Towards a Theory of the Organism

MAE-WAN HO
Bioelectrodynamics Laboratory, Open University, Milton Keynes, U.K.

Abstract—A tentative theory of the organism is derived from McClare's (1971) notion of *stored energy* and Denbigh's (1951) thermodynamics of the steady state, as a dynamically closed, energetically self-sufficient domain of cyclic non-dissipative processes coupled to irreversible dissipative processes. This effectively frees the organism from thermodynamic constraints so that it is poised for rapid, specific intercommunication, enabling it to function as a coherent whole. In the ideal, the organism is a quantum superposition of coherent activities over all space-time domains, with instantaneous (nonlocal) noiseless intercommunication throughout the system. Evidence for quantum coherence is considered and reviewed.

Introduction

ORGANISMS ARE SO ENIGMATIC from the physical, thermodynamic point of view that Lord Kelvin, co-inventor of the second law of thermodynamics, specifically excluded them from its dominion (Ehrenberg, 1967). As distinct from heat engines, which require a constant input of heat energy in order to do work, organisms are able to work without a constant energy supply, and moreover, can mobilize energy *at will*, whenever and wherever required, and in a perfectly coordinated way. Similarly, Schrödinger (1944) was impressed with the ability of organisms to develop and evolve as a coherent *whole*, and in the direction of increasing organization, in defiance of the second law. He suggested that they feed upon "negative entropy" to free themselves from all the entropy they cannot help producing. The intuition of both physicists is that energy and living organization are intimately linked.

Schrödinger was reprimanded, by Linus Pauling and others, for using the term "negative entropy," which does not correspond to any rigorous thermodynamic entity (Gnaiger, 1994). However, the idea that open systems can "self-organize" under energy flow became more concrete in the discovery of *dissipative structures* (Prigogine, 1967) that depend on the flow and dissipation of energy, such as the Bénard convection cells and the laser (Haken, 1977). In both cases, energy input results in a phase transition to global dynamic order in which all the molecules or atoms in the system move coherently.

From these and other considerations, I have identified Schrödinger's "negative entropy" as "stored mobilizable energy in a space-time structured system" (Ho, 1993, 1994b, 1995a), which begins to offer a possible solution to the enigma of living organization.

In this article, I outline a theory of the organism as a dynamically and energetically closed domain of cyclic nondissipative processes coupled to irreversible dissipative processes. This effectively frees the organism from thermodynamic constraints so that it is poised for rapid, specific intercommunication, enabling it to function as a coherent whole.

Address for correspondence: Mae-Wan Ho, Bioelectrodynamics Laboratory, Open University, Walton Hall, Milton Keynes, MK7 6AA, UK.

Integrative Physiological and Behavioral Science, October–December 1997, Vol. 32, No. 4, 343–363.

In the ideal, the organism is a quantum superposition of coherent activities over all space-time domains, with instantaneous (nonlocal) noiseless intercommunication throughout the system.

Stored Mobilizable Energy

The concept of *stored energy* in this article derives from McClare (1971), who attempted to formulate the second law of thermodynamics so that it can apply, not only to ensembles of molecules as is conventionally the case, but also to a single molecule. He was motivated to do so because organisms are by no means large ensembles of identical molecules. Instead, a cell typically has one or two molecules of DNA, and a few molecules of specific ligands binding to receptors on its membrane are sufficient to initiate a cascade of increasingly macroscopic changes. Furthermore, all energy transductions in the living system are dependent on enzymes and other proteins functioning individually as "molecular energy machines," transferring energy directly from the point of release to the point of utilization.

McClare introduced the notion of a characteristic time interval, τ, for a system at temperature θ, which partitions the energies in the system into *stored* versus *thermal* energies. Thermal energies are those that exchange with each other and reach equilibrium in a time less than τ, so technically they give the so-called Boltzmann distribution characterized by the temperature θ. Stored energies are those that remain in a non-equilibrium distribution for a time greater than τ, either as characterized by a higher temperature, or such that states of higher energy are more populated than states of lower energy. So, stored energy is any form that does not thermalize, or degrade into heat in the interval τ.

McClare then restated the second law as follows: *useful work is only done by a molecular system when one form of stored energy is converted into another. In other words, thermalized energy is unavailable for work and it is impossible to convert thermalized energy into stored energy.*

The above restatement of the second law seems unnecessarily restrictive, and possibly untrue, for thermalized energy from an enzyme molecule embedded in a membrane, or a matrix such as the cytoskeleton, is likely to cause conformational changes in neighbouring enzyme molecules, resulting in further work being done. Thermalized energy from burning coal or petrol is routinely used to run generators and motor cars. However, they do so against an *external* constraint, such as a piston, which, in taking up the thermalized energy, is in a position to do work against the system external to the combustion chamber. This suggests that "the system" must be more explicitly defined in relationship to the extent of equilibration.

A more adequate restatement of McClare's second law, which improves on my previous attempts (Ho, 1994a, 1995a), might be as follows: *Useful work is done by molecules by a direct transfer of stored energy, and thermalized energy cannot be converted into stored energy within the same system, the system being the extent over which thermal and other rapidly exchanging energies equilibrate.*

The first half of the formulation, much as McClare has proposed, is new and significant for biology. The second half of the statement, which I have modified, introduces the concept of a "system" defined as the extent to which thermalized and other rapidly exchanging energies equilibrate. It allows for the possibility that thermalized energies from one (sub)system can do work in a larger encompassing system for which the thermalized and other energies are in a nonequilibrium distribution. This is highly relevant for living

systems (Ho, 1993) which are now known to have a nested dynamic organization of compartments and microcompartments down to the interior of cells and organelles (Welch and Clegg, 1987) where single molecular energy machines may cycle autonomously without equilibrating with its environment.

The major consequence of McClare's ideas arises from the explicit introduction of time, and hence *time-structure*. For there are now two quite distinct ways of doing useful work at maximum efficiency, not only slowly according to conventional thermodynamic theory, but also quickly—both of which are reversible as no entropy is generated. This is implicit in the classical formulation, $\delta S \geq 0$, for which the limiting case is $\delta S = 0$, the attention to time-structure making much more precise what the limiting conditions are. A slow process is one that occurs at or near equilibrium. A reversible thermodynamic process merely needs to be slow enough for all thermal, or other exchanging energies to equilibrate, i.e., slower than τ, which can in reality be a very short period of time, for processes that have short time constants. Thus, for a process that takes place in 10^{-12}s, a microsecond (10^{-6}s) is an eternity. So high efficiencies of energy conversion can still be attained in thermodynamic processes which occur quite rapidly, provided that equilibration is fast enough. Compartmentation and microcompartmentation effectively restrict the volume within which equilibration occurs, thus reducing the equilibration time. Thus, the living system is both thermodynamically optimized in terms of efficiency of energy transformation and transfer, and kinetically optimized in terms of the speed with which reactions can occur (Ho, 1995a).

At the other extreme, there can also be a process occurring so quickly that it, too, is reversible. In other words, provided the exchanging energies are not thermal energies in the first place, but remain stored, then the process is limited only by the speed of light. Resonant energy transfer between molecules is an example of a fast process. It occurs typically in 10^{-14}s, whereas the molecular vibrations themselves die down, or thermalize, in 10^{-9}s to 10^{1}s. McClare (1972) suggests that a form of resonant energy transfer may occur in muscle contraction, where it has been shown that the energy released in the hydrolysis of ATP can be almost completely converted into mechanical energy in a molecular machine that can cycle autonomously without equilibrating with its environment. Ultrafast, resonant energy transfer takes place between the light-trapping antenna complex and the reaction center of the photosynthetic system in the thylakoid membrane, and is also involved in the first step of the separation of positive and negative charges across the membrane (Fleming et al., 1988).

McClare's ideas have been taken up and developed by Blumenfeld (1983), and more recently, Welch and Kell (1986), among others (see many Chapters in Welch, 1986), particularly in the the concept of *non*equilibrium, "quantum molecular energy machines," which is now increasingly accepted among protein biochemists and biophysicists. I suspect, however, that most molecular energy machines may be functioning in the quasi-equilibrium mode (see Ho, 1995a).

I have generalized McClare's notion of "characteristic time" of energy storage to "characteristic space-time," which captures the space-time differentiation of living processes more precisely. Stored energy, being capable of doing work, is also mobilizable energy or *coherent* energy. (Coherent energy comes and goes together so it can do work, as opposed to incoherent energy which goes in all directions and cancel itself out.) As the energy is stored over all space-times, so it is mobilizable all over the system. Stored energy is really a more precise formulation of the usual "free energy" which has no space-time characterization. Detailed arguments for energy storage in living systems is presented elsewhere (Ho, 1993; 1995a).

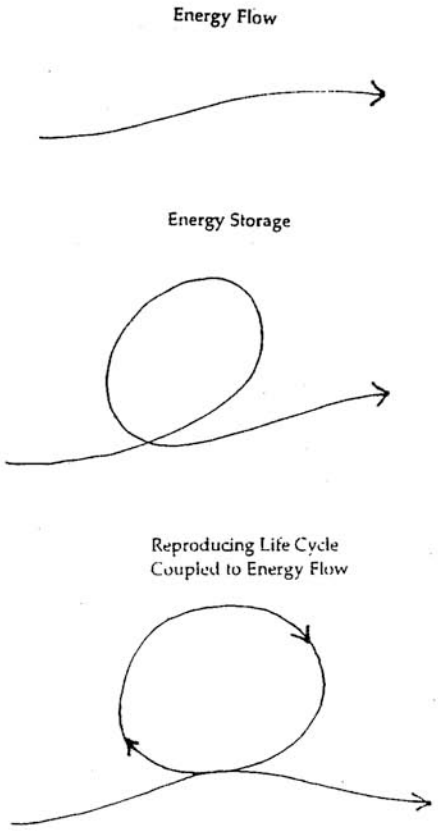

FIG. 1. Energy flow, energy storage and the reproducing life-cycle.

Energy Storage Frees the Organism from Thermodynamic Constraints

Energy Storage and Mobilization in Living Systems

The key to understanding the thermodynamics of the living system is neither energy flow nor energy dissipation, but energy storage under energy flow (Figure 1). Energy flow is of no consequence unless the energy is trapped and stored within the system where it circulates to do work before being dissipated. A reproducing life cycle, i.e., an organism, arises when the loop of circulating energy closes. At that point, we have a life cycle within which the stored energy is mobilized, *remaining stored as it is mobilized*, and coupled to the energy flow.

Energy storage depends on the highly differentiated space-time structure of the life cycle, whose predominant modes are themselves cycles of different sizes, spanning many order of magnitudes of space-times, all coupled together, and feeding off the one-way energy flow (Ho, 1993; 1994a,b; 1995a). The more cycles there are, the more energy is stored, and the longer it takes for the energy to dissipate. The average residence time of

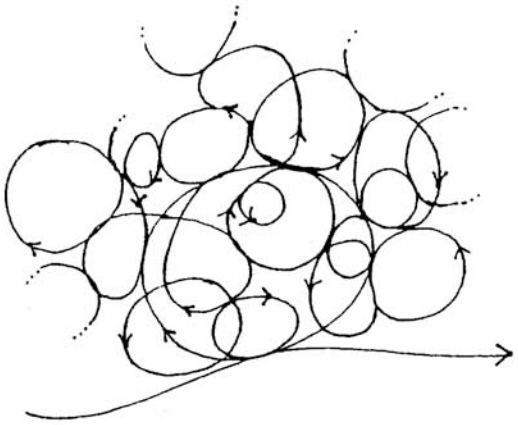

FIG. 2. The many-fold cycles of life coupled to energy flow.

energy (see Morowitz, 1968) is therefore a measure of the *organized* complexity of the system. An intuitive representation is given in Figure 2.

Coupled processes are familiar in biochemistry: practically all thermodynamically uphill reactions (ΔG positive) are coupled to the thermodynamically downhill ones (ΔG negative). The ATP/ADP couple, ubiquitous to the living system, effectively turns all biosynthetic and other energy requiring uphill reactions *downhill* (c.f. Harold, 1986). Life is literally downhill, or effortless, all the way (Ho, 1995a).

That living processes are organized in cycles is also intuitively obvious by a casual examination of the metabolic chart. Apart from the prominent cycles, such as the tricarboxylic acid cycle and the cyclic interconversion of ATP/ADP, NADH/NAD and other redox intermediates, many more cycles and epicycles are entangled in the metabolic network. Another prominent way in which cycles appear is in the familiar form of the wide spectrum of biological rhythms—with periods ranging from milliseconds for electrical discharges of single cells to circadian and circa-annual cycles in whole organisms and populations of organisms (Breithaupt, 1989; Ho, 1993). These cycles interlock to give the organism a complex, multidimensional, entangled space-time, very far removed from the simple, linear Newtonian space and time (Ho, 1993; 1994b). That these rhythms are indeed entangled is indicated by the remarkable observations that mutations in two genes of *Drosophila*, *period* and *timeless*, which speed up, slow down or abolish circadian rhythm, also cause corresponding changes in the millisecond wing beat cycle of the male fly's love song (see Zeng et al., 1996). This correlation spans seven orders of magnitude of characteristic timescales, reflecting the full extent of storage and mobilization of energy in the living system. Energy is stored and mobilized over all space-times according to the relaxation times and volumes of the processes involved. The result, as mentioned above, is that organisms can take advantage of two different ways to mobilize energy with maximum efficiency-nonequilbrium transfer in which stored energy is transferred before it is thermalized, and quasi-equilibrium transfer, in which the free energy change approaches zero according to conventional thermodynamic considerations.

As all the space-time modes are coupled together, energy input into any mode can be

readily delocalized over all modes, and conversely, energy from all modes can become concentrated into any mode. In other words, energy coupling in the living system is *symmetrical* (see Ho, 1993, 1994b, 1995a,b) as argued later in more detail.

Symmetrical Coupling of Cyclical Flows

Symmetrical energy coupling and cyclical flows are both key aspects of the living system that are actually predicted from the thermodynamics of the steady state, in the form, respectively, of Onsager's reciprocity relationship (see Denbigh, 1951 for an accessible exposition), and of Morowitz's (1968) theorem.

Onsager's reciprocity relationship is well known. It states that for a system of many coupled linear flows under conjugate forces,

$$\mathbf{J}_i = \Sigma_k L_{ik} \mathbf{X}_k \tag{1}$$

where $\mathbf{J}_i$ is the flow of the i^{th} process (i = 1, 2, 3.....n), $\mathbf{X}_k$ is the k^{th} thermodynamic force (k = 1, 2, 3,.....n), and L_{ik} are the proportionality coefficients (where i = k) and coupling coefficients (where $i \neq k$), the couplings for which the $\mathbf{X}_k$s are invariant with time reversal (i.e., velocity reversal) will be symmetrical; in other words,

$$L\text{ik} = L\text{ki} \tag{2}$$

so long as the **J**s and the **X**s satisfy $T\theta = \Sigma \mathbf{J}_i \mathbf{X}_i$ where θ is the rate of entropy increase per unit volume (I thank Denbigh (personal communication) for this formulation).

Morowitz's (1968) theorem, much less known, states that the flow of energy through the system from a source to a sink will lead to at least one cycle in the system at steady state, *provided that the energy is trapped and stored within the system* (italics mine). This important theorem is, as far as I know, the only attempt to account for cycles in the living system, it implies that the steady state—at which global balance is maintained-must harbour nonlinear processes (see Ho, 1993). I present a shortened version of Morowitz's proof below.

For a canonical ensemble of systems at equilibrium with i possible states, where f_i is the fraction of systems in state i (also referred to as occupation numbers of the state i), and t_{ij} is the transition probability that a system in state i will change to state j in unit time. The principle of microscopic reversibility requires that every forward transition is balanced in detail by its reverse transition, that is,

$$f_i\, t_{ij} = f_j\, t_{ji} \tag{3}$$

If the equilibrium system is now irradiated by a constant flux of electromagnetic radiation such that there is net absorption of photons by the system, i.e., the system is capable of *storing* energy, a steady state will be reached at which there is a flow of heat out into the reservoir (sink) equal to the flux of electromagnetic energy into the system. At this point, there will be a different set of occupation numbers and transition probabilities, $f_i'$and t_{ij}'; for there are now both radiation induced transitions as well as the random thermally induced transitions characteristic of the previous equilibrium state. This means that for some pairs of states i and j,

$$f_i' t_{ij}' \neq f_j' t_{ji} \tag{4}$$

For, if the equality holds in all pairs of states, it must imply that for every transition involving the absorption of photons, a reverse transition will take place involving the

radiation of the photon such that there is no net absorption of electromagnetic radiation by the system. This contradicts the original assumption that there is absorption of radiant energy (see previous paragraph), so we must conclude that the equality of forward and reverse transitions do not hold for some pairs of states. However, at steady state, the occupation numbers (or the concentrations of chemical species) are time independent (i.e., they remain constant), which means that the *sum* of all forward transitions is equal to the *sum* of all backward transitions, that is,

$$df_i'/dt = 0 = \Sigma\,(f_i't_{ij}'-f_j't_{ji}') \qquad (5)$$

But it has already been established that some $f_i't_{ij}'-f_i't_{ji}'$ are non-zero. That means other pairs must also be non-zero to compensate. In other words, members of the ensemble must leave some states by one path and return by other paths, which constitutes a cycle. Hence, *in steady state systems, the flow of energy through the system from a source to a sink will lead to at least one cycle in the system.*

Morowitz's theorem also implies that the steady state *necessarily* violates the principle of microscopic reversibility, which, as Onsager originally argued, is a principle extraneous even to thermodynamic equilibrium (see Denbigh, 1951).

Onsager's reciprocity relationship has been extended to the far from equilibrium regime by Rothschild et al. (1980) for multi-enzyme systems and more recently, by Sewell (1991) for infinite quantum systems. However, the validity and the theoretical basis for the extension of Onsager's reciprocity relationship to biological systems are still under debate (Westerhof and van Dam, 1987).

I believe some form of Onsager's reciprocity relationship *does* hold in living systems if only to account for the ready mobilization of energy on the one hand—why we can have energy at will—and on the other hand, for the linear relationships between steady-state flows and conjugate thermodynamic forces outside the range of equilibrium, *which is actually observed in many biological systems* (Berry et al., 1987, and references therein).

According to Rothschild et al. (1980), linearity in biological processes can arise in enzymes operating near a multidimensional inflection point far away from thermodynamic equilibrium, if some of the rate constants are linked. That is realistic for living systems which are now known to have highly organized flows in the cytoplasmic matrix due to dynamic compartmentation and microcompartmentation (Welch, 1986, and references therein). In common with Rothschild et al. (1981), Sewell shows how Onsager's reciprocity relationship applies to locally linearized *combinations* of forces and flows, which nonetheless behave globally in nonlinear fashion. Again, that is relevant for the living system, where nested compartments and microcompartments ensure that many processes can operate locally at thermodynamic equilibrium even though the system or subsystem as a whole is far away from equilibrium (Ho, 1995a). Furthermore, as each process is ultimately connected to every other in the metabolic net through catenations of space and time, even if truly symmetrical couplings are localized to a limited number of metabolic/energy transducing junctions, the effects will eventually be shared or delocalized throughout the system, so that symmetry will apply to appropriate *combinations* of forces and flows (Sewell, 1991) *over a sufficiently macroscopic space-time scale*. That is, perhaps, the most important consideration. As real processes take time, Onsager's reciprocity relationship cannot be true for an arbitrarily short instant, but must apply at a sufficiently macroscopic time interval when overall balance holds.

Thermodynamics of the Steady State vs. Thermodynamics of Organized Complexity

Denbigh (1951) defines the steady state as one in which "the macroscopic parameters, such as temperature, pressure and composition, have time independent values at every point of the system, despite the occurrence of a dissipative process." (p.3) That is too restrictive to apply to the living system, which, as mentioned earlier, has coupled processes spanning the whole gamut of relaxation times and volumes.

A less restrictive formulation—one consistent with a "thermodynamics of organized complexity"—might be to define the living system, to first approximation, as a *dynamic equilibrium in which the macroscopic parameters, such as temperature, pressure and composition have time-independent values despite the occurrence of dissipative processes* (see Ho, 1993, 1994a, 1996a). The present formulation omits the phrase, "at every point of the system" on grounds that *microscopic homogeneity is not crucial for the formulation of any thermodynamic state, as the thermodynamic parameters are macroscopic entities quite independent of the microscopic interpretation* (Ho, 1993). Like the principle of microscopic reversibility, it is extraneous to the phenomenological laws of thermodynamics as Denbigh (1951) himself has convincingly argued.

The first incursion into the thermodynamics of the steady state was W. Thomson's (Lord Kelvin) treatment of the thermoelectric effect (see Denbigh, 1951). This involves a circuit in which heat is absorbed and rejected at two junctions (the Peltier heat), and in addition, heat is absorbed and given off due to current flows between two parts of the same metal at different temperatures (the Thomson heat). Both of these heat effects are reversible, in that they change sign but remain the same in magnitude when the direction of the current is reversed. On the other hand, there are two other effects which are not reversible: heat conduction along the wires and dissipation due to the resistance. It is, thus, impossible to devise a reversible thermoelectric circuit even in principle. Nevertheless, Thomson took the step of assuming that, at steady state, those heat effects that are reversible, i.e., the Peltier heat and Thomson heat, balance each other so that no net entropy is generated,

$$\Delta S_p + \Delta S_T = 0 \tag{6}$$

On that basis, he derived the well-known relations between the Peltier and Thomson heats and the temperature coefficient of the electromotive force. It was a bold new departure in the application of the Second Law, but one which was subsequently justified by experimental evidence.

Very similar methods were used later by Helmholtz in his treatment of the electromotive force and transport in the concentration cell, where he states clearly that the two irreversible process in the cell, heating and diffusion, are to be disregarded and the second law to be applied to those parts of the total process which are reversible. Most modern accounts of this system follow the same procedure. A virtual flow of current is supposed to take place across the liquid junction, resulting in a displacement of the ions. The process is taken to be reversible and to generate no net entropy. The justification, according to Guggenheim (cited in Denbigh, 1951), is that the two processes, diffusion and flow of current across the junction, "take place at rates which vary according to different laws" when the composition gradient across the boundary is altered. So it seems reasonable to suppose that the two processes are merely superposed, and that the one may be ignored when considering the other. Thus, the steady state is treated *as if there were no dissipative processes*, and it is this assumption which is later validated by Onsager's reciprocity relationship.

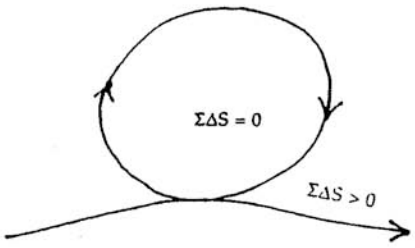

FIG. 3. The organism frees itself from the constraints of energy conservation and the second law of thermodynamics.

The Organism is a Superposition of Cyclic Non-dissipative Processes Coupled to Dissipative Processes

In the same spirit, I propose to treat the living system as a superposition of non-dissipative processes and dissipative irreversible processes, so that Onsager's reciprocity relationship applies only to the former. In other words, it applies to coupled processes for which the net entropy production is balanced or zero,

$$\Sigma_k \Delta S_k = 0 \tag{7}$$

This will include most living processes because of the ubiquity of coupled *cycles*, for which the *net* entropy production balances out to zero. The principle applies, in fact, to the smallest unit cycle in the living system—enzyme catalysis—on which all energy transduction in the living system is absolutely dependent. Over the past thirty years, Lumry and his coworkers (see Lumry, 1991) have shown convincingly how the flexible enzyme molecule balances out entropy with enthalpy to conserve free energy (i.e., *stored* or coherent energy in the present context) during catalysis, in accordance with the relationship for isothermal processes,

$$\Delta G = \Delta H - T\Delta S = 0 \tag{8}$$

The organism is, in effect, a closed, self-sufficient energetic domain of cyclic non-dissipative processes coupled to irreversible dissipative processes (Ho, 1995b). In the formalism of conventional thermodynamics, the life cycle, or more precisely, *the living system in dynamic equilibrium, consists of all cyclic processes for which the net entropy change is zero, coupled to dissipative processes necessary to keep it going, for which the net entropy change is greater than zero* (Figure 3).

In other words, there is an *internal entropy compensation* as well as coherent energy conservation due to the predominance of coupled cyclic processes and the nested space-time organization of the processes.

The Principle of Internal Entropy Compensation Implies the Principle of Minimum Entropy Production

Prigogine derived a theorem of minimum entropy production (see Glandorff and Prigogine, 1967), which states that entropy exported from a system reaches a minimum, or

becomes zero, at thermodynamic equilibrium and at steady states close to thermodynamic equilibrium. The theorem is a direct consequence of Onsager's reciprocity relationship which holds at steady states close to thermodynamic equilibrium. The principle of internal entropy compensation proposed here is in addition to, and implies the principle of minimum entropy production, and may even be valid in regimes far from thermodynamic equlibrium.

Prigogine's theorem of minimum entropy production was derived for homogeneous systems where all volume elements are uniform and locally at equilibrium. On the contrary, internal entropy compensation applies to systems with organized heterogeneity—such as organisms—so that positive entropy production in some space-time elements may be compensated by negative entropy production in other elements. Alternatively, positive entropy flows in some directions may be compensated by negative entropy flows in other directions, or else some form of enthalpy-entropy compensation could take place, as mentioned before, so that coherent energy is conserved. The system could be arbitrarily far from equilibrium, so long as, at some sufficiently macroscopic spacetime of interest, overall balance is attained, and the net entropy production of the system either vanishes or reaches a minimum. The internal balance of entropy production means that the system maintains its organized heterogeneity or dynamic order. It is in turn dependent on energy flow being symmetrically coupled, and cyclically closed over the system as a whole. This is the same as the argument presented earlier for the validity of Onsager's reciprocity relationship in systems far from thermodynamic equilibrium.

While most current thermodynamical analyses ignore space-time structure, the "thermodynamics of organized complexity" applying to living systems (Ho, 1993) is dependent on space-time heterogeneity, which allows "free" variation of microscopic states within macroscopic constraints. Thus, stability criteria which apply to the system as a whole need not be satisfied in individual space-time elements. Each element may be defined by the extent of equilibration according to the characteristic timescale of its constituent process(s), and so the local equilbrium assumption can still be satisfied. But each space-time element need not be in equilibrium with other elements.

Consequences of Dynamic Closure

The dynamic closure of the living system has a number of important consequences. First and foremost, it frees the organism from the immediate constraints of energy conservation—the first law—as well as the second law of thermodynamics, thus offering a solution to the enigma of the organism posed by Lord Kelvin and Schrödinger. *There is always energy available within the system, for it is stored and mobilized at close to maximum efficiency over all space-time domains.*

The other consequences are that, the organism is also free from mechanical constraints, and satisfies, at least, some of the basic conditions for quantum coherence. I shall deal with these in the following sections.

The present formulation converges formally with several other representation of living organization: Maturana and Varela's (1987) concept of life as *autopoesis*—a unitary, self-producing entity; Eigen and Schuster's (1977) hypercycle of RNA-directed protein synthesis, in turn directing RNA polymerization; and Kauffman's (1993) catalytic closure of polypeptide formation in the origin of life. However, unlike the present formulation, none of the previous representations is based explicitly on physical, thermodynamic principles, which offer new and important physical insights into the living system.

The Exquisite Sensitivity of the Organism that is Free from Mechanistic Constraints

One of the hallmarks of the living system is that it is exquisitely sensitivity to specific, weak signals. For example, the eye can detect single photons falling on the retina, where the light sensitive cell sends out an action potential that represents a million-fold amplification of the energy in the photon. Similarly, a few molecules of pheromones in the air is sufficient to attract male insects to their mates. No part of the system has to be pushed or pulled into action, nor be subjected to mechanical regulation and control. Instead, coordinated action of all the parts depends on rapid *intercommunication* throughout the system. The organism is a system of "excitable media" (see Goodwin, 1994; 1995), or excitable cells and tissues poised to respond specifically and disproportionately to weak signals, because the large amount of energy stored everywhere automatically amplifies weak signals, often into macroscopic actions.

As mentioned earlier, stored energy is *coherent* energy capable of doing work. The organism, therefore, is a highly coherent domain possessing a full range of coherence times and coherence volumes of energy storage. In the ideal, it can be regarded as a quantum superposition of coherent space-time modes.

The Coherence of Organisms

The ultimate problem of living organization is to account for the irreducible *wholeness* of the organism, which, as as Needham (1936) states, encompasses the activities of elementary particles and atoms, of molecules and cells, tissues and organs, up to the organism itself, and beyond. The problem has never been adequately addressed until Fröhlich (1968; 1980) presented the first detailed theory of *coherence* of the organism. He argued that as organisms are made up of strongly dipolar molecules packed rather densely together, they approach the "solid state," where electric and elastic forces will constantly interact. Metabolic pumping will excite macromolecules such as proteins and nucleic acids as well as cellular membranes, which typically have an enormous electric field of some 10^7V/m across them. These will start to vibrate and eventually build up into collective modes, or *coherent excitations*, of both phonons and photons extending over macroscopic distances within, and perhaps also outside, the organism. Coherent excitations are possible precisely because the system does not dissipate its energy immediately, but *stores* it and circulates it among the different modes in the system, as described in the previous Section.

The dynamic, energetic closure of the living system, together with the "solid-state" nature of organisms, do provide the conditions for coherent excitations (see Ho, 1993; 1995b), and the closest analogy is the solid state laser. There, the reflective cavity is the closure required, and continued input of energy beyond the laser threshold will maintain the lasing action or coherent excitation of the emitting atoms. The closure itself is significant in that it enables the creation of a macroscopic quantum system (Leggett, 1986) with effectively a single degree of freedom, in other words, a quantum coherent domain. Such a system possesses a Hamiltonian and can therfore be represented in terms of a macroscopic wave function (c.f. Fröhlich and Hyland, 1995).

Quantum Coherence in Living Organisms

I have presented detailed heuristic arguments elsewhere on why the wholeness of organisms is to be understood as quantum coherence (Ho, 1993; 1995b). First, there is increas-

ingly compelling evidence that the organisms and in particular cells are organized to approach the "solid state" (or, more accurately, the liquid crystalline state, as I shall describe later on) in which much of the cell water is structured on the large amount of surfaces available in the "microtrabecular matrix" that fill up the so-called cytosol (see Clegg, 1985). That, plus the dynamic and energetic closure of the living system argued before, would seem to me to provide both the necessary and sufficient conditions for coherent excitations to occur, rather as suggested. Second, the predominant interactions in the solid state organism, as in any solid state, are electric and electromagnetic, and necessarily so, for those are the *only* ways in which molecules interact and form the various hierarchies of supramolecular assemblies that make up living organisms themselves. Third, living organisms depend on quantum reactions, not only in the sense that quantum tunneling is explicitly recognized in electron and proton transfer, but especially in the sense that all energy transductions are carried out by individual enzyme and other molecules acting as "quantum energy machines" in which individual quanta of energy released are directly transferred from the point of release to the point of use (McClare, 1971; see also Ho, 1993; 1995a). The coordination of such activities requires nothing short of quantum coherence, especially in view of the rapidity and specificity with which responses or *intercommunication* can take place in the living system.

By far the most persuasive argument, to my mind, is the nature of the coordination that is achieved in the organism, where every single part in this magnificently diverse and pluralistic multiplicity, down to an individual quantum molecular energy machine, seems to be able to work autonomously while keeping in step and in tune with the whole. So perfectly do all the parts work together that, as Schrödinger (1944) has remarked, we never experience ourselves as the multiciplicity that we are, but always in the singular "I." That requires no other than the *factorizability* of the quantum coherent state, which I shall explain below.

The Factorizability of Quantum Coherence

A quantum coherent state is a *pure* state—a state of oneness—that has the property of factorizability. This can be understood by considering Young's two-slit experiment (Figure 4) in which a source of monochromatic light is placed behind a screen with two narrow slits. As is well known, light behaves as either particles or waves according as to whether one or both slits are open. When both slits are open, even single photons behave as waves in that they seem to pass through both slits at once, and, falling upon the photographic plate, produce a pattern which indicates that each photon, in effect, interferes with itself.

The intensity or brightness of the pattern at each point depends on the sum of four correlation functions:

$$I = G(t,t) + G(b,b) + G(t,b) + G(b,t) \tag{9}$$

where $G(t,t)$ is the intensity with only the top slit opened, $G(b,b)$ the intensity with only the bottom slit opened, and $G(t,b)+G(b,t) = 2G(t,b)$ is the additional intensity (which take on both positive and negative values) when both slits are opened. At different points on the photographic plate, the intensity is

$$I = G(t,t) + G(b,b) + 2|G(t,b)|\cos\theta \tag{10}$$

where θ is the angle of the phase difference between the two light waves.

The fringe contrast in the interference pattern depends on the magnitude of $G(t,b)$. If

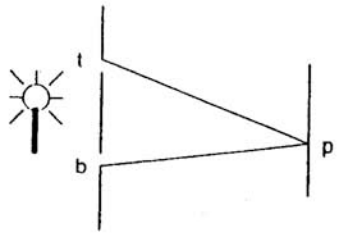

Fig. 4. Young's two-slit experiment.

this correlation function vanishes, it means that the light beams coming out of t and b are uncorrelated; and if there is no correlation, we say that the light at t and b are incoherent. On the other hand, an increase in coherence results in an increase in fringe contrast, i.e., the brightness of the bands. As $cos\theta$ is never greater than one (i.e., when the two beams are perfectly in phase), then the fringe contrast is maximized by making $G(t,b)$ as large as possible and that signifies maximum coherence. But there is an upper bound to how large $G(t,b)$ can be. It is given by the Schwarz inequality:

$$G(t,t,)G(b,b) \geq |G(t,b)|^2$$

The maximum of $G(t,b)$ is obviously obtained when the two sides are equal:

$$G(t,t)G(b,b) = |G(t,b)|^2 \tag{11}$$

Now, it is this equation that gives us a description of quantum coherence. A field is coherent at two space-time points, say, t and b, if the above equation is true. Furthermore, we have a coherent field if this equality holds for all space-time points, X_1 and X_2. This coherence is called first-order coherence because its refers to correlation between two space-time points, and we write it more generally as,

$$G_{(1)}(X_1, X_1)G_{(1)}(X_2, X_2) = |G_{(1)}(X_1, X_2|^2 \tag{12}$$

The above equation tells us that the correlation between two space-time points in a coherent field *factorizes*, or decomposes neatly into the product of the self-correlations at the two points separately, and that this *factorizability is both a necessary and a sufficient condition for quantum coherence*. Factorizability does not mean that the pure state can be factorized into a mixture of states, but it does lead to something quite unusual—any two points in a coherent field are correlated but they will still behave statistically independently of each other. If we put two photon detectors in this field, they will register photons independently of each other. It is the direct consequence of how perfectly they are correlated!

Coherence can be generalized to arbitrarily higher orders, say, to m approaching ∞, in which case, we shall be talking about a fully coherent field. If mth order coherence holds, then all of the correlation functions which represent joint counting rates for n-fold coincidence experiments (where $m<n$) factorize as the product of the self-correlations at the individual space-time points. In other words, if we put n different counters in the field, they will each record photons in a way which is statistically independent of all the others with no special tendency towards coincidences, or correlations (see Glauber, 1970).

$$G_{(m)}(X_1, \ldots\ldots, X_m, \ldots\ldots, X_j)^m = \prod_{j=1}^{m} G_{(1)}(X_j, X_j) \tag{13}$$

In practice, because the system is always under decohering influences from the environment, such high order coherences will never be achieved. One may still expect a species of factorizability, with a coefficient g_n, which is generally less than unity,

$$G_{(m)}(X_1, \ldots\ldots, X_m, \ldots\ldots, X_j)^m = g_n \prod_{j=1}^{m} G_{(1)}(X_j, X_j) \tag{14}$$

Nevertheless, there is now a lot of experimental evidence that lasers can achieve at least six orders of factorizability (Glauber, 1970).

The key to understanding the coherence of organisms is in the factorizability of the quantum coherent state (Ho, 1993; 1995b; 1996a). The coherence of organisms entails a quantum superposition of coherent activities over all space-time domains, each correlated with one another and with the whole, and yet independent of the whole. In other words, the quantum coherent state, being factorizable, *maximizes both global cohesion and local freedom*. It is that which underlies the sensitivity of living systems to weak signals, and their ability to intercommunicate and respond with great rapidity. Within the coherence volumes and coherence times of energy storage, there is no space-like, nor time-like separation, and that is why organic space-time can be nonlocal. Factorizability is also why we can attend to all the different vital functions simultaneously and separately, and yet remain an undivided whole. I propose that: *The organism is, in the ideal, a quantum superposition of coherent activities over all space-time scales, this pure coherent state being an attractor, or end state towards which the system tends to return on being perturbed.*

The fully coherent state (to order m, where m approaches ∞) is an idealization which is almost never realized. This is because the system, despite its dynamic, energetic closure, is constantly interacting with its environment, which would tend to decohere the system, or take it away from the fully factorizable pure state. Nevertheless, it will tend to return to the fully coherent pure state, which is an attractor, as stated above. In quantum optics and quantum electrodynamic theory, the coherent state is indeed asymptotically stable (Goldin, 1982). Duffield (1988) has provided a proof that the "Fröhlich state" of coherent excitation also exhibits global asymptotic stability. In the analogy with the pumped laser, one might even consider the stronger hypothesis that phase correlations between different modes in the living system are *actively* determined and maintained (c.f. Haken, 1977).

Another useful representation of the organism is in terms of a coherent quantum electrodynamical field of many modes (Ho, 1996c), with an uncertainty relationship between energy and phase (Preparata, 1994), such that when phase is defined, energy is indeterminate, and vice versa. This captures the phase-amplitude relationships between macroscopic physiological rhythms characteristic of many systems (Kelso, 1991; Breithaupt, 1989; Freeman and Barrie, 1994).

Evidence for Quantum Coherence in Organisms

Evidence for Factorizable Correlations of Activities

The problem of demonstrating macroscopic quantum coherence such as that of the living system, seems at first, an impossible task, as it would involve finding correlations and factorizability among the large number of degrees of freedom, m, characteristic of even the most simple organism (c.f. Leggett, 1986). However, this need not be impossible for an organized system, and in particular, a coherent system would not have the infinite degrees of freedom of a totally random collection of molecules. A coherent system is one with the highest degree of *algorithmic simplicity* (Zurek, 1989), in that the instructions specifying it is a macroscopic wave function (c.f. Fröhlich and Hyland, 1995), and is hence, much, much shorter than, say, a complete specification of its microstate, volume element by volume element, which would be required if the system were completely random (c.f. Saunders and Ho, 1981). In the limit of a fully coherent system, its algorithmic entropy is zero, as there is effectively a single degree of freedom (Ho, 1993). Away from the fully coherent ideal, there should still be plenty of evidence of correlations between different activities. Some hint of these correlations are already found in the physiological literature.

The integral relationships between heart beat and respiratory cycles, for example, are well known in physiology (Breithaupt, 1989). Similarly, accurate phase relationships are maintained among the four limbs during locomotion, which are also in phase with the pattern of electrical activities in the motor areas of the brain (Kelso, 1991). The remarkable nature of these familiar physiological rhythms are generally overlooked. Each of the subsystems involved—the limb or the respiratory system—is a macroscopic domain consisting of billions of cells each engaged in myriads of enzyme activities. Yet, each behaves as a macroscopically coherent domain capable of maintaining phase correlations with one another.

The correlations between different physiological rhythms are almost never perfect, especially in the state of health, that is because all parts of the system are essentially intercommunicating. Thus, "deterministic chaos" has been used to describe many living functions from the complex, locally unpredictable behaviour of ant colonies (Goodwin, 1994) to unrepeatable patterns of brain activities (Freeman, 1995). An example is the heart beat, which is found to be much more irregular in healthy people than in cardiac patients. Goldberger (1991) came to the conclusion that healthy heartbeat has "a type of variability called chaos," and that loss of this "complex variability" is associated with pathology and with aging. Similarly, the electroencephalogram or electrical activities associated with the active functional brain also contains many frequencies whereas during epileptic fits, the spectrum is characteristically greatly impoverished (Kandel, Schwarz and Jessell, 1991). There is much debate at present as to whether these complex variabilities associated with the healthy, functional state constitute chaos in the technical sense (Glass and Mackey, 1988).

Another way to understand the complex activity spectrum of the healthy state, I suggest, is that it is polychromatic, approaching "white" in the ideal, in which all the modes of energy storage are equally represented. It corresponds to the so-called $f(\lambda)$ = const. rule that Popp (1986) has generalized from the spectrum of light or "biophotons" which have been found to be emitted from all living systems. It is a state of both maximum and minimum entropy—maximum because all the space-time modes are equally populated

(over a sufficiently macroscopic timescale), but minimum because the modes are all coupled together to give in effect a single degree of freedom (see Ho, 1993; 1994a, 1996b). In a system where there is no impedance to energy mobilization, all the modes are intercommunicating and hence all the frequencies will be represented. Instead, when coupling is imperfect, or when the subsystem, say, the heart, or the brain, is not communicating properly, it falls back on its own modes, leading to an impoverishment of its activity spectrum.

If my conjecture is correct, then analyses of autocorrelations and cross correlations of physiological rhythms may begin to reveal interesting patterns suggestive of factorizability or near-factorizability. Equation (14) may be used for this purpose.

Evidence for Nonlocal Intercommunication

Another important class of evidence for quantum coherence is nonlocal, intercommunication, as in the limit of coherence time and coherence volume, intercommunication is instantaneous, nonlocal, and noiseless (Ho, 1996a). Spatial coherence of brain activities has been observed by, among others, Freeman and Barrie (1994), have recorded electrical activities of the rabbit brain which are phase-coherent, at least over an area of several square millimeters, for which no obvious source can be identified, nor obvious means of intercommunication by known neural mechanisms. Singer and his coworkers, similarly, have recorded electrical activities in widely separated areas of the cat's brain—in the same or different hemispheres—which are phase coherent to a high degree (see Gray et al., 1989; Singer, 1990, 1994). These findings have spurred speculations on novel mechanisms mediating coherence, including microtubules (Hameroff and Penrose, 1995) or water trapped inside microtubules acting in the manner of optical fibres (Jibu et al., 1994). In contrast, I have proposed that those findings are manifestations of nonlocal intercommunication (see Ho, 1997), which suggests that the brain is a coherent domain, to begin with. Of course, current measurement techniques are yet unable to distinguish between communication at the speed of light, and genuine instantaneous (nonlocal) intercommunication. This applies also to the macroscopic phase correlations between physiological rhythms in widely separated organs of the body mentioned above, where it would be virtually impossible to intercommunicate by means light signals sent via water trapped inside microtubutes acting as optical fibres.

Other more esoteric demonstrations of nonlocality should also be sought, such as biological analogues of the physical phenomena reviewed by Aharonov (1986). We have produced preliminary evidence that *Drosophila* embryos may serve as biological detectors of the Aharonov-Bohm effect (Ho et al., 1994), in that body pattern abnormalities typically induced by static magnetic fields (see later), are found to be inducible in a region where the magnetic flux is nearly zero, but the vector potential is nonvanishing. However, these results are perhaps not easy to interpret precisely.

Evidence for Coherent Excitations

Experimental attempts have been made to detect Fröhlich's (1968; 1980) coherent excitations that are presumably associated with different biological states, with several claims of success (recently reviewed by Wu, 1994). A lot of the experiments are based on "resonance" responses to external electromagnetic fields of different frequencies and variously modulated frequencies which are notoriously difficult to analyze, let alone repro-

duce. I suspect that these highly nonlinear results require a different kind of statistical analysis that detects *patterns* of responses, like the strange attractors of chaos theory, rather than single value responses. Nevertheless, the "Fröhlich state" is now an active area of theoretical as well as experimental research (see Pokorny, 1995). I mentioned that coherent excitations can exist in both phonons and photons extending over macroscopic distances within, and perhaps also outside the organism. Emitted photons can be detected relatively easily, and may present a more feasible experimental system.

The emission of electromagnetic radiation from coherent lattice vibrations in a solid-state semiconductor has recently been experimentally demonstrated for the first time (Dekorsy et al., 1995). The possibility that organisms may use electromagnetic radiations to communicate between cells was already entertained by Soviet biologist Gurwitsch (1925) early this century. This hypothesis was revived by Popp and his coworkers in the late 1970s, and there is now a large and rapidly growing literature on "biophotons" believed to be emitted from a coherent photon field (or energy storage field) within the living system which are indeed involved in "nonsubstantial" intercommunication between cells and organisms (see Popp, Li, and Gu, 1992).

Working in Popp's laboratory, we found that a single, brief exposure of synchronously developing early fruitfly embryos to white light results in the re-emission of relatively intense and prolonged flashes of light, some tens of minutes and even hours after the light exposure (Ho et al., 1992b). The phenomenon is reminiscent of phase-correlated collective emission, or *superradiance*, in atomic systems, although the time-scale is orders of magnitude longer, perhaps in keeping with the energy storage coherence times of the organism. For phase-correlation to build up over the entire population, one must assume that each embryo has a *collective* phase of all its activities, in other words, each embryo must be considered a highly (quantum) coherent domain, despite its multiplicity of activities (Ho, Zhou and Haffegee, 1995; Zhou, et al., 1996). This is not unlike the phase-locking of macroscopic physiological rhythms described above.

During the same period of early development in *Drosophila*, exposure of the embryos to weak static magnetic fields also cause characteristic global trans-formation of the normal segmental body pattern to helical configurations in the larvae emerging twenty-four hours later (Ho et al., 1992a). As the energies involved are several order of magnitude below the thermal threshold, we conclude that there can be no effect unless the external field is acting on a coherent domain where charges are moving in phase, or where magnetically sensitive liquid crystals are undergoing phase alignment globally (Ho et al., 1994). Liquid crystals may indeed be the material basis of many, if not all aspects of biological organization (Ho et al., 1996).

Organisms are Dynamic, Polyphasic Liquid Crystals

The importance of liquid crystals for living organization was recognized by Joseph Needham (1936) among others. He suggested that living systems actually *are* liquid crystals, and that many liquid crystalline mesophases may exist in the cell although they cannot then be detected. Indeed, there has been no direct evidence that extensive liquid crystalline mesophases exist in living organisms or in the cytoplasm until our recent discovery of a noninvasive optical technique (Ho and Lawrence, 1993; Ho and Saunders, 1994; Newton, Haffegee and Ho, 1995; Ross et al., 1997). This enables us to obtain high resolution and high contrast coloured images of live organisms based on visualizing just the kind of coherent liquid crystalline mesophases which Needham and others had predicted.

The technique amplifies small birefringences typical of biological liquid crystals, enabling us to see the whole living organism down to the phase alignment of the molecules that make up its tissues. Brilliant interference colours are generated, specific for each tissue, dependent on the birefringence of the molecules and their degree of coherent phase alignment. The colours are generated *even as the molecules in the tissues are busily transforming energy*. That is possible because visible light vibrates at 10^{14}Hz, much faster than the molecules can move, so the tissues will appear indistinguishable from static crystals to the light passing through so long as the movements of the constituent molecules are sufficiently coherent. The brightness (intensity) of the colours actually increases with increasing activity, suggesting that the degree of coherence is higher the greater the energy input. With this imaging technique, one can see that the organism is *thick with activities at every level, coordinated in a continuum from the macroscopic to the molecular*. And that is what the coherence of the organism entails.

These images also bring out another aspect of the wholeness of the organism: all organisms, from protozoa to vertebrates without exception, are polarized along the antero-posterior (or oral/adoral) axis, so that all the colours in different parts of the body are maximum when the axis is appropriately aligned, and they change in concert as the organism is rotated from that position. The major body axis is the *optic axis* of the whole organism, which is, in effect, a single (uniaxial) crystal. This leaves us in little doubt that the organism is a singular whole, despite the diverse multiplicity and polychromatic nature of its constituent parts.

Conclusion

I have presented theoretical considerations and experimental evidence to support the idea that the living system can be conceptualized as a dynamically closed, self-sufficient energetic domain of cyclic nondissipative processes coupled to irreversible dissipative processes. This effectively frees the organism from thermodynamic constraints, as there is always coherent energy available within the system which is mobilized at maximum efficiency over all space-time domains. Because of that, all parts of the system are poised for rapid, specific intercommunication, enabling it to function as a coherent whole. In the limit of the coherence time and coherence volume of energy storage, intercommunication is instantaneous (nonlocal) and noiseless.

The organism can be regarded, in the ideal, as a quantum superposition of activities—organized according to their characteristic space-times—each itself coherent, so that it can couple coherently, i.e., nondissipatively, to the rest. Quantum superposition enables the system to maximize its potential degrees of freedom so that the single degree of freedom required for coherent action can be *instantaneously* accessed.

The main implication of quantum coherence for living organization is that, in maximizing both local freedom and global intercommunication, the organism is in a very real sense completely free. Nothing is in control, and yet everything is in control. An organic whole is an *entangled* whole, where part and whole, global and local are so thoroughly implicated as to be indistinguishable, and where each part is as much in control as it is sensitive and responsive. There is no choreographer orchestrating the dance of molecules in the living system. Ultimately, choreographer and dancer are one and the same.

Acknowledgments

This article grew out of discussions and correspondences with many colleagues over the past year who have given me new ideas, taught me more about physics, or drew my attention to relevant publications: Geoffrey Sewell, Kenneth Denbigh, Rufus Lumry, Rickey Welch, Franklin Harold, Peter Marcer, Peter Saunders, and Brian Goodwin. Helpful comments are gratefully acknowledged from Walter Freeman and Stewart Wolf.

References

Aharonov, Y. (1986). Non-local phenomena and the Aharonov-Bohm effect. In R. Penrose and C.J. Isham, (eds.). *Quantum concepts in Space and Time* pp. 42–56. Oxford: Oxford Science Publication, Clarendon Press.

Berry, M.N., Gregory, R.B., Grivell, A.R., Henly, D.C., Phillips, J.W., Wallace, P.G. & Welch, G.R. (1987). Linear relationships between mitochrondiral forces and cytoplasmic flows argue for the organized energy-coupled nature of cellular metabolism. *FEB* 224, 201–207.

Blumenfeld, L.A. (1983) *Physics of Bioenergetic Processes.* Heidelberg: Springer-Verlag.

Breithaupt, H. (1989). Biological rhythms and communications. In F.A. Popp, U. Warnke, H.L. Konig and W. Peschka (eds.). *Electromagnetic Bioinformation 2d. ed.*, pp. 18–41. Berlin: Urban & Schwarzenberg.

Clegg, J.S. (1985). Properties and metabolism of the aqueous cytoplasm and its boundaries. *American Journal of Physiology.* 246, R133–151.

Dekorsy, T., Auer, H., Waschke, C., Bakker, H.J., Roskos, H.G. & Kurz, H. (1995). Emission of submillimeter electromagnetic waves by coherent phonons. *Physical Review Letters* 74, 738–741.

Denbigh, D. (1951). *The Thermodynamics of the Steady State.* New York: Methuen & Co., Ltd.

Duffield, N.G. (1988). Global stability of condensation in the continuum limit for Fröhlich's pumped phonon system. *Journal of Physics A: Mathematical and General* 21, 625–641.

Ehrenberg, W. (1967). Maxwell's demon. *Scientific American* 217, 103–110.

Eigen, M. & Schuster, P. (1977). The hypercycle: a principle of natural self-organization Part A; Emergence of the hypercycle. *Naturwissenshaften* 64, 541–552.

Fleming, G.R., Martin, J.L. and Breton, J. (1988). Rates of Primary Electron Transfer in Photosynthetic Reaction Centres and Their Mechanistic Implications, *Nature* 333, 190–192.

Freeman, W.J. (1995). *Societies of Brains. A Study in the Neuroscience of Love and Hate.* New Jersey: Lawrence Erlbaum Associates.

Freeman, W.J. & Barrie, J.M. (1994). Chaotic oscillations and the genesis of meaning in cerebral cortex. In: G. Bizsaki, (ed.) *Temporal Coding in the Brain.* Berlin: Springer-Verlag.

Fröhlich, H. (1968). Long range coherence and energy storage in biological systems. *International Journal of Quantum Chemistry* 2, 641–649.

Fröhlich, H. (1980). The biological effects of microwaves and related questions. *Advances in Electronics and Electronic Physics* 53, 85–152.

Fröhlich, F. & Hyland, G.J. (1995). Fröhlich coherence at the mind-brain interface. In: J. King and K.H. Pribram (eds.). *Scale in Conscious Experience: Is the Brain Too Important To Be Left To Specialists to Study?* pp. 407–438. Mahwah, New Jersey: Lawrence Erlbaum Associates.

Glansdorf, P. and Prigogine, I. (1967). *Thermodynamic theory of Structure, Stability and Fluctuations.* London: Wiley.

Glass, L. & Mackey, M.C. (1988). *From Clocks to Chaos: The Rhythms of Life.* Princeton, New Jersey: Princeton University Press.

Gnaiger, E. (1994). Negative entropy for living systems. Controversy between Nobel laureates Schrödinger, Pauling and Perutz. *Modern Trends in BioThermoKinetics* 3, 62–70.

Glauber, R.J. (1970). Coherence and quantum detection. In R.J. Glauber, (ed.). *Quantum Optics.* New York: Academic Press.

Goldberger, A.L. (1991). Is the normal heartbeat chaotic or homeostatis? *NIPS* 6, 87–91.

Goldin, E. (1982). *Waves and Photons, An Introduction to Quantum Optics.* New York: John Wiley and Sons.

Goodwin, B.C. (1994). *How the Leopard Changed Its Spots: The Evolution of Complexity.* London: Weidenfeld and Nicolson.

Goodwin, B.C. (1995). Biological rhythms. In: *Biocommunication. S327 Living Processes*, pp.183–230. Milton Keynes: Open University Press.

Gray, C.M., Konig, P., Engel, A.K. and Singer, W. (1989). Oscillatory responses in cat visual cortexexhibit inter-columnar synchronization which reflects global stimuls properties. *Nature* 338, 334–337.

Gurwitsch, A.G. (1925). The mitogenic rays. *Botanical Gazette* 80, 224–226.
Haken, H. (1977). *Synergetics*. Berlin: Springer-Verlag.
Harold, F.M. (1986). *The Vital Force: A Study of Bioenergetics*. New York: W.H. Freeman.
Ho, M.W. (1993). *The Rainbow and the Worm: The Physics of Organisms*. Singapore: World Scientific.
Ho, M.W. (1994a). What is Schrödinger's negentropy? *Modern Trends in BioThermoKinetics* 3, 50–61.
Ho, M.W. (1994b). Towards an indigenous western science—the organism as a coherent space—time structure. In: W.Harman and J. Clark, (eds.). *New Metaphysical Foundations of Modern Science,* pp. 179–213. Sausalito: Institute of Noetic Sciences.
Ho, M.W. ed. (1995a) *Bioenergetics, S327 Living Processes, An Open University Third Level Science Course*. Milton Keynes: Open University Press.
Ho, M.W. (1995b). Bioenergetics and the coherence of organisms. *Neural Network World* 5, 733–750.
Ho, M.W. (1996a). Bioenergetics and biocommunication. In: R. Paton (ed.). *Proceedings IPCAT95* (in press). Singapore: World Scientific.
Ho, M.W. (1996b). The biology of free will. *Journal of Consciousness Studies* (in press).
Ho, M.W. (1996c). Bioenergetics, biocommunication and organic space-time. Proc. British Computing Society Symposium on Living Computers, Greenwich University.
Ho, M.W. (1997). Quantum coherence and conscious experience. Kybernetes.
Ho, M.W., French, A., Haffegee, J. & Saunders, P.T. (1994). Can weak magnetic fields or potentials affect pattern formation? In: M.W. Ho, F.A. Popp, and U. Warnke, (eds.). *Bioelectrodynamics and Biocommunication*, pp.195–207. Singapore: World Scientific.
Ho, M.W., Haffegee, J., Newton, R. & Ross, S. (1996). The organism as a polyphasic liquid crystal. *Bioelectrochemistry and Bioenergetics* (in press).
Ho, M.W. & Lawrence, M. (1993). Interference colour vital imaging—a novel noninvasive technique. *Microscopy and Analysis* (September 26).
Ho, M.W., Popp, F.A. & Warnke, eds. (1994). *Bioelectrodynamics and Biocommunications*. Singapore: World Scientific.
Ho, M.W. & Saunders, P.T. (1994). In: M.W. Ho, F.A. Popp and U. Warnke, (eds.). Liquid crystalline mesophases in living organisms. In: *Bioelectromagnetism and Biocommunication,* pp. 213–225. Singapore: World Scientific.
Ho, M.W., Stone, T.A., Jerman, I., Bolton, J., Bolton, H., Goodwin, B.C., Saunders, P.T. & Robertson, F. (1992a). Brief exposure to weak static magnetic fields during early embryogenesis cause cuticular pattern abnormalities in *Drosophila* larvae. *Physics in Medicine and Biology* 37, 1171–1179.
Ho, M.W. Xu, X., Ross, S. & Saunders, P.T. (1992b). Light emission and rescattering in synchronously developing populations of early *Drosophila* embryos—evidence for coherence of the embryonic field and long range cooperativity. In: F.A. Popp, K.H. Li and Q. Gu, (eds.). *Advances in Biophotons Research,* pp. 287–306. Singapore: World Scientific.
Ho, M.W., Zhou, Y.M. & Haffegee, J. (1995). Living organization, the coherence of organisms and the morphogenetic field. In: L. Trainor and C. Lumsden, (eds.). *Physics in Biology* (in press). New York: Academic Press.
Jibu, M., Hagan, S., Hameroff, S.R., Pribram, K.H., Yasue, K. (1994). Quantum optical coherenc in cytoskeletal microtubules: implications for brain function. *Biosystems* 32, 95–209.
Kandel, E.R., Schwarz, J.H. & Jessell, T.M. (1991). *Principles of Neural Science*, 3rd ed. New York: Elsevier.
Kauffman, S.A. (1993). *The Origins of Order, Self-Organization and Selection in Evolution.* New York: Oxford University Press.
Kelso, J.A.S. (1991). Behavioral and neural pattern generation: The concept of neurobehavioral dynamical systems. In: H.P. Koepchen and T. Huopaniemi, (eds.). *Cardiorespiratory and Motor Coordination*, pp. 224–234. Berlin: Springer-Verlag.
Leggett, A.J. (1986). The superposition principle in macroscopic systems. In: R. Penrose and C.J. Isham, (eds.). *Quantum concepts in Space and Time*, pp. 28–40. Oxford: Oxford Science Publication, Clarendon Press.
Lumry, R. (1991). Mechanical, force, Hydration and Conformational fluctuations in Enzyme Catalysis. In *A Study of Enzymes, vol. II, Mechanisms of Enzyme Action* (S.A. Kuby, ed.). Boca Raton, Florida: CRC Press.
Maturana, H.R. and Varela, F.J. (1987). *The Tree of Knowledge*. Boston: Shambala.
McClare, C.W.F. (1971). Chemical machines, Maxwell's demon and living organisms. *Journal Theoretical Biology* 30, 1–34.
McClare, C.W.F. (1972). A molecular energy muscle model. *Journal Theoretical Biology* 35, 569–575.
Morowitz, H.J. (1968). *Energy Flow in Biology*. New York: Academic Press.
Needham, J. (1936). *Order and Life*. Cambridge, Mass: MIT Press.

Newton, R., Haffegee, J. & Ho, M.-W. (1995). Colour-contrast in polarized light microscopy of weakly birefringent biological specimens. *Journal of Microscopy* 180, 127–130.

Pokorny, J. ed. (1995). Biophysical Aspects of Coherence, Conference 1995 (Special Issue), *Neural Network World* 5 (5).

Popp, F.A. (1986). In: C.W. Kilmister, (ed.). *Disequilibrium and Self-Organization*, p.207. Dordrecht: Reidel.

Popp, F.A., Li, K.H. & Q. Gu, eds. (1992). *Recent Advances in Biophoton Research and its Applications*. Singapore: World Scientific.

Preparata, G. (1980). What is Quantum Physcis? Back to the QFT of Planck, Einstein and Nernst. Lecture given at the IX Winter School on Hadron Physics, Folgaria, Italy.

Prigogine, I. (1967). *Introduction to Thermodynamics of Irreversible Processes*. New York: John Wiley & Sons.

Ross, S., Newton, R. Zhou, Y.M., Haffegee, J., Ho, M.W., Bolton, J.P., and Knight, D. (1997). Quantitative image analysis of birefringent biological material. *Journal of Microscopy* 187, 72–67.

Rothschild, K. J., Ellias, S.A., Essign, A. and Stanley, H.E. (1980). Nonequilibrium Linear Behavior of Biological Systems. *Biophysics Journal*, 30, 209–230.

Saunders, P.T. & Ho, M.-W. (1981). On the increase in complexity in evolution. II. The relativity of complexity and the principle of minimum increase. *J. theor. Biol.* 90, 515–530.

Schrödinger, E. (1944). *What is Life?* Cambridge: Cambridge University Press.

Sewell, G.L. (1991). Non-equilibrium statistical mechanics: Dynamics of macroscopic observables. In: W. Gans, A. Blumen and A Amann (eds.). *Large-Scale Molecular Systems: Quantum and Stochastic Aspects*, pp. 1–48. New York: Plenum Press.

Singer, W. (1990). Self-organization of cognitive structures. In: J. Eccles and O. Creutzfeld, (eds.). *The Principles of Design and Operation of the Brain*. Berlin: Springer.

Singer, W. (1994). Organizing principles of cortical function. *3rd Annual BRA Decade of the Brain Lecture*, University of Oxford, December.

G.R. Welch and D.B. Kell. (1986). In *Fluctuating Enzyme* (G.R. Welch, ed.), p. 451. New York: John Wiley & Sons.

Welch G.R. & Berry, M.N. (1985). Long range energy continua and the coordination of multienzyme sequences *in vivo*. In: G.R. Welch, (ed.). *Organized Multienzyme Systems*. New York: Academic Press.

Welch, G.R. & Clegg, J.S. eds. (1987). *The Organization of Cell Metabolism*. New York: Plenum Press.

Westerhof, H.V. & Van Dam, K. (1987). *Thermodynamics and Control of Biological Free-energy Transduction*. Amsterdam: Elsevier.

Wu, T.M. (1994). Fröhlich's theory of coherent excitation—a retrospective. In: M.-W. Ho, F.A. Popp and U. Warnke, (eds.). *Bioelectrodynamics and Biocommunication*, pp. 387–409. Singapore: World Scientific.

Zeng, H., Qian, Z., Myers, M.P. & ROSBASH, M. (1996). A light-entrainment mechanism for the Drosophila circadian clock. *Nature* 380, 129–135.

Zurek, W.H. (1989). Algorithmic randomness and physical entropy. *Phy. Rev. A* 40, 4731–4751.

Zhou, Y.M., Ho, M.-W., Bolton, J.P., Milani, M., Costato, M. & Musumeci, F. (1996). Biophoton emissionin synchronously developing populations of early *Drosophila* embryos. *Proc. BIOS Europe '96*.