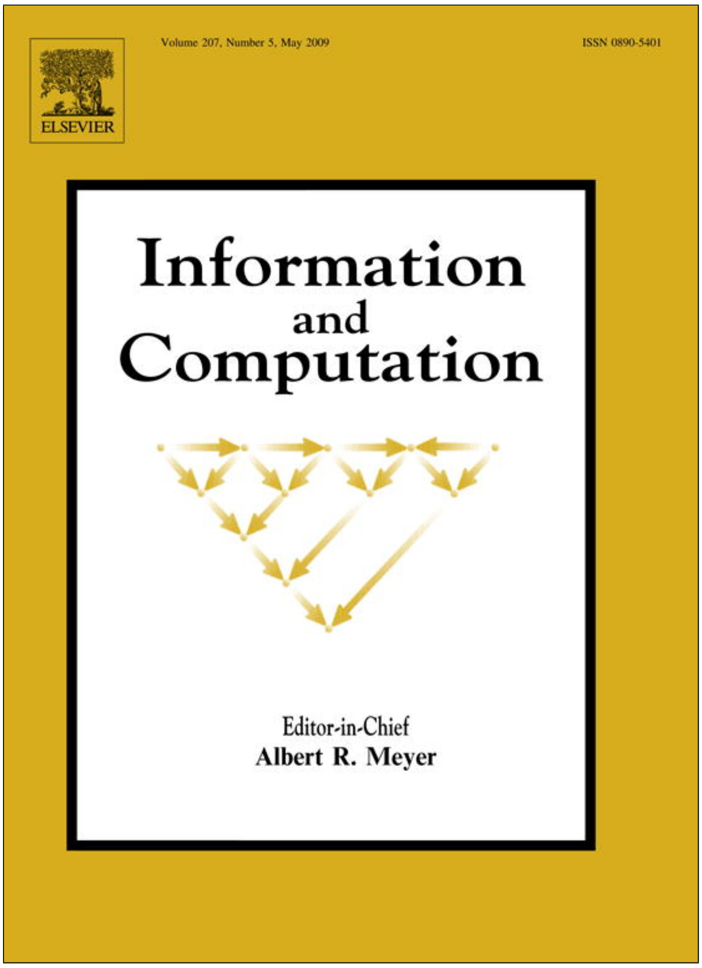

Volume 207, Number 5, May 2009
ISSN 0890-5401
ELSEVIER
Information and Computation
Editor-in-Chief
Albert R. Meyer

Information and Computation 207 (2009) 545–558

Contents lists available at ScienceDirect

Information and Computation

journal homepage: www.elsevier.com/locate/ic

From exact sciences to life phenomena: Following Schrödinger and Turing on Programs, Life and Causality

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ARTICLE INFO

Article history:
Received 15 October 2007
Revised 6 November 2008
Available online 23 January 2009

ABSTRACT

This text presents a survey and a conceptual analysis of a path which goes from Programming to Physics and Biology. Schrödinger's early reflections on coding and the genome will be a starting point: by his (and Turing's) remarks, a link is explicitly made between the notion of program and the analysis of causality and determination in Physics. In particular, Turing's work in Computing and in Morphogenesis (his 1952 paper on continuous dynamics) will be seen as part of a scientific path which goes from Laplace's understanding of deterministic predictability to the developments of Poincaré's analysis of unpredictability in non-linear systems, at the core of Turing's 1952 work. The relevance of planetary "resonance", in Poincaré's Three Body Theorem, and its analogies and differences with logical circularities will then be discussed. On these grounds, some recent technical results will be mentioned relating algorithmic randomness, a strong form of logical undecidability, and physical (deterministic) unpredictability. This will be a way to approach the issue of resonances and circularities in System Biology, where these notions have a deeply different nature, in spite of some confusion which is often made. Finally, three aspects of the author's (and his collaborators') recent work in System Biology will be surveyed. They concern an approach to biological structural stability, as "extended criticality", the structure of time and of biological rhythms and the role of a proper biological observable, "organization". This is described in terms of "anti-entropy", a new notion inspired by a remark by Schrödinger.

1. Introduction

The impact of notions stemming from programming and digital machines into the understanding of Biology has been very important and we will discuss some of its methodological roots and consequences. The idea is that computing implicitly suggests a "causal structure" ("what causes what?") by the input–output relation in programming or by the nature of interactions in computer's networks. More precisely, we will refer to the notion of "structure of determination" proposed by a mathematical model and distinguish between model and imitation, following Turing. The point is that a physical process may be fully *determined* by a set of equations that do not need to possess or to be uniquely associated with a solution, that is to an evolution function, which, if computable, would yield a program. In mathematical physics, the existence of (analytic) solutions or the nature of these solutions is a key problem; the reference to dynamical systems, beginning with Poincaré's fine analysis, will be a relevant aspect of our discussion.

Several major scientific figures will be mentioned here. Schrödinger first, by his pionering intuitions about life, which started a lively debate, but also by a recent application we made of his wave equation and operatorial approach in Biology. Poincaré will be recalled, in particular, by the invention of the geometry of dynamical systems and the induced radical change

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doi:10.1016/j.ic.2008.11.002

in what “determination" means in mathematical physics. The relevance of his work will be hinted also for the foundations of mathematics by his critique of Hilbert and by a subtle relation to Gödel’s work, on epistemological and technical grounds. Turing will often appear, by his role in Computability, of course, but also by his analysis of Morphogenesis (the dynamics of the generation of forms), in a little known paper by Computer Scientists, yet a foundation for an entire branch of applications of Physics to Biology.

In Biology, the “structures of determination", at the various levels of organization of life, are far from clear (morphogenetic fields, phylogenetic drifts ... are some of the many ideas at work). Even less so regarding the organism, where these different levels of organization, often treated by different mathematical tools, happen to be reciprocally integrated and regulated. Without any attempt of completeness, a few recent proposals for modelling some features of the living state of matter will be hinted here, in the perspective of “Systems Biology” (the organism/the species analysed from a global view point).

In summary, Section 2 introduces Schrödinger’s ideas on codings in Biology and his hints towards a “global analysis” of organisms (to be further developped in Section 8.3). Section 3 moves from Schrödinger to Turing, on the grounds of their common understanding of the “Laplacian” nature of the ideas they were proposing, in particular in comparison with Turing’s work on Morphogenesis. These action/reaction systems, studied by Turing, are related to Poincaré’s analysis that took us away from Laplace’s understanding of determination; in both cases non-linear interactions or “resonance effects” play a major role. Section 4 contains a methodological reflection and an opening towards the complexities of the living state of matter, where causal interactions and circularities are also massively present. Yet, Section 5 introduces a warning against the too easy transfer of the relevant circularties in Logic and Computing towards Biology and it does this by an analysis of Gödel’s and the λ-calculus’s use of self-reference. More on the role of continuous modeling is said in this section as well as in Section 6, where some recent results relating deterministic unpredictability (in Poincaré’s sense) and algorithmic randomness are presented (a form of strong undecidability, à la Gödel thus, for infinite strings). Section 7 goes back to some of the peculiar challenges posed to mathematizing in Biology, in view of the interactions between different levels of organization (and of mathematization). Section 8 briefly introduces the ongoing attempts, with F. Bailly, to face this challenge by a global approach to the very notion of “organism” and “evolutive system”. In particular, the section argues that the common feature of the three different viewpoints from which we look at life phenomena is their being “mathematical extensions” of current physical theories, by some, possibly original, concepts (extended criticality, two dimensional time, anti-entropy).

The interplay between Computing, Physics, and Biology is the thread connecting the various parts of this survey/methodological paper. This story in part reflects the author’s personal history, which has been ponctuated by many collaborations with extraordinary colleagues in Logic and Computing, and, more recently, in Physics and Biology, some mentiond in the acknowledgements. But, even more importantly, this history has been marked by the collaborations with his students who thaught him much more than he could teach them.

2. Preliminaries on the Program and Organization in Biology

In a short informal book of 1944, *What is Life?* [50], Schrödinger explores some possible theoretical ways for understanding the phenomenon of life. Schrödinger is a founding father of one of the most advanced areas of exact sciences, Quantum Physics, in particular by his proposal of the “wave equation” over the complex field. In his reflections on Biology, he brings in a search for *general principles*, in an area, the not yet fully born Molecular Biology, where scattered observations could at most correlate local genomic differences (mutations, say) to teratogenics effects (pathologies or anormalities) in the phenotype (the form, functions or behavior of a living being).

His book on Life is mostly known as one of the first attempts to characterize the chromosome as a structure bearing a “code-script” for the architecture of an organism:

> “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 ... *(omitted)* ... But the term code-script is, of course, too narrow. The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are law-code and executive power – or, to use another simile, they are architect’s plan and builder’s craft – in one.” (pp. 22–23).

Thus, this code-script must be understood at least in the sense of a “program”, including a “compiler”, perhaps even as supporting an “operating system”. This is a very general and original perspective, as these notions were new at the time: computing, at least under the modern conception of “programs coded and transformed like data” in the sense of Turing, had just started (the very concept of Universal Turing Machine as at once program, compiler, and operating system). Similarly, it is the War effort that had pushed the art of coding–decoding at the limelight: World War II has truly been a War of the Code, with Turing himself at the core of this effort, by his work on the Enigma Machine and the breaking of the German codes. Schrödinger captures the novelty and the richness of this paradigm: since then, the science of coding–decoding over sequences of 0s and 1s, and their computations, has been changing the world. However, the idea of genome as a program has long lived, yet some still use it as a metaphor. Its inadequacy, even as a metaphor, have been evidentiated by many in Biology. We will briefly get into this below and refer to [41] for an extended critique, from a computer scientist view point, and more references.

The second half of this booklet contains further speculations, as original as those on the code-script. Schrödinger attention switches from an analysis of heredity to a questioning on the local and global stability of Life. More precisely, sometimes by remarks in contradiction with previous ones in his own book, he hints to a rather different understanding of the organism, away from the programming paradigm and centered on an analysis of entropy vs. “organization” as its negative counterpart (see Section 8.3 below). This second half of his book did not receive as much attention as the first, yet it follows the same need for a Theory as the first: to enrich the collection of uncorrelated facts and local interactions, by an analysis of the “global structure” of an organism and by a pertinent theoretical proposal. And, in contrast to the early pages on codings, whose proposal is now easy to grasp and to refer to, by common sense (everything is encoded today), the second part of the book opens new and more original perspectives.

Schrödinger’s contradictory, but very rich and stimulating observations will be “used” here to introduce some ongoing reflections. These range from a critique of the computational perspective concerning heredity and development to some hints towards current work, which brought the author from the exact frame of Logic and its applications to Computing all the way towards theoretical attempts in System Biology, meant as an analysis of organisms and biological organization. This long way goes through some remarks on what one may mean by “determination” in Physics, which are crucial to understand the challenges posed by biological theoretizing.

3. The Program and the “structure of determination” in Physics

3.1. From Laplace to Poincaré

Let us look now at the “omitted” part in Schrödinger’s quotation above:

> “ . . . In calling the structure of the chromosome fibres 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 . . . ” (pp. 22–23).

Schrödinger, by his experience in Physics, understands that, by transferring the linguistic-symbolic nature of the notion of *discrete code* over a natural system, one obtains a structure of determination of Laplacian type. What does this mean? Laplace’s key conjecture, at the beginning of the XIX century, was that determination, in Physics, implies predictability. In other words, when a system of equations or an evolution function for a physical process is given, one should be able to predict all future states. Of course, Laplace was aware that in some cases (the critical ones, we would say today – a ball on top of a hill, for example), “des nuances insensibles” (a variation or fluctuation possibly below the interval of physical measure) could yield unpredictable developments. Yet, he thought that this was possible only on isolated points, in the mathematical sense, not to be found in such a stable and predictable system as the revolving planets around the Sun, his main concern. Thus, he developed, on one side, an investigation of equational physico-mathematical determination and, on the other, an independent analysis of unpredictable events as non-deterministic randomness, and invented by this also modern Probability Theory [18]. This distinction between determinism, which would imply predictability, and randomness, as non-deterministic unpredictability, is at the core of the so called “Laplacian” understanding of determination. As we shall, see it passed over to programming and, less soundly, to molecular approaches to Biology as long as they refer to the DNA as a “code-script” or program or alike.

Some time later (1880–1892), Poincaré stepped in. He looked closely at the system of equations that *determine* the movements of three celestial bodies, subject to Newton’s law of gravitation, and . . . deduced the intrinsic unpredictability of their trajectories, against Laplace program. The system, in general, has no analytic solution, since infinitely many increasing coefficients make the approximating series diverge: by this, one shows that very small variations, below observability, can macroscopically affect the trajectories over time. The analysis of deterministic dynamical systems, which are “sensitive to initial conditions” and thus provably unpredictable, was born and, surprisingly enough, the Solar System was one of them, actually the first discovered. Modern developments confirm its chaotic nature and actually compute the time beyond which any prediction is provably impossible (not much, in astronomical terms: a few millions years, see [35]). By Poincaré’s approach and contrary to Laplace’s distinction, in classical (and relativistic) dynamics, randomness boils down to unpredictability in *deterministic* chaotic systems.[1]

3.2. Turing: from the Machine to Morphogenesis

It happens that a major mathematician of Computing, A.M. Turing, has been deeply involved in this passage from Laplace predictable dynamics to the modern Geometry of Dynamical Systems. As a matter of fact, Turing worked also at continuous dynamical systems, in particular at some morphogenetic processes relevant to Biology. In order to mention his role in both themes, we summarize shortly some remarks and quotations in [37], which deal with the intended Laplacian “determination” in computing machines.

We all know that Turing invented the Logic Computing Machine, as he first named his Machine in the seminal paper of 1936. The idea was to describe the least act of computation (or even of “logic thought”) by the most elementary and simplest

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[1] Contemporary Physics proposes a further and distinct (intrinsic) character to randomness in Quantum Mechanics (see [6,40] for a recent comparisons of the two notions of randomness).

steps: read/write 0 or 1, move right/left the writing head on the tape, like a man computing on the squares of a child's exercise book. Borrowing Gödel's idea of number-theoretic coding, he then could encode the very set of instructions, the program, into the tape and invent the Universal (Turing) Machine. Surprisingly enough, this machine was fully general: any Hilbertian finitistic system and its representable functions could be encoded in it. And the Church–Turing thesis was born. Well beyond Physics, that is with no reference to the "material structure", all those who believed that the brain is a logic machine and nothing else, considered Turing's model of computing a complete model of the brain: what else could ever be logically computed/deduced by an intelligent device, independently of the hardware?

However, about 12 years later Turing got interested (again) in Physics and started to work on some physical aspects of life: Morphogenesis, the genesis of shapes and regularites in chemical reactions. This new research interest led him to another seminal paper [54]. At that time, in a parallel 1950 paper in the journal Mind, an "imitation game" between a machine and a brain, Turing defines differently his invention: a *Discrete State Machine*. This name is used in several places of [53]; indeed, a Turing Machine, the former Logic Machine, is, from the point of view of its *physical* states, a *Discrete State* Machine, DSM as Turing writes for short.

Morphogenesis instead is "*modeled*" as a dynamics of forms in a "*continuous system*", his words again [54] (but also in [53]). Now, a (mathematical) model is meant to propose a *structure of determination* of a physical phenomenon (may be a wrong one, he says): in [54], an action/reaction/diffusion system of equations mathematically models the chemical genesis of forms in organs (the distribution of colors on the furs of some animals, typically). The main property of teh non-linear case of this model is "the exponential drift", as Turing calls the sensitivity to initial conditions (a very pertinent name as it is a matter of the so called Lyapounov exponents): a minor variation exponentially modifies the evolution of forms over time, this is what interests Turing in those continuous dynamics.

In that paper he observes that also the brain is a continuous system, subject to the exponential drift. This observation is already hinted in the other article on the "imitation game" [53]:

> " ... the nervous system is surely not a DSM ... a small error in the information about the size of the nervous impulse ... " may induce major changes ([Turing, 1950, p. 57]).

The change of perspective is dramatic: once Logic is put aside, the DSM becomes an *imitation* of the brain, not a model. It may though play a game which does not pretend to provide an intelligibility (to suggest a structure of determination), but where the Machine may cheat an observer and pretend to behave like a brain. A sound paradigm for Classical AI: cheating the observer, even if no understanding of the brain is proposed. But why it is not a model?

In a DSM, Turing observes,

> " ... it is always possible to predict all future states ... This is reminiscent of Laplace's view ... The prediction which we are considering is, however, rather nearer to practicability than that considered by Laplace" [Turing, 1950; p. 47].

In fact, he explains, the Universe and its processes are subject to the exponential drift, as defined and analyzed in the 1952 paper (in 1950, Turing uses the following example: "The displacement of a single electron by a billionth of a centimeter at one moment might make the difference between a man being killed by an avalanche a year later, or escaping."). To the contrary, and there lies the greatest effectiveness of his approach,

> " ... It is an essential property of ... [DSMs] that this phenomenon does not occur. Even when we consider the actual physical machines instead of the idealized machines, ... ", prediction is possible, [Turing, 1950; p. 47].

Of course, Turing stresses, there may be such a long program that it is hard (practically impossible) to predict its behavior; yet, this is a *practical* issue, a very different one from the core *theoretical* property, deterministic unpredictability, in chaotic dynamical systems. By the exponential drift, over approximated physical measures, the (equational) non-linear determination does not imply prediction: minor perturbations or fluctuations may induce very different genesis of forms [54].

Turing, thus, is fully aware, exactly like Schrödinger, that once the discrete linguistic-symbolic paradigm of computation is used as (or to understand) a physical device, we switch to a Laplacian regime. But what is the mathematical difference with respect to continua? The point is that "discrete" means that the "discrete topology is natural" over the intended mathematical structure. Thus, points are isolated and *exactly* accessible. This is the core property of discrete code-scripts and DSM's, as both Schrödinger and Turing understand: programs, data types, everything is exactly given and determination implies predictability. The effects of the *exponential drift* may be avoided. In Mathematical Physics, this drift engenders unpredictability in deterministic systems because of perturbations or fluctuations below the level of physical measure, which is never exact, by principles (there is at least the thermal fluctuation), thus *necessarily* an approximation by an interval. And the interval of measure is better mathematized by Euclidean (or *interval*) topologies over continua or dense structures: this is the deep link between Physics and the mathematics of continua (see below for more).

Computability Theory instead is a theory of *repeatable calculations* over integer numbers as discrete data types, beginning with Herbrand-Gödel Primitive Recursion, which is iteration plus a register update. Ending with portability of software: even on different, but suitable environment, a fortiori over identical environments, programs may be repeated at will. And it works. A classically random, yet deterministic, process may be in contrast defined as a process that *is not* repeatable, in general, when re-launched on the same initial conditions as *intervals* of physical measure. That is, by definition, a deterministic continuous dynamics in a sensitive regime (almost) never repeats itself when restarted over the same physical initial conditions, as these are given, by principle, by an interval and a fluctuation or variation within that interval *causes*, in general, a different evolution. This is unpredictability and it is grounded on a difference *in principle* concerning access to the intended data types: the exact code-scripts vs. the approximated interval in a continuum.

Note that, taking as input the discrete extremes of an interval does not help for these purposes, as non-linear dynamics are "mixing" (that is, the extremes are soon no longer such). Thus, one may program on a digital machine the wildest turbulence and still be able, by a "restart" on the same *discrete data*, to iterate the strangest of its attractors at will (more on this in [37,38]). And identical repetition itself, as a time shift, is a form of predictability.

In short, a model proposes an "intelligiblity" by formalizing the forces at play (or, more generally, the symmetries and symmetry-breakings, see [5]) and, even, by evidentiating "unpredictability", if it applies: we know more over a double pendulum after an analysis of the Lyapounov exponents in its evolution function, which quantify the unpredictability of its deterministic evolution. Similarly, we know more about the Solar System since Laskar's results quantifying its unpredictability [35]. The mathematical understanding of a physical process, since Poincaré, does not coincide with predicting: the qualitative analysis, in terms typically of the Geometry of Dynamical Systems, may be very informative.[2] An imitation is not committed to this. For example, the computer implementation of a double pendulum, though very suggestive, misses to provide us with a key information: the irrepeatability of its evolutions, as you may iterate at will its creazy (chaotic) trajectories by relaunching each of them on the *identical* initial data (iteration, as we said, is a form of prediction: just try again). And this has no physical sense: it is an imitation (a fantastic one, in contrast to brain DSM imitations, which are rather poor …).

In summary, in deterministic frames, randomness as unpredictability is due to the *conjunction* of deterministic chaos (a precise mathematical notion: sensitivity, topological transitivity and density of periodic orbits (see [21]) *and* of the non-null interval of physical measure. It is amazing and very sad to observe that the founders of modern Molecular Biology, Jacob and Monod (see [44] for example), still counterpose determination and randomness exactly like Laplace. Thus, they view determination as predictability and (re-)propose the Laplacian notion of program for the DNA.

As it is well known, we now have computability over continua, hybrid systems and a lot more, but this is not what is meant, even today, when referring to the discrete structure of the DNA as a "code", which uses its own discrete data base, the bases or the nucleotides, to run the program of Life.

What happens though when we embed programs in physical continua? Concurrent processes over networks already face this challenge, as these happen to be distributed in physical space-time, that we better understand by the mathematics of continua. Synchronization issues and a lot more make the situation very different [1]; yet, the still discrete data types allow networks' programs to repeat rather well. We may open a remote web page hundreds of times and get always the same result. Indeed, identical repeatability of a programmed process is still the main *aim* of Concurrency and Networks Programming (the enormous amount of research on reliability and portability of software is part of this effort). And, in general, it works.

And what if we embed the undoubtly discrete structure of the DNA into an organism, beginning with the cell's cytoplasm, which happens to be (almost) a turbulence, in contact with the quasi-fluid structure of enthalpic oscillations of macromolecules? As a matter of fact, more than 60% of fertilizations in mammals fail (do not lead to a birth): this is not a great achievement for the (Intelligent) Designer or Programmer (see [41] for more details). In contrast to programming, one of the main invariants in Biology is variability, non-repeatability, within "structurally stability". The later is a hard to grasp notion, extensively studied by Thom in topological terms [52]. Our notion of "extended criticality" in Section 8 is a modest attempt in this direction (living beings are modelled as "extended critical transitions").

4. From the program to the organism

As already mentioned, Schrödinger theoretical thinking, the attitude towards knowledge that brought him to revolutionize microphysics, lead him also to a search for a general frame to understand life, in his dissatisfaction for the pure collections of "differential" data. As for this crucial issue, Schrödinger refers to the already known mutants of the *Drosophila* (observed or induced mutations *cause* teratogenic effects in the phenotype, such as strange eye colors) and observes:

> "We call … "locus", or, if we think to the hypothetical material structure which serves as support of it, a "gene". In my opinion, the fundamental concept is more the *difference of properties* than the property it-self."

Schrödinger is perfectly aware that the differential method, in Natural Sciences (an observed or induced difference in a parameter induces a difference in an observable), does not lead, per se, to a *direct causal relation*, from the parameter to the observable (in this case: from the *wild* gene to the *normal* phenotype). Why the locus, whose mutation induces a change in the color of the eye of the *Drosophila*, should ever support the normal structure leading to the normal eye? In Physics, under this experimental protocol, one immediately tries to theoretize and *use* or *invent* general principles, in order to propose a possible direct determination. One observes, say, that different weights fall in (roughly) identical times and … Galileo proposed a general law for falling bodies. Observations on different frictions brought him to invent the law of inertia, a limit principle (he could never observe the absence of friction, yet he proposed the only pertinent, fully general *principle*, at the limit). Later, the geodetic principle unified both phenomena, gravitation and inertia, in Relativistic Physics. In suitable phase-spaces, it

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[2] Hadamard's seminal work on the geodetic flow on negative surfaces is the other fundamental, largely qualitative, approach to unpredictable dynamics.

is in the background also in Quantum Physics, as for conservation laws at least, see [5]. Instead, a large amount of DNA loci inducing the white eye mutant were later observed in the *Drosophila*. Moreover, teratogenic effects, such as displacements of wings and legs, identical to those induced by mutations, were induced by changing the magnetic field or the pressure on the embryo . . . , [51]. Where is the (wild) “gene" causally related to the (normal) phenotpe of eyes, wings and legs?

Thus, Schrödinger first proposes the original notion of code or program as for the chemical level, as a general principle of intelligibility. This is a tentative and rather unsatisfactory idea by, in particular, its Laplacian nature, as we observed and we know from Schrödinger himself. It is even more so, since the DNA of many animals has been fully “decoded”: besides a few exceptions, which do not provide a law, in no general way we know how to relate the *wild* DNA to the normal phenotype. Yet, in the rest of the book, he goes further. In spite of several remarks, in the first part, on the possible relevance of quantum effects in genomic, he later wonders whether we should expect a theoretical autonomy of Biology, “ . . . irreducible to the ordinary laws of physics”. As a matter of fact, he recalls that “ . . . the classical laws of physics are modified by the Theories of Quanta . . . ”. An analogy better clarifies the problem: Schrödinger suggests considering

> “ . . . an engineer who is only familiar with steam engines. After having inspected the construction of an electric motor, he would be willing to admit that the latter functions according to *principles* that he does not yet understand”.

Of course, some principles such as energy conservation, entropy growth and so on do unify the Physics of these engines, yet electromagnetism has proper laws, hardly derivable, by direct connection, from the thermodynamics of the steam engine.[3]

Of course, both Schrödinger and Bohr search for the unity of knowledge, but their experience tells them that this is a difficult conquest: in no way one gets for free the *unification* of the quantum field and the relativistic one, by imposing one as the only possible (mathematical) frame. The two phenomenal levels have been first organised by pertinent theories, then unity is searched and . . . it is a matter of “unity” not reduction. That is, the attempts towards unification do not erase one theory in favour of the other, but redesign both from a novel perspective. So, String Theory radically revisits quantum objects and Non-Commutative Geometry (the other main contemporary path towards unification [17]) entirely reorganises the geometry of physical space.

Similarly, one has to explore the global context of the organism, with respect to the local chemical effects: unity will be a further conquest. This is exactly what Schrödinger claims:

> “ . . . let’s try to hint to the possible meaning of the principle of entropy at the *global scale* of a living organism, while forgetting for the time being all what we know on chromosomes and heredity . . . ”.

The motivation for looking at entropy is clear, for Schrödinger:

> “Life . . . is not only based on the tendency to go from order to disorder, but also on an existing order that maintains itself.”

Thus, first Schrödinger suggests explicitly a change in the phenomenal level, by forgetting molecules. Then he looks at order or organisation at the global scale as a form of *negative entropy*. In no way Schrödinger analyses this decrease of entropy as growth of “information”, in particular of the kind he was discussing in reference to the molecular “code”. But he explicitly refers to it as a form of Gibbs free energy, a completely different perspective (see Section 8.3). Let me go now to some important reactions to Schrödinger audacious conceptual explorations.

In a 1987 volume in honour of Schrödinger two major bio-chemists, L. Pauling and M. Perutz (Nobel winners as well) aggressively address Schrödinger lucubrations: Schrödinger on organism is “vague . . . superficial” since for example, according to Pauling, we have

> “the ‘one gene one enzyme hypothesis’ . . . Schrödinger does not seem to have heard of this.[4]”

Now, as such, this key remark either is trivial or it is blatantly false. If one takes it as a *definition* of “gene”, as many seem to do (a gene is “what engenders” one enzyme or one protein), then it would please M. de Lapalisse and it is analogue to the notion of XVIII century phlogiston (that “which engenders” the flame). If, instead, it is to be considered as referring to a gene as a sequence in the DNA, as in this debate on chromosomes, it is well know that it does not work (see, for example [22], where one may learn that the “one gene – many proteins” fact was known since the ‘80s). But more can be said today since the work on alternative splicing, whose consequences may be briefly described as the “one gene - many proteins; some proteins – no gene” hypothesis (see Brett [13] and Bartel [12] among others, or Longo and Tendero [41] for further reflections on the current situation).

And here comes the prevailing dogma in molecular circles: “Life can be explained on the basis of the existing laws of Physics” [48].

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[3] It is worth recalling that another great physicist of Quantum Mechanics, shares a similar viewpoint in a short paper on the issue. “The intrinsic impossibility of an analysis of the stability of atoms in mechanical terms, presents a strict analogy with the impossibility of a physical or chemical explanation of the characteristic vital function.” [14].

[4] The hypothesis was proposed by Baedle and Tatum in the ‘30s, by a (pioneering) differential analysis and the typical conceptual drift, since a *mutation* was observed as inducing a *dysfunctional* enzyme [19]. This issue of induced/observed differences (mutations) and their causally incomplete explicatory role is exactly the point raised by Schrödinger (see the quotation at the beginning of this section).

Personally, this author is a monist and a materialist. We have no doubt, or it is our main metaphysical assumption, that the reader as well, and the many bacteria in and out both of us, we are all physical matter. The issue is *theoretical* not *ontological*: which *theory* may better help to understand those active, living organisms? Quantum Physicists, on the ground originally of very few experiments (the discrete spectrum of the hydrogen energy, the photo-electric effect, the strange behaviour of the three bodies of the helium ...), dared to propose a radically different theoretical frame, just because of a change of physical scale. And Darwin, in order to propose the only biological theory that, up to today, has the breath and generality of the major physical theories, totally disregarded the Physics of his time. Perutz's dogma has nothing of the unifications of the kind we mentioned above and towards which we need to go. It is just a prejudice.

More precisely, it corresponds to the largely financed myth that the *stability* and the *organisation* of the DNA and the subsequent molecular cascades completely determine the *stability* and the *organisation* of the cell and the organism. This is false, since the *stability* and the *organisation* of the cell and the organism causally contribute to the *stability* and the *organisation* of the DNA and the subsequent molecular cascades. Thus the issue of the global order of the cell (and the organism) must parallel the absolutely crucial molecular analyses.

But ... do not we get in a conceptual vicious circle by this view on life? yes, of course, we do. Yet, even metabolic cycles in a cell are circular and the bootstrapping of life is not better understood by looking only at their, molecular, level. There is a lot of fuss concerning circularities either in the attempts to avoid them (while they are the salt of intelligibility) or by putting them all in the same farandole, from Gödel to baroque music, Escher or life phenomena. Let us shortly focus on this, in order to avoid confusion and too easy conceptual abuses.

5. Circularities and dimensions in Logic and Computing

Logicians and Computer Scientists are well aware that our business begun by the invention of a major vicious circle. In 1931, Gödel constructed a proposition G of Peano Arithmetic (PA), which is provably equivalent to its own unprovability. He invented for this the notion of Gödel-numbering, the coding by numbers of propositions over numbers ($\underline{G}$, say, is the number-code for G), and of computable or recursive function. This allowed him to express formal deductions as number-theoretic, computable, functions (they go from coded propositions to coded propositions, as numbers) and, thus, to "flatten down" the meta-theory of PA into PA itself. In other words, deductions *over* PA are encoded by Theor, a predicate *of* PA, that is $\mathrm{PA} \vdash A$ (Arithmetic proves A) yields $\mathrm{PA} \vdash \mathrm{Theor}(\underline{A})$. Thus, G is constructed in order to realize

$$\mathrm{PA} \vdash (G \leftrightarrow \neg\mathrm{Theor}(\underline{G})).$$

Unprovability of G and of its negation, $\neg G$, easily follows from these very difficult and original coding tricks.

The following year, Church invented the λ-calculus, where any formal sign x can be applied to any other sign, including x itself. This is understood, semantically, by a so called reflexive object in categories, that is by an object D (a non-trivial mathematical structure) which is isomorphic to its own space of (endo-)morphisms (formally: $(D \Rightarrow D) \equiv D$). Once more, a higher type object is flattened down by some sort of coding: the functions *on* D are identified with or encoded by elements *in* D (see [11]).

More recently, an impredicative Theory of Types (1970, see [25]) dared to define types also by a universal quantification over types themselves (for all X which is a type, formally $\forall X$:Type) referring to the very collection of types which is being defined (formally: ($\forall X$:Type.A) is in Type). The relative consistency of this theory was first assured by a difficult consistency or normalization theorem, then by a non-obvious categorical meaning. In short, the universal quantification above may be understood by a beautiful symmetry with respect to existential quantification. Grothendieck toposes are used for this, following Lawvere, and the meaning of quantification pops out as the right/left adjunction with respect to a fundamental functor (the diagonal functor: see [4] for details). In short, impredicativity is understood as "closure under indexed products", that is in categories that contain, as objects, products indexed over all objects. Once more though, this latter construction relies on a reflexive object, where functions are coded by elements (the categories closed under universal quantification as indexed product are built over a D with $(D \Rightarrow D) \equiv D$, an isomorphism see [29,39]).

In summary, by coding, one embeds the higher level structure into the lower one in all different senses of "structure". In Gödel theorem, the metatheory of PA is encoded as a subtheory of the theory (PA); in particular, the internal predicate Theor encodes/embeds metatheoretic provability into PA (see [36] for more on incompleteness). In type-free theories, meaning is given over a structure D such that $(D \Rightarrow D) \equiv D$. Thus, a function on D may be coded as an element of D and its mathematical behaviour is fully represented by that of the coding element. And this gives (categorical) meaning also to Impredicative Type Theories. The first circularity, Gödel's one, is at the core of the main single theorem of the XX century Logic and originated Computability Theory, thus, with Church, Turing and many more, modern Computer Science. The others contributed to the design of major programming paradigms, besides their logical and mathematical interest.

Let us insist, "just" codings originated and explain these circularities. And these very codings are changing the world: by Gödel-numbering as 0's and 1's, texts, images, music ... we are letting Mankind access to memory and knowledge of Mankind, over the Web of our arithmetic computers, an historical change comparable to the invention of writing. Yet, does this resemble to the circularities that one may describe in Natural Sciences? Not at all, as we shall see in Sections 6 (Physics) and 7 (Biology).

Before moving towards other disciplines, let us conclude this section by one more observation. The notion of (Cartesian) dimension does not apply in the frames mentioned above (Arithmetic, type-free and impredicative theories, the main logical contexts for circularities). Infinite discrete structures, the natural numbers $\mathbb{N}$ in particular, are isomorphic to any finite product: $\mathbb{N} \equiv \mathbb{N}^m$, by a computable isomorphism. That is, any finite string of integers can be encoded as an integer, and this is crucial for Gödel's and Turing's approach to computability and their applications.

Moreover, as a consequence of the isomorphism at the core of the other two frames, that is of $(D \Rightarrow D) \equiv D$, one has $D \times D \equiv D$ for any such D (in general, one only has an isomorphic embedding, a retraction to be precise, but this is the same for our purposes). Then, of course, any finite product D^m of the working space D is isomorphic to (can be isomorphically embedded into) D, within the intended category. Thus, the proper of the notion of dimension disappears.[5]

This makes no sense in Physics, as it would simply destroy most of its theories: the dimensional analysis, that is the analysis of the number and type of variables in a function $f(x_1, \ldots, x_n)$, is crucial in Physics and theories radically change when changing dimension. From the analysis of heat propagation (Poisson equations), whose characteristics are very different in one, two or three dimensions, to the "mean values theories", which differ radically from two, three or four dimension, and a lot more. Not to quote Relativity Theory where the unified *four* dimensional structure of space-time is crucial or String Theory, where intelligibility is given by moving to 10 or more dimensions. And Mathematics proves it beautifully, in relation to the "natural topology" on $\mathbb{R}$, the real numbers, that is in relation to the so-called Euclidean or interval topology, which we already mentioned. Recall first that the interval topology is "natural" since it comes from physical measure, which is, by principle, an interval. Then, and this is fantastic, one can prove the following:

$$\text{if } A \subset \mathbb{R}^n \text{ and } B \subset \mathbb{R}^m \text{ are open sets and } A \equiv B, \text{ then } n = m.$$

This theorem says that dimension is a topological invariant, when one takes the natural topology in a space manifold, in the sense of Riemann. This result is false when considering, for example, the discrete topology on $\mathbb{R}$, or, say, a weakly separated topology. This is a remarkable connection between Mathematics and Physics, via measure. As we have seen above, any similar fact provably fails in arithmetical, type-free or impredicative frames, as for cartesian products.[6]

As a side remark, one should also observe that the bottom line of computing is always type-free (shall we directly say "dimension-free"?): the machine language is eventually encoded by finite and undistinguishable sequences of 0's and 1's, the bits in the digital core of every computer. They must be undistinguishable, as they code data, programs, compilers, operating systems ... everything, in a way that one can act on all of them by programs – everything may be used as a data for a suitable program (of course, some important "bricolage" is required in order to distinguish some subsets of 0's and 1's and implement, say, some aspects of von Neumann architecture or ... bootstrapping in a computer, but these are some needed technical details, principles and theorems are a different matter).

With the richness and the limits of mathematical circularities in mind, let us now go further.

6. "Resonance" as circularity in Physics?

It is well-known, since Newton, that the universal law of gravitation, by mutual attractions between planets (resonances), may induce diversions from their elliptic orbits. Technically, planetary resonance means that two planets are on the same line with respect to the Sun, a situation of maximal gravitational interference. As already mentioned at length, interaction is expressed by the non-linearity of the equations. In conjunction to physical measure, as an interval, this gives the unpredictability of this deterministic system (even planetary ones, as we said) in short astronomical times (see [35]). We will discuss here the relation between dynamical unpredictability and logical undecidability.

In a sense, it is the systemic unity of this "simple" gravitational system that produces chaos: the global structure of interactions affect each body's evolution. One may see in this some analogies with the global game of signs that affects single signs in, say, impredicative theories: the collection of types appears in the very definition of some individual types. Or, even, the meta-theory vs. theory interaction may be evocated or other (reciprocal) coding techniques in Logic, following the circularity in Gödel's theorem.

Technically, though, there seem to be no direct relation (at least that one could see: the 12 equations of the three gravitational bodies examined by Poincaré are, logically, a flat and simple first order system, no way to spot logical circularities). Yet, there can be found an epistemological and an indirect mathematical connection.

Epistemologically, though, the Three Body Problem is a predecessor of Gödel's theorem. Consider the 12 equations as a formal system; make an assertion, as a formal proposition, on the situation of the system after enough time. Poincaré showed the existence of a finite time of unpredictability and, since Laskar's work, we can compute this time on the grounds of the best

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[5] This motivates the need for weakly separated topologies viz. T_0-topologies over the "geometric" structures interpeting type-free theories: interval topologies, see below, do not allow these isomorphisms. More generally, Cartesian Closed (topological) Categories, even as models of typed calculi, force global continuity from componentwise continuity, which is impossible in continuous manifolds with interval or "physically" meaningful, enough separated, topologies.

[6] In concurrency, exactly because physical space is in the background, some suggest to give a role similar to dimension to the notion of "level of interaction", two for functional application (sequential systems), more for concurrent systems, see [15] among others; this is a relevant paradigm shift in computing.

conceivable approximation or measure interval of the baricenters' coordinates of the planets (these are elastic, of course, and subject to many deformations, including thermal fluctuations). The (formal) assertion on the future is then "undecidable" with respect to the given formal frame of the equations, if one wants to express in this way, as undecidability, the modern quantification of unpredictability.

Poincaré had thus a competent feeling of this peculiar "undecidability" and firmly, even violently, opposed Hilbert's philosophy of Mathematics, a search for complete and decidable knowledge (a view of "Mathematics as the Chicago sausage machine, automatically producing theorems and sausages from pigs and axioms", observed Poincaré). Of course, he could not formalize his philosophy more precisely, as Gödel was not yet born, but the right intuition was there. That very intuition which led him to conjecture, in a letter to Zermelo, the independence (undecidability) of the Axiom of Choice from Formal Set Theory, as depending on structural (model-theoretic we would say today), not just formal properties of Sets [42].

As a matter of fact, this philosophical remark cannot be pushed further. Undecidability is an internal issue of formal systems (it concerns a purely mathematical assertion), while unpredictability, as already mentioned, pops out in the interplay between a mathematical (possibly formalized) system, as a model, and a physical process: the evolution of the latter cannot be predicted, beyond a certain time limit, by the intended model. And this by the conjunction of *mathematical* chaoticity and the intrinsic, theoretical, limitation of (classical) *physical* measure, an approximation by principles. However . . .

Mathematically, an indirect connection may be given. Martin-Löf, in [43], gave a very interesting notion of randomness, for infinite sequences of integers (0's and 1's, say), relative to a probability measure. His definition is "à la Gödel", since, following early ideas of Kolmogorov, it is only based on Recursion Theory (in short: an infinite sequence is random if it passes all *effective* "statistical tests"). For physically meaningful probability measures, an infinite ML-random sequence is (strongly) undecidable (i.e., non recursively enumerable – it actually contains no infinite recursively enumerable subsequence).

Now, dynamical systems yield internally a notion of "typicality" (or genericity): a point is typical if its orbit describes the dynamics from a statistical viewpoint, in Birkhoff's ergodic sense (phycisists would also say: a typical point is "randomized" or it is "generic" for the dynamics). M. Hoyrup and C. Rojas (in collaboration with S. Galatolo and as Ph.D theses, under this author's supervision), generalizing a result by V'yugin [57], have shown in [23] that in a metric space, every ML-random point is "typical" in this dynamical sense. Moreover, under suitable but interesting conditions, also the reverse holds. In short, and as conjectured by this author and proved in [23,24], the ML-randomness of symbolic orbits,[7] in effectively measurable dynamical settings, is equivalent to the chaoticity of the intended dynamical system.[8] And, as already observed, chaoticity yields deterministic unpredictability, in classical dynamics.

In conclusion, physical systemic unity as a specific form of resonance or circularity, has no direct connection with the "circularities by coding" proper to Logic and probably to all linguistic constructions ("this phrase is false" also encodes the meaning of the phrase into itself; the negation along the path from meaning to syntax, gives the contradiction, Gödel's style – well, it is Gödel who was inspired by the Liar's paradox). Yet, epistemologically, Poincaré's and Gödel's negative results may be related and this relation has a technical counterpart. That is, by defining arithmetical randomness via Recursion Theory, as a strong form of undecidability, one may show its equivalence to deterministic unpredictability as randomness (under suitable measures) in dynamical systems, via Birkhoff approach to ergodicity.

Hilbert, also a remarkable mathematician of Physics, could not see the conceptual continuity between his foundational views on the completeness and decidability of formal systems of signs for Mathematics and Laplace's philosophy of Physics concerning the predictability of deterministic systems. But this was one hundred years ago, in a time of growth of "positive knowledge". It is amazing that, decades later, many still look for a complete determination of the phenotype by the discrete sequences in DNA, the formal alphabetic signs of a reinvented Laplacian–Hilbertian formalism for life.

7. Circularities in life phenomena

Democritus used to annotate atoms by letters of the alphabet. The elementary, undivisible components of matters had to be understood in analogy to the elementary and simple components which encode the sounds of language. By putting letters together we get to meaning, by phonemes, similarly as systems of atoms produce visible, meaningful objects.

Theoretical Chemistry has been transforming Democritus idea into a science, indeed into an alphabetic "rewriting system" for atoms and molecules, in the sense of Computing. Also its experimental counterpart, in vitro, is largely understood by rewriting techniques, which are extensively developed today also in bio-informatics. Unfortunately (or fortunately? otherwise we would not be here . . .), in Biology, interacting molecules are embedded in turbulent active frames, enclosed into semi-permeable membranes, with highly unpredictable effects on the formal dynamics of chemical signs.

A large amount of relevant work has been focusing on the "emergence by circularities" in metabolic cycles, see [49] for example. These cycles are extremely complex even in the simplest prokaryotic cell, yet they seem to lead to circularities that may be understood in formal terms and by computable dynamics, as long as they are considered "per se" by excluding the role of contexts (see [45]). It is difficult though to elaborate with rigour about possible technical connections between metabolic cycles, their emergent properties, and dynamic unpredictability. It is largely acknowledged that emergent properties are a form of unpredictable phenomena, in the sense of Poincaré, of these molecular systems (see also [30] on non-linear dynamics in life phenomena, among others); this is why many systemic approaches go well beyond the chemical

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[7] A symbolic orbit, thus a sequence of digits, may be obtained by construcing a finite partition of the phase space.

[8] A weaker notion of algorithmic randomnes, due to Schnorr, was used for this reverse result [24].

level. We claim that, from these perspectives, a form of incompleteness of the molecular approach in Biology is derivable (a “causal" incompleteness [41]). Of course, the incompleteness of formal systems with respect to meaning or of the analyses of chemical cascades with respect to phenotypes, does not mean “useless”: formal deductions and computations are essential to Mathematics, as well as DNA activities and their formal investigations are the main components of any analysis of life.

We will focus here on a different, possibly more complex kind of circularity, the one due to the mutual interactions of different levels of organization in a cell and, even more so, in an organism. The project is to “complete” (or, better, *complement*) the incompletable. The idea is that the challenging circularities in Biology are not found at the molecular levels, where they are more or less easily modelled by computable tools (see [16,45]), including the many “feedback" effects in metabolic cycles, but in the interactions between different levels of organisations (cells, tissues, organs, organism . . .).

Organelles (microtubules, mythocondria . . .) are part of cells, which compose tissues, and thus organs. These are integrated in organisms, which regulate them in various ways (by hormones, immune and nervous systems . . .). Beautiful Mathematics has been developed for the analysis of some of these different levels of organization. Morphogenesis and Phyllotaxis mostly deal with shape and structure of *organs*. Far from trivial non-linear systems analyse optimal distribution of colors or forms, along the regular shapes of shells and plants, see [32]. As we recalled, Turing has been one of the pioneers in this area, beginning by his 1952 paper, but D’Arcy Thompson, Waddington, Thom and many others should also be quoted. The fractal structures of lungs and vascular systems, for example, have been closely analyzed and their fractal dimension formally derived by optimality criteria in *energy* exchange by surface or volume, within constraints in volume.

As for the level of tissues, the dialogue of cells has been analyzed by “mathematical nets” (one should quote here Von Neumann, Hopfield, G. Parisi . . .). In particular, neural nets have been largely leading the mathematical analysis of brain, by a non-trivial use of tools from Mathematical Physics, statistical approaches in particular. The difference here is that *gradients of energy* are exchanged, more than energy as in the previous case (many call “information” a gradient of energy). This is a crucial mathematical difference, as in the latter frame stable structures are obtained by attractors, say, or other related form of limit dynamics, in contrast to the geodetics that preside most of the descriptive aims of Morphogenesis or Phyllotaxis. The result is that these two different levels of organization (organs as shapes vs. tissues as functionalities of cells’ networks) do not talk to each other, both the Mathematics and . . . the communities. This is due, first, to the different role of individual cells given in the two different frames (they are the support of any activity, in networks, while they are largely neglected, as individuals, in Morphogenesis and Phyllotaxis – “organs form cells, not cells organs”, as claimed in [32]. Second, it is the different physical dimension of what is exchanged (energy vs. gradient of energy) that engenders very different mathematical analyses. And both these analysis are far away from the metabolic cycles and molecular cascades that take place within or between cells.

Now, it happens that organs are made out of tissues and that tissues are part of organs and both are integrated in organisms that regulate them in various modes, as we said, by many ways “upwards-and-downwards" causal effects. We should perhaps talk here even of “resonance effects” between different levels of organization. These interactions give unity and contribute to the stability, as well as to the dynamic instability, of the organism. And they seem to propose a much more complex form of circularity than the one can find in the (relatively simple) resonance effects between gravitational bodies. These are situated in just one level of organization, governed by just one mathematical law, Newton’s universal law of gravitation. Moreover, there is surely no way to encode organs into tissues nor conversely and mimic by this the logical construction and understanding of circularities.

As for the remote molecular level, we are far from any general understanding of the *direct* role of the DNA in the formation of the organism. As already observed, following Schrödinger, the analyses which relate in vivo the genotype to the phenotype are of a differential nature, with a few exceptions (a genetic difference engenders a teratogenic effect or just a difference). Consider the difference of sex, to take the most well known case: the chromosomes XX and XY do not contain a coding of female or male sexual organs respectively, but act as switches that change the sensitivity of the embryo to hormones. In no way it would be right to say that chromosomes “code" for the structure of sex organs: these are the result of an interactive process where the proteins, largely, but not exclusively, originating in DNA, are the (essential) bricks, but not the “law-code" nor the “executive power", as still many claim following Schrödinger’s early Laplacian views (see the quotation in the introduction).

8. Some work directions

In the second half of his 1944 book, Schrödinger deals with his concern for a theory of organism as “structure maintaining organization”. In particular, he stresses the tension between the usual growth of entropy, proper to all thermodynamic processes, and the formation and maintenance of an entropy of opposite sign, a *negative entropy*, related to the formation and maintenance of organization.[9] Below, we will discuss some possible developments of Schrödinger hint towards a suitable notion of negative entropy, that we named *anti-entropy*. Let us first refer to two recent reflections which tackle this issue of organic unity, from different, though related, view-points.

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[9] Entropy is associated to a downgrading in the “organization” of energy: mechanical energy, typically, is more organized than heat. Negative entropy is produced when energy or matter, solar heat or food for example, are used to produce organized matter. And this, according to Schrödinger, also in plants and animals.

The main observable in Physics is surely energy. From Galileo inertia, to the energy spectrum as key Quantum observable, energy conservation principles unify 400 years of an extraordinary variety of theories. Hamilton least action principle and the geodetic principle (see [5]), in their full generality, refer to "action", which is energy × time.

In Biology instead, *organisation* is the primary, astonishing observable. Energy seems more a parameter: food is surely needed, one gets fatter, but how does energy become organization, that is the question (in nine months and with a few watts, a woman can make a baby, an incredibly complex structure). One of the main claims in several papers by Bailly and this author is that Theoretical Biology may need a change in the observables and parameters with respect to current Physical Theories. It is a matter of a change of perspective or "just" of the pertinent phase (or reference) space proposed while theoretizing. We will shortly see below some ongoing work, where organization, time, and anti-entropy will be added as observables or looked upon in a different way from what is usually done in theories of the inert. As an example, but more discussions will be developed below, observe that Thermodynamics, by inventing *entropy*, a new observable, relevantly enriched or even modified the analysis of *energy* as carried on in classical Physics.

8.1. Extended Criticality

There exists an area of Physics where organisation matters. It may be roughly defined as the Physics of critical transitions (or of Criticality). The formation of crystals, obtained by passing through a critical point, a phase transition, is an old and paradigmatic case. Yet, the analysis of self-organization in Physics was first turned into an autonomous approach by Prigogine. Since the late '40s, he stressed the interest of "far from equilibrium" Thermodynamics, a discipline still now called by many "the science of systems at equilibrium" in spite of Prigogine's work and the Nobel Award associated to it, and he invented the notion of dissipative system. Then, by the analysis of "self-organized far from equilibrium systems", Prigogine, Nicolis and others (mostly from the Bruxelles' school, see [46] for a relevant reference) opened the way to a broad area relating some aspects of the physics of criticality to possible analyses of life.

The idea is that, far from equilibrium, in systems that are dissipative or in a permanent exchange of energy (and matter) while producing internal and external entropy, changes of state may occur which correspond to a (sudden) formation of a "structure of coherence". This pops out from more or less disordered state, under random fluctuations. Thus the slogan "order by fluctuations (or noise)" was proposed, that so much displeased R. Thom. As a matter of fact, Thom was the great mathematician of the genesis of forms ruled by equational determinations of global structures, punctuated by singularities [52] – indifferent to noise (see [2] for the debate Prigogine vs. Thom).

In self-organised criticality, during the process of change of state, the global structure is involved in the behaviour of its elements: the local situation depends upon (is correlated to) the global situation. Mathematically, this may be expressed by the fact that the correlation length formally tends towards infinity (the case with second order transitions, such as para-/ferro-magnetic transition); physically, this means that the determination is global and not local. In a very synthetic way, in Physics, a critical transition is related to a change of phase and to the appearing of critical behaviors of some magnitudes of the system's states – magnetization, density, for example – or of some of its particular characteristics – such as correlation length. It is likely to appear at equilibrium (null fluxes) or far from equilibrium (non-null fluxes). If, in the first case, the mathematico-physical processing is rather well-understood (thermodynamics for the bridge between microscopic and macroscopic description), on the other hand, in the second case, we are far from having theories as satisfactory.

Some specific cases, without much stress on the far from equilibrium situation nor reference to Prigogine, have been extensively publicized by Bak, Kaufmann and others (see [10,30]). The sand hips, whose criticality reduces to the angle of formation of avalanches in all scales, percolation (see [33]) or even the formation of a snow flake are interesting examples. The perspective assumed is, in part, complementary to Prigogine's one, usually: it is not fluctuations within a weakly ordered situation that matter in the formation of coherence structures, but order stems from chaos. Yet, in both cases potential correlations are suddenly made possible by a change in one or more control parameters. For example, the forces attracting water molecules towards each other, as ice, are potentially there: the passage below a precise temperature, as decreasing Brownian motion, at a certain value of pressure and humidity, allows these forces to apply and, thus, the formation of a snow flakes, typically. Local and global symmetry breakings give the variety of organized forms and their regularities.

In recent work [8], we propose to analyze the organization of living matter as "extended criticality". The idea is that matter, in its living state, is in a permanent critical transition, constantly reconstructing its organization. All the physics of criticality necessarily deals with point-wise critical transitions: this is part of the very definition of phase transition and it is used in an essential way by the main mathematical tool in the approach, the "renormalization methods" (see [20]). We consider, instead, a set (whose closure is) of null-measure, an extended interval of criticality with respect to all pertinent parameters (time, temperature, pressure ...). It is as if a snow flake could stand variations within a relatively large interval of its control parameters by continually reconstructing itself, in a permanent "going through" the critical transition (in an "autopoietic" manner if the reader likes the notion [55]). One then has an extended, permanently reconstructed *global* organization in a dynamic interaction with *local* structures, as the global/local interaction is proper to critical transitions.

So far, our analysis, in the paper quoted above, has been largely conceptual, since, by the loss of the mathematics of renormalization, there seem to be little known Mathematical Physics that applies to this physically singular situation.[10]

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[10] M. Montevil is making remarquable mathematical progresses by his ongoing thesis work.

We are thus trying to tackle the issue by looking also at two fundamental aspects of organized living matter: time and (anti-)entropy. The latter is our current attempt to develop Schrödinger's idea on negative entropy, by a related but different concept, as we shall explain below.

8.2. Protension and the Rhythms of Life

When a paramecium is surrounded by a circle of salt (and it really does not like that), it tries various directions then ... it launches itself and tries to go beyond the circle. Of course, sometimes it works, sometimes it does not. The number of trials and errors, before the "jump", may depend on the individual. One has to be careful, in these analyses, not to be exceedingly anthropomorphic (we always are, somehow) and project on a unicellular our complex behaviour. It is equally wrong though to claim that an amoeba or a paramecium (a huge unicellular animal: more than 1/3 of a millimetre diameter) just move only along a gradient. In vitro it is trivially so, but in their very polluted natural and preferred environments they continually arbitrate between a large amount of different concentrations of matter, of diverse interest for them: different chemical gradients, a small bacterium ... (the paramecium has about 2000 flagella and uses some of them to push food towards an opening, used as a mouth).

Experimental workers in the areas admit that these animalcules have some sort of "memory". We prefer to call *retention* this "trace" left by action. But retention makes sense (it is used for a selective advantage, in Darwinian language), if used for action. Call then *protension* this "leaning towards" or expectation that makes action guided by retention.

Of course, there must be some molecular mechanisms supporting these activities, this is a triviality for a monist like this author. Similarly, Democritus atoms or Planck's quanta composed and compose Galileo's falling bodies or Einstein's celestial ones, and these scientists were well aware of this. Yet, the autonomous and fundamental theories they developed, totally disregarding the atomic/elementary components, gave us very informative frames for knowledge. Today, in view of the richness and autonomy of these theories, the problem of their unification (recall: unification, not reduction) with Quantum Physics is well posed and we can soundly work at it. If they had been waiting for the explanation in terms of "atomic or quantum fields" of the phenomena they were witnessing and that led them to fundamental theoretizing, we would still be with Aristotle's Physics. (As a matter of fact, why "fundamental" should always mean "elementary"?)

These very pretentious analogies are just mentioned here to justify the method. Our theory of retention/protension and rhythms, in [7], is a little, very simple mathematical frame for accommodating this crucial observable of life, time. Retention is mathematically defined by a relaxation function, a very common tool in Physics to represent processes going back to an equilibrium (besides, some physical material present "memory" effects). Protension is given by a time-symmetry, corrected in order to make it monotonically depend on retention (our assumption: there is no protension without retention). The paper continues by proposing an embedding of biological time into a *two dimensional manifold*, a mathematical "scheme" for understanding time. In short, we propose to understand internal rhythms in animals (plants do not seem to have any, but the debate is open) by accommodating them in an orthogonal fiber, with respect to the oriented dimension of thermodynamical time. Following a technique developed for space in physics (Kaluza–Klein), this extra time-dimension is compactified, that is, it is a line with an extra point and closed onto itself, a circle thus.

The simple mathematics used is an attempt to pursue a crucial aspect of extended criticality, the unity by correlations given by rhythms. As a matter of fact, synchronization, from metabolic rhythms to neural oscillations, seems at the core of the structural coherence of living individuals.

8.3. Anti-entropy

Extended criticality makes sense if the intended coherence structure or global organization is permanently reconstructed. Both the formation and maintenance of organization goes in the opposite direction of entropy increase, as we already observed in reference to Schrödinger remarks on the need for an analysis of *negative entropy*. The idea, closely developed in [9]), is to decompose entropy in a positive (thermodynamical) component, S^+, ruled by the Second Principle of Thermodynamics, and a negative one, S^- (anti-entropy), governed by a new principle. This extra "law" applies only to living beings, as we consider anti-entropy identical to organization or biological complexity, K, but by opposite sign ($K = -cS^-$), modulo a dimensional constant. Thus, anti-entropy is a new observable, not just entropy with a negative sign, as negative entropy. A purely conceptual analogy may be done with anti-matter in Quantum Physics: this is a new observable, relative to new particles, whose properties (charge, energy) have opposite sign with respect to matter. We hint very briefly here to the formal principles only, and even more shortly to their consequences.

The principle of "existence and maintenance of anti-entropy" simply says, by two inequalities, that (internal) organization cannot decrease (it increases, during embryogenesis, or is conserved):

$$-K = cS^- \leq 0 \; and \; -dK/dt = dS^-/dt \leq 0 \qquad (1)$$

On one side, then, the many thermodynamical processes in living beings increase entropy (by the second principle of thermodynamics), on the other, organization is added or maintained, by (1).

In a footnote Schrödinger observes that the negative entropy he is talking about should be considered as (a component of) Gibbs free energy, G. Now, $G = H - TS$, where S is entropy, T is temperature, $H = U + PV$ is the system's enthalpy (U is the internal energy, P and V are pressure and volume). Without getting into the technical details, we just mention that from the analysis of metabolism, R, as free energy flux, and the identification of H with the mass, M, modulo a dimensional constant a $(H = aM)$, we derived a balance equation relating R to entropies:

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

A fundamental and new term here is σ, the speed of entropy production related to the *irreversibility of all processes involved* (including the variation of S^+ and of $K = -cS^-$).

Let me just mention here that, by analysing closely $T\sigma$, we could derive a diffusion equation which seems to fit surprisingly well Gould's diagram relating biomass, complexity and time, along the evolution of species [27]. The idea is that $T\sigma$ is the global effect produced by evolution. That, it is one of the (rare?) observables or "dimensions" which result from evolution as a global process (energy consumption and degradation, increasing organization – species formation and differentiation). This is why it gives a qualitative, yet mathematical description of the entire process, with the peculiar growth of organization due to a simple mathematical reason: the original symmetry breaking in evolution, the formation of the archeobacteria, that is the origin of life, propagates as an asymmetry along time and increasing biomass. In our interpretation, the increasing complexity of life (of phenotype, not of DNA!) is just a mathematically easy to understand consequence of the symmetry breaking corrisponding to the big-bang of life. Yet, this had to be described equationally. We did so by writing a diffusion equation inspired by Schrödinger famous equation. As a matter of fact, the determination of the source term in the equation (and an alternative derivation of it) is given by adapting Schrödinger wave equation, with real instead of complex coefficients, to our context. The consequences of this balance analysis allows also to develop some remarks on ontogenesis and aging, which further relate our two forms of entropy to biological processes. The interested reader should consult [7] for details.

9. Conclusion

Beyond the many technical details which are required to make sense of this, let me conclude by observing that a common methodology underlies the three approaches in previous section. We did not propose an incompatible theoretical frame with current physical theories, even though we acknowledged that this has been done within Physics itself (by Quantum Physics) and, if needed, it may be envisaged for Biology. Our "theories" happen to be "just" extensions of physical theories, in the logical sense. If, in Extended Criticality, the interval of critical transition is brought to measure 0, we are back to the Physics of Criticality. If the diameter of the second, compactified dimension of time in Section 8.2 is brought 0, we are back to the one dimensional arrow of thermodynamical time. Finally, equalities to 0 in the inequalities in (1) above, thus null value for K and its derivative, bring us back to physical frames (including in the balance equation for R): no extra principle nor extended balance equations including K. This flattens Gould's diagram to 0 and, thus, ... the evolution of species: we are back to Physics, no observable life around. If a tentative conclusion can be made of this synthetic presentation of a many years path, we would summarize it by referring to "incompleteness" as a pervasive fact in Science. Our theoretical attempts must always be enriched by complementary components of knowledge, by "meaningful" constructions: in Logic we must draw from Physics, say, or Cognition. And even more so, in the many possible interactions between different disciplines.

In [5], we distinguish, both in Mathematics and in Physics, between Construction Principles and Proof Principles. In Mathematics, meaningful conceptual constructions escape to formal theories (the Proof Principles), or the latter are provably incomplete with respect to the former: this is "concrete" incompleteness, see [36]. Mathematical construction principles join physical principles as for symmetries and order principles, which become geodetic principles in their various physical forms. The purely molecular analyses in Biology seem, once more, to assume the completeness of formal games of signs: the complete alphabetic description of organisms in the DNA. They lend themselves as some sort of Formal or Computational Principles, but often of a rather naive theoretical nature, in spite of the difficult and sometimes extraordinary empirical practices of Molecular Biology. So, we heard for too long that the DNA is a "program" or that it contains "the complete hereditary information" – it completely encodes the form of the ear or ... conjugal fidelity (in Young et al., Nature 400 (1999) 766–788). The friction between disciplines is a good tool for appreciating the relative incompleteness of internal paradigms. By working at a "tissue of knowledge" (and only the collaboration with researchers of various disciplines can allow this), mutually enriching proposals in different areas may help in our effort towards theoretical constructions, in each of them.

Acknowledgments, see http://www.di.ens.fr/users/longo for pictures, references and papers

My former students, now professors in Italy and France, organized this meeting and this special issue: my past work with them was the most passionating part of my scientific activity. They are too many to be mentioned here (see the conference pictures on my web page) and I already hinted to my debt to them in the abstract; yet, Giuseppe Castagna deserves a further acknowledgement for his commitment and affection in both birthday initiatives. As for my new research directions, words are not enough to express my gratitude to the many that in the last 10 years made possible a, sometimes wild, interaction with other disciplines. First of all Francis Bailly, my collaborator and guide in Physics for more than 8 years, but also other physicists, such as Thierry Paul, deserve most credit. Jean-Yves Girard gave to many of us the example of an audacious and deep thinking within Logic and, recently, in novel interactions between Logic and Physics. I hope I could transfer this attitude towards "daring to think" to the PhD students who graduated in my new team, CIM, since 2002 (M. Mossio, B. Saulnier,

M. Hoyrup, C. Rojas), as they helped me to discover each time new scientific paths. The discussions, meetings and projects with Jean Petitot and Jean Lassegue were essential for the work on an epistemological perspective. Biologists such as Lamberto Maffei, Nadine Peyreras, Carlos Sonneschein, Ana Soto, Evelyn Fox Keller, and a few others, in many discussions, meetings and exchanges, gave me many concrete hints towards "what is life".

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