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Genetic Information, Physical Interpreters and Thermodynamics; The Material-Informatic Basis of Biosemiosis

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Abstract The sequence of nucleotide bases occurring in an organism's DNA is often regarded as a codescript for its construction. However, information in a DNA sequence can only be regarded as a codescript relative to an operational biochemical machine, which the information constrains in such a way as to direct the process of construction. In reality, any biochemical machine for which a DNA codescript is efficacious is itself produced through the mechanical interpretation of an identical or very similar codescript. In these terms the origin of life can be described as a bootstrap process involving the simultaneous accumulation of genetic information and the generation of a machine that interprets it as instructions for its own construction. This problem is discussed within the theoretical frameworks of thermodynamics, informatics and self-reproducing automata, paying special attention to the physico-chemical origin of genetic coding and the conditions, both thermodynamic and informatic, that a system must fulfil in order for it to sustain semiosis. The origin of life is equated with biosemiosis.

Keywords Genetic information · Molecular biological interpreter · Self-construction · Coding self-organisation · GRT systems · Informed generation

Introduction

One of the most vexing questions in biology and the philosophy of biology is the character of information and its relevance to our understanding of the nature of living systems as physico-chemical entities. Much of the vexation is caused by the multi-faceted character of information, not least its relationship to "meaning", of which we have immediate experience in language and the perpetual confrontation of multiple interpretations of even

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the simplest perceptions. Although the manifestation of meaning in the physical universe is inextricably linked to biology, there is little agreement, except within alternative schools of biosemiotic thinking, as to how that link is to be understood. In this paper, a critical analysis of the link between biology and meaning will be attempted from the point of view of the theories of molecular biology, physics and complex systems, especially as they have been applied to the question of the origin of life. A heuristic approach will be taken, in which terms with rigorous, formal definitions will be tested for their relevance, with a view to clarifying the standing of physical, computational and semiotic theory in biology.

The feature of organisms that distinguishes them most strikingly from everything non-living is the process of hereditary reproduction. Organisms are able to breed true, one generation after another, because their characteristics are, at least in part, encoded in chromosomal DNA that somehow carries a wide variety of information about them. This is true to the extent that a large animal can be cloned simply by transferring a nucleus containing its chromosomes to a denucleated zygote of the relevant taxon (Wilmut et al. 1997). We understand that an apparently accurate copy of the DNA-donor animal can be grown, virtually from scratch, because the chromosomal DNA "contain[s] in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state" (Schrödinger 1944). When the base-paired heteropolymeric structure of DNA was first elucidated (Watson and Crick 1953), Delbrück's idea of hereditary information being stored in a form resembling an "aperiodic crystal" (Timoféeff-Ressovsky et al. 1935) was vindicated. Thereafter certain molecular moieties, first nucleotide bases and then amino acids, came to be conceived of as letters of physico-chemical alphabets; and it quickly became apparent that in all organisms a simple molecular code operates whereby specific sequences of nucleotide triplets are translated into specific sequences of amino acids comprising the primary linear structure of proteins.

A vivid demonstration of the natural function of DNA bases as letters from an alphabet has been provided by Gibson et al. (2010) who chemically synthesized DNA molecules with sequences closely resembling those normally found in *Mycoplasma mycoides* cells. They then substituted the artificial DNA for the chromosomes of a *M. capricolum* cell, after which the genetically modified cells transformed and bred true, through many cycles of reproduction, as a form of *M. mycoides*. The identity of the cells changed according to the source of the information in the DNA with which they had been supplied. The DNA synthesis was conducted as an exercise in information processing—the copying and assembly of a suite of nucleotide sequences found in cells of *M. mycoides*, much of the process being controlled electronically. The suite of synthesized DNA sequences included some with completely arbitrary base sequences, which are not found in *M. mycoides* or *M. capricolum*, and which would not be expected to serve any predictable biological function. However, when transliterated using a chosen Roman-alphabet interpretation of base-triplets (Shirriff 2010), these extra DNA sequences spell out various messages in English (Saenz 2010).

It has long been known that the finely differentiated characteristics that distinguish one organism from another are exquisitely dependent on the detailed sequences, sometimes down to the last nucleotide base or amino acid, of the macromolecules found within their cells. Soon after the functionally determinative features of the genetic material (DNA) and the ribosomal translation of nucleotide sequences into the amino acid sequences of proteins (genetic code) were first discovered, Crick (1958)

enunciated two principles to provide a universal molecular explanation of biological specificity: the Sequence Hypothesis and the Central Dogma.

While it is true that aspects of both of these principles have required modification (Crick 1970), the framework of thought that they established still serves as the *lingua franca* of modern molecular biology and derivative disciplines like bioinfomatics. Thus, while claiming the heritage of atomic physicists and their empirical analysis of the purely material aspect of natural processes, soon after its inception as a scientific discipline molecular biology departed from a discourse that relied solely on descriptions of the physico-chemical properties of molecules and admitted, in addition, that abstract, immaterial features of components of cells, namely, sequences of letters—chemical moieties construed as hieroglyphics—were causes of biological phenomena.

Although the theoretical perspective of physics and chemistry has been radically modified in molecular biology through introduction of the idea of antecedent informational control and processing at the level of single molecular events, practitioners of the discipline generally resile from either admitting that such modification is of anything other than merely formal significance, or considering it as a theoretical problem. Thus, the new discipline of bioinformatics has developed as a branch of information science devoid of any necessary connection with molecular processes except that the symbols being manipulated entail implicit chemical representations. What was intended in the original definition of the term "bioinformatics" has been forgotten, save in some theoretical work that is far from the mainstream of molecular biology (Hogeweg 2011).

Molecular biology has failed to articulate the general theoretical problem of the relationship between material causation and meaningful information. As a consequence it has become not much more than a set of techniques, largely indistinguishable from biotechnology, for determining how biological systems can be manipulated for commercial gain, curiosity or other ends. It takes little account of the coincidence of molecular-level physical and informatic processes which differentiates the phenomena of life from everything else found in nature.

While the recent elevation of technology above science by global society is by no means restricted to molecular biology (Forman 2010) it is of particular significance in that field simply because systems lacking an essentially biological aspect cannot easily be construed as having any capacity to produce technology. Neither simple matter nor any simple non-living material object carries the sort of autonomous functionality with respect to which some external or internal structure could be seen as being actively used by it. However, very basic forms of the capacity for technology are evident in the emergent functional relationships among molecular components of the primitive prebiotic systems from which terrestrial life first arose. A theoretically critical molecular biology could, based on detailed empirical analysis of natural processes, contribute a great deal to the development of fundamental concepts needed for a responsible understanding of the planetary transformations that *Homo sapiens* is enabling with the capacities of many new technologies, among them "living technology" (Bedau et al. 2010; Wills et al. 2013).

This brings us to the problem of semiotics. When can some atomic-level physical configuration be said to have acquired the function of a sign and how can potentially meaningful signs emerge naturally (as opposed to being designed and produced artificially) in physical systems? What conditions must be fulfiled before signs can exist in the physical universe?

This paper starts from the premise that a new theoretical approach to these questions is needed, hopefully a theory that brings to light new phenomena or provides for a decisive test relative to extant theory. After a discussion of the definition of information commonly used in the quantitative natural sciences, a view of the circumstances under which such information can have meaning is articulated in a sequence of four theses.

1. The existence of disembodied (non-physical) information about the physical world is incompatible with the second law of thermodynamics.
2. Any body of information can be given any meaning whatsoever, by creating a device that functions as an interpreter to deliver the specified meaning upon reception of that information.
3. The spontaneous emergence of the algorithmically meaningful interpretation of information in molecular systems is only possible in self-organised non-equilibrium physical systems whose component structures satisfy certain relational constraints of a purely formal, informatic character.
4. Biological evolution consists in the emergent generation and development of autonomous triadic {information, interpreter, meaning}-systems, in which the interpreter is comprised of components produced by its own output—naturally occurring interpreters are self-constructing.

The conclusion reached is that both life and meaning originate in physical systems through a process of information-based self-construction from functionally differentiated component parts.

Information and Thermodynamics

Information was given a rigorous, quantitative definition by Shannon (1948). Although he was concerned with the faithful communication of differentiable patterns of signals, his information measure can be applied to any set of differentiable patterns. The amount of information H produced by a process that has n separately recognisable outcomes, each of which has an independent probability p_i, is given by the formula

$$H = -K\sum_{i=1}^{n} p_i \log p_i$$

The constant K specifies the units in which H is measured: if the logarithm is taken to base 2, then K=1 and the unit of measurement as the shannon (Battail 2013), which corresponds to a single toss of a fair two-sided coin. Thus, any defined set of events, measurements, states, symbols or any other possible real-world outcomes whose occurrence is characterized by a discrete probability distribution,[1] is the potential source of an amount of formless information H.

The reasons for adding the qualification "formless" to this measure of information are (i) that it relates to a set of numerical probabilities and has no necessary relation to anything having a material form; and (ii) that any set of abstract forms or qualitative

[1] The definition is easily extended to continuous probability distributions.

patterns of which an actual distribution of outcomes may be an instantiation is lost in the reduction to a single numerical value that specifies nothing but the quantity of information. The formlessness of Shannon information can be compared with the formlessness of energy, conceived as a measure of the amount of the most basic substance of which everything in the physical universe is necessarily comprised.[2]

Shannon information begs the question of its definition: why should it be called "information?"[3] Answering this question requires that we consider the relevance of Shannon's measure to our more familiar experience of the association of information with representation and meaning. Tossing a fair coin has two possible outcomes of equal probability of 1/2, and so produces one shannon of information. The alternative outcomes can the represented in terms of a simple binary digit, or bit, usually specified as the set {0,1} (Battail 2013). However the meaning of the information, "1" rather than "0", or vice versa, the fact that it is being taken to represent the outcome of a coin toss, depends completely on some arbitrary historical event or convention whereby the information is associated with those real-world outcomes. Tossing the coin twice has four distinguishable outcomes and produces two shannons of information, and so on. In each case the information in question is a formulaic representation of the qualitative pattern of a particular (set of) outcome(s) whereby it is distinguished from any other (set of) outcome(s): for example, heads rather than tails for one toss; two heads rather than any of the other three possible outcomes for two tosses, and so on. This differentiation of the pattern of individual outcomes, with reference to which the probability distribution over members of a set of outcomes is specified, is the manner in which information has form in any particular context. The quantity of information given by Shannon's formula specifies the overall degree of differentiation between outcomes, but it is silent concerning (i) the manner of differentiation; (ii) the number of possible outcomes associated with the relevant probability distribution; and (iii) details of the range of possibilities in the set of outcomes under consideration, or more significantly, their consequences.

It is possible for information to be produced in the real world only because the physical universe is not homogeneous and not in thermal equilibrium. In a universe having the same temperature and composition at every location, no information could be produced, because every process would have the same outcome—no change from the initial condition. A process that has only one possible outcome produces no information. However, in this instance we have used the term "process" rather loosely; no thermodynamic processes occur in a system at equilibrium, so there is no probability distribution of outcomes to which Shannon's formula could apply, except the instantaneous occurrence of maximally disordered molecular movements and collisions. The production of information envisaged by Shannon requires the sampling of the probability distribution in question, the determination of something temporally real from among a set of possibilities—an actual occurrence. The probability distribution can be sampled

[2] Energy has had the status of the formless *Urstoff* of the cosmos since Einstein derived his celebrated relation, $E=mc^2$, in which he demonstrated the quantitative equivalence of energy and mass. Mass, identified with weight in pre-Newtonian physics, is the classical measure of the amount of substance, whether divisible (compound) or indivisible (atomic), comprising anything in the physical universe.

[3] There are alternatives to this probabilistic definition of Shannon information (Muller 2007), most importantly the algorithmic definition which measures the minimum number of bits needed to specify a procedure for generating a given string of letters.

by any system for which each defined possibility has some distinguishable, consequential effect. In other words, the production of information through the sampling of a set of possible outcomes requires a physical interaction between the system producing the outcomes and the system that is said to do the sampling.

Szilard (1929) and Brouillon (1956) gave detailed consideration to the thermodynamics of the necessary interaction between the information-producing process ("system") and the sampling system ("observer") and were thereby able to exorcise Maxwell's Demon from the physical universe. Maxwell's Demon was a hypothetical entity that could, through the judicious use of information gained by sampling the local fluctuations (microscopic inhomogeneities) occurring in a system at thermal equilibrium, take heat from a cold region of the system and deliver it to a warm region without doing work and then use the temperature difference to do useful work at no net thermal cost, in violation of the second law of thermodynamics. The significance of Szilard and Brouillon's results, and all who have followed them, is that both the production and utilization of information, conceived in any scientific way, are bound to events in the physical world and the laws that govern it. Any purely sentient entity able to gain, through non-interactive observation, the information needed to construct a sufficiently accurate representation of the microscopic details of a physical system would be able to use the mechanism of Maxwell's Demon to create a perpetual motion machine in direct violation of the second law of thermodynamics. In other words, as we currently know them, the laws of physics, especially the second law of thermodynamics, would no longer hold universally if information-generating observation of a material system could be carried out without any physical connection between the observer and the system under observation. The existence of Descartes' immaterial *res cogitans* is incompatible with the thermodynamics of his *res extensa*.

Meaning

We now have the task of determining what sort of causal connection between real world outcomes and their representations is able to make information meaningful in any way. Take the information contained in the human genome as an example. It comprises some 6×10^9 bits, but does not contain the same number of shannons (Yockey 1992). When the physical form of this information consists of a concatenated sequence of nucleotide bases chosen from the canonical four-letter alphabet, that is, comprising DNA molecules such as those found in human chromosomes, an obvious real-world interpretation of this information is the specification of a particular specimen of the biological genus *H. sapiens*. In the case of the standard sequence published by the Celera Corporation (Venter et al. 2001) it turns out that the human being so specified would be a near clone of the individual known internationally as "J. Craig Venter" rather than a hypothetical individual corresponding to a consensus sequence drawn from a wide range of unique specimens of *H. sapiens* (Levy et al. 2007). There is no reason to believe that humans cannot be cloned in the way other animals have been (Wilmut et al. 1997), in which case the means already exist for the production of an individual human organism as a particular interpretation of some selected body of information of size $\sim6\times10^9$ bits embedded in DNA sequences. However, there exists a multitude of other interpretations of the information in the human genome, the range of which is restricted

only by the ingenuity of whoever wishes to build a device capable of giving effect to their potentially perverse imaginings.

The rationale for genome sequencing is to represent the relevant information in some easily accessible and manipulable form, usually electronic or optical, thereby averting the need to deal continually with samples containing particular DNA sequences. This transformation of the information storage medium brings new possibilities to light. When information is stored in particular structures it becomes readily available for use in the service of any purpose whose fulfilment depends on processes that make reference to that form of information. It was this aspect of information that the Venter Institute took advantage of when they encrypted messages into the DNA sequence of their engineered strain of *M. mycoides*. They implemented an arbitrary information-processing algorithm (the mapping from trinucleotides to an ASCII-like character set) whereby part of the genome of their organism can be interpreted as English language messages relevant to certain societal activities. Whether the particular DNA sequence had come into existence by accident or design, it would still be open to interpretation as messages in English: the transformation of the information into that form requires only the existence of some physical entity, or constellation of entities, that can execute the relevant algorithm.

This discussion is not intended to pre-empt argumentation about whether the processes of nature, from the elementary quantum events in the early hot universe to the neurological dynamics of a thinking person's brain, operate in an algorithmic fashion. Algorithms are (usually compact) specifications of transformations of patterns of information, either real or potential. They can be representations of mechanisms, often general mechanisms, according to which natural processes appear to be ordered. As Barbieri (2013) points out, mechanisms serve as scientific models in the realm of natural philosophy. Even the most ardent modern reductionists, who seek complete and final knowledge of nature's unity in the form of a uniquely defined quantum field, eschew the idea that the operation of the relevant mechanism/algorithm is deterministic (Weinberg 1992). According to this view, all meanings, including beliefs about nature, are irrelevant to the algorithmic operation of the (albeit indeterministic) quasi-Laplacian universe. Exactly to the contrary, others seek creative freedom in the belief that nature's operation is non-algorithmic and is bound ultimately to confound the efforts of all model-building that relies on descriptions of operational mechanisms (Penrose 1989; Kauffman 2012).

Possible Interpretations

I now wish to state a strong claim: *Any body of information of non-zero magnitude can be interpreted as, and therefore function as a sign for, any meaning whatsoever. The possible meanings of any body of information depend only on the availability of physical interpreters that generate those meanings.* I do not distinguish between "meaning" and "interpretation", restricting both to the outcome of a physical process within a well-defined system. Either is regarded as the output, potentially generic, of a physical system whose operation varies according to different informational inputs.

Given an elaborate enough description of what is naturally possible and what is observed in the physical world, the occurrence (as opposed to the non-occurrence) of a single event, that is a body of information comprised of a single bit, could be interpreted as

a sign that God exists, an answer to one of the most vexing philosophical questions that has ever been posed. This example is provided to illustrate that the meaning of information can often be ascribed almost entirely to the internal structure and rules of the interpreter. However, in attempting to understand how systems of meaning are associated with particular physical structures and processes, focussing especially on elementary biomolecular systems, I wish to restrict application of the word "interpreter" to a physical system that transforms information, a way of mapping one pattern of information onto another, what Barbieri (2003, 2013) calls a "code". I prefer to use "code" to refer to the simplest transformations of information or parts of algorithms, just as we refer to the universal genetic code as a mapping from 64 codons onto 20 canonical amino acids and the STOP signal. The molecular biological interpretation of a genetic sequence as the primary structure of a protein, known as its "translation", can be regarded as the output of a ribosome-centred computer, on which operates an algorithm involving recognition of an ATG-trinucleotide START signal, repeated translocation and code-table assignment (peptidyl transfer) operations and finally STOP signal recognition.[4] Looking at arbitrary non-biological meanings of genetic information will give us a deeper appreciation of the biosemiotic processes through which these and other systems of interpretation of genetic information have arisen as a result of natural processes.

I will now consider the interpretation of the information in the human genome as the sound produced by a performance of Beethoven's Ninth Symphony. It is easy to construct a machine that takes the information in the human genome and produces an audio file record of such a performance. All one need do is create a bitwise alignment of the two sets of information, the human genome (A) and the audio record (B), perform the "exclusive or" binary operation across the entire length of the alignment to produce their XOR cross (C), and then embed C in a Turing machine that accepts an input stream and XOR crosses it with its internal record of C to produce an output. If the sequence of the human genome (A) is given as input, then a recording of Beethoven's Ninth (B) will be the output. This is because the XOR function has the property that if XOR(A,B)=C, then XOR(A,C)=B and XOR(B,C)=A.

A Turing machine constructed in this way would appear to have very little use, relying as it does on a system of states dictated by the information contained in C, but its interpretation of the information in the human genome is likely to be quite robust in respect of input errors. One could no doubt corrupt the human genome input information in special ways to an extent that it became completely meaningless from a biological point of view, incapable, when instantiated as a DNA sequence, of allowing a human cell to maintain life. However the audio output of the symphonic performance generated by the machine would, to the human ear, probably be indistinguishable from the original soundtrack used to produce C. There are many single point mutations that render a human zygote unviable, but changing the corresponding bit in an audio recording will be of no significance.

First Objection

"The machine already contains Beethoven's Ninth in the embedded information (C). The symphony is not an interpretation of the input (the human genome)." Does the

[4] The integrity of the code part of the algorithm is not maintained directly by the ribosomal mechanism, but by an independent suite of enzymes known as aminoacyl-tRNA synthetases (AARSs).

machine contain Beethoven's Ninth or the human genome? If the symphonic performance is given as input then the output is the human genomic sequence. This raises the question whether any body of information has an inseparable meaning that is intrinsic to it as information. We have already answered that question in the negative, without precluding the possibility that information can have an origin that is practically inseparable from it. What is important concerning the interpretation of the human genome as the sound of a performance of Beethoven's Ninth, B=XOR(A,C), is that it would not be possible to create the interpreter that produces the sound of the performance if the Symphony did not already exist. The chance appearance of our hypothetical Turing machine in the universe without the historical occurrence of Beethoven having written the symphony is inconceivable. However, if we consider the complementary interpretation, A=XOR(B,C), obtaining the human genome from a recording of the symphony, then the way in which information can be bound to its origin becomes much clearer. The human genome first has to exist and be known by us for it to be possible for us to construct the C-dependent Turing machine that retrieves it (A) from the symphony (B). [5]

Second Objection

"It would be possible to build a special machine to produce the symphony using any chosen suitably-sized body of information as input. The Turing machine cannot reasonably be conceived of as an interpreter of any kind." We have allowed the interpreting algorithm to be of about the same informational complexity as an intended input (the human genome) and its corresponding output (the sound of a symphonic performance). This leads us to inquire into the complexity of the natural process (viewed as an algorithm) that produces a human being when it is given a human genome sequence as input information, as would occur if a human were cloned. The idea that the sequence of the human genome is all that is needed for the construction of a human being, that it has such an intrinsic meaning, is untenable. However, it is still believed by many molecular biologists that the human DNA sequence somehow pre-specified the existence of *H. sapiens* as an animal in some Platonic mathematical space of biological forms.[6] The work of Gibson et al. (2010) is relevant to the question of the extent to which diverse organisms possess the same interpreter of genetic information: if one organism is similar enough to another, its interpreter may be compatible with the other's genome, within the bounds of current techniques for genomic transplantation.[7]

Third Objection

"The proposed genome-symphony machine lacks any general functionality as an interpreter." The output I=XOR(C,J), produced by the machine with an arbitrary

[5] The dependence of the origin of Beethoven's Ninth on the pre-existence of the human genome (the fact of Beethoven's humanity) obfuscates the main question and arises only because the symphony is a human artifact and not some other complex object.

[6] This fallacy is expounded by Dawkins (1986, p73).

[7] As discussed elsewhere (Wills 2009), when supplied with information within a certain range of compatibility, a cellular interpreter executes the extraordinary feat of transforming itself into a new self-constructing interpretation of the supplied information.

input J not resembling either the A and B used to produce C=XOR(A,B), would not be recognisable as either a genomic sequence or an audio record. Although it could be instantiated as either, the output information could hardly be expected to function either biologically or musically, or in any other functional domain, except by an accident of inconceivably low probability, a "miracle". Something which acts as an interpreter, even within the restricted definition of the term accepted within computer science, takes information from one domain, where the information has the status of a sign, or representation, and maps it directly into another domain, where it comes to be the thing whose existence was encrypted in the form of the sign. An interpreter is a device that constructs a wide range of objects from their encrypted descriptions.[8] On this basis, the genome-symphony Turing machine we have described could indeed be used as a general interpreter of a sign J for any information I whatsoever that had been encrypted through the process J=XOR(C,I). One could even conceive of a device incorporating some hidden C being used for the retrieval of information I from encrypted proprietary records J. The information I could be bioinformatic records, music, books, photographs, anything at all that can be represented digitally. The functional operation of the machine would define the convention for the retrieval of the information, just as there are conventions for the further interpretation of digital records as chromosomes or audio signals or whatever.[9]

Precursors to Semiosis

Having established that a physical system comprising an interpreter is required for information ever to have meaning, we now proceed to enquire into the natural origin of interpreters that are capable of decoding information in physical structures of a specific kind. The first observation to be made is that most bodies of information of any size are associated in some way with what can only be regarded as cosmically unique events or structures. In this sense a body of information, like the pattern of apparently random atomic defects in an otherwise perfectly regular crystal, can be construed as having a natural meaning; merely by existing it "represents" or "signifies" the occurrence of its creation. By the same token, it is possible to create bodies of information, like the cross between the human genome and a soundtrack of Beethoven's Ninth Symphony, in which "references" to more than one essentially unique occurrence or structure are embedded. Thus, systems of meaning can become very complex, especially when an object that is the product of a functioning interpreter comprises or contributes to a structure which is taken as a source of information by a second interpreter—all the more so when the second interpreter recognises completely different types of structures as bits of information. However, in biology there are quite simple, natural systems of meaning, what Barbieri (2003; 2013) calls

[8] An audio CD player is a general interpreter for the transfer of information from spatial patterns of information on an optically readable disc to corresponding audio "objects", commonly comprised of temporal patterns of voltages and currents in the solenoids of electromagnetically driven speakers.

[9] The XOR encryption system described here would be ineffective against attempts (code-breaking) to circumvent it. However, all of the same arguments apply to much more sophisticated systems of encryption. The XOR system has been chosen only for illustrative purposes.

"organic codes", whereby information is transferred between well-defined domains in which it occurs or functions.

The execution of each organic code relies upon the existence of an interpreter, which is typically comprised of quite special but generic structural components. The question in theoretical biology that we now want to address is how interpreters, which give specific and detailed meaning to bodies of information as large as the sequence of the human genome, can evolve from an initial state of complete molecular disorder. The fact of genetic information's existence finds a reasonably satisfactory explanation in terms of a molecular theory of Darwinian selection (Eigen 1971, 2013), but the disposition of its functional meaning, above and beyond the fact that the information has accumulated, begs an enquiry into the character and emergence of natural systems of interpretation.

At its most elementary level, an interpreter is a dynamic physical system in which information is transferred from one form, or domain, to another. At its most complex level, what we commonly call a "language", a system of interpretation is not restricted to transfers of information between existing domains and the meanings that can be can expressed through extant modes of transfer. Using a language, people can generate not only novel assemblages of input information, perhaps from disparate domains, but also previously non-existent domains for the output of information. This can all occur without the underlying physical structures altering to any internally significant or currently determinable extent. In the extreme case of the socially constructed meaning of our everyday lives, the interpretation of the information constituting the patterns of differentiable perceptions open to us seems to be completely emancipated from any physical or mechanical determination, except for the apparently incidental fact that it would not arise without the prior existence of our brains. So, our task is to locate the possibility of meaningful information transfer within the constraints imposed by the structure of physical reality, but not in such a way that physical laws prescribe, dictate or determine what the meaning or interpretation of any body of information should be.

We first face the fact that information cannot be transferred within a system at thermodynamic equilibrium. At the very least, some sort of far-from-equilibrium system is required. Far-from-equilibrium systems display a wide variety of ordered macroscopic behaviours, the identifying characteristics of which depend on details of the couplings between molecular processes in the system (Glansdorff and Prigogine 1971). For example, the system described by Turing (1952) displays macroscopic spatio-temporal patterning as a direct result of coupling between molecular reaction and diffusion processes. In some far-from-equilibrium systems the internal dynamics are coupled to a particular internal "relaxed" or "inert" molecular state, detailed aspects of the system that affect, but are not changed by, the molecular processes that take place in it (Pattee 1972, 1995). Alternative relaxed molecular states of this sort serve directly as information that the system interprets—the coherent dynamics of the system producing different outcomes from different "initial conditions" supplied in the form of potentially different inert state "inputs". This is how heritable DNA sequences serve as information for the construction, maintenance and evolution of organisms.

In seeking to explain the molecular genetic origin of biological self-organisation Eigen (1971) examined systems of polymer-sequence copying in which the domains of information and its interpretation were identical. When the fidelity of sequence

replication exceeds a defined threshold value, such a system can generate information, in the form of a predominant (or consensus) polymer sequence. This occurs in a homogeneous mixture of molecules simply as a result of Darwinian selection among polymer species that have different rates of reproduction and loss. In describing how polymer sequence information can accumulate, essentially *ex nihilo*, Eigen (1971) assumed that any molecules responsible for the process of copying, e.g., replicase enzymes, were supplied and maintained externally, in no way controlled by the system. In the extended system of the hypercycle (Eigen 1971; Eigen and Schuster 1979) the replicases came to be produced within the system and strict Darwinian competition between polymer information carriers was circumvented. The hypercycle demonstrated the possibility of coexistent information carriers surviving when their dependence on one another was arranged in a closed cycle of mutual amplification. However, the hypercycle introduced a new level of interpretation of molecular sequence information, above and beyond the "zeroth order interpretation" entailed in the process of copying. In the hypercycle, the information in each replicating polymer is interpreted, through some unspecified means, to produce a specific replicase enzyme that preferentially catalyses replication of the next polymer, making a directed hyper-connection from one cyclical process (replication of a specified polymeric information carrier) to the next.

The work of Kauffman (1986, 1993, 1995) is representative of a quite different approach to the problem of physico-chemical self-organisation, one in which any information-carrying capacity of macromolecules is quite secondary to the virtually inevitable emergence of a more basic protobiological order in dynamic populations of polymers. Kauffman's autocatalytic sets of polymers rely on the propensity of molecules like proteins to act as catalysts of specific ligation and/or cleavage reactions, using highly specific recognition processes to select substrates and concatenate them together to form new sequences, which in turn may catalyse other reactions. In its original conception (Kauffman 1971, 1986) the propensity of proteins for catalysis and their capability for specific substrate recognition were considered to be so high that nearly every possible polymeric sequence could be expected to participate in an enormous network of coincidentally reinforcing cross-catalytic interactions. Although each reaction was conceived as highly selective and specific, the surviving population was the same as would be obtained by a random reaction process.

An alternative approach to the problem (Wills and Henderson 2000) adopted the implicit view that catalytic polymers should be construed as monadic interpreters that take the substrate sequence motifs they specifically recognize as input, and produce their concatenation as output. Model autocatalytic systems based on this principle can only exist as a result of what might be called "chemical coincidence". The structure of each monadic interpreter in an autocatalytic subset of polymers must be comprised of only the selected substructures that the chosen monadic interpreters can produce. The degree of functional specificity that can be supported in systems of this sort is limited on one side by a complete lack of selection—everything possible is made and no information is preserved—and on the other side by the improbability of a very specialized function being associated with an undifferentiated structure—in the extreme, a homopolymer being able to differentiate among different monomers and selectively catalyse just one ligation reaction.

Eigen (1971, 2013) insists that the level of catalytic specificity typical of biological systems cannot be achieved by self-organisation of autocatalysis alone; rather, that the replication of information carriers is necessary. Recent reconsiderations of Kauffman-type

systems (Hordijk et al. 2011) have been more realistic than the original (Kauffman 1986), but take little account of the potentially symbolic character of polymer sequence information. The process of local sequence-complement matching has been incorporated as one constraint on catalysis, but like DNA copying, which is actually a monadic two-step process, it doesn't amount to more than "zeroth order interpretation". Hordijk et al. (2013) have attempted to bridge the conflicting positions (Eigen 1971, 2013; Kauffman 1971, 1986; Hordijk et al. 2011) but only with partial success.

The significance of this gamut of work is that it demonstrates the possibility of the emergent interpretation of polymer sequence information, at least of the zeroth order type, in autocatalytic systems. However, the inherent system-wide control of process and structure specificity is much less than can be achieved in biological systems that rely on polymers that serve as information carriers (Eigen 1971).

Coding Systems

The first direct investigations of the evolution of systems that support the autonomous interpretation of molecular sequence information are due to Bedian (1982) and Wills (1993). The basic assumption made by these authors was that simple chemistry includes the possibility of a class of polymer (such as a protein) being synthesised in such a way that molecules belonging to some other class of polymer (like a nucleic acid) act as information-carrying templates that function as "instructions": construction of a polymer molecule from the first class is collinear with the sequence of an extant polymer molecule from the second class. However, a mechanism of collinear synthesis does not of itself require or guarantee the transfer of information from the template to the polymer molecules of the first class.

Information transfer requires that the selection of the monomer added to the growing polymer chain at any position be influenced by the identity of the monomer located at the collinear position on the template. By means of such influence, coded information transfer is able to emerge as a self-organised behaviour of the system, generating itself *de novo* from an initial state in which the sequences of the polymers being synthesised are completely random. In this disordered initial state there is no net template-influenced selectivity of the monomer concatenated to the growing polymer chain at any position, because all assignments are equally probable.

Coding self-organisation works as follows. Suppose we are dealing with binary alphabets of amino acids $\{a,b\}$ and template sequence elements $\{A,B\}$ that act as "codons"; and that two particular proteins (assignment catalyst enzymes) with (arbitrarily chosen) sequences E_1=*baababbaaab* and E_2=*abbbaababba* are able to catalyse the two assignment functions $\{A \rightarrow a\}$ and $\{B \rightarrow b\}$ when proteins (amino acid polymer chains) are synthesised in a manner collinear with extant nucleic acid templates (sequences of codons).

In a thermodynamically driven system in which proteins are synthesised from energetically activated amino acids a^* and b^*, the presence of nucleic acid templates with sequences T_1=*BAABABBAAAB* and T_2=*ABBBAABABBA* will enable the two coding enzymes to produce themselves autocatalytically.[10] Coding self-organisation

[10] Reverse-order complementary sequences for T_1 and T_2 (and therefore E_1 and E_2) have been chosen in recognition of the possibility discussed by Chandrasekaran et al. (2013).

occurs when a population of proteins with random sequences and very weak catalytic activity for all of the possible assignments $X \rightarrow y$ uses the specified templates for synthesising further protein molecules. The newly synthesised population is also random until stochastic fluctuations occur that simultaneously increase the concentrations of E_1 and E_2 above some critical threshold, after which self-amplification of these two species proceeds until they dominate the protein population and the system executes the coded transfer of individual bits of information according to the rules $\{A \rightarrow a\}$ and $\{B \rightarrow b\}$.

From the point of view of physics and chemistry there is nothing mysterious about the process of self-organisation in Bedian-Wills systems—it occurs as a result of the inexorable operation of physico-chemical laws. On the other hand it can only occur when there is a particular formal relationship, which has nothing to do with energetic or thermodynamic constraints, between (i) the sequence information carried by the template species available to the system (e.g., T_1 and T_2) and (ii) the structure-dependent (catalytic) properties of molecules of the synthesied polymer species (e.g., E_1 and E_2). The required relationship is that the information (in T_1 and T_2) must be "reflexive" in the sense that when it is interpreted according to the rules of an emergent code the polymers that are synthesised have sequences corresponding to catalysts (E_1 and E_2) that happen to carry out, virtually exclusively, the subset of assignments belonging to the code $\{A \rightarrow a, B \rightarrow b\}$ and not the subset of other (non-code) assignments $\{A \rightarrow b, B \rightarrow a\}$.[11] The required coincidence of cause and effect is extraordinary and in simulations of coding self-organisation it is set up in advance by the programmer (Bedian 1982; Wills 1993).[12]

When the templates are reflexive *vis-à-vis* the coding catalysts, the possibility of semantic closure (Pattee 1982, 1995) emerging through the process of coding self-organisation is built into the system as an effect of autocatalysis: polymers of the sort being synthesised play a role in the synthetic process that produces them, in effect serving as adaptors, influencing the choice of monomer to be concatenated to the partially synthesised polymer chain according to the particular monomer present at the collinear position on the template.

Coding self-organisation is a selection process in which the population of polymers being synthesised becomes enriched in molecules that catalyse particular monomer assignments, while molecules that catalyse alternative monomer assignments, destructive of the emerging code, are progressively diluted out of the population. Through appropriate template choice, the required trans-species information-function correlation is a possibility even if the relationship between the structures and catalytic properties of the second polymer species is essentially random (Wills 1993). However, the formal correlation between the sequence information of molecules of the template polymers and the structure-determined properties of the catalytic polymers remains as an indispensable extra-physical requirement for thermodynamically driven coding self-organisation.

[11] The information-function relationship of coding reflexivity is not always unproblematic. It can only be unambiguously established for classes of polymers whose structure-function relationship (mapping from polymer sequence to catalytic properties) is sufficiently asymmetric (Nieselt-Struwe and Wills 1997).

[12] This is accomplished by symbolically "back-translating" the sequences of E_1 and E_2 to determine the sequences of T_1 and T_2. A similar procedure must be followed to produce self-reproducing automata (Von Neumann 1949). The "description" tape must be devised and specified by the programmer.

The formal trans-species information-structure correlation that enables the emergence of semantic closure in systems that undergo coding self-organisation can rather easily be attributed to the template sequence alone: the template sequence is required to have the special, and extremely rare, property of "reflexivity" *vis-à-vis* the sequences of catalysts that execute the coding assignments (Wills 2001). However, adopting this perspective on the origin of coding condemns us to a "miraculous" view of the appearance of template polymers with the necessary sequence properties. Under any physically realistic assumptions, the chance appearance of reflexive template sequences turns out to be far too improbable for it to play any useful role in the scientific explanation of biosemiosis. But the theoretical situation then turns out to be even more dire. If a reflexive template sequence were provided to such a system, it would quickly be lost and replaced by inferior species as a result of errors in its reproduction and the extant coding system would be lost (Wills 1994). Finally, to top it off, it can be demonstrated analytically that natural selection cannot provide for survival of the required species in an ordinary, spatially homogeneous physical system, even when template reproduction is catalysed by a polymer that is integral to the system (Füchslin and McCaskill 2001). At this stage it seems hopeless: the theory of coding self-organisation suggests that some sort of continuous physico-chemical miracle, the unlawful material intervention of an immaterial agency, is required for a molecular-level interpreter to be able to exist by maintaining (copying) and interpreting a stored description of its components. A self-reproducing chemical automaton (Von Neumann 1949) cannot exist in, let alone emerge from, an ordinary homogeneous chemical system.

Spatio-Temporal Self-Organisation

In his classical treatment of reaction-diffusion systems, Turing (1952) described the spontaneous emergence of macroscopic chemical patterns, spatial inhomogeneities, in systems that are initially homogeneous. The result is counter-intuitive—as is the existence of biological systems—given a superficial understanding of the second law of thermodynamics. The slowness of the scientific community to accept the reality of the Belousov-Zhabotinsky (BZ) reaction attests to this difficulty (Winfree 1984; Frank-Kamenetskii 2012). Prigogine (1978) considered the manner in which nonlinearities in system dynamics can give rise to "dissipative structures" like Turing or BZ structures to be so extraordinary that he dubbed them "a new state of matter".

As noted above, the correspondence between template information and sequences of populations of catalytic polymers is an extra-physical condition required for the joint selection of polymers from two classes whose sequences are associated through a coding relationship. The mechanism of Turing (1952) provides a means whereby a constraint fulfilling that condition can emerge as a "miraculous" property of a physical system. This was first demonstrated by Füchslin and McCaskill (2001). If one considers the movement of molecules as well as their chemical structure and properties, and the possibility of coupling between molecular diffusion and chemical reactions, then it is found that individual molecular template sequences can be localised for long enough in the immediate vicinity of limited subsets of second-species polymer catalysts for natural selection to favour the joint survival of reflexive information and the corresponding autocatalytic set of catalysts comprising an

interpreter. Model systems of this sort have been called gene-replicase-translatase (GRT) systems (Füchslin and McCaskill 2001; Markowitz et al. 2006; Wills 2009).

The theoretical significance of GRT systems resides in the way in which the self-organisation of information processing (coupled accumulation of template information and emergence of its interpretation) is dependent on the self-organisation of physico-chemical processes (emergence of macroscopic order as a result of reaction-diffusion coupling). At first sight the connection between the two linked modes of self-organisation, pattern formation in reaction-diffusion systems and coding self-organisation in GRT systems, defies any simple mechanistic description. Nonetheless, the connection exists, and was carefully analysed by Füchslin and McCaskill (2001). The Turing mechanism operates essentially to colocalize templates with catalysts in a manner that establishes a codependency between them to the extent that their association defines them as belonging to an identifiably integrated system.

A similar effect has been achieved in other model systems, such as the autopoietic systems of Maturana and Valera (1980) or the chemoton system of Gánti (2003). These systems are endowed with a membrane-forming capability for colocalizing molecular components. Autonomous creation of a system boundary allows the system as a whole to become the unit of selection, rather than the dynamic behaviour being dictated by internal competition for survival within or between classes of polymers. GRT systems are simpler in that the required spatial localization is given "for free" by the physically lawful system dynamics and does not have to be set up as an explicit feature of the model. Neither autopoietic or chemoton models demonstrate the emergence of coding or any other system for the interpretation of polymer sequences as meaningful information. They therefore lack a genotype-phenotype mapping of the sort characteristic of systems that undergo Darwinian selection as a result of genetic inheritance—in terms of Von Neumann (1949) they do not carry a "description" of themselves and in terms of Füchslin and McCaskill (2001) they do not have a general system for decoding (interpreting) template information.[13] The process whereby systems of interpretation self-organise during biological evolution has been described elsewhere as "informed generation" (Wills 2009).

Finally, it would be remiss not to point out that the Turing mechanism is only capable of mitigating the need for a minor miracle in relation to the emergence of the complex system of molecular biological coding observed in every living cell. Kick-starting the universal genetic code through Turing-type reaction-diffusion self-organisation would require simultaneous fluctuations that selectively increased the concentrations of the "correct" 20 out of 400 or more possible distinct assignment catalysts, along with a template bearing the corresponding reflexive information and correct coding for the replicase enzyme. Such an event is so improbable that its occurrence would qualify as another "miracle", placing the main event of life's origin beyond any useful scientific analysis.

However, the GRT systems in which self-organisation from an initially disordered state has been observed involve very modest amounts of template information, only

[13] Gánti did not consider that a von Neumann-type "description" was necessary for biological inheritance and epigenetic effects prove him correct. However, it is hard to envisage how the extraordinarily detailed control of processes in biological systems could be achieved without the logarithmic reduction in the complexity of the system's specification that an information-based mapping from cause to effect makes available (Schrödinger 1944; Eigen 1971, 2013).

the most rudimentary coding systems (one-bit codon and amino acid analogues) and simultaneous fluctuations in two out of four coding-assignment functions. When this is taken together with previous analysis of the hierarchy of nested constraints that would allow coding to emerge in a stepwise fashion, becoming increasingly complex and specific (Nieselt-Struwe and Wills 1997), and the observation that the dynamics of coding self-organisation allow it to occur progressively (Wills 2004, 2009), we see that the GRT model indeed provides a plausible explanation of the emergence of semiosis in prebiotic physico-chemical systems and the genotype–phenotype mapping necessary for biological evolution involving Darwinian selection.

The conclusions to be drawn from studies of GRT systems are (Wills 2009):

(i) genetic information is created through the competitive process of natural selection;
(ii) functional interpreters construct themselves through a cooperative process of "informed generation": systemic self-organization of their component parts;
(iii) the natural selection of apposite genetic information requires the operation of an interpreter;
(iv) the generative construction of a functional interpreter requires a store of apposite genetic information;
(v) the increasing complexity and specificity of biological forms requires the progressive coevolution of genetic information and a corresponding system of functional interpretation.

The perspective that GRT systems offer on the emergence of genetic coding may also prove amenable to empirical investigation.

Empirical Considerations

I now present a brief summary of an argument, to be developed in more detail in a separate paper (Wills and Nieselt, forthcoming), to the effect that the present day enzymes that serve the role of "translatases" in GRT systems are an example of a phenomenon that has a more plausible explanation based on semiotic principles than on reductive physico-chemical reasoning supplemented with Darwin's principle.

Every cell contains a suite of 20 aminoacyl-tRNA sythetase (AARS) enzymes, one for each of the 20 canonical amino acids from which proteins are made. The functional role of these enzymes is the same as the model translatases that catalyse codon to amino acid assignments in GRT systems. However, there is an apparent paradox in the molecular biological inference that the specificity of codon-to-amino-acid assignments displayed by the AARSs depends on the specificity of their structures, which cannot be maintained without the pre-existing specificity of their assignment functions (due to the essentially autocatalytic character of their production as an outcome of their interpreting reflexive sequence information in part of the cell's genome template).[14]

Every cell signals its status as a 'living' entity by existing in a thermodynamically privileged state that has arisen as a result of not only the naturally selected DNA

[14] The expectation that errors in the production of protein components of the translation apparatus will be self-amplifying was framed by Orgel (1963; 1970) as an "error catastrophe" problem.

template information it contains but also the highly organised constellation of molecular functionalities it inherited from its parent(s) (Wills 2009). The amino acid sequences of the AARS enzymes carry what can reasonably be construed as a palimpsest of (i) primordial digital codon and amino acid alphabets; and (ii) the structural core of the corresponding molecular biological interpreter that executed an elementary binary code (Fig. 1). This primæval binary code is hypothesized to have emerged at a time that can be thought of as the origin of life, perhaps before anything remotely like an integrated single-cell organism had appeared on the planet. Whether an imprint of the entire pathway from an ancient binary code to the universal genetic code can be found in the sequences of present day AARS proteins is still an open question.[15] However, the unfolding of the genetic code in a tree of bifurcations in the amino acid recognition/differentiation process is clear in the inferred phylogenies of the AARSs (O'Donoghue and Luthey-Schulten 2003; Fournier et al. 2011) as well as transfer RNAs (Delarue 2007).

The suite of AARS enzymes found in present-day cells is divided into two disjoint classes whose division is as universal as the genetic code. While the structure of all of the Class I enzymes from species belonging to all of life's kingdoms resemble one another, as do the Class II structures, there is nothing obvious in common between any structures of enzymes from the two separate classes (Fig. 1). On the other hand, both classes of AARSs fulfil the same generic biochemical function, catalysis of the attachment of an amino acid to a tRNA molecule. This chemical reaction is the process whereby the genetic code is executed. Code execution requires an AARS protein catalyst uniquely to recognise both an amino acid and a tRNA incorporating a cognate codon and then specifically to attach them to one another. The accuracy with which this task is accomplished is a measure of the fidelity of the universal genetic code.

Why do the cells of organisms from all branches of the tree of life, some of which diverged from one another nearly 4 billion years ago, all still carry versions of two solutions to a single biochemical problem, the ligation of an amino acid and tRNA molecule? The fundamental tenet of Darwinian evolution, survival of the fittest as a result of competition among variants generated in an error-prone production process, engenders the expectation that variation among and competition between the Class I and Class II solutions to the AARS problem would have led rapidly to the dominance of the gene for one and the demise of the gene for the other in the struggle for reproductive superiority. If the value to a system of a primitive AARS lay in its various capabilities of accurately discriminating and ligating specific amino acids and tRNAs, then differences in the fitness of prototypical Class I and Class II AARSs would have left a single survivor, not a pair of alternatives acting in concert.

However, if entities as complex as organisms cannot exist without the prior invention of some means of meaningful computation, i.e., the storage of information and the execution of a coded interpretation of it, then the cooperative survival of Class I and II AARS prototypes (Fig. 1) can be viewed as a locked-in feature of molecular biological systems that is left over from the invention of the first-ever chemical code. That is to say, cooperative survival of structurally dissimilar entities offered the only chemically feasible means of producing the two functionalities, $A \rightarrow a$ and $B \rightarrow b$, needed to preserve bits of

[15] The endpoint of coding evolution may not have been reached before different threads separated into the first semi-autonomous organisms.

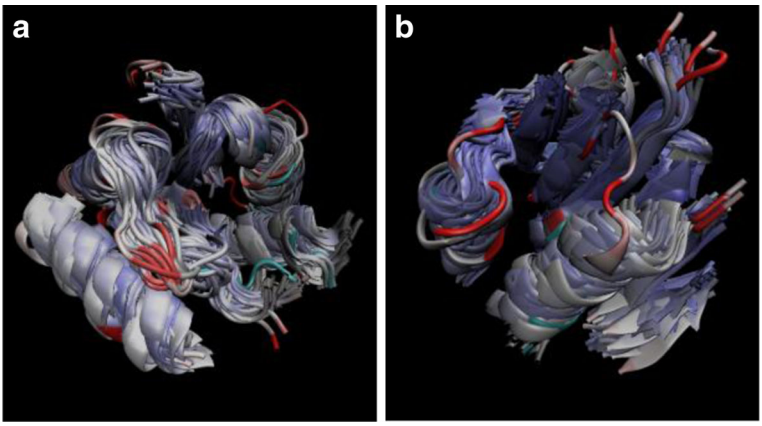

Fig. 1 Superimposed core structures (peptide α-carbon chains) of representative (**a**) Class I and (**b**) Class II AARS enzymes of all catalytic specificities from organisms belonging to diverse taxa from all biological kingdoms. Images were produced by using the VMD software (Humphrey et al. 1996)

information using the limited "bandwidth" then available (for the storage and transmission of genetic information) in such a way that neither functionality was significantly confused with either of its alternatives, $A \rightarrow b$ or $B \rightarrow a$. Thus, we infer that the first physico-chemical coding system in which information per se was created and simultaneously interpreted was as simple as possible, consisting of an elementary code linking two binary alphabets, one comprised of two distinguishable types of amino acids $\{a,b\}$ and the other comprised of two distinguishable types of nucleic acid codons $\{A,B\}$.

The coded mapping from one binary alphabet to the other allowed information stored in nucleic acid sequences to be interpreted as proteins, whose collective catalytic functions corresponded to the restricted subset of codon-to-amino acid assignments $\{A \rightarrow a, B \rightarrow b\}$ comprising the code. There is no reason in principle why the enzymes catalysing these primitive assignments by means of tRNA amino-acylation should have been as vastly different from one another as the Class I and II AARSs,[16] but a system containing a structure that strongly preferred both A over B and a over b as substrates, and a completely different structure with complementary substrate preferences of equal strength, would more easily have staved off the corroding effects of the alternative coding assignments $\{A \rightarrow b, B \rightarrow a\}$ (Nieselt-Struwe and Wills 1997).[17]

Concluding Discussion

We began with the Shannon definition of information: a pattern that can to some degree be distinguished from other patterns in some arbitrarily defined class of possible properties of an equally arbitrarily defined class of objects. Shannon information can

[16] The bifurcation of the sets of codons and amino acids into functionally distinct subsets did not necessarily require the emergence of two structures as distinct as those portrayed in Figure 1, but that is what appears to have happened and become locked into all subsequent molecular biological evolution.

[17] There is increasing evidence that the Class I and II core structures were encoded in the complementary strands of a single nucleic acid gene (Chandrasekaran et al. 2013).

most simply be represented, and then measured, by using an alphabet of symbols (or letters), of which the simplest example is the set of the binary digits {0,1}. We then enquired into the meaning of any body of information and determined that absolutely any meaning is possible, any actual meaning depending only on the existence and operation of a physico-computational system called an interpreter that takes the information as input and produces the chosen meaning as output. This perspective was used to frame the fundamental problem of the origin of biological systems: what minimal conditions are needed for interpreters capable of assigning meaning to physical patterns, in particular, polymeric sequences, to emerge from disordered molecular systems? We found that the gene-replicase-translatase (GRT) model possesses all of the features needed satisfactorily to answer the question. In GRT systems genetic information is created through a process of natural selection in which the survival-value of information-carrying polymers is determined by their aptitude to serve as templates for the self-construction of a functional interpreter through a process of informed generation. The first molecular biological interpreter appears to have operated a simple binary code. Every living cell carries a palimpsest of this primordial system of interpretation, in the dual structural cores of its Class I and II AARS enzymes. Life originated in the spontaneous creation of alphabet-symbolic information and its interpretation. It was a result of thermodynamically driven self-organisation, the coupling of natural selection and informed generation, in an autocatalytic system of nucleic acids and peptides.

At the centre of every cell's operation there exists a pair of structures (Fig. 1) whose forms have been preserved through every new generation in countless branches of life for nearly 4 billion years. These forms appear to have been the joint producers and products of the original elementary difference that was recognised and exploited by nature to create bits of meaningful symbolic information. "*A difference that makes a difference*" (Bateson 1972) emerged out of the sea of disordered chemical reactions and apparently enslaved the flow of energy to serve the purpose of its own existence. The chemically effectual distinctions made simultaneously between two classes of nucleic acid codons and two classes of amino acids allowed codon sequences to be taken as symbolic representations of the amino acid sequences of the proteins that functioned to make the necessary distinctions. This semantic closure (Pattee 1982, 1995) was achieved through a thermodynamically driven process of computational self-organisation and a primitive system of meaning came into existence on this planet where no such thing had existed previously.

Now, you, the reader are looking at these words and an optical image of the letters is stimulating cells on the surface of your eyes' retinae and an astronomically more complex process of information processing is taking place as you register ("understand") the meaning of the words that I, the writer, have previously composed. The detailed process of communication and understanding is conditioned not only by the common structure of our participating brains, but the long process of cultural evolution that has resulted in the conventions that define the English language. All of this live information processing is sustained by and occurs in systems that incorporate in their most basic nanoscopic operating structures truly bred offspring of the molecules in which a bit of meaningful information first came into being.

Eigen (2013; p 449) claims to have answered the question of how complex interpretations of information originate by characterising the dynamics of biological evolution as movement in a high dimensional "I-space" of genetic information (Eigen

2013, pp354–387; 404–423), the very same space through which Dawkins (1986, pp72–73) believes an engineer could cobble a pathway from a pigeon to a dodo. Both of these authors seem to admit that information per se can function causally in physical systems: Dawkins (1986, p111) in his proclamation of the "plain truth" that willow seeds are equivalent to floppy discs; and Eigen (2013, p 480) when he says "In order for life to come about, there must be some physical principle that controls complexity" and goes on to ascribe the beginning of evolution to the origin of genetic information.

According to Eigen (2013, p 479) we are in possession of the general law of which life is a consequence. Natural selection generates genetic information of which the apparently purposeful functional order of biological systems is a product. Neither Dawkins nor Eigen looks at the other side of the coin and engages seriously with the possibility that information is the product of the functional order of biological systems. Thus, Eigen (2013) devotes hundreds of pages to the task of explaining how natural selection generates information but, even though some relevant work has been conducted under his patronage (Hoffmann 1974, 1975; Wills 1993; Füchslin and McCaskill 2001), makes no mention of processes whereby the functionally ordered interpretation of genetic information confers a survival value that makes its accumulation as such in biological systems possible through natural selection. And when it comes to the genetic code, it is nucleic acids (tRNAs) rather than proteins (AARS enzymes) that he claims "take care of the correct assignment of each of the 20 natural amino acids used in proteins to their cognate codons in messenger RNA (mRNA), as is necessary for error-free translation" (Eigen 2013, p 489). According to this view, functional order in biological systems is not capable of generating anything fundamental, only epigenetic phenomena, which ultimately gain their significance from the principle of natural selection and that principle alone.

In complete contrast to Dawkins (1986) and Eigen (2013) I have described how the epigenesis of molecular biological interpreters points to the kernel of nature's generative activity, what the ancients Greeks called *physis* (Heidegger 1939), an aspect of the physical universe as fundamental as those aspects embodied in the fixed mechanical laws of physics and Darwin's principle. The transition to a self-organised state in GRT-type systems or the more primitive quasi-species systems (Eigen 1971) could be described in a reductive physico-chemical narrative that didn't even acknowledge Darwin's natural selection as a principle. However, in spite of its validity, such a description would fail to signal the semi-autonomous role of information in biological systems (Schrödinger 1944), without which genetic engineering would be impossible. By the same token, the narrative of Dawkins and Eigen fails to signal the semi-autonomous role of generative computation in the universe, the crucial distinguishing feature that separates biological systems from the other products of nature. It is necessary to combine the natural selection of polymer template sequences (Eigen 1971) with the informed generation of interpreters (Wills 2009) to explain how either information or function can come naturally to reside in molecules. In biological systems there is no information without function, or vice versa. The two co-evolve and neither has complete executive or operational control.

The origin of semiosis in natural systems has been the subject of a great deal of philosophical argument, little of which has gained any significance from, or contributed any significance to, current theories of the elementary molecular properties of biological systems or features of protobiological systems. On the other hand, the main

argument of this paper is that only by taking account of the semiotics of molecular biological coding, the origin of genetic information and its interpretation, can biological systems be investigated in a properly scientific manner. For more than half a century scientists have peddled the idea that DNA genes,[18] selfish or otherwise, are the key to the understanding, and even more importantly now, the manipulation, of information in biological systems. Without doubt, DNA has served as a medium for information storage through æons of evolution. The base-paired structure of DNA, usually represented in its iconic double helical form, displays the aptitude of this polymer for this function—the complementary strands can be separated, allowing the sequence to be read and a new complementary copy to be written. However, DNA replication is what we have characterised as a "zeroth order" process of interpretation. Biology is replete with processes that confer much greater meaning on DNA sequence information. Correspondingly, the evolutionary maintenance and development of meaning and interpretation have been the domain of other special structures, created and sustained by various modes of thermodynamic self-organisation. The first non-trivial interpretation of molecular information seems to have been the catalytic capability of conferring meaning: the execution of a code to produce entities with code-executive capabilities. Molecular biological self-construction and semiosis have a common origin in the simultaneous emergence of genetic information and its associated interpretation through the operation of a binary code.

Semiosis requires not just physical stability of sign system instantiation (so that information can be inherited and serve as a codescript for the creation and maintenance of a daughter system), but also the dynamic stability of the system of interpretation (execution, utilization) of the information. The interpreter system of any biological species is a complex network of processes that has been built up through numerous symmetry breakings, phase transitions and self-organising "decision processes" during æons of evolution (Wills 2009). During reproduction inheritance of the interpreter is as important as that of the genetic information. Inherited genetic information is useless in the absence of a functioning molecular biological interpreter. On the other hand genetic information serves as a fixed and necessary "boundary condition" or constraint (Pattee 1972, 2013), without which the interpreter system would undergo thermodynamic collapse ("die").

We have characterised biological systems primarily as natural systems that carry and interpret information. Their most important feature, their "life", is that they possess a codescript description of themselves (Schrödinger 1944), which they are able to interpret (execute) as instructions for their own construction (Von Neumann 1949). Their physical structure embodies a system of correlation (genotype-to-phenotype mapping) whose existence requires the satisfaction of conditions (semantic closure) that can only be expressed in terms of extra-physical informational relationships. We have pointed to the origin of the genotype-phenotype mapping as the most important problem in theoretical biology. How does this orderly relationship, necessary for Darwinian selection as a result of variation in the inheritance of traits, arise? Our provisional answer: first in the emergence of a self-constructing system of genetic coding, and the self-representation of the code interpreter in genetic information.

[18] Darwin's principle of natural selection has been applied successfully to the understanding of autocatalytic macromolecules (Eigen 1971) and somewhat less successfully to single genes (Dawkins 1976; Hubbard 2013; Newman 2013).

Endorsement

It is the author's wish that no agency should ever derive military or purely financial benefit from the publication of this paper. Authors who cite this work in support of their own are requested similarly to qualify the availability of their results.

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Since this paper went to press, new evidence has been presented to support the view that the cores of the Class I and II AARS enzymes played a fundamental role in the origin of life. [Li, L., Francklyn C., & Carter, C. W. (2013) Aminoacylating urzymes challenge the RNA World hypothesis. J. Biol. Chem., 288, 26856–26863].

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