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THE ROLE OF NON-GENOMIC INFORMATION IN MAINTAINING THERMODYNAMIC STABILITY IN LIVING SYSTEMS

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Abstract. Living systems represent a local exception, albeit transient, to the second law of thermodynamics, which requires entropy or disorder to increase with time. Cells maintain a stable ordered state by generating a steep transmembrane entropy gradient in an open thermodynamic system far from equilibrium through a variety of entropy exchange mechanisms. Information storage in DNA and translation of that information into proteins is central to maintenance thermodynamic stability, through increased order that results from synthesis of specific macromolecules from monomeric precursors while heat and other reaction products are exported into the environment. While the genome is the most obvious and well-defined source of cellular information, it is not necessarily clear that it is the only cellular information system. In fact, information theory demonstrates that any cellular structure described by a nonrandom density distribution function may store and transmit information. Thus, lipids and polysaccharides, which are both highly structured and nonrandomly distributed increase cellular order and potentially contain abundant information as well as polynucleotides and polypeptides Interestingly, there is no known mechanism that allows information stored in the genome to determine the highly regulated structure and distribution of lipids and polysacchariedesin the cellular membrane suggesting these macromolecules may store and transmit information not contained in the genome. Furthermore, transmembrane gradients of H^+, Na^+, K^+, Ca^+, and Cl^- concentrations and the consequent transmembrane electrical potential represent significant displacements from randomness and, therefore, rich potential sources of information.Thus, information theory suggests the genome-protein system may be only one component of a larger ensemble of cellular structures encoding and transmitting the necessary information to maintain living structures in an isoentropic steady state.

1. **Introduction.** A living cell is a highly ordered structure that employs information and energy to maintain a stable entropy state in a universe that requires entropy, by the second law of thermodynamics, to monotonically increase with time. In general, the entropy state of a cell may be considered temporally and spatially stable, acknowledging, of course, that mammalian cells do age at variable rates and ultimately die. Thus, more accurately, the entropy increase in normal living systems is much slower than that of nonliving systems beginning at the same time

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point with an identical level of complexity. Thus, cells maintain steep and relatively stable transmembrane entropy gradients.

The global order of a cell is comprised of various components. Perhaps the most obvious component is the large number of macromolecules synthesized from smaller precursors such as DNA, RNA, proteins, lipids, and polysaccharides. Further reduction of entropy is obtained from organization of these molecules into subcellular structures such as the cell membranes, ribosomes, and endoplasmic reticulum. Somewhat less obvious sources of order include transmembrane gradients of anions and cations. For example, the intracellular concentration of Na^+ is about 20 mM while the extracellular concentration is usually similar to that of the ocean (140 mM).

Maintenance of order requires energy. For example, while the total protein content of a cell is typically stable, there is a continuous degradation and synthesis of polypeptides that, because of inevitable thermodynamic inefficiency, requires a net expenditure of energy through hydrolysis of ATP. Furthermore, the transmembrane ion gradients require a continuous, energy dependent flow of ions to counter diffusion forces that will tend to move atoms along the concentration gradients. Thus, maintenance entropic stability requires continuous generation of energy and export of the products of the associated chemical reactions including heat, CO^2, H_20 or lactic acid that result from aerobic or anaerobic metabolism of glucose.

A critical source of cellular order is the specificity of the synthesized macromolecules. That is, the addition of monomers to macromolecules is not random but rather they are added in a specific sequence that allows the macromolecule to serve a specific function. For example, a protein that consists of 100 randomly distributed amino acids represents a decrease in entropy compared to that of a solution of 100 amino acids. However, this protein will likely have no function so that its contribution to overall cellular order is much less than a functional protein that, for example, catalyzes some step in the metabolism of glucose and thus increases the rate of energy production. The latter protein can be obtained only through information that constrains the polypeptide to a specific order of 20 amino acid "building blocks." The nonrandom ordering of subunits into a functioning ensemble with a predictable function separates living systems from other natural processes, such as crystal formation, that also represent local, transient decreases in entropy. This unique property of living systems is dependent on information.

Thus, storage and processing of information are central to the ability of the cell to maintain a stable entropy state. Fisher, Shannon, and others [1–4] have clearly demonstrated that information and entropy are deeply interrelated. Conventionally, intracellular information is encoded in the triplet code of DNA as the four nucleotides are grouped in nonrandom ways. This displacement from randomness contains information that can be transmitted within the cell through RNA intermediates to form proteins or to future generations of cells through direct synthesis of identical DNA sequences. Long-standing biological dogma presumes cellular information storage and processing is entirely determined by the DNA maintained in the genome. Interestingly, however, this is not necessarily supported by information theory, which states that any component of a system that contains subunits described by a nonrandom probability function will contain information and thus reduce entropy. While proteins and DNA clearly fulfill this definition of information, so do other macromolecules, such as lipids and polysaccharides (the membrane of a typical mammalian cell contains 10^9 lipids or glycolipids [5]). Furthermore, cells

typically maintain large transmembrane ion gradients including Na^+, H^+, Cl^-, Ca^+, and other [5]. This deviation from randomness represents a significant decrease in Shannon entropy and, thus, an increase in cellular information content. While these gradients are facilitated by protein pumps in the membrane, the magnitude of the gradients appears to be dictated by other control mechanisms, since loss of function of the membrane proteins does not significantly alter the gradients [5].

Thus, these structures represent potentially abundant sources of information unrelated to DNA. In fact, the entire cell may be considered a package of information, and we propose the genome represents only one component of a much larger ensemble of information resources.

2. **Information content of cells.** Morowitz [5] has estimated that about 2 x 10^{11} bits of information are required to describe the three-dimensional structure of Escherichia coli. A similar estimate of information content in *E. coli* is obtained from calorimetric data [7]. This is considerably larger than the estimated information capacity of DNA in *E. coli* of 10^7 bits [7]. However, this stored information is expanded through manifold translations, so that one gene can be translated into hundreds or thousands of proteins (although the average is twenty to thirty proteins per mRNA [8,9]). Thus, the total cellular information content derived from the genome includes the sum of that stored in DNA, RNA, and proteins. This can be estimated, because the average molecular composition of *E. coli* is known. The mRNA content of *E.coli* is four times larger than DNA, indicating a significant information expansion because of repeated transcriptions of some genes (note the number of intracellular mRNA transcripts for each gene at any given time may range from 0 to over 1,000; 4 represents the average number). However, the greatest expansion of information is due to multiple transcriptions of each mRNA molecule to proteins. This can be estimated by using the experimentally determined typical protein content of *E. coli,* which is 1.56 x 10^{-13} gram/cell. Assuming the average molecular weight of amino acids is 110, we can calculate that approximately 8.4 x 10^8 amino acids have been incorporated into the intracellular proteins of *E. coli.* Using Shannon information ([2]; also see below) it can be estimated that 4.2 bits of information are gained with each incorporated amino acid, for a total protein information content of about 3.4 x 10^9 bits. Note that this represents two orders of magnitude expansion of the DNA information content. Some further reduction in entropy can be obtained through tertiary folding of the protein although this appears to represent a relatively small contribution.

Thus, the combined information content of the polypeptides and polynucleotides within the *E. coli* is more than an order of magnitude less than that of the entire cell, suggesting either some unknown mechanism by which the information in proteins is further expanded to other cellular components or that separate information systems must exist within the cell.

Having examined the static information content of living systems, we turn to the dynamics of information and entropy flow next.

3. **Information dynamics.** The living cell maintains a stable entropy state only because it is an open thermodynamic system. A closed system, governed by the Clausius equation [10] cannot maintain life:

$$\frac{dS}{dt} \geq 0 \tag{1}$$

where S is a measure of entropy. However, in an open system Prigogine [11] has shown that

$$\frac{dS}{dt} = \frac{dS_T}{dt} + \frac{dS_i}{dt} \tag{2}$$

where dS_T/dt is the increase in thermodynamic entropy due to irreversible processes such as chemical reactions, and $\mathrm{dS}_i/\mathrm{dt}$ is the negative entropy unique to biological processes and thus a measure of information. Although some negative entropy potentially could be "imported" through ingestion of polypeptides, under normal conditions biological negative entropy completely depends on translation of information. That is, cellular information is conventionally regarded as a closed system [6] and the intracellular negative entropy necessary for maintenance of life depends entirely on the information stored within the cell.

It is intuitively obvious that, although a living cell requires continuous function of biochemical processes that are irreversible or reversible but far from equilibrium, the cell must on average maintain a stable global entropy state ($\mathrm{dS}_{cell}/\mathrm{dt}$ of 0 or very nearly 0). A sustained $\mathrm{dS}_{cell}/\mathrm{dt} > 0$ is a presumptive indication that the cell is dead or dying. [1]

4. **Negative Entropy Production.** In culture conditions, cells are maintained in an environment of basic molecules and are unable to "feed" on the negative entropy of proteins and other macromolecules. That is, macromolecules are not available in the environment to be imported into the cell and incorporated directly into the cellular structure. Thus, all macromolecules in a cell maintained in standard culture media must be synthesized from small molecules using cellular information to determine the structure and quantity of proteins, lipids, polysaccharides, DNA, and RNA. Therefore, to maintain $\mathrm{dS}_{cell}/\mathrm{dt} = 0$ in a quiescent (non-cycling) cell, the Shannon entropy from information transmitted from DNA to the cytoplasm and nongenetic nuclear structures must quantitatively equal the thermodynamic entropy from [3]. In a cell that is actively reproducing, additional information must be generated to counter the approximately fourfold increase in entropy that will result from each cell doubling.

In a quiescent (nonreplicating) mammalian cell, about 200 x 10^6 nucleotides of DNA are polymerized into hnRNA per minute [12] Only approximately 5% of the hnRNA nucleotides subsequently flow into the cytoplasm as mRNA—the remaining sequences are removed during processing of the hRNA in the nucleus [13]. The mRNA is then quickly degraded so that the quiescent cell is typically in a steady state of information flow such that the total content of mRNA remains constant. Since the nucleotide triplet code is degenerate, the actual information transmitted is best measured in the resulting polymerization of amino acids. That is, although each sequence of three nucleotides transcribed by the DNA contains six bits of information, they result in only one (of 20) amino acids added to a growing polypeptide. Thus, only $-\log_2 1/20$ bits of information (about 4.2 bits) is actually transmitted. Each mRNA molecule will produce approximately 20 to 30 proteins before it is degraded [8,9]. This yields a total flow of information from the DNA to the cytoplasm of about $0.2\text{x}10^8$ bits/sec. A potential additional source of information from the

[1] The point of transition here is interesting. If S_o is the initial entropy value and entropy $[\mathrm{S}_{cell}]$ increases with time so that $\mathrm{S}_{cell} > \mathrm{S}_o$, at what value of S_{cell} is the cell dead?

DNA is the mitochondrial genome. However, in mammalian cells mitochondrial DNA is less than 10^{-5} the amount of nuclear DNA, so that the contribution from this source should be negligible [5].

Information theory has extensively studied the "entropy" of information flow. Although some authors have vehemently disagreed [14], investigators commonly use Shannon entropy as designated in information theory as the negative equivalent of entropy defined by the second law of thermodynamics (see the discussion by Pierce [15]). In an ideal system, information entropy and thermodynamic entropy have been shown to be linearly related so that 1 bit = . 693kT joules, where k is Boltzman's constant and T is absolute temperature [7, 15]. This yields a cost in energy to the cell of at least 3 x 10^{-21} joules for each bit of information. This cost is recouped by the accumulation of negative entropy in the remainder of the cell through utilization of the information. The value of this information-derived negative entropy equals (in an ideal system) the energy cost divided by T (i.e., about 1 x 10^{-23}J/^{o}K/ bit). These results indicate negative entropy flux gained through information transcribed from the genome can, at most, negate an increase of thermodynamic entropy of 2 x 10^{-16} J/cell/s/^{o}K. This, of course, represents an ideal and therefore maximum value since the thermodynamic coupling will undoubtedly be imperfect, and some information is certainly lost through errors in transcription or translation.

5. **Cellular Entropy Production.** The thermodynamic entropy of a cell at steady state (i.e., at constant volume and pressure and the same temperature as its environment) will be increased by irreversible and reversible intracellular reactions far from equilibrium. In this inhomogeneous, nonequilibrium system Daut [15] and Gibbs [17,18] have demonstrated that thermodynamic entropy production in mammalian cells under physiologic conditions is primarily the result of glucose metabolism for energy and can be approximated as

$$\frac{dS_T}{dt} = \frac{\Delta G_{gluc} J_{ATP}}{(N_{ATP})(T)} \tag{3}$$

where ΔG_{gluc} is the free energy of glucose oxidation, $J_{ATP}$is the flux of intracellular ATP (assuming that in a steady state the rate of ATP synthesis is identical to the rate of hydrolysis), N_{ATP} is the number of ATP molecules synthesized from one molecule of glucose and T is the absolute temperature. Thus, dS_T/dt is a positive quantity linearly related to free energy dissipation from glucose combustion lost during ATP synthesis or subsequently released in ATP hydrolysis (i.e., not stored in the construction of macromolecules or used to perform cellular work).

The free energy of glucose oxidized at physiologic concentration and physiologic conditions (ΔG_{gluc}) is 2790 kJ/mol. ATP synthesis (J_{ATP}) cells has been measured to range from 997 μmol/10^{10}cells/hr in quiescent cells to 2100 umol/10^{10}cells/hr in proliferating cells [19-21]. Using the smaller value, ATP synthesis is assumed to be a minimum of about 3 x 10^{-17}mol/cell/sec. T is taken to be 37^O. The number of molecules of ATP synthesized per molecule of glucose will vary depending on the relative utilization of glycolytic versus aerobic metabolism but will not typically exceed 31. This yields an estimated rate of increase in thermodynamic entropy of about 5 x 10^{-15} J/cell/sec/^{o}K.

In summary, even the idealized maximal benefit of information from the genome is more than one order of magnitude less than the amount necessary for maintaining thermodynamic stability. In both bacteria and mammalian cells it would appear

that the information necessary to drive the transmembrane entropy exchange mechanisms must include structures in addition to the DNA-protein axis.

6. **Non-genomic intracellular information.** Thus. application of information theory to living systems suggests that information sources other than DNA are necessary to maintain an isoentropic state. While these results are initially quite surprising, they are, upon reflection, consistent with a variety of observations, including that the role of lipids in cellular membranes is precisely regulated. About 10^9 lipid and glycolipid molecules are typically present in the mammalian cell membrane, composing approximately 60% of its mass [5]. In mammalian cells, the quantity and distribution of the 100 different species of lipids are precisely controlled and vary considerably between different cell types and even between the inner and outer layers of the membrane [5]. Lipids consist of saturated and unsaturated carbon chains of varying length (usually 14 to 20 carbons per chain) as well as different polar and nonpolar head groups. Clearly, considerable information is required to control the length and saturation of the carbon chains, to add the correct polar or nonpolar head group, and to regulate the quantity and distribution of each lipid species. Furthermore, there is no clear mechanism by which the structure and distribution of membrane lipids is controlled by DNA.

The information content of lipids can be roughly estimated using Shannon methods. The addition of a carbon at the end of a growing fatty acid side chain in a lipid involves at least four configurations: the null possibility (i.e., no carbon is attached and this ends the side chain); a single bond carbon addition (CH_2-CH_2) in cis configuration, a single bond carbon addition in trans configuration; or a double bond carbon (CH=CH) addition to form an unsaturated chain. Assuming an approximate typical side chain length of about 16 carbons, a crude estimate of at least 50 x 10^9 bits of information are contained in the lipid component of the membrane in a typical mammalian cell.

In addition, the distribution of lipids in the inner and outer cell membranes is consistently different [5]. This asymmetry, as a deviation from randomness, may also encode information and could play a controlling function in membrane synthesis and recognition of intra- and extracellular pH [22]. Finally, the physicochemical state of the membrane depends highly on environmental factors, including temperature and the concentration of certain small molecules [23,24]. These alterations may allow information from the environment to be transmitted into the cell, perhaps through lipid phase transitions in membrane microdomains [25].Similar analysis can be applied to the other macromolecules including polysaccharides and glycolipids. From this it is clear that considerable information is present in these cellular components—information apparently unrelated to the genome.

To find other potential sources of information flow for the nonprotein components of a cell, it is useful to recall that information requires energy. Therefore, the site of substantial information flow should also be a site of large expenditures of energy. Since about 50% of the energy utilized by a cell is expended at the membrane, primarily for ion exchange [20,21], it seems likely that a significant source of the negative entropy required for cell maintenance could be encoded in the flow of ions across the membrane or the resulting transmembrane potential. In fact, an ion pumped across the membrane against a gradient adds a measure of certainty to the statistical probability of locating the atom. That is, if concentrations were equal across the membrane, no information would exist relative to the probability

of finding an ion (Na^+ for example) on one side or the other. The asymmetric distribution of a Na^+ atom across the membrane increases the probability of finding a Na^+ atom in one compartment over the other and thus decreases cellular entropy and increases the information content. The marked concentration gradients of K^+, Na^+, Ca^+, and CI^-across the cell membrane may, thus, encode substantial quantities of information possibly transmitted as a nondiscrete source, perhaps through variations in transmembrane potential and intracellular pH. Furthermore, while the transmembrane gradient is facilitated by membrane protein transporters, the actual size of the gradient is heavily influenced by the lipid content of the membrane, either directly, through formation selective permeability or formation of ion pores [26,27], or indirectly, by influencing the function of protein pumps [28,29]. Thus, the information source that "encodes" the transmembrane ion gradient is probably not genetic. Furthermore, this encoded information can be transmitted to the cell as changes in the transmembrane ion gradient perturb the intracellular potential, which may substantially alter the cell morphology and function [30].

The theoretical finding that significant quantities of non-genomic intracellular information are required for maintenance of a living state is supported by a variety of experimental observation. One example is the significant and persistent alterations of cell behavior, including DNA transcription following changes in transmembrane potential and cytoplasmic pH [30]. As a second example, the transmembrane potential of a sea urchin egg rises from -70 mV to +10 mV after fertilization. The change in the positive direction occurs less than 1 second after the fertilizing sperm contacts the egg and is the first measurable event following fertilization [31]. Development of a malignant phenotype is observed when the nucleus of a normal cell is transplanted into the cytoplasm of a transformed cell, but not vice versa [32]. Two other instances are the transformation of cells to a malignant phenotype following irradiation of only the cytoplasm [33] and the stability of red blood cells over a life span of 120 days following extrusion of the nucleus.

7. **Summary.** Application of information theory and elementary thermodynamics to cellular function, using extant experimental data, demonstrates that the content and flow of information from the genome is insufficient to provide the negative entropy necessary to construct and maintain a living cell. We identify potentially rich cellular information resources in lipids and polysaccharides, as well as the asymmetric distribution of ions across the cell membrane. No currently known mechanism allows the information in DNA or proteins to be transmitted to these information reservoirs, suggesting they act as independent ensembles whose function may be primarily the detection and translation of critical environmental factors such as temperature, pH, and substrate concentrations.

These additional information sources are interrelated as, for example, transmembrane ion gradients are controlled by both protein pumps and the lipid content and configuration in the membranes. The intracellular ion concentrations, in turn, appear to represent an analog system that transmit information about the environment from the membrane to the nucleus and vice versa. Thus, perturbations in these gradients, through alterations in the transmembrane potential, play a significant role in maintaining cell morphology and function.

These theoretical results inicate non-genomic information plays a significant but unrecognized role in maintenance of a stable entropic state in living systems. This information encoded in macromolecules other than DNA and proteins such as lipids

and polysaccharides as well as transmembrane gradients undoubtedly interacts with the genome but also probably actcindependently. Indeed, it seems reasonable to hypothesized from these resulst that the first living sysems were self-replicating membranes and that such systems might still be extant in nature. As outline above, these results are consistent with current experimental data and may be explicitly tested through the simultaneously measurement of free energy utilization, heat flow, DNA transcription, and protein synthesis in cultured cells.

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