Eric Drexler, space-systems researcher at MIT, published *Engines of Creation* in 1986, predicting machine parts the size of molecules that could be assembled into machines much smaller than biological cells and interact directly with the ‘machinery’ of biology (1), and even the fulfillment of the computer scientist’s dream - the self-reproducing automaton - at the nanoscale, the nanobot. After all, Drexler says, biology is nothing more than a bunch of molecular machines created and honed by evolution.

This frightened many people, including Bill Joy, chief scientist of Sun Microsystems, who wrote a long article in *Wired* in 2000, proposing we should consider halting the developments of nanotechnology, for fear of being overrun by a mass of “grey goo”, the self-replicating nanobots.

Nanobots that can repair damaged cells, or self-replicate and run amok, remain in the realm of science fiction (2). Many scientists are sceptical, including Richard Smalley, Nobel laureate for ‘buckminster fullerene’ - a new form of carbon in the shape of the geodesic dome named after the dome’s inventor, architect Buckminster Fuller - and George Whitesides, Professor of Chemistry in Harvard University.

There are no examples of molecular machines that work outside living cells, and those in living cells are made and assembled on totally different principles from the way chemists make them in the laboratory.

In the lab, the atomic force microscope can be used to pick up and move individual atoms, but that doesn’t mean one can make molecular-size machines, let alone those that assemble other molecular machines or reproduce themselves. The atomic force microscope is a macroscopic device that can be precisely controlled to manipulate individual atoms. Molecular size machines, on the other hand, will be subject to quantum forces that are uncontrollable.

Drexler appears to be struggling towards the idea that the artificial molecular machines are like those of the living system, about which very little is generally known.

Let me show you an image of living molecular machines working together so perfectly in the organism that the entire organism appears liquid crystalline (3) (Figure 1).

The colours appear under the polarised light microscope with which earth scientists identify rock crystals, but using slightly different settings discovered in our laboratory in 1992 (3,4) that turn out to be especially suited for ordered molecular states in living organisms. Crystals show up in brilliant colours because they have an orderly arrangement of atoms and molecules. But how can a living, squirming worm be like a crystal, when the molecular machines in its body must be moving about, transforming energy?
The answer, which came after a series of investigations, is both simple and revealing. The macromolecules, bound with lots of water, are indeed in a liquid crystalline state, where all the molecules, including bound water, are macroscopically aligned to form a continuum linking up the entire body, throughout the connective tissues, the extracellular matrix and into the interior of every single cell (5). Most importantly, the molecules, including the water, are moving coherent together as a whole. Living molecular machines are made up of at least twice their weight of ‘biological’ water – water that’s an integral part of their structure and function (6-8), as our recent collaborative work on collagen with Franco Musumeci’s laboratory has demonstrated (see Chapter by Agata Scordino).

I said all the molecules are ‘macroscopically aligned’. This is not an exaggeration. The anterior-posterior axis of the body actually defines a global polarizing axis, as though the organism is one single (mono-axial) crystal. When that axis is aligned between the two polaroids, the organism’s muscle and other structures all adopt a single colour, blue, green, orange, red, etc. But when that axis is rotated 90 degrees, blue turns to red or orange, green to yellow and so on, as typically of interferérence colours arising from birefringent or doubly refracting crystals such as quartz.

Thus, when the little fruitfly larva curls around to form a circle, its global axis is correspondingly circularised, and the body musculature and other prominent structures switch colours, from blue to red or green to orange and vice versa.

Light in the visible range vibrates at $10^{14}$ cycles per second. Molecules, however, move much slower, probably at least ten thousand times slower. So the molecules will appear to the light coming through as though motionless. And, as long as all the molecules in each muscle and tissue are moving coherently together, it will give the appearance of static alignment and order, i.e., a crystal. It is like being able to take a sharp image of a very fast moving object with a sensitive film that requires only the briefest exposure time.

![Figure 1. The organism consists of molecular machines working coherently together. Live image of first instar fruitfly larva.](image)
The colours are telling us that the living organism is coherent and whole beyond our wildest dreams; that all the parts are co-ordinated from moment to moment, down to the motion of individual molecular machines.

We’ve done the detailed physical, optical analyses to demonstrate that the brightness of the colour is linearly dependent on the degree of coherent alignment. In the live organism, the brightest parts are always the most active, suggesting that coherence increases with activity. As consistent with this finding, the colours fade when the organism dies.

Living molecular machines, densely packed and embedded in the liquid crystalline matrix, runs in almost perfect cycles, drawing on coherent energy extracted and stored from metabolism. Living molecular machines essentially borrow coherent energy and return it only slightly degraded to the matrix. Their efficiency is such that very little waste heat is generated, which is why they can be packed so densely, and work without burning out.

The two biggest unsolved problems for artificial molecular machines are the energy supply and energy dissipation, which living molecular machines have solved most elegantly, as I shall show in the rest of this article. But there’s a deeper problem.

I am going to offer a series of heuristic arguments to explain the image of the living organism you see, that indicate to me the organism possesses a special kind of wholeness, one that approaches quantum coherence. And - this is the sting in the tail – the molecular machines cannot be individually controlled, just as the whole organism cannot be controlled. Instead, the organism is, to a large degree, a system of molecular democracy of distributed control. Each individual molecular machine operates with maximum freedom, but is at the same time, correlated with the freedom and spontaneity of the whole.

That sounds like a Chinese conundrum. I’ll start at the beginning of the story with the thermodynamics of molecular machines, which offers a new way of looking at living energy and organisation.

Maxwell’s Demon and ‘molecular energy machines’

There are many ways in which living systems appear to go against the second law of thermodynamics. Not only do they resist decay to thermodynamic equilibrium - death by another name - but grow and develop and increase their organisation, even to the extent of being able to reproduce future generations.

Most of all, they can summon energy at will, whenever and wherever required, and in a perfectly coordinated way. That alone was enough to persuade Lord Kelvin, co-inventor of the second law, to exclude them from its dominion (9),

“The animal body does not act as a thermodynamic engine... whatever the nature of these means [whereby mechanical effects are produced in living organisms], consciousness teaches every individual that they are, to some extent subject to the direction of his will. It appears therefore that animated creatures have the power of immediately applying to certain moving particles of matter within their bodies, forces by which the motions of these particles are directed to produce derived mechanical effects.”

In its usual interpretation, the second law of thermodynamics applies to systems consisting of large numbers of identical molecules. A major difficulty with the living system, as first pointed out by Schrödinger in his book, What is Life? (10), is that single molecules, or very few of them, are often the active agents.

Thus, a cell has only one or two molecules of each sequence of DNA in the nucleus that specifies all its proteins. The E. coli bacterium has but several molecules of the protein that enables it to respond to the presence of lactose in its environment, which is enough to induce enzymes that metabolise the sugar, enabling it to grow and to multiply; and that is
typical of whole classes of metabolic regulators. Similarly, it takes no more than a few molecules of a given hormone to bind to specific receptors in the cell membrane in order to initiate a cascade of biochemical reactions that would radically change the whole cell. Does that mean the second law really does not apply to living systems?

Schrödinger drew attention to two key features of living systems. The first - that ‘aperiodic’ crystals are responsible for the heredity of organisms - led directly to the discovery of DNA. The second - the requirement of an additional principle of coherence to account for life - had been relatively neglected by the scientific community. But its time may have come, as evidenced by the overwhelming support for this conference.

Actually, the problem with the second law of thermodynamics is not restricted to biology, but may also appear in physical systems. The most colourful statement of the problem is in the form of Maxwell’s demon - an hypothetical intelligent being who can operate a microscopic trapdoor between two compartments in a container of gas at equilibrium, so as to let fast molecules through in one direction, and the slow ones in the other, as the kinetic energies of the molecules fluctuate statistically around the equilibrium state. Soon, a temperature difference would be created by the accumulation of fast, energetic molecules on one side and slow molecules on the other. At that point, work can be extracted from the system (Figure 2).

The equilibrium state, by definition, has no free energy available to do work. Maxwell’s demon has in effect created a non-equilibrium state out of the thermodynamic equilibrium, which is not only theoretically impossible, but no one has succeeded in so doing.

![Figure 2. Maxwell's demon converting equilibrium to non-equilibrium](image)

The physicist James Maxwell invented this demon in 1867 to illustrate his belief that the second law is statistical, and had no intention of questioning the second law itself. The trapdoors, after all, would be subject to the same statistical fluctuations as the molecules, and would open and close indiscriminately so that the separation of fast from slow molecules could never be achieved, unless we had the magical demon - small and clever enough to observe the fluctuations.

Thirty-eight years later, however, Einstein showed that the fluctuations can be observed, and in fact, were first observed in 1827 by Robert Brown, as Brownian motion, the random movements of microscopic particles (observable under the microscope) jostled about by the thermal fluctuations of the water molecules.
The problem of Maxwell's demon is generally considered as having been ‘solved’ because the demon would require information about the molecules, in which case, the energy involved in obtaining information would be greater than that gained and so the second law remains inviolate.

But that argument fails to take account of the special structure or organization of the system that can supply the ‘information’. Biological membranes, ubiquitous in living systems, are just this kind of informational structures. The cell membrane has an electrical potential gradient of some $10^7$ Vm$^{-1}$ across it. Bound within it are enzymes – molecular machines - catalysing the vectorial transport of ions and metabolites from one side to the other, as for example, the transport of Na$^+$ out of, and K$^+$ into the cell, against their respective concentration gradients, by the Na$^+$/K$^+$ ATPase.

The unidirectional transport of ions and metabolites depend on the asymmetric properties of the membrane itself as well as the enzymes embedded in the membrane. For example, the membrane enzyme Na$^+$/K$^+$ ATPase normally transports Na$^+$ out of the cell and K$^+$ into the cell using the energy from splitting ATP into ADP and Pi. It was found, however, that weak alternating electric fields could drive this directional active transport by the enzyme without ATP being broken down (11). This implies that the energy from the external electric field is directly transduced - specifically transformed - into transport work by the membrane-bound enzyme. Moreover, randomly fluctuating electric fields are also effective, precisely as if Maxwell’s demon were involved in making good use of the fluctuations.

Biophysicist Tsong has offered a model to explain this phenomenon in terms of an enzyme that extends across the membrane, which changes its conformation (shape) and binding affinities for the inorganic ion(s) at the two sides of the membrane (11) (Fig. 3).

![Figure 3. How trans-membrane enzymes effectively act as Maxwell's demon (11).](image)

Astumian and coworkers showed that any system with a saw-tooth potential could respond to random fluctuations in the electric field to transport charged species up a concentrations gradient by a ratchet mechanism (12) (Fig. 4).

It is interesting to note that macromolecules in liquid crystalline mesophases (the prefix *meso-* indicates they are in between the liquid and solid crystal phase) have their dipoles aligned, and could well satisfy the ‘saw-tooth’ potential required of the ratchet mechanism. One is reminded of linear structures such as microtubules, along which molecular motors such as kinesins transport their cargo. This alone tells us that there is something quite special about energy in living systems.
It does not mean that the second law is violated, however. The cell membrane is a non-equilibrium structure with an enormous electrical potential gradient across it. Furthermore, it forms a selective boundary, by virtue of the molecular machines embedded in its matrix, which have affinities for different molecular or ionic species on either side of the membrane (see above). Such membranes are therefore, full of ‘information’.

Information is first and foremost the mobilisation of energy with specificity, efficiency and coordination. How is that achieved? The clue lies in the organism’s space-time structure.

**Figure 4.** Two realizations of the ‘saw-tooth’ potential that can provide a ratchet mechanism for uphill transport. Top, electrical circuit with interdigitating positive and negative electrode; middle, row of oriented dipoles. Bottom, saw-tooth energy diagram (12).

**Space-time structure of living processes and the second law**

It is usually said that the organism is an open system whose organization is maintained in some kind of ‘steady state’ by a flow of energy and chemicals. As soon as that flow is interrupted, disintegration sets in and death begins. That steady state, however, is not a static bulk phase in a rigid container, far from it.

Within the organism, one finds organized heterogeneities or dynamic structures on all scales. There is no homogeneity, nor static phase held at any level. Even a single cell has a characteristic dynamical structure, with all its parts in constant motion. Its electrical potentials and mechanical properties are subject to apparently cyclic and non-cyclic changes as it responds to and counteracts environmental fluctuations.

Spatially, the cell is partitioned into numerous compartments by cellular membrane stacks and organelles, each with its own ‘steady states’ of processes that can respond directly to ‘external’ stimuli and relay signals to other compartments. I put ‘external’ between quotation marks because, in the nested structure of the organism, the environment of a small compartment is enclosed within a larger one, which is in turn enclosed by yet a more inclusive domain, and so on. And within the smallest compartment, ‘microdomains’ with no obvious boundaries can be separately energized to give local circuits; and
complexes of two or more molecules can function as ‘molecular machines’ that can cycle autonomously without immediate reference to its surroundings.

There is now good evidence that the cell is meticulously organised dynamically, down to individual molecular machines (3, 8), that metabolites are ‘channelled’ through successive enzymes working in close proximity to and in correlation with one another. Hardly any molecule exists in bulk solution, and there cannot be any ‘bulk solution. For most, if not all of the water molecules inside the cell, and outside, in the extracellular matrix and connective tissues such as tendons, cartilage and bones, are associated with macromolecules and membranes as ‘biological water’, water that behaves even more strangely than ‘bulk’ water.

In other words, the steady ‘state’ is not a state at all but a conglomeration of processes spatio-temporally organized. The organism has a deep space-time structure, and cannot be represented as an instantaneous state or even a configuration of states. At the very least, it implies that if thermodynamics were to apply to living systems, it must apply at all levels, ultimately, even to individual molecules, and not just to statistical ensembles of molecules. That is what physiologist Colin McClare said, some 30 years ago (14).

The second law restated
In order to formulate the second law of thermodynamics so that it applies to single molecules, McClare introduced the important notion of a characteristic time interval, $\tau$, within which a system reaches equilibrium at temperature $\theta$. The energies contained in the system can be partitioned into *stored* energies versus *thermal* energies (Fig. 5).

![Figure 5. Stored versus thermal, equilibrated energies.](image)

Thermal energies are those that exchange with each other, equilibrate throughout the system and reach equilibrium in a time, $t_e$, less than $\tau$. Stored energies are those that remain in a non-equilibrium distribution, within a time interval $t_s$ greater than $\tau$, either localized within the system, or such that states of higher energy are more populated than states of lower energy for the temperature $\theta$. So, stored energy is any form that does not equilibrate, or degrade into heat in the interval $\tau$.

McClare went on to restate 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 thermal energy into stored energy.

The immediate objection to this formulation is that it is wrong. What does the motor-car depend on if not thermalized energy?
McClare is right to stress that useful work can be done by a molecular system via a direct transfer of stored energy without thermalization. The process of photosynthesis, on which most of life on earth depends, involves the direct, non-thermal absorption of the energy of photons, which is why typical thermodynamic calculations based on the temperature of the sun may be irrelevant. Besides, non-thermal energy transfer is the rule in living processes.

McClare’s restatement of the second law is also unnecessarily restrictive, for thermal energy can be directed or channelled to do useful work in a cooperative system, as in the case of molecular machines embedded in a non-equilibrium membrane mentioned earlier.

Most important of all, in a system with space-time organization, ‘thermalized’ energy from a small compartment is still stored energy within the larger compartment encompassing it (see Figure 6).

![Figure 6. Equilibrium and non-equilibrium in the nested dynamic compartments of the living system.](image)

I have proposed that a more adequate restatement of the second law might be as follows (3, 9):

*Useful work can be done by molecules by a direct transfer of stored energy, and thermalized energy cannot be converted into stored energy in the same system, the system being defined as the (spatial) extent to which thermalized energies equilibrate in a characteristic time.*

The first part of the statement is the same as McClare’s, the second part is new, and offers a way of defining a ‘system’ - in terms of the extent of thermal equilibration in a characteristic time - that may be quite useful.

Thus, the motor-car works on thermalized energy from the combustion engine. But the piston is doing work external to the system containing the thermalized energies of the expanding gases generated from the combustion.

**Slow, quick, quick.**

The major consequence of McClare’s ideas arises from the explicit introduction of time, and hence time-structure, which I have generalised to space-time, and space-time structure. For there appears two quite distinct ways of doing useful work most efficiently, not only
slowly according to conventional thermodynamic theory, but also quickly - both of which are reversible and at maximum efficiency as no entropy is generated. This is implicit in the classical formulation, \(dS \geq 0\), for which the limiting case is \(dS = 0\). The attention to space-time-structure, however, makes much more precise what the limiting conditions are.

Let us take the slow process first. A slow process is one that occurs at a rate matching the time it takes to go to equilibrium, in other words, slow compared to the time required for all exchanging energies to equilibrate, or distribute themselves evenly in the whole system. According to classical thermodynamics, such a process occurs reversibly, and is the most efficient in terms of generating the maximum amount of work without generating any entropy. By taking explicit account of characteristic time, a reversible thermodynamic process merely needs to be slow enough for all thermally-exchanging energies to equilibrate, i.e., slower than \(\tau\), which can in reality be a very short period of time, for processes that are intrinsically fast.

For example, a protein molecule can undergo some \(10^6\) or more conformational fluctuations per second at physiological temperatures, which gives a rough idea of how fast thermal energies equilibrate throughout the molecule. For a protein that’s an enzyme, it will catalyze \(10^3\) reactions during that time. Thus, most catalysis is a ‘slow’ process compared with the time it takes for thermal equilibration. In fact, each enzyme molecule is a ‘microdomain’ isolated from its surroundings for the duration of the catalytic reaction, which can thus be regarded as occurring at equilibrium. So high efficiencies of energy conversion can still be attained in thermodynamic processes that occur quite rapidly, provided that equilibration is fast enough.

The nested compartment structure of the living system is therefore optimised for thermodynamic efficiency, as well as kinetically, for rapid energy transfer. It effectively restricts the spatial extent within which equilibration occurs, thus reducing the equilibration time while increasing the local concentration of reactants.

Thus, local equilibrium may be achieved for most biochemical reactions carried out by molecular machines in the living system. We see that thermodynamic equilibrium is really a subtle concept, depending on the level of resolution of time and space.

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, the process is limited only by the speed of light. Resonant energy transfer between molecules is an example of a fast process. As is well known, excited chemical bonds will vibrate at characteristic frequencies, and any two or more bonds that have the same intrinsic frequency of vibration will resonate with one another. (This happens also in macroscopic systems, as when a tuning fork is struck near a piano, the appropriate string will begin to vibrate when it is in tune.) More importantly, the energy of vibration can be transferred through large distances, theoretically infinite, if the energy is radiated, as electromagnetic radiations travel through space at the speed of light, though in practice, it may be limited by nonspecific absorption in the intervening medium.

Resonant energy transfer occurs typically in \(10^{-14}\)s, whereas the vibrations themselves die down, or thermalize, in \(10^{-9}\)s to \(10^1\)s. It is 100% efficient and highly specific, being determined by the frequency of the vibration itself; and resonating molecules (like people) can attract one another. By contrast, conventional chemical reactions depend on energy transfer that occurs only at collision, it is inefficient because a lot of the energy is dissipated as heat, and specificity is low, for non-reactive species could collide with each other as often as reactive species.

Does resonant energy transfer occur in the living system? McClare suggested it does, especially in muscle contraction, where it has already been shown that the energy released in the hydrolysis of ATP is almost completely converted into mechanical energy in
a molecular machine that can cycle autonomously without equilibrating with its environment. Recent experiments with isolated muscle proteins show that the energy of one ATP molecule split into ADP and Pi may support up to 5 cycles of cross-bridge formation between actin and myosin (15). This goes against the conventional view that each cross-bridge cycle is strictly coupled to the splitting of one ATP molecule, and suggests that the energy is stored either in the myosin head or the actin for more than 100ms – a long, long time from the point of view of molecules - after the release of the bound nucleotide.

This mechanism is especially important within the organism, as it offers a way of synchronising the contraction cycles so the entire muscle fibre and ultimately, the entire muscle can work as a unit.

Ultrafast, resonant energy transfer processes also operate in photosynthesis. The first step is the separation of positive and negative charges in the chlorophyll molecules of the reaction centre, which has been identified to be a readily reversible reaction that takes place in less than $10^{-13}$s (16). And it has been argued by McClare and others that, protein-protein interactions and protein-DNA interactions are not due to complementary shapes – the ‘lock and key’ model – as generally thought, but to electromagnetic resonance recognition (17), which is much more specific, and works at a distance.

To recapitulate, the living system may be using both means of efficient energy transfer: slow and quick reactions, always with respect to the characteristic space-time of the processes involved. Living systems may simultaneously satisfy both quasi-equilibrium and far from equilibrium conditions for minimum entropy production. This important insight has come from taking account of the characteristic space-time of processes.

It also makes explicit the large amount of energy stored in a range of nested space-times. Any system with a dynamic space-time organization is an energy storage depot maintained as a whole far away from thermodynamic equilibrium. Energy is stored in complex chemical molecules, in macromolecular conformational fluctuations, concentration gradients across membranes, in electric fields created by charge separation, in viscoelastic fields due to mechanical strain that could be global to the entire cell or organism, or local to individual proteins. The energy storage times range from $10^{-9}$s or shorter intervals to minutes, hours, days or longer.

It is in dealing with organized complexity that conventional thermodynamic principles are most inadequate. And yet, space-time structure is crucial to the organization of living processes, and cannot be ignored if thermodynamics were to be made applicable to living systems. In fact, our enquiry so far has suggested that this space-time structure may hold the key to the efficiency and rapidity of energy transfer in the living system.

**Quantum molecular machines**

Another important insight is the fundamental quantum nature of biological processes. McClare defined a molecular energy machine as one in which the energy stored in single molecules is released in a specific molecular form and then converted into another specific form so quickly that it never has time to become heat. It is also a quantum machine because the macroscopic effect is the sum of the effects produced by single molecules. Muscle contraction is the most obvious example. But it is becoming clear that all enzymes work in the same way. They are efficient molecular energy machines each capable of storing and transducing a finite quantum of energy in a specific manner (8).

Enzymologist Lumry has produced compelling evidence that enzymes work in a manner that minimizes change in free energy, $\Delta G$, through being flexible (18). The reason enzymes have to be so large, relative to the active site, is because energy released from the substrate is directly transferred via deformation of the protein molecule to where the energy
is needed. The energy released is stored transiently in the protein molecule before it is delivered to where it is used. Hence, there is little or no dissipation of the energy.

Very few reactions that take place in the organism involve thermalization of stored molecular energy. This does not preclude thermal excitation where the activation energy barrier is sufficiently low, as for example, in the hydrogen bonds that maintain the three-dimensional shapes of protein molecules. Indeed, such fluctuating changes in conformation occur in nanoseconds (10^-9 s), and have been observed in a large number of proteins. But, in order to do useful work, the fluctuations have to be coordinated. Otherwise there will be equal probability for the reaction to go forwards as backwards - as predicted in statistical mechanics.

There seems to be no escape from the fundamental problem of biological organization: how can individual quantum molecular machines function in collective modes extending over macroscopic distances, ultimately the whole organism? Just as bulk phase thermodynamics is inapplicable to the living system, so perforce, some new principle is required for the coordination of quantum molecular machines. This principle is coherence. The coherence of quantum molecular machines entails quantum coherence.

Let’s stay with thermodynamics, to see how it could apply to the living system as a whole.

The organism as an energy storage domain
The new concept of ‘stored energy’ developed above is a good starting point, as opposed to the usual ‘free energy’. ‘Free energy’ cannot be defined a priori, much less can it be assigned to single molecules. Even changes in free energy cannot be defined unless we know how far the reaction is from equilibrium.

‘Stored energy’, originally defined by McClare with respect to a characteristic time interval, has been extended to a characteristic space-time. As such, stored energy is explicitly dependent on space-time differentiation, hence it is a precise concept, defined on the space-time domain of the processes involved. Stored energy has meaning with respect to single molecules as much as it has with respect to the whole organism. The organism can be considered, first and foremost, as an energy storage domain, and stored energy is coherent energy capable of doing work at the specific space-time domain in which it is stored.

Many physicists and chemists have stressed the importance of energy flow and dissipation to living systems. Prigogine made ‘dissipative structures’ a house-hold name by calling attention to the possibility of dynamic organisation arising out of energy flow and energy dissipation (19).

The archetypal dissipative structure is the Bénard-Raleigh cells that appear in a shallow pan of liquid heated uniformly from below. At a critical temperature difference between the top and the bottom, a phase transition occurs, the lighter warm water rises to the top while the denser cold water sinks, giving a coherent pattern of convection cells that look like a honeycomb from the top of the pan. This dissipative structure is a collective activity that extends over all the molecules - some 10^{23} of them - in the system (Figure 7).
Figure 7. The Bénard-Raleigh convection cells, a ‘dissipative structure’.

Prigogine emphasized energy flow and dissipation in the phase transition to collective behaviour that makes the ‘dissipative structure’, but the phenomenon depended on the liquid being able to absorb and store the heat energy, and to expand. In order to benefit from energy flow, the system must capture and store the energy to lift it up from thermodynamic equilibrium, at which nothing ever happens by definition.

Similarly, solar energy flows through Mars and Venus as much as earth, but only earth can capture the energy by means of the chlorophyll of green plants to support most of the biosphere, which is one big energy store maintained far away from thermodynamic equilibrium.

The key to understanding the thermodynamics of organisms is, therefore, not energy flow or energy dissipation, but energy storage under energy flow (Figure 8).
Figure 8. Energy flow, energy storage and the reproducing life-cycle

Energy flow is of no consequence unless the energy is trapped within the system where it circulates, to do work and to build up structures for storing the energy before it is dissipated (3). ‘Dissipative structures’ is a misnomer for what are really ‘energy storage structures’.

An organism arises when the loop of circulating energy somehow closes on itself to give a regenerating, reproducing life-cycle. Within the life-cycle, energy is mobilized, remaining largely stored as it is mobilized. The energy goes into complex cascades of coupled cyclic processes within the system before it dissipates to the outside. These cascades of cycles span the entire gamut of space-times from slow to fast, from local to global, that all together make up the life-cycle. An intuitive representation is given in Figure 9.

Each cycle is effectively a domain of coherent energy storage defined by the characteristic space-time of the process involved (see Figures 5 and 6.) Coherent energy is energy that can do work because it is all coming and going together. The cycles within the life-cycle are all interlinked in a very special way in order to feed off the one-way energy flow and to transfer the energy so it remains largely stored as it is transferred. Think of the cycles as eddies forming in a pool off the main river stream. The more eddies there are, the more energy is stored, and the longer it takes for the energy to dissipate. The average residence time of energy is correlated with the organised complexity of the system, and is therefore a measure of it.
Coupled processes are familiar in biochemistry: practically all thermodynamically uphill reactions - those requiring energy - are coupled to the thermodynamically downhill ones - those yielding energy. The ATP/ADP couple, ubiquitous to the living system, effectively turns all biosynthetic and other energy requiring uphill reactions downhill.

Another prominent way in which cycles appear in the living system is in the familiar spectrum of biological rhythms, with periods ranging from milliseconds for work cycles of molecular machines to circadian and circa annual cycles of whole organisms and populations of organisms.

These cycles interlock to give the organism a complex, multidimensional, entangled space-time very far removed from the simple, linear Newtonian space and time of mechanical physics. Each cycle, when enlarged, will have a structure similar to the whole. This self-similar fraction structure is characteristic of living processes. A fractal structure has fractional dimensions rather than the usual one, two or three. Organic space-time is fractal as opposed to structureless, uniform Newtonian time (see later).

There are some suggestive observations that all biological rhythms may indeed be entangled or coupled and correlated. Geneticists have discovered that mutations in at least two genes of the fruitfly, 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 (20). This correlation spans seven orders of magnitude of characteristic time scales, reflecting the full extent of coupled energy storage and mobilisation in the living system.

**Energy storage and mobilisation is symmetrical**

Energy is stored and mobilized over all space-times according to the relaxation times and volumes of the processes involved. The result, as stated earlier, is that the organism can take advantage of two different ways to mobilize energy with maximum efficiency – non-equilibrium transfer in which stored energy is transferred before it is thermalized, and quasi-equilibrium transfer, which is slow enough to allow all thermalized and other exchanging energies to equilibrate, for which the free energy change approaches zero, in accordance with conventional thermodynamic considerations.

Because all the modes of activity are coupled together, energy input into any mode can be readily shared, or delocalised over all modes; and conversely, energy from all modes can become concentrated into any mode. Another way to express the same thing is
that energy from any point can spread throughout the system, and can also become concentrated to any point from all over the system. Energy transfer is reciprocal and reversible.

I have argued (3) that these and other properties of the living system can be derived from a certain interpretation of the thermodynamics of the steady state, beginning with Onsager’s reciprocity relationship and Morowitz’ theorem (see Box 1 and Box2).

Onsager’s reciprocity relationship predicts that symmetrical couplings will arise in a multi-component system of coupled linear processes at steady state, while Morowitz’ theorem predicts that at steady state, the flow of energy from source to sink will lead to at least one cycle in the system.

Box 1
Onsager’s Reciprocity Relation
Let \( J_1 \) and \( J_2 \) represent two coupled flow processes, and \( X_1, X_2 \), the corresponding forces, then,

\[
J_1 = L_{11}X_1 + L_{12}X_2
\]

\[
J_2 = L_{21}X_1 + L_{22}X_2
\]

Where \( L_{11} \) and \( L_{22} \) are proportionality constants relating the flows each to their respective force, \( L_{12} \) and \( L_{21} \) are coupling coefficients representing the extent to which coupling occurs: in other words, how the force of one process influences the flow of the other process. For example, the two flows could be electricity and inorganic ions, due respectively to an electric potential gradient and an ionic concentration gradient. The cross coefficients tell us the extent to which the electric potential gradient influences the diffusion of ions, and conversely, how the ionic concentration gradient affects the flow of electricity.

Onsager shows that if the principle of microscopic reversibility is true for a system in equilibrium and near equilibrium, it implies that,

\[
L_{12} = L_{21}
\]

This means that the coupling of the two processes becomes completely symmetric, even in states of non-equilibrium at the molecular level. In other words, the force of each process has the same reciprocal effect on the other process. This result can be generalized to a system of many coupled processes described by a set of linear equations of the same form,

\[
J_i = \Sigma_k L_{ik}X_k
\]

where \( J_i \) is the flow of the \( i^{th} \) process \((i = 1, 2, 3,...n)\), \( X_k \) 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 \( i \neq k \)). It may happen that some of the coupling coefficients are zero (in cases where the processes do not interact at all). Some may be positive while others are negative. Still, for such a multicomponent system, certain of the couplings will be symmetrical; in other words, for some \( i \) and \( k \), \((i \neq k)\),
Linear processes are those for which the ‘flows’ are proportional to the ‘forces’, and are usually found in the near-equilibrium regime, where Onsager’s reciprocity relationship is considered to apply. In this regime, every reaction in the system is in detailed balance, i.e., going the same rate backwards as forwards. This principle of microscopic reversibility has long been considered fundamental to the steady state. Onsager showed, however, that the principle is really not necessary for the reciprocity relationship to hold; that symmetrical couplings will arise even when detailed balance is not obtained for every reaction, so long as balance is attained at some level.

That has opened the way for suggestions that the reciprocity relationship may also apply in regimes far from equilibrium, provided quasi-equilibrium assumptions hold locally, as they would in a system with the nested space-time differentiation envisaged here (3). Furthermore, combinations of non-linear forces can also give linear effects, thus expanding the possibilities for reciprocity and reversible energy transfer.

Box 2  
Morowitz’s Theorem
A canonical ensemble of systems is 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, i.e,

$$f_i t_{ij} = f_j t_{ji}$$

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, 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 $j$,

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

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 our original assumption that there is absorption of radiant energy, so we must conclude that the equality of forward and reverse transitions does 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 equals to the sum of all backward transitions, i.e,
\[ \frac{df_{ij}}{dt} = 0 = \sum (f_{ij}' - f_{ji}') \]

But it has already been established that some \( f_{ij}' - f_{ji}' \) 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.

The above line of reasoning led Morowitz to an important theorem:
*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.*

As for cycles, biologists have long wondered why biological activities are so predominantly rhythmic or cyclic, and a lot of effort has gone into identifying the centre of control, or master genes that set biological rhythms; all to no avail.

Cycles pervade the organism because they make thermodynamic sense for sustainable systems like organisms. Cycles involve perpetual returns to the same states, thus giving dynamic stability, the characteristic of steady states. Cycles are dynamic ‘boxes’ to all intent and purposes. They also enable the activities to be coupled, or linked together, so that those yielding energy can transfer the energy directly to those requiring energy, and the direction can be reversed when the need arises. These symmetrical, reciprocal relationships are most important for sustaining the system. That’s how our metabolism and physiology is actually organised: closing the cycle and linking up.


He defined 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”.

Denbigh’s definition is too restrictive, however, to apply to the living system, and, as I have been arguing, unnecessarily so. By now it will have become clear that thermodynamics was invented for macroscopic systems and says nothing about the microscopic details. The microscopic details can vary freely so long as the macroscopic parameters are satisfied.

A less restrictive formulation – one consistent with the space-time differentiation of the living system described here – is as follows (3, 22,23):

*The living system tends towards a dynamic equilibrium in which the macroscopic parameters such as temperature, pressure and composition have time-independent values despite the occurrence of dissipative processes.*

My formulation omits Denbigh’s phrase, “at every point of the system”. Microscopic homogeneity is not crucial for the formulation of any thermodynamic state, on the contrary, it is irrelevant to the living system and probably all real processes.

But how does the dynamic equilibrium arise?

The clue lies within the history of the thermodynamics of the steady state, which began with W. Thomson's (Lord Kelvin) treatment of the thermoelectric effect. This arises in an electrical 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 that 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,

\[ \Delta S_p + \Delta S_T = 0 \]

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 that 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 that 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, 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, and 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 that is later validated by Onsager’s reciprocity relationship.

**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 cyclic 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 out to zero,

\[ \sum_k \Delta S_k = 0 \]

This will include most living processes on account of the ubiquity of coupled cycles, for which the net entropy production may indeed balance out to zero. Cycles are states of perpetual return, so entropy does not accumulate, and also, no net entropy need to be generated.

Thus, the living system tends towards a dynamic balance at the macroscopic level, or as a whole (Fig. 10). The simple equation \( \sum \Delta S = 0 \) inside the life cycle represents the overall internal balance and compensation of entropy so that the system’s organisation is maintained, while the necessary dissipation and entropy are exported to the outside, as represented by \( \sum \Delta S > 0 \).

That’s the abstract ideal. In practice, dissipation within the system goes to a minimum, not quite zero. The system does grow old, and eventually dies, but only slowly.
The organism can be regarded, to first approximation, as a closed, self-sufficient energetic domain of cyclic non-dissipative processes coupled to irreversible dissipative processes. This can be stated thermodynamically as follows.

The living system tends towards a dynamic equilibrium that 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.

The principle of entropy balance internal to the system actually applies in the smallest unit cycle of the living system – the molecular machine – as enzyme chemist Rufus Lumry and his coworkers have shown convincingly (18). The flexible enzyme molecule balances entropy with enthalpy change to conserve free energy (or stored coherent energy in the present context), in accordance with the relationship for isothermal processes (processes at constant temperature),

\[
\Delta G = \Delta H - T \Delta S = 0 \quad [1]
\]

where \( \Delta G \) is the change in free energy, \( \Delta H \) is change in enthalpy, \( T \) is temperature on the absolute scale and \( \Delta S \), the change in entropy.

The balance can also occur at more macroscopic levels. The important point is that entropy is balanced out internally and coherent energy conserved. This completes my account of the thermodynamics of organisms.

Before I go on to consider quantum coherence, I would like to clarify two important conjectures regarding entropy that I have presented: minimum entropy production and internal entropy balance. The one does not follow directly from the other, though they may well be related.

**Minimum entropy production and internal entropy balance**

Prigogine had earlier proposed a theorem of minimum entropy production, 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 basis of Prigogine’s theorem is unclear. It may be a direct consequence of Onsager’s reciprocity relationship, though this has to be investigated.

Prigogine’s theorem of minimum entropy production at steady state was derived for homogenous systems where all volume elements are uniform and locally at equilibrium. I have shown, instead, how local equilibrium can indeed obtain in a system with nested space-time differentiation – organised heterogeneity - even though the system as a whole is far from equilibrium.
The minimum entropy production that I have proposed depends explicitly on both the organism’s nested space-time differentiation, that enables it to satisfy both quasi-equilibrium and far from equilibrium conditions for the most efficient energy transfer, i.e., that generate little or no entropy, and the predominance of cycles in the organism, for which the net entropy production, is again effectively zero.

The principle of internal entropy compensation, is perhaps in addition to, and implies the principle of minimum entropy production; and may even be valid in regimes far from thermodynamic equilibrium.

Chandresekhar is responsible for a balance theorem (25), which states that for the Bénard-Rayleigh convection cells (Figure 7) to appear, there must be a minimum (critical) temperature gradient at which a balance can be steadily maintained between the kinetic energy dissipated by viscosity and the internal energy released by the buoyancy force (of the rising warm water).

Glansdorff and Prigogine (24), for their part, state that the Bénard-Rayleigh instability occurs at the minimum temperature gradient that can be steadily maintained between the entropy generated through heat conduction by the temperature fluctuations, and the corresponding entropy flow “carried away” by the velocity fluctuations.

Prigogine’s theorem of minimum entropy production at steady state was derived for homogenous systems where all volume elements are uniform and locally at equilibrium. I have shown how local equilibrium can indeed obtain in a system with nested space-time differentiation – organised heterogeneity - even though the system as a whole is far from equilibrium.

The internal entropy compensation I have proposed also applies to systems with organized heterogeneity of coupled processes, 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 can be compensated by negative entropy flows in other directions. And compensation will be especially perfect in cyclic processes. Another possibility is enthalpy-entropy compensation, as in enzyme catalysis, so coherent energy is conserved, and no net entropy is generated.

Thus, the system as a whole can be arbitrarily far from equilibrium and yet remain stable and sustainable, so long as, at some sufficiently macroscopic space-time of interest, or on the whole, overall balance is attained, and the net entropy production of the system either vanishes or reaches a minimum. The system thereby maintains its organized heterogeneity or dynamic order.

Some consequences of the thermodynamic model of the organism

My formulation of the organism in terms of dynamic (and physical) closure – to form cycles - converges formally with several other representations of the living state: the concept of autopoesis, representing a unitary, self-producing entity, proposed by theoretical biologists Maturana and Varela (26); theoretical chemists Eigen and Schuster’s hypercycle (27) of RNA-directed protein synthesis in turn directing RNA polymerisation; and theoretical biologist Kauffman’s catalytic closure of polypeptide formation in the origin of life (28).

However, none of those concepts was based on physical thermodynamic principles, and it is that which distinguishes the present formulation. It can offer new and important insights into the living state (22), some of which are highlighted below.

a. There is always energy available

The dynamic, energetic closure of the living system gives rise to 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 clue to the enigma of the organism first posed by Lord Kelvin (see earlier). There is always energy available within the system, for energy is stored coherently and ready for use over all space-time domains. That is also the basis of the autonomy of organisms. It does not explain when and how the organism decides to exercise its will to use energy, only why it can do so.

On account of the coherent energy stored, organisms are never simply at the mercy of their environments. Thanks to that, we don’t have to eat constantly, leaving plenty of time for other useful, pleasurable activities.

b. Intercommunication, not control
One of the hallmarks of an organism is its exquisite sensitivity to specific, subtle signals. 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 are sufficient to attract male insects to their mates from miles away. This sensitivity is characteristic of all parts of the living system, and is a direct consequence of the coherent energy stored locally at every point.

No part of the system has to be pushed or pulled into action, or be subjected to mechanistic regulation and control. Instead, coordinated action of all the parts depends on rapid intercommunication throughout the system. The organism is an excitable matrix filled with molecular machines, organised in cells and tissues, that are poised to respond specifically and disproportionately to weak signals, because large amounts of coherent energy are available everywhere to amplify the weak signals into macroscopic actions. The basis of biological information depends as much on the specificity of the signal as on the organisation of the coherent energy store.

On this account alone, the organism is radically anti-mechanistic. Mechanical systems work by a hierarchy of controllers and the controlled that returns to system to set points. Our social institutions, for example, are run on mechanistic principles, and are undemocratic and non-participatory. Bosses issue commands that are relayed through line-managers in one direction down to the workers, and no answer back is allowed. Organic systems, by contrast, operate by intercommunication and total participation. Everyone acts and pays attention to everybody else. Each is simultaneously boss and worker, or better yet, choreographer and dancer, and as much in control as she is sensitive and responsive.

There are no predetermined set points to which the system has to return, even though its predominant cyclic organisation makes for a remarkable degree of homeostasis automatically. Instead, organisms live and develop from moment to moment, freely and spontaneously. All of that is made possible by the energy stored, aided and abetted by the special liquid crystalline medium that’s optimised for energy storage and inter-communication, a topic for another full paper in itself (3-8).

Chemist George Gray, who studied liquid crystals for many years, referred to liquid crystals as “tunable responsive systems” (30), and as such, ideal for making organisms. They respond to electric and magnetic fields, to temperature and pressure. Especially important are the layers of biological water associated with proteins and other macromolecules, which are not only essential for the workings of molecular machines, but also support jump conduction of protons. Protons may have a key role in regulating metabolism through oxidation and reduction reactions.

c. The organism has a full range of coherence times and coherence volumes
I have stressed that stored energy is coherent energy. As energy is stored over all space-times, the organism possesses a full range of coherence times and coherence volumes. In
the ideal, it may be regarded as a special quantum coherent state with many, many modes of activity. We shall explore that possibility further in the next Section.

All that I have described above constitutes a ‘thermodynamics of organised complexity’ that’s applicable to organisms as well as sustainable ecological and economic systems, as argued in detail elsewhere (31).

**Coherent excitations of the body electric**

The living system is a bewildering mass of organised heterogeneity. Its molecular diversity alone would defy description in terms of statistical mechanics that depend on large numbers of identical molecular species.

The *E. coli* bacterium is less than one micron in its longest dimension. Within the confines of its minute body protected by a cell wall of complex proteins and carbohydrate fibres, it has a single gigantic DNA molecule of several million base pairs coding for thousands of different proteins, the majority of which exists in no more than 100 copies and some considerably less. There are thousands of different RNAs, most represented by a few copies. In addition, there are diverse membrane lipids, carbohydrates, fats and other metabolites, small molecular weight cofactors and inorganic ions, all embedded in a minute, highly indented and worm-holed droplet of water.

And yet, this vastly complicated, seemingly random mixture of molecules within a volume smaller than a pinhead behaves with such order and intent that Schrödinger concluded it must be “guided by a ‘mechanism’ entirely different from the ‘probability mechanism’ of physics” (10).

The mechanism that Schrödinger had in mind is none other than the collective behaviour of physical systems, of which the Bénard-Rayleigh cells is a classic example.

Among the first collective phenomena in physical systems to be discovered were *superfluidity* in liquid helium – when all the molecules move as one - and *superconductivity* in various pure metals and alloys - which conduct electricity with zero resistance - both occurring at temperatures near absolute zero. In the early 1990s, materials were discovered that superconduct at much higher temperatures, at least 125K.

Low temperature superfluidity and superconductivity are both equilibrium phase transitions dependent on the exclusion of random thermal energies that would destroy the collective state.

A better physical metaphor of the organism is perhaps the solid-state laser, which relies on *non*-equilibrium phase transition to dynamic order from energy pumping, rather more like the organism.

In the solid-state laser, specific atoms are embedded in a block of solid-state material, at the ends of which are reflecting mirrors. Energy can be supplied in the form of light, electric current, or heat, in order to excite the atoms. The atoms re-emit light tracks, and those running perpendicular to the mirrors will be reflected back and forth several times before going out. At low levels of energy pumping, the laser operates as an ordinary lamp, and the atoms emit randomly. As the pumping power is increased, a critical level is reached, called the *laser threshold*, when all the atoms will oscillate in phase and emit together, sending out a giant wave train that is a million times or more as long as that emitted by individual atoms.

As in the Bénard-Rayleigh cells, there is a transition from a regime of random motion of atoms and molecules to one where all the atoms and molecules are moving coherently together. In both systems, random energy is channelled into coherent modes of activity at phase transition, as characteristic of non-equilibrium phase transitions. It is that which makes them stable to thermal noise or other perturbations, as distinct from
equilibrium phase transitions such as low temperature superconductivity, which is destroyed by thermal energies.

However, the two non-equilibrium phase transitions are different in an important respect. The Bénard-Rayleigh cells result from a classical phase transition, which typically occurs over a long timescale. The solid-state laser, by contrast, results from a quantum phase transition, which occurs very rapidly. This difference in timescale tips the balance in favour of biological organisation being essentially a quantum rather than a classical phenomenon.

Could such quantum phase transitions happen in the living system? Solid-state physicist Herbert Fröhlich (32, 33) proposed that it could. Living organisms, being packed densely with dielectric or dipolar molecules, are rather like solid-state systems in which electric and viscoelastic forces constantly interact. Under those conditions, metabolic pumping may result in a build-up to collective modes of vibration, rather like the laser action just described.

Fröhlich thought that thermal energies arising from metabolism may be retained in the system by the excitation of giant dipolar molecules such as proteins, nucleic acids and cellular membranes that typically have an enormous electric field of $10^7$ V/m across them. The excited molecules and structures vibrate at various characteristic frequencies depending on the interaction between displacement of electric charges and mechanical deformation of the molecular chains. This eventually builds up into collective modes of both electromechanical oscillations (phonons or sound waves) and electromagnetic radiations (photons) that extend over macroscopic distances within the organism and perhaps also outside the organism.

Electromagnetic radiation from coherent lattice vibrations in a solid-state semiconductor has been experimentally demonstrated (34). The radiative mode arises because oscillating charges always emit electromagnetic waves. Fröhlich refers to all these collective modes of vibrations as ‘coherent excitations’.

There are three kinds of coherent excitations. The first is a stable or metastable, highly polarized state where the separation between positive and negative charges is maximum. This results from ‘mode-softening’ of interacting frequencies towards a collective frequency of zero.

The second is limit-cycle oscillation, a limit-cycle being a cycle with a stable orbit that neither becomes smaller nor bigger.

The third mode arises when the energy supply exceeds a certain threshold, and oscillations of much higher frequencies occur in many modes. Each collective ‘mode’ can be a band of frequencies, with varying spatial extents, as consistent with the space-time structure of the living system. Nevertheless, the frequencies are coupled together through a ‘heat bath’, so that random energy fed into any specific frequency can be communicated to other frequencies. One must remember that the ‘heat bath’ is no ordinary heat bath but a highly efficient medium for energy conservation and mobilization on account of its liquid crystalline structure.

Although Fröhlich based his theory on the solid-state and not the liquid crystalline state, I believe his general argument will apply even better in the liquid crystalline state. In liquid crystalline mesophases, all the dipoles and dielectrics will be aligned, so charge displacements can potentially grow macroscopically, by inter-molecular interactions both directly, and through resonance. At the same time, the ‘plasticising’ effects of biological water on proteins and other macromolecules will also amplify viscoelastic deformations. The biological water will contribute further to electrical displacements by supporting jump conduction of protons. Macroscopically coherent oscillations, giant excitons and solitons (see Chapter by Larissa Brzhik) may propagate throughout the liquid crystalline matrix.
These are possibilities that should be taken very seriously and investigated both theoretically and experimentally.

It is of considerable interest that theoretical physicist Duffield (35), a student of Fröhlich, has proved that under the most general conditions of energy pumping, the Fröhlich state of coherent excitations is ‘globally, asymptotically stable’. That means the system will tend to evolve towards that state, and more over, stay in that state and return to it on being perturbed.

Our enquiry thus far has shown that the living system has all the thermodynamic and other physical characteristics for the highest degree of coherence to arise, perhaps quantum coherence.

Quantum coherence

The properties of the quantum state considered most paradoxical are all connected with quantum coherent states, and these are also of the greatest importance for the living organism. We start by considering the usual two-slit experiment (Figure 11).

Figure 11. The two-slit experiment.

In the simplest version, a beam of light is shone through a screen containing a pair of narrow slits onto a photographic plate. When only one slit is opened, an image of the slit is recorded on the photographic plate, which, when viewed under the microscope, would reveal tiny discrete spots. And this is consistent with the interpretation that individual particle-like photons, on passing through the slit, have landed on the photographic plate, where each photon causes a single silver grain to be deposited.

When both slits are opened, however, an interference pattern forms on the photographic plate, which is consistent with a wave-like behaviour of the light: the two wave trains, on passing through the slits, arrive at different parts of the photographic plate either in phase, when they reinforce each other to give a bright zone, or out of phase, so they cancel out to give a dark zone (Figure 12). On examining the plate under the microscope, however, the same graininess appears, as though the light waves become individual particles as soon as they strike the plate.
The result is the same even if the intensity of the light is reduced to such an extent that only individual photons will pass through the slits and arrive on the screen one at a time. That means each photon must have passed through both slits and interfered with itself, in wave-like fashion, and yet on encountering the photographic plate, instantly becomes a particle again.

If one tried to be clever and put a photon-detector at one of the slits so the observer can tell which slit the photon has passed through, then the interference pattern will disappear. The interference pattern will only happen if we remain ‘ignorant’ as to which slit the photon has ‘actually’ passed through.

Similar experiments have been done with electrons and even neutrons that are 1800 times as massive as the electron, with essentially the same results. Numerous other more sophisticated experimental configurations have been devised to investigate this phenomenon, and always the conundrum remains. Photons are split into superposed reflected and transmitted states, or into opposite polarized states, that are nonetheless capable of interfering when brought together again.

The way quantum mechanics explains this result is to ‘say’ mathematically that the photon has a ‘probability amplitude’ – expressed as a complex number - of passing through the top or the bottom slit. These amplitudes express the quantum mechanical alternatives available to the photon. But they are not probabilities in the classical sense. In order to get the correspondence to classical probabilities (and hence the correct interference pattern), one must square those amplitudes or complex number weightings.

The fundamental picture of reality in quantum mechanics is that all possibilities open to the system co-exist in a ‘pure state’- not a mixture of states - until the instant when observed. A ‘pure state’ is indivisible, it is a unity representing the quantum superposition of all the possible alternatives. The act of observation seems to put an end to his dream-like pure state into one of the possibilities that previously existed only as a potential.

Quantum superposition in the pure state is usually represented as the parable of Schrödinger’s cat, shut in box with a radioactive nuclide, which might undergo radioactive decay and trigger a mechanism releasing cyanide gas to kill it. The quantum state of the cat, therefore, is a superposition of being dead and being alive, until the instant when the observer opens the box. Then, and only then would it be definitely dead, or alive.

My own interpretation rejects this ‘collapse’ of the wave function of the pure state (3) by the human observer for reasons including it being ‘human chauvinist’.

I shall not go into the mysteries of entangled states associated with the Einstein Poldosky and Rosen (EPR) paradox, because it is just another aspect of quantum coherence. Different parts of a coherent state, even when separated by macroscopic space-
time dimensions, will remain correlated or entangled, so that observation or measurement of one part simultaneously determines the state of the entangled part if the same measurement were applied, as though some instantaneous message is sent through the ether in non-local intercommunication.

However, and this is important, the unmeasured quality remains indeterminate, hence the ‘collapse’ of the wave function interpretation is overly simplistic, and there are other recent indications that observation does not destroy entanglement.

There has been great progress in experimental quantum optics recently. Not just elementary particles, but the ‘long-lived’ entanglement of two ‘macroscopic objects’ has been reported (36). Admittedly, by long-lived, the physicists meant 0.5 milliseconds, and ‘macroscopic objects’ referred to two samples, each containing about $10^{12}$ caesium atoms. In order to be entangled, each ‘object’ has itself to be coherent. Could macroscopic quantum objects exist? Until a few years ago, the answer was no. Admittedly, $10^{12}$ caesium atoms is not quite the size of an organism, even the simplest organism.

**Maximum local freedom and global correlation in quantum coherence**

The usual properties of the coherent quantum state are mysterious enough: superposition, nonlocal interaction and entanglement. But there is one other property relevant for the living system that has seldom been mentioned, which can be deduced from the two-slit experiment. It is the *factorizability* of the quantum coherent state (see Box 3).

This means that two or more separate space-time points are so perfectly correlated that their cross-correlation can be expressed exactly as the product of the self-correlations at the separate points. So, paradoxically, each behaves as though it is totally uncorrelated with the other.

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**Box 3**

**The factorizability of the quantum coherent state**

In the two-slit experiment, the intensity or brightness of the interference pattern on the photographic plate at each point depends on a ‘probability’ that light falls on to that point.

The ‘probability’ is not probability in the ordinary sense, but *quantum* probability, as explained earlier. One way of representing these special probabilities is as correlation functions consisting of the product of two complex amplitudes. Light arriving at the point p on the photographic plate (Fig. 10) has taken different paths, tp and bp. The intensity at p is then given as the sum of four such correlation functions:

$$I = G(t,t) + G(b,b) + G(t,b) + G(b,t)$$

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 (the interference term which take on both positive and negative values) when both slits are opened. At different points on the photographic plate, the intensity is

$$I = G(t,t) + G(b,b) + 2|G(t,b)|\cos \theta$$

where $\theta$ 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 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, 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 obtained when the two sides are equal:

$$G(t,t)G(b,b) = |G(t,b)|^2$$

This equation 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 it refers to correlations between two space-time points, and we write it more generally as,

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

The significance of the above equation is that it tells us the correlation between two space-time points in a coherent field factorizes, or decomposes neatly into the self-correlations at the two points separately, and that this factorizability is a sufficient condition for coherence.

It is important to stress that factorizability does not mean the coherent state can be factorised into a mixture. It says that the cross correlation between separate space-time points is so perfect that it can be expressed as the product of the self-correlations at the separate points. So, if two photon detectors are placed in this field, they will register photons as if they were independent of each other.

Coherence can be generalised to arbitrarily higher orders, say, to $n$ approaching $\infty$, in which case, we shall be talking about a fully coherent field. If nth order coherence holds, then all of the correlation functions that represent joint counting rates for $m$-fold coincidence experiments (where $m<n$) factorise as the product of the self-correlations at the individual space-time points. In other words, $n$ different photon counters in the field will each record photons statistically independently of all the others, with no special tendency towards coincidences, or correlations.

This is essentially the theory of quantum coherence developed by quantum physicist Roy Glauber (37). It does not require the existence of a single mode or frequency of light, nor does it require the existence of high intensities of light. Indeed, multimode lasers are already commercially available.

The factorizability of coherence states has been experimentally verified, and high degrees of coherence – six or more orders (see Box) – have also been measured in commercial lasers.

**Could organisms be quantum coherent?**

Let me summarise my arguments for answering in the affirmative.
First, coherence is directly observed in the living organism using an imaging technique based on detecting molecular order. Second, molecular machines are quantum machines, and quantum coherence is necessarily involved in their coordination. Third, the rapidity of long-range coordination in the living system is such as to rule out classical coherence due to classical phase transitions to coherent dynamic order as exemplified by the Bénard-Rayleigh convection cells. Fourth, thermodynamically, the living system is optimised for coherent energy storage over all space-times. Fifth, the nature of living matter – its dielectric properties and liquid crystallinity - predisposes the living system to coherent excitations as proposed by Fröhlich. Finally, theoretical considerations suggest that the coherent Fröhlich state is globally and asymptotically stable.

The organism is, in the ideal, a quantum superposition of coherent activities over all space-times, constituting a pure coherent state towards which the system tends to return on being perturbed.

Some consequences of the quantum coherent model of living organisms

a. The coherent sensitive whole
I have earlier drawn attention to the extreme sensitivity of organisms to weak signals, which depends on the large amount of coherent energy stored locally everywhere within the system.

We have carried out extensive experiments demonstrating that brief exposures of fruitfly embryos to static magnetic fields so weak that the energy is below the ‘thermal threshold’, the amount of random energy characteristic of the ambient temperature. Those weak fields can nonetheless cause dramatic global transformations of the body pattern of the fruitfly larva hatching 24 hours later (38). These and other experiments cannot be explained unless there is a high degree of coherence within the developing organism.

Quantum coherence may indeed underlie the extreme sensitivity of organisms to weak electromagnetic fields in general. The biological effects of cell phones must be considered in this light.

This same degree of sensitivity underlies the perfect intercommunication within the organism that enables it to function as a coordinated whole.

b. Quantum coherence and conscious experience
There has been a great deal written on whether ‘consciousness’ requires an explanation in terms of quantum theory ever since Roger Penrose suggested that might be the case (39). One aspect that seems to have been missed is that quantum coherence is a pre-requisite for conscious experience.

Schrödinger invited us to think of the “I” that each of us experiences of our own being, the person “who controls the ‘motion of the atoms’” in our body. This consciousness is “never experienced in the plural, only in the singular”.

That is just what the state of coherence entails: a multiplicity that is singular. The ‘self’ is a domain of coherence, a pure state that permeates the whole of our being. And that is responsible for the unity of experience, without which there can be no ‘consciousness’. There is more to the conscious experience and quantum coherence that I have described elsewhere (40).
c. The “quantum jazz” of life
Perhaps the most paradoxical property of the ideal living system is that both local freedom and global correlation are maximum. This is the consequence of the factorizability of the quantum coherent state. Coherence in the living system does not mean uniformity, quite the opposite: compartments, micro-compartments and micro-domains, right down to molecular machines, all working autonomously, doing different things at different rates, generating flow patterns and cycles of different spatial extensions, yet all coupled together, in step with one another and hence, with the whole organism. I have referred to this hive of coordinated yet autonomous living activities as the “quantum jazz” of life (41).

The organism, defined as a domain of coherent activities, opens the way to envisaging a super-organism such as a population or a society engaging in coherent activities. As coherence maximizes both local freedom and global cohesion, it defines a relationship between the individual and the collective that has previously been deemed contradictory or impossible. The ‘inevitable’ conflict between the individual and the collective, between private and public interests, has been the starting point for all social as well as biological theories of western society. Quantum coherence tells us it is not so inevitable after all. In a coherent society, such conflicts do not exist. The problem is how to arrive at such an ideal state of organization that in a real sense, nurtures diversity (and individuality) with universal love.

d. Organic space-time distinct from Newtonian space-time
Organic space-time is big subject to which I have devoted an entire Chapter in my book, The Rainbow and the Worm (3), and written more on elsewhere. Newtonian space and time are linear, infinitely divisible, and independent of real processes. In contrast, organic space-time is non-linear, heterogeneous, multi-dimensional and mutually entangled, being created by real processes. I considered the possibility that, as action is already quantized, so organic space-time should be quantized. Instantaneous, depthless Newtonian time is a figment of the mechanistic imagination.

I also considered the possibility that space-time, being tied to organic processes, may have a fractal structure like organic processes and be “continuous but non-differentiable” (42). All that opens the way to some remarkable consequences.

e. Nonlocality in organic space-time
Coherence is associated with a time and a volume over which phase correlation is maintained. The coherence time for a quantum molecular process is just the characteristic time interval over which energy remains stored in McClare’s formulation of the second law. A coherent space-time structure theoretically enables ‘instantaneous’ correlations over a range of time scales and spatial extents. For, within the coherence time there is no volume separation, just as within the coherence volume there is no time separation. Thus, nonlocal correlations may be a fact of life.

In addition, quantum physicist Wolfgang Schommers invites us to consider a time-energy uncertainty relationship that has the same form as the usual position-momentum uncertainty relationship (43). What that implies in practice is a vast unexplored area. Could time decrease or maybe go backwards?

And if coherence were to become established over a population of organisms, a society or an entire ecosystem, would that give the possibility for nonlocal correlation in the extended domain?

f. Time and entropy
As coherent energy is stored over a range of space-times, the organism can be regarded as a totality of coherent activities in the ideal. Coherent activities generate no space-time or entropy. Thus, one comes to the startling conclusion that space-time may be generated by the incoherence of action (3). Time and entropy turns out to have the same cause and direction. All the more reason to act coherently that one may fend off entropic decay for another day.

**Conclusion**

This article is the inside story of how molecular machines really work in the coherent organism. It was inspired by a vision of the coherent, liquid crystalline organism that challenges the usual mechanistic interpretation in the most profound way.

And so I began by reformulating the second law of thermodynamics so that it can apply to single molecules as much as to complex systems with nested space-time differentiation.

I then presented other heuristic arguments on why the most general considerations of energy pumping from metabolism would result in a phase transition to a state of quantum coherence for the organism’s molecular machines, a state that tends to be restored when perturbed. These arguments apply all the more so to the liquid crystalline nature of living matter.

The quantum coherent organism offers exciting new vistas into the secret of life that invites us to transform the way we could live our own lives.

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