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## **Life is a self-organizing machine driven by the informational cycle of Brillouin**

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### **Abstract**

Acquiring information is indisputably energy-consuming and conversely, the availability of information permits greater efficiency. Strangely, the scientific community long remained reluctant to establish a physical equivalence between the abstract notion of information and sensible thermodynamics. However, certain physicists such as Szilard and Brillouin proposed: (i) to give to information the status of a genuine thermodynamic entity ( $k_B T \ln 2$  joules/bit) and (ii) to link the capacity of storing information inferred from correlated systems, to that of indefinitely increasing organization. This positive feedback coupled to the self-templating molecular potential could provide a universal basis for the spontaneous rise of highly organized structures, typified by the emergence of life from a prebiotic chemical soup. Once established, this mechanism ensures the longevity and robustness of life envisioned as a general system, by allowing it to accumulate and optimize microstate-reducing recipes, thereby giving rise to strong nonlinearity, decisional capacity and multistability. Mechanisms possibly involved in priming this cycle are proposed.

### **Keywords**

Thermodynamics, Information, Positive feedback, Microstates reduction, Nonlinearity, Multistability, Organization.

## Introduction

A recently conducted experiment of accelerated evolution (Marlière et al., 2011) revealed that the structure of DNA from contemporary cells is purely contextual and could have been different if conditions had been different. This instructive study, ruling out previous speculations about the rational of nucleotide composition, shows that life has the potential to take many different molecular forms. Hence, in order to analyse life as a general phenomenon, not restricted to particular terrestrial circumstances, one is led to examine the innermost physical principles underlying this puzzling form of matter organization. Even if current physical models are incapable of recapitulating the complexity of life, life is however expected to obey the same physical laws as any other piece of matter (Trevors, 2010). The most amazing feature of life is its apparent capacity to climb back up the chemical randomisation expected from the second law of thermodynamics. This fact has long been pointed by Ludwig Boltzmann himself, who envisioned life as a struggle for entropy. In this article, the progressive intrusion of information in thermodynamics is first reviewed by pointing out the historical contributions of physicists. In this context, life is characterized by its unbeaten capacity to manage, retrieve and store information through a positive feedback, corresponding to the cycle of Brillouin that is proposed to be a fundament of life. Then, the modes of coupling between information archival and biochemical intelligence are examined and finally the delicate question of the priming of the cycle of Brillouin is addressed.

## Life is a struggle for low entropy

The second law, connecting the time arrow and the maturation of the universe (Coveney and Highfield, 1990), is perhaps the most puzzling law of physics because it is basically probabilistic: (i) inexistent at the microscopic level, (ii) leaky at the mesoscopic level (Wang et al., 2002) and (iii) insurmountable at the macroscopic level (Lebowitz, 1993). A reasonable assumption is that living systems are larger than the threshold scale of emergence of the second law, but strangely they seem to violate it. To perceive this long-standing problem, consider the two upper panels of Fig. 1 and let us try to order them in time. The correct answer obviously depends on the existence of life. In absence of life, Fig. 1B is necessarily posterior to Fig. 1A, because the components of the sand castle can only disintegrate with time, according to the statistical approach to the second law (Coveney and Highfield, 1990; Lebowitz, 1993). Conversely, living beings can build the castle by clustering and organizing sand particles at the expense of free energy inputs. This reasoning no longer applies to life, that is assumed to have spontaneously emerged from a primordial disorganized organic soup, reminiscent to that obtained in the Miller's experiment (Miller and Urey, 1959) and symbolized in Fig 1C, suggesting that the second law of thermodynamics should be refined to incorporate living systems.

## Towards an explanation

### *Multifaceted entropy*

The progress towards reconciling life with thermodynamics has been marked out by successive contributions of physicists. Of course the first one was Ludwig Boltzmann, who revolutionized our approach to our world by recovering the Clausius thermodynamics through the rigorous enumeration of matter microstates, that is to the say the sum of all relative configurations of the different objects in a system (macrostate)  $X$ . The entropy ( $S$ ) previously defined as the extent of heat dissipation in the differential form  $dS = dQ/T$ , proved to be equivalent to the Gibbs-Boltzmann relationship  $S(X) = k_B H(X)$  where  $k_B$  is the Boltzman constant giving the units to entropy (joules/kelvin) and  $H(X)$ , the dimensionless statistical entropy of  $X$ , is defined as a function of the probabilities  $p(x_i)$  of all possible configurational states  $x_i$  of the system through  $H(X) = -\sum_i p(x_i) \ln p(x_i)$  (Gibbs, 1878). This use of probabilities in classical thermodynamics can appear puzzling because probabilities are generally associated with the notion of knowledge of an observer, but it will turn out to have a profound significance.

The next step of this story was the establishment of a connection between entropy and information. Leo Szilard first introduced the concept of intelligence in thermodynamics after revisiting the Maxwell's demon experiment (Szilard, 1929), translated in (Szilard, 1964), of which a simplified

version is presented below. Szilard concluded that if we do not wish to admit that the second law has been violated, we must conclude that acquiring knowledge is a dissipating process (Szilard, 1929). Then, Claude Shannon, a mathematician and electronic engineer built a mathematical theory of communication and a quantification of information inspired by the Gibbs equation of entropy (Shannon, 1948), following the logarithmic measure of information introduced by Hartley (Hartley, 1928). Shannon named his formula of information "entropy" because of its mathematical similarity with the Gibbs entropy (Rothstein, 1951). This analogy between dimensionless informational entropy and thermodynamics was subject to debates to determine if it is fortuitous or reflects underlying relationships (Jaynes, 1957). However a problem with the dimensionless equation of entropy is that it turned out to be singularly useful in many unrelated research areas, including computing systems, spatial patterns or the informational content of DNA sequences, thus blurring the connection with thermodynamic entropy. Szilard, Jaynes, Brillouin and, before them, Boltzmann himself (Rothstein, 1951), considered that the entropy of thermodynamics is actually related to missing information. Brillouin crossed the Rubicon by considering information as a genuine physical notion (Brillouin, 1949; 1950; 1953). Other authors met this view, such as Landauer who considered that information is physical (Landauer, 1996). At first glance, information seems to be purely cognitive and unrelated to the classical quantities of thermodynamics such as energy, heat or work, but the correspondence between information and the Boltzmann's entropy can in fact be concretely illustrated by the Maxwell's demon experiment, slightly modified below. This celebrated thought experiment, originally suggested by Maxwell and re-used here because of its historical popularity, simply reflects the macroscopic nature of the second law. The instantaneous motion of an individual particle is oriented and thus potentially capable of generating work, but on a larger scale this possibility is cancelled by other particles with opposite trajectories, so that there is no sustained net flux at equilibrium.

Consider a chamber containing an ideal monoatomic gas, inevitably made of higher and lower energy particles moving randomly. Let us fix an arbitrary median energy threshold over which particles are represented in black and below which they are represented in white. Now imagine that this chamber is separated into two equivalent compartments by a wall (Fig. 2A) with a door (Fig. 2B, C) and that this door is controlled by the Maxwell's demon. The demon is supposed to have the capacity to perceive the speed of the particles moving towards the door, allowing him to apply a systematic game rule: He opens the door for every high energy particle coming from the right-hand compartment (Fig. 2B) and for every low energy particle coming from the left (Fig. 2C). When an asymmetric distribution is generated by this strategy (Fig. 2C), the door is then closed, the separating wall is unlocked and transformed into a piston freely moving upon particle impacts (Fig 2C to D). This piston is of course expected to move from left to right because of the thermal dilatation of the left compartment (Fig. 2, large arrow). Hence, some exploitable macroscopic work seems to be extractable from the spontaneous thermal agitation of the gas in absence of work input, thereby generating a perpetual motion machine. This experiment basically contradicts the second law which stipulates that extracting work from random motion at equilibrium is impossible.

### ***Solving the Maxwell's demon experiment imposes to assume an analogy between information and negative entropy***

The explanation of the above experiment is that the selective action of the demon is based on his knowledge about the speed of the particles. To cancel the unacceptable outcome of this theoretical experiment, one should admit that some equivalence exists between information and work. In absence of specific information, any particle has the probability  $\frac{1}{2}$  to be black and  $\frac{1}{2}$  to be white, giving a probabilistic entropy per particle of  $S_1 = -k_B (\frac{1}{2} \ln \frac{1}{2} + \frac{1}{2} \ln \frac{1}{2}) = k_B \ln 2$ . To take the decision to open the door or to let it remain closed, the Maxwell's demon should cancel the uncertainty about the particle energy to reduce its entropy to zero, which requires acquiring an information capable of providing a "negentropy" (using the neologism of Brillouin) of at least  $N_1 = -k_B \ln 2$ , thus reconciling the Maxwell's demon experiment with thermodynamics. The reconnection of information to classical physics becomes more than a concept once the cost of a quantum of information (or bit) is quantified using traditional physical units (Brillouin, 1953). On the one hand, Brillouin understood that obtaining information is never for free in all aspects of knowledge, including scientific investigations for which heat-dissipative reasoning power and costly experiments are necessary. On the other hand, acquired

information allows designing subsequent experiments and undertaking new prior work actions, thereby creating an iterative chain of information retrieval (Brillouin, 1949; 1950; 1956). Information acquisition, which has a cost, should not be confused with information processing, which can in theory be achieved through adiabatic reversible logic operations (Landauer, 1961). In turn, given its latent energy content, erasing one bit is expected to dissipate  $k_B T \ln 2$  joules of heat. The main lesson of the Maxwell's demon experiment is that selecting, filtering or discerning activities, are thermodynamically expensive operations. They are the hallmark of living matter and the direct consequence of underlying information. In the same manner that a well informed Maxwell demon can break macroscopic symmetry and generate work, living matter has patiently accumulated information during evolution, allowing it to behave with seeming intelligence.

### ***The physical meaning of information***

The idea of Szilard and Brillouin to confer to information a thermodynamic meaning is a conceptual jump more considerable than it appears. Establishing an equivalence between the immaterial information theory and physical thermodynamics led to debates in the scientific community because of the widespread idea that there are no counterparts in information theory to concrete thermodynamic dimensions (temperature, energy). This connection can be simply established by the Boltzmann's constant for classical physics but in quantum physics, entropy is dimensionless and corresponds to no more than the logarithm of the number of microstates. It is ironic that this long standing reluctance is similar to the rejection of the approach to entropy of Boltzmann, who failed to convince his peers that the abstract mathematical counting of postulated gas particles can describe sensible physical notions, sometimes more accurately than the previous approaches. The reticence to introduce information in physical laws can also be related to the anthropic connotation of this word, confusedly associated to the capacity to decode and interpret information, suggesting that some observers are involved in the story, according to the statement of William Stanley Jevons "probability belongs wholly to the mind" (Jevons, 1877). In absence of a new word devised for the circumstance, one should just admit that information can be separated from the idea of intention. For example, information does exist, even in absence of conscious conceivers and translators, in the non-monotonic arrangement of nucleotides in DNA (Avery, 2003; Church et al., 2012), the famous macromolecule selected at least on earth as the vector of heredity (Avery et al., 1944).

### **Entropy and information**

The configurational entropy of a given system  $X$ , can be decreased if the system is conditioned on another system  $Y$  that can specify its own microstates. Information can then be defined as the fraction of entropy shared by non-independent systems  $X$  and  $Y$ . In other words, the system  $Y$  can be used as a correlated "controller" system of  $X$  if there is a mutual information ( $I$ ) between  $X$  and  $Y$ , defined by

$$I(X; Y) = H(X) + H(Y) - H(X, Y) = H(X) - H(X|Y) \quad (1)$$

Where  $H$  is the dimensionless configurational entropy and  $H(X|Y)$ , the entropy of  $X$  conditioned on  $Y$ , is obtained from conditional probabilities,

$$H(X|Y) = - \sum_{x,y} p(x, y) \ln p(x|y) \quad (2)$$

where  $p(x|y)$  is the probability of realizing state  $x$  given its outcome  $y$ . The terms "given" or "knowing that" of conditional probabilities clearly reflect a transfer of information allowing to infer a priori probabilities from *a posteriori* probabilities through the Bayes theorem.

$$p(x_j|y) = \frac{p(y|x_j)p(x_j)}{\sum_i p(y|x_i)} \quad (3)$$

The Bayes theorem has general application in feedback controls, including physical devices (Sagawa and Ueda, 2012), cellular decision making, for example by regulating the appropriateness of gene expression (Libby et al., 2007) and Darwinian evolutionary game theory (Harper, 2009).

## Memory devices and information assimilation

### *Storage of information*

Brillouin explained that the amount of information provided by a significant number of bits contributes for a short period of time and to a very small fraction of the entropy of a fluctuating system, so that the equivalence between information and negentropy has in fact importance only for the theory of information but not really for thermodynamics (Brillouin, 1953). But this question becomes radically different in the case of a system capable of recording and accumulating information, what is precisely Life, for which the amount of stored information largely exceeds system fluctuations. The spontaneous emergence of highly organized living structures from a random chemical soup (Fig. 1C, D) seems to contradict the general statement of the second law  $\Delta S \geq 0$ , but no longer the modified formulation  $\Delta(S-N) \geq 0$ , where  $N$  is the invisible negentropy stored in the system. The apparent organization materialized by a decrease of  $S$  can be compensated by an increase of the absolute value of  $N$ , generated by the conversion of information inferred from past experiences (Brillouin, 1953). The surprising prediction of Schrödinger that life should involve "other laws of physics", inspired by the apparent capacity of life to give rise to "negative entropy" (Schrödinger, 1943), could be precisely related to  $\Delta(S-N) \geq 0$ . In this respect, Szilard and Brillouin, who wrote their studies before the discovery of the genetic code, were particularly clear-sighted. In practice, terrestrial life uses several information-storage devices: long-term genetic (DNA) and short-term epigenetic, in the form of either chemical or structural modifications or of active circuits (Nicol-Benoît et al., 2012). The DNA that we received at the stage of the egg should be appreciated as an invaluable gift, because it contains digitally-engraved information concentrating billions of cycles of Brillouin. Life is an utmost manifestation of a generalized tendency of correlation between subsystems, but  $\Delta S \geq 0$  remains of course valid for closed systems and at the level of the "whole universe", if this notion has some relevance. In this respect, Brillouin recalled that energy is never converted one-to-one. Acquiring information has a cost higher than  $k_B T \ln 2$  joules per bit and converting bits into negentropy is also dissipative.

### *NeoDarwinism*

Two main modes of species evolution, Darwinian and Lamarckian, both contribute to various extents to evolution (Koonin and Wolf, 2009). Darwinism, or natural selection, is the main mechanism officially admitted in the frame of the central dogma of molecular genetics (Crick, 1970), according to which DNA delivers archived information in a blind manner while remaining unaware of its appropriateness. Hence, Darwinian evolution mainly proceeds through random non-repaired DNA modifications, which are *a posteriori* filtered by the environment. This mechanism allows self-replicating systems to extract and record information about the environment (Elitzur, 1994; Krakauer, 2011). Let us consider a gene for which different promoter sequence rearrangements are possible to modify its expression. How to select the optimal modification improving the role of this gene in the system? Since the system itself cannot predict the outcome, the decision is relegated to the environment, which pitilessly punishes the wrong proposals. Individuals who made the bad choice die or fail to mate, but this waste is the price to be paid for reinforcing the species. In this evolutionary game, the player is the species because neodarwinism is by essence populational and dissipative, inseparable from the incessant turnover of individuals.

### *NeoLamarckism*

Systematic blind tests of mutational combinations through the previous mechanism could take an amazingly long time compared to the observed species evolution rate, which has led certain authors to conclude that additional mechanisms must intervene to introduce some orientation and acceleration in the evolutionary process. Such mechanisms would lead to profound revisions of the central dogma and support the concept of genetic assimilation of Waddington (Waddington, 1952). Certain existing mechanisms, including horizontal gene transfers, the prokaryotic CRISPR-Cas system of defense against mobile elements and certain modes of RNA interference, can be classified as quasi-Lamarckian (Koonin and Wolf, 2009). The phenomenon of gene amplification (Nunberg et al., 1978) is also clearly an inducible genome modification. One can even imagine other such mechanisms: (i)

transgenerational transmission of epigenetic information, itself resulting from the experience of the previous generation; (ii) backward arrows towards DNA added to the basic scheme of the central dogma. For example, the alteration of RNA sequences by editing enzymes provides a means for proteins to generate new, non-genome-encoded proteins capable of adjusting the phenotype, that can be subsequently fixed by retroposition. About 30 to 60% of nuclear DNA from higher eukaryotes result from RNA retroposition and this process is not a relic of ancient evolutionary stages, but is still active (Maestre et al., 1995). It is responsible for the appearance of new genes such as *SRY* or Hominidae-specific *PMCHL1* transcribed in the developing human brain (Courseaux and Nahon, 2001) and for the rapid outbreak of new biological activities (Michel et al., 1997). Although they are fascinating in their principle, these mechanisms remain poorly substantiated but open the door to interesting future investigations.

### ***Self-evolution***

The basic principles of evolution described above could be incomplete. Although the same entropy formula is used to calculate the theoretical information content of DNA and the phenotypic and behavioural complexity of living structures, care should be taken to not to draw a bijective relationship between these entities because cooperative phenomena can emerge without need to increase the size of DNA, even of coding and signal DNA. The similar number of genes observed in *C. elegans* and in humans is illuminating in this respect. As explained in the following section, the management of information is not specific to genome archiving but can also be epigenetic. The notion of emergence precisely describes the property of systems for which global complexity exceeds the sum of its individual components (Ricard, 2004; 2006). Besides, over a certain degree of organization, the environmental controller system could to some extent be set by the living system itself, controlling its own environment. An example is the transformation of the atmosphere of the earth by cyanobacteria, marked by the accumulation of oxygen, of course unintentional but then opportunistically used by animals, and of the ozone shield which reduced DNA-damaging ultraviolet light. In addition, it can be speculated that evolution could not only be driven by mining information from the environment but also from other types of systems. For example, how to explain certain puzzling phenomena such as the genius of Gauss and Mozart and the feeling of harmony engendered by their oeuvres. Music could be inherited from sexual behaviours, but the role in the Darwinian struggle for life of the purely gratuitous addicting satisfaction provided by the discovery of new mathematical equations, remains to be clarified. If species fitness has primarily been acquired by encountering environment, the recombination of environment-inspired capabilities could generate more abstract secondary forms of intelligent design and reward systems.

### **How to convert stored information into biochemical intelligence.**

Somewhat magically, decreasing statistical entropy by reducing or removing certain microstates can generate intelligence (Michel, 2011), a notion early connected to thermodynamics by Leo Szilard (Szilard, 1929). It would be too restrictive to believe that intelligence is a matter of brains and complexity and is confined to higher organisms or civilizations. In fact, intelligence can be considered as the innermost property of life, distinguishing it from the inanimate world and existing in all living structures including the most elementary ones. The recipes of biochemical intelligence based on microstate reduction listed in Michel (2011), share the common property to generate nonlinear outputs in response to linear inputs. Then, strongly nonlinear or ultrasensitive functions create Boolean-like networks, which are the input ingredients, together with positive feedbacks, of multistability (Thomas, 1998; Ferrell, 2012), which are themselves the basic components of cellular decision making, differentiation and multicellular systems. Transfers of information are obvious in all these recipes. For example the dynamic cooperativity of slowly relaxing macromolecules such as glucokinase, corresponds to a transfer of information through time since the enzyme remembers the shape of the substrate bound in the recent past (Rabin, 1967). In the phenomenon of multimeric cooperativity, there is a transfer of information through space between the different stereochemically linked subunits. Strikingly, this latter mode of nonlinear response is obtained in subsystems at equilibrium, highlighting the possibility of conversion postulated above between visible organization and hidden negentropy. This type of cooperativity relies on the existence of highly preorganized macromolecules,

typically resulting from the storage of information progressively optimized along generations. Beside the popular case of hemoglobin oxygenation, equilibrium cooperativity is in fact widespread in biochemistry. For example, transcription factor (TF) dimerization is a simple and typical generator of nonlinearity responsible for gene regulatory network multistability (Michel, 2010). The fact that near all TFs have been selected to be active only as dimers is certainly not fortuitous. The explanation often given is that TF hetero-dimerization allows to integrate multiple signalling pathways, but this role could not be the main one, since homodimers remain numerous in the cell and are likely to have appeared first, before gene duplications and TF family diversification. The essential role of TF dimerisation could in fact be that it provides a natural mechanism to eliminate microstates: those made of DNA bound by TF monomers. This simple fact is sufficient to generate nonlinearity, indispensable to design conditional memory circuits (Nicol-Benoît et al., 2012). The need for nonlinearity is basically related to integrative networks. To illustrate this principle in the field of gene regulatory networks, it is clear that the cell-type specificity of gene expression (such as that of the growth hormone in somatotroph pituitary cells) cannot be dictated by a single TF, because the problem of cell-type specificity would just translate to this TF. Instead, specificity is generated by a combination of TFs, because a general way to solve the question of the regulation of a lot of parameters by a limited number of actors is to have recourse to combinatorials. To ensure the "unlocking" or threshold effect of the full TF combination on switching the target gene on, transcriptional activity should not be simply proportional to the number of TFs bound to the promoter (linear), but should be much more than additive (strongly nonlinear, sigmoidal, S-shaped or cooperative). In this way, the same TFs could participate to different combinations. For example, the prolactin and growth hormone genes are active in different pituitary cells, prolactotroph and somatotroph respectively, although their TF combination share common TFs reflecting their embryonic origin, including Pit1 and Ptx1 present in all the cells deriving from Rathke's pouch, the phylogenetic and embryonic ancestor of the pituitary gland. Their differential expression is due to additional TFs differentiating the combinations.

The notion of complexity often associated with life can be misleading because complex systems should not be understood as necessarily made of a large number of components, as illustrated by parasites whose apparent complexity tends to decrease (Krakauer, 2011). Elementary, two-component systems such as glucokinase with glucose, or hemoglobin with oxygen, are small but complex since they have refined, intelligent concentration-dependent behaviours, resulting from a reduction of configurational entropy inscribed in the genome (Michel, 2011). Conversely, large dynamic networks cannot be living if their numerous nodes obey only to merely follow linear interactions, since nonlinearity is necessary to give rise to life.

### **Generalization: the organizational potential of positive feedbacks in open systems**

Cells, surrounded or not by semi-permeable membranes (Trevors and Pollack, 2005), are open systems (Trevors, 2010). This property is an unescapable condition for life.

#### ***Nonequilibrium***

The importance of nonequilibrium in spontaneous organization has been shown for physical systems and extended to life (Nicolis and Prigogine, 1977). A direct illustration of nonequilibrium is the permanent birth and death of individual organisms. The robustness of the global life system contrasts with the perishability of its members, in the same manner that mRNA and protein molecules should be continuously degraded and resynthesized in the cell. In this respect, life is more characterized by its immaterial plan of action, than by its material substance. It is remarkable that the only persistent molecule throughout cellular lifespan is DNA, which can be marginally repaired but is not replaced, contrary to all the other cellular components. These permanent turnovers allow the multistability of biochemical networks and the shaping of the epigenetic landscape of Waddington (Ferrell, 2012; Nicol-Benoît et al., 2012). Multistability can emerge only out of equilibrium whereas at equilibrium, only one final state is possible when starting from the same ingredients.

#### ***Positive feedbacks***

It is a commonplace that (i) feedbacks are transfers of information and that (ii) injecting information in a system allows to increase its organization. The pivotal importance of positive feedbacks for breaking



symmetry holds at different levels of complexity, from molecular deracemisation providing the substrates for synthesizing homochiral macromolecules (Wattis and Coveney, 2005; Viedma, 2007), to cellular differentiation and social education. The capacity of asymmetrization of positive feedbacks is particularly well illustrated by the in vitro process of "protein misfolded cyclic amplification" (PMCA) set up to amplify small amounts of scrapie Prion proteins (PrP)(Morales et al., 2012). It is also involved in crystallisation, a phenomenon more closely related to life than it appears (Monod, 1972), in which the structure initiated by certain conformers favours their own recruitment. Positive feedbacks are obvious in self-templating phenomena such as the propagating and evolving Q $\beta$  replicase system (Otsuka and Nozawa, 1998) and amplification-selection in general (Dewey, 2000). Positive feedbacks are sometimes hidden behind the apparent complexity of phenomena, but careful inspection shows that they are rarely absent from self-organization mechanisms, including the non-monotonic patterns generated by reaction diffusion and Turing bifurcations (Turing, 1952). Life upgrading that occurred between unicellular organisms and metazoans, also required positive feedbacks. Multiple and specialized cell types reflect the multistability of a biochemical regulatory network and are generated from the same genome by successive splitting events (Foster et al., 2009; Ferrell, 2012) requiring positive feedbacks (Kaufman et al., 2007). The positive feedback of Brillouin has also such a role, by splitting matter into inanimate and living forms. It predicts the indefinite upgrading of life, necessarily associated to dissipation. Intense dissipation is envisioned here as a by-product of self-sustained positive feedbacks, whereas it is considered as a driving force in the currently debated theory of maximum entropy production, assumed to govern the evolution of physical-chemical systems out of equilibrium, including life but not specific to life (Dewar, 2009; Volk and Pauluis, 2010; Ross et al, 2012).

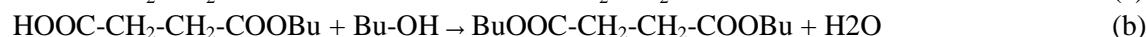
### Priming the cycle of Brillouin

The definition of life is a source of interminable controversy in the absence of a theory about the nature of living systems (Cleland and Chyba, 2002). Information storage, whatever its molecular modes, is proposed here to be a fundamental principle satisfying  $\Delta(S-N) \geq 0$ . But unfortunately, the initialization of the cycle of Brillouin is by essence refractory to experimentation, since this activity is specific to intelligent designers with plenty of scientific knowledge and as such, will be of little help to solve the fundamental question of the initial, spontaneous priming of the cycle. Experiments can allow to verify the capacity of positive feedbacks out of equilibrium to generate secondary forms of intelligence and self-learning, and will certainly constitute a keystone of synthetic life; but by definition, an experimenter belongs to a previously established information retrieval system. The same problem of an anterior priming of the cycle of Brillouin holds for the seeding by preexisting life in the panspermia hypothesis. Alternatively, it could be tempting to look for information-managing systems in alternative forms of life that could have independently arisen, but this strategy is also problematic. Indeed, it is likely that the first onset of life in a given planet precludes any chance of novel life emergence on the same planet, through evolutionary competition or simply by mineralizing the prebiotic organic soup. A first step to evaluate the mode of initiation if the cycle of Brillouin would be to look for: (i) natural cases of non-programmed self-perpetuating positive feedbacks such as PrP propagation and (ii) purely chemical cooperative phenomena.

The capacity of positive feedbacks to amplify initial fluctuations is well recognized but to be amplifiable, the amplitude of these fluctuations should be high relative to the size of the system. This could be achieved through scale reduction of encapsulated systems near the limit of validity of the second law, to avoid the mutual inhibition between conflicting conformers. Considering again the example of prion amplification (resembling an autonomous parasitic alien), the resistance to sporadic Creutzfeldt-Jacob disease of persons heterozygous for the 129th amino-acid of PrP (Alperovitch et al., 1999) illustrates such a feedback inhibition. The problem raised by too faint spontaneous initial partitions has been examined in the case of deracemisation and crystallisation. One tridimensional configuration can be naturally more prone to self-templating and impose its shape on the other ones, as observed for scrapie PrP(Sc) compared to properly folded healthy PrP(C) (Colby and Prusiner, 2011).

Stored information optimizes molecular cooperativity, that is in turn necessary for subsequent information retrieval, which explains the gradual complexification of life. But the first steps of negentropy storage remain an open question, that would be partially solved by proving the existence of

abiotic molecular cooperativity, since the activities of information retrieval and archiving are themselves the products of previous nonlinear activities. These behaviors could result from fortuitous specific binding or intramolecular transitions. Contemporary equilibrium cooperativity could have progressively arisen by optimization of naturally occurring cooperative phenomena and it would be fundamental to identify initial, non-encoded nonlinear behaviours. Minimal forms of equilibrium cooperativity can already exist for relatively simple molecules, which can respond to environmental variation and involve different kinds of intramolecular transfers of information. As an example, let us consider the chemical case of the two-step esterification of succinic acid by butanol into dibutylsuccinate:



Succinic acid initially displays two carboxy binding sites for the nucleophilic butylate ligand BuO- with exactly the same affinity. However, in the second reaction step, the binding constant of reaction (b) cannot be the same as reaction (a) for the unliganded succinic acid because of a change in the intramolecular electronic structure and then a still larger change in the solvation of the monoester as compared to the initial acid. This example is a primitive version of cooperativity in which the asymmetric electronic states of partially liganded succinic acid, could be similar to the hierarchical binding cooperativity of hemoglobin (Michel, 2008) and play the role of large scale tridimensional change. It would be interesting to determine if cooperativity is negative or positive in this precise case, but one cannot exclude that situations of positive cooperativity appear in relatively simple molecules.

### Piling-up layers of emergence

The visionary perception of Boltzmann shed a new light on the notion of emergence between the different levels of matter organization. Indeed, Boltzmann's statistics developed for discernable particles are very efficient for describing the macroscopic world and independent of quantum statistics established later. As a matter of fact, the behaviour of a monoatomic gas can be determined with an extreme degree of precision by modeling atoms as ordinary hard spheres, without regard to their quantum components. Life is also a higher order level of emergence, that will eventually be followed by still higher order levels such as synthetic life. A general rule is that when the combinatorial limit of a given level of organization is reached, then a new layer of information encoding emerges. This phenomenon is already perceptible at our scale. At the subcellular level, biochemical systems can self-organize through simple statistical recipes owing to the capacity of asymmetric macromolecules to eliminate microstates (Michel, 2011). The resulting nonlinear relationships allow the genesis of network multistability, that is itself the basis of cellular differentiation etc. Once the cycle of Brillouin is primed, the different forms taken by life are just a matter of circumstances, of chance and of tinkering (Jacob, 2001). The quasi-universal propensity of matter to self-organize does not contradict the second law of thermodynamics but reveals an intriguing mode of universe maturation through subsystem correlation and information storage. Beyond its current use in evolution dynamics, information theory could be extended as a founder thermodynamic principle of life.

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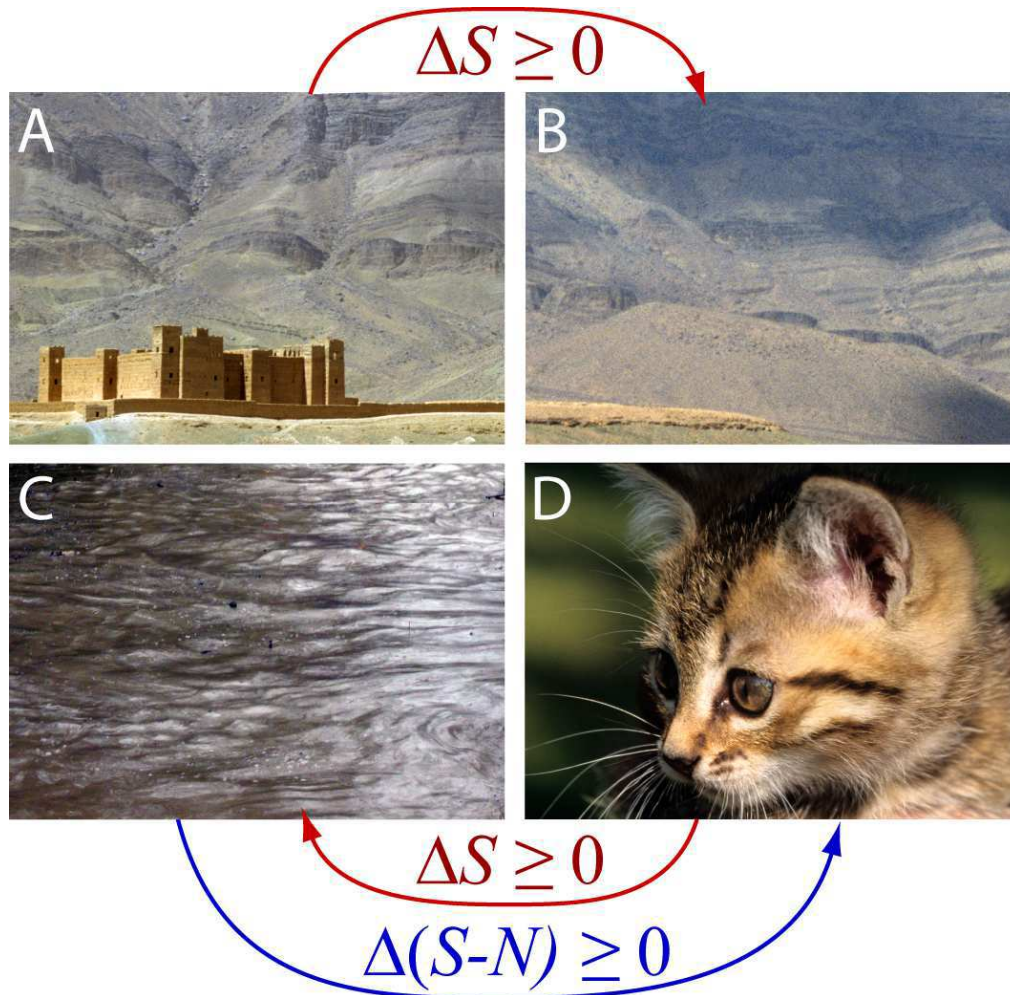
### References

- Alperovitch A, Zerr I, Pocchiari, M, Mitrova E, de Pedro Cuesta J, Hegyi I, Collins S, Kretzschmar H, van Duijn C, Will RG (1999). Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease. *Lancet* 353:1673–1674
- Avery, J (2003). *Information theory and evolution* (Singapore).

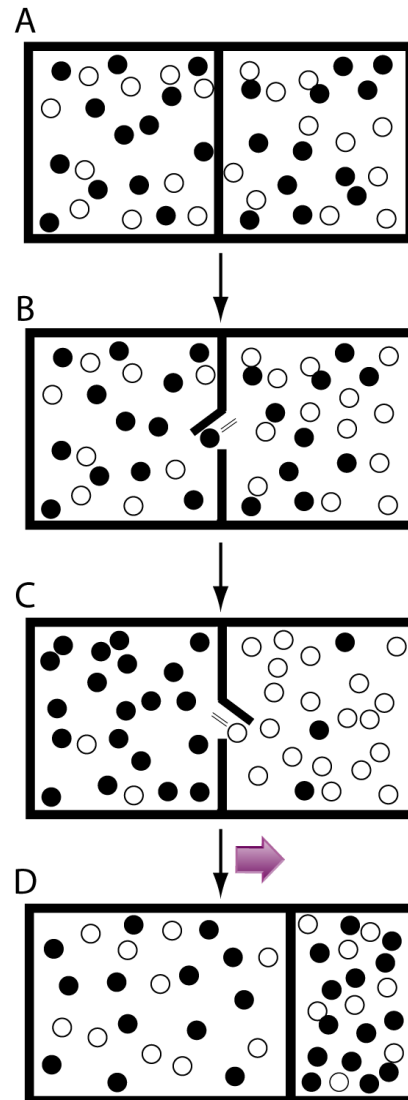
- Avery, OT, Macleod, CM, McCarty, M (1944). Studies on the chemical nature of the substance inducing transformation of pneumococcal types: Induction of transformation by a desoxyribonucleic acid fraction isolated from *Pneumococcus* type III. *J Exp Med* 79:137–158
- Brillouin, L (1949) Life, thermodynamics, and cybernetics. *Am Sci* 554–568.
- Brillouin, L (1950) Thermodynamics and information theory. *Am Sci* 594–599.
- Brillouin, L (1953) The negentropy principle of information. *J Appl Phys* 24:1152–1163.
- Brillouin, L (1956) *Science and Information Theory* (New York).
- Church GM, Gao Y, Kosuri S (2012) Next-generation digital information storage in DNA. *Science* 337:1628.
- Cleland CE, Chyba CF (2002) Defining 'life'. *Orig Life Evol Biosph* 32:387–393.
- Colby DW, Prusiner SB (2011) Prions. *Cold Spring Harb Perspect Biol* 3:a006833.
- Courseaux A, Nahon JL (2001) Birth of two chimeric genes in the Hominidae lineage. *Science* 291:1293–1297.
- Coveney PV, Highfield R (1990) *The arrow of time: A voyage through science to solve time's greatest mysteries*. Allen WH. Virgin Books
- Crick F (1970) Central dogma of molecular biology. *Nature* 227:561–563.
- Dewar RC (2009) Maximum entropy production as an inference algorithm that translates physical assumptions into macroscopic predictions: Don't shoot the messenger. *Entropy* 11:931–944.
- Dewey TG (2000) Information dynamics of in vitro selection-amplification systems. *Pac Symp Biocomput* 602–613.
- Elitzur AC (1994) Let there be life. Thermodynamic reflections on biogenesis and evolution. *J Theor Biol* 168:429–459.
- Ferrell JE Jr (2012) Bistability, bifurcations, and Waddington's epigenetic landscape. *Curr Biol* 22: R458–466.
- Foster DV, Foster JG, Huang S, Kauffman SA (2009) A model of sequential branching in hierarchical cell fate determination. *J Theor Biol* 260:589–597.
- Gibbs JW (1878) On the equilibrium of heterogeneous substances. *Transactions of the Connecticut Academy of Arts and Sciences* 3: 108–248; 343–524.
- Harper M (2009) The replicator equation as an inference dynamic. *arXiv:0911.1763*.
- Hartley RVL (1928) Transmission of information. *Bell System Technical Journal* 7:535–563.
- Jacob F (2001) Complexity and tinkering. *Ann N Y Acad Sci* 929:71–73.
- Jaynes (1957) Information theory and statistical mechanics. *Phys Rev* 106:620–630.
- Jevons WS (1877) Theory of probability. In *The Principles of Science* 224–225.
- Kaufman M, Soulé C, Thomas R (2007) A new necessary condition on interaction graphs for multistationarity. *J Theor Biol* 248:675–685.
- Koonin EV, Wolf YI (2009) Is evolution Darwinian or/and Lamarckian? *Biol Direct* 4:42.
- Krakauer DC (2011) Darwinian demons, evolutionary complexity, and information maximization. *Chaos* 21:037110.
- Landauer R (1961) Irreversibility and heat generation in the computing process. *IBM Journal of Research and Development* 5:183–191.
- Landauer R (1996) The physical nature of information. *Physics Letters A* 217:188–193.
- Lebowitz JL (1993) Boltzmann's entropy and time's arrow. *Physics Today* 46:32–38.
- Libby E, Perkins TJ, Swain PS (2007) Noisy information processing through transcriptional regulation. *Proc Natl Acad Sci USA* 104:7151–7156.
- Maestre J, Tchénio T, Dhellin O, Heidmann T (1995) mRNA retroposition in human cells: processed pseudogene formation. *Embo J*. 14:6333–6338.
- Marlière P, Patrouix J, Döring V, Herdewijn P, Tricot S, Cruveiller S, Bouzon M, Mutzel R (2011) Chemical Evolution of a Bacterium's Genome. *Angewandte Chemie International Edition* 50:7109–7114.
- Michel D (2008) An alternative theoretical formula for hemoglobin oxygenation. *Eur Biophys J* 37:823–827.
- Michel D (2010) How transcription factors can adjust the gene expression floodgates. *Prog Biophys Mol Biol* 102:16–37.
- Michel D (2011) Basic statistical recipes for the emergence of biochemical discernment. *Prog Biophys Mol Biol* 106:498–516.

- Michel D, Chatelain G, Mauduit C, Benahmed M, Brun G (1997) Recent evolutionary acquisition of alternative pre-mRNA splicing and 3' processing regulations induced by intronic B2 SINE insertion. *Nucl Acids Res* 25:3228–3234.
- Miller SL, Urey HC (1959). Organic compound synthesis on the primitive earth. *Science* 130:245–51.
- Monod J (1972) *Chance and Necessity* (Mass Market Paperback).
- Morales, R, Duran-Aniotz C, Diaz-Espinoza R, Camacho MV, Soto C (2012) Protein misfolding cyclic amplification of infectious prions. *Nat Protoc* 7:1397–1409.
- Nicol-Benoît F, Le-Goff P, Le-Dréan Y, Demay F, Pakdel F, Flouriot G, Michel D (2012) Epigenetic memories: structural marks or active circuits? *Cell Mol Life Sci* 69:2189–2203.
- Nicolis G, Prigogine, I (1977) *Self-organization in nonequilibrium systems: from dissipative structures to order through fluctuations* (Wiley).
- Nunberg JH, Kaufman RJ, Schimke RT, Urlaub G, Chasin LA (1978) Amplified dihydrofolate reductase genes are localized to a homogeneously staining region of a single chromosome in a methotrexate-resistant Chinese hamster ovary cell line. *Proc Natl Acad Sci USA* 75:5553–5556.
- Otsuka J, Nozawa Y (1998) Self-reproducing system can behave as Maxwell's demon: theoretical illustration under prebiotic conditions. *J Theor Biol* 194:205–221.
- Pulselli RM, Simoncini E, Tiezzi E (2009) Self-organization in dissipative structures: a thermodynamic theory for the emergence of prebiotic cells and their epigenetic evolution. *BioSystems* 96:237–241.
- Rabin BR (1967) Co-operative effects in enzyme catalysis: a possible kinetic model based on substrate-induced conformation isomerization. *Biochem J* 102:22C–23C.
- Ricard, J. (2004). Reduction, integration and emergence in biochemical networks. *Biol Cell* 96, 719–725.
- Ricard J (2006) *Emergent collective properties, networks, and information in biology* (Elsevier).
- Ross J, Corlan AD, Müller SC. (2012) Proposed principles of maximum local entropy production. *J Phys Chem B* 116:7858–7865
- Rothstein J (1951) Information, measurement, and quantum mechanics. *Science* 114:171–175.
- Sagawa T, Ueda M (2012) Nonequilibrium thermodynamics of feedback control. *Phys Rev E Stat Nonlin Soft Matter Phys* 85:021104.
- Schrödinger E (1943) *What Is Life?*
- Shannon CE (1948) A mathematical theory of communication. *Bell Syst Tech J* 379–423 and 623–656.
- Szilard L (1929) Über die Entropieverminderung in einem thermodynamischen System bei Eingriffen intelligenter Wesen. *Zeitschrift Fur Physik* 53:840–856.
- Szilard L (1964) On the decrease of entropy in a thermodynamic system by the intervention of intelligent beings. *Behav Sci* 9:301–310.
- Thomas R (1998) Laws for the dynamics of regulatory networks. *Int J Dev Biol* 42:479–485.
- Trevors JT (2010) Generalizations about bacteriology: thermodynamic, open systems, genetic instructions, and evolution *Antonie Van Leeuwenhoek* 97:313–318.
- Trevors JT, Pollack GH (2005) Hypothesis: the origin of life in a hydrogel environment. *Prog Biophys Mol Biol* 89:1–8.
- Turing AM (1952) The Chemical basis of morphogenesis. *Philos Trans Roy Soc B* 237:37–72.
- Viedma C (2007) Chiral symmetry breaking and complete chiral purity by thermodynamic-kinetic feedback near equilibrium: implications for the origin of biochirality. *Astrobiology* 7:312–319.
- Volk T, Pauluis O (2010). It is not the entropy you produce, rather, how you produce it. *Philos Trans R Soc Lond B Biol Sci.* 365:1317–1322.
- Waddington CH (1952) Selection of the genetic basis for an acquired character. *Nature* 169:625–626.
- Wang GM, Sevick EM, Mittag E, Searles DJ, Evans DJ (2002). Experimental demonstration of violations of the second law of thermodynamics for small systems and short time scales. *Phys Rev Lett* 89:050601.
- Wattis JAD, Coveney PV (2005) Symmetry-breaking in chiral polymerisation. *Orig Life Evol Biosph* 35:243–273.

## Figures



**Figure 1.** Illustration of the apparently paradoxical thermodynamic behaviour of life. Structuring of soil particles into a castle (A) or a pile (B). Arrangement of organic molecules into an isotropic solution symbolizing an organic soup similar to that of the Miller's experiment (C) or an animal, a masterpiece of organization (D). In absence of life, the second law predicts spontaneous evolution from (A) to (B) and from (D) to (C), that is to say towards higher entropy. But accumulation of "negentropy" ( $N$ ) by injection of information, can increase its organization without modifying the second law (bottom arrow). This conversion of information into negentropy can be considered as a hallmark of living systems and the accumulation of information is proposed to proceed through the positive feedback of Brillouin.



**Figure 2.** An energy extraction machine realisable only if a Maxwell's demon can operate (which is not the case). Two equivalent compartments containing moving particles with high (black) or low (white) energy, are separated by a wall (A) into which a door can be opened. If the demon opens the door only to let the black particles to go from right to left (B) and the white particles in the opposite direction (C), then, an asymmetric distribution (of lower configurational entropy) is obtained. This provides work due the selective dilatation of the left compartment when transforming the separating wall into a piston (D).