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Review

Entropy Perspectives of Molecular and Evolutionary Biology

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Abstract: Attempts to find and quantify the supposed low entropy of organisms and its preservation are revised. Absolute entropy of the mixed components of non-living biomass (around -1.6 x 10^3 J K^{-1} L^{-1}) is the reference to which other entropy decreases would be ascribed to life. Compartmentation of metabolites and departure from the equilibrium of metabolic reactions account for 1 and 40-50 J K^{-1} L^{-1}, respectively, decreases of entropy and, though small, are distinctive features of living tissues. DNA and proteins do not supply significant decreases of thermodynamic entropy, but their low informational entropy is relevant for life and its evolution. No other living feature contributes significantly to the low entropy associated to life.

The photosynthetic conversion of radiant energy to biomass energy accounts for the most of entropy (2.8 x 10^5 J K^{-1} carbon kg^{-1}) produced by living beings. The comparative very low entropy produced in other processes (around 4.8 x10^2 J K^{-1} L^{-1} day^{-1} in human body) must be rapidly exported outside as heat to preserve the low entropy decreases due to compartmentation and non-equilibrium metabolism. Enzymes and genes are described whose control minimize the rate of production of entropy and could explain selective pressures in biological evolution and the rapid proliferation of cancer cells.

Keywords: cancer; DNA informational entropy; cell compartmentation; evolutionary Biology; lactate dehydrogenase (LDH); lactic acid; metabolism; thermodynamic entropy; Warburg effect

1. Introduction

Thermodynamically, organisms are open systems that maintain their assumed low entropy by exporting as heat the metabolically produced entropy [1,2]. Production, influx and outflux rates of entropy by the whole organism have been frequently determined experimentally and estimated theoretically (see [3] for a review). However, there are uncertainties about the magnitude of entropy content of organisms, the value to which the low entropy is compared, the molecules to which low entropy is associated, and about the relative contribution of each living reactions to generate or save entropy.

Bioenergetics investigations have been mainly focused on values and changes of Gibbs free energy (G, ΔG) and enthalpy (H, ΔH) that have a physiological significance more evident than entropy (S, ΔS) which, in this regard, may be approached as indicative of how much enthalpy cannot be recovered as free energy according to the relations:

$G = H - T \times S$ and $\Delta G = \Delta H - \mathrm{T} \times \Delta S$

for, respectively, actual values and changes (Δ) in processes at the absolute temperature T.

Free energy and enthalpy have a clear physic significance which determines the course of biological processes. However, a role of entropy *per se* has barely been assigned in Biology. Recent theoretical and experimental investigations are uncovering aspects of development, cancer, and biological evolution whose understanding benefits from entropy approaches and, still more, that entropy content and changes determine their occurrence.

For well-defined chemical components, the absolute entropy of formation from their constituting atomic elements [4] (https://homepages.wmich.edu › ~choPDF) has become the usual reference. However, the low entropy associated to one organism structure has been approached diversely. Sometimes, the low entropy of one macro-structure is referred in respect to the entropy of their disassembled molecules. Frequently, it is referred to the magnitude of entropy produced when the components of the organism are oxidized to $CO_2 + H_2O$. Usually, for well-defined chemicals and for reactions, the entropy content and production (respectively) are expressed per mole. But, for some specific purposes, they are expressed per carbon atom gram, total mass, volume and, even, energy content or produced involved.

When referred to one unit of carbon weight, the entropy of formation at room temperature (25-30ºC) of the dry matter of cells is in the same range than that of glucose and amino acids commonly feeding the growth of cells [3,5], around 2 x 10^3 J K^{-1} carbon kg^{-1}, and of the same living cell [6], and lower than CO_2 gas (4.8 x 10^3 J K^{-1} carbon kg^{-1}). Then, supposedly, living features additional to that of chemical biomass should account for minor contributions to low entropy of organisms, however they are decisive for life. Compartmentalization of components, sequences of nucleic acids and proteins, ordered membrane structure, …, although keys for life, have minor contribution to the low relative entropy of the whole organism. In fact, the standard entropy of formation of dry glucose, -2.12 x 10^2 J K^{-1} mol^{-1} [7] (equivalent to -2.95 x 10^3 J K^{-1} carbon kg^{-1}) decreases in aqueous solution to -1.16 x 10^3 J K^{-1} glucose mol^{-1} (calculated from [4]), equivalent to -6.44 x 10^3 J K^{-1} glucose kg^{-1} or -1.61 x 10^4 J K^{-1} carbon kg^{-1}. Considering that carbon accounts some 9% (w/w) of fresh living matter (one liter, L, weighting 1.1 kg), this has -1.6 x 10^3 J K^{-1} L^{-1} entropy attributable to biomass standard formation *in situ*.

The comparison of the entropy of chemical components and structures with the rate of entropy production in different metabolic reactions and with the entropy fluxes in organisms permit an approximate evaluation of the role of entropy export, and the contribution of structure/function entropies to support life and biological evolution.

2. Entropy Fluxes in Photosynthesis

Plants, where radiant energy play a key role in energy and entropy fluxes, are good model to compare a wide range of entropy fluxes with low-entropy reservoirs and physiological processes. Yourgrau and Van Der Merwe early [8] made clear that plant photosynthesis agrees the thermodynamics second principle of the increase of entropy and, despite more recent polemics related with the primary photochemical stages [9,10], the increase of entropy is widely accepted for the entire process and all stages of photosynthesis [11,12].

Starting from the low-entropy energy of the absorbed light, its full conversion to the high-entropy of heat energy is diminished by successive stages of the use, storage, and export of energy by plants that, synthesizing low-entropy chemicals, decreases the export of entropy as heat. Potential entropy is trapped in radiant energy, and photosynthesis captures part of this potential entropy (sometimes named negentropy) tied to the free energy of the biosynthesized chemicals. Energy, as heat, and associated entropy are released from these chemicals through respiratory firing in the same plants or in non-photosynthetic organisms.

The entropy (S_R) associated to radiant energy (E_R) reaching the plants may be approximated as that of non-diffuse sunlight [13] by: $S_R = E_R/5 \times 10^3$ J K^{-1}. For several purposes, the ratio of energy to its associated entropy (E/S) is a measure of the quality of the energy and has dimension of absolute temperature (K). Hence, the ratio $E_R/S_R = 5 \times 10^3$ K, is a value corresponding to high quality energy. In contrast, when E_R is completely converted to heat at ambient 300 K temperature the new (thermal) entropy is $S_T = E_R/3 \times 10^2$ J K^{-1}. The quality of the conserved energy (E_R/S_R) decreases to 300 K. The entropy associated to the free energy of most photosynthesized chemicals lays between a minimum $E/5 \times 10^3$ J K^{-1} and a maximum $E/3 \times 10^2$ J K^{-1} differing by a factor 15.7.

Photosynthesis saves a small fraction (less than 1%) of the absorbed radiant energy as biomass supporting the reaction:

$$6\ CO_2 + 6\ H_2O \longrightarrow C_6H_{12}O_6 + 6\ O_2 \qquad (1)$$

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$\Delta G_0 = 2.88 \times 10^6$ J glucosa mol^{-1} [14].

Dividing by the standard entropy loss in the formation of glucose, 1.16×10^3 J K^{-1} glucose mol^{-1} [4], the free energy gain in photosynthesis as bonds in the glucose molecules has a quality $2.88 \times 10^6 / 1.16 \times 10^3 \sim 2.5 \times 10^3$ K, lower than radiant energy but far above of heat energy. Although differing among the high variety of metabolites and macromolecules, the 2.5×10^3 K ratio may be a reference quality of the energy of stored in cell molecules. However, in contrast to radiation energy, ΔG^0 and ΔH^0 are widely used in bioenergetics bibliography and comparison with photo-physics bibliography is immediate by: $\Delta G^0 / \Delta S^0 = (\Delta H^0 / \Delta S^0)$ - T.

Most of the radiation energy absorbed by the leaf is dissipated as heat for water transpiration [15]. Even, at the best, around 77% energy radiation absorbed by the photosynthetic machinery is dissipated as heat. Thus, assuming a minimum 50 photons needed to photosynthesise one molecule of glucose, photosynthesis converts, 10^7 J radiation energy (2×10^3 J K^{-1} entropy) to recover 2.88×10^6 J as free energy of one glucose mol endowed with 1.16×10^3 J K^{-1} entropy, approximately half of that in the used radiation. Considering the entropy associated to heat, the photosynthesis results in an increase of entropy:

$$\left((10^7 - 2.88 \times 10^6) / 300\right) - 2 \times 10^3 - 1.16 \times 10^3 \quad \sim \quad 2 \times 10^4 \text{ J K}^{-1} \text{ glucose mol}^{-1}$$

that is only indicative because no correction of concentrations has been applied to the free energy and entropy standards and, in most cases, photosynthesis of glucose requires more than 50 photons per molecule [16]. Notwithstanding, the 2×10^4 J K^{-1} glucose mol^{-1} supplies a reference value of the minimum production of entropy associated to photosynthesis. Sato [17] calculated lower, but in the same order (1.15×10^4 J K^{-1} glucose mol^{-1}), entropy production considering the use of 48 photons and slightly lower entropy of radiation. Light excess over the capacity of the photosynthetic machinery increases the production of entropy through nonphotochemical quenching (NPQ) by monomeric dispersed photosystem II (PSII) and light harvesting (LHCP) complexes. These seem to assembly under low light intensities to multimeric macro-complexes that, hiding involved pigments, decrease energy dissipation (entropy production) through zeaxanthin in NPQ [18].

Most of the entropy produced in photosynthesis takes place at the photophysical stages in the light-harvesting complexes and the photosystems, since the absorption of photons to charge separation. The last occurs by transfer of one electron excited in one chlorophyll dimer to one monomeric chlorophyll and then to pheophytin [19]. As the entropy content of most metabolites are in the same range than glucose on a carbon atom gram basis, energetic considerations show that next electron transfers and pumping of protons in thylakoid, as well as conventional enzyme catalysed reactions in chloroplast and cytosol, account a minor fraction of the 2×10^4 J K^{-1} glucose mol^{-1} of entropy produced in photosynthesis. Then, when compared with the first "Élan Vital" [17] of photosynthesis, the changes of entropy associated to metabolic reactions are very low, falling in the range +10 to -30 J K^{-1} mole^{-1} as deduced from ΔG and ΔH data [4] of representative reactions.

3. Structural and Metabolism Entropy

The entropy change associated to the folding of polypeptide chain to form the three-dimensional structure of protein has been estimated experimental and theoretically. The reported values vary within a one order of magnitude range [20-24]. Typical values are -1.25×10^3 J K^{-1} mol^{-1} conformational entropy for mean globular proteins. However, the decrease of entropy by protein folding is accompanied by similar or higher increase of the translation entropy of the solvent water molecules [25], which leaves a negligible global effect of protein folding on the entropy balance of the living cell. In other systems, Jia et al. [26] investigated changes of entropy in the transition of lamellar to grana stacked thylakoid and concluded that it is driven by increase of entropy. Therefore, evidence suggests that assemblages of protein and lipid in supra-macromolecular complexes are

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entropy driven and that they account for more entropy to the cellular medium than their unfolded or dispersed components.

When DNA double strand melts entropy increases around 50 JK^{-1} (mol bp)$^{-1}$ [27]. However, the low number of DNA molecules and the entropic increase due to the small molecules crowding around DNA molecules make negligible the possible entropy decrease associated to the double strand structure of DNA or, in general, the aggregation of components of the genetic machinery [28]. Thus, similarly to protein folding and lipid assemblage, secondary DNA and RNA folding do not significantly contribute to endow a low entropy distinction to life.

Compartmentation of metabolites within the different cell organelles and between cells and extracellular medium implies a decrease of entropy which was evaluated in the range of 1.0 J K^{-1} L^{-1} below the hypothetical homogeneous solute distribution [6]. Compared with the standard entropy of formation of the biomass *in situ*, -1.6 x 10^{3} J K^{-1} L^{-1}, the compartmentation of metabolites, although essential for life [29], barely decreases the entropy of living matter one-thousandth the yet negative standard entropy of formation of their molecular components. As there is no evidence that folding, and assemblage of macromolecules contribute in a higher proportion than compartmentalization to low the entropy of living matter, the question is still whether other cell structures significantly contribute to the supposed low entropy of organisms [1,30].

Adult organisms absorb nutrients and metabolize them to products that are excreted. Despite the turnover of its components, mass and entropy of the organism open system remain constant. However, the metabolism inside produces entropy, mainly as heat and, in a lower amount, as chemicals that have more entropy than the nutrients. An adult human body may produce 10^{7} J day^{-1} as heat carrying 4.8 x10^{2} J K^{-1} L^{-1} day^{-1} entropy. In other words, the human body exports with heat in one hour around 20-folds the small entropy deficit associated to the subcellular compartmentation key for life. Otherwise, the heat produced would duplicate in one day the body temperature (from 36.5 to 73º). Obviously, heat must be quickly exported (dissipated) to avoid membrane disassembly, protein denaturation, and then, cell die. Entropy export is a consequence of the high entropy of heat, it has no connection to the low entropy of compartmentation. In contrast to mass and energy, entropy is not conserved neither it can be transferred. Except for entropy of radiation, it is a state function that depends on the distribution of energy within molecules, and it can only increase as time run ahead. The frequent expressions “imported” and “exported” entropies, that myself use, are not truly correct because entropy as such is not transferable. The organism exchanges heat energy and mass that have associated entropy. In doing so, entropy stays constant in the organism and increases in the environment. By no mean, the entropy that increases in the environment is extracted from the structures of organism that remain unchanged. The heat and the final molecules produced in the metabolism are exported carrying their high entropy content.

Obviously, metabolic reactions are not in equilibrium and then, these non-equilibriums have associated low-entropies intrinsic to organisms that, have been poorly investigated. The lower entropy associated to the non-equilibrium is cancelled at equilibrium and should equal to the increase of entropy produced when the equilibrium is reached. Thus, the metabolism intrinsic entropy of one organism is a measure of how far from equilibrium is the whole metabolism of the organism. At the equilibrium, almost all intermediaries of the whole metabolism have been converted to products, the ΔG of the reaction equal 0, and entropy reaches the maximum value. The metabolism intrinsic entropy (S_i) of a living tissue may be estimated as the negative value of the entropy gained when the equilibrium of the whole metabolism is reached. Approximately: $\Delta S = -\Delta G/T$.

The main question is what cell components count to evaluate the ΔG from live body to metabolically equilibrate death body. One possibility is to consider only the intermediaries subjected to rapid metabolic turn-over. However, the wide range of metabolite turnovers and the variety of intermediaries and concentrations make the estimation of ΔG gross approximate. Thus, with rude approach, stored starch and triglycerides should not count in an organ as liver to calculate ΔS_i. To compare with the contribution of compartmentation to low entropy associated to life, let consider the entropy associated to the continuous metabolization of glucose to CO_2:

$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O \qquad \Delta G_0 = -2.88 \times 10^6$ J glucosa mol^{-1} (2)

Discarding the effect of concentrations of substrates and products on ΔG, the entropy decrease associated to the non-equilibrium of metabolizing 5 mM glucose at 308 K would be:

$2.88 \times 10^6 \times 5 \times 10^{-3} / 308 = 47$ J K^{-1} tissue L^{-1}. That is around 50-fold higher than the decrease of entropy associated to compartmentation but only 2.5-fold the rate production of entropy by human body per hour, calculated around 20 J K^{-1} L^{-1} $hour^{-1}$ (Figure 1).

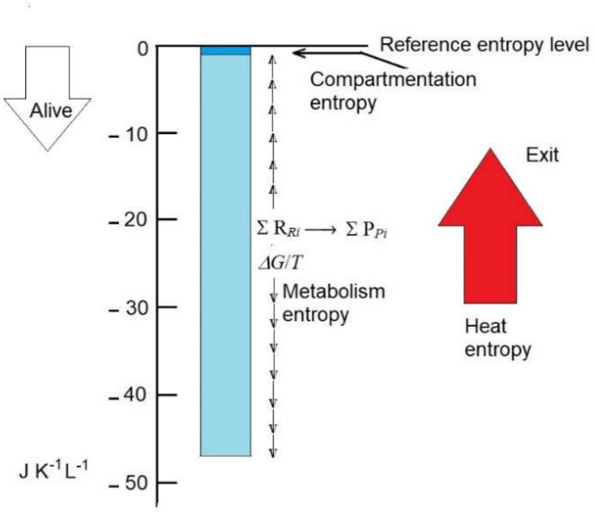

Figure 1. Compartmentation entropy and metabolism entropy are plausibly the main contributors that, decreasing entropy of non-living biomass (reference entropy level), convert it to alive biomass. Entropy values in the scale may be representative for human body. Compartmentation entropy is essentially constant and metabolism entropy (due to the departure from reaction equilibrium) is variable. Exportation of heat entropy (red arrow) prevents the collapse to 0 of compartmentation and metabolism entropies.

The calculations are gross approximated (possibly within one order size), but they emphasize the relevance of the intrinsic metabolism entropy and the need for its furthermore accurate calculation, as it is defined here, because it is probably the major contributor of the low entropy claimed for organisms.

When the whole cell metabolism approaches to equilibrium, intrinsic metabolism entropy increases and becomes 0 at death. In the sequential reactions of a metabolic path (e.g.: glycolysis), enzyme inhibition, like glyceraldehyde-3-phosphate dehydrogenase by iodoacetamide [31], led the precedent reactions to equilibrium, but hold off equilibrium the following reactions, thus keeping transitorily low intrinsic metabolism entropy until cell death. Metabolism is one characteristic feature of living tissue that caries linked a relative low entropy and, thus, it contributes variably to decrease the total entropy of life.

4. Production of Entropy

Metabolism produces heat that is transferred outside with in chemicals with their associated entropy, produced at a rate, P, [32]:

$$P = dS/dt = \Sigma v_i A_i / T \qquad (3)$$

Where summation Σ extends to all reaction rates, v_i, and affinities, A_i, as given by: $A_i = \Sigma n_i \mu_{Ri} - \Sigma n_i \mu_{Pi}$; where μ_is are the chemical potentials of substrates, R_R, and products, P_P, of the metabolic reactions i: $\Sigma R_{Ri} \longrightarrow \Sigma P_{Pi}$

The rate of production of entropy differs widely among organisms and physiological states, increasing, according to equation (3), with the metabolic rate and the affinity of the global metabolic reaction. Affinity and rate are higher as farther from equilibrium the reaction is. Therefore, departure from equilibrium has opposite effects in the rate of production of entropy, that increases, and in the content of entropy of the organism that decreases due to the negative contribution of the intrinsic metabolism entropy. When approaching to equilibrium, rates, v_is, become linearly dependent of chemical potentials, μ_is, and the rate of production of entropy, P, can only decrease [32,33].

In response to variable environments, the open thermodynamic systems of organisms change the separation from equilibrium of specific metabolic pathways and, sometimes, of the whole organism metabolism, then affecting its rate of entropy production and its entropy content within ranges compatible with life. Life compatible ranges vary among organisms and decide to be alive and evolutionary selection.

5. Evolution and Entropy

Relations between biological evolution and entropy have been often investigated. Organized structures and functions are characteristic of life and evidence suggests that they became increasingly complex during the evolution of organisms. Not such as evidently, the higher organization and complexity are supposed to imply lower entropy. This would imply the paradox that during the evolution of living beings the entropy of biomass decreases, in contrast to the second principle of thermodynamics. The paradox appears from the ambiguous, when not arbitrary, identification of organization and complexity with low entropy and high information, and of entropy with disorder [34-36]. Then, information-based models of organisms propose that evolution is associated to increased organism diversity and entropy of ecosystems [37-39], higher entropy production [40,41] and, often, that entropy production would be maximized in fully evolved enzymes [42]. In contrast to barely quantifiable qualities (like order and complexity) in molecular and cell biology, others as information, and entropy, quantifiable and statically based, must be analysed, and distinguished [43]. In this line, several alternative models support the trend to lower rates of the production of entropy by organisms during evolution [33,44-48].

Interpreted statistically, entropy is a measure of the uncertainty of the distribution of energy according to the equation of Boltzmann and Shannon:

$$S = - k \text{ x } \Sigma p_i \text{ x } \ln p_i$$

where k is the Boltzmann constant ($1.381 \text{ x } 10^{-23}$ J K^{-1}) and p_i is the probability of one distribution, i, of the total energy among different molecules, electron excitations, bond vibration energy, and so on. The statistical interpretation of entropy as a characteristic distribution of energy is relevant in biological issues, like the understanding of the entropy content of the different biomolecules.

One similar formulation is used in information theory, and the so-called informational entropy measures the uncertainty of one statement or information of a system. The informational entropy analysis is often used in Biology, but its meaning should be distinguished from thermodynamic entropy in molecular biology and evolution. The genetic information in DNA supplies straightforward examples for informational entropy concepts. The characteristic nucleotide sequence of the four bases (adenine A, guanine G, cytosine C, and thymine T) in the DNA of one organism is the same in all cells of the organism and results of the combination of random mutations and functional selection during biological evolution. *A priori* there is no preference for a specific sequence, 4^n different DNA sequences are equally possible and the actual DNA sequence has only a 4^{-n} probability (p), where “n” (the number of bases in the DNA sequence) ranges from one million in bacteria to billions in many animals and plants. Hence, according to the Shannon formula [49-51], the evolutionary events leading from unspecified base sequence to the sequences of today organisms result in a gain of information (a decrease of entropy, negative ΔS_{DNA}) in “bit”:

$\Delta S_{DNA} = \Sigma\, p \log_2 p = \Sigma\, 4^{-n} \log_2 4^{-n} = 4^{n} \times 4^{-n} \log_2 4^{-n} = -2n$; or $\Delta S_{DNA} = -2n$ bit

Then, 2n bit is the informational entropy loss (information gain) associated to the choice of the specific DNA sequence of n bases.

Accumulation of mutations in the cells of one multicellular organism or in individuals of one specie, increases the informational entropy of, respectively, the organism or the specie. In the last case, natural selection will cut most mutants, evolutionarily decreasing again the informational entropy or genetic diversity of the specie, also named populational entropy [37,52].

Informational and thermodynamic entropies are not equals although the two are statistically based. Then, as statistics alone cannot justify thermodynamic entropy determinants in evolutionary Biology, less at all informational entropy could explain biological evolution without reference to the physiological and physic-chemist properties of the organisms. For the example of DNA, the key question of the choice of one specific sequence is not only a statistical issue, but also a molecular biology issue with its physic-chemicals and thermodynamic determinants.

The evolutionary transition of procaryotic to eucaryotic decreased the thermodynamic entropy of the new organisms [6] due to added compartmentalization of metabolites, which look like a type of organized system. As show in sections **3** and **4**, compartmentation-dependent decrease of entropy is small when compared with the variable decrease of metabolism entropy, but it is measurable and sufficiently stable to be considered characteristic of living beings and their evolution. It seems unescapable the paradox that the highly compartmentalized eucaryotic organisms were selected despite they had lower entropy than their predecessors. A close look to the evolution of the rate of production of entropy could resolve de paradox.

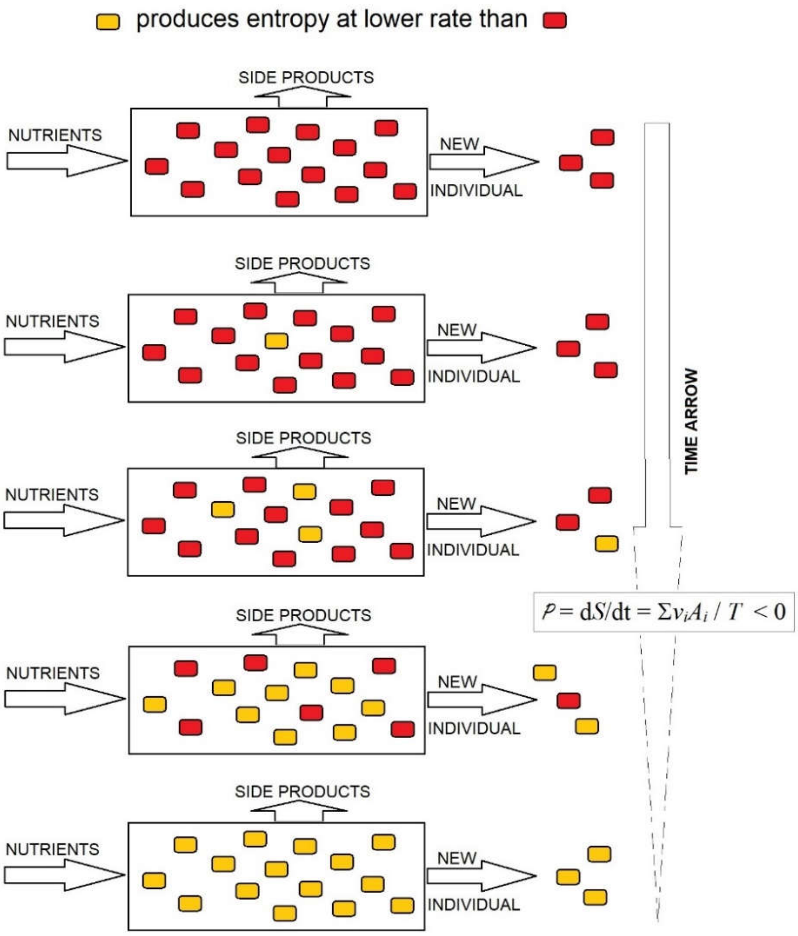

Figure 2. Decrease of the rate of production of entropy in an open system saturated of organisms. Under limiting supply of nutrients, the system is close to equilibrium and can only evolve to decrease the rate of production of entropy, which is achieved by progressive substitution of organisms that produce entropy at high rate (red 🟥) by organisms producing entropy at low rate (yellow 🟨).

As equation (3) shows, in the stationary state of the open system of organisms, the rate of production of entropy is $\mathcal{P} = \mathrm{d}S/\mathrm{d}t = \Sigma v_i A_i / T$, where v_i is the rate of consumption of nutrient substrate by the organism i and A_i the affinity of the global reaction in the organism i. If proliferating organisms compete for the same nutrient, this became limiting, and the reactions approach equilibrium, when v_is depend linearly on affinities A_is. Under these conditions, the rate of entropy production in the complete system of competing organisms cannot increase, it can only decrease to a minimum [32]. As I yet pointed [33], the decrease of entropy in a system of competing organisms may be conducted by rapid proliferation of organisms that produce entropy at the lowest rate and progressive disappearance of organisms that produce entropy at high rate, the opposite is not possible (Figure 2). That is not other than the evolutionary choice of organisms producing entropy at the lowest rate, at least at limiting conditions, and supplies a thermodynamic foundation for the evolution of organisms by natural selection. Therefore, the evolutionary trend to lower rates of entropy production in an organism system implies that the entropy of organisms per mass unit of consumed substrate should decrease in the evolution.

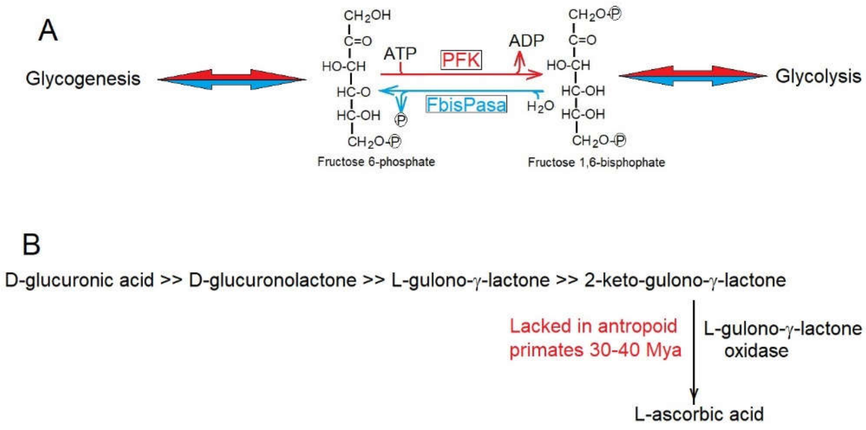

Figure 3. A) Phospho-fructose kinase (PFK) and fructose 1,6-bisphosphatase (FbisPase) would provide a futile metabolic cycle in glycolysis and glycogenesis consuming ATP and producing entropy. Strict metabolic controls ensure that they do not function simultaneously. **B)** Biosynthetic pathway for the synthesis of L-ascorbic acid. Anthropoid primates lack the enzyme L-gulono-γ-lactone oxidase.

To decrease the rate of production of entropy, enzymes have evolutionarily acquired metabolic controls avoiding futile cycles like that of phospho-fructose-kinase (PFK) and fructose 1,6-bisphosphatese (FbisPasa) (Figure 3A) in, respectively, glycolysis and gluconeogenesis (https://microbiochem.weebly.com/gluconeogenesis.html), that avoiding their simultaneous activity, decrease the production of entropy by continuous waste of ATP.

Sometimes, decreases of the rate of production of entropy was reaches in evolution by elimination of metabolic routes that became non-necessary. Thus, the synthesis of ascorbic acid was loss The loss of ascorbic acid synthesis 30-40 Mya (Figure 3B) in the line of anthropoid primates [53] by accumulation of inactivating mutations in the gene encoding L-gulono-γ-lactone oxidase, which catalyses the synthesis of L-ascorbic acid. Very probably, intense herbivore feeding of these ancestral primates supplied enough L-ascorbic acid that made dispensable its synthesis; thus, saving entropy production in anthropoid. Many other examples of conservation, elimination, and recovery of specific genes during evolution are easily explained [54-56] for their consequences to decrease the rate of production of entropy as predicted by the Prigogine theorem [32,33].

The entropy produced by proliferating organisms is usually simplified as that of their main metabolism. For example, in the respiratory consumption of glucose by yeast the only reaction considered is:

$$C_6H_{12}O_6 + 6\ O_2 \longrightarrow 6\ CO_2 + 6\ H_2O \qquad (4)$$

Where low entropy substrates (glucose, $C_6H_{12}O_6$ and oxygen, O_2) are converted to high entropy products (CO_2 and H_2O), therefore increasing the production of entropy that add to the entropy of the heat produced in the reaction. However, due to the proliferation of organisms, new individuals must be added to the right side of reaction (4) as products having entropy. Then, the true rate of entropy production should be lower as lower is the entropy of the new individuals. Consequently, theory predicts that, other factors equal, organisms with lower content of entropy (with increased structure-function organization?) would be selected on preference over those with high entropy.

6. Cancer and Entropy

Cancer has been a recurrent theme to confront entropy models of development, mostly of informational entropy. The development of higher plants and animals from the single cell zygote to fully differentiated adult organisms implies growth and construction of new structures anatomic and functionally organized that, supposedly, have less entropy than original zygote on a mass unit basis. Cancer cells leaves from the ordered development by rapid cell multiplication without specialized differentiation. Anatomically, cancer tissue appears to be disorganized and, therefore, having high entropy. The assignment of high entropy to cancer tissue seems sound and, with right definition of information, models of cancer growth have been linked to the expected increases of informational entropy and decreases of information [57] and to higher [58] or lower [59] rates of the production of thermodynamics entropy. However, the relation of cancer anatomy and growth with thermodynamic entropy is not as clear and it has difficulties like that yet mentioned to evaluate the entropy decrease associated to protein folding or of supra-macromolecular structures of the cell.

Another bioenergetic approach to cancer focuses on the Warburg effect. Cancer cells fermentatively metabolize glucose to lactate at high rate when compared with non-cancer cells that mainly consume glucose by respiration to produce CO_2 [60-62]. Typically, cancer cells metabolize by fermentation 95% glucose [63] while health liver or kidney cells ferment only 15% glucose [64]. The preferent fermentative metabolism in cancer is known as the Warburg effect. The fermentative metabolism, that only yields two moles of ATP per glucose mole, is at first glance surprising for rapidly growing cancer cells when compared with non-cancer cells, that presumably have a lower demand of energy and consume glucose by respiration that yields 36 moles of ATP per glucose mole. The association of fermentative metabolism with rapid cell proliferation was yet pointed by [60] in cancer cells as in microorganisms. To place facts in perspective, with current ATP yields, it must be noted that respiration still accounts around 50% of the ATP synthesized in typical cancer cells. Therefore, although cancer cells could metabolize 4 to 20-folds more glucose by fermentation than by respiration, they get by respiration between 80 and 48% ATP [65]].

The molecular bases of the physiological switch, from mainly respiratory to mainly fermentative of glucose, going with the transformation from normal to cancer cells have been investigated intensely [60-62,66,67] fitting them within the genetic and metabolic reprograming of cancer, and hardly explaining the advantages conferred to cancer cell by the fermentative metabolism.

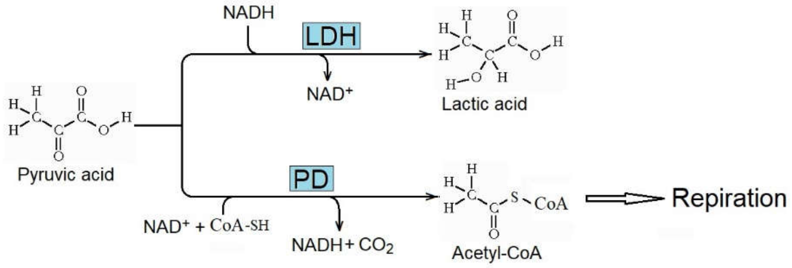

Figure 4. Conversion of pyruvic acid to lactic acid and acetyl-CoA catalysed by lactate dehydrogenase (LDH) and pyruvic dehydrogenase (PD), respectively. Enhanced activity of LDH is critical for the Warburg effect and production of lactic acid in cancer.

The Warburg effect has been considered as an early and distinctive sign of cancer cells [68] linked to stem cell model and the genetics instability of cancer cells.

The enhanced metabolism of pyruvic acid by lactate dehydrogenase (LDH) to produce lactic acid (Figure 4) is essential for the Warburg effect. It decreases the metabolism of pyruvic acid to acetyl-CoA by pyruvic dehydrogenase (PD) and its further respiratory consumption. Consequently, the concentration of lactic acid increases in cancer tissue and metabolic inhibition of LDH decreases the rate of tumour progression [66,67].

The association between the Warburg effect and cancer is thermodynamically intelligible [69] in a model where the total rate of entropy production tends to a minimum [70] in agreement to the Prigogine principle.

Within a thermodynamics approach, I suggested [65] that lower rate of entropy production of fermentative metabolism of glucose could supply a selective advantage for the proliferation of cancer cells. At the usual temperature (37º = 310 K), pH 7.4, concentrations

(5 x 10^{-3} M glucose; 2.9 x 10^{-3} M lactate) and CO_2 (380 ppm = 38 Pa) in human tissues, the entropy produced, per glucose mol metabolized, is lower in fermentation than in respiration:

respiration: Glucose + 6 $O_2 \longrightarrow 6\ CO_2 + 6\ H_2O$ ΔS = 403.9 J K^{-1} glucose mol^{-1}

fermentation: Glucose $\longrightarrow$ 2 Lactate + 2 H^+ ΔS = 359.4 J K^{-1} glucose mol^{-1}

which is a consequence of the lower entropy of lactate than of CO_2.

Thus, like competing organisms for limited nutrients in evolutionary Biology, the fermentative metabolism bought by cancer cells allows them increased proliferation over non-transformed cell to conduct the trend of the tissue mass to lower the rate of entropy production. Lactate is a low-entropy side-product that confers the cells producing it advantage when competing for limiting glucose.

7. Concluding Remarks

Since the book of Schrödinger [1] the relation between life and entropy has been a matter of discussions and speculations barely shadowed by the impressive advances in molecular biology. Organisms supposedly have low entropy, although their activity produces entropy for the environment. Today, progresses in the understanding of entropy nature and production parallel molecular biology insights, supplying scientific background for the two questions raised by the proposal of Schrödinger on organismal entropy: a) how much low entropy is? b) what molecular and structural features account for low entropy? In addition, the distinction between informational and thermodynamic entropies, and the rate of production of entropy was revealed as keys to understand the dynamic of life.

Remembering that entropy is an energy-associated variable, photosynthesis, the first stage leading to life down-grades sun energy to glucose-associated energy whose entropy may be estimated around 1.6 x 10^4 J K^{-1} carbon kg^{-1} or 1.6 x 10^3 J K^{-1} per body litre (L) alive or death. Energy conversion in photosynthesis conforms the thermodynamic second principle and barely reaches 2-3 % efficiency while it increases entropy around 2.8 x 10^5 J K^{-1} carbon kg^{-1}, mainly produced in the photo-physical stages of light energy conversion.

By taking as reference the 1.6 x 10^3 J K^{-1} L^{-1} of life mass, the assumed low thermodynamic entropy distinguishing alive from death biomass seems associated to decreases in the range of 1 J K^{-1} L^{-1}, due to compartmentation of metabolites, and 40-50 J K^{-1} L^{-1} estimated for the departure of metabolic reactions from equilibrium. The decreases are slight but their need, like those of the structural and informational designs of metabolites and macromolecules, demands further precise quantifications to define the limits between health and pathology. The two are temperature sensible, which compels continuous export of heat with its associated entropy. Intense experimental and theoretical investigations suggest that there is no other living feature that contribute significantly to the low entropy associated to life.

Recent investigations on the rate of production provide entropy with added relevance in molecular biology of evolution and development. The central question is whether organism metabolism trends to maximize or minimize the rate of production of entropy. The two possibilities have been theoretically and experimentally proved for specific biological systems and non-living models. The trend to minimize the rate of production of entropy is based on the theorem of Prigogine, who seems applicable for organisms or cells competing for one nutrient and concludes the choice of those producing entropy at the lowest rate and the elimination of those that produce entropy at high rate. The minimization model could resolve the old question of the physical bases of the evolution by natural selection and supply the thermodynamic background to understand the rapid proliferation of cancer cells.

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