BIOLOGICAL ORGANIZATION AND ANTI-ENTROPY[1]

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Abstract

This paper proposes a systemic perspective for some aspects of both phylogenesis and ontogenesis by expressing biological organization in terms of "anti-entropy", a notion to be defined below and which conceptually differs from the common use of "negative entropy". To this purpose, we introduce two principles, in addition to the thermodynamic ones, which are (mathematically) compatible with traditional principles but which have no meaning with regard to inert matter. A traditional balance equation for the metabolism will then be extended to the new notion as specified by these principles. We examine far from equilibrium systems and we focus in particular on the production of global entropy associated to the irreversible character of the processes. A close analysis of anti-entropy will be performed from the perspective of a diffusion equation of biomass over "complexity" and, as a complementary approach and as a tool for specifying a source term, in connection to Schrödinger's method regarding his equation in the field of Quantum Mechanics. We borrow only the operatorial approach from this equation and do so using a classical framework, since we use real coefficients instead of complex ones, thus outside of the mathematical framework of quantum theories. The first application of our proposal is a simple mathematical reconstruction of Gould's complexity curve of biomass over complexity as it applies to evolution. We then present, based on the existence of different time scales, a partition of ontogenetic time, in reference to entropy and anti-entropy variation. On the grounds of this approach, we analyze the metabolism and scaling laws. This allows to compare various relevant coefficients appearing in these scaling laws, which fit empirical data. Finally, a tentative and quantitative evaluation of complexity is proposed, also in relation to some empirical data (caenorhabditis elegans).

1. **Introduction**

The issue of biological organization, of its emergence, its evolution and of its sustainability has been approached from widely varying perspectives: molecular biology, genetics, open dynamical systems far from equilibrium, etc. One of the aspects which remain the most controversial is the thermodynamic one: biological organization, beyond the molecular level, will be interpreted here in terms of "anti-entropy", a concept which is not proper to (thermo-)dynamics, where entropy is defined, statistically speaking, using a distribution of probabilities and, macroscopically speaking, according to the direction of heat exchanges. Note that the notion of "negative entropy" is the object of debates between several authors among whom we find Schrödinger, Pauling, Brillouin, Atlan, Nicolis and Prigogine. We will basically depart from this type of discussion, by attempting to introduce a different

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perspective partly inspired by Quantum Mechanics (but not reduced to its terms, see §. 4 and 8), and a method of approach that are, in our view, closer to the phenomenology of life and its proper observables.

1.1 Schrödinger and negative entropy as organization

We will use as starting point Schrödinger's informal and original remarks concerning entropy [Schrödinger, 1944]. Schrödinger's short text is often quoted for its first part, which was quite innovative at the time but is now obsolete. In that part of the text, he proposed to apply the notion of "code-script", even that of program, to chromosomes. Such computational views of the genome have now been made obsolete by many analyses: a synthesis of recent overviews and critiques may be found namely in [Fox Keller, 2003] and many others (see also [Longo, Tendero, 2007] for a discussion and references). It must be noted, however, that the notion of program was new at the time, just as was cryptography, the theory of "coding". Moreover, a Laplacian deterministic viewpoint dominated the period's genomics, and continued to do so for a long time, yet, it had never been explained with such clarity as it had been with Schrödinger. This great physicist, had at least understood the consequences of this application of the discrete symbolism of formal calculus to nature: "It is these chromosomes that contain in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state. Every complete set of chromosomes contains the full code. In calling the structure of the chromosome fibers a code-script we mean that the all-penetrating mind, once conceived by Laplace… could tell from their structure whether the egg would develop, under suitable conditions, into a black cock or into a speckled hen… They are the law-code and executive power… they are architect's plan and builder's craft in one" (pp 22-23).

Since the success of the genome project and the decoding of the DNA of several animal species, we have at last arrived to the position of Laplace's God but, unfortunately (?), without the associated predictive power; the least we can say is that we lack the "compiler" and the operating system, even the knowledge of the "executive power". Or maybe is it a case of insufficient knowledge of the *global structure* within which this discrete sequence operates, a sequence apparently so symbolic and computational, yet embedded in the very complex organization, the cell or even the organism, (re-)acting on it?

This brings us back to chapter IV of Schrödinger's book where he will "… try to sketch the bearing of the entropy principle on the large-scale behavior of a living organism - forgetting at the moment all that is known about chromosomes, inheritance, and so on…" From this premise, Schrödinger develops considerations that are as preliminary as audacious and that are based on a view of the organism as a whole. His idea is that what counts for a living organism is its organization and that the problem which poses itself is not only its establishment (the formation of "order based on disorder"), but also its maintenance ("order based on order"). He emphasizes the importance, still unclear today, of the acquisition of organization as *negative entropy*, including by means of food. This acquisition will participate to the ongoing tension between the increase of entropy, specific to any irreversible thermodynamic process and generating disorder, and the maintenance of order.

It is both the formation and the maintenance of order, its continuous regeneration, that interest us and that we propose to frame '*in abstracto*' by means of a mathematical concept of anti-entropy, as "organization" or "biological complexity", specified by two new theoretical principles and used in a balance equation. Anti-entropy differs from what is usually meant by negative entropy in view of its characterization by proper formal principles, which extend (but are compatible with) the thermodynamic ones. This will be done independently of any causal analysis which would quite probably require unification with molecular approaches; but if we do not have (at least) two theories, with their own conceptual autonomy, there is nothing to unify.

Notions of negative entropy have been introduced on several occasions, both in physics and in biology. In general, they have been understood as a *decrease* of entropy, compensating the entropy increase, either within thermodynamic approaches or in reference to information theory and Shannon's entropy principle. *In a final section, sect. 8, we will discuss the relations of our approach to existing ones.*

Following Schrödinger's focus on the "large-scale behavior of a living organism", we propose a global view point, by an important change of observables and of parameters with respect to current physical theories. To briefly mention one of these changes, maybe our main contribution, we will examine the relationship between the evolution of the biomass and that of organization or complexity of organisms, as anti-entropy, by taking into account both the phylogenetic and the ontogenetic levels (we will see that this relationship corresponds to an analysis in terms of diffusion, but within a phase space which is uncommon for physics). This requires a (perhaps arbitrary, yet) rather precise quantification of phenotypic (or epistemic) complexity for a living organism and its use in balance and diffusion equations.

1.2 The theoretical autonomy of life phenomena and the methodological perspective

As a matter of fact, as for negative entropy, Schrödinger does not propose any specific and mathematically formalized principle, yet he shortly suggests that it should be understood in terms of Gibbs free energy, an idea that we will further develop (sect. 3). He also insists on the necessity of investigating statistical phenomena, these already being extremely important in physics for understanding thermodynamic entropy. These analyses could help establish correlations with physical theories, among which the bio-chemistry of macromolecules. In particular, he believes that it would be necessary to strive towards the unification of two "different mechanisms, which would enable orderly processes, a statistical mechanism producing order based on disorder and the new method, producing order based on order". And here lies, in our view, the complexity of biological phenomena: order as an *organized unity, differentiated and interacting, which creates and maintains itself.* From the seminal works of Prigogine and of several others on thermodynamics far from equilibrium and on self-organization (see [Nicolis, Prigogine, 1977], [Kauffman, 1993]) to the recent attempt in [Bailly, Longo, 2008]), which analyses structural stability as a coherence structure specific to an "extended critical situation", many tried to grasp these aspects of the complexity of living organisms (see sect. 8 for more references and comparisons). Concerning the second organizing mechanism ('order from order'), Schrödinger outlines the idea, which we have mentioned, according to which it would use the absorption of negative entropy from the

environment, particularly by food. We will not make any assertions concerning the relevance of this idea.

We will instead take a path which, without exploring the 'causes' – possibly molecular – will attempt to postulate and develop some new principles. These, as we already mentioned, could help to establish a, partly mathematical, conceptual framework for the analysis of the role of anti-entropy in the play between order and disorder within the living organism, starting at the level of the cell (which is, obviously, made up of molecules, in the same way as the classical or relativistic falling bodies are made up of quanta, in their own field: *unification* is indeed progressing today, but it is far from being accomplished[2]).

We will begin by a "principle of establishment/maintenance" of anti-entropy (sect. 2), which has no analogy (nor meaning, we believe) in current physical theories. We will consider this anti-entropy as a measurement of the organizational complexity of life phenomena; on such bases, we will outline a few mathematical consequences of this identification, which will be compared to empirical data. The relation of biological complexity or organization to a notion of anti-entropy, modulo a dimensional coefficient, will allow us to consider it as a component of a Gibbs free energy, which depends on entropy, in particular in a balance equation (sect. 3); we will thus decompose entropy in a positive and a negative part, our anti-entropy, of the same physical dimension.

By the addition of a new entropic principle in sect. 2, which is specific to life phenomena, and of its consequences on a metabolic balance equation, we will by no means change "the laws" of any physical theory, but "just" extend them by new principles. The limit case (the value 0 of the components of the "biological type") of the equations and the inequalities below brings us back to classical physical frameworks, of which these formulae are, therefore, nothing but a *mathematically compatible extension*. Yet, this will deeply modify the conceptual space (or the phase spaces) of the considered phenomena and their evolutions. The focus on some observables, which happen to be unusual from the point of view of current physical theories, and the compatible mathematical extensions are the core methodological issues in our approach.

As for the mathematics, Schrödinger's ideas will play an even more important role in the application we will make of his "wave equation". This will be used as a diffusion equation with real numbers coefficients, in contrast to Schrödinger's definition over the complex field, and it will be applied to a mathematical investigation of the diffusion of biomass over complexity, following Gould's analysis of evolution (sect. 4 and 5). Some applications of our approach to ontogenetic processes will be given in sect. 6 and 7. Comparisons with existing approaches to "negative entropy" and various analogies and differences w.r. to physics are presented in sect. 8.

2. Organization as anti-entropy: a few principles

From here onwards we will equally use the terms of anti-entropy $-S^-$ (a negative magnitude) and of complexity K, opposite to S^- (so $K = -S^-$); complexity K will thus be a positive

[2] Let's note, passingly, that even the most elegant *theoretical reduction*, that of thermodynamics to statistical physics, was accomplished when thermodynamics and its principles were already quite solid.

magnitude, a different observable from negative entropy, yet still with the dimension of an entropy. We will also be led to distinguish processes of complexification in the course of ontogenetic development (internal to the organism and strongly dependent on genetic determinations) from phylogenetic processes of complexification (apparently much more dependent on random phenomena and external conditions).

The initial situation (cell-egg in the first case, isolated bacterium in the other) will be characterized by a very small K (epistemic) complexity (an anti-entropy approaching 0, therefore, from a global standpoint, a negligible one). So we then propose as *structural principle* for life phenomena during its organization and the maintenance of its organization the two following inequalities:

$$\mathbf{-K = S^- \leq 0} \quad \textit{and} \quad \mathbf{-dK/dt = dS^-/dt \leq 0} \qquad \mathbf{(1)}$$

$S^- < 0$ would correspond to "anti-entropy" associated to the system's internal organization processes (existence *and* establishment of order, respectively). For purposes of comparison with the physical situation and in order to include life phenomena, we will write the physical entropy corresponding to disorder as $S^+ > 0$. The relevance of this distinction will be clear later on, but let's mention for now that each component is associated to time constants that are sufficiently different to be separated according to the time scale considered (typically, the frequency of metabolic cycles vs. that of cellular reproductions).

The inequations in (1) thus express, in our view, the principles of the maintenance and tendency towards organization, respectively, within life phenomena, the only context, in our approach, where non null $K = -S^-$ would make sense. We will see that the canceling out to 0 of the second equation, $dS^-/dt = 0$, in presence of $S^- < 0$, can only concern the accomplished organism resulting from ontogenesis. This is never achieved in the case of phylogenesis, because, in principle and on average, following Gould (see sect. 4), we consider organisms as becoming increasingly complex, along evolution.

To remain closer to empirical reality, in the last part of this text we propose to consider the complexity K as composed of three main components which can either be of equivalent importance or which can, to the contrary, be clearly dominated by the one or the other according to the situation and we will write:

$$K = \alpha K_c + \beta K_m + \gamma K_f$$

α, β, and γ are the respective "weights" of the different types of complexity within the total complexity (we will have $\alpha + \beta + \gamma = 1$). These weights are likely to present temporal variations over the course of an ontogenetic development or of phylogenetic evolution.

K_c ("combinatorial" complexity) corresponds to the possible cellular combinatoric without any other consideration than the differentiations between cellular lineages as structuring element; indeed, inasmuch as cells from a same lineage are interchangeable, it is less their number which is important than the differentiations associated to the apparition of these lineages (although, we will see, their number does intervene). For example, we will consider the analysis of the embryogenesis of *Caenarhobditis Elegans* from this angle (see Appendix 2).

K_m ("morphological" complexity) is associated to the topological forms and structures which arise; it can in principle be mathematically evaluated from the way in which organic

structures of a same level of organization present themselves and combine. We will evoke in particular the properties of connexity and more or less fractal structures.

K_f ("functional" complexity) is, for its part, associated to the relationships established and to the fulfilled biological functions; metabolic relations, neuronal relations, interaction networks. In this regard, we will examine in particular the examples from the nervous system on the one hand, and from metabolic networks on the other. In [Edelmann, Tononi, 2000], a measure of biological complexity is proposed, as differentiation of the neural system, by an information theoretic approach, based on Shannon's entropy. This also gives a pure number and it may be seen as a component of our K_f.

This tripartition of K is more closely developped in sect. 7. It is greatly qualitative for the moment, but it should help to understand why an increase of K cannot be treated as a decrease of S^+, which is physical entropy : K is to be associated to biological organization, particularly to the *alternation of levels of organization*, and to the structuring specific to life phenomena (organites, cells, organs, multicellular biological organism), which is foreign to physical theorizations. As for the instauration of order, critical transitions, studied in physics and acting as starting point for our reflections on "extended criticality" in [Bailly, Longo, 2008], the establishment of coherent structures (percolation, the formation of a crystal, of a snowflake… [Binney et al., 1992; Kauffman, 1993; Jensen, 1998]), corresponds to a decrease of S^+, but there is nothing there to allow to speak as such of "different organization levels", nor of the K_c, K_m, K_f partition introduced above. Once more, the point of this paper is to propose a distinction between the decrease of a specific part of the entropy, due, for example, to a pre-existing physico-chemical potential (molecular interactions, typically, that become actual links because of a decrease of Brownian motion – crystals, snowflakes formation…) and the establishment of biological organization.

As we have already evoked earlier, it is necessary to distinguish the processes of ontogenesis from those of phylogenesis, which, although they may present formal similitudes, are not reducible to ones to the others. Recapitulation theory (ontogenesis would recapitulate phylogenesis) has not really been verified, even if embryos do present, at a given stage of their development, indubitable resemblances in their form and functioning (the morphological "bottleneck"). It indeed appears that the framing of random processes by strong internal (DNA) or external (cell, organism, ecosystem) determinations is very different in each of the two cases.

3 – Metabolism and anti-entropy

Living matter, beyond its reproductive, generative and plastic capacities, among many others, distinguishes itself by the existence of a metabolism which, on account of various exchanges with its environment and of its internal biochemical reactions, enables it to remain dynamically far from equilibrium and to structurally stabilize the "extended critical situation" which characterizes it. In this paragraph, we attempt to analyze, from a thermodynamic standpoint, the dynamics of this metabolism.

Although the approach proposed here takes on a character which heavily borrows from the concepts of physics, a biological specificity will appear from the moment we take into

account the evolutive autonomy of its organization and of the resulting "order", in the schematic and highly abstract form of anti-entropy.

So let's consider a system far from equilibrium and note as G its Gibbs free energy. In general, we have G = H –TS, where T is temperature, S is entropy and H = U + PV is the system's enthalpy (U is the internal energy, P and V are respectively pressure and volume). By definition, the R *metabolism*, when it exists (in living organisms for instance), corresponds to the difference between the fluxes of generalized *free energy* entering and exiting through the surface Σ:

$$R = \Sigma[J_G(x) - J_G(x+dx)]$$

So we have:

$$R = - \Sigma dx(divJ_G)$$

(in what follows, we will forget the element of volume Σdx, which we consider to be unitary).

Besides, the conservation equation (or the balance equation) is expressed in the general form:

$$-divJ_G = dG/dt + T\sigma$$

where G is an extended expression of Gibbs free energy and where σ represents the speed of production of entropy associated to irreversible processes.

So let's return to our distinction which, once more, has no reason to appear in current physical theories, proposing to decompose[3] the S entropy in the two different parts which are S^- and S^+. With these notations in mind, we then obtain from G = H –TS (see note[4]):

$$R = dH/dt - T(dS^-/dt + dS^+/dt) + T\sigma$$

Moreover, given the relationship between mass and energy, we have H = aM where M is the mass (and a is a coefficient which has the magnitude of a speed squared). So R can be rewritten, by highlighting four contributions to the metabolism: first, the variation of mass, the increase of organization, as a decrease of S^-, plus the tendency towards disorder resulting in the increase of S^+; then, and crucially, we add the production of entropy σ (its speed) due to the *irreversibility of the global process*. We thus have:

$$\mathbf{R = adM/dt - T(dS^-/dt + dS^+/dt) + T\sigma} \qquad \mathbf{(2)}$$

Equation (2) is the *fundamental equation* which will be the basis of the development of a great part of later discussions. Let's note that the inequalities in (1) are to be read as a "principle" which we propose for a theoretization of life phenomena that is to be *added* to physical (thermodynamic) principles, whereas (2) is a balance equation, based upon classical principles of conservation, yet extended to S^-. Note that the possibility to derive this equation, from the expression of G, is what forces us to consider biological organization, K, as given in terms of anti-entropy S^-, a notion with the same dimension as entropy.

Before examining the consequences of this, we will focus on a particularly important term of equation (2), Tσ, the inevitable production of global entropy associated to the irreversible character of the processes. More specifically, it is the speed of production multiplied by the temperature (σ obviously has the magnitude of an entropy applied to time, so Tσ is a power).

[3] This decomposition, $S = S^- + S^+$, is not relevant for purely physical phenomena, as, in theories of inert, $S^- = 0$, and remains thus specific to biological ones.

[4] In a footnote to [Schrödinger, 1944], Schrödinger proposes to analyze the negative entropy of which he speaks of as a form of Gibbs free energy G. In view of our decomposition of $S = S^- + S^+$, we consider G here as a "generalized" free energy. Of course, the metabolism R has the physical dimension of a power.

We will take into account the fact that, account taken of all irreversibilities, Tσ is associated to *all* processes at hand presenting such a trait, *including the variation of anti-entropy*, dS^-/dt. In a *spirit* that is close to those found in Prigogine's works, whose theorems we will not need to use however, the production of entropy, often considered as a "side effect", in particular near equilibrium, becomes for us one of the main analytical tools. The idea is that in very complex far from equilibrium dynamics, Tσ in provides a "synthetic view" of the global dissipative process : as we said, it is a correlated to *all* ongoing irreversible processes and it is one of the few observables with this characteristic of "globality".

In the sequel, another relevant observable for our analysis will be the mass (global, M, the biomass, or the individual mass, W, the "weight", see 6.1). Let's then analyse Tσ in its relation to the mass. Now, Tσ is a power and corresponds, thus, to the product of forces by fluxes (of matter, of energy – chemical, for instance – etc.; a flux is proportional to a force, thus to a mass), and is hence proportional to a mass squared. It can therefore be written, up to a coefficient ζ_b and a term $T\sigma_0$ as:

$$\mathbf{T\sigma \approx \zeta_b M^2 + T\sigma_0} \qquad \mathbf{(3)}$$

$\boldsymbol{\zeta_b}$ is therefore a constant which depends only on the global nature of the living entity under study and it is 0 in absence of living matter. We will discuss, for example, the different issues of the biomass and of the mass of an organism. $T\sigma_0$ corresponds to the limit of a purely physical irreversible functioning, that is, one where the *living* mass, as part of M, would be null (thus $\boldsymbol{\zeta_b = 0}$). This limit situation does not apply in biological world where such mass is at least equal to that of the elementary biological entity, the isolated bacterium, but it may be relevant for a dead organism, with a decomposing chemical structure.

To use this equation, we will inspire ourselves again from Schrödinger but, this time, regarding his physical methodology and his famous equation from an operational viewpoint.

We will focus on equations (2) and (3), because we will consider them to be specific to life phenomena, as they contain terms that *cancel out* when we pass from the description of life to physical phenomena. In (2), it is obviously with regard to S^- and to its variation in relation to time; in (3) the main term belongs to our approach to life phenomena and we will give an important role to this equation, a sort of balance between global entropy and biomass. Once more, the inert would be a limit case, the null value of the observables relative to life (S^-, dS^-/dt and ζ_b). In short, we are "just" proposing a (mathematically compatible) *extension* of current physical theories, as our approach is not incompatible with them, just not reducible. To our physicalist friends in biology, we recall that the quantum field is not only irreducible, but also *incompatible* with the relativistic field – and conversely, so far.

Intermezzo: Schrödinger's equation and operators (recall)

One of Schrödinger's great ideas was the introduction of the "wave function" in quantum mechanics. Many aspects characterize the originality of this equation, which has changed the course of microphysics. In our approach, we will highlight here its *operational aspect* that later played a determinant role in quantum physics.

Schrödinger's view, at the time of his equation, centered around the wave function as a description of the quantum state. He came to substitute transformation *operators* to *measured quantities*, specific to the mechanics of classical particles.

To understand, *a posteriori*, this very audacious passage, we consider the following wave function, where **p** is the moment and E is the energy:

$$\Psi(\mathbf{x},t) = \exp(i(\mathbf{px} - Et)/h)$$

(it is a solution of Schrödinger's equation for an isolated quantum particle but... this does not matter here).

Since **p** and E appear as coefficients of space **x** and time t, respectively, it is very easy to see that multiplying a spatio-temporal evolution function (this function in particular) by **p** or by E is equivalent to differentiating it with respect to **x** or t, that is $\partial/\partial\mathbf{x}$ and $\partial/\partial t$**,** respectively (up to a coefficient: i/h).

Thus, to these physical *quantities*, **p** and E, can be associated *differential operators*: the derivative with respect to space and time, respectively, the two parameters of physical evolution. Let's then consider the (classical) law of conservation (Hamilton's equation: total energy is the sum of kinetic energy and of potential energy):

$$E = K_E + P_E$$

More specifically, $E = \mathbf{p}^2/2m + V(\mathbf{x})$, where $V(\mathbf{x})$ is the pertinent potential[5].
Now, if we associate

$$\mathbf{p} \rightarrow -i\hbar\partial/\partial\mathbf{x} \equiv -i\hbar\mathbf{grad}$$

$$E \rightarrow i\hbar\partial/\partial t$$

and to space **x** the multiplication by **x** or by its functions, such as $V(\mathbf{x})$, we obtain Schrödinger's equation (ħ is Plank's h divided by 2π and $\partial^2/\partial\mathbf{x}^2$ is the usual laplacian operator Δ) :

$$i\hbar\partial\psi/\partial\mathbf{t} = -(\hbar^2/2m)\partial^2\psi/\partial\mathbf{x}^2 + V(\mathbf{x})\psi$$

($V(\mathbf{x})$ is the potential in x, but its expression is not important for the moment, we will return to this).

The operational association performed may be synthesized, very abstractly, as the application of Schrödinger's operator:

$$\mathbf{\hat{O}Sch} \equiv \{i\hbar\partial/\partial t = -(\hbar^2/2m)\partial^2/\partial\mathbf{x}^2 + V(\mathbf{x})\}.$$

We propose to follow, *mutatis mutandis*, a similar approach for the very different case we have at hand, relatively to temporal operationality in life phenomena. Let's also observe, following many others, that we can also understand Schrödinger's equation as a *diffusion equation*: it has its "parabolic" form (a quantity diffuses, over time, proportionally to a variation of its gradient in space, plus, if applicable, a source or sink term). It presents however two traits which are essentially different from classical diffusion equations: it operates on the field of complex numbers and not only on the field of real numbers, and the "diffusion coefficient" is itself complex. Let's note that by this approach, Schrödinger invented a phase space which was appropriate to the phenomenal domain which interested him. We will indeed take a similar approach, but basing ourselves however on diffusion laws and then justifying the result by a "Schrödinger-styled" method of operational transformations.

4 – The "diffusion" of biomass with respect to complexity

[5] In the case of the one-dimensional harmonic oscillator, we would have: $E = p^2/2m + kx^2/2$.

Let's attempt here to explain our strategy, even if it means anticipating certain results and making a few repetitions. Empirical data, to which we will return below, seem to indicate that the *qualitatively* representative graph of the evolutions of biomass in function of complexity takes on a half-Gaussian form. Now, we know that there is a relationship between this form and random processes as well as with solutions for diffusion equations. We will therefore write the corresponding equation which we also expect to be interpretable in all its terms from the biological standpoint. Once this stage has been reached, in view of introducing an operational representation, in accordance with what we consider to be an essential property of the temporality of life phenomena, we will look for the metabolism's relevant quantities to serve as foundation for such operators. To this end, we will follow a method which is similar to that which we have encountered to define **ÔSch**. Our purpose is of using them much more generally later on, by showing that their use may, indeed, characterize a diffusion process in the adequate space, based on the great generality of metabolic processes.

Let's now be more specific; we will first attempt to fulfill this program in the case of the evolution of biomass. Why give precedence to the case of biomass? Firstly, it deals with life phenomena as a whole without us needing at this stage to take into account the whole variety of its manifestations; then, and to return to the empirical bases which we mentioned earlier, it so happens that the works by S.J. Gould provide us, as we will see, with a starting point and with a very interesting work direction. We will see that the adequate spaces neither correspond with normal physical space, such as in classical physics, nor with the abstract Hilbert spaces of quantum mechanics, but are rather related to this new basic variable which is complexity K, associated to organization. We may call this complexity phenotypic or, more generally, *epistemic*, in contrapposition to the "objective" complexity of physico-chemical processses (see [Bailly, Longo, 2003] for more on this distinction).

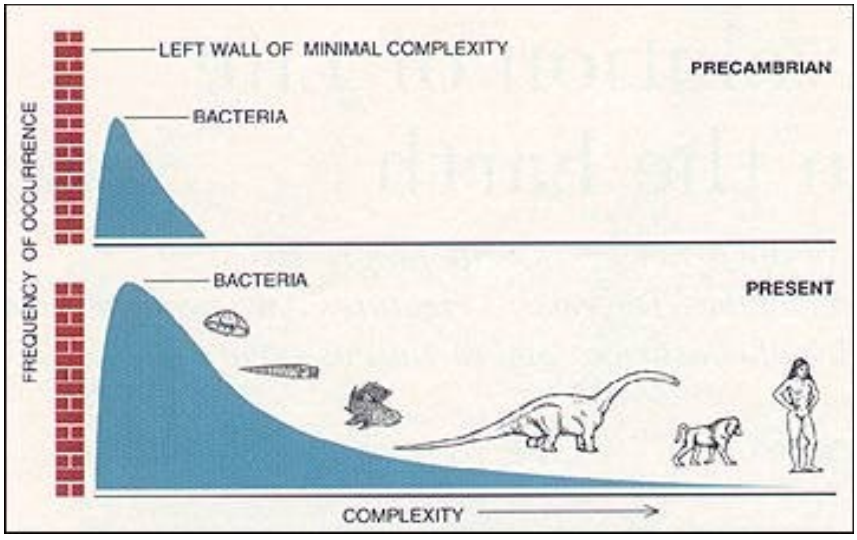
The analytical results will then enable us to return to a "diffusional" character for the basic equation in this new space which is specific to life phenomena. In order to establish these results, we will take inspiration from the aforementioned approach and from works by S.J. Gould, such as presented in [Gould, 1991]. In particular, it will be an issue of modeling two of the main aspects of such work: on the one hand, the idea of random processes of evolution in function of the complexity of life phenomena – and of the quasi-Gaussian aspect taken by the occurrence graph of biomass in function of this complexity (figures 1 and 1') – and on the other hand, that of the existence of what Gould calls a "left wall" which imposes itself upon these processes. This left wall expresses the impossibility of characterizing life phenomena below the elementary level of the bacterium. Random evolution then only takes place "towards the right", meaning in the direction of a higher epistemic complexity than that of the bacterium: in fact,

any random walk, bounded on one side, statistically progresses ("diffuses") in the direction opposite to the wall.

In other words, the global structure of diffusion is the average result of the local interactions, which transitively "inherit" the orientation due to the original symmetry breaking. In our case, where this breaking corresponds to the formation of the first bacteria, there can then be local

inversions of complexity, but, on average, it can only increase[6]. We are thus applying a general mathematical principle, largely applied in physics, over a non physical phase space.

FIGURES 1 AND 1' ([Gould, 1991the "frequency of occurrences" corresponds to our "biomass"):



Gould's drawing is based on a remarkable idea: the space of observable and parameters is given by the biomass and the "complexity". More precisely, it hints on how the biomass "diffuse over complexity, a rather original phase-space. Yet, it is a confusing hint because of its unclear reference to time. "Present" should be the instantaneous picture of the current situation: what are the dinosaurs doing there? An advantage of our mathematical approach will be to provide a consistent treatment of time as well (see figure 1b).

The idea is to define operators derived from equation (3) according to a real-numbers variant of Schrödinger's operatorial approach (over real numbers, in our case).

4.1 Dynamics and modeling

To propose an equation which interpolates, on the basis of general principles, paleontological data, we will use, as observables and reference parameters, the epistemic "density" of the biomass m, physical time t and relative epistemic complexity K: here lies our change of reference space where we will express m in function of t and of K. The isolated bacterium then corresponds to the origin ($K \approx 0$) and the existence of the left wall always imposes $K > 0$, which is consistent with our principle (1). The studied state function will therefore be chosen as the "density" of the biomass relatively to K and will be written m(t, K)

[6] To put it into biological terms, "the spreading of the curve can only be explained by the existence of the left wall and by the multiplication of species; the right part of the distribution is a *consequence* and not a cause of this spreading"… "the notorious progression of life throughout history is therefore a random movement introducing distance between organisms and their tiny ancestors, and not a unidirectional impulse towards a fundamentally advantageous complexity" [Gould, 1991]. Of course, we are only thinking here of biological evolution, while neglecting the last few thousands of years, the short history of humanity's invasion of the planet.

of which the integral over all accessible K's will give the temporal evolution of the overall biomass M(t). Time, of course, is an orthogonal dimension relatively to the plane of the figures above: its increase induces a deformation of the curve on this plane, just as in the passage, described by Gould, between the Precambrian time and today.

The dynamics involved and the aspect of the effects which it provokes (Gould's qualitative curve) lead us to propose to determine m(t, K), as a first attempt, by a diffusive equation with a source (a second approach to equation (4) below, inspired by Schrödinger's operator, will further justify and specify it). Indeed, one must take into account an irreversibility with regard to time, an expression stemming from a "random walk" as well as the fact that, by means of growth and genesis, the biomass tends to increase with time. The corresponding "diffusion" equation (which may be interpreted as a balance equation) will thus be written as:

$$\partial m/\partial t = D\partial^2 m/\partial K^2 + Q(t,K) \qquad (4)$$

D represents the "diffusion coefficient", associated to the random evolution process of this biomass density in terms of epistemic complexity K, and Q is the biomass's source term. The total biomass M(t) at time t will therefore be the integral in dK of m(t, K).

But… how may we justify this equation more specifically and give an expression to Q(t,K)? A Schrödinger type operational approach will enable us to derive this diffusion equation from general considerations made regarding the issue of the production of entropy in metabolic processes and will also enable to propose an expression for the Q(t,K) function.

So let's return to the metabolism equation (2). As we have already recalled, equation (2) in our far from equilibrium frameworks has enabled us to introduce the speed of entropy production σ, which we have then correlated, by means of equation (3), to the system's energy variation. The latter, let's recall, being proportional to the mass squared, takes the following form in the case of biomass, where M is now the total biomass (as we were saying, Tσ is a power and the coefficients must, of course, take it into account) :

$$T\sigma = \zeta_b M^2 + T\sigma_0$$

By analogy with what is done in quantum physics regarding energy, that is the association $E \rightarrow i\hbar\partial/\partial t$, it then does not seem artificial to put into relationship the speed of the production of entropy, which is related to the irreversible character of all processes, with the variation in relationship to time, which is also unidirectional, by means of the partial derivation operator $\partial/\partial t$. Once more, the analysis of the speed of entropy production, far from equilibrium, plays a very important role, from our point of view, one which is quite similar to that of the variations of energy close to equilibrium (see Sect. 3).

So let's set the correspondence - in the manner of Schrödinger, if we may allow ourselves such an abuse of language and… of dimension:

$$T\sigma \rightarrow \rho_b \, \partial/\partial t \, ,$$

where ρ_b is a dimensional coefficient (see appendix 1 for the dimensional analysis). Similarly as for ζ_b, also ρ_b is different from 0 only in presence of biological activity.

In the same order of ideas, now in analogy to $(\mathbf{p} \rightarrow -i\hbar\partial/\partial\mathbf{x})$ in quantum physics, let's then correlate the growing biomass with what may be considered to be its dual or its necessary complement, that is the organization of which it is the locus. Thus, we propose, for

K epistemic complexity, and by means of the $\partial/\partial K$ differential operator, the following association:

$$M \rightarrow \partial/\partial K \quad \text{(see Appendix 1)}$$

Of course, our parameters and observables as well as the constants (see below) have totally changed: entropy variation, multiplied by temperature, $T\sigma$, instead of physical energy; mass M instead of momentum (which is proportional to a mass, though) and, most of all, complexity K instead of space. From the formal point of view, and with regard to the physical Hamiltonian, $T\sigma$ then plays the role of energy (it is actually a power) and M plays the role of momentum p (M squared indeed intervenes in $T\sigma$, just as p does in E). Likewise, for Schrödinger, p is associated to the space x, as explained in the Intermezzo, under the form of $\partial/\partial x$, also in relationship to the duality, characteristic of quantum physics, which correlates momentum and position. In our approach, mass is associated to complexity, as the structural organization within which it develops, under the form of $\partial/\partial K$. As we will see below, this component disappears in the equation, exactly when there is only a growth of mass, without any change of organization – in the case of the free proliferation of bacteria, for instance.

In accordance with Schrödinger's approach then, the source term Q(t,K) may be considered as a "potential" and in our case expresses itself, up to a dimensional constant, by the simple multiplication by $T\sigma_0$, the source term, which is constant in relation to t and K. This gives us for Q(t,K) a linear expression in m, which we will write as $\alpha_b m$.. Intuitively, Q, representing a source term, must be compatible with the tendency towards free proliferation (reproduction) of organisms, which is roughly proportional to the number of existing organisms, therefore, to m (that is, linear in m, see also the following note).

By concluding with the introduction of the "diffusion coefficient", D_b, in epistemic complexity, and by posing $\alpha_b = T\sigma_0/\rho_b$ for the source term, we get an operator which takes the form of :

$$\mathbf{\hat{O}} \equiv \{\, \partial/\partial t = D_b \partial^2/\partial K^2 + \alpha_b \,\}$$

By using as state function, or "biological evolution function", the density m(t,K) over K, this operator corresponds to the equation:

$$\partial m/\partial t = D_b \partial^2 m/\partial K^2 + \alpha_b m \qquad (5)$$

Of course, α_b makes sense (is non zero) only in presence of non null biological activities ($\rho_b \neq 0$). In the case of the inert, one also has m(t,K) = 0. Observe finally that, w.r. to Schrödinger's operator, a crucial difference is given by the coefficients. These happen to be real numbers, not complex ones, as the latter contribute to produce the typical effects of Quantum Mechanics (superposition, among others).

To summarize, in the case of biomass, it was thus possible to associate operators to the relevant magnitudes and to thus obtain a dynamic equation. The recourse to Schrödinger's approach on the one hand justifies, by means of a different method, the same equation obtained as a diffusion, (4); on the other hand, it has enabled us to give an expression to Q(t,K), the source function of the dynamics. One of our concerns will now be to examine if, how, and with which results this approach may be applied and generalized to the other cases considered.

5. Phylogenetic aspect

We have thus proposed, for the density m of biomass, the evolution equation (5) on the epistemic complexity K, or, more explicitly:

$$\partial m/\partial t = D\partial^2 m/\partial K^2 + am(t,K) \qquad (5)$$

Let's recall that D represents the "diffusion coefficient" associated to the random evolution process of this biomass density over the epistemic complexity and that am(t,K) is the source term of the biomass (D will then have the magnitude of a squared complexity divided by a time value; am(t,K) is that of the mass density divided by a time value, so a is the reciprocal value of a time value). As intuitively considered above, this would amount to supposing that the proliferation speed ($\partial m/\partial t$) is proportional to the mass[7]. So a solution[8] to (5) would be written as (A is still a dimensional constant, a mass density multiplied by the square root of a time value):

$$m(t,K) = (A/\sqrt{t})\exp(at)\exp(-K^2/4Dt) \qquad (6)$$

To a constant biomass density $m = m_c$, we can thus solve in K to get $K(m_c,t)$, that is :

$$K^2\big|_{mc} = 4aDt^2 - 2DtLogt + 4Dt(LogA - Logm_c) \qquad (7)$$

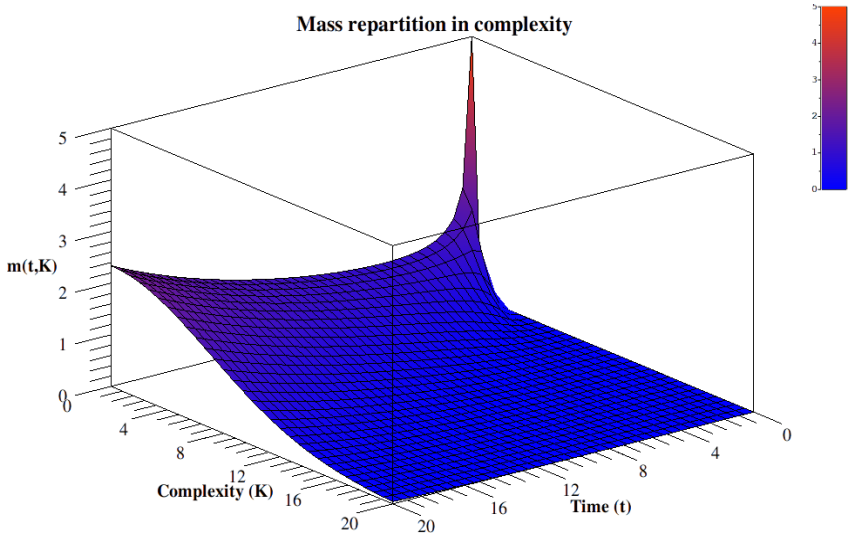
and for high values for time, the epistemic complexity would increase linearly in function of such time:

$$K(t\to\infty) \sim 2t\sqrt{(aD)} \qquad (8)$$

So, for a given biomass density, the epistemic complexity would not stop to increase (and anti-entropy would not stop to decrease: $dS^-/dt \sim -2\sqrt{aD}$). We could comment this by saying that evolutive processes tend towards a regular increase of the epistemic complexity of a given biomass.

It should be clear that our approach mathematically justifies Gould's approach, gives a source term and a consistent dependence on time, including the exponential free proliferation of bacteria in early times of life:

FIGURE 1b (courtesy of Maël Montevil):



[7] This hypothesis, to reiterate once again, is perfectly compatible with the analysis of the processes of free proliferation undergone by living matter. That is, with no constraints and without regard to complexity and its variations (so, for D = 0), it leads to an exponential increase in time (for example, in the case of the free reproduction of bacteria).

[8] Other solutions exist, but they do not answer to the constraints that are *a priori* implicit for the object we are examining here.

Let's recall in this respect that the "left wall" proposed by Gould for the evolution of the biomass with regard to complexity involves an asymmetry in the whole evolutive process, which is given by the form, asymptomatically exponential in t and Gaussian in K, of our m(t,K) function. As a mater of fact, for purely mathematical reasons, a random walk with a boundary produces an *oriented* diffusion. In our case, this introduces a bias in the variation that is available to selection. So, we obtain an increase, *on average*, in complexity and in mass with the progression of time as well as a (half) bell curve, in what concerns the ratio between the two. This seems to correspond well enough to the empirical evidence and it is contrast to the working hypothesis of the modern synthesis in theory of evolution. According to this hypothesis, the supply of variation, as purely and locally random, is not biased. That is, it was supposed that the variation in a trait is disributed uniformely, in all directions, and without bias around the current mean. As a matter of fact, a simple analysis of the "phylogenetic drift" in terms of random mutations, without principles such as those which we postulate, does not enable to deduce the asymmetry stressed here, following Gould. In fact, the random mutations could induce, at each moment of the evolution and on average, as great an increase as a decrease in epistemic complexity as well as an initially uniform distribution of complexity in relation to mass. Darwinian selection of the incompatible alone would not suffice to explain the overall increase of complexity, because "simpler" may also be compatible with the ecosystem (bacteria are still happily there), nor to explain the empirically observed distribution of biomass over complexity. On the other hand, the mathematical justification of asymmetry highlighted by Gould, and that we develop here, accounts for natural complexification: an asymmetry at the origin in the diffusion propagates by local interactions in the phase space. To conclude, it appears to us that these remarks are not necessarily in opposition to (neo-)Darwinian theories. In short, the *a posteriori* judgment that evolution complexifies organisms because more complexity provides a "selective advantage", is transformed (or, at least, enriched) by a mathematical *a priori* principle on the propagation of a symmetry breaking. Thus, our approach inserts (neo-)darwinian views within a framework where the structure of evolution is made (more) intelligible by being derived from general principles, among which the (in)equalities in (1) and (2), and by very solid methods (diffusion and operator-based approach). In particular, they give a mathematical foundation to the remarks, revisited by Gould and quoted in Sect. 4, remarks which, for many biologists, are at the center of the modern vision of evolution.

6. Ontogenetic aspect

6.1 Three characteristic times and four metabolic regimes

In the case of ontogenesis, the situation is different than that outlined for phylogenesis. Let's start by noting that *embryogenesis*, with the setting of the various functions and a (strong) increase of the complexity of the organism, is completed rather quickly, with a characteristic time which we will call τ_K, to produce an organism which continues to grow without necessarily diversifying further on.

There comes a moment, where the anti-entropy ($S^- = -K$) stops decreasing (or where the complexity K stops increasing) and where it stabilizes at the value at which the organization maintains itself (at the cost, of course, of the continuing energetic exchanges with the exterior

and of a consumed power P for reaching the final and relatively stable mass)[9]. Of course, the setting of the organization is practically over with (end of embryogenesis) a long time before the final mass is attained. Let's call W the individual mass[10] and τ_W the characteristic time necessary to reach the adult's mass (we will thus have $\tau_W >> \tau_K$).

In what concerns entropy S^+ related to aging, we will propose an exponential increase, with its own characteristic time:

$$dS^+/dt = S^+/\tau_{S+}$$

This increase corresponds, due to the nature of the exponential, to a cumulative effect, with no antagonism (see 6.2.1). The characteristic time τ_{S+} therefore refers to aging and consequently $\tau_{S+} >> \tau_W$ because the adult mass is reached far before biologically detectable aging begins.

These three characteristic times ($\tau_{S+} >> \tau_W >> \tau_K$) divide the evolution of the organism into the *four distinct periods* below, within which one or another of the relevant aspects is dominant (without excluding the others) : (2.1) establishment of organization (embryogenesis, with a τ_K characteristic time); (2.2) mass increase (τ_W) ; (2.3) adult life and, finally (2.4), aging (τ_{S+}).

We can therefore distinguish reduced and different forms for the metabolism's equation (2) in function of each of these periods:

(2.1) $R_1 \sim adW/dt - TdS^-/dt + T\sigma_1$ (the effect of S^+ remains negligible : embryogenesis)

(2.2) $R_2 \sim adW/dt + T\sigma_2$ (organization $K = -S^-$ no longer changes, the mass increase continues and the effects of aging remain negligible : childhood/adolescence)

(2.3) $R_3 \sim T\sigma_3$ (now the mass remains more or less constant and all is governed by exchanges with the environment which ensure structural stability: adulthood)

(2.4) $R_4 \sim -TdS^+/dt + T\sigma_4$ (the effect of aging starts to be felt and becomes predominant: old age ; it is even possible to add a negative adW/dt term, accounting for a possible loss of weight)

Let's summarize by observing that:

- (2.1) above is the ($dS^+/dt = 0$) case of equation (2) ;
- we go from (2.1) to (2.2), when there is no more increase of organization ($dK/dt = 0$);
- from (2.2) to (2.3), when there is no more increase of mass ($dw/dt = 0$) ;
- from (2.3) to (2.4), when the increase of internal entropy is no longer negligible possibly accompanied by a loss of weight.

It must also be noted that the (speed of the) production of entropy σ_i, for i = 1,...4, remains present. It could be relevant to consider it as being minimal in σ_3, at the adult stage – an age of relative "stationarity", but that would lead us to considerations regarding the applicability of Prigogine's "theorem of minimum entropy production" (see [Nicolis, Prigogine, 1977]), which does not affect the work done here.

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[9] For accounting such a qualitative situation, the simplest is to propose that the evolution of K is also governed by some logistic equation, such as $dK/dt = 1/\tau_K K(1-K/K_f)$ (see paragraph 6.2.1.)

[10] We called m the biomass density, M its integral (the overall biomass) and W the individual mass (or weight). The apparent inconsistency in names is due, in part, to the lack of more consistent letters, but also to the very different mathematical dynamics of these three entities. In particular, only W admits a notion of approximately "maximal" or adult mass to be associated to scaling laws; moreover, its growth is qualitatively given by the logistic function. None of these properties applies to the dynamics of m and M, which we previously described.

6.1.1 Remarks on aging

Without neglecting the genetic aspects of aging, which molecular theories often associate to the shortening of telomeres, we would like to emphasize the importance of this persistent production of entropy during all the stages of life and, particularly, during the last stages. It is a matter, we reiterate, of the internal entropy S^+ which has a physical nature (related to thermodynamic processes and to the exchange of matter and of energy) as well as of the (speed of) entropy production σ_i due to *all* irreversible processes, including the dS^+/dt variation of entropy and that specific to life phenomena, the *variation* of complexity $dK/dt = -dS^-/dt$. Now, in a monocellular organism, for which there are no stages 2.3 or 2.4, given that maturity normally triggers mitosis, the entropy produced is released in the exterior environment and there is practically no reason to speak of aging. On the other hand, in a metazoan, the entropy produced, under all of its forms, is also but inevitably transferred to the environing cells, to the tissue, to the organism. In particular, during the adult stage (2.3) and during aging (2.4) the σ_3 and, respectively, the S^+, σ_4 components, eminently entropic, dominate. The effect of the accumulation of entropy during life is that which contributes, mathematically, to the exponential increase of S^+, with a very large τ_S**+** (which corresponds to its very tardive sensible manifestation). But entropy implies, in principle, disorganization, including the gradual disorganization of cells, of tissues, of the organism.

But of course, this very general analysis says nothing about *how* this disorganization takes place, nor anything about its specific "timetable". Today, there are at least two competing theories regarding aging (see [Olshansky et al., 2005] for an overview): the first, more classical, based on the cumulative ravages of "oxidative stress", the second, based on the loss of metabolic stability (essentially attributable to [Demetrius, 2004]). These specific analyses account, though differently, for the experimental data and for the observations which are sometimes contradictory. They require, from our standpoint, significant adjustments with regard to our characteristic times, in function of the species and of their ecosystems, but it seems to us that the framework of principles proposed here would be compatible *a priori* with both points of view, yet enriching both, we believe, by their embedding into a more general theoretical frame.

6.2 Temporal evolution of the metabolism and scaling laws

In this section, we will compare theoretical observations and empirical data, and this will lead us to a strong hypothesis concerning the correlation between the role of the individual mass, W, and the speed of entropy production, σ, in the evolution of the metabolism. This hypothesis will be strengthened by a correlation between different magnitudes (coefficients) corresponding to empirical observations.

6.2.1 Mathematical forms of growth: complexity and mass

As a premise to Section 6.2.2, the main application of our approach to ontogenesis, we recall that, in order to describe in a mathematically simple way the increase of the individual mass W, in biology, we would represent it in the form of the logistic function, as commonly done:

$$dW/dt = (W/\tau_W)(1 - W/W_f)$$

This is the simplest among functions describing an "ago-antagonistic" process, since Lotka and Volterra's work and even more so since the seminal work in ecology by [May, 1976] (a linear increase which multiplies a decay, the antagonistic factor which limits increases, as in the diagram below, in W and t; see [Sprott, 2003] for a recent introduction and survey). This factor is normalized by dividing W_f, the final mass (asymptotic) reached by the adult organism. In the preceding notation, τ_W is its characteristic time.

Now, we may assume a maximal or final value to the complexity K of a multicellular organism and we formally describe also the evolution of the complexity over the course of ontogenesis, as an ago-antagonistic process, by the logistic function where τ_K is its characteristic time (low speed of complexification during early cell reproduction, followed by a faster tissue differentiation and, finally, slow stabilization):

$$dK/dt = (K/\tau_K)(1 - K/K_f)$$

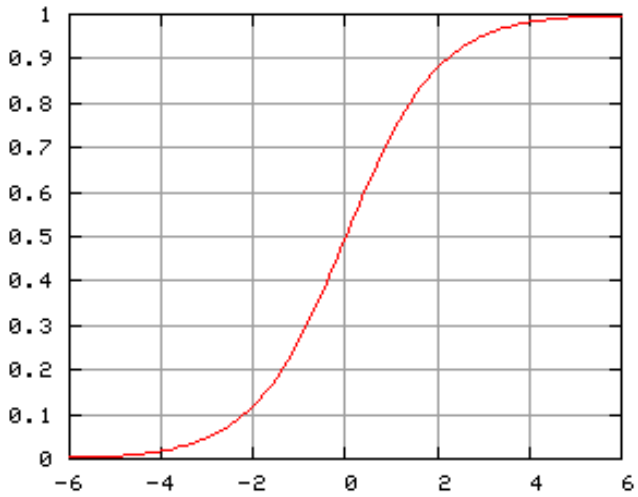

Figure 2.

In other words, we could comment this qualitative diagram, common to dK/dt and to dW/dt, by reminding that, in the case of K, complexity increases over the course of embryogenesis because the structure complexifies and the system becomes increasingly organized. More specifically, after a first phase of simple cellular reproduction, we observe a great increase of organization. This increase slows down, after an inflection point which we have set here at 0, until it then reaches a maximal level of organization, K_f, at the end of embryogenesis and of development, here at an approximate "time" 4. We will understand the mathematical form of the increase of mass in a similar way, but with a much longer characteristic time (the two curves only differ by the constant values τ_K, τ_W, K_f, W_f).

6.2.2 The metabolism and scaling laws[11]

The following analysis firstly bases itself on the existence of scaling laws in biology, that is, on the fact that certain magnitudes behave (give or take the coefficients) like powers of the adult mass of organisms and sometimes in a very interspecific way [Peters, 1983; Schmidt-Nielsen, 1984]. First, the existence of these scaling laws may have been thrown into doubt, but it happened to be corroborated by a number of observations and reinforced in some ways by the demonstration of allometric laws [Weibel 1991; West et al. 1997; Gayon 2000;

[11] The calculations in this section were established with the collaboration of Boris Saulnier.

Andresen et al. 2002]. Secondly, it is the value of the scaling exponents, generally fractional, which has been the subject of controversies, but a relatively wide consensus, not only based on experimental observations, but also on theoretical constraints, has finally arisen regarding the acceptance of a set of values [Wieser 1984; Denne et al. 1987; Kurz et al. 1998; Gilloly et al. 2001; Andresen et al. 2002; Brown et al. 2002]. It is these values which we will use later on. In particular, for the issue at hand, most of the important characteristic times and biologically important durations (life span, gestation period) or the periods (reciprocal frequency values) that are associated to the biological rhythm scale as the ¼ power of the adult mass, W_f. On the basis of this, and for the characteristic times which interest us here, we can write, for $j = S^+, W, K$:

$\tau_j \sim u_j W_f^{1/4}$ (scaling of the times as a ¼ power of the adult mass).

In particular, we have, for the characteristic time of growth:

$\tau_W \sim u_W W_f^{1/4}$.

As for metabolism, the analyses and the observations show that, over *the course of the increase of mass*, it grows linearly with the mass, [Peters, 1983], that is

(R) R_1 et R_2 (of equations (2.1) and (2.2) above) depend *linearily* on the mass W.

On the other hand, the *adult* metabolism itself very generally obeys the scaling law:

$R_3 \sim v_R W_f^{3/4}$.

We will see that the linearity of the dependence of the metabolism over the course of growth and this last equation are correlated: this will only be the limit case of the increase (when the adult mass is reached). In particular, by using $R_3 \sim v_R W_f^{3/4}$ and (2.3), that is, $R_3 \sim T\sigma_3$, we will have:

$T\sigma_3 \sim v_R W_f^{3/4}$.

We will now focus on the presumed linearity of R_2, in relationship to W, by comparing it to the expression we get when developing equation (2) at stage (2.2), thanks to the logistic expression which modelizes the increase of mass:

$$dW/dt = (W/\tau_W)(1 - W/W_f)$$

We then get:

(2.2b) $R_2 \sim adW/dt + T\sigma_2 = (a/\tau_W)W(1 - W/W_f) + T\sigma_2$

Let's firstly note that, for $W = W_f$, we go back, obviously, to the expression for R_3. However, we have a problem here: we have just said, see (R) above, that during period (2.2) corresponding to the increase of mass, metabolism R_2 linearly depends on the mass, whereas (2.2b) gives a quadratic expression for this dependency.

This apparent contradiction isn't one if the quadratic terms reciprocally cancel each other out, that is, if

(9) $(a/\tau_W)W^2/W_f \sim T\sigma_2$

From the physical point of view, equation (9) is *dimensionally* plausible, because the speed of entropy production is proportional to the mass squared (see eq. (3)). From a logical standpoint, the inference is correct: if the hypotheses are true and if $(a/\tau_W)W^2/W_f \neq T\sigma_2$ leads to a contradiction, then $(a/\tau_W)W^2/W_f = T\sigma_2$. What appears to validate the hypotheses, in particular (2.2b) which stems from (2), taken together with the current observations regarding the linearity of R_1 and of R_2, in relationship to mass, is that our deduction (from the hypothesis) *implies* a relation between empirically corroborated magnitudes, as we will see in the following section.

Note, now, that (9) trivially implies the following simplified form of (2.2b):

$R_2 \sim (a/\tau_W)W$.

This expression, at the threshold value, when the adult mass $W = W_f$ is reached, that is, when R_2 becomes R_3, gives us, on the one hand :

$$R_2 = R_3 \sim (a/\tau_W)W_f = (a/u_W)\, W_f^{3/4} \text{ since } \tau_W \sim u_W W_f^{1/4} .$$

On the other hand, we know that $R_3 \sim v_R W_f^{3/4}$, therefore $v_R W_f^{3/4} \sim (a/u_W)\, W_f^{3/4}$, and this implies

(10) $$u_W v_R \sim a.$$

We will see, in the following section, that $u_W v_R \sim a$ is empirically corroborated at least in the case of the human organism where we have a sufficient amount of data, and this reinforces the given hypothesis.

For the moment, let's use the expressions $R_2 \sim (a/\tau_W)W$, $\tau_W \sim u_W W_f^{1/4}$ and relation (10) to put R_2 in the form of

(11) $$R_2 \sim v_R(W/W_f^{1/4})$$

At the adult stage, when $W = W_f$, the scaling of R_3 in $W_f^{3/4}$ is widely recognized. As promised, in our approach, this scaling becomes a particular case (a particular regime, the adult threshold $W = W_f$) of our more general relation (11). In any event and moreover, we will obtain, in the considered regimes and by using (9), (10) and $\tau_W \sim u_W W_f^{1/4}$, the expression

$$T\sigma_2 \sim v_R(W^2/W_f^{5/4}).$$

This result, at the limit of $W = W_f$, further reinforces our hypotheses and equality (9) which results from it because it gives, by another path, the expression $T\sigma_3 \sim v_R W_f^{3/4}$ obtained above.

In fact, the crucial remark, over the course of this reasoning which is logically and physically plausible, is indeed that the speed of entropy production $T\sigma_2$ (quadratic in W) intervenes in these regimes in such a way as its contribution to the metabolism *compensates* for the "antagonistic" component specific to the mass increase, that is, $-(a/\tau_W)W^2/W_f$ (equation (9) above). It appears that there is something interesting to understand here and which arouses open questions concerning the role of the speed of the increase of entropy, due to all the irreversible processes at play, in the computation of the metabolism in relation to mass. At the $T\sigma_3$ limit, we were saying, and therefore for $W = W_f$, all is in order; meaning, once more, that our general equations, in limit cases, produce widely acknowledged scaling laws.

6.3 Comparisons with observations and with biological data

We are now at the stage of verifying that the relation ($a = v_R u_W$), which we have established by using theoretical hypotheses and empirical references, is compatible with the biological data which we may have at hand, the most complete ones seeming to be those relative to the human being. We will proceed in several steps.

Firstly, let's give an explicit expression to the evolution of mass over the course of development; we know that it satisfies the logistic equation and, after integration, we get:

(12) $$W(t) = (W_i W_f)/[W_i + (W_f - W_i)\exp(-t/\tau_W)]$$

where W_i and W_f represent the initial and final masses, respectively.

The graph of the growth curve for mass, represented in figure 2, shows an inflection point. We can easily calculate that it is reached at time t_r such that $W(t_r) = W_f/2$.

If the maximal mass of the average adult male is around 70 kg, the usual growth curves show that a child reaches a mass of 35 kg around the age of 12 (= t_r). Also, we evaluate the fertilized ovule to have a mass of $W_i \sim 1{,}4.10^{-3}$ mg (an ovule has on average a diameter of 140µm and a density of approximately $1 Kg/dm^3$). Finally, we use the relationship between t_r

and W_f by applying it to equation (12) to get the approximate value of τ_W, that is, $\tau_W \sim 0.5$(life span)[12]. By then using the scaling formula for τ_W, we finally get $u_W \sim 63$ days/kg$^{1/4}$.

Also, it is possible to evaluate v_R. Indeed, the R_3 human metabolism is of the order of 100w (100J/sec or 2000 Kcal/day). With $W_f \sim 70$Kg and knowing by the scaling law that $v_R = R_3/W_f^{3/4}$, we /compute $v_R \sim 360$KJ/(day.Kg$^{3/4}$).

Now, if the sought relation ($a \sim u_W v_R$) is verified, we should get $a \sim 22.5$KJ/g. This result is indeed in accordance with the evaluations conducted experimentally which propose the interval of variation $20\text{KJ/g} < a < 26\text{KJ/g}$, see [Mitchell, Seymour, 2000; Zelter, 2004].

Of course, the satisfying aspect of this result does not enable in itself to prove the full generality of the model which we have just proposed, but gives it, besides its relatively simple thermodynamic clarity, a biological plausibility that is not simply abstract. Of course, it would be necessary to complete this sort of result by means of more numerous and general observations and biological experiments. This would allow to be totally convinced that this approach based on the role of entropy, far from equilibrium, without entering into details of the underlying cycles of chemical reactions. These are of course very important and may analytically account for the metabolic phenomena that we considered at the thermodynamic level for the whole organism or set of organisms.

7. The components of complexity

Let's now return to the tripartition of the complexity K introduced in Sect. 2:

$$K = \alpha K_c + \beta K_m + \gamma K_f \qquad (13)$$

Our main aim is to propose a "quantitative" approach to "epistemic complexity" of organisms, as we called it. This very arbitrary and sketchy attempt is only justified by that aim, which should turn organization as complexity into a major observable in biology, and a mathematizable one. Our starting point will lie in a parallelism with the classical treatment of the thermodynamic entropy as considered from a statistical mechanic point of view, i.e. $S = k_B \text{Log} Z$, where k_B is the Boltzmann constant and Z is the number of complexions (discernable microstates). In our case, instead of just "one kind" Z of microstates, we will consider Z as a global "complexion number", made out of three components, $Z = Z_c^{\alpha} Z_m^{\beta} Z_f^{\gamma}$ such that $S^- = -k_B \text{Log} Z$, thus $K = k_B \text{Log} Z$. Thus, equation (13) may be derived by:

$$K = k_B \text{Log} Z = k_B(\text{Log} Z_c^{\alpha} + \text{Log} Z_m^{\beta} + \text{Log} Z_f^{\gamma}) = \alpha K_c + \beta K_m + \gamma K_f$$

where each component is given by a logarithm, multiplied by the dimensional constant, k_B, as we will observe and justify in the following subsections. We will further motivate this definition of anti-entropy in sect. 8, by more comparisons to physics.

7.1 The combinatorial component K_c

The distinction between anti-entropy, related to growth as such, and differentiation, related to morphogenesis, have a cellular equivalent. We propose to consider the processes of cellular division and proliferation to be associated to the first aspect, growth, and the processes of

[12] Life span of humans in the wildness (all these data refer to wild animals: our agriculture and civilization largely changed data).

cellular differentiation for their part to be associated to combinatorial complexity. We then consider them to mainly intervene in the context of the establishment of organization under the aspect of K_c.

We will first simplify the problem by adopting the following combinatorial approach: if N(t) represents the number of cells at time t and if we designate by n(t) the number of differentiated cellular lineages, lineage j (j = 1, …, n) comprising $n_j(t)$ cells ($\sum_j n_j = N$), we define the combinatorial component of the complexity K_c, up to the dimensional constant k_B, by the logarithm of multinomial $M(t) = N!/\prod_j(n_j!)$, that is:

(14) $$K_c \sim k_B[Log(N!) - \sum_j Log(n_j!)]$$

Now if we posit that $n_j = N/q_j$, where each q_j is a bounded integer ($\sum_j(1/q_j) = 1$) and, as N is very large compared to 1, we may use Stirling's approximation; (14) can then be simplified and, per cell, we get:

(15) $$K_c/N \sim k_B\sum_j[Log(q_j)/q_j]$$

Why are we giving this relevant role to Boltzmann constant k_B? The point is that k_B follows from the analysis of perfect gazes. Thus, it provides, in full generality, a possible "least value of information" in terms of entropy, due to the assumed "perfect" independence of particles (see also Brillouin's or Shannon's approach to information as negative entropy[13]). In any case, we use it here both as a dimensional constant and in order to fix a scale, but other scales are of course possible.

In the Appendix, we illustrate this approach by studying the case of the multicellular organism *Caenorhabditis elegans* of which we precisely know the temporal development, in both terms of number of cells as well as of distinct lineages.

7.2 The morphological component K_m

In what concerns the morphological complexity K_m, we will simply refer to current mathematical analyses which take into account the connexities of organs as well as the existence of critical geometric points (maxima and minima, inflections and curvatures...) characterizing their forms and topologies. For example, and very provisionally, we could evaluate K_m as follows:

$$K_m = k_B [Log(1+n_1) + Logn_2 + Logn_3 + Logn_4]$$

where n_1 represents the number of changes in the sign of the local curvature (for example in the case of complicated geometrical shapes[14]), n_2, the number of singular situations (corners, bifurcations, etc), n_3, the number of non connate parts of a same organ (for example, the number of separate muscles or bones taking into account the number of different such organs) and n_4, the number of group links (wreath) in the sense of [Leyton, 2004] which enable to define, for biology, at least closely, the geometric construction of forms (for instance, for the digestive system - very roughly – the group of the sphere (for stomach) and that of the curved cylinder - for oesophage and intestine). This does not mean, of course, that biology is itself constructed according to these procedures, but that the results of such biological constructions may be described using the method proposed by Leyton… possibly a venue to explore further.

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[13] More precisely, Brillouin's evaluation of this least value is $k_B Ln2$ (one needs at least 2 discernable microstates).

[14] Of course in the case of "fractal" structures (which are actually fractals only at the infinite limit), we have to take into account only the final result at the relevant limiting scale (number of bifurcations for trees - like the bronchial tree, for instance - size of minimal elements for interfaces - like the alveolar terminal structure of the lung for instance -).

7.3 The functional component K_f

Finally, the part of K_f complexity which we have called "functional" corresponds to the *relations* (metabolic, nervous, etc.) which are established between cells and organs in order to ensure the organism's physiology, the integrations and regulations between levels of organization, motor, cognitive and behavioral controls. It is obviously quite difficult to evaluate this contribution but, by proposing some specific formalizations, we nevertheless present a few ideas which may contribute to mathematize the discussion, thus to clarify its terms on rigorous conceptual grounds.

To do so, we will consider that this set of relations and networks can be represented by means of graphs where, for example in the case of the nervous system, the nodes correspond to neurons and the edges to synapses. K_f will then correspond to the (logarithm of the) number of such graphs. So if we designate the number of neurons (approximately 10^{11} for the human brain) as m and designate the number of synapses as km (k being between 10^3 and 10^4), the theory of Erdös-Renyi graphs shows that there are G graphs such as:

$$G = \binom{\binom{m}{2}}{km} = \binom{\frac{m(m-1)}{2}}{km}$$

with the $\binom{a}{b}$ symbols corresponding to the combination of a objects taken b to b; and we will therefore postulate:

$$K_f \sim k_B \mathrm{Log} G$$

If m is very large in comparison to 1, Stirling's successive approximations then give us:

$$K_f \sim k_B km(\mathrm{Log} m)$$

And for each neuron, we get: $K_f/m \sim k_B k \mathrm{Log} m$

One may notice that in this elementary model the complexity per neuron increases (logarithmically) with the number of neurons once such a number is sufficiently high. This situation may be distinguished from that encountered with the combinatorial complexity per cell which remains – roughly – independent from the number of cells. This effect is of course associated to the global effects that are induced by the functional relations between elements[15].

A more general approach may also be proposed: let $\langle k \rangle$ be the average number of edges per node and N the number of nodes; the total number of relations will therefore be $\langle k \rangle N$ and the number of associated permutations is $(\langle k \rangle N)!$. For a large N the corresponding K_f would therefore be approximately $k_B \langle k \rangle N \mathrm{log} N$ and, per node (per neuron, for example, or per support within a metabolic network) we get $K_f/N \sim k_B \langle k \rangle \mathrm{Log} N$, with the same qualitative remarks as before regarding the dependency in terms of the average number of edges per node and of the number of nodes. The advantage of this point of view enables to integrate the case of networks which are independent of scale, of which, in general, the probability of edges per node evolves in k^{-p}. By taking the normalization factors into account, we get $\langle k \rangle = \zeta(p-1)/\zeta(p)$ where ζ represents the Riemann function. A number of studies pertaining to variegated networks show that p is close to 2 (for metabolic networks for

[15] This case is the simplest because we have taken into account only combinations of the sets of pairs of interacting neurons. If we had considered the totality (or even an asymptotic significant part of this totality) of the possible sub-sets, we would have obtained $K_f \sim k_B km^2 \mathrm{Log} 2$ and a complexity per neuron proportional to m.

example, we have p ~ 2.2). For the nervous system, the fact that the average number of synapses is of the order of the thousands, even of the tens of thousands, indicates that in this case p is very close to 2 (up to 10^{-3} or even 10^{-4}).

7.4 Conclusion

We have attempted to define, to analyze and to propose a way for measuring the quantity what we can designate as the complexity K of a living organism. To do so, we have distinguished between three possible components: a combinatorial component where the important factor is the number of differentiated cellular lineages, a morphological component which takes into account the more or less elaborate form of structures and their connexities and, third, a functional component relative to the relations established by the networks formed by the organism's cells or parts. Depending on the given situation, the dominant terms may vary: for example, in less evolved organisms, the combinatorial aspect, based on the number of cells concerned, may play a major role. Likewise, relatively to the morphological component, the existence of more or less significant symmetries, of more or less numerous connex components, of more or less singular structures (fractal or not) plays an essential role which, in certain cases this may be the main component of (may mathematically dominate) the complexity of the organism. Consider, for example, the variety of organisms involved in the "explosion" of the Burgess fauna. Conversely, in highly evolved organisms, for example those endowed with a sizable and developed nervous system, the relational/functional aspect, logarithmically dependent on the number of concerned cells, seems to clearly dominate.

These different ways in which a same overall complexity K can occur in living phenomena illustrates in our view the genericity of the biological trajectories in contrast with the singular geodesics of physics, inasmuch as this same complexity is, in our view, an essential component of the conceptual space specific to any analysis of life phenomena.

8. More on negative entropy in physics and anti-entropy in biology. Concluding remark.

All irreversible physical processes produce entropy: positive, growing entropy. In some cases though, in particular in the cases of phase transitions from disorder to order, one can witness a decrease of this quantity. The point is that entropy, in thermodynamics, corresponds to a *degradation of energy* and a suitable energy input, in some cases, or a change of the system as a whole (phase transitions) may compensate this degradation. It is then possible, within thermodynamics, to develop an analytical framework for both increasing and decreasing entropy without having recourse to anything else than its general principles (usually in the number of three: the conservation of energy, the non decrease of entropy in isolated systems, the absence of any movement and therefore of any form of energy[16], at the absolute zero of temperature). Unification with classical dynamics was made possible by means of statistical physics, by the analysis, at the infinite limit, of particle trajectories, hence of geodesics, as optimal trajectories for action (energy × time).

When used in biology, the concept of negative entropy has been also considered as contrasting, *by a negative sign*, the growth of (thermodynamic) entropy. So, viewed as a non-isolated system, an organism may absorb solar radiation and decrease entropy (typically, in photosynthesis, [Brittin, Gamow, 1961; Jennings et al., 2007]) or it may absorb energy from

[16] At least from a non-quantum standpoint.

high temperature thermal sources, in deep sea far from solar radiation ([Lopez-Garcia P., 2003]) and contrasts by this entropy decrease, in particular by building organic molecules. These are very interesting approaches, but we find them mathematically insufficient for describing living organization: they focus on the molecular level, a most relevant one, yet exactly the one that Schrödinger (and us) propose to put temporarily aside, in order to develop a systemic approach to live phenomena[17]. Reduction, as in thermodynamics, or unification as in relativistic vs. quantum fields is a further, very relevant and difficult issue.

And now a crucial point: energy and its up- *and* down-grading are the key *observables* in these molecular analyses. As a matter of fact, the prevailing perspective regarding the inert, in thermodynamics just as in any physical theory, focuses on energy and derived or correlated notions ("least action principles", typically). Also entropy, as recalled above, can be expressed in terms of the degradation of energy (and/or of the dispersion of trajectories), thus, in some cases, it may be compensated by a suitable absorption of energy. The many very relevant analysis on entropy decrease in building processes of organic molecules belong to these approaches, as we said, and focus on energy exchanges (see also [Kier, 1980], [Roy et al., 2003] for more on the role of decreasing entropy in molecular processes).

In our opinion, autonomous mathematical investigations, concerning the "multilevel entangled structure" of living organisms, also deserve to be carried on, in the more complex sense of different but interacting levels of organization, even in a cell, beyond the molecular level. In particular, cellular differentiation leads to an organism where the "structure of correlation" (as defined in [Bailly, Longo, 2008]) is based on *integration and regulation between levels*. This proposes a relatively new and crucial observable, from the perspective of the "large-scale behavior of a living organism". Our aim has been to propose a tentative quantification of this observable, which is compatible with, but adds up to the ones used in physical theories. As we stressed several times, it is related to energy via a balance equation derived from metabolism and an extension of the notion of Gibbs free energy G, but our focus is on the $K = -S^-$ component in equation (2), and on entropy production, $T\sigma$, equation (3). As we mentioned in sect. 2, the possibility of writing these equations, in terms of G, motivated our tentative correlation of biological organization (or complexity) to a notion of anti-*entropy*.

Of course, there exists at least an area of physics where the concept of "organization" massively steps in. This is the theory of "critical phase transitions" ([Binney et al., 1992], [Kauffman, 1993], [Jensen, 1998] and many others). In sect 1.2 and 2, we already hinted to the relevance of and the correlations to these analyses, which we "extended" in [Bailly, Longo, 2008].

Many also tried to analyze biological organization in terms of (Shannon's) information: since entropy increase may characterize loss of information, its negation should provide (an increase of) information. Besides its relevance in transmission theory, this approach has inspired new analyses also as for negative entropy in quantum systems (see, among others, [Cerf, Adami, 1997]). Yet, both classical and quantum information basically refer to classical or quantum bits, as the discrete mathematical frames are at the core of information and computation theories. In contrast to this, we tried to deal with equations (balance and

[17] As quoted in sect. 1.1: "…entropy principle on the large-scale behavior of a living organism - forgetting at the moment all that is known about chromosomes…".

diffusion, typically) that are better understood in (differentiable) continua and where Shannon's theory and its quantum variants hardly apply. Moreover, our guiding reference to anti-entropy as a component of a Gibbs free energy, following but beyond Schrödinger, also departs from the understanding of our notion in terms of (Shannon's) information.

The best, yet very informal, analogy we can propose within physics is not with the many current uses of negative entropy, as far as we can see, but it concerns the notion of *anti-matter*. Anti-matter has the same physical dimension of "matter", but it is *not* mathematically correlated to a decrease of energy in matter. It is one of the possible solutions of Dirac's equation ([Schiff, 1955]) and the lowering of energy, towards equilibrium or far from equilibrium stationarity, for example, does not lead nor is related to "anti-matter". Thus, anti-matter has the same dimension and the opposite sign w.r. to *energy* in correspondence to the opposite sign of *charge* of matter, but it is a different *concept*, since *it refers to different observables*: typically, the positron (anti-electron) yields negative energy (positive charge), the anti-proton yields negative energy (negative charge) but they are not just a different state of the electron or the proton, but different quanta. When anti-matter encounters matter, the annihilating result of quanta produces a large amount of energy, under the form of gamma-rays, not zero nor least energy[18]. The prevailing of matter over anti-matter has been analyzed as a breaking of the CP symmetry, in reference to the TCP symmetry, [Sakharov, 1982].

Similarly, for us, anti-entropy has the same (physical) dimension as entropy, with the opposite sign, yet it is a different concept, as it provides a different observable: in our approach, anti-entropy is correlated to the formation of *multilevel, integrated and regulated organization*, and *not only* to the appearing of order corresponding to a lowering of physical entropy, a relevant and largely studied issue, which is already present at the molecular level and in critical transitions in physics. Moreover, this conceptual analogy of our notion of anti-entropy to physical anti-matter justifies our computations in sect. 7, sect. 7.1 in particular. As for anti-matter, its values of energy and charge are computed in the "same" way as those for matter, but they have opposite value and provide a different observable (the anti-particles). Similarly we computed S^- by $-k_B LogZ$ and thus, K, by the "same" computations as physical S^+. Yet, our Z and the objects are very different: the discernable states are the cells and their differentiated lineages (whose ratio gives the measurable value, see eq. (14), sect. 7.1), the complexity of their shapes, their connexity, etc. and the functional structures of the relevant networks (enzymatic, neuronal, etc.).

By these tools, we insist, with many other authors including Schrödinger, but along our proper lines, on the necessity to develop, in parallel to the richness of the analyses of molecular biology, systemic frameworks specific to the global activity of organisms. These could suggest, even for phenomena that occur within the cell, a *structure of determination* that is more adequate for the physical singularity of life phenomena (see [Bailly, Longo, 2006] for an analysis of the various forms of physical determination and an outline of their relationship to life sciences).

In conclusion, it has not been a question here of discussing the current stability of the cell as such, or even that of the organism, as meaningful coherence structures within which to set

[18] Let's recall that Dirac's equation also engenders Pauli-matrices representing the spin of the particles and, from this point of view, it *organizes* some key properties of the matter.

the causal analyses themselves, if possible, of proteins' cascades. Our project is one of the many theoretical efforts proposing the systemic perspective of which the notion of "extended criticality" should also be part (see [Bailly, Longo, 2008]). In this paper, we focused on a simple mathematical description of a new observable, as "determined by" and "applied in" a few inequalities and equations.

Observe finally that anti-entropy is "just" a tool for our approach, as we aim at quantifying K, epistemic complexity, and mathematically work on it. We suggested that it may defined as $K = -S^-$, so that we could work on it as a component of the equational definition of metabolism, in terms of Gibbs free energy.

It should be clear that the method is largely derived from the practice of physical theoretizing, yet, we (strictly) extended current physical theories, thermodynamics, in particular, by new principles which we consider proper (only) to the phenomenality of life.

Appendix 1: Some dimensional analyses

Let's recall that the application of the $\hat{O}$ operator leads to the equation of the generic g density function's general form:

$$\partial g/\partial t = D_g \partial^2 g/\partial \kappa^2 + (T\sigma_{0g}/\rho_g)g = D_g \partial^2 g/\partial \kappa^2 + \alpha_g g$$

The dimensional analysis of the various intervening coefficients may present some interest and reveal itself to be enlightening. The dimensions will be denoted in brackets [...], and we will denote, as usual, mass as [M], length as [L], time as [T] (not to be mistaken for temperature which is usually written as [°K]), and, by convention, $[C \equiv ML^2T^{-2}(°K\text{-})^{-1}]$ for complexity. We will then have:

$[\sigma] = [ML^2T^{-3}(°K)^{-1}]$ (power per Kelvin – and per mole -)

$[\rho] = [ML^2T^{-2}]$ (energy)

$[(°K) \times \sigma_0] = [ML^2T^{-3}]$ (power)

$[\alpha] = [(°K) \times \sigma_0 / \rho\ ] = [T^{-1}]$ (reciprocal time value = frequency)

$[D] = [M^2L^4T^{-5}(°K)^{-2} \equiv C^2T^{-1}]$ (square of a complexity divided by time).

Let's recall that in the case of thermal or matter diffusion, the diffusion coefficient has a magnitude which is the square of a length divided by time ($[L^2T^{-1}]$; here, it is therefore the epistemic complexity which serves as length, that is, of space. This is in accordance with or main equation (5) and its derivation "a la Schrödinger".

Finally, we have introduced, over the course of these definitions, within the framework of the evaluation of the speed of entropy production, the coefficient ζ_b ; given the way in which it intervenes (see relation (7) for example), its dimensionality is less "classical"

$[\zeta] = [M^{-1}L^2T^{-3}]$

The other magnitudes which appear in the text are endowed with their usual dimensions (direct: time, mass, numbers, or derived: entropies, energies, densities over the epistemic complexity).

Appendix 2: The case of *Caenorhabditis elegans.*

The interest of examining the case of *Caenorhabditis elegans* in terms of combinatorial complexity stems from the fact that, as we have already evoked, we have a thorough knowledge of this organism's development, cell by cell and ensuing lineage by lineage (see [Ehrenstein, Schierenberg, 1980]). The results we have obtained using the empirical data present some interest and provoke a few questions which may prove to be relevant to other cases.

It is an issue of examining the behavior of K_c over time, which is defined by relation (14) (in this case, there are not always enough cells in each lineage in order to apply approximation (15)). Table 1 presents these results. It is striking to observe that K_c increases very quickly from 0 (a single cell) to 1 and that it stabilizes around this value over the course of its development from the moment where all cellular lineages are represented, as if it was effectively the number of active cellular lineages which would essentially set K_c, independently of their number of cells and hence of the size of the organism.

Time t (mn)	Total number N	AB lineage	MST lineage	C lineage	E lineage	D lineage	P lineage	K_c/k_B
70	6	4	1				1	0.57
100	24	16	2	2	2	1	1	0.92
130	31	16	4	4	4	2	1	1.2
150	81	64	8	4	2	2	1	0.71
170	102	64	16	8	8	4	2	1.10
250	182	128	16	8	8	4	2	0.97
Pre-*lima bean*	434	256	64	64	32	16	2	1.19

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