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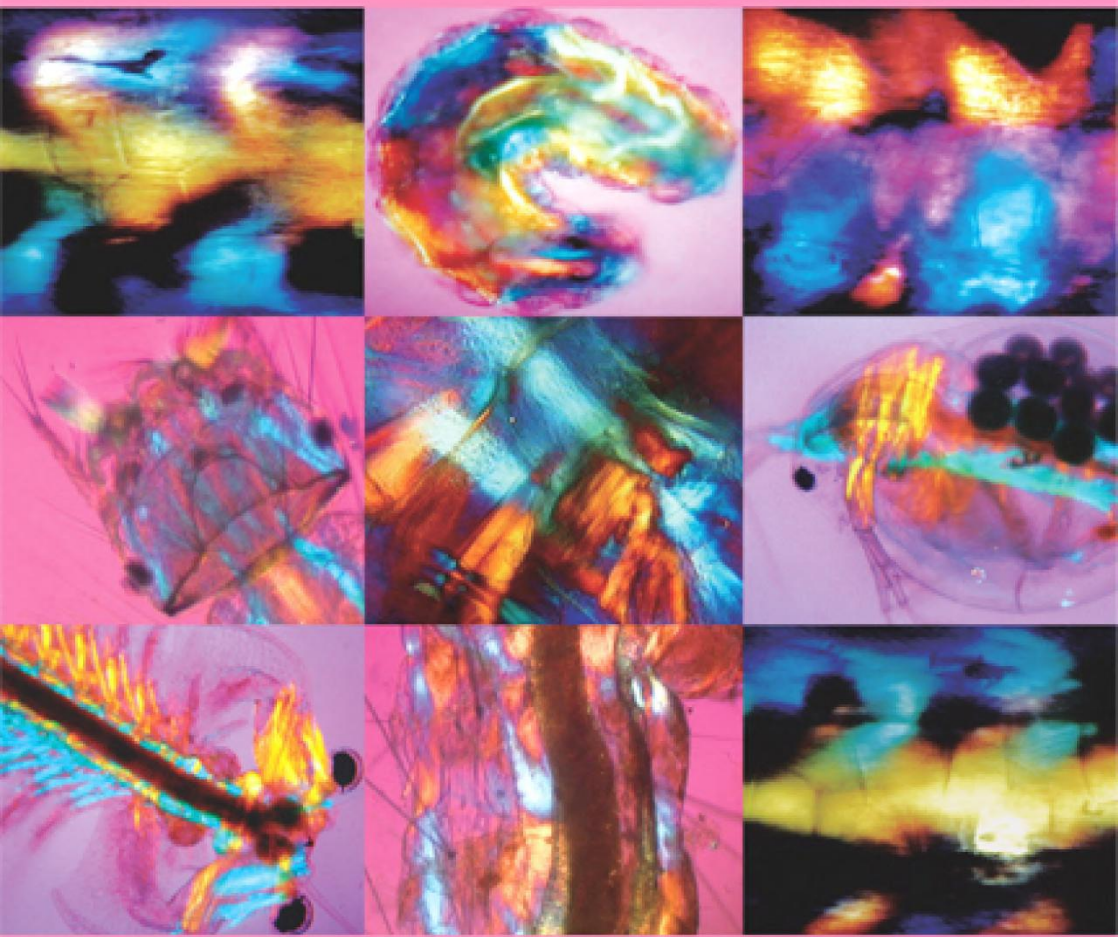

THE RAINBOW AND THE WORM

The Physics of Organisms

Mae-Wan Ho

World Scientific

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3RD EDITION

Mae-Wan Ho
Institute of Science in Society, UK

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CHAPTER 1

What is It to Be Alive?

The 'Big' Questions in Science

There are 'big' questions and 'small' questions in science. Most scientists in their work-a-day life confine themselves to asking small questions such as: Which gene is involved in a given hereditary defect? How will a certain organism react to such and such a stimulus? What are the characteristics of this or that compound? What is the effect of A on B? How will a given system behave under different perturbations? Yet, it is not a desire to solve particular puzzles that motivates the scientist, but rather the belief that in solving those little puzzles, a contribution will be made to larger questions on the nature of metabolic or physiological regulation, the generic properties of nonlinear dynamical systems, and so on. It is ultimately the big questions that arouse our passion, both as scientists and as ordinary human beings. They can inspire some of us as the most beautiful works of art that nature has created, whose meaning is to be sought as assiduously as one might the meaning of life itself.

For me, the big motivating question is Austrian quantum physicist Erwin Schrödinger's *What is life?*[1] That it is also a question on the meaning of life is evident to Schrödinger, who closes his book with a chapter on philosophical implications for determinism and freewill. This is as it should be. I do not agree with those scientists for whom

scientific knowledge has no meaning for life, and must be kept separate from real life in any event; perhaps an attitude symptomatic of the alienation that pervades our fragmented, industrial society. I will not dwell on that here, as it is not the main thesis of my book. Instead, I want to concentrate, for now, on Schrödinger's original question:

> 'How can the events *in space and time* which take place within the spatial boundary of a living organism be accounted for by physics and chemistry'?[2]

The same question has been posed in one form or another since the beginning of modern science. Is living matter basically the same as non-living only more complicated, or is it something different altogether. In other words, are the laws of physics and chemistry necessary *and sufficient* to account for life, or are additional laws outside physics and chemistry required. Descartes is famous not only for separating mind from matter; he also placed living matter, alongside with non-living matter, firmly within the ken of the laws of physics; more specifically, of mechanical physics. Since then, generations of vitalists, including German embryologist Hans Driesch and French philosopher Henri Bergson, have found it necessary to react against the mechanical conception of life by positing with living organisms an additional *entelechy*, or *elan vital*, which is not within the laws of physics and chemistry.[3]

The vitalists were right not to lose sight of the fundamental phenomenon of life that the mechanists were unable to acknowledge or to explain. But we no longer live in the age of mechanical determinism. Contemporary physics grew out of the breakdown of Newtonian mechanics at the beginning of the present century, both at the submolecular quantum domain and in the universe at large. We have as yet to work out the full implications of all this for biology. Some major thinkers early in the last century, such as British philosopher-mathematician Alfred North Whitehead, already saw the need to explain physics in terms of a general theory of the organism,[4]

thus turning the usually accepted hierarchy of reductionist explanation in science on its head. Not everyone has accepted Whitehead's thesis, but at least, it indicates that the traditional boundaries between the scientific disciplines can no longer be upheld, if one is to really understand nature. Today, physics has made further in-roads into the 'organic' domain, in its emphasis on nonlinear phenomena far from equilibrium, on coherence and cooperativity, which are some of the hallmarks of living systems. The vitalist/mechanist opposition is of mere historical interest, for it is the very boundary between living and non-living that is the object of our enquiry, and so we can have no preconceived notion as to where it ought to be placed.

Similarly, to those of us who do not see our quest for knowledge as distinct from the rest of our life, there can be no permanent boundary between science and other ways of knowing. Knowledge is all of a piece. In particular, it is all of a piece with the knowing consciousness, so there can be no *a priori* dualism between consciousness and science. Far from implying that consciousness must be 'reduced' to physics and chemistry, I see physics and chemistry evolving more and more under the guidance of an active consciousness that *participates* in knowing.[5] Some of these issues will be dealt with in the final chapters.

The Physicochemical Underpinnings of Life

Schrödinger's preliminary answer to the question of what is life is as follows:

> 'The obvious inability of present-day [1940s] physics and chemistry to account for such events [as take place within living organisms] is no reason at all for doubting that they can be accounted for by those sciences'.[6]

He is saying that we simply do *not* know if events within living organisms could be accounted for by physics and chemistry because

we have nothing like living systems that we could set up or test in the laboratory. There is a serious point here that impinges on the methods and technologies we use in science. Until quite recently, the typical way to study living organisms is to kill and fix them, or smash them up into pieces until nothing is left of the organization that we are supposed to be studying. That has merely reinforced the Newtonian mechanical view of organisms that has proven thoroughly inadequate to account for life. The situation should change with great advances in the development of non-invasive technologies within the past thirty years. We can 'listen in' to nature without violating her. I shall have more to say on that in later chapters.

Another reason for not doubting that physics and chemistry can account for living systems is surely that they are both evolving disciplines. Who knows what the subjects will look like in twenty years time? Already, physics and chemistry now look quite different from the subjects in the 1940s. The transistor radio, the computer and lasers have been invented since Schrödinger wrote his book. Whole new disciplines have been created: synergetics, the study of cooperative phenomena, nonequilibrium thermodynamics, quantum electrodynamics and quantum optics, to name but a few. In mathematics, nonlinear dynamics and chaos theory took off in a big way during the 1960s and 1970s. Perhaps partly on account of that, many nonlinear optical phenomena associated with quantum cavity electrodynamics and coherent light scattering in solid-state systems have been actively investigated only within the past 25 years. Hopes for high temperature superconductivity, which flared brightly in the 1990s, have dimmed considerably since. A major current obsession is nanotechnology, or technology precise to the molecular level, which is finding many applications in photonics and electronics.[7] The quantum information revolution is also with us, holding out promise of quantum cryptography and computers that rely on quantum entanglement to solve problems much faster than conventional computers.[8]

There have been suggestions since the early 1990s that the recent developments in physics and chemistry are particularly relevant for our understanding of biological phenomena. But a serious attempt

to re-examine Schrödinger's question was not made until the first edition of this book, published in 1993, and especially the second edition published in 1998. Since then, there has been further stunning progress in physics and chemistry, which has made the physics of organisms all the more relevant for our understanding of the big question.

Be prepared for an intellectual odyssey that takes off from equilibrium to nonequilibrium thermodynamics and extensions of quantum theory, with incursions into solid state physics, the physics of liquid crystals, as well as the relevant physiology, developmental biology, biochemistry and molecular biology of cells and organisms. I shall not be referring much to the details of molecular genetics and gene control mechanisms, which already fill volumes, including one that I have written in 2003 on how genetic engineering and much of molecular biology is still stuck in the mechanistic paradigm, and failing to catch up with the new, organic genetics of the fluid genome.[9] Genes and molecules are all part of the rich tapestry of life that will find their rightful place when our life-picture has been sufficiently roughed out. I am more concerned here with the fundamental physical and chemical principles that make life possible, rather than the molecular nuts and bolts.[10]

I promise neither easy nor definitive answers. Our education already suffers from a surfeit of facile, simplistic answers which serve to explain away the phenomena, and hence to deaden the imagination and dull the intellect. An example is the claim that the natural selection of random mutations is necessary and sufficient to account for the evolution of life. As a result, whole generations of evolutionary biologists are lulled into thinking that any and every characteristic of organisms is to be 'explained' solely in terms of the 'selective advantage' it confers on the organism. There is no need to consider physiology or development, nor indeed the organism itself; much less the physical and chemical basis of living organisation.[11]

To me, science is a quest for the most intimate understanding of nature. It is not an industry set up for the purpose of validating existing theories and indoctrinating students in the correct ideologies.

It is an adventure of the free enquiring spirit that thrives not so much on answers as unanswered questions. It is the enigmas, the mysteries and paradoxes that take hold of the imagination, leading it on the most exquisite dance. I should be more than satisfied, if, at the end of this book, I have done no more than keep the big question alive.

What is life? Can life be defined? Each attempt at definition is bound to melt away, like the beautiful snowflake one tries to look at close-up. Indeed, there have been many attempts to define life, in order that the living may be neatly separated from the nonliving. But none has succeeded in capturing its essential nature. Out of the sheer necessity to communicate with my readers, I shall offer my own tentative definition for now, which to me, at least, seems closer to the mark: *life is a process of being an organising whole*. In the course of this book, you will come across other more precise or more encompassing definitions.

It is important to recognize that life is a *process* and not a thing, nor a property of a material thing or structure. As is well known, the material constituents of our body are continually broken down and synthesized again at different rates, and yet the whole remains recognizably the same being throughout life. So much so that a profound sense of grief will overtake loved ones whenever that unique life history comes to an end. Life resides in the pattern of dynamic flows of matter and energy that somehow makes the organism alive, enabling it to grow, develop and evolve. The 'whole' does not refer to an isolated, monadic entity. On the contrary, it refers to a system open to the environment, which it enfolds and organizes into highly reproducible or dynamically stable forms.[12] To be alive and whole is a very special being. Let us dwell on that for a while.

On Being Alive

Biology textbooks often state that the most important characteristic of organisms is the ability to reproduce, and then proceed to give an account of DNA replication and protein synthesis as though that

were the solution to the fundamental problem of life. The ability to reproduce is only one of the properties of living organisms, and it could be argued, not even the most distinguishing one. For there are a number of other characteristics, scientifically speaking, which leave us in no doubt that they are alive: their extreme sensitivity to specific cues from the environment, their extraordinary efficiency and rapidity of energy transduction, their dynamic long range order and coordination, and ultimately, their wholeness and individuality.[13]

For example, the eye is an exquisitely sensitive organ, which in some species can detect a single quantum of light, or photon, falling on the retina. The photon is absorbed by a molecule of *rhodopsin,* the visual pigment situated in special membrane stacks in the outer segment of a rod-cell (Fig. 1.1). This results eventually in a nervous impulse coming out at the opposite end of the cell, the energy of which is at least a million times that contained in the original photon. The amplification of the incoming signal is in part well understood as a typical 'molecular cascade' of reactions: the specific receptor protein, *rhodopsin*, on absorbing a photon, activates many molecules of a second protein, *transducin*, each of which then activates a molecule of the enzyme *phosphodiesterase* to split many molecules of cyclic guanosine monophosphate or cGMP. The cGMP normally keeps sodium ion channels open in the otherwise impermeable cell membrane, whereas the split non-cyclic GMP cannot do so. The result is that the sodium channels close up, keeping sodium ions out of the cell and giving rise to an increased electrical polarisation of the cell membrane, from about –40 mV to –70 mV, which is sufficient to initiate the nerve impulse.[14]

Figure 1.1. Diagram of a light sensitive rod cell. The top part (to the left) is the 'rod' containing membrane stacks in which the light sensitive pigments are situated; the resultant nervous impulse goes out at the bottom.

Molecular cascades are common to all processes involved in signal transduction, and it is generally thought that one of their main functions is to amplify the signal. Let us examine the visual cascade reactions more closely. There are notable caveats in the account given in the last paragraph. For one thing, the component steps have time constants that are too large to account for the rapidity of visual perception in the central nervous system, which is of the order of 10^{-1} s. Thus, it takes 10^{-2} s just to activate *one* molecule of phosphodiesterase after photon absorption. Furthermore, much of the amplification is actually in the initial step, where the single photon-excited rhodopsin molecule passes on the excitation to at least 500 other molecules of transducin within one millisecond. How that is achieved is still a mystery, except that as rhodopsin and transducin molecules are bound to a common membrane, the membrane must play a crucial role in both the amplification and the long-range, coherent transfer of excitation.

Another instructive example is muscle contraction.[15] About 40% of our body is made of skeletal muscle, i.e., muscle attached to bones, like those in our arms and legs and trunk. Another 5 to 10% is smooth muscle such as those in the gut and body wall, and cardiac muscle in the heart. Skeletal muscle consists of bundles of long, thin muscle fibres, which may be discerned under a magnifying glass. These fibres are several centimetres in length, each of which is actually a giant cell formed by the fusion of many separate cells. A single muscle fibre, magnified a hundred times or more under the light microscope, can be seen to be made up of a bundle of 20 to 50 much smaller fibres, or *myofibrils*, each 1 to 2 μm (micrometre, one-millionth of a metre) in diameter. A myofibril has regular, 2.5 μm repeating units, called *sarcomeres*, along its length. Adjacent myofibrils are aligned so that their sarcomeres are in register. Under the much higher magnifications from the electronmicroscope — thousands to tens of thousand times — one will see extremely regular arrays of the periodic structures (Fig. 1.2). One will also see that each sarcomere consists of alternating thin and thick filaments, made up respectively of the two main muscle proteins, *actin* and *myosin*. In three dimensions,

there are actually six thin actin filaments surrounding each thick myosin filament, and the six actin-filaments are attached to an end-plate, the Z-disc. Contraction occurs as the actin filaments surrounding the myosin filaments slide past each other by cyclical molecular tread milling between myosin 'head' groups and serial binding sites on the actin filament, forming and breaking cross-bridges between the filaments, in all three dimensions in the entire array.[16]

The actin and myosin molecules are packed and arranged very precisely, approaching the regularity of crystals, and the study of the detailed structure of resting *as well as contracting* muscle is done by means of X-ray crystallography. There are 624 myosin head groups on each myosin filament, and when the entire muscle contracts, each sarcomere in it shortens proportionately. Thus, when a myofibril containing a chain of 20 000 sarcomeres contracts from 5 to 4 cm, the length of each sarcomere shortens correspondingly from 2.5 to 2 μm. The energy for contraction comes from the hydrolysis of a special molecule that acts as the universal energy transacting intermediate in the body. In its 'charged up' form, it is ATP, or adenosine triphosphate, with three phosphate groups joined one to another in series and then to the chemical group adenosine. ATP 'discharges' its energy by splitting off a phosphate group at the end, to give the partically 'discharged' form, ADP or adenosine diphosphate.

Muscle contraction is triggered by an *action potential* at the site where a nerve impinges on the muscle-cell membrane. An action potential is a quick electrical discharge followed by recovery of the pre-existing baseline electrical potential. This releases calcium ions, Ca^{2+}, from intracellular calcium ion stores to initiate contraction simultaneously in the entire cell within a millisecond.[17] Contraction involves numerous autonomously occurring cycles of attachment and detachment of all the individual myosin heads to and from the binding sites on the actin filaments at the rate of 50 cycles or more per second[18] — each of which molecular event requiring the transfer of energy contained in one molecule of ATP — precisely coordinated over the whole cell.[19]

In a typical muscle contraction, *all* the cells in the muscle — billions of them at the very least — are executing the same molecular

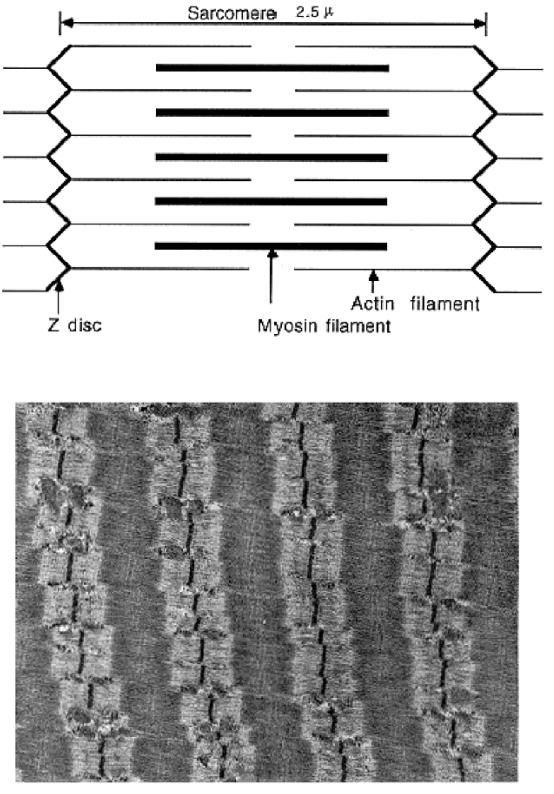

Figure 1.2 Ultrastructure of rabbit muscle. Top, diagram of a sarcomere; bottom, electronmicrograph.

treadmilling in concert. Simply waving our arms about is a veritable feat requiring a series of actions coordinated instantaneously over a scale of distances spanning nine orders of magnitude from 10^{-9} metre (nanometre, one billionth of a metre) for intermolecular spacing between the actin and myosin heads, to about one metre for the length of our arm; each action, furthermore, involving the coordinated splitting of 10^{19} individual molecules of ATP. Now, then, imagine what has to happen when a top athlete runs a mile in under four minutes; the same instantaneous coordination over macroscopic distances involving astronomical numbers of molecules, only more so, and sustained for a long period without break.

It is truly remarkable how our energy should be available to us *at will*, whenever and wherever we want it, in the amount we need. Moreover, the energy is supplied at close to 100% efficiency. This is true for muscle contraction, in which the chemical energy stored in ATP is converted into mechanical energy,[20] as well as for all the major energy transduction processes, as for example, in the synthesis of ATP itself in the mitochrondria[21] where carbon compounds are oxidised into carbon dioxide and water in the process of respiration. If that were not so, and energy transduction can only occur at the efficiency of a typical chemical reaction outside living organisms, which is 10 to 30% efficient at best, then we would literally burn out with all the heat generated.

To summarise, then: being alive is to be extremely sensitive to specific cues in the environment, to transduce and amplify minute signals into definite actions. Being alive is to achieve the long-range coordination of astronomical numbers of submicroscopic, molecular reactions over macroscopic distances; it is to be able to summon energy at will and to engage in extremely rapid and efficient energy transformation.

So, how is the sensitive, vibrant whole that is the organism put together? An organism that develops from a relatively featureless fertilised egg or seed to a complicated shapely creature that is nonetheless the same essential whole until it dies?

We have certainly not exhausted the wonders of being alive, and shall continue our investigations from the standpoint of thermodynamics in the next few chapters.

Notes

1. Schrödinger (1944).
2. Schrödinger (1944) p. 3.
3. Needham (1935).
4. Whitehead (1925).
5. I have written several papers recently on the need to recover a way of knowing in science that involves the complete participation of the knowing being: intellect and feeling, mind and body, spirit and intuition. Authentic science and art

are both creative activities arising out of this total engagement of nature and reality. See Ho (1989a, 1990a, 1993).

6. Schrödinger (1944) p. 4.
7. I have reviewed nanotechnology and many other new scientific developments in successive issues of the quarterly magazine *Science in Society* (*SiS*) published by the Institute of Science in Society (www.i-sis.org.uk). See for example Ho (2002a, 2002b, 2006h).
8. See Ho (2002a, 2004h).
9. Ho (2003a).
10. Ho (2004b).
11. For alternative approaches to neo-Darwinism in the study of evolution, please see Ho and Saunders (1984); Pollard (1984); Ho and Fox (1988); Kauffman (1993); Goodwin (1994); Cohen and Stewart (1994); Saunders (1998).
12. See Ho (1988a).
13. See Ho (1989b).
14. See Stryer (1987).
15. See Alberts *et al.* (1983).
16. The precise details of myosin-action interactions in muscle contraction remains unclear to this day. Force appears to be generated by the myosin head even when it is detached from the rest of the molecule, see Ho and Harris (1995).
17. Rios and Pizarro (1991).
18. See Pollard (1987).
19. The claim of energy transfer from ATP is strongly challenged by many. See Ho (1995a) Chapters 4 and 7.
20. Hibbard *et al.* (1985); but see Note 19 above.
21. Slater (1977).

CHAPTER 2

Do Organisms Contravene the Second Law?

Life and the Second Law

Many scientists have remarked that whereas the physical world runs down according to the Second Law of thermodynamics such that useful energy continually degrades into heat, or random molecular motion (expressed in the technical term, *entropy*), the biological world seems capable of doing just the opposite: increasing its organisation by a flow of energy and matter. Physicists and chemists have long felt that as all biological processes require either chemical energy or light energy and involve real chemical reactions, the Second Law, as much as the First Law of thermodynamics (the conservation of energy) ought to apply to living systems. So, what is the secret of life? Schrödinger[1] pointed out that because living systems are open to the environment, they could create a local decrease in entropy at the expense of the surroundings, so that the entropy of living systems plus the surroundings always increases in real processes, and there is no violation of the Second Law. But there are more fundamental problems, as Schrödinger was well aware of, as were the founding fathers of thermodynamics. We cannot appreciate those problems before we know what the laws of thermodynamics are, and to which systems they are supposed to apply.

The Laws of Thermodynamics

Classical thermodynamics deals with the laws governing the conversion of heat into work or other forms of energy. It arose as a science giving an exact description of macroscopic systems of gases expanding against an external constraint such as a piston driving a steam engine, for example, for which the important parameters are pressure, volume and temperature. Its major foundations were laid long before detailed atomic theories became available. The possibility that the thermodynamic behaviour of matter could be derived from the mechanical properties (such as mass and velocity) of its constituent molecules forms the basis of *statistical mechanics*, which is supposed to give a rigorous deductive framework for thermodynamics.[2]

There are two main laws of thermodynamics. The First Law is usually written as the equation,

$$\Delta U = Q + W \tag{2.1}$$

It says that the change in the total internal energy of a system, ΔU, is equal to the heat absorbed by the system from its surroundings, Q, plus the work done on the system by the surroundings, W. (The sign Δ (Greek letter *delta*) is shorthand for 'change in'.) It is based on the law of the conservation of energy, which states that energy is neither created nor destroyed in processes, but flows from one system to another, or is converted from one form to another, the amount of energy 'in the universe' remaining constant. The total internal energy U is a function of the particular state of the system, defined by temperature and pressure, and does not depend on how that state is arrived at. The heat absorbed Q and the work W are by contrast, *not* state functions and their magnitudes depend on the path taken. The First Law tells us that energy is conserved but it does not tell us which process can occur in reality; as the Second Law does.

The Second Law of thermodynamics tells us why processes in nature always go in one direction. Thus, heat flows from warm to

cold bodies until the two are at the same temperature, but nobody has ever observed heat flowing spontaneously from cold to warm bodies. A drop of ink placed into a jar of water soon diffuses to fill the whole jar. And we would be surprised indeed, if, some time later, the original ink drop were to reconstitute. In the same way, machines run down unless constantly supplied with energy. Nobody has ever succeeded in building a perpetual motion machine that turns heat into mechanical work, then turns mechanical work back to its original equivalent in heat and so on, over and again, which does not contradict the First Law of thermodynamics.

Thus, spontaneous processes in nature appear to define a time's arrow: they go in one direction only, never in reverse. Physical systems evolve from order to homogeneous disorder, eventually running down until no more useful work can be extracted from them. To explain these phenomena, the Second Law defines a quantity, entropy, which increases in real processes and never decreases. Thus, at the end of a process, the change in entropy is always positive, or in the limiting case of a process that is reversible, the change in entropy is zero. This is expressed in the equation,

$$\Delta S_{sys} + \Delta S_{surr} \geq 0 \tag{2.2}$$

It says that the sum of the changes in entropy in the system, ΔS_{sys}, and its surroundings, ΔS_{surr}, is greater than or equal to zero in all real processes. The change in entropy in each case is equal to the heat absorbed in a reversible process divided by the temperature at which the process occurs in degrees Kelvin, or K (which starts at –273.15°C, so that for example, 25°C would be 298.15 K). For simplicity, we consider an *isothermal* process, i.e., one occurring in a system at constant temperature T,

$$\Delta S = Q_{rev}/T \tag{2.3}$$

A reversible process, in thermodynamic terms, is one that occurs very, very slowly, so that it is at *equilibrium* the whole way through. This means that the heat energy absorbed at every stage has time

enough to spread or *equilibrate* throughout the system. In a reaction occurring reversibly, the net change of entropy in the system is exactly compensated by the change in entropy of the surrounding in the opposite direction, so that the net change in entropy is zero:

$$\begin{aligned} \Delta S_{sys} &= -\Delta S_{surr} \\ \Delta S_{sys} + \Delta S_{surr} &= 0 \end{aligned} \tag{2.4}$$

Another point about entropy is that it is a state function (like internal energy U above), and is therefore independent of the path taken to arrive at the particular state. If the process occurs irreversibly, the heat, Q, absorbed is less than that in the reversible process, but the entropy production does not change, so,

$$Q_{irrev}/T < \Delta S_{sys} \tag{2.5}$$

On account of the reduction in the amount of heat lost by the environment to the system, the required compensatory change in entropy in the environment cannot take place in accordance with Eq. (2.4). That means the increase in entropy in the system is not compensated by an equal decrease in entropy in the environment, so

$$\begin{aligned} \Delta S_{sys} &> -\Delta S_{surr} \\ \Delta S_{sys} + \Delta S_{surr} &> 0 \end{aligned} \tag{2.6}$$

An example of an irreversible process is the expansion of a perfect gas against a vacuum. Here, no heat is absorbed from the surroundings and no work is done. The change in entropy of the system is the same as if the process occurred reversibly, but the change in entropy of the surroundings is zero, and so a net increase in entropy (so to speak, 'of the universe') results.

We can see that living systems may indeed *decrease* in entropy at the expense of a compensating *increase* in entropy in its surroundings, and there is no need to contravene the Second Law in that respect.

Another way to state the Second Law is that all isolated systems (those that exchange neither energy nor matter with their surroundings)

run down so that useful energy is degraded into entropy. The point at which all useful energy is degraded into entropy is the state of *thermodynamic equilibrium*. Thermodynamic equilibrium is thus an end-state characterised by a maximum in entropy, when no useful energy is left. Entropy arises from a kind of incoherent 'wasted' energy that is no longer available for work. (Entropy is technically not the same as energy, as it has different dimensions, Joules per deg. K instead of Joules.)

We can then define a number of functions for the *free energy*, or energy that is extractable for work: the Helmholtz free energy A for systems at constant volume, and the Gibbs free energy G for other systems.

$$A = U - TS \tag{2.7}$$

$$G = U + PV - TS \tag{2.8}$$

(Note that for simplicity, we have dropped the subscript '*sys*', for all the symbols referring to the system.) For isothermal processes at constant temperature T, the changes in free energies are,

$$\Delta A = \Delta U - T\Delta S \tag{2.9}$$

and,

$$\Delta G = \Delta H - T\Delta S \tag{2.10}$$

ΔH is the change in a quantity called *enthalpy*, or heat content, which is defined as,

$$H = U + PV \tag{2.11}$$

$$\Delta H = \Delta U + \Delta(PV) = \Delta U + P\Delta V + V\Delta P + \Delta P\Delta V \tag{2.12}$$

U, P and V are the internal energy, pressure and volume of the system. At constant pressure, the last two terms disappear, and,

$$\Delta H = \Delta U + P\Delta V \tag{2.13}$$

If volume is constant, the last three terms of Eq. (2.12) disappear; we get,

$$\Delta H = \Delta U \tag{2.14}$$

The free energy change of the system is ΔA, as given in Eq. (2.9).

Equations (2.7) and (2.8) tell us that 'free energy' is just that part of the internal energy or enthalpy that can be extracted for work. The part that is unavailable for work is entropy. So, as entropy increases in a system, free energy decreases, until, at thermodynamic equilibrium, entropy reaches a maximum and there is no free energy left. The concept of thermodynamic equilibrium is central to the Second Law. It is a state of maximum entropy towards which all isolated systems evolve. A system at equilibrium is one in which no more changes can occur unless it is removed from isolation and placed in contact with another system.

The laws of classical thermodynamics essentially describe how one equilibrium replaces another. They say very little about the changes that happen in between when systems are not in equilibrium. In that respect alone, classical thermodynamics is quite inadequate to deal with living systems where things are happening all the time. (In Chapter 4, we shall see how thermodynamicists try to overcome that limitation with some success). A more serious problem is that the laws of thermodynamics, as usually formulated, apply to homogeneous, or 'bulk phase' systems consisting of a large number of identical components.[3]

Entropy as Disorder

Entropy can be given an exact formulation in statistical mechanics in terms of a large ensemble of identical systems at a given internal energy, volume and composition, referred to as a 'microcanonical ensemble'. Each member in the microcanonical ensemble can exist in a vast number of different *microstates* or more precisely, 'quantum states'. The entropy of the system is given as,

$$S = k \ln W \tag{2.15}$$

The Boltzmann's constant, $k = 1.3805 \times 10^{-23}$ J K^{-1}, is a measure of the thermal energy in Joules associated with each molecule per degree K. W is the number of possible microstates that the system can exist in, and ln is the natural logarithm. (It should be apparent to you by now that physicists may use the same symbols for different entities: I have used W for work in the First Law of thermodynamics, whereas here it stands for microstates.) It can be readily appreciated that the greater the number of possible microstates, the greater the entropy, hence, of 'randomness', or 'disorder'. The system consisting of the ink drop in a jar of water, for example, starts from a state of low entropy because the ink molecules are confined to a small region in the glass. Entropy increases as the ink molecules diffuse, so that finally, at equilibrium, a given ink molecule has the probability of being found in a small volume located anywhere in the glass. The equilibrium state is thus the one in which the entropy function given in Eq. (2.15) is a maximum. Another way to say the same thing is that the equilibrium state is the most probable state.

Similarly, the total energy of a system corresponds to the sum of all the molecular energies of translation, rotation, vibration, plus electronic energy and nuclear energy (see Chapter 5), whereas temperature is proportional to the sum of the kinetic energies of all the molecules. For a monatomic system (a system of molecules each containing one atom), the total energy is:

$$nkT = \sum_{i=1}^{n} m_i C_i^2 \tag{2.16}$$

Here, n is the total number of molecules, m_i is the mass of the ith molecule and C_i its velocity. The term kT is often referred to as the thermal energy of a molecule at temperature T.

The translation of macroscopic parameters into microscopic properties of molecules is by no means straightforward. For example, the statistical entropy function, elegant though it is, cannot easily be used for systems involving chemical reactions, which include all living systems as well as all chemical systems. It is only an analogue

of the macroscopic entropy. As physical chemist Kenneth Denbigh[4] reminds us in his excellent textbook, there is no *necessary* connection between entropy and either 'orderliness' or 'organisation'. Along with concepts like energy, work, heat and temperature, entropy does not bear up to rigorous analysis.[5] We shall leave these difficulties aside for the moment (to be dealt with in Chapter 5), and concentrate on the limitations of the Second Law of thermodynamics that arise from its statistical foundations.

Is Maxwell's Demon in the Living System?

In his physical chemistry textbook, Samuel Glasstone[6] expresses a very commonly held view that the Second Law of thermodynamics is a statistical law, and can only be applied to a system consisting of a large number of particles. And furthermore, 'If it were possible to work with systems of single, or a few, molecules, the law might well fail'.

A major difficulty already identified by Schrödinger is that single molecules, or very few of them, are the active agents in living systems. Thus, each cell contains only one or two molecules of each sequence of DNA in the nucleus. Each bacterium of *E. coli* contains several molecules of the protein that enables it to respond to the presence of lactose in its environment, resulting in the induced synthesis of several enzymes involved in metabolising the sugar, enabling the bacterium to grow and to multiply. This is typical of whole classes of metabolic regulators. Similarly, it takes no more than several molecules of a given hormone to bind to specific receptors in the cell membrane in order to initiate a cascade of biochemical reactions that alter the characteristics of the whole cell. Does that mean the Second Law cannot be applied to living systems?

Actually, this difficulty is not restricted to biology, but occurs in physical systems as well. The most colourful statement of the problem is in the form of Maxwell's demon[7], an hypothetical intelligent being that can operate a microscopic trapdoor between two compartments of a container of gas at equilibrium so as to let

fast molecules through in one direction, and the slow ones in the other. Soon, a temperature difference would be created by the accumulation of fast, energetic molecules on one side and slow ones on the other, and work can then be extracted from the system. Scottish physicist James Clerk 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 also 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, German-born physicist Albert Einstein, who invented relativity theory and probably the most famous scientist in recent generations, showed that the fluctuations *can* be observed, and in fact, were first observed in 1827 by Scottish botanist Robert Brown, and hence named after him as Brownian motion. This is the random movement of microscopic particles (observable under the microscope) as they are jostled about by the fluctuations of the water molecules. It also became evident in the 1950s that something like a Maxwell's demon could be achieved with little more than a trapdoor that opens in one direction only and requires a threshold amount of energy (activation energy) to open it. This is realisable in solid-state devices such as diodes and transistors that act as rectifiers.[7] Rectifiers let current pass in one direction only but not in reverse, thereby converting alternating currents to direct currents. That means they can convert randomly fluctuating currents, in principle, into an electrical potential difference between the two sides from which work can then be extracted.

Similar situations are commonly found in biological membranes, which have electrical potential gradients of some 10^7 V/m across them and bound enzymes involved in the directional transport of ions and metabolites from one side to the other. For example, Na^+ is transported out of, and K^+ into the cell by the Na^+/K^+ ATPase (but see Chapter 17, p. 264). The conventional account is that the chemical energy in

ATP is used to 'pump' Na^+ out of the cell in exchange for K^+, which is why Na^+ concentration remains low inside the cell while K^+ concentration is high.

However, it has been demonstrated that weak alternating electric fields can drive unidirectional active transport by this enzyme without ATP being broken down. In other words, the energy from the electric field is directly transduced into transport work by means of 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![8] Actually, there is no violation of the Second Law here simply because cells and organisms are not at thermodynamic equilibrium.

The problem of Maxwell's demon is generally considered as having been 'solved' by Hungarian born physicist Leo Szilard, and later, French-American physicist Léon Brillouin, who showed that 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 (see Chapter 19). What they have failed to take account of is that the so-called information is already supplied by the special *structure* or organisation of the system. In the next chapter, I shall concentrate on how the problem of Maxwell's demon might be solved.

Notes

1. Schrödinger (1944).
2. See Penrose (1970).
3. Statistical mechanics can be formulated to deal with a mixture of chemical species, and to a limited extent, with space-time structure, but not yet of the kind that exists in living systems. I thank Geoffrey Sewell for pointing this out to me.
4. See Denbigh (1989) pp. 323–332.
5. See Bridgman (1941). Geoffrey Sewell disagrees with my statement, pointing out that a lot of effort has since been devoted to translating/relating macroscopic entropy to degree of molecular disorder either in a system (von Neumann entropy) or in a process (Kolmogorov entropy). However, I believe it is still

true to say that the relationship between the macroscopic and microscopic entities remain conjectural; there is no *necessary* logical connection between the two (see Chapter 5).

6. Glasstone (1955).
7. Ehrenberg (1967).
8. See Astumian *et al.* (1989). The authors are at pains to point out that noise internal to the system, however, cannot be used in the same way to generate work, because electrical correlations would be induced to oppose it, and hence the second law is by no means violated. A more detailed model of how 'non-equilibrium fluctuations' can bias the Brownian motion of a particle in an anisotropic medium without thermal gradients is presented by Astumian (1997). See also Tsong and Gross (1994) for an electroconformation model of membrane-bound enzymes that can efficiently carry out vectorial transport with random electrical energy. Wiggins (2003) has proposed a more interesting model based on water changing states, as described in Ho (2006i).

CHAPTER 3

Can the Second Law Cope with Organised Complexity?

The Space-Time Structure of Living Processes

One cannot fully appreciate the problem of Maxwell's demon in the context of living organisms without taking account of the organism's complex space-time structure, which also demonstrates clearly the limitations of thermodynamics as applied to living systems.

To begin, we can take it as obvious and given that the organism is an open system, which moreover, qualifies as a *dissipative structure*[1] in the sense that its organisation is maintained in some kind of 'steady state' by a flow of energy and chemicals. (We shall say more about energy flow in the next chapter.) 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 such as the physical chemist's continuously stirred tank reactor (CSTR) or, as microbiologists prefer to call it, the *chemostat*. The CSTR has long served as the model for the steady state, and many useful analyses have been done. But as far as a representation of living organisation is concerned, it introduces some quite misleading features. Indeed, in typical models of dissipative structures such as the Bénard cells (see the next chapter), which develop in a shallow pan of water heated from below, or the Beloussov-Zhabotinsky oxidation-reduction reaction,

which gives oscillating, concentric red and blue rings and various spiralling patterns in a petri-dish (see Fig. 3.1), the dynamical structures, the patterns that can be seen, are obtained precisely because the system is not stirred. Stirring would obliterate those structures, resulting in featureless homogeneity.[2]

What do we find in the organism? There is organised heterogeneity, or dynamic structures on all scales. There is no homogeneity, no static phase held at any level. Even a single cell has its characteristic shape and anatomy, all parts of which are in constant motion; its electrical potentials and mechanical properties similarly, are subject to 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 state' of processes that can respond directly to external stimuli and relay signals to other compartments of the cell. Within each

Figure 3.1 The Beloussov-Zhabotinsky reaction.[3]

compartment, microdomains[4] can be separately energised to give local circuits, and complexes of two or more molecules can function as 'molecular energy machines' that can cycle autonomously without immediate reference to its surroundings. In other words, the steady 'state' is not a state at all but a conglomerate of processes spatiotemporally organised, i.e., it has a deep space-time structure, and cannot be represented as an instantaneous state, or even a configuration of states.[5] Characteristic times of processes range from $<10^{-14}$ s for resonant energy transfer between molecules to 10^{7} s for circannual rhythms. The spatial extent of processes, similarly, spans at least ten orders of magnitude from 10^{-10} m for intramolecular interactions to metres for nerve conduction and the general coordination of movements in larger animals.

The processes are catenated in both time and space: the extremely rapid transient flows (very short-lived pulses of chemicals or of energy), which take place on receiving specific signals, are propagated to longer and longer time domains of minutes, hours, days, and so on via interlocking processes that ultimately straddle generations. These processes include the familiar enzyme activation cascades (see Chapter 1) that occur in response to specific stimuli and often end in the expression of different genes and in morphological differentiation.

For example, repeated stimulation of the same muscles encourages the growth of those muscles and make them function more efficiently, as body builders are well aware! The intermediate events include changes in innervation, and the expression of genes that code for different sets of muscle proteins.[6] Figure 3.2 depicts the catenated sequence of events and their approximate timescales.

A transient pulse of a chemical signal, *acetylcholine*, sent out by the nerve cell at its junction with the muscle, opens the sodium ion channels in the membrane of the muscle cell and depolarises the cell membrane within 10^{-3} s (peak 1), triggering an influx of Ca^{2+} from the sarcoplasmic reticulum (special membrane stacks of the muscle cell) which lasts for 10^{-2} s (peak 2). This in turn sets off the reactions between the muscle proteins, actin and myosin, in a contraction, which

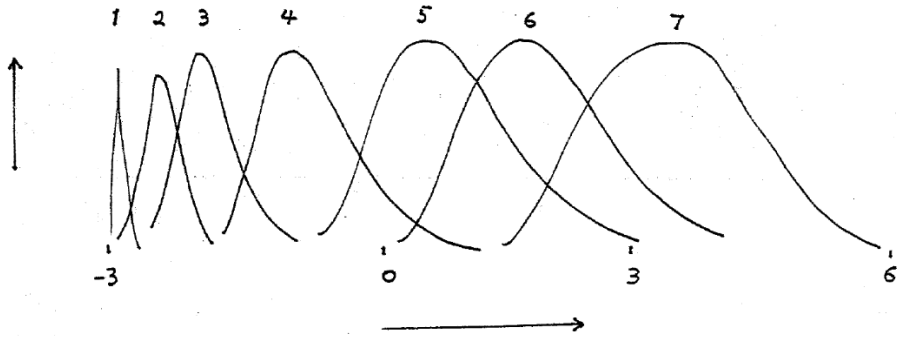

Figure 3.2 Catenation of living processes in time. The horizontal axis is time in seconds, in logarithm to the base ten. The amplitudes in the vertical axis are represented as equal for all the processes, but in reality, they may be progressively amplified or diminished at longer and longer time scales (see text).

involves many cycles of molecular tread-milling where ATP is split into ADP and Pi. Each individual cycle is some 10^{-2} to 10^{-1} s long (peak 3), whereas a contraction may last 1 to 10 s (peak 4). Sustained muscular activities, consisting of numerous cycles of contraction and relaxation of entire muscles, go on typically for 10^2 to 10^3 s (peak 5). This stimulates transcription of specific genes to increase the synthesis of special muscle proteins in 10^3 s or longer (peak 6). Over a period of days, weeks and months, repetition of the same sequence of activities in regular exercises gives rise to the desired changes to the muscles involved (peak 7): enhancement in anatomy and improvement in performance.

These catenated processes are responsible for the phenomenon of 'memory' so characteristic of living systems. In reality, the processes are projections or propagations into the *future* at every stage. They set up influences to determine how the system develops and responds in times to come. Typically, multiple series of activities emanate from the focus of excitation. The mere *anticipation* of muscular activity is accompanied by the secretion of adrenaline, which in turn causes the blood vessels to dilate, increasing the heart rate, and thus enhancing the aeration of muscles and the synthesis of more ATP to supply the

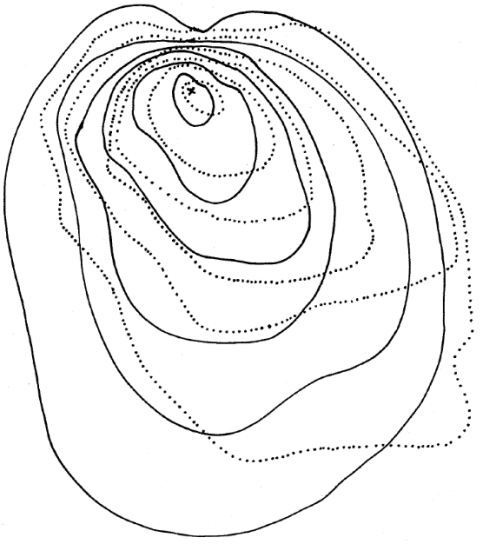

Figure 3.3 Processes propagating in many dimensions of space and time. The spot marked × is the initial signalling process. The dotted lines and solid lines represent two series of catenated processes spreading out from the initial event.

sustained activity of the muscle. While the array of changes in the positive direction is propagating, a series of negative feedback processes is also spreading, which has the effect of dampening the change. It is necessary to think of all these processes propagating and catenating in parallel in many dimensions of space and time (see Fig. 3.3). In case of disturbances that have no special significance for the body, homeostasis (a kind of dynamic balance) is restored sooner or later as the disturbance passes. On the other hand, if the disturbance or signal is significant enough, a series of irreversible events brings the organism to a new 'steady state' by developing or differentiating new tissues. The organism also acts to alter its environment appropriately and in myriad ways, by moving, building nests, secreting slime or other chemical substances.

The living system is so thoroughly dynamic that each single cell in the body is simultaneously criss-crossed by many circuits of flow,

each circuit with its own time domain and direction, specified by local pumping, gating and chemical transformation. Thus, classical equilibrium constants are quite irrelevant, for each 'constant' is in reality a continuous function of variables including the flow rates, the electrical and mechanical field intensities and so on. Furthermore, as the reaction products change the chemical potentials of all the components by altering the variables, the equilibrium 'constants' will also be functions of time. How can we describe such a space-time structure?

Inorganic chemist R.J.P. Williams[4] at Oxford University in the UK has considered this problem with the refreshing eye of 'first looking into nature's chemistry', and advocates a shift from a conventional thermodynamic approach to a dynamic approach, which would involve a description of the living system in terms of forces and flows rather than a succession of equilibrium states. This has already begun to some extent with non-equilibrium thermodynamics (see next chapter). But the fundamental difficulty of the statistical nature of a thermodynamic description remains practically untouched. There is as yet no science of organised heterogeneity or complexity — apart from that presented in this book — such as would apply to living systems.

As is clear from the foregoing description, living systems consist of nested compartments and microcompartments down to single macromolecules that can cycle autonomously as efficient molecular energy machines. At the very least, this implies that if thermodynamics were to apply to living systems, it must apply to individual molecules. Such was British physiologist Colin McClare's[5] contention.

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, τ, within which a system reaches equilibrium at temperature θ. The energies contained in the system are then partitioned into *stored* energies versus *thermal* energies.

Thermal energies are those that exchange with each other and reach equilibrium in a time t_e less than τ, so technically they give the so-called Boltzmann distribution characterised by the temperature θ. Stored energies, on the other hand, are those that remain in a non-equilibrium distribution for a time t_s greater than τ, either as characterised 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 thermalise, equilibrate throughout the system or degrade into heat in the interval t (see Fig. 3.4).

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, thermalised energy is unavailable for work and it is impossible to convert thermalised energy into stored energy.

McClare was right in identifying the problem of Maxwell's demon in relation to the living system, and in stressing that useful work can be done by a molecular system via a direct transfer of stored energy *without thermalisation*. The significance of this alone requires much more thought. Photosynthesis, on which practically all life on earth depends, involves the direct, nonthermal absorption of the energy of photons, and non-thermal energy transfer may indeed play a much larger, if not fundamental role in living processes than hitherto

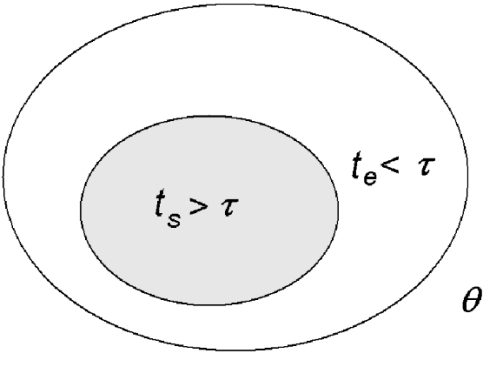

Figure 3.4 Stored *versus* thermalised equilibrated energies of a system.

recognised. However, his restatement of the Second Law is unnecessarily restrictive, and possibly untrue, for thermal energy *can* be directed or channelled to do useful work in a cooperative system, as in the case of enzymes embedded in a membrane described at the end of the previous chapter. Furthermore, thermalised energy from burning coal or petrol is routinely used to run machines such as generators and motorcars (which is why they are so inefficient and polluting). There is a way out of this.

Let's take the case of the motorcar. The hot gases expand against a constraint,[6] the piston, which, in taking up the thermalised energy, is in a position to do work against the system *external* to the combustion chamber. This suggests 'the system' must be more explicitly defined in relationship to the *extent* of equilibration, which naturally brings into the Second Law considerations of space as well as time. A more adequate restatement of the Second Law, is as follows:

> *Useful work is done by molecules by a direct transfer of stored energy, and thermalised 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.*[7]

The first half of the formulation, much as McClare has proposed, is new and significant for biology, as well for the non-equilibrium phase transitions associated with laser action, for example (see Chapter 9). The second half of the statement, which I have modified, introduces the concept of a 'system', defined as the spatial extent to which thermalised and other rapidly exchanging energies equilibrate. Importantly, this allows for the possibility that thermalised energies from one (sub)system can do work in a larger encompassing system for which the thermalised and other energies are in a non-equilibrium distribution. This is highly relevant for the nested dynamic organisation of the living system (see Fig. 3.5).

What I am proposing is that the living system is effectively partitioned into systems encompassing systems within, rather like Russian dolls, each defined by the spatiotemporal extent to which rapidly exchanging energies equilibrate (see below).

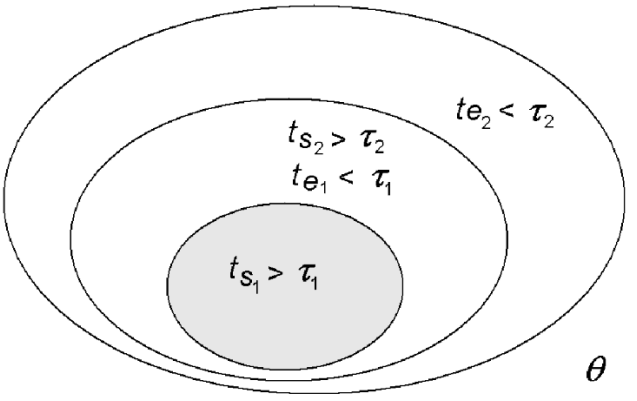

Figure 3.5 Energies equilibrated or thermalised in system 1 are still stored in the larger encompassing system 2.

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, 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 $dS = 0$, as explained in the previous chapter. But the attention to time-structure makes much more precise what the limiting conditions are.

Let us take the slow process first. A slow process is one that occurs at or near equilibrium. According to classical thermodynamics, a process occurring at or near equilibrium is reversible, and is the most efficient in terms of generating the maximum amount of work and the least amount of entropy (see p. 15). By taking explicit account of characteristic time, a reversible thermodynamic process merely needs to be slow enough for all exchanging energies to equilibrate, i.e., slower than τ, which can in reality be a very short period of time, for processes that have a short time constant. Thus, for a process that takes place in 10^{-12} s, a millisecond (10^{-3} s) is an eternity. Yet for the cell in which it occurs, it is about the 'normal' timescale, and for us, a millisecond is about two orders of magnitude below the level of our time awareness. So high efficiencies of energy conversion can still be attained

in thermodynamic processes that occur quite rapidly, provided that equilibration is fast enough.

Seen in this light, the nested dynamic structure of the living system is thermodynamically (as well as kinetically) extremely important. It effectively restricts the spatial extent within which equilibration occurs, thus reducing the equilibration time.[8] This means that *local equilibrium may be achieved for many biochemical reactions in the living system*. We begin to see that thermodynamic equilibrium itself is a subtle concept, depending on the level of resolution of time *and* space. I shall have more to say on that in Chapter 6.

At the other extreme, there can also be processes occurring so quickly that they too are 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, chemical bonds when excited 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 non-specific absorption in the intervening medium. Resonant energy transfer occurs typically in 10^{-14} s, whereas the vibrations themselves die down, or thermalise, in 10^{-9} s to 10^{1} s. (On our characteristic perceptive time-scale — roughly 10^{-2} s — the vibrations would persist for as long as one year to one thousand years!) 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, at least as perceived by conventional chemists, 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[9] was the first to suggest it occurs in muscle contraction. Subsequently, it has been found that the energy released in the hydrolysis of ATP is almost completely converted into mechanical energy (see above). Experiments with isolated muscle proteins show that the energy of one ATP molecule may be effectively shared over four cycles of cross-bridge formation between actin and myosin. That would indeed involve a form of resonant energy transfer.[10] Ultrafast, resonant energy transfer processes are well recognised in photosynthesis.[11] Chlorophyll molecules in the light harvesting 'antenna complex' transfer the energy of the photons absorbed to the 'reaction centre' by a form of resonant energy transfer known as exciton migration. In the reaction centre, the separation of positive and negative charges in the 'special pair' of chlorophyll molecules has also been identified to be a readily reversible reaction that takes place in less than 10^{-13} s. This is possibly the fastest chemical reaction on earth, as well as being 100% efficient. Molecular and electronic engineer Irena Cosic[12] has put forward the radical idea that protein-protein, as well as protein-DNA interactions are not due to complementary shapes as in the mechanical 'lock and key' model still accepted by the vast majority of molecular biologists, but due to electromagnetic resonance recognition. In other words, the molecules attract one another by vibrating at the same frequencies. We shall look at this idea in more detail in a later chapter.

Thus, by virtue of its nested space-time differentiation, the living system can simultaneously exploit equilibrium and non-equilibrium energy transfer with minimum dissipation.[13] It also optimises the rapidity of energy mobilisation. Biochemical reactions depend strictly on local concentration of reactants, which could be enormously high, as their extent of equilibration is generally quite restricted. Cell biologists are beginning to take seriously the view that the cell is more like a solid state, or more accurately, a liquid crystalline matrix, where nothing is freely diffusible, and even the cell water is organised. You will read about these fascinating developments in later chapters.