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The Perennial Question

Available energy is the main object at stake in the struggle for existence and the evolution of the world.

—Ludwig Boltzmann, 1886

Gain in entropy always means loss of information, and nothing more.

—Gilbert Lewis, 1930

The perennial question – what is life? The simple answer is that life, either considered in the totality of all its incredible diversity or even in the context of an individual organism, is a highly complex chemical system with a capacity for self-reproduction. But what fuels this system, and what drives the evolution of such extreme apparent complexity? The principle underlying the answer to the first question was initially propounded by Ludwig Boltzmann, the nineteenth-century physicist and natural philosopher. Boltzmann had a tremendous admiration for Darwin and suggested, ‘Available energy is the main object at stake in the struggle for existence and the evolution of the world’.

Thirty-six years later, Alfred Lotka (1922a, 1922b) interpreted Boltzmann’s view to imply that available energy could be the central concept that unified physics and biology as a quantitative physical principle of evolution, stating, ‘In accord with this observation is the principle that, in the struggle for existence, the advantage must go to those organisms whose energy-capturing devices are most efficient in

Box 1.1 Darwinism and Darwinian

Two of the most overused, and possibly abused, terms in the evolutionary lexicon. Although there exist notable exceptions (for example, Koonin, 2009; Koonin & Wolf, 2009), as with Lamarckism the precise meaning of the terminology can depend on the interpretation of an individual protagonist and may result in semantic quibbling. In this book the word is used in the strict contexts of variation and the process of natural selection as originally proposed by Darwin and Wallace. It is not, and cannot be, restricted to purely genetically driven evolution. Lamarckism is here defined as describing the inheritance of acquired characteristics, including somatic mutations. Because both Darwin and Lamarck predated the discovery of DNA, these definitions of Darwinism and Lamarckism here assume a more modern perspective.

directing available energy into channels favorable to the preservation of the species'. But, by themselves, such statements left unanswered the question of how different life forms could successfully reproduce themselves and also change. The question became, if available energy is the fuel, what is the directing force behind evolution? Although Boltzmann framed his comments in the context of Darwinian evolution (Box 1.1), his thoughts preceded the publication of Mendel's work on the genetics of peas. Consequently in the 1940s it fell to another physicist, Erwin Schrödinger, to combine Boltzmann's concept of available energy with that of a requirement for a heritable informational 'code-script' that specifies the form and function of all biological organisms. Life as we know it thus rests on the twin pillars of energy and information – consideration of both is essential for an adequate appreciation of the essence of life.

Today virtually all living organisms depend on deoxyribonucleic acid, DNA, as their primary source of genetic information – their 'code-script'. Some viruses utilise ribonucleic acid, RNA, a related nucleic acid, but these are very much the exception, and the amount of information encoded in RNA genomes, relative to that in DNA, is minute. So how did DNA achieve this dominant position? Why DNA – and not RNA? The current paradigm of information transfer in living organisms posits that the genetic information encoding proteins in

DNA is first copied into RNA, and the RNA copies are then translated into functional proteins by an elaborate molecular machinery (Box 1.2). But it was probably not always thus. In the initial stages of the evolution of life, it is believed that there was no DNA – it was an ‘RNA world’ – and possibly the appearance of RNA even preceded or was concomitant with the evolution of proteins themselves.

Both DNA and RNA are nucleic acids. They are both polymers consisting of a backbone of a long strand of alternating sugar and phosphate residues (Box 1.3).

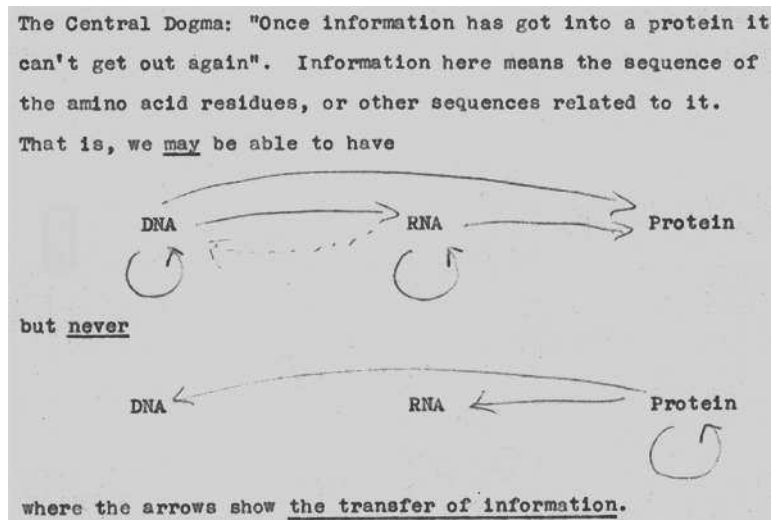
An organic base is attached to each of the sugars. In RNA there are four principal types – adenine, cytosine, guanine and uracil. In DNA thymine replaces uracil. In any given chain of RNA or DNA the specific order of these bases in the polymer constitutes the genetic information. As famously pointed out by Watson and Crick, particular combinations of these bases have the ability to form complementary pairs with each other by forming hydrogen bonds. Adenine can pair with uracil or thymine, while guanine can pair with cytosine (Figure 3.1). This property allows two nucleic acid strands to base-pair with each other provided that the base sequence of one strand is complementary to that of its neighbour. It is the formation of this double helix that provides the fundamental basis for genetic inheritance. Today DNA exists almost exclusively in a double-stranded form. It is the ‘double helix’. In contrast RNA molecules are predominantly single stranded, although this does not preclude the formation of double-stranded regions depending on base-pairing within a single strand. Chemically RNA and DNA differ principally in the nature of the sugar in backbone. The RNA sugar is ribose (hence RiboNucleic Acid), whilst that in DNA is deoxyribose (hence DeoxyriboNucleic Acid). This difference confers important different chemical and physical properties on the two nucleic acids, differences that allow DNA to function more efficiently as a genetic information store.

By itself a description of the components of biological systems fails to capture the intrinsic nature of the process of life. The key to understanding life is that it is dynamic. It is not an ordered crystal structure but rather should be regarded as a system in constant flux where an elaborate organisation of multifarious chemical reactions is involved in maintaining individual organisms and enabling their

Box 1.2 Biological Information Transfer

The process of the transfer of genetic information in a biological system was initially formulated by Francis Crick in 1956 and subsequently published in 1958 (for an illuminating historical perspective, see Cobb, 2017): The Central Dogma. This states that once 'information' has passed into protein, it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein.

Although commonly interpreted as implying a unidirectional transfer of information from DNA to RNA to protein both Crick's text and the accompanying diagram in his notebook clearly envisaged, albeit cautiously, that in principle information could be transferred not only from DNA to RNA but from RNA to DNA.



Source: Reproduction from Francis Crick's 1956 notebook (Credit: Wellcome Collection)

This caution was rewarded by the subsequent discovery that the RNA genome of certain viruses, the aptly named retroviruses, could be copied as DNA and inserted into nuclear DNA.

Box 1.3 DNA and RNA

The biological nucleic acids, DNA and RNA, are both polymers in which the monomeric units are nucleotides. Each nucleotide contains a 5-carbon sugar, usually ribose in RNA or deoxyribose in DNA, as well as a phosphate group and a heterocyclic nitrogenous base. The four bases most commonly found in RNA are adenine, cytosine, guanine and uracil, while in DNA thymine is found in place of uracil. Although the base-pairing rules – adenine pairs with uracil or thymine and guanine pairs with cytosine – are specific and conserved, modified variants of the bases often occur in both DNA and RNA. These include 5-methylcytosine, N6-methyladenine, uracil, hydroxymethyluracil and glucosylated hydroxymethyluracil in double-stranded DNA as well as N6-methyladenine and other variants in transfer RNA.

replication for future generations. This concept of energy flux is again attributable to Lotka. Replication is dependent on the conservation of information within any biological system but, by the same logic, can allow small informational changes to determine changes in the characteristics of the chemical reactions and so direct the evolution of biological forms. In this context RNA initially had two essential attributes. Not only could it carry information in the form of a defined sequence of nucleotides, but it could also, by virtue of its chemical structure, catalyse a (rather restricted) set of chemical reactions. So by analogy to protein catalysts, aka enzymes, it could act itself as an enzyme, and indeed some RNA molecules still perform biologically crucial such functions in cells. Indeed the synthesis on the ribosome of the peptide bonds connecting individual amino acids in a protein chain is RNA-catalysed. That such an important feature of cellular information flow is still extant is one of the major indications that RNA catalysis is evolutionary ancient and likely developed in a world devoid of DNA.

In principle, given appropriate precursor chemicals, RNA can maintain itself by self-catalysed copying and processing. Such a process is likely inefficient. With the advent of the ability to synthesise protein molecules – even simple ones – the biological world would be transformed. Instead of the four basic structural units – the bases – in RNA, present-day proteins can contain up to at least

20 different fundamental units – as amino acids – in a polypeptide chain. Consequently not only is the repertoire of chemical reactions that can be catalysed by proteins very much greater than that of RNA molecules but also protein molecules either individually, or in collaboration with each other, can construct a scaffold that facilitates the close approaches of the chemical participants in a reaction. Or put another way, proteins can act to increase the local concentrations of reactants not only by possessing catalytic properties themselves – this is, after all, an essential attribute of enzymatic catalysis – but also by stabilising the structures of other catalytic macromolecules – be they RNA or protein – to effect the close spatial proximity of chemically reactive groups.

Ultimately all these chemical reactions that build an organism require energy (Lane, Allen, & Martin, 2010). But how can the process of life be reconciled with physical laws? At the heart of this question lies the apparent paradox first broached by the eminent physicist Erwin Schrödinger nearly 70 years ago. Like Boltzmann and Lotka before him, he addressed the fundamental issue of the nature of life itself as seen through the lens of a physicist. How is it that although Boltzmann's Second Law of Thermodynamics (Box 1.4) dictates that the universe ultimately approaches a state of maximum disorder, or entropy, that biological systems, as we observe them, appear to be, at the very least, minimising disorder or creating a system within themselves where order is actually increasing – or in Schrödinger's terminology – creating *negentropy* (see also Brillouin, 1953, 1956) The key to this apparent paradox is that biology operates in a thermodynamically 'open' system in which any local decrease or minimisation of entropy is more than compensated by an entropy increase elsewhere so that, on balance, overall entropy increases. In other words, because overall the system is heterogeneous, it is energetically possible for different parts of a connected system to gain or lose entropy, provided that there is no net loss of entropy. Indeed, because the energy required to reduce entropy locally is not utilised with 100% efficiency, there must overall be an increase in entropy. In this context what is important is Boltzmann's 'available energy' and not the overall energy content of a system. Energy is useless if it cannot be utilised. A tautology maybe but as Boltzmann put it in defining available energy:

Box 1.4 Second Law of Thermodynamics

The Second Law of Thermodynamics concerns processes that involve the transfer or conversion of heat energy. It posits that because such processes are not 100% efficient, some energy is ‘wasted’ and therefore a system progresses in the direction of increasing disorder, also known as **entropy**. This statement implies irreversibility and is the basis for the ‘arrow of time’. There are many varied formulations of the Law. That of Planck states, ‘Every process occurring in nature proceeds in the sense in which the sum of the entropies of all bodies taking part in the process is increased. In the limit, i.e., for [ideal] reversible processes, the sum of the entropies remains unchanged’. In the context of the Second Law, living organisms are never in states of thermodynamic equilibrium and must be considered as ‘open’ systems because they take in nutrients and give out waste products. A biological system is not reversible but operates within a non-equilibrium ‘open’ thermodynamic environment. Nevertheless, to satisfy the requirement of the Second Law that entropy increases as energy, there is, overall, a net increase in the system comprising an organism and the total environment in which it operates. A further crucial characteristic of the Second Law is that, as discussed in Chapter 2, it is statistical and thus probabilistic in nature. The Second Law has been, and to some extent still is, scientifically controversial, but as Arthur Eddington once said,

The law that entropy always increases, holds, I think, the supreme position among the laws of Nature. If someone points out to you that your pet theory of the universe is in disagreement with Maxwell’s equations – then so much the worse for Maxwell’s equations. If it is found to be contradicted by observation – well, these experimentalists do bungle things sometimes. But if your theory is found to be against the Second Law of Thermodynamics I can give you no hope; there is nothing for it but to collapse in deepest humiliation.

(Although, for a dissenting view, see Hemmo and Shenker [2012].)

The general struggle for existence of animate beings is not a struggle for raw materials – these, for organisms, are air, water and soil, all abundantly available – nor for energy which exists in plenty in any body in the form of heat, but a struggle for [negative] entropy, which becomes available through the transition of energy from the hot sun to the cold earth.

Schrödinger (1944) points out very clearly that this statement is best appreciated in thermodynamic terms by invoking the technical definition of ‘free energy’ or, as he puts it, ‘[considering entropy alone] cannot account for [a biological system which feeds] on matter in the extremely well-ordered state of more or less complicated organic molecules]. But this balance differs between organisms. It is true for animals but much less so for plants and of course, both are part of the same complex system.

A fundamental question is then what is the nature of the molecular mechanisms that drive the creation of negentropy and the establishment of organisation? The creation of negentropy, otherwise a reduction in the intrinsic entropy of a system, implies increased order, a property of complex systems. But what do we understand by complexity? Complexity can be a slippery concept, distinct from, but related to, diversity but here is defined as a physical system containing a number of distinct components that interact directly or indirectly (Box 1.5). These components usually constitute a network. Diversity, a necessary condition for complexity, simply specifies the number of components without regard to their ability to interact. It is effectively a scalar property while by analogy complexity has some of the attributes of a vector. Although life is arguably one of the most extreme examples of a complex system, there are many other examples of such a phenomenon, for example, a galaxy cluster, an atom or even a city. In these cases available energy is used to create organisation in an open thermodynamic system. For a city the available energy would have been provided in early times by the agricultural harvesting of light energy and more latterly by fossil fuels.

The evolution of complexity in biological systems was also highlighted in Erwin Schrödinger’s *What Is Life?* In his seminal lectures in 1943, he claimed that the laws of heredity required that the genetic material must contain a ‘code-script’ that determined ‘the entire pattern

Box 1.5 Complexity and Diversity

A succinct and relevant definition of complexity and complex states has been provided by Chaisson (2015) – ‘a state of intricacy, complication, variety or involvement among the networked, **interacting** parts of a system’s structure and function; operationally, a measure of the **information** needed to describe a system, or of the rate of energy flowing through a system of given mass’. This definition emphasises not only that interactions between different parts of a system are a core component of complexity but also that the system can be described by information or by energy flux, as originally postulated by Lotka. For biological systems, at least, the intimate connection between information and complexity is discussed in Chapter 2. A related concept is that of ‘complexification’ (see Huxley in de Chardin, 1959), visualised as a process that is ‘accompanied by an increase in energetic tension in the resultant corpuscular organisation, or individualised constructions of increased organisational complexity’. For further discussion of the concept, see Adami (2002; Adami, Ofria, & Collier, 2000).

Non-biological examples of complex systems share characteristics with biological systems. A simple example is an atom, composed of three different interacting sub-atomic particles – electrons, protons and neutrons – which like biological systems, form a dynamic structure. But this picture represents only one level of complexity. In the atomic nucleus both protons and neutrons are themselves made up of a mixture of three other sub-atomic particles – quarks. The precise flavour of the mixture determines whether the nucleon is a proton or a neutron. And again, the strong force between nucleons is mediated by apparently massless particles termed gluons. Like atoms, most complex systems can be considered to be a hierarchy of different levels of complexity.

Diversity, as the word implies, is a measure of difference and is shorthand for the number of distinguishable components in a system – for example, an ecosystem. Commonly used in the context of biodiversity as popularised by E. O. Wilson (1992), it is often broadly interpreted to include interactions between components and therefore complexity. Nevertheless, although it does not by itself imply interactions, diversity is the basis for complexity.

of the individual's future development and of its functioning in the mature state'. In other words, the individual's and by extension the biological system is specified by 'information'. At that time the nature of this code-script was obscure. Schrödinger appreciated that the encoding molecules must contain a non-repetitive molecular structure, but the experiments characterising the molecules that carried genetic information were only in their infancy – and in fact the first, from Oswald Avery and his collaborators implicating DNA as the responsible molecule, would not be published until the following year. Nevertheless, the concept that biological information is encoded chemically provided an essential link between the heritability and the thermodynamics of living biological systems. This mirrored Boltzmann's implied view that available energy could be the central concept that unified physics and biology as a quantitative physical principle of evolution.

This link is indeed central to the mechanism of the evolution of biological systems. In this context the overriding concept of natural selection, although usually discussed in relation to organisms, actually applies to the molecules that specify by their function the phenotype of an organism. At one level it is the thermodynamic characteristics of the molecules, particularly the macromolecules, that determine the properties of a biological system as a whole – however that system is defined. Most biological macromolecules, be they DNA, RNA or proteins, are long polymeric chains whose length is very much greater than their width. Superficially they may be compared to long lengths of flexible string such that the length of an individual molecule can be accommodated by many different pathways in three dimensions. It is this variety of pathways – more technically, configurations – that is one component of the intrinsic entropy – or disorder – of the molecule. Some of these long polymers, particularly RNA and proteins, perform structural roles. Others catalyse chemical reactions. Yet others combine these roles. But for those that catalyse chemical reactions, the close approach of the chemical groups required for catalysis within the molecule is essential. And because these groups have, in general, to be much closer to each other than the corresponding lengths along the backbone of the polymer only a few configurations out of a multitude will enable efficient catalysis. Selection for efficient reaction rate will thus inevitably result in a tightening of the frequency spectrum of the range of available configurations and so in a reduction of the intrinsic entropy.