

ENTROPY VERSUS INFORMATION: IS A LIVING CELL A MACHINE OR A COMPUTER?

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In this paper we discuss the entropy and information aspects of the living state. Particular attention is paid to the information gain on assembling and maintaining a living cell. Numerical estimates of the information and entropy reduction are given and discussed in the context of the cell's metabolic activity. Difference between information and instruction are given. Finally, a brief overview is provided of the possibilities of bio-computing.

1 Introduction

The current explosion of interest in the future of computing is strongly motivated by an imminent approach of the limit of classical computing as extrapolated from Moore's Law stating that the number of transistors that can be fabricated on commercially available silicon integrated circuit doubles every 18-24 months. This amazingly fast trend towards miniaturization has been valid in the microelectronics sector for close to four decades. Today, the smallest available silicon chips contain up to 100 million transistors on a few cm² of a wafer translating into linear dimensions on the order of 200 nm or less. To reach the dimensions of small clusters of several atoms, approximately 2 nm in length requires a 10,000-fold miniaturization of micro-circuitry, and according to Moore's Law, is expected to occur some time between 2019 and 2028. However, there is a growing concern heretofore unexplored technologies will have to be found even before this limit is reached. There is already substantial effort underway in an area referred to as quantum computation since nanometer-size objects reach into the realm of quantum mechanics and entirely different physical laws apply. Unfortunately, practical considerations such as the so-called entanglement of the system's wave function with the environment pose a serious challenge to any practical applications of quantum computing.

Simultaneously with an effort to build the first quantum computer, a quest has been pursued to use biological materials provided to us by nature itself, or perhaps in combination with silicon-based technology, to come up with not only smaller

electronic devices but also with devices that are more flexible structurally and functionally. It is hoped that one day soon a biological computer will be built that is fast, small and evolvable. Of course, we are already intimately familiar with its prototype, our brain, which can be held as proof of concept. The human brain is composed of 10 billion nerve cells interconnected with as many as 1000 neighboring neurons communicating via signals in the form of electric potential differences that travel along axons, with speeds in the m/s range. We know that waves of electric activity are correlated with the brain's cognitive functions but do not know which structures and/or process are responsible for consciousness or even what constitutes memory. This is sometimes referred to as the mind-body problem. Without getting too far into this hotly debated topic these days, we might just add that there is a camp of researchers galvanized by the Oxford mathematician Sir Roger Penrose who believes that the fundamental nature of the mental processes lies in quantum mechanics. If true, this would, in a way, provide a neat conceptual link between the two routes towards a new type of computing: nano-scale in-silico computing and also nano-scale biological or in vivo computing. The process of nerve excitation involves a passage of the electrical signal from one nerve cell to another in the form of synaptic transmission. Synapses are connections between nerve cells, their axons or dendrites and form nanometer size gaps which are crossed by neurotransmitter molecules stored in vesicles that open when stimulated. Here again is a point of contact with quantum mechanics. In addition there is a very intricate structure of protein filaments filling both the nerve cell's body and its axons. Inside the axons one finds a parallel architecture of microtubular bundles interconnected with other proteins, a structure that resembles parallel computer's wiring (Hameroff, 1987) leading to the hypothesis that this microtubular structures may be involved in subcellular (nano-scale, possibly quantum) computation. Brown and Tuszynski (1999) demonstrated theoretically their feasibility as information storing and processing devices. There is a great promise that protein networks are strongly involved in both information processing and storage.

This then suggests that living cells perform significant computational tasks. If so, can we reconcile laws of thermodynamics and information theory with our knowledge of cell biology? Furthermore, can we gain insights into the inner workings of the cell such that in the future hybrid computers can be designed that harness the power of biological computational elements being integrated with silicon technology? We address these issues in the remainder of this paper.

2 Cell Energetics - The Cell as a Machine

In order to function, every machine requires specific parts interconnected in an intelligent fashion in order to perform the desired function. In addition, a steady supply of energy must be provided to convert it, with some level of efficiency, into useful work. Likewise, all biological cells, like machines, must have many well-

engineered parts to work. Indeed, cells are constructed from yet smaller machines known as organelles. Cell organelles include mitochondria, Golgi complexes, endoplasmic reticulum and the protein filaments of the cytoskeleton. Even below this level there are machine-like parts of the cell, such as motor proteins and enzymes, that perform specific functions involving energy input and power output, e.g. transport (Alberts et al, 1994). A critically important macromolecule is ATP that is a complex nano-machine that serves as the primary energy currency of the cell. ATP is used to build complex molecules, provide energy for nearly all living processes such that it powers virtually every activity of the cell. Nutrients contain numerous low-energy covalent bonds but unfortunately these are not very useful to do most type of work in the cell. Thus, low energy bonds must be translated into high-energy bonds using ATP energy by removing one of the phosphate-oxygen groups, turning ATP into ADP. Subsequently, ADP is usually immediately recycled in the mitochondria where it is recharged and re-emerges again as ATP. At any instant each cell contains about one billion ATP molecules. Because the amount of energy released in ATP hydrolysis is very close to that needed by most biological reactions, little energy is wasted in the process. Generally, ATP is coupled to another reaction such that the two reactions occur nearby utilizing the same enzyme complex. Release of phosphate from ATP is exothermic while the coupled reaction is endothermic. The terminal phosphate group is then transferred by hydrolysis to another compound, via a process called phosphorylation, producing ADP, phosphate (Pi) and energy. Phosphorylation often takes place in cascades becoming an important signalling mechanism within the cell. Importantly, ATP is not excessively unstable, but it is designed so that its hydrolysis is slow in the absence of a catalyst. This insures that its stored energy is released only in the presence of an appropriate enzyme. The mitochondrion, where ATP is produced, itself functions to produce an electro-chemical gradient—similar to a battery—by accumulating hydrogen ions between the inner and outer membrane. This electro-chemical energy comes from the estimated 10,000 enzyme chains in the membranous sacks on the mitochondrial walls. As the charge builds up, it provides an electrical potential that releases its energy by causing a flow of hydrogen ions across the inner membrane into the inner chamber. The energy causes an enzyme to be attached to ADP which catalyses the addition of a third phosphorus to form ATP

3 Entropy Reduction in Living Systems

Living cells are dissipative, open and far-from-equilibrium systems that lower the entropy utilizing an influx of energy and molecular material in a multi-compartment structure with specific functional characteristics. Entropy reduction was discussed early on by Schroedinger (1967) and it relies on both energy supply to create a metastable non-equilibrium state and electrical, pressure and chemical potential gradients across semi-permeable membranes. Electric potential differences also assist in the process. As an open system, a cell operates cyclically exchanging

material and heat with the environment. High-energy molecules are absorbed through pores in the membrane and their energy used to synthesize components of the cell and maintain ambient temperature. Heat is dissipated and waste products excreted so that excess entropy in the environment is balanced by structure- and information-production lowering the entropy inside the cell. This, of course, leads overall to a net entropy change in the cell fluctuating quasi-periodically close to the zero value. Cell death would manifest itself in the breakdown of structures and functions leading to a continuous entropy production. Overall, the entropy changes in the cell can be attributed to: (a) chemical reactions, (b) mass transport in and out of the cell, (c) heat generation and (d) information processing. Morowitz (1995) estimated that approximately 2×10^{11} bits of information are contained in the structure of E.coli bacteria, the simplest and best documented organism, a number which agrees with calorimetric data (Gilbert, 1966). However, the estimated information capacity in the E.coli's genome is only 10^7 (Johnson, 1970) which is at first surprising but on closer examination, to be expected, as will be argued below.

Living cells, as all matter, must obey the energy conservation principle which in this case takes the form of the first law of thermodynamics, i.e.

$$dU = DQ + DW \quad (1)$$

In this thermodynamic sense, cells can be viewed as a machine, exactly the way we discuss the thermodynamics of a combustion engine engaged in a Carnot cycle, performing work and generating heat, thus requiring constant supply of energy and matter, more precisely, energy-giving molecules like glucose (see below). A more appropriate formulation of the energy balance is therefore through the Gibbs free energy that accounts for a change in the numbers of molecules and the presence of several molecular species.

$$G=U-TS+PV=\mu N \text{ or } dG=-SdT + V dP +\mu dN \quad (2)$$

Hence, the entropy differential can be written as:

$$dS=dU/T+PdV/T-\mu dN/T \quad (3)$$

which indicates that entropy changes can be achieved through heat production, change of volume or a flux of molecules. All of the above is relevant in the context of a cell.

Since the entropy of an ideal gas of N particles with total energy E, of mass m each, is (Landau and Lifshitz, 1969)

$$S/k=N\{\ln(V/N)+ 3/2 \ln (mE/3\pi \hbar^2 N) + 5/2\} \quad (4)$$

this means that confining molecules within space, as is the case with building a cellular structure reduces the exploration volume V and thus reduces the entropy of the system accordingly. Conversely, mixing two molecular species with numbers N_1 and N_2 in a fixed volume V by opening a partition between their compartments V_1 and V_2 , increases the entropy by the amount given below:

$$\Delta S = N_1 \ln(N/N_1) + N_2 \ln(N/N_2) \quad (5)$$

Therefore, keeping various molecular species separated in individual compartments (such as the mitochondria, the nucleus, the endoplasmic reticulum, etc) is an entropy reducing process since our information about the system's internal distribution is enhanced.

Enzymatic catalysis against the energy barrier is a process that typically helps achieve such a deliberate separation of molecular species. In fact, a variety of solute molecules are contained within cells. The cellular fluid (cytosol) has a chemical composition of 140 mM K^+ , 12 mM Na^+ , 4 mM Cl^- and 148 mM A^- where the symbol A stands for protein. Cell walls are semipermeable membranes and permit transport of water but not of solute molecules. We use Dalton's Law to determine the osmotic pressure inside a cell. A mixture of chemicals, with concentrations c_1, c_2, c_3, \dots dissolved in water has the total osmotic pressure equal to the sum of the partial osmotic pressures, Π , of each chemical. The total osmotic pressure inside a cell, Π_{in} , is therefore

$$\begin{aligned} \Pi &= \Pi_1 + \Pi_2 + \Pi_3 + \dots = RT(c_1 + c_2 + c_3 + \dots) \\ \Pi_{in} &= RT \frac{(140 + 12 + 4 + 148) \times 10^{-3} \text{ mol}}{1 \text{ liter}} \times \frac{1 \text{ liter}}{10^{-3} \text{ m}^3} = 7.8 \times 10^4 \text{ Pa} \end{aligned} \quad (6)$$

The cell exterior is composed of 4mM K^+ , 150 mM Na^+ , 120 mM Cl^- and 34 mM A^- . As a consequence the total osmotic pressure of the cell exterior, Π_{out} , is given by

$$\Pi_{out} = RT \frac{(4 + 150 + 120 + 34) \times 10^{-3} \text{ mol}}{1 \text{ liter}} \times \frac{1 \text{ liter}}{10^{-3} \text{ m}^3} = 7.9 \times 10^4 \text{ Pa} \quad (7)$$

Because Π_{in} and Π_{out} are quite close in values, the osmotic pressure difference between the exterior and interior part of the cell is very small, as it is the net pressure exerted on the cell wall that matters. For fragile animal cells, it therefore becomes vitally important to keep their interior and exterior osmotic pressures

closely matched. The cell therefore has a sophisticated control mechanism to do this. This can, again, be seen as an entropy reduction mechanism.

Looking deeper into the issue of entropy reduction by the cellular process, in the production of macromolecules such as proteins, naturally the atoms that are assembled lose their degrees of freedom by being joined together. In the simplest case of a peptide chain viewed as a semi-flexible rod, each amino-acid prior to the assembly process possesses three translational and three rotational degrees of freedom, in addition to some internal degrees of freedom which by and large survive the assembly process. After a peptide has been assembled, only small rotations around the backbone are permitted effectively wiping out five degrees of freedom per amino-acid. Consequently, one can view this as an entropy reduction process. This negative entropy, call it structural for want of a better word, is created in addition to the combinatorial contribution that described the probability of selecting a particular sequence of amino-acids in the peptide, let's say $k \ln (20^n)$ where n is the number of amino-acids in a peptide. The folding of a chain into a globular protein restricts the motion of its member groups eliminating some rotations altogether and limiting others. This, again, can be seen as a reduction of the phase space whose volume changes from Ω to Ω' with an attendant entropy reduction of $\Delta S = k \ln(\Omega/\Omega')$. For illustration purposes, we have used here a somewhat simplistic approach via a micro-canonical ensemble where all states in the phase space have the same probability while in reality, due to the interactions between molecules, a canonical ensemble should be used leading to a more accurate but also a more complicated formula, namely:

$$S = kT \frac{\partial}{\partial T} \ln Z + k \ln Z \quad (8)$$

Where $Z = \sum_i e^{-\frac{E_i}{kT}}$ is the partition function of the system (treated as an isolated one). Indeed, since the system is open (albeit the openness is not complete), a grand canonical ensemble technique should be used in the evaluation of the resultant entropy change.

Much has been said about the effect of the second law of thermodynamics on living systems since the latter seem to defy it. However, the second law of thermodynamics is valid for closed systems and it basically states that in closed systems irreversible processes such as heat generation lead to entropy increases while and reversible processes involve no heat and no entropy change. No provision is made for entropy reduction but once again, a living cell is an open system and taken together with its surroundings the total entropy change will never be negative. In closed systems conditions for equilibria are expressed as either minima of the

appropriate thermodynamic potentials (e.g. Gibbs free energy) or maximum entropy requirements (Landau and Lifshitz, 1969). In open systems, there is no such rule except one looks for stability conditions of a given state, i.e. whether under a small perturbation the state will evolve or retain its equilibrium value.

Another way of discussing entropy is in terms of order and disorder. The most pertinent physical transformations between states of matter that are ordered and disordered are called phase transitions. Continuous (second order) phase transitions involve no entropy change at the critical point and ordering in the system sets in gradually as seen through the bifurcation of an associated order parameter. In first order phase transitions, on the other hand, an entropy jump is always present at the transition point. Since $Q = T \Delta S$ is the latent heat of transition, this entropy jump is proportional to the latent heat of transition. Phase transitions with both positive and negative latent heats exist, i.e. entropy creation or reduction takes place in the system on supplying or withdrawing heat, but always $\Delta G = 0$ at the transition point. This does not violate the second law of thermodynamics since the system is not isolated thermally from the environment that may receive excess heat. This example is, of course, relevant to a living cell, if one were to speculate about jump-starting a living process by physical means.

In non-equilibrium systems such as auto-catalytic chemical reactions of the Brusselator type (Prigogine, 1980), order is created and sustained spontaneously by means of non-linear interactions. Since these are open and driven systems, the second law of thermodynamics does not need to be invoked. Another important properties of non-linear systems is the possibility of self-assembly, for example in pattern forming crystal growth. This provides an example where there is no necessity for an instruction-driven creation of order and structure. Sometimes, when discussing the assembly of bio-matter, concern is unduly given to the need for instruction in putting the building blocks of matter together. While there are clear instructions for the amino-acid sequences in the genome, the details of higher order structure formation need no special encoding. They may emerge spontaneously as an attractor in non-linear dynamical system that we call a living cell as a result of biological self-organization (Kauffmann, 1993).

As emphasized earlier, a living cell constantly consumes energy to maintain its structure and vital functions. The energy comes basically in two forms: photons (in plants) and glucose-containing compounds (in animals). Glucose is easily utilized to synthesize ATP that, together with its analog GTP, is the common currency of biological energy as discussed in Sec.2. An ATP molecule, under standard conditions carries 7.3 kcal/mol of energy and its less common analog GTP somewhat less. Each glucose molecule gives rise to approximately $N=30$ ATP molecules and the associated entropy production is given by the equation (Daut, 1987)

$$dS/dt = \Delta G(\text{glucose}) J(\text{ATP})/NT \quad (9)$$

Where $\Delta G(\text{glucose}) = 3 \times 10^6$ J/mol is the free energy of glucose oxidation and $J(\text{ATP}) = 10^{-13}$ mol/hr is the flux of resultant ATP for a single cell (Kim et al, 1991). Taking $T = 310$ K results in roughly an entropy rate of change for a single cell in the range of 10^{-14} J/K s. This can be compared to only 0.7×10^{-17} J/K s of entropy reduction due to DNA transmitted information, i.e. less than one thousandth. This is not surprising since many other processes are at work to keep the cell in its metastable (low entropy) state. First of all, the membrane itself consisting of phospho-lipids comprises some 60% of the cell's mass and presents a highly ordered structure requiring an entropy reduction to be put in place. Likewise, proteins and peptides are composed of up to several thousand atoms each with fairly well specified positions leading to a net entropy drop compared to a non-living state. Finally, approximately 50% of the metabolic energy of a cell is utilized in the process of ion pumping across the membrane (Rolfe and Brown, 1997), mainly as a result of trans-membrane potential and the work of ion pumps. The latter resemble in its function the Maxwell demon, except of course, they do not possess a thinking function. Instead, they rely on molecular recognition mechanisms. These mechanisms, when a pump is activated, lower the entropy by binding the two molecules together. The subsequent placement of an ion or a macromolecule within the confines of a membrane permanently lowers the entropy by volume of exploration reduction as discussed above. A release of a waste product into the environment results in a precisely opposite effect.

Chemical reactions may either absorb or release heat much like first order phase transitions, i.e. they may be either exothermic or endothermic. Since almost all living processes are in essence chemical reactions or cascades thereof, it is worth analysing them from the point of view of entropy. The most interesting reactions from the viewpoint of information theory are catalytic reactions of the special types of functional proteins called enzymes. Enzymes use a fine-tuned selection mechanism of molecules that have shapes complementary to a recognition pocket. This is called a lock-and-key mechanism and, by forcing particular orientations of the catalytically reacting molecules, enzymes increase the reaction rates by several orders of magnitudes. Consequently, this process can be viewed as information processing whereby the shapes of binding domains are recognized, the molecules are optimally positioned for binding and in some cases particular bonds are broken and others created. Some enzymes belonging to the class of allosteric proteins may adopt two or more stable conformations acting like switches, being activated in one conformation and inactive in some others. Following a binding and a catalysis event, enzymes return to their original conformation thereby participating in their active promotion of a particular reaction cyclically. From the point of view of information and entropy reduction, they do not overall decrease the entropy of the

cell (Lowenstein, 1999). At best, they break even since any piece of information that an enzyme invests in a catalytic reaction is re-collected at the end of a cycle. Furthermore, it is important to stress, that the information necessary to perform a particular function (molecular recognition) is not entirely contained in an enzyme. In order for an enzyme to be effective, it must be activated by the environment in which it resides: the water, the inorganic ions, etc. Thus, one may say that the information is contained in the entire system, i.e. the cell.

4 Biological Information

Shannon defined information as negative entropy given by the formula

$$I = k \ln W = -k \sum p_i \ln(p_i) \quad (10)$$

Its introduction has enabled the resolution of the long-standing paradox referred to as Maxwell's demon. The problem involved a creature that operated a small door between two compartments of a container with two types of gas molecules, for example high- and low-energy ones. The end result would be a separation of the gas into hot and cold with no energy expenditure thus contradicting the second law of thermodynamics. Szilard's solution (Szilard, 1929) of the problem endowed the demon with information, i.e. Shannon's information which is negative entropy balancing out the changes in the entropy of the gas. In quantitative terms, the energy cost of 1 bit of information at physiological temperature is $\ln 2 kT = 3 \times 10^{-21} \text{J} = 18.5 \text{ meV}$ which should be kept in mind discussing biological functions that are replete with information content. Information about the structure and composition to be developed, such as protein sequences and folding patterns, is of major importance in this context.

Production of DNA takes place even in non-replicating cells. A typical mammalian cell polymerizes approximately 2×10^8 nucleotides of DNA a minute into hnRNA (Brandhorst and McConkey, 1974) out of which only 5% end up in the cytoplasm coding for protein synthesis (Dreyfuss et al, 1993). Since there is redundancy in coding of nucleotide triplets for the 20 amino acids, the original 6 bits of information in DNA translate into $\log_2(20) = 4.2$ bits in a protein. Consequently, on the order of 0.7×10^6 bits/s are transmitted from the nucleus to the cytoplasm. This is augmented by a small fraction of information due to mitochondrial DNA (Alberts et al 1994). As we have shown above, this is but a small fraction of the total information production (understood as negative entropy) of a living cell. The vast majority of information is contained in the organized structure of the cell and its components.

Since the Shannon information formula employs probabilities of particular states, there are inherent dangers of selecting these probabilities, especially when this is done purely combinatorially as is often the case, for example in an amino-acid or nuclei acid sequence determination. This is not necessarily a random choice situation akin to tossing a coin. This means that taking $p=1/W$ for a single element selection, where W is the number of possible choices, may not be correct giving an excessively improbable (or high information) estimate. This would be the case if the choices of elements in a sequence are not of the same statistical weight, but instead are biased statistically, so that a more appropriate probability value is given by the canonical ensemble Boltzmann distribution formula $p_i=p_0\exp(-E_i/kT)$. Of course, in order to make this estimate, one needs to know the energies E_i and hence the Hamiltonian for the system. Therefore, the apparent information estimate of $I=(k\ln N)^n$ where n is the number of members in a string may be significantly larger than the true value of $-S$ from thermodynamic estimates of a given state- a maximum entropy state for equilibrium and hence a minimum information content. For a string of choices (e.g. amino acid sequence in a peptide or a nucleic acid sequence in a DNA or RNA), this may lead to "basins of attraction" favoring some combinations strongly over others. There could be evolutionary retention of favored choices and the establishment of hierarchies of order. An immense number has been defined as $I=10^{110}$ and represents a clear computational barrier even from the point of view of cataloguing such an enormous number of objects. Immense numbers commonly appear in biology: both DNA and protein sequences are immense numbers arising from the sheer numbers of possible combinations in which these macromolecules may be formed. However, in view of the argument above, restricting the phase space by forming basins of attraction due to intra-molecular interactions may result in a hugely reduced number of combination one would encounter in practice.

Another comment we wish to make is that regarding a clear distinction between information and instruction. While the former was introduced on purely statistical grounds as a measure of the number of choices possible when making a selection for a string of elements, instruction implies the existence of a message, a messenger and a reader who would the execute the message. A classic example of this would the synthesis of amino-acids contained in the triples of DNA and RNA base pairs. While there is the same information value in every triplet, namely $k \ln(4^3)=6$ bits, some amino-acids are coded uniquely by a single triplet, some by two different ones and some triplets do not encode anything. This is obvious in view of the fact that there are 64 possible triplets of base pairs while only 20 distinct amino-acids, hence the redundancy. A similar difference between information and instruction can be found in the genome where in addition to the coding sequences of DNA, some of which are of vital importance to the very survival of a given organism, one finds so-called junk DNA that has apparently no coding value but represents a vast majority of the DNA sequence. The main thing to stress here is that information is often

confused with instructions. However, in the sense of Shannon's information, it is a more general concept that includes purely structural aspects such as combinatorial entropy reduction and chemical entropy changes. Instruction, on the other hand, implies a message and a message reader that executes a command. In this sense, this is similar to computer commands and operations. DNA and RNA are thought to be such biological messengers and so are hormones and various signaling molecules. However, as shown in previous sections, it appears that a vast majority of information content is not instructional in nature. This is akin to simple algorithms like the logistic map or fractal recursive relations which give rise to great mathematical complexity of the results that follow. Similarly, DNA can be viewed as an algorithm that spans an awe-inspiring complexity of a living cells. While coding for protein synthesis is contained in the genetic code, it is most improbable that details of structure formation need special coding. They most likely unfold due to self-organization inherent in the dynamics of the synthesized products

In view of the discussion presented in this paper regarding information content and processing in a living cell, we wish to postulate the existence of two types of information in biological systems: (a) structural information- i.e. negative entropy and (b) functional information. The former is simply related to a neat and tight packing of the various molecules into macromolecules and macromolecules into organelles that comprise the cell. The latter on the other hand, pertains to the functioning of the cell and hence the rate and amount of chemical reactions taking place. The two forms are somewhat related but not identical. Imagine the construction of a car as an analogy. It may look perfectly good but if the gas line is cut, it won't function. The same holds true of a living cell. Some key reactions like synthesis of tubulin, if not properly executed, will lead to the cell death. While structural information should be maximized meaning entropy reduction by the cell, functional information is concerned with how rapidly information is being exchanged. Therefore, the cell's tendency should be to increase the speed of biochemical reactions and the amount of molecular interactions if possible. Living processes are cyclical in nature, so one is expecting to maximize the rate of information (or entropy) change over time for maximum functionality. In order to optimize both aspects: structure and functionality, a living system such as a cell, should strive to maximize the product of the two quantities, i.e. achieve:

$$\text{Max } \{I^2(t) (dI(t)/dt)^2\} \quad (11)$$

where we have squared the quantities in the product due to the cyclicity of life's processes. Note that some aspects of this distinction between structural information and functional information in biological systems were already emphasized more than three decades ago by H. Froehlich (1968) who coined the term biological coherence to draw attention to both the holistic and functional integration of the information flow in living matter.

5 Conclusions

The various points of reference regarding the nature of the living state undoubtedly reflect the prevailing Zeitgeist of the period in which a given theory has been created. The viewpoint of representing the cell as a machine, or even a factory, closely mirrors the worldview of the industrial revolution of the 19th century. Likewise, the currently popular opinion that living cells are intensely engaged in some type of computation is closely linked with the technological revolution ushered into in the late 20th century as a result of the proliferation of computer technology. Both points of view have merits, i.e. the cell obeys the laws of physics such as the first law of thermodynamics and hence can be viewed as a thermodynamic machine and simultaneously it acts against the second law of thermodynamics by creating structural and functional order. In other words, it creates and maintains information. Furthermore, it most certainly processes information and engages in signaling thereby actively performing computation. It is safe to say that living cells can be viewed as both micro-factories (with nano-machines performing individual tasks) and biological computers whose nano-chips are the various proteins and peptides in addition to DNA and RNA. Most of the cell is what we might call hardware while a small fraction is software (for example the genetic code in the DNA that instructs for the synthesis of proteins). Probably only a small fraction of the cell can be seen as pure information content. Is there something else in living systems that neither machines nor computers possess? Probably yes. At least two properties distinguish animate matter from inanimate objects: procreation and autonomy expressed by free will (to move against the whims of thermal noise, in the very least)

On a more practical note, can biomimetics be used to enhance our computational capabilities? The answer is yes, although progress in this area has been slow. In general terms, a chemical computer is one that processes information by making and breaking chemical bonds, and it stores logic states or information in the resulting chemical (i.e., molecular) structures. A chemical nano-computer would perform such operations selectively among molecules taken just a few at a time in volumes only a few nanometers on a side. An alternative direction has been to adapt naturally occurring biochemicals for use in computing processes that do not occur in nature. Important examples of this are: Adleman's DNA-based computer, Birge's bacteriorhodopsin-based computer memories as briefly discussed below.

Adleman first used DNA, to solve a simple version of the "traveling salesman" problem where the task is to find the most efficient path through several cities. Adleman (1994) demonstrated that the billions of molecules in a drop of DNA contained significant computational power. Digital memory can be seen in the form of DNA and proteins. Exquisitely efficient editing machines navigate through the cell, cutting and pasting molecular data into the stuff of life. Has evolution

produced the smallest, most efficient computers in the world? Even if this is an exaggeration, the innate intelligence built into DNA molecules could help fabricate tiny, complex structures using computer logic not to crunch numbers but build things. Furthermore, DNA computers may use a billion times less energy than electronic computers, while storing data in a trillion times less space. Moreover, computing with DNA is highly parallel: in principle there could be billions upon trillions of DNA or RNA molecules undergoing chemical reactions, performing computations, simultaneously. Molecular biologists have already established a toolbox of DNA manipulations, including enzyme cutting, ligation, sequencing, amplification, and fluorescent labeling. The idea behind DNA computing springs from a simple analogy between the following two processes: (a) the complex structure of a living organism ultimately derives from applying sets of simple instructed operations (e.g. copying, marking, joining, inserting, deleting, etc.) to information in a DNA sequence, (b) any computation, is the result of combining very simple basic arithmetic and logical operations. Eric Winfree intends to create nanoscopic building blocks out of DNA that are designed—to carry out mathematical operations by fitting together in specific ways. DNA is not the only candidate for a biological computer chip. Birge (1994) proposed to use of the light-sensitive protein dye bacteriorhodopsin, that is produced by some bacteria. He and his collaborators have shown that it could provide a very high density optical memory that could be integrated into an electronic computer to yield a hybrid device of much greater power than a conventional, purely electronic computer. In conclusion, electronic computers assembled using DNA and run on organic nutrients instead of electricity are another science-fiction idea that may soon become reality.

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