlinear systems: small changes can have striking and unanticipated effects. Every physician knows that the response of a given patient to a drug is sometimes unpredictable. More importantly, it cannot be calculated beforehand from any known physical or biological principle (17). By the same token, nonlinear systems cannot be understood by analyzing their components individually.

One of the most insightful theories of biological organization is that of *complementarity.* It has been analyzed recently by Root-Bernstein and Dillon (16,18) and from their extensive analysis has resulted a more profound understanding of the dynamics of life. The theory has implications far beyond the ones to be discussed here.
Complementarity, as defined by the above authors, is the non-random, reversible coupling of the components of a system, which could be a molecule, a cyclic chemical system, a cell or an organism. Of particular interest is *molecular complementarity*, a non-covalent interaction between molecules. The forces involved in the transient molecular binding are at least ten times weaker than those involved in covalent interactions. Examples of these weak forces are Van der Waals forces, hydrogen bonds, charge-transfer complexes and similar reversible chemical interactions. We already encountered them in the water-water and water-electrolyte interactions of Wiggins, the wave-cluster-domain interactions of Watterson and the piezoelectric interactions of the hydrogen bonds of biopolymers. What this new theory has done was to integrate all these interactions by way of a single unifying principle – that of molecular complementarity.

According to complementary theory, there are four different types of *coupling* in living processes and only one of those is thermodynamic. Thermodynamic coupling occurs, for instance, when energy in sunlight is captured and converted to chemical bond energy. Living systems, however, not only must capture energy in reproducible energy cycles but they must also convert the captured energy into stable, reproducible structures that can perform mechanical and information functions. The couplings involved in these latter processes, which are required for life to exist, are non-thermodynamic. Therefore, thermodynamic theory alone cannot explain the functioning of living systems (16).

Another insight from complementary theory is that which relates structural coupling with function. For instance, we know that DNA carries genetic information, although we do not yet know how it came to carry this function. But, in itself, the DNA sequence has no intrinsic meaning. Outside of an organism, a gene would have no more meaning than a particular set of cards has outside the context of a particular game. Both information value and biological function are context-dependent. Similarly, molecules so-called “receptors” or “second messengers” have these properties only in specific contexts, not intrinsically. Function is dictated by the specific structural interactions. If a molecule has different interactions, it may have more than one function. This is the rule rather than the exception. Structure and function are thus intimately related. An unanticipated result of this intrinsic structural-functional coupling is that living systems are less, not more, than the possible sum of their parts. Complementarity reduces the possible states a system can achieve and in the process makes possible the harnessing of free energy fluxes into ordered sets of functions (16).

There are both chemically reversible and irreversible systems in biology. Because of constraints imposed by increasing entropy, irreversible systems are temporarily limited, ie, they are dissipative or unstable. Long-term survival in biology, therefore, requires stable systems. Complementarity is able to confer stability to chemically reversible systems.

If the components of a system are reversibly linked, they will respond to environmental changes by reversible reactions that tend to maintain equilibrium. Systems possessing this kind of reactions are known as *buffer systems* or *homeostatic systems.* Buffer systems are those that manifest only a very small rate of change in response to a much larger one of an external parameter affecting them. Homeostatic systems are those that tend to return to a local equilibrium (local free energy minimum, in the case of biological systems) after being pushed away from it. Homeostasis and buffering are expressed in all molecular interactions in complementary systems (16).

Complementary molecules buffer one another and their environment and they can self-assemble in non-random ways. Presumably, this was the critical mechanism that made possible the aggregation of molecules in stable sub-assemblies during evolution. These sub-assemblies later organized in assemblies of sub-assemblies which in turn further organized into still bigger assemblages of assemblies and so on. Living structure is organized in this hierarchical fashion. The critical point about hierarchies is that as one moves from one hierarchy to a higher level hierarchy, new or *emergent properties* become evident that are not predictable from the microscopic properties of the components of the previous hierarchy. The development of a new hierarchy is critically dependent on the interaction of these emergent properties with the overall functioning of the hierarchy below. Emergent properties, however, are not a singular characteristic of biological systems. They can originate in any hierarchically organized system – be it chemical, physical, mechanical, biological or even electronic (16).

The nature of molecular complementarity is basically physical, ie, electrostatic. However, biological systems have characteristics not found in pure physical systems. This is particularly true for proteins (enzymes), where internal interactions among components and external interactions and reactions with other proteins are very slow as they involve changes in conformation. The time delay in the structural rearrangements is much greater than the minimum required by physical laws (19), which also operate in the surrounding physical space. It is these significant internal delays that allow for information to be processed, structure to be self-organized and energy to be flowed continuously through the hierarchical levels that make up the living structure. Seen in this light, life is in effect an ultimate function of time.

When molecules interact complementarily, there is an hidden direction in the binding. The molecules simply associate at the orientation that produces the lowest free energy for the coupled molecular state. Deviations from this position must require an input of external energy. The result of this directional binding is the production of a natural *vector.* Depending on the systems that are coupled and on other factors, molecular vectors can lead, for instance, to the generation of concentration gradients or to the conversion of scalar biochemical reactions into vectorial physiologic processes. A case in point is the vectorial nature of membrane-bound ion pumps. A pump which is complementary to the membrane is able to alter the intracellular and extracellular concentrations of the pumped ions. If the pump were not imbedded in the membrane, futile cycling of the pump would move the ions around within the cell, but not change their concentrations. Binding of the pump and membrane is central to production of the gradient vector. Molecular complementarity between enzymes with product exchange also results in generation of a chemical vector. This occurs when reversible complements interact in solution, eg, when the product of one enzyme is “handed off” to another enzyme to use as substrate, without release to the environment and therefore without exposure to anti-directional effects in the solution (18).

Complementary theory is based on short-range interactions but it is capable of demonstrating long-range effects, as exemplified by the generation of vectorial processes. Its major power, however, derives mostly from being a unifying principle, bringing together seemingly diverse but basically similar theories, such as those of Wiggins and of Watterson. It is, however, a peripheral theory imposed on matter and not derived from an intrinsic property of matter. Although it is considered a vector theory, it still treats interactions as being reversible processes. We will discuss later an even more general theory, the *unitary theory*, based on the electrical properties of matter, which treats complementary theory as a special case.

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8

CELL ENERGY METABOLISM AND ITS ORGANIZATION

Metabolism is a type of material self-organization which involves the autonomous use of matter and energy in building, growing, developing, and maintaining the bodily fabric of a living thing
Margaret A. Boden

Metabolism concerns the role of matter-energy in organisms considered as physically existing things. The matter is needed as the stuff of which the body is made. And the energy is needed to organize and maintain this matter. Metabolism localizes life in the physical world (1).

Every living organism represents the successful integration of many biomolecular machines that take up energy from the environment and convert it into some substance ("currency") that can be used to provide energy for whatever the organism needs – motion, heat or construction and maintenance of internal structure. These functions imply a continuous metabolism capable of capturing, using, storing and budgeting that energy, thus making possible for living beings to engage in their activities.

Metabolism involves material embodiment, not mere physical existence. Being more fundamental than reproduction or even evolution, metabolism is the vital property that better differentiates real (biological) life from the artificial "life" of a computer or a robotic machine (1). It necessarily involves a delicate balance between anabolism and catabolism. To effect these vital functions, a complex biochemistry is required.

This biochemistry is the result of several thousands of chemical reactions involving complex feedbacks and taking place simultaneously in a condensed space of a few cubic micra. Current models of metabolic regulation are still based on concepts drawn from solution chemistry. Cellular reactions are viewed as scalar in nature, involving diffusion and random collision between enzyme and substrate. Modern concepts, however, favor a highly organized energy metabolism, based on electrochemical processes involving vectorial flows, which are far more efficient and easily harnessed for biological work (2).

8.1 Electrochemistry and the redox concept

Electrochemistry is the branch of chemistry concerned with the relation between electricity and chemical change. Many spontaneously occurring chemical reactions liberate electrical energy and, conversely, electrical current can be utilized to bring about many chemical reactions that do not occur spontaneously. Reactions involving electron transfer from one substance to another are known as *oxidation-reduction,* or redox*,* reactions. They are ubiquitous in life but have a special role in energy transducting processes, such as in photosyntethic and mitochondrial electron transport chains. Their quantitative significance to the body economy is comparable to that of acid-base reactions, which involve proton transfer.

The proper understanding of oxidation-reduction processes requires the introduction of two essential concepts – *electronegativity* and *oxidation number* (3). Electronegativity is a measure of electron affinity. The more electronegative an atom is, the more tendency it has to take away electrons from other less electronegative atoms. Pauling electronegativities are based on bond dissociation energies using a scale in which fluorine, the most electronegative element, has a value of 4 (Fig.9).
Oxidation number is a measure of the degree of oxidation of an element or atom. In forming chemical bonds, atoms donate, acquire or share electrons. This makes possible to assign one number to every atom which specifies how many of its last orbital electrons are involved in forming bonds with other atoms. In electrochemistry, chemical bonds are considered to be ionic, that is, bond electrons are completely transferred to the most electronegative atom of the bond. If the bond is between atoms with the same electronegativity, each atom shares one electron.
The oxidation number (oxidation state) is calculated as the difference between the number of electrons the element retains when combined and the number of electrons that it possesses when in the fundamental state (the number of its group in the Periodic Table). The calculated number will be negative if there is an excess of electrons and positive if there is a lack of them.

There is no physical reality to oxidation states. They simply represent the results of calculations based on a formal rule. The method can be illustrated by considering the reaction of water formation from its elements, oxygen and hydrogen (Fig. 9). This reaction takes place continuously in mitochondria and it is

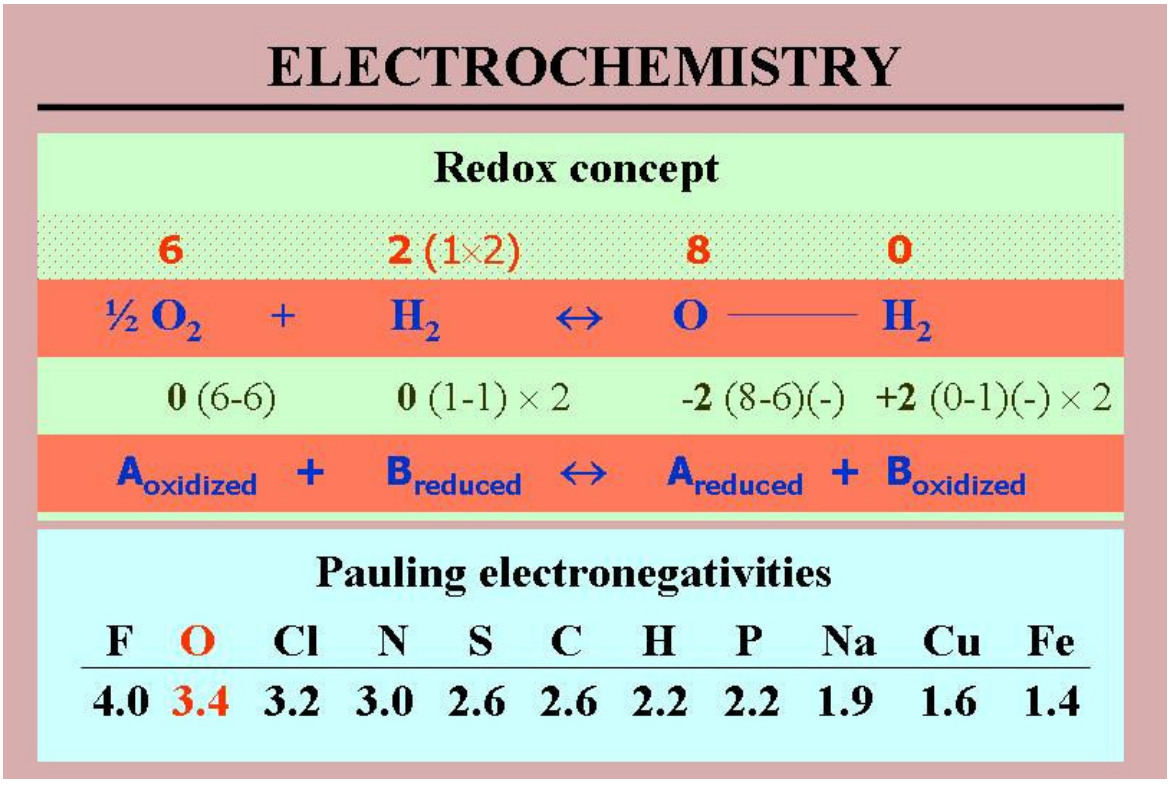

Fig. 9. Illustration of the redox process by the reaction of water formation. The line above the reaction displays the number of electrons in the last atomic orbital and the line below shows the calculated oxidation numbers. The negative charge of the electron has to be considered, as indicated. In the water formation reaction, oxygen is reduced (decreases its oxidation number from 0 to –2 by the gain of 2 electrons) and hydrogen is oxidized (each atom increases its oxygenation number from 0 to +1 by losing its single electron). The redox process can be considered a binary equation. Values for the electronegativity table were taken from ref (3) with some modifications. Further explanation in text.

an essential step in the production of free energy in aerobic living organisms. In the reaction, oxygen is reduced and hydrogen is oxidized. In a redox process, the atom or ion that is oxidized increases its oxidation number (loses electrons) and the atom or ion that is reduced decreases its oxidation number (gains electrons). Simply stated, oxidation is a loss of electrons and reduction is a gain of electrons (3,4).

Oxidation and reduction are coupled processes in the sense that in any oxidation reaction a reciprocal reduction occurs. Because of their complementarity, the oxidation and reduction processes together are referred to as *redox reactions.* The reactant that brings about the oxidation, the oxidizing agent, is itself reduced by the other reactant, the reducing agent. In the example given, ½ O_2 is the oxidizing agent and H_2 the reducing agent.

A particular oxidation or reduction can often be carried out by a wide variety of oxidants or reductants. This has led to a generalization of the redox concept by writing it without specifying the identity of the reducing agent:

$$\text{oxidant} + n\ e^- \rightarrow \text{reductant}$$

The symbol e^-, which stands for electron, serves as a reminder that an unspecified reducing agent is required to bring about the change; n is the number of electrons transferred. In our water formation example, the oxidant would be $(1/2\ O_2 + 2\ H^+)$ and the reductant H_2O. Although hypothetical, this type of reactions, known as *half-reactions,* are properly balanced chemical processes.

All redox reactions can be broken down into a complementary pair of hypothetical half-reactions. These cannot be studied in isolation but when two half reactions are linked they form an electrochemical cell, a device in which chemical energy is converted to electrical energy and vice-versa. Oxidation and reduction half reactions can be carried out in separate compartments (half-cells) of electrochemical cells, with the electrons flowing through a wire connecting the electrodes and the circuit completed by some arrangement for ion migration between the two compartments, usually an agar bridge. (4).
Analysis of the electrical potential, or voltage, developed by pairing various half-reactions in electrochemical cells, has led to the determination of redox potentials for many common half reactions. Electrochemical cells finally provided some physical reality to the half-reaction concept.

At equilibrium, the redox potential (in reality, reduction potential), E_h, is related to the concentrations of oxidant and reductant by the Nernst-Peters equation,

$$E_h = E_0 + R\,T / n\,F\,.\,ln\,(oxidant / reductant)$$

In this equation, R is the gas constant, T the absolute temperature, and F the Faraday (the charge of a mole of electrons). E_0 is the standard potential of the redox system, measured with respect to a hydrogen electrode immerse in a 1M H^+ solution, pH 0, when the concentrations of oxidant and reductant are equal (1M). Both E_0 and E_h are expressed in volts. (The standard state in biochemistry is referred to a solution of 10^{-7} M H^+, pH 7, and this is denoted by a prime in E_0, E'_0).

The similarity between the Nernst-Peters equation and the familiar Henderson-Hasselbach equation used in acid-base balance is obvious, and there are other analogies between acid-base and redox chemistry. The redox potential, E_h is a measure of the capacity of a chemical system to exchange electrons with its environment, just as the pH of a chemical system, according to Bronsted theory, measures its capacity to exchange protons (or hydrogen ions) with the environment. Lower E_h values imply that the system gives up electrons more readily, as lower pH values imply that the system gives up protons more readily. The

standard potential, E_0 is the analog of the pK_a in acid-base chemistry. It is specific to the particular system.
In a mixture of redox systems at equilibrium, there exists only one E_h, which may be measured from the (oxidant)/(reductant) ratio and E_0 of any of the systems, just as the pH of an equilibrium mixture of various acid-base systems can be obtained from the concentrations of unionized acid and free base in any one acid-base pair, and the pK_a of that system (5).

8.2 Photosynthetic energy transfer

Biological systems are intimately connected with the universe, from where they originated. One area that demonstrates this connectivity quite strikingly is energy metabolism. Essentially, all free energy consumed by biological systems arises from solar energy.

Solar energy is nuclear energy. Nuclear interactions occur only at very high temperatures where atomic nuclei have sufficiently high speeds to overcome their mutual electric repulsion. Nature displays two types of nuclear forces, strong and weak. It is the latter type that is involved in the solar reaction. In the sun's central core and by the action of the weak force, ordinary hydrogen is fused into helium by thermonuclear reactions which generate vast quantities of electromagnetic energy. This energy is radiated into space and only a tiny proportion of it falls on earth with all the light and heat necessary for life.

Life on earth is ultimately sustained by *photosynthesis.* This process occurs in the thylakoid membrane of chloroplasts present in the leaf cells of green plants. Photosynthesis is powered by light and uses water as ultimate donor of electrons for the reduction of CO_2 to yield carbohydrates. It makes use of a process known as excitation-energy transfer. Light photons of given energies are singly absorbed by a photoreceptor protein, chlorophyll, converting it into the "excited state". The process involves conformational motions of the protein occurring in the femtosecond time scale. Excited chlorophyll electrons are then transferred with great efficiency to a distant reaction site where the excitation energy is used to split (oxidize) liquid water molecules in the leaves, according to the net reaction:

$$H_2O - 4e^- \xrightarrow{\text{Light}} O_2 + 4H^+$$

The hydrogen derived from water oxidation (which steps through five increasingly oxidized states) reduces atmospheric CO_2 and in the process the oxygen of water generates O_2, which diffuses into the atmosphere. These gases move along pores present in the leaves. The overall equation can be written as:

$$H_2O + CO_2 \rightarrow (CH_2O) + O_2$$

The electrons with their energy are trapped in CH_2O which represents carbohydrate, primarily sucrose and amylose. The protons are released into the thylakoid lumen to form a proton gradient across the membrane that is subsequently used to drive ATP production (4,6,7). Through the remarkable chemistry of photosynthesis, atmospheric carbon is fixed to the leaf as biomass and solar energy is stored as carbohydrate. All organisms on earth are made up of organic polymers of carbon compounds. Life, as we know it, is carbon-based.

Photosynthesis closely resembles oxidative phosphorylation, to be described later. The principal difference between these energy transduction processes is the source of high-potential electrons. In

oxidative phosphorylation, they come from the oxidation of foodstuffs; in photosynthesis, they are produced by photoexcitation of chlorophyll.

8.3 The metabolic network for energy transformation

Energy flows from sun to earth as heat flows from a hotter to a colder body. Photosynthesis transduces the radiant solar energy into chemical energy. It does so by trapping the electron energy in the C – H bond. Carbohydrates, fats and proteins are then formed – the foodstuffs.

For energy to be used by a living cell, it must be stored in a phosphate bond. To the effect, the foodstuffs are first hydrolyzed in the intestine to amino acids, sugars, and fatty acids, in a series of non-ATP requiring exothermic reactions. These small molecules are then degraded to a few simple units, the most important being the acetyl unit of acetyl CoA, a carrier of activated acyl groups. Acetyl CoA is then metabolized to the electron carriers NADH (reduced nicotinamide adenine dinucleotide) and $FADH_2$ (reduced flavin adenine dinucleotide), which are oxidized by the electron transport chain with generation of ATP (adenosine 5'-triphosphate), a compound with high-energy phosphate bonds. ATP is the carrier of free energy in the body, to be used in energy-requiring reactions (4). Among those reactions are the ones that initiate the metabolic pathways of glycolysis and fatty acid oxidation, which require an input of energy. In other words, to generate ATP we need ATP.

In a broad sense, metabolism refers to the total inflow and outflow of matter and energy and their intermediary transformations. It is carried out by a complex network of cellular constituents and reactions – the metabolic network. Although details of its structural and functional organization are lacking, it is understood to be composed of a series of interconnected metabolic cycles, some with more reactions than others, functioning in a state of dynamic equilibrium. The network is extremely heterogenous but its fundamental design is identical for all living systems (8). The cycling nature adds efficiency to the network.

At the center of the interconnected cycles of energy transfer is the citric acid cycle, also called tricarboxyllic acid cycle or Krebs cycle. It is a highly organized complex with six of its eight enzymes interacting with each other, all known to be bound to the inner surface of the mitochondrial inner membrane (9). The cycle is fuelled by glycolysis and by the catabolism of fatty acids and many amino acids. Its dominant reactions are oxidation-reduction, hydration-dehydration, carboxylation-decarboxylation, and splitting (Fig. 10).

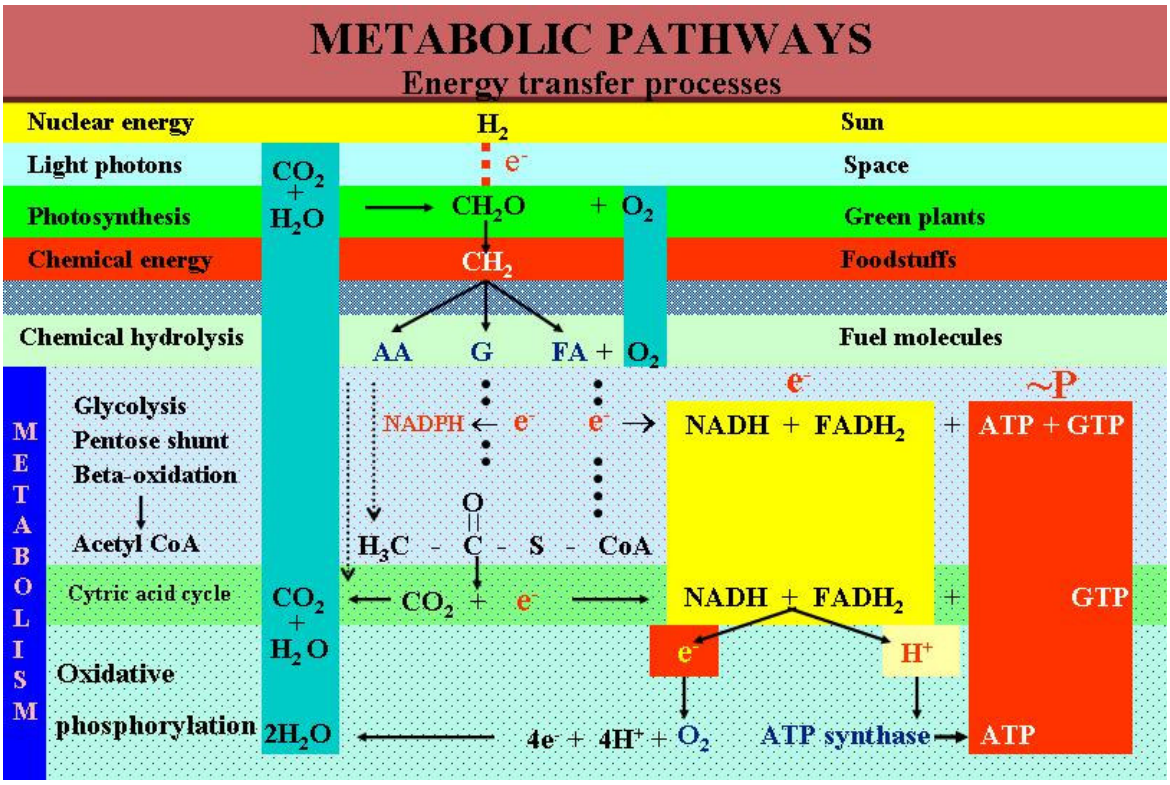

Fig. 10. Simplified overview of the major metabolic cycles for energy transformation. Photonic energy is transduced to chemical energy in the process of photosynthesis and stored in the C-H bond (in the hydrogen's electron). Ingested foodstuffs are first hydrolyzed in the gut to aminoacids (AA), glucose (G) and fatty acids (FA). G and FA, containing most of the C-H bonds, enter their respective metabolic cycles where some energy is freed (ATP, GTP) but most it is transferred to electron acceptors (NADP+, NAD+, FAD) as redox energy. G and FA metabolites, together with some AA, then converge to the mitochondrial citric acid cycle via acetyl CoA, for complete oxidation to CO2, under aerobic conditions. In this cycle, some more energy is freed (GTP) but the bulk of it is transferred to electron acceptors (NAD+, FAD). The electron carrier NADPH (reducing power), formed in the pentose phosphate pathway, stays behind for use in reductive biosynthesis; the electron carriers NADH and FADH2 enter the electron transport chain where, through the process of oxidative phosphorylation, all energy is finally released and momentarily conserved as proton-motive potential difference (osmotic energy) until used in the synthesis of ATP (free energy). Further details in text.

The principal function of the citric acid cycle is to oxidize the two-carbon acetyl group of acetyl CoA. A coenzyme, so called because it functions with enzymes, is a special type of substrate molecule that enables substances, hydrogen for instance, to be exchanged. It is a kind of metabolic shuttle. Acetyl CoA is coenzyme A (A standing for acetylation) with an acetyl unit linked to it by a thioester (C-S) bond. It is the special characteristics of this bond that gives acetyl CoA its high acetyl transfer potential. Acetyl CoA carries an activated acetyl group, just as ATP carries an activated phosphoryl group (4). The balance of the overall reaction of the citric acid cycle is that three molecules of water react with acetyl CoA to form carbon dioxide, CoA and reducing equivalents (hydrogen atoms or electrons). Four pairs of electrons [4 (2H)] are transferred (three to NAD^+ and one to FAD) for each acetyl group that is oxidized. The cycle directly yields one high energy phosphate bond, which becomes incorporated into GTP (guanosine triphosphate). GTP itself can be used as a phosphoryl donor or its high-energy phosphate bond can readily be transferred to ADP to form ATP. Besides providing the ingredients for ATP synthesis, the cycle also provides precursors for the synthesis of carbohydrate, amino acids, purine and pyrimidine nucleotides, and porphyrins (10,11).

Some of the high-potential electrons of fuel molecules must be conserved for biosynthetic purposes rather than transferred to oxygen to generate ATP. The currency of readily available reducing power in cells is NADPH (reduced nicotinamide adenine dinucleotide phosphate). Generated in the pentose phosphate pathway, NADPH serves as an electron donor in reductive biosynthesis, in plasma membrane redox systems and in the electron transport chain of adrenal mitochondria and liver microsomes where cytochrome P450 is the terminal component. The reaction carried out by this chain *is oxidative hydroxylation* rather than oxidative phosphorylation (4).

The adaptation of metabolism to the energy requirements of exercise is achieved mainly by increasing flux rates rather than substrate pools in the energy cycles of skeletal muscle. During moderate to intense exercise, it has been calculated that ATP turnover rate – and hence citric acid cycle flux - increases 60-100-fold whereas pool size increases only 4-fold (8). Only glucose and fats are directly related to metabolic energy. The amino acids derived from ingested proteins function primarily as building blocks for the cell's own proteins and are not a primary source of energy.

8.4 Oxidative phosphorylation and ATP synthesis

Life began without oxygen. Anaerobically, high energy phosphate bonds can only be formed in a metabolism with no net oxidation-reduction, as in the conversion of glucose to lactate. This primitive metabolism requires one NAD^+ which is regenerated later in the pathway, allowing the process to be self-sustaining (4). Anaerobic glycolysis persists to this day in the cytoplasm of every cell in the body. Only later, when photosynthesis had introduced enough oxygen into the atmosphere, did oxidative chemical pathways develop. These are found in mitochondria, which may have invaded the primitive cell as parasitic microorganisms in past eons and stayed there ever since.

Mitochondria came to be the respiratory power plants for ATP generation. A liver cell contains about 1,000 of them. Their inner membrane is a bi-directional energy transducing membrane capable of converting electrical to mechanical to chemical energy or the other way around. The structural elements that enable this process to be carried out are the electron transfer chain and the ATP synthase.

The electron transfer chain comprises four enzyme complexes (I-IV), the last two belonging to the cytochrome system. They are arranged in order of redox potential, from negative to positive, so the electrons can flow smoothly with a steady stepwise release of energy during the transfer process. In these enzyme complexes, the hydrogen atoms of the electron carriers are split into protons and electrons. The electrons are then passed down the chain. The electron-carrying groups are flavins, iron-sulfur clusters (a total of 13 or 14), hemes and copper ions. Sometimes the whole hydrogen atom, not just its electron, is transferred. From the point of view of energy this makes no difference because the energy of the hydrogen atom available to the cell resides in the electron. Protons thus enter or leave the chain as needed. All enzyme complexes, except the less energetic complex II, itself a component of the Krebs cycle, are electron-driven proton pumps. They actively transport protons from the matrix side to the cystosolic side of the inner membrane and in this way a transmembrane proton gradient (proton-motive potential difference) is generated (Fig. 11). The energy is conserved in this gradient until used for the synthesis of ATP (12,13).

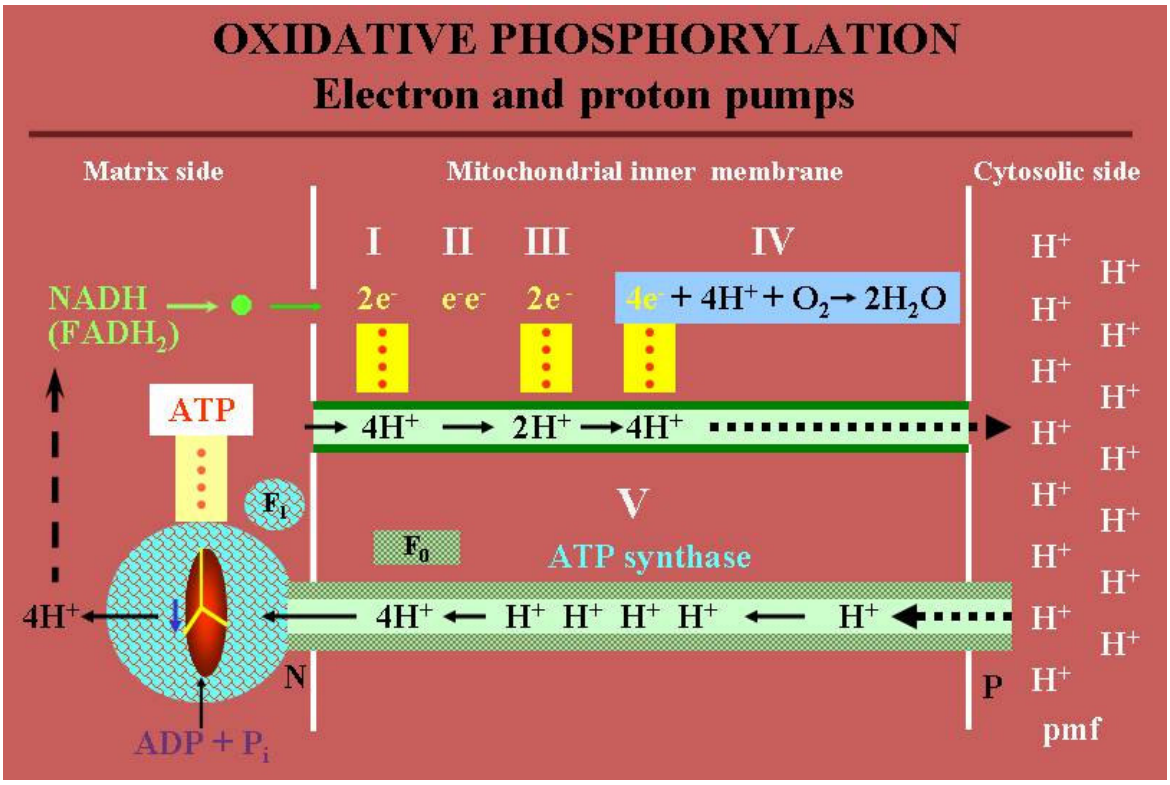

Fig. 11. Schematic view of the process of oxidative phosphorylation emphasizing the dual proton pump concept. All components of the electron transfer chain are transmembrane proteins as it is ATP synthase. High-energy electrons from NADH and FADH2 are transported down the four-component electron transfer system to their final acceptor, oxygen. The energy released as they pass from one carrier molecule to the next is used to pump protons across the inner membrane, from matrix (negative site, N) to intermembraneous space (positive side, P). An electrochemical proton-motive force (pmf) is thus created that is used to release ATP from the F1 motor of ATP-synthase where the counterclockwise rotatory synthesis of ATP from ADP and Pi takes place. The electron transfer system and the ATP synthase can be viewed as two proton pumps, both coupled to the proton-motive force and connected in series by a proton circuit. Further insights in text.

In the overall, the electrons, with their relatively high energy content, flow from the electron carriers NADH and $FADH_2$ and other minor substrates to component IV of the electron transfer chain, the enzyme cytochrome oxidase. Within this enzyme, at a site involving heme a_3 and Cu_B, electrons finally meet their final acceptor, oxygen. The reaction catalyzed by cytochrome oxidase is the four-electron reduction of dioxygen (O_2) to two water molecules (Fig. 11). This reaction is exactly the opposite of the first reaction of photosynthesis. For every turnover of the enzyme, eight protons are taken from the inside aqueous compartment, four protons being used to make two water molecules, and the remainder four protons are pumped to the opposite site of the membrane. This particular reaction couples redox chemistry to proton pumping (14).

The driving force of *oxidative phosphorylation* is the electron-transfer potential difference between NADH (E'_0 = -32 V), the strongest reducing agent, and O_2, the strongest oxidizing agent (E'_0 = + 0.82 V), which is +1.14 volts. This is about ¾ of the voltage obtained from a regular AA size home battery. The total power output generated in the electron transfer process, in a moderately active person, ranges from 68-220 watts, depending on physical activity. It corresponds to the power produced by a 3-10 watt bulb, a miniscule amount of energy by our living standards.

The *ATP synthase,* the other major element of oxidative phosphorylation, has been a special target of research in recent times and much is known about its inner workings. The enzyme is a multisubunit complex with distinct extramembraneous and transmembrane domains, termed F_1 and F_0, respectively. Functionally, these domains are rotary molecular motors, linked by a common drive shaft, the core subunit of F_1 known as gamma subunit. F_1 is driven by ATP and F_0 is driven by the proton-motive potential difference (generally known as proton-motive force) generated in the electron transfer process. Rotational catalysis takes place in F_1 where three nucleotide binding sites act in sequence. The motors are reversible and so, depending on which one is driving, the enzyme can either hydrolyze or synthesize ATP (15) (Fig. 11).

When F_1 is the driver, while one site binds ATP, the other one hydrolyzes it, and the third releases the hydrolysis products, ADP and phosphate. The rotation, therefore, involves three steps of 120^o each (each step is itself accomplished in two substeps of 90^o and 30^o each, approximately (16)). F_1 thus functions as a stepper motor (maximum speed, 130 rev/s) but the stepping mechanism is still unknown. When F_0 is the driver, ATP is synthesized. One catalytic site binds ADP and Pi, the next makes tightly bound ATP and the third releases this ATP (15-18). The proton-motive force is used not to form ATP but to release it from the synthase. How protons move through F_0 is still unclear but the stoichiometry of translocated protons over synthesized ATP is normally 3-4/1, which amounts to 9-12 protons per full turn in F_1. So, if F_0 also functions as a stepper motor, it will be nine or twelve stepped (17). The motor rotation, however, is not simply mechanical. In reality, it is statistical mechanical and this means that the flow of individual protons is indirectly and loosely coupled to the motor rotation. The H^+/ATP stoichiometry, therefore, is not fixed but variable and dependent on the electrochemical potential of the proton and other factors (19).

The ATP synthase and the electron transfer chain work in concert. In their operation, they behave as *proton pumps* that can work in the forward direction as well as backwards. Both pumps are coupled to proton translocation and are linked in series via a proton circuit, akin to the classic electron conducting circuit. They differ in their energy supply: one is propelled by electrons, the other by ATP. Under physiologic conditions, with energy consumption and substrate availability, the electron-propelled pump is the stronger one and forces the ATP-propelled pump to run backwards. To be more precise, the ATP synthase is not pumping but is running as a generator. It is using the proton-motive force, which the flow of electrons is yielding, to produce ATP from ADP and phosphate. When substrate supply is inadequate or oxygen delivery impaired, the electron-propelled pump becomes the weaker and the pumping operation is reversed. It now generates an electrochemical potential at the expense of the hydrolysis of ATP (20). Oxygen consumption and ATP synthesis are thus functionally coupled.

Enzymes, however, do not work in the vacuum. They are immerse in an aqueous medium where the chemical reactions take place. There is evidence that transient changes in water structure, occurring locally in the vicinity of the catalytic sites in F_1, work in concert with the proton motive force to promote the synthesis and release of ATP (21).

8.5 Uncoupling of oxygen consumption from ATP synthesis

The coupling of oxygen consumption to ATP synthesis, or more precisely, of the electron and hydrogen transfer chain to the ATP synthase, is mediated by the translocation of electrons, H^+ and OH^- across the coupling membrane. All these enzymes have a dual action, one of chemical catalysis and the other of osmotic vectorial transport and are thus called *chemiosmotic enzymes.* The process by which a

chemiosmotic enzyme establishes a gradient of a substance across a membrane to be used as source of energy is generally known as *chemiosmosis* (12,22).

For a chemiosmotic process to be effective, it must be tightly coupled. In the case of mitochondria, this means that the inner mitochondrial membrane should be impermeant to protons. It turns out that there is a significant basal proton leak, constantly dissipating the electrochemical proton potential. Its magnitude is too high to be solely explainable by consequences of osmotic exchange through a living membrane. An important consequence of the mitochondrial proton leak is that it allows oxygen consumption to occur without ATP synthesis. The process burns off significant amounts of energy and generates a lot of heat. And here lies one of its functions, that of basal thermogenesis. It accounts for 20% or more of the standard metabolic rate and heat production, most of it from proton leak in skeletal muscle (23).

The mechanism of basal proton conductance does not depend linearly on its driving force (the proton motive force), as described by Ohm's law (24), which suggests that it is subject to regulation. This regulation must be subtle to meet variable and changing requirements of the cell. Long-chain fatty acids are known to be involved and carrier proteins and permeability pores have been described but the overall regulatory process remains obscure.

8.6 Excitation and incomplete reduction of molecular oxygen

In the energy-producing processes of mitochondria, molecular oxygen is completely reduced by four electrons to yield two molecules of water as end products. However, in these and other oxidative processes in the body, partially reduced oxygen species or excited forms of oxygen may be produced.

Molecular oxygen is a very unique compound. Unlike most molecules, the oxygen molecule is a *biradical* in the ground state. It has two unpaired electrons in its molecular orbitals, one in each atom. Luckily, this biradical is not very reactive, otherwise it would spontaneously oxidize the carbon- and hydrogen-rich organic molecules of living organisms. This relative stability of molecular oxygen is due to the parallel spin state of its unpaired electrons, which, in quantum language, is called a *triplet state.* When this kinetic restriction is removed, oxygen becomes activated and oxidation ensues (25-27).

Oxygen activation can be accomplished in one of two ways: by inverting the spin of one of the unpaired electrons or by incomplete reduction. In the first case, an excited species of oxygen with antiparallel spin, known as *singlet,* is formed; in the second case, one-electron stepwise reduction of oxygen gives rise successively to superoxide, hydrogen peroxide, hydroxyl radical and eventually water.

All these forms of oxygen, known as *reactive oxygen species,* are potentially toxic, but the hydroxyl radical is by far the most aggressive of them all. Chemically, it is a water molecule without one hydrogen atom and with a missing electron (and thus, one unpaired electron) on the oxygen atom. When an atom or molecule contains one or more unpaired electrons and is capable of independent existence it is called a *free radical.* The hydroxyl free radical owes its high aggressiveness to the lonely electron which wants to pair with electrons in other molecules. Its lifetime in vivo is vanishingly small because it reacts at the site of formation with whatever it is next to.

In the four electron water reduction by cytochrome oxidase, a number of oxygen intermediates are known to be formed but they are so strongly bonded to the enzyme that are not released into the ambient medium. Even so, about 1.5% of the consumed oxygen is not reduced to water via the cytochrome oxidase but undergoes stepwise single electron reduction caused by *"electron leaks"* in the preceding

parts of the respiratory chain. Most of the active oxygen thus formed is superoxide, which is quickly dismutated to hydrogen peroxide by mitochondrial superoxide dismutase. Hydrogen peroxide is a stable molecule capable of diffusing out through the mitochondrial membrane. However, under normal circumstances, is scavenged by mitochondrial catalase and converted into water (26,28).

8.7 The free energy of ATP and bioenergetics

With the mammalian thermostat set at 37.5^{o} C, there is constant thermal agitation of single molecules (Brownian motion) at microscopic level. This basal level of energy upon which life is built is usually known as *kT* (Boltzmann's constant times absolute temperature), a quantitative approximation of its kinetic energy (3/2 kT).

To separate the energy of a living system from the environmental energy, at least two *energy minima* are required. A living system must possess at all times: (1) a local energy minimum above kT, to provide for physical stability and homeostatic control and (2) a sufficient amount of free energy (free energy state), greater than kT, to maintain local order and to provide energy for chemical reactions. Loss of either of these control conditions will drive the system to the global basal energy minimum (kT) and death will result (29). If the system is irreversible, an additional constraint must be met: a continuous input of free energy to maintain it away from thermodynamic equilibrium.

The supplier of free energy is usually ATP and, therefore, the ATP/ADP system must be coupled to each living system. In this way, whenever there is a change in the balance of a given system, a counter-change of free energy is given to bring the system back to the stable state. This is the reason why ATP has so prominent a role in bioenergetics.

The local energy minimum is a function of the free energy state, which is controlled by the available energy of ATP. In order to keep energy requirements low, there is a relation between the range of kT and the range of the chemical reaction energies, that is to say, between kT and ATP. To illustrate this point, smooth muscle, for which direct measurements have been made, has a free energy of ATP of 2.5 kcal/mol, while kT is approximately 0.6 kcal/mol (29). Our biological chemistry has been adapted to our kT, which dictates the minimal limits of energy required for life processes. This puts limits on the binding energies of molecular complementarity, which should be on the order of or slightly greater than kT and not higher. A binding energy that is too high would be associated with very tight, and thus prolonged, binding and one that is too low, below kT, would lead to quick dissociation of the molecules.

8.8 Kinetics and transduction of free energy

ATP and related phosphoryl compounds are carriers of free energy in the body, the ATP/ADP cycle being the fundamental mode of energy exchange. Biological systems tend to be in a state of lowest possible free energy and so the ATP inventory of the cell is very low (1-3 mM). The amount of ATP in resting skeletal muscle can only sustain contractile activity for less than one second. Even in the heart there is only enough ATP for 1-2 contractions. The ATP synthesized in diastole is used in the next systole. It is the inventory turnover rate (of the order of 100,000 times/day) or ATP flux that is very high. In effect, it is mostly by maximizing metabolic fluxes that the high efficiency of the metabolic machinery is achieved (30).

Since there are physicochemical limitations in the rate of enzyme action, the above tissues possess a local store of readily available energy to be used in conditions of abrupt high demand. The energy

reservoir is of creatine phosphate, also known as *phosphagen.* With a phosphoryl potential higher than ATP, creatine phosphate readily transfer one phosphoryl group to ADP to form ATP. In skeletal muscle, the creatine phosphate store (25 mM) is exhausted in the first 6-7 seconds of extreme exertion, such as the 100 meters sprint (31). By that time, glycolytic and lipolytic ATP energy is already available.

The high phosphoryl potential ("high energy") of phosphate compounds is due to their large free energy of hydrolysis. The "high energy" status comes with two requirements: the phosphate molecule must be easily cleaved and its hydrolytic products must be prevented from binding again. If these requirements are met, at equilibrium of the hydrolytic reaction, there is much higher concentration of products (B, C) than of reactant (A) and the equilibrium constant for the hydrolysis ($k = [B] . [C] / [A]$) is high. The higher is the equilibrium constant, the higher will be the energy of hydrolysis. The ATP/ADP system owes its "high energy" not only to special intramolecular characteristics (less resonance forms and therefore less stability in ATP than in ADP or P_i) but and foremost to its reactivity with solvent water. The solvation shell around ADP and P_i is much thicker than that around ATP and, therefore, ADP and P_i are much more stable in solution than ATP (32).

The hydrolysis of ATP is catalyzed by enzymes capable of *energy transduction.* These enzymes use the chemical energy derived from the cleavage of ATP to perform mechanical work, to build up ionic gradients across membranes or to promote the synthesis of new molecules. The process of energy transduction is complex and still obscure but seems to involve the following steps: (1) loose coupling of ATP to enzyme, (2) energy transfer from ATP to enzyme, (3) hydrolysis of ATP and (4) release of hydrolysis products. The energy is used to change the enzyme conformation, and in the transition state chemical or mechanical work is performed.

As in the synthesis of ATP, water around the catalytic site of the enzyme appears to play an active role in the process of energy transduction. It changes its density (structure) twice, before and after the change in enzyme conformation, presumably to prevent and then favor ATP hydrolysis (32). It may even play a direct role in actual energy transfer but this has not been clarified. Although these events are of extreme importance, their flickering nature has so far prevented their proper study.

8.9 Nature and organization of metabolism

The metabolism of oxidative phosphorylation is electrochemical in nature. The charges of hydrogen ions are separated into two currents, one of electrons (electricity) and another of protons (proticity) by the action of chemiosmotic enzymes. To effect charge separation, the enzymes must be bound to a surface, in this case the inner surface of the mitochondrial inner membrane, and organized in a specific order which allows sequential reactions to occur. This kind of metabolism with a built-in directionality is called *vectorial.* It is now believed that vectorial metabolism occurs throughout the cell.

Redox enzymes are present in almost all major membranes of the cell and therefore electrochemistry is widespread. In addition, ion-transporting enzymes are bound to most membranes and ionic currents (ionicity) are going on incessantly across membranes. All currents of charge generate and are influenced by vectorial electric fields. The electric field across membranes is extremely large, not because of the magnitude of the potential difference, which is about 50-100 mV, but because the thickness of membranes is quite small. The closer together the charges are, the greater the attraction force between them. So, a potential difference of 70 mV across a cell membrane of 5 nm thickness generates a field of 140,000 volts/cm. The potential across a membrane may in fact reflect the existence of numerous localized regions of charge separation in it. Thus, a number of separate fields may exist within a single

membrane, extending into adjacent cytoplasmic areas. It can be anticipated that they will affect the vectorial movement of charge within their domains. The formation and maintenance of electric fields appears to be a general feature of cellular membrane function (2).

There is now compelling evidence that fields and vectorial metabolism also occur in the interior of the cell. The surfaces required for the organization of such a metabolism are supplied by the cytoskeletal structures and the microtrabecular lattice. These proteinaceous structures are made of dipoles and charged groups which interact strongly with the dipoles of water to produce localized electric fields. In the new concept of metabolism, the enzymes, perhaps in the form of protein-water clusters, are adsorbed onto the surface of the cytoskeletal filaments in a way that the product of a given reaction is "handed off" to the next enzyme in the pathway without release to the aqueous medium. A chemical vector is thus established which is characteristic of chemical reactions based on molecular complementarity (29).

In the electrochemical interpretation of metabolism, a substantial part of the free energy arising from the cleavage of ATP is associated with the liberation of a proton:

$$ATP^{4-} + H_2O \leftrightarrow ADP^{3-} + P_i^{2-} + H^+$$

The field generated by this proton current, which is vectorial, could influence the equilibrium of the associated chemical reaction (2).
In addition to the link between electrical and chemical events, the close physical association of enzymes with the prestressed structures of the cytoskeleton, which are known to be signaling pathways, raises the possibility of a purposeful *mechanochemical metabolism.* Indeed, a dynamical interplay between cytoskeletal geometry and the kinetics of biochemical reactions, including gene activation, is thought to occur (33). Calculations show that the energy liberated by contraction of an actin filament is higher than that of kT. It is possible, therefore, that mechanical energy is involved in enzyme activation, or more specifically, in the triggering of the *transition state,* which in the old biochemistry was attributed to kT energy (34).

We have a new kind of metabolism, still awaiting study, where chemical, mechanical and electrical energies are interlinked, all working towards an integrated function. The old biochemical concept of diffusion of chemical species, random collisions of enzymes with substrates in solution and scalar chemical reactions is no longer accepted. The metabolic charts on the walls of biochemistry laboratories need to be revised with new data obtained, not by studying isolated enzymes in solution, but by studying them in their interactive milieu where reaction rates and even pathways may be quite different. This may prove to be a daunting task.

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9

PHYSICAL STRUCTURE, TENDENCY TO SYMMETRY AND THE UNIVERSAL UNITY OF NATURE

The unity of nature lies in the operation of one general law of change, while the differences of particular systems lie in their individual structures
Lancelot L. Whyte

We live in a universe of structure and form. Forms appear, transform and disappear in accordance with still unknown laws. Similarly, living systems are continually changing their complex structure. All their molecules, and virtually all cells, are continually being transformed in a cycle of life and death, which goes on from the moment of conception until the death of the organism as a whole (1). Present physical theories cannot account for the changes continually occurring in organic structure.

The ideal theory should be applicable to all systems, physical and biological, be simple and capable of explaining all existent theories. A gigantic step in that direction was taken more than half a century ago but the concept has not received the wide exposure and attention it undoubtedly deserves. One of the reasons for this may be that the physical foundations of the concept differ from those of accepted physics, yet its assumptions are simpler and therefore with more generality.

The basic idea is hundreds of years old but it was Lancelot Whyte that, in the middle part of last century, brought it to light, dissected its physical roots and envisioned how far its ramifications could reach. In simple terms, the concept is based on properties of matter rather than on energy. Specifically, it rests on the axiom that there is an inherent tendency in fundamental micro-structures towards three-dimensional symmetry or minimal asymmetry. Saying it another way, there is a fundamentally irreversible tendency for asymmetry to decrease in isolable processes and it is this one-way principle that accounts for the changing of structure and ultimate stability of regular form. Whyte called it *"unitary principle"* (2).

The unitary principle has two aspects: a spatial (asymmetric relations) and a temporal (persistent tendency). The temporal process modifies and extends the concept of entropy. In effect, the principle is more powerful than thermodynamics, quantum mechanics and complementary theory. It is a proposed law of nature which is still waiting for mathematical expression and validation. However, recent experiments at quantum level of observation appear to confirm its predictions.

As it stands, the unitary principle is nonquantitative and is considered just a blueprint for a future exact theory of science. The latter requires a change in present atomic theory, in terms defined by Whyte himself (3). In what follows, we will attempt to introduce the theory and present a very simplified view of some of its aspects, particularly in regards to the development of form and order, and to reconcile its energy conception with that of classic theories.

9.1 Structure, dimensionless physics and one-way processes

Structure is the only physical entity we can observe and mathematically express. We can conceive of it as a complex of relations taking place in the four dimensions. To represent these space-time relations, non-unitary theories, which are based on dimensional laws, require four-coordinate metric frames and external measurements. These requirements put limits on the scope and accuracy of these theories. The high complexity of the hierarchically ordered structure of living systems further complicates the problem making dimensional theories unable to provide insight into biological systems in incessant change. What Whyte has proposed is a theory devoid of dimensions of length, time and mass (so-called "dimensionless") and directly based on the changing asymmetrical relations of structure. The theory is logically simpler and more general, and can be more powerful than any dimensional theory, known or ever conceived (2-4).

The theory is simpler than previous theories because it does not require the device of a metrical frame, the measurements and their interactions being incorporated into the system. It is more general since it assumes only the fact of a widespread tendency (one-way process) toward equilibrium. It also makes use of asymmetrical relations, which are more general than the symmetrical relations of reversible physics. A relation is said to be asymmetric if it is incompatible with its converse and symmetrical if it implies its converse. The asymmetrical relation $A \neq B$ comprises the special case of the symmetrical relation $A = B$, when the difference between A and B becomes nil. Thus, one-way physics, based on asymmetrical relations, is more general than, and can contain as a special branch, reversible physics (2).

Whyte's theory expresses the changing asymmetrical relations in structure by a dimensionless number. It is known that certain types of dimensionless expressions, such as ratios of lengths, ratios of trigonometric functions or even angles, can be physically more powerful than, and cannot be represented by, any dimensional expression. We have seen (chapter 3.1) that to define the position and orientation of the atoms of hydrogen in relation to that of oxygen in the water molecule the angle of 104.5^{o} was used. Constant angles and not linear relations better determine the stable structure of matter and, since they are expressed in degrees or radians, they can be used advantageously in dimensionless theory (2-4).

9.2 The unitary principle and biological systems

The theoretical foundations of the unitary principle rest on the principles of causality and symmetry. The principle of causality – *every effect must have a cause* – is used as a rule for selecting isolable (on the way to becoming isolated) processes. A process is isolable if it displays causal continuity, that is, if does not contain arbitrary features.

Unitary theory is based on the inequality of cause and effect relationship. In a one-way isolable process with these characteristics, the symmetry principle dictates that causal continuity be traceable from earlier to later stages and not necessarily the other way round. Expressed in more general terms, in isolable processes earlier distinctions can disappear but new distinctions cannot arise.

The unitary principle, as science of decreasing asymmetry, can thus be stated: *symmetry is preserved and can increase, but asymmetry can only decrease, in isolable processes.* By asymmetry it is meant an observable deviation from some type of tri-dimensional spatial symmetry. It follows that if an existent specific symmetry disappears or a characteristic asymmetry does not wholly disappear in the course of any process, the process is not isolable and must be treated as a component of a more extensive process. There is, thus, a meaningful order underlying change in a unitary process.

Viewing these causal relations other way, isolable processes (or systems) will tend to perfect their symmetry and non-isolable processes to adjust their symmetry to conform to the average level of asymmetry of their environment. Biological systems are too complex and too intermingled functionally with their environment. This makes them unable to achieve complete isolation. Under these conditions, and in a universe in constant change, biological systems have a tendency for local symmetry and a tendency towards extended uniformity of asymmetry. These two tendencies are often in fluctuating balance (2).

9.3 The central role of protein dynamics in unitary theory

Organisms combine in a unique manner the properties of stability and instability. They are due to special characteristics of the structure of proteins which is intimately linked to that of water. This remarkable combination of properties receives an immediate interpretation in unitary theory where stability implies symmetry and instability asymmetry.

Protein stability is due to tendency to form symmetrical patterns from a basic main polypeptide chain. In complex proteins, stability is reinforced by hydrogen bonding and other linkages to neighboring complementary structures. Protein instability, on the other hand, is due to tendency to undergo characteristic structural transformations (fluctuations) following a slight stimulus. It arises from the activity of asymmetrical (polar or polarizable) side and end groups, containing charges and electric dipoles as described in chapter 6.4. These protein dipoles interact coherently with the electric dipoles of adjacent water molecules. But with some simplification we can just say that it is the protein framework, in interaction with its changing environment, that determines the normal state of polarization in any region, and therefore the normal orientation of all polarized constituents. Protein, thus, constitutes the basis of the *functional pattern* of an organism (2).

9.4 The unitary field and the energy states of life

Physical reality is just one but different theories interpret it in different ways. This is the case of the *field* which by classical theories is a function of space and time coordinates but by unitary theory becomes a function of the polarizable structures of systems. As a result, while the classic field produces changes in momentum in inertial entities, the unitary field describes changes of shape, orientation and position in the structure of proteins. The unitary field is unique on two accounts: (i) it is linked to structure and so it is a structured field, and (ii) its operation tends to bring all component parts of a system into conformity with the resultant polarization of the whole (2). Before we consider in more detail the unitary field in full operation, it is instructive to have an insight into the energy states of a biosystem. These are schematically represented in Fig.12 which integrates the dynamics of all proteins.

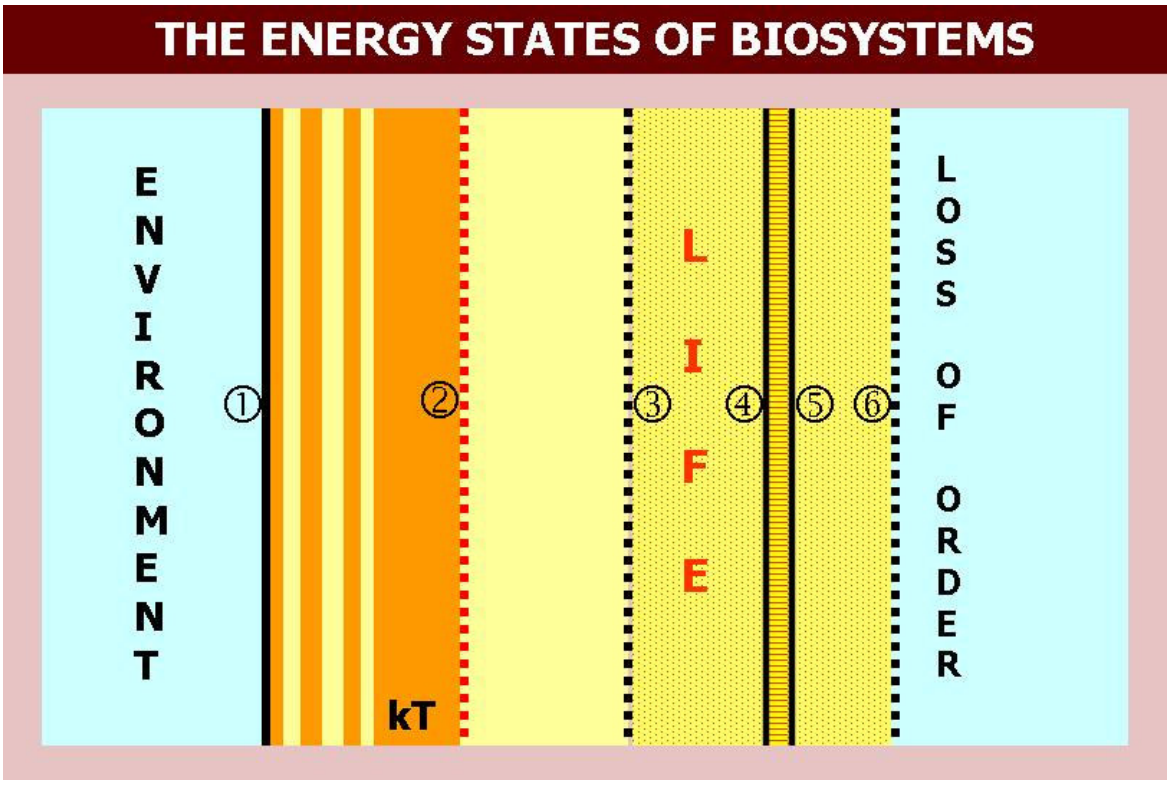

Fig.12. Perspective representation of the coherent energy states of a functioning biosystem. The states are indicated by numbers close to their boundaries: 1 – physical ground state or vacuum (unchangeable); 2 – thermodynamic equilibrium state; 3 – living ground state (vacuum of the organism); 4 – the more symmetric state of the net oscillation of protein dipoles (normal stable state); 5 – the sensitive metastable state of the net oscillation of protein dipoles (normal state); 6 – critical unstable state.

Functionally, a protein structure of certain complexity manifests two characteristic states, separated by a relatively low threshold. Under normal conditions, that is, in the undisturbed state, the protein molecule is maintained in its higher metastable state (state 5 in the diagram) by the resultant field of the region. This is the *normal state*, a compromised polarization state at which differences of polarization among all components of a system are at a minimum. Following a slight stimulus, of external or internal origin, depolarization occurs as the molecule tends to move into a more symmetrical and *stable state* (state 4).

Protein molecules are thus in perpetual oscillation (fluctuation) from a less stable to a more stable state and back and this occurs at every level of organization, in small and large systems and in the organism as a whole. These protein fluctuations can only occur within a certain energy range where depolarizations are possible. When maximal structural symmetry is achieved (state 3) or critical structural instability is reached (state 6) no energy can be stored in the structure and no depolarization takes place. These energy states are difficult to define but they represent the range of life.

Proteins do not work in a dry environment. They are embedded in an aqueous medium maintained at a certain temperature – the thermodynamic heat bath. Without its stimulating influence life would not be possible. In terms of energy, however, there is a buffer zone between the thermodynamic equilibrium state (state 2) and the minimum energy state compatible with life (state 3).

9.5 The functional cycle of one-way processes and the relation of parts to whole

In dynamical theories, all processes are viewed as relative motions of ultimate particles and changes in these motions are ascribed to interactions between pairs of particles. Unitary theory pictures processes differently. Instead of constant particles, a complex system is viewed as made up of single structural units, each with its tendency to symmetry. These ultimate units are arranged in hierarchies of sub-systems within complex systems. So, the relation of static parts to one another is broadened in unitary theory to the relation of the process of the whole to the processes of its component units (2).

An individual protein (and other cooperating molecules) is constantly undergoing closed transformation cycles which involve both a change in net polarization and a change in shape of the protein structure or, more specifically, of its structural component units. When polarization occurs, an energy-requiring deformation takes place in the structure of each unit leading to the transition of the protein from the *stable* to the more energetic but sensitive metastable state. This structural distortion (expressed in theory by a dimensionless ratio) is held by a narrow threshold. When depolarization occurs, this threshold is overcome and the structural deformation is now free to continually decrease until full relaxation is reached at the normal stable state (inner tendency towards symmetry).

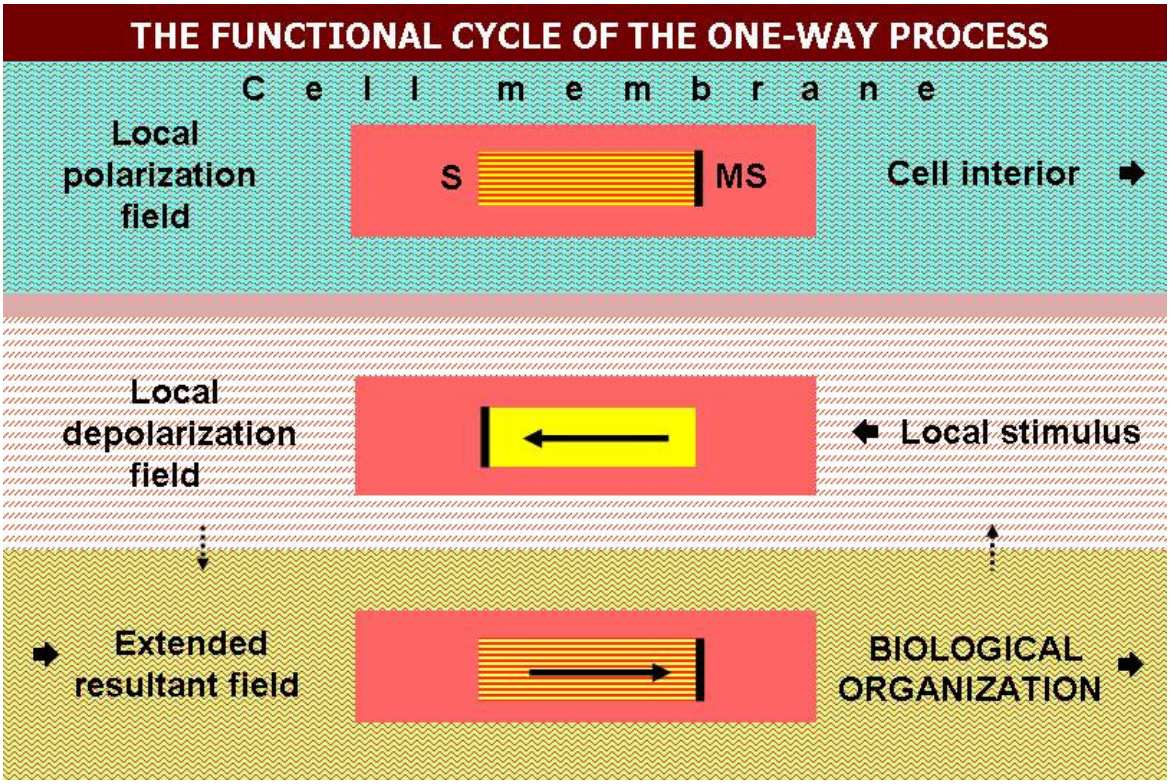

Fig. 13. Schematic view of the cycle of changes occurring in a cell membrane-associated protein following a disturbing stimulus. The upper part of the figure represents a protein will all its structural units in the normal metastable state (MS). A local polarization field surrounds the protein. The lower part of the figure depicts the two phases of the cycle of changing structural asymmetry, each phase having a one-way directed character. A local stimulus brings the system over its functional threshold, triggering electric depolarization and releasing structural asymmetry. The system is brought to the normal stable state (S) by its inner tendency towards symmetry. The local depolarization field spreads towards the membrane and triggers an outer extended resultant field which brings energy and inductive influences from neighboring molecules and local environment. This resultant field (outer tendency towards asymmetry) restores protein polarization and asymmetry and tends to

establish uniformity of polarization in the region. On its propagation to the cell interior, it organizes structure and induces order (further explanation in text).

Each transformation cycle has therefore two phases, schematically represented in Fig. 13, which are induced by one-way pulses of depolarization or repolarization. The depolarization or relaxation pulse is a wave of disturbance triggered by an exciting stimulus which could be a small change in a local variable (thermal, chemical, mechanical or electromagnetic), perhaps initiated by the functional activity of a neighboring system. In contrast to this, the repolarization pulse is a wave of normalization resulting from a regional aggregate of protein structure (functional system). This normal resultant field is itself a component of an organism-wide continuous normalizing process, the unitary counterpart of the endogenous coherent electromagnetic field. Free energy from local respiratory systems (the source of polarization) and information from regional proteins (ultimately from the hereditary units) and from environment are inducted into the normal resultant field which restores protein polarization and asymmetry and tends to achieve uniformity of polarization in the region (2).

Thus, inner structural processes decrease and outer field processes increase asymmetry in local structures. With rare exceptions (p.e., oscillations of an enzyme system), the rhythm of this cycle is not precisely regular. In general, the completion of the cycle does not bring the system back to the same energetic state, even in the adult organism. The normal state is not a static condition but a pattern of processes, each one with its own rhythm. And the latter varies according to the environmental situation, that is, with season, hour, current activity, etc.

The relation of any organic system to its component parts is determined by the states of polarization of the system and of the parts. The details of intraprotein dynamics are still not known but the cycles of depolarization-polarization take place on the time scale of tens of femtoseconds (5). Under normal conditions of operation, only a small number of parts are depolarized and the system as a whole tends to normalize itself. In this normalizing process the parts appear to “cooperate’ with the whole.

But besides the depolarization-repolarization cycles, which leave no net change, the process of structural deformation and relaxation is associated with an all-important one-way organic transformation – the extension or multiplication of organic parts. It is this formative (or *morphic* (6)) process that is unique to unitary theory. The two functional aspects, cyclic and progressive, are interdependent and always present. As a result, it is not possible to describe organic phenomena in terms just of cycles alone or one-way transformation alone.

9.6 The process of formation and the concept of structural order

Structure is *spatial form* and stabilized structure is the final result of a continuous process going from simpler to more and more complex form. So, the process of formation, the stabilized structure and the cycles of function are three inseparable components of a single comprehensive process – the unitary process.

Every system displays a morphic tendency, which is realized if it is consistent with the tendencies of all the larger systems of which it is a part. This universal tendency is for asymmetrical (or less symmetrical) forms to become more symmetrical. It is, therefore, the fundamental factor underlying all development and maintenance of structural patterns. Functionally, patterns (ordered arrangements) are more important than their individual component units because it is their configuration that most often

determines the properties of complex structure. Tendency to symmetry is the basis of all biological organization (2).

More symmetrical structures are more stable and durable than less symmetrical ones. As a consequence, their pattern tends to dominate and to extend itself at the expense of that of their less symmetrical counterparts. *Dominance* is control and control implies one-way causal influence. The latter must then be exerted by the more on the less stable and, similarly, by the whole on its constituent parts.

Besides dominance, another asymmetrical relation contributes to the stability of organic form. It is that of *facilitation*, a property of certain types of protein molecules (genes, autocatalytic enzymes) to self-duplicate by repetition of the process by which they were formed. Facilitation underlies all development and extension of form and is of fundamental importance to the development of order (2).

Normalizing processes are intrinsically self-facilitating. When a wave of normalization passes through any partly disordered system of polarizable molecules it tends to adjust their positions and orientations in order for them to become more symmetrically and regularly arranged. This ordering tendency is not due to any special long-range force but to the energy quanta of the repolarizing field. A similar concept of structural order is held by quantum field theory, a derivation of unitary field theory to be described in the next chapter.

9.7 The unitary interpretation of energy and entropy

The unitary principle of Whyte is built on a solid scientific foundation. An eminent unitary theorist that recognized this fact was Leo Baranski who approached the same principle by way of energy concepts and, in the process, clarified and extended the unitary structured field conceived by Whyte (8).

Energy as an entity separated from a structure does not exist. In the unitary concept, energy becomes *structural asymmetry*. Whenever energy is manifest there is a structure in the process of change from asymmetry to symmetry. The unitary field, therefore, is conceived to be composed of three-dimensional free-energy field structures whose asymmetry is the basis of all energy of all systems (7). This conception of field is deeper than that of quantum theory and statistical thermodynamics which rests on the random motions of atoms and molecules.

The division of energy into field energy and system energy is therefore no longer valid. Consequently, the thermodynamic property of “internal energy” of a system does not exist as a separate entity. The potential energy of a system is ultimately traceable to the field asymmetry inducted into the system and the kinetic energy is the system in process.
Free energy and entropy are just two different aspects of the same process – the decrease in structural asymmetry, in isolable processes. Baranski relates the property of free energy to the change in structural configuration of the system and that of entropy to the conversion of structural field asymmetry to symmetry.

In unitary theory it is structure and structural changes that are fundamental. Energy is not a conserved quantity. What is conserved is structural symmetry. There is also no tendency towards entropy and disorder. There is only the unitary field displaying its tendency towards uniformity of asymmetry and increasing order (7).

9.8 Matter, energy and atomic microstructure

Under enough magnification, every object seems to have some hidden structure. As the magnification level increases, a deeper level of structure with its own characteristic pattern is revealed. Proteins resolve into molecules, molecules into atoms, and atoms into electrons and quarks. According to unitary theory, as the ultimate molecular and atomic levels are approached, the pattern of organization should become more exactly geometrical (8).

These theoretical predictions have been confirmed by James Watson, at the Cellular Dimorphism Institute (CDI), Los Angeles, California. This investigator has built a powerful and sound imaging technology which has pushed the frontier of biology beyond the atomic level. The cellular microstructure of our time, the magnificent end product of a continuous process of development over more than a thousand million years, can finally be seen clearly, in real space-real time multicolored photographs (9). At this quantum level of observation, the texture of the different structural patterns is easily appreciated, the ultimate structure of native enzymes is revealed, new patterns in the process of formation can be seen (Fig 14), and even molecular crystals have been caught in the marvelous act of self-duplication (Fig 15). All this is proceeding with an impressive degree of order. Unitary theory, thus, appears to describe reality quite closely.

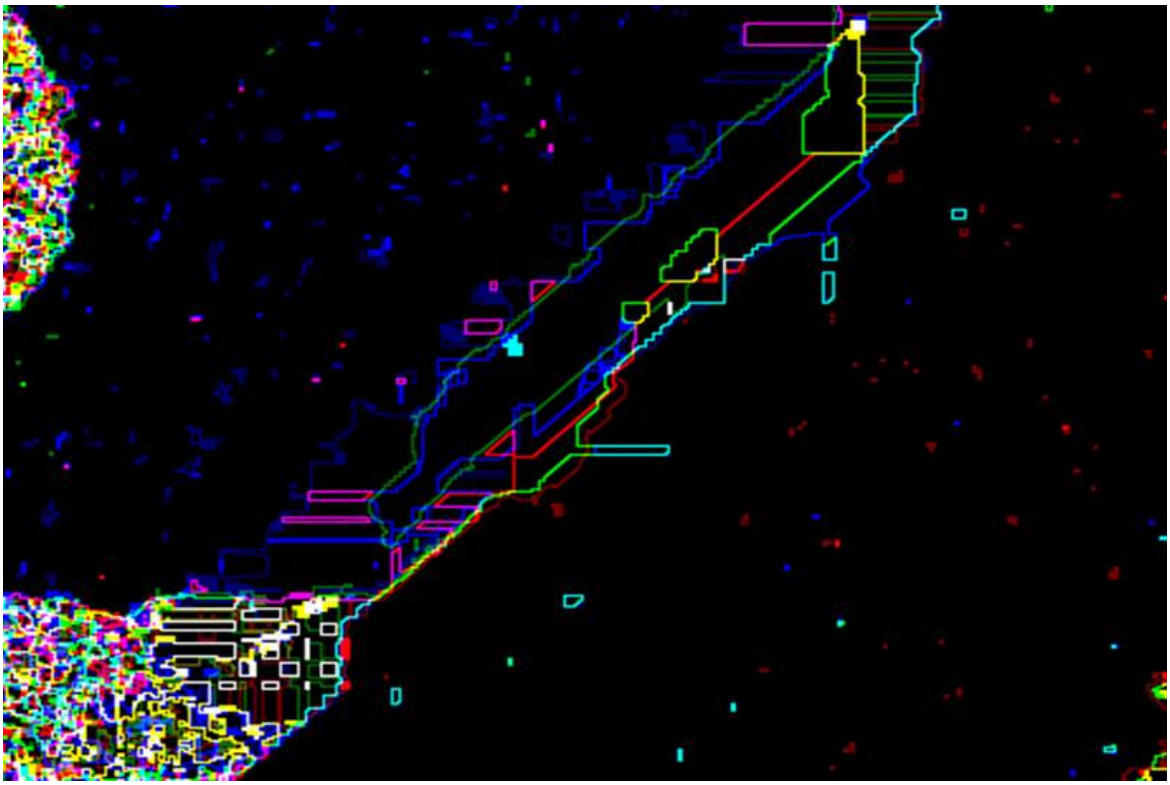

Fig. 14. The process of synthesis - transformation of energy into biomatter, presumably carried out under the influence of space-controlled resultant polarization pulses. The photograph above, courtesy of Dr. James Watson, was obtained by CDI technology, at 1700×38 to the minus 10th power of magnification. It shows a quantum bridge being constructed which appears to serve as scaffold for extension of existent structure. A primary vector axis is evident which, according to unitary theory, coincides with the direction of propagation of polarization and transport of materials. The polarized parts, each with its own element of asymmetry, are mutually oriented, aligned, brought closer and finally assembled into a more symmetric whole.
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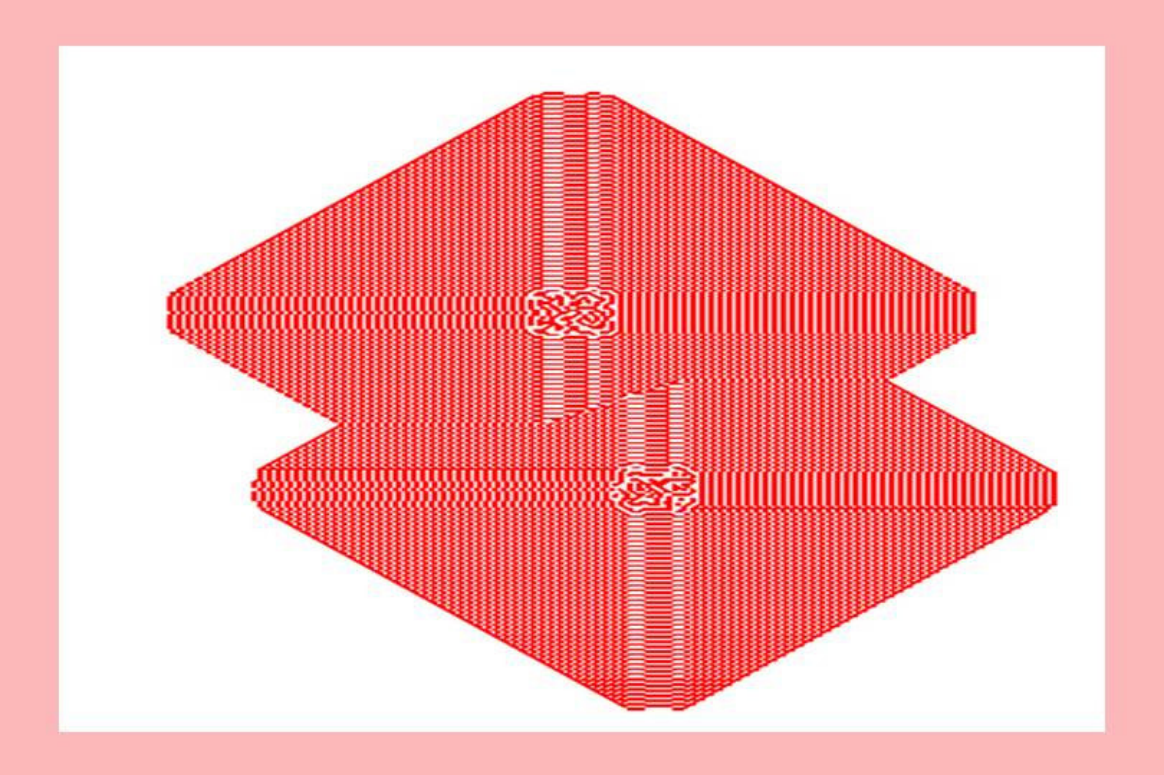

Fig. 15. The morphic process of autocatalysis. This photograph, as the previous one, was taken by Dr. James Watson at CDI. It shows two self-constructing pyramidal crystals (tensegrity structures – see chapter 4.2) slowly separating out of, or morphing into, each other. Their structural pattern is identical. According to unitary theory, this pattern has been brought to their characteristic symmetrical form. It is stable and therefore displays no inner tendency towards further change.
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In the saying of Watson, the photographs and electronic data clearly show "the never ending birth, growth, and death cycle being played out by wave-particle energy as it converts energy into matter, in essence, reversing $E = mc^2$" (9,10). The CDI evidence conclusively shows the electromagnetic nature of life.

The technology is an open window to the quantum world of living structure, but its application to other fields surely lies ahead. So far, it is showing a new kind of science, where physics meets biology and where environment and life, through matter-energy, are in constant transformation to mutually adjust their respective structures. It is this natural process, revealed to us by changing forms, that unitary theory tries to understand and describe.

9.9 The unity of nature

As clearly stated by Baranski, the essential idea of Whyte's unitary theory is that one structured field underlies, and comprises, the whole universe. The field operates on one single process – the unitary formative process. Both the inorganic and organic realms illustrate the properties of this universal process but in systems of different orders of complexity.

The unitary process applies directly to ultimate structure. Macroscopic phenomena represent the indirect results of its operation. Matter, energy, life and mind are names that man has given to different aspects of this universal process (2,7).

Our organism and environment (local space) form just one single system which is influenced by the rest of the universe, most particularly by the dynamics of sun and earth. The rhythms of night and day, sleep and wake, left handedness and right-handedness and many other phenomena evident in living systems are all manifestations of the interdependence of life and nature.

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10

LIFE AND SPACE ENERGY

Space can be thought of as making as important a contribution to chemical and biochemical reactions as do the reactants themselves
Bevan L. Reid

Space and biomatter are intimately interlinked, structurally and functionally. Matter and energy are exchanged at their interface. Classical thermodynamics recognizes this fact but space energy has characteristics different from the heat-type energy of thermodynamics. Heat energy, as well as sound and light energy, is readily appreciated by one of the senses. It is real. On the contrary, space energy, at similar frequencies, escapes sensory detection. For this reason, this form of energy is known as virtual, imaginary or intangible.

In spite of these qualities, or because of them, virtual energy is believed to have a central role in the structuring of living systems and in the control of the chemical reactions that sustain life. Indeed, we have already found concealed effects of virtual energy in the biological actions of ELF electric fields and in the chemical oscillations of dissipative structures. Life would not be possible without the organizing guidance of space, that is to say, of the universe.

Space energy is a conceptual product of the mathematical formalisms of quantum mechanics and our knowledge of the function of this energy in living processes derives mostly from the interpretations of the quantum equations by theoretical physicists. Some experimental work does exist, particularly that of Bevan Reid and co-workers (1), but the subject matter, although no longer mystical, remains largely speculative. Nevertheless, its inclusion in this book, whose central theme is energy, appears to us justified.

For the sake of clarity, only a simplified version of physical concepts can be given. The discussion, based for the most part on Reid's ideas, will be limited and directed toward the understanding of space-induced metabolic control and molecular structuring.

10.1 A working model for the photon

As carrier of the electromagnetic field, the *photon* is understood as a linear, transversal sine wave of infinite dimensions. This classical wave model of mathematics and physics is appropriate for field propagation but it does not fit well with the concept of wave-particle duality. Reid as used a more mechanical model of the photon, that of de Broglie, to base his hypothesis of space-matter interactions (2). This working photon is a discontinuous structure, a composite of mutually interactive real and virtual waves of finite dimensions. The exterior waves, the envelope, are classical, two-dimensional sine waves of real energy; the interior waves, the core, are non-linear longitudinal waves of virtual energy. It is as if a real electromagnetic wave envelops and transports a miniscule package of space energy. It is

this package of virtual energy that supposedly does the active biological work, be it electron or ion transport, cell component motility or metabolic work.

The core waves are sensitive to any phase perturbation encountered by their envelope in its flight, which could send them into rapid interaction which de Broglie likened to Brownian motion. Being of longitudinal type, the envelope-free virtual waves need only one dimension to travel, or to put it differently, they have a trajectory of a bullet. So, they can cross hollow cylindrical structures, such as membrane pores and enter into the DNA axis without being destroyed.

According to Reid, living matter was specially designed to interfere with incident photons. Transmembrane proteins are seen as traps for the electromagnetic envelope, allowing virtual energy to be released and delivered into the cell (2).

10.2 Space energy and the creation of matter

Space is all pervasive. It exists inside and outside matter. The space-matter interface, at atomic level, is an inextricable, almost unscrutable frontier, out of reach from our observable world. So, any hopes of increasing our understanding of biomatter-space interactions must reside on knowledge of the structure and function of space. Since space cannot be scrutinized directly by any known or conceivable means of observation, our knowledge of it can only be hinted indirectly, mainly by mathematical means.

Most of our knowledge of space structure comes from the theories of quantum field and quantum electrodynamics. The unique structured space (field) of unitary theory described in chapter 9 is purely conceptual.
According to quantum ideas, there is no matter in the vacuum, just energy in the form of a quantum potential, a sort of force of potentiality. By some unclear reason, this background energy is not perceived by any of the five senses. Cosmologists call it “dark energy” because it does not absorb or emit light (3). It is still present at zero absolute temperature and is therefore also known as “zero-point energy”. Associated with this type of energy, there is an electromagnetic field and a tiny force known as *Casimir force.*

In the undisturbed state, the energy sea of the vacuum may be thought of as an infinite symmetric array of intermingled tiny tornados, called *vortices,* spinning around randomly and incessantly. As they intermingle by coalescence, they provide for hybridization of each one’s information. The vortex is the basic structure of space. It constitutes a gradient of energy, formed from a multitude of energy levels or waves of increasing frequency, from zero at apex to maximum at base.

In the mathematical formulations, transmission in the energy field of the vacuum requires no energy and no time. On contact with highly ordered biomatter, particularly of polymer-type, or with an electromagnetic field, the symmetry of space is broken. When symmetry is broken a fluctuation of the vacuum in the form of an infinitely long filament instantaneously occurs. The filament, made of a collection of coherent vortices, corresponds to a virtual massless particle, called *boson* (a virtual photon). The boson contains information derived both from the originating matter and from that previously stored in the energy of the vacuum. According to circumstances, this extremely unstable virtual particle (or wave) can either revert into the energy sea or, alternatively, it can increase its coherence, acquire mass and become a real filament containing matter in the form of electrons. Finally, this real filament breaks down in the non-observable world and becomes manifest in the real world as nascent matter. A biologist might say that growth has occurred because the particles begin to attract other matter to the site.

According to theory, the cytoskeletal filamentous structures of the cell, where most of metabolism is now thought to occur, have their origins in local space (4,5).

If the abstract world of mathematics corresponds to the real world of physics, matter can be created from the "energy" construct of space. Life, directly or indirectly, would be under space control and ultimately under the control of the forces of nature. This is a profound and powerful concept, one that goes beyond physics proper.

10.3 Virtual flow-biomatter interactions

According to theory, biomatter is itself inert. The valency electrons of atomic orbitals are moved by space energy in the form of continuous fluctuations. Reid visualizes fluctuations as energy loops propelled from space which interact with matter before their eventual return to space (6).

Being of quantal nature, space energy must be associated with some waveform. This waveform loses its symmetry (symmetry breaking) upon exiting from space, in response to the real gravitational and electromagnetic influences. Upon collision with matter, fractions of the original space waves and of their intrinsic spin are produced and it is these wave patterns that ultimately activate valency orbitals. To complete the cycle, these wave patterns must then return to the same space. This step involves complex restorative arrangements of the wave, to fit the symmetry requirements of space, a process known as *resonance* (6).

Although theoretically connected to light photons, quantum flows in biosystems carry waves (bosons) of longer wavelengths. These flows are formed on contact with matter in the form of repeat arrangement of its constituents, as occurs in the polymer state, and so the wavelengths of their components are greater than atomic and molecular dimensions. Most of the virtual flow is made up of millimeter and micrometer waves belonging to the acoustic range of the classic electromagnetic spectrum (Fig. 12). Their properties of control over atomic and molecular systems derive from this wavelength advantage. As in the case of the photon, this virtual flow is enveloped by magnetic fields and by heat, the act of envelopment being considered as the conversion into real flow.

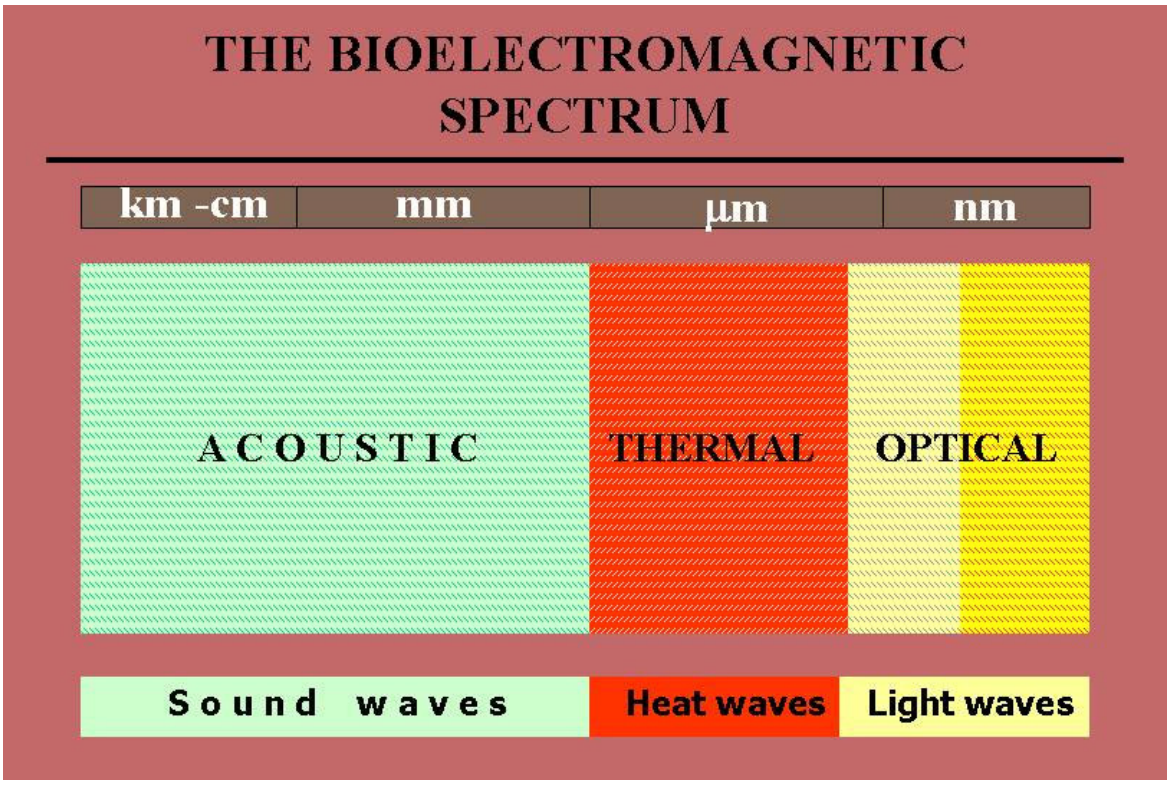

Fig. 16. Unconventional schematic perspective of that part of the electromagnetic spectrum more involved in biological effects. In the absence of specific definitions, boundary wavelengths should be taken as somewhat arbitrary. The spectrum of visible light in the optic range is shown as bright yellow.

These long period waves, with their content of energy and information, encompass distances much greater than those of the valence electron clouds of atoms. In this way, they can bring spatial and temporal coherence to interacting atoms and molecules, thus providing for global control of chemical reactions. Since the virtual flow does not exhibit temperature or pressure per se, its biochemical control is temperature-independent and therefore very different from the Arrhenius-type control of classical biochemistry (7).

Because of their long period, these virtual waves travel very fast. In terms of energy levels, they are comparable to the vibrations of atomic lattices of bulk matter known as *phonons,* with which they exchange energy. In effect, the whole spectrum of virtual flow is seen as a standby energy ladder, a source of endogenous energy capable of rapid frequency shifts, from phonon to photon and vice-versa, to accommodate specific local energy needs. These energy conversions may require the input of metabolic energy.

The high speed virtual waves have the tendency to attract mobile real electrons, possibly derived from atomic cores, to their flight. They cooperate with each other in their progression through space and tend to condense on coherent ensembles of similar frequency and phase known as *Bose condensates.* A condensate flow may contain so high numbers of electrons as to reach meso- or macroscopic status. Once constituted in condensed form, the virtual flow is exquisitely sensitive to environmental effects, such as changes in temperature and to magnetic fields, including even miniscule variations of the magnetic field of the earth. The low amplitude ELF electric fields discussed in subchapter 6.7 may achieve their biologic effect by coupling to virtual flows, followed by amplification by condensation.

For certain reasons, the virtual waves can be considered as flowing in two dimensions in these high density condensates. This restricts the degrees of freedom available to electrons so that they can no longer repel each other by Coulomb repulsive forces between their like charges. They can now aggregate in the stream and flow resistanceless in pairs of antiparallel spin, a process known as *superconductivity.* This form of electron transport, with its intrinsic magnetic fields, typically occurs on the surface of proteins.

Besides superconductivity, the condensates can generate other novel wave patterns which can lead all the way from stimulation to termination of chemical reactions. It is through these nonlinear dynamic processes, involving multiple interfering wave patterns capable of reorienting dipoles and rearranging molecules and macromolecules, that molecular structuring and self-organization are finally achieved. Virtual flows extended to the whole bulk would provide the cells with an elaborate system for their control and integration into an organism (7,8).

According to these concepts, space creates living matter and drives its structural order. In turn, highly ordered matter imposes its order on local space. Under the wave concept, a biopolymer could be considered a *memory* of a previous wave state of the environment. If this particular wave state has had a part in the original structuring of this biopolymer, then, the energy it emanates would be expected to simulate the wave pattern of the environment. Hagan and Reid believe that it was this property, the ability of biopolymers to re-radiate coherent waveforms derived from the environment, that gave evolved systems the autonomy which has allowed a free and prolific evolution (9).

In addition to structural order, there is also *electrical order.* Biological macromolecules are microstructures containing dipole moments and free mobile electrons which endow them with high electrical capacity and high permittivity, properties that permit the storage of, and interference with, outside electric fields. It is through the dielectric properties of biomatter that the interaction with the electrical properties of space takes place (1).

If further investigation proves the validity of these theoretical concepts, its implications to the field of clinical medicine would be enormous. For instance, many causes could compromise the return of a given fluctuation to space, a situation that would lead to persistent activation of the related atomic orbitals. A state of autonomy would then exist in place of the normal cyclic reaction. The defective resonance could however be replaced by a normal resonance introduced therapeutically (6).

The space virtual electromagnetic field is the counterpart predecessor of the endogenous, material electromagnetic field. Its function is to maintain the structure of living matter in continuing consistency with the structure of the environment. To understand life, then, a correct description of the relationship living system-environment is as fundamental as the internal description of the system itself.

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11

THE BRAIN PHOTONIC SYSTEM AND CONSCIOUSNESS

The electron is the basic component of all matter, life and consciousness.
Jerry I. Jacobson

At present stage, unitary theory is only relational. Quantum field theory, on the other hand, has a mathematical treatment, albeit complex, which can be applied to specific biological problems. Its power of explaining macroscopic ordered phenomena from their disordered microscopic origins makes quantum field theory particularly suited to the self-organizing hierarchical nature of living systems. A phenomenon recently proposed is that of weak, coherent *photon emission* from living matter. It is postulated to occur in the microtubules of the cytoskeletal framework of all cells but a similar mechanism may take place in all protein filamentous structures of cytoskeletons and extracellular matrices. Derived from cooperative water-protein quantum dynamics, microtubular photon emission is seen as a reliable long-range signal transfer network (1,2).

Its high transmission speed, although less than the velocity of light in the vacuum, is particularly useful in the central and peripheral nervous systems of large animals, where neuronal axons may extend for distances of over one meter. The photonic information network has revolutionized brain dynamics where it has been primarily studied. Recently, its possible involvement in the emergence and maintenance of consciousness has been proposed and convincingly argued (1).

The theory of photon emission is supported by a sound structural foundation, but generation and emission of coherent photons is yet to be shown to occur in microtubules or in any other microscopic biological structure. The concept so far has remained purely theoretical but its implications are so profound that it merits serious consideration. A full discussion of this theory cannot be presented here but an insight into the mechanisms involved is given, together with a brief account of the neural photonic network and its implications for brain function.

11.1 The structure and physical properties of microtubules

Among the cytoskeletal filamentous polymers, *microtubules* are the most central to cellular organization and information processing. They are very dynamic structures which self-assemble and disassemble by mechanisms still not fully elucidated. They are interconnected with other microtubules and cell structures by linking proteins (microtubule-associated proteins) which are of particular importance to the stability of the microtubule assembly.

Microtubules are hollow (water containing) polymeric cylinders comprising filaments, typically of 1-10 μm in length, made up of tubulin dimer subunits of $4 \times 5 \times 8$ nm, arranged in a slightly twisted hexagonal lattice. It is interesting to note that the size of a tubulin dimmer is comparable to that of two

water clusters. The cylinders, whose diameter is about 25 nm, accommodate on average 13 filaments together with water molecules. The tubulin dimmer is made of alpha- and beta-monomers, of slightly differing shape, each containing several alpha helices. It has a very high dipole moment resulting from an excess of negative charges localized to the alpha monomer. The tubulin dimmer has two quantum states, resulting from the jumping of electrons from one monomer to the other at speeds of 10^{-9} to 10^{-11} sec. These states are piezoelectrically coupled to tubulin conformational changes which are brought about by energy provided by the hydrolysis of GTP and ATP (1,2)

11.2 Microtubular coherent photon emission and transmission

When switching their location from the alpha- to the beta-monomer, the electrons reverse the orientation of the associated dipole moment of the tubulin dimmer. These dipolar oscillations interact strongly with the intrinsic electric dipoles of adjacent water molecules and a nearly uniform quantized electromagnetic field is generated, parallel to the axis of the microtubule. It is from the interaction of the quantum dynamic system of water molecules with the quantized electromagnetic field confined inside the hollow microtubule core that coherent photon emission is produced.

According to the proponents of the theoretical formalism, there is a certain symmetry property in the quantum equations whose dynamics in the ground state is known to manifest long-range order creating phenomena due to spontaneous symmetry breaking. Specifically, energy derived from the thermal fluctuation of tubulins energizes more and more water molecules, raising them from the lowest rotational energy state to the first excited rotational energy state, until a point is reached where the system's symmetry suddenly breaks down. When this occurs, a group of water molecules in rotationally excited states loses its energy collectively, and creates a pulse mode of non-linear, long-range, coherent photons in the quantized electromagnetic field inside the microtubule. In other words, any incoherent and disordered energy distribution among the water molecules, resulting from the macroscopic thermal dynamics of tubulin dimmers, is gathered collectively into coherent and ordered dynamics ready to emit coherent photons cooperatively. This special, laser-like process of coherent photon emission is called *superradiance* (1). Its characteristic times are much shorter than those of thermal interactions and, consequently, optical signaling in microtubules is free of thermal noise and loss.

The long-range coherence of the pulse mode photons is preserved during propagation through the water filled hollow core of microtubules which play the role of dielectric waveguides. Photons propagate along this internal core as if the optic medium inside it were made transparent by the photons themselves. This phenomenon is known in quantum optics as *self-induced transparency* (1). Propagation is carried out at constant speed, which is less than the speed of light in the vacuum.

11.3 The brain microtubule system as physical basis for consciousness

In the classical neuronal theory, transmission of information is carried out electrically in neuronal membranes and chemically in synapses. Conduction of neural impulses is the sole pathway for signal transfer and information processing. The control mechanism for creation and conduction of impulses resides in each neuron and is therefore of local nature (3). This theory may explain activities localized to certain areas of the brain, such as sensation and motor and speech functions, but it is difficult to conceive how could it possibly account for nonlocalized activities, such as memory, perception and consciousness. Indeed, the resistance of aspects of these activities to relatively extensive brain damage indicates that memory storage, perceptual processing and conscious thought are distributed procedures.

In regards to consciousness, despite its extension in space, it has a "unity", which again is difficult to explain by classical means (1). These shortcomings of the classical theory have been recognized by several workers who have proposed a purely chemical, non-ionic mechanism, to explain intelligence, which would avoid drastic interactions with the electrical nature of neuronal membranes (4) or a capillary-neuron electrical pathway through the neuroglia, to explain fast, long-range interactions (5).

The distributed, photographic-like, nature of memory had defied all reasonable explanations until *optical holography* and later the lasers came about. Holography is, in principle, a means of creating a unique image without the use of a lens. It uses only a recording material (pe, a photographic plate) and coherent light (pe, two pulsed lasers). Direct light from the coherent source, called the reference beam, and reflected light from the object are allowed to interfere and the resultant pattern is recorded. The recording of the image (intensity and phase of reflected light) is called a hologram. This appears to be an unrecognizable pattern of stripes and whorls but, when illuminated by coherent light, it organizes the light into a three-dimensional representation of the original object.

Some lensless method of holography could underlie the mechanism of memory, if coherent waveforms and recording materials were available in the brain. Coherent waves have long been known to occur in all living matter and recording structures could conceivably be supplied by some cytoplasmic structures. The recent proposal, by several renown theoretical physicists, of long-range correlation waves of coherent photons in microtubules of neurons and other brain cells, if confirmed by experiment, would make optical holography in brain tissue a very likely possibility. In this view, images would be obtained from cytoplasmic interference of coherent sources from and among multiple microtubules, with other finer components of the cytoskeleton and the microtrabecular lattice serving as recording structures (1). Photon coherence in microtubules is capable of superposition of states. Billions of microtubules distributed over hundreds of micrometers could be in superposition with billions of microtubules hundreds of micrometers away in other directions and so on leading to a coupling of microtubule dynamics over wide areas and ultimately over the whole brain. This in turn could account for a unity of thought and consciousness (1).

In brain tissue, there may be two interacting communication systems - the incoherent, local, macroscopic classical neuronal system and the coherent, non-local microscopic quantum system. The macroscopic behavior of the quantum system exhibits the long-range order or coherence needed for autonomous information processing in the brain. This system involves not only neurons but also the more numerous astrocytes and given the high number of microtubules per cell (10^7 for neurons (6)), its capacity for dynamical exchanges would be astonishingly high. This extremely vast network, if its existence can be confirmed, could certainly provide a basis for biomolecular recognition and a substrate for consciousness.

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In preparation.