Perspectives on Organisms: Biological Time, Symmetries and Singularities. Introduction

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August 8, 2013

Chapter 1
Introduction

The historical dynamic of knowledge is a permanent search for "meaning" and "objectivity". In order to make natural phenomena intelligible, we *single out* objects and processes, by an active knowledge construction, within our always enriched historical experience. Yet, the scientific relevance of our endeavors towards knowledge may be analyzed and compared by making explicit the principles on which our conceptual, possibly mathematical, constructions are based.

For example, one may say that the Copernican understanding of the Solar system is the "true" or "good" one, when compared to the Ptolemaic. Yet, the Ptolemaic system is perfectly legitimate, if one takes the Earth as origin of the reference system, and there are good metaphysical reasons for doing so. However, an internal analysis of the two approaches may help for a scientific comparison in terms of the *principles* used. Typically, the Copernican system presents more "symmetries" in the description of the solar system, when compared to the "ad hoc" constructions of the Ptolemaic system: the later requires the very complex description of epicycles over epicycles, planet by planet .... On the opposite, by Newton's universal laws, a unified and synthetic understanding of the planets' Keplerian trajectories and even of falling apples was made possible. Later on, Hamilton's work and Noether's theorems (see chapter 5) further unified physics by giving a key role to optimality (Hamilton's approach to the "geodetic principle", often mentioned below) and to symmetries (at the core of our approach). And Newton's equations could be derived from Hamilton's approach. Since then, the geodetic principle and symmetries as conservation principles are fundamental "principles of intelligibility" that allow to understand at once physical phenomena. These principles provide objectivity and even define the objects of knowledge, by organizing the world around us. As we will extensively discuss, symmetries conceptually unified the physical universe, far away from the ad hoc construction of epicycles on top of epicycles.

Physical theorizing will guide our attempts in biology, without reductions to the "objects" of physics, but by a permanent reference, even by local reductions, to the *methodology* of physics. We are aware of the historical contingency of this method,

yet by making explicit its working principles, we aim at its strongest possible conceptual stability and *adaptability*: "perturbing" our principles and even our methods may allow further progress in knowledge construction.

1.1 Towards biology

Current biology is a discipline where most, and actually almost all, research activities are — highly dextrous — experimentations. For a natural science, this situation may not seem to be an issue. However, we fear that it is associated to a belief that experiments and theoretical thinking could be decoupled, and that experiments could actually be performed independently from theories. Yet, "concrete" experimentations cannot be conceived as autonomous with respect to theoretical considerations, which may have abstract means but also have very practical implications. In the field of molecular biology, for example, research is related to the finding of hypothesized molecules and molecular manipulations that would allow to understand biological phenomena and solve medical or other socially relevant problems. This experimental work can be carried on almost forever as biological molecular diversity is abundant. However, the understanding of the actual phenomena, beyond the differences induced by local molecular transformations is limited, precisely because such an understanding requires a theory, relating, in this case, the molecular level to the phenotype and the organism. In some cases, the argued theoretical frame is provided by the reference to an unspecified "information theoretical encoding", used as a metaphor more than as an actual scientific notion, [Fox Keller, 1995, Longo et al., 2012a]. This metaphor is used to legitimate observed correlations between molecular differential manipulations and phenotype changes, but it does so by putting aside considerable aspects of the phenomena under study. For example, there is a gap between a gene that is experimentally necessary to obtain a given shape in a strain and actually entailing this shape. In order to justify this "entailment", genes are understood as a "code", that is a one-dimensional discrete structure, meanwhile shapes are the result of a constitutive history in space and in time: the explanatory gap between the two is enormous. In our opinion, the absence or even the avoidance of theoretical thinking leads to the acceptance of the naive or common sense theory, possibly based on unspecified metaphors, which is generally insufficient for satisfactory explanations or even false — when it is well defined enough as to be proven false.

We can then informally describe the reasons for the need of new theoretical perspectives in biology as follows. First, there are empirical, theoretical and conceptual *instabilities* in current biological knowledge. This can be exemplified by the notion of the gene and its various and changing meanings [Fox Keller, 2002], or the unstable historical dynamics of research fields in molecular biology [Lazebnik, 2002]. In both cases, the reliability and the meaning of research results is at risk. Another

issue is that the molecular level does not accommodate phenomena that occur typically at other *levels of organization*. We will take many examples in this book, but let's quote as for now the work on microtubules [Karsenti, 2008], on cancer at the level of tissues [Sonnenschein & Soto, 2000], or on cardiac functions at its different levels [Noble, 2010]. Some authors also emphasize the historical and conceptual shifts that have led to the current methodological and theoretical situation of molecular biology, which is, therefore, subject to ever changing interpretations [Amzallag, 2002, Stewart, 2004]. In general, when considering the molecular level, the problem of the composition of a great variety of molecular phenomena arises. Single molecule phenomena may be biologically irrelevant *per se*: they need to be related to other levels of organization (tissue, organ, organism, . . .) in order to understand their possible biological significance.

In no way do we mean to negate that DNA and the molecular cascades related to it play a fundamental role, yet their investigations are far from *complete* regarding the description of life phenomena. Indeed, these cascades may causally depend on activities at different level of analysis, which interact with them and deserve proper insights.

Thus, it seems that, with respect to explicit theoretical frames in biology, the situation is not particularly satisfying, and this can be explained by the complexity of the phenomena of life. Theoretical approaches in biology are numerous and extremely diverse in comparison, say, with the situation in theoretical physics. In the latter field, theorizing has a deep methodological unity, even when there exists no unified theory between different classes of phenomena — typically, the Relativistic and Quantum Fields are not (yet) unified, [Weinberg, 1995, Bailly & Longo, 2011]. A key component of this methodological unity, in physics, is given by the role of "symmetries", which we will extensively stress. Biological theories instead range from conceptual frameworks to highly mathematized physical approaches, the latter mostly dealing with *local* properties of biological systems (e. g. organ formation). The most prominent conceptual theories are Darwin's approach to evolution — its principles, "descent with modification" and "selection", shed a major light on the dynamics of phylogenesis, the theory of common descent — all current organisms are the descendants of one or a few simple organisms, and cell theory — all organisms have a single cell life stage and are cells, or are composed of cells. It would be too long to quote work in the second and third group: they mostly deal with the dynamics of forms of organs (morphogenesis), cellular networks of all sorts, dynamics of populations . . . when needed, we will refer to specific analyses. Very often, this relevant mathematical work is identified as "theoretical biology", while we care for a distinction, in biology, between "theory" and "mathematics" analogous to the one in physics between theoretical physics and mathematical physics: the latter mostly or more completely formalizes and technically solves problems (equations, typically), as set up within or by theoretical proposals or directly derived from empirical data.

In our view, there is currently no satisfactory *theory* of biological organization as such, and in particular, in spite of many attempts, there is no theory of the organism.

Darwin's theory, and neo-Darwinian approaches even more so, basically avoid as much as possible the problem raised by the organism. Darwin uses the duality between life and death as selection to understand why, between given biological forms, some are observed and others are not. That is, he gave us a remarkable theoretical frame for phylogenesis, without confronting the issue of what a theory of organisms could be. In the modern synthesis, since [Fisher, 1930], the properties of organisms and phenotypes, fitness in particular, are predetermined and defined, in principle, by genetics (hints to this view may be found already in Spencer's approach to evolution [Stiegler, 2001]). In modern terms, "(potential) fitness is already encoded in genes". Thus, the "structure of determination" of organisms is understood as theoretically unnecessary and is not approached[1].

In physiology or developmental biology the question of the structure of determination of the system is often approached on qualitative grounds and the mathematical descriptions are usually limited to specific aspects of organs or tissues. Major examples are provided by the well established and relevant work in morphogenesis, since Turing, Thom and many others (see [Jean, 1994] for phillotaxis and [Fleury, 2009] for recent work on organogenesis), in a biophysical perspective. In cellular biology, the equivalent situation leads to (bio-)physical approaches to specific biological structures such as membranes, microtubules, ..., as hinted above. On the contrary, the tentative, possibly mathematical, approaches that aim to understand the proper structure of determination of organisms as a whole, are mostly based on ideas such as autonomy and autopoiesis, see for example [Rosen, 2005, Varela, 1979, Moreno & Mossio, 2013]. These ideas are philosophically very relevant and help to understand the structure of the organization of biological entities. However, they usually do not have a clear connection with experimental biology, and some of them mostly focus on the question of the definition of life and, possibly, of its origin, which is not our aim. Moreover, their relationship with the aforementioned biophysical and mathematical approaches is generally not made explicit. In a sense, our specific "perspectives" on the organism as a whole (time, criticality, anti-entropy, the main themes of this book) may be used to fill the gap, as on one side we try to ground them on some empirical work, on the other they may provide a theoretical frame relating the global analysis of organisms as autopoietic entities and the local analysis developed in biophysics.

In this context, physiology and developmental biology (and the study of related pathological aspects) are in a particularly interesting situation. These fields are directly confronted with empirical work and with the complexity of biological phenomena; recent methodological changes have been proposed and are usually described as "systems biology". These changes consist, briefly, in focusing on the systemic properties of biological objects instead of trying to understand their components, see [Noble, 2006, Noble, 2011, Sonnenschein & Soto, 1999] and, in partic-

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[1] By the general notion of structure of determination we refer to the theoretical determination of a conceptual frame, in more or less formalized terms. In physics, this determination is generally expressed by systems of equations or by functions describing the dynamics.

ular, [Noble, 2008]. In the latter, it is acknowledged that, as for theories in systems biology:

> There are many more to be discovered; a genuine "theory of biology" does not yet exist.
>
> *[Noble, 2008]*

Systems biology has been recently and extensively developed, but it also corresponds to a long tradition. The aim of this book can be understood as a theoretical contribution to this research program. That is, we aim at a preliminary, yet possibly general theory of biological objects and their dynamics, by focusing on "perspectives" that shed some light on the unity of organisms from a specific point of view.

In this project, there are numerous pitfalls that should be avoided. In particular, the relation with the powerful physical theories is a recurring issue. In order to clarify the relationships between physics, mathematics and biology, a critical approach to the very foundations of physical theories and, more generally, to the relation between mathematized theories and natural phenomena is most helpful and we think even necessary. This analysis is at the core of [Bailly & Longo, 2011] and, in the rest of this introduction, we just review some of the key points in that book. By this, we provide below a brief account of the philosophical background and of the methodology that we follow in the rest of this book. We also discuss some elements of comparison with other theoretical approaches and then summarize some of the key ideas presented in this book.

1.2 Objectivization and Theories

As already stressed, theories are conceptual and — in physics — largely mathematized frameworks that frame the intelligibility of natural phenomena. We first briefly hint to a philosophical history of the understanding of what theories are.

The strength of theoretical accounts, especially in classical mechanics, and their cultural, including religious, background has led scientists to understand them as an intrinsic description of the very essence of nature. Galileo's remark that "the book of nature is written in the language of mathematics" (of Euclidean geometry, to be precise) is well known. It is a secular re-understanding of the "sacred book" of revealed religions. Similarly, Descartes writes:

> Par la nature considérée en général, je n'entends maintenant autre chose que Dieu même, ou bien l'ordre et la disposition que Dieu a établie dans les choses crées. [By nature considered in general, I mean nothing else but God himself, or the order and tendencies that God established in the created things.]   *[Descartes, 1724]*

Besides, in [Descartes, 1724], the existence of God and its attributes legitimate, *in fine*, the theoretical accounts of the world: observations and clear thinking are truthful, as He should not be deceitful. In this context, the theory is thus an account

of the "thing in itself" (das Ding an sich, in Kant's vocabulary). The validity and the existence of such an account are understood mainly by the mediation of a deity, in relation with the perfection encountered in mathematics — a direct emanation of God, of which we know just a finite fragment, but an identical fragment to God's infinite knowledge (Galileo).

Kant, however, introduced another approach [Kant, 1781]. In Kant's philosophy, the notion of "transcendental" describes the focus on the *a priori* (before experience) conditions of possibility of knowledge. For example, objects cannot be represented outside space, which is, therefore, the *a priori* condition of possibility for their representation. By this methodology, the thing in itself is no longer knowable, and the accounts on phenomena are given, in particular, through the *a priori* form of the sensibility that are space and time. Following this line, mathematics is understood as *a priori* synthetic judgments: it is a form of knowledge that does not depend on experience, as it is only based on the conditions of possibility for experience, but neither is it based on the simple analysis of concepts. For example, $2 + 3 = 5$ is neither in the concept of 2 nor in the concept of 3 for Kant: it requires a synthesis, which is based on *a priori* concepts.

The transcendental approach of Kant has, however, strong limitations, highlighted, among others, by Hegel and later by Nietzsche. Hegel insists on the status of the knowledge of these *a priori* conditions, which he aims to understand dialectically, by the historicity of Reason and more precisely by the unfolding of its contradictions. Similarly, with a different background, Nietzsche criticizes also the validity of this transcendental knowledge.

> Wie sind synthetische Urtheile *a priori* möglich? fragte sich Kant, — und was antwortete er eigentlich? Vermöge eines Vermögens [. . .]. [How are *a priori* synthetic judgments possible?" Kant asks himself — and what is really his answer? By means of a means (faculty) [. . .]]
> *[Nietzsche, 1886]*

For Nietzsche, it is essential, in particular, to understand the genesis of such "faculties", or behaviors, by their roots in the body and therefore by the embodied subject [Stiegler, 2001]. One should also quote Merleau-Ponty and Patocka as for the epistemological role of our intercorporeal "being in the world" and for reflections on biological phenomena (for recent work and references on both these authors in one text, see [Marratto, 2012, Thompson, 2007, Pagni, 2012]).

In short, for us, the analysis of a genesis, of concepts in particular, is a fundamental component of an epistemological analysis. This does not mean fixing an origin, but providing an attempted explicitation of a constitutive paths. Any epistemology is also a critical history of ideas, including an investigation of that fragment of "history" which refers to our active and bodily presence in the world. And this, by making explicit, as much as it is possible, the purposes of our knowledge construction. Yet, Kant provided an early approach to a fundamental component of the systems biology we aim at, that is to the autonomy and unity of the living entities

(the organisms as "Kantian wholes", quoted by many) and the acknowledgment of the peculiar needs of the biological theorizing with respect to the physical one[2].

One of the most difficult tasks is to insert this autonomy in the unavoidable ecosystem, both internal and external: life is variability *and* constraints, and neither make sense without the other. In this sense, the recent exploration in [Moreno & Mossio, 2013] relates constraints and autonomy in an original way and complements our effort. Both this "perspective" and ours are only possible when accessing living organisms in their unity and by taking this "wholeness" as a "condition of possibility" for the construction of biological knowledge. However, we do not discuss here this unity *per se*, nor directly analyze its auto-organizing structural stability. In this sense, these two complementary approaches may enrich each other and produce, by future work, a novel integrated framework.

As for the interplay with physics, our account particularly emphasize the *praxis* underlying scientific theorizing, including mathematical reasoning, as well as the cognitive resources mobilized and refined in the process of knowledge construction. From this perspective, mathematics and mathematized theories, in particular, are the result of human activities, in our historical space of humanity, [Husserl, 1970]. Yet, they are the most stable and conceptually invariant knowledge constructions we have ever produced. This singles them out from the other forms of knowledge. In particular, they are grounded on the constituted *invariants of our action*, gestures and language, and on the *transformations* that preserve them: the concept of number is an invariant of counting and ordering; symmetries are fundamental cognitive invariants and transformations of action and vision — made concepts by language, through history, [Dehaene, 1997, Longo & Viarouge, 2010]. More precisely, both ordering (the result of an action in space) and symmetries may be viewed as "principles of conceptual construction" and result from core cognitive activities, shared by all humans, well before language, yet spelled out in language. Thus, jointly to the "principles of (formal) proof", that is to (formalized) deductive methods, the principle of construction ground mathematics at the conjunction of action and language. And this is so beginning with the constructions by rotations and translations in Euclid's geometry (which are symmetries) and the axiomatic-deductive structure of Euclid's proofs (with their proof principles).

This distinction, construction principles vs. proof principles, is at the core of the analysis in [Bailly & Longo, 2011], which begins by comparing the situation in mathematics with the foundations of physics. The observation is that mathematics and physics share the same construction principles, which were largely co-constituted, at least since Galileo and Newton up to Noether and Weyl, in the XXth century[3]. One may formalize the role of symmetries and orders by the key notion

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[2] For a recent synthetic view on Kantian frames, and many references to this very broad topic, in particular as for the transcendental role of "teleology" in biological investigations, one should consult [Perret, 2013].

[3] Archimedes should be quoted as well: why a balance with equal weights is at equilibrium? for symmetry reasons, says he. This is how physicists still argue now: why is there that particle? for

of group. Mathematical groups correspond to symmetries, while semi-groups correspond to various forms of ordering. Groups and semi-groups provide, by this, the mathematical counterpart of some fundamental cognitive grounds for our conceptual constructions, shared by mathematics and physics: the active gestures which organize the world in space and time, by symmetries and orders.

Yet, mathematics and physics differ as for the principles of proof: these are the (possibly formalized) principles of deduction in mathematics, while proofs need to be grounded on experiments and empirical verification, in physics. What can we say as for biology? On one side, "empirical evidence" is at the core of its proofs, as in any science of nature, yet mathematical invariance and its transformations do not seem to be sufficiently robust and general as to construct biological knowledge, at least not at the level of organisms and their dynamics, where variability is one of the major "invariant". So, biology and physics share the principles of proofs, in a broad sense, while we claim that the principles of conceptual constructions cannot be transferred as such. The aim of this book is to highlight and apply some cases where this can be done, by some major changes though, and other cases where one needs radically different insights, from those proper to the so beautifully and extensively mathematized theories of the inert.

It should be clear by now, that our foundational perspective concerns in priority the methodology (and the practice) that allows establishment of scientific objectivity in our theories of nature. As a matter of fact, in our views, the constitution of theoretical thinking is at the same time a process of objectivization. That is, this very process co-constitutes, jointly to the empirical friction on the world, the object of study in a way that simultaneously allows its intelligibility. The case of quantum mechanics is paradigmatic for us, as a quanton (and even its reference system) is the result of active measurement and its practical and theoretical preparation. In this perspective, then, the objects are defined by measuring and theorizing that simultaneously give their intelligibility, while the validity of the theory (the proofs, in a sense) is given by further experiments. Thus, in quantum physics, measurement has a particular status, since it is not only the access to an object that would be there beyond and before measurement, but it contributes to the constitution of the very object measured. More generally, in natural sciences, measurement deals with the questions: where to look, how to measure, where to set borders to objects and phenomena, which correlations to check and even propose .... This co-constitution can be intrinsic to some theories such as quantum mechanics, but a discussion seems crucial to us also in biology, see [Montévil, 2013].

Following this line of reasoning, the research program we follow towards a theory of organism aims at finding ways to constitute theoretically biological objects and objectivize their behavior. Differences and analogies, by conceptual continuities or dualities with physics will be at the core of our method (as for dualities, see, for

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symmetry reasons — see the case of anti-matter and the negative solution of Dirac's equations, [Dirac, 1928].

example, our understanding of "genericity vs. specificity" in physics vs. biology in chapter 7), while the correlations with other theories can, perhaps, be understood later[4]. In this context, thus, a certain number of problems in the philosophy of biology are not methodological barriers; on the contrary, they may provide new links between remote theorizing such as physical and social ones, which would not be based on the transfer of already constructed mathematical models.

1.2.1 A critique of common philosophical classifications

As a side issue to our approach, we briefly discuss some common wording of philosophical perspectives in the philosophy of biology — the list pretends no depth nor completeness and its main purpose is to prevent some "easy" objections.

PHYSICALISM   In the epistemic sense (i.e. with respect to knowledge), physicalism can be crudely stated as follows:

> the majority of scientists [recognize] that life can be explained on the basis of the existing laws of Physics .   *[Perutz, 1987]*

The most surprising word in this statement is "existing". Fortunately, Galileo and Newton, Einstein and the founders of quantum mechanics, did not rely on *existing* laws of physics to give us modern science. Note that Galileo, Copernicus and Newton where not even facing new phenomena, as anybody could let two different stones fall or look at the planets, yet, following different *perspectives* on familiar phenomena, they proposed radically new theories and "laws"[5].

There is no doubt that a wide range of isolated biological phenomena can be accommodated in the main existing physical theories, such as classical mechanics, thermodynamics, statistical mechanics, hydrodynamics, quantum mechanics, general relativity, . . . , unfortunately, some of these physical theories are not unified, and, *a fortiori*, one cannot reduce one to the other nor provide by them a unified biological understanding. However, as soon as the phenomena we want to understand differs radically or are seen from a different perspective (the view of the organism), new theoretical approaches may be required, as it happened along the history of physics. There is little doubt that an organism may be seen as a bunch of molecules, yet we, the living objects, are rather funny bunches of

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[4] The "adjacent" fields are, following [Bailly, 1991], physical theories in one direction and social sciences in another. The notion of "extended criticality", say, in chapter 7, may prove to be useful in economics, since we seem to be always in a permanent, extended, crisis or critical transition, very far from economic equilibria.

[5] What an unsatisfactory word, borrowed from religious tables of laws and/or the writing of social links — we will avoid it. Physical theories are better understood as the explicitation of (relative) reference systems, of measures on them and of the corresponding fundamental symmetries, see [Weyl, 1983, Van Fraassen, 1989, Bailly & Longo, 2011].

molecules and the issue is: which *theory* may provide a sound perspective and account of these physically singular bunches of molecules? For us, this is an epistemic, a knowledge issue, not an ontological one.

Such lines are common within physics as well, in particular in areas that are directly relevant for our approach. For example, the understanding of critical transitions requires the introduction of a new structure of determination, as classes of parameterized models and the focusing on new observables, such as the critical exponents, see chapter 6. Similarly, going from macrophysics (classical mechanics) to microscopic phenomena (quanta) necessitates the loss of determinism, while the understanding of gravity in terms of quantum fields leads to a radical transformation of the classical and relativistic structure of space-time (e. g. by non-commutative geometry, [Connes, 1994]) or radically new objects (string theory, [Green et al., 1988]). It happens that these audacious new accounts of quantum mechanics, which aim to unify it with general relativity, are not compatible with each other. Moving backwards in time, another example is the link between heat and motion, which required the invention of thermodynamics and the introduction of a new quantity (entropy). The latter allowed to describe, in particular, the irreversibility of time, which is incompatible with a finite combination of Newtonian trajectories. Notice, though, that the current physical understanding of systems far from thermodynamical equilibrium is seriously limited because there is no general theory of them, see for example [Vilar & Rubí, 2001]. And biological entities, if considered as physical systems, would most probably fall at least in this category.

VITALISM   For similar reasons, the question and the debates around the notion of vitalism lead to a flawed approach to biological systems. We exclude, by principle, the various sorts of intrinsic teleologism (evolution leading to our human perfection), internal living forces, encoded homunculi in DNA or alike. From our theoretical point of view, what matters is to find ways to objectivize the phenomena we want to study, similarly as what has been done along the history of physics. However, the fear of negatively connoted vitalist interpretations leads to blind spots in the understanding of biological phenomena, since it hinders original approaches, strictly pertinent to the object of observation. If the search for an adequate theory for the living state of matter, in an autonomous interplay of differences and analogies with theories of the inert, is vitalism, then the researchers in hydrodynamics may be shamefully accused to be "hydrodynamicists" as, so far, there is no way to reduce to (nor to understand in terms of) elementary particles that compose fluids, of quantum mechanics say, the incompressibility and fluidity in continua at the core of their science. Those are understood in terms of new or different symmetries from the one founding the theory of particles (quanta): the suitable symmetries yield radically different and irreducible equations and mathematically objectivize the otherwise vague notions of fluidity and incompressibility in a continuum. Our colleagues in hydrodynamics are not "dualist" for this, nor they believe in a "soul" of fluids, against the

vulgar matter of particles. Similarly, in thermodynamics, the founding fathers invented new observable quantities (entropy) and original phase spaces (P, V, T, pressure, temperature and volume) for thermodynamic trajectories (the thermodynamic cycle). By this, they disregarded the particles out of which gases are made. Later, Boltzmann did not reduce thermodynamics to Newton-Laplace trajectories of particles. He assumed molecular chaos and the random exploration of the entire intended physical space (ergodicity, see chapter 8), which are far away from the Newton-Laplace mathematical frame of an entailed trajectory in the momentum / position phase space. The new unit of analysis is the volume of each microstate in the phase space. He then unified asymptotically the molecular approach and the second principle of thermodynamics: given his hypotheses, in the thermodynamic integral, an infinite sum, the ratio of particles over a volume stabilizes only at the infinite limit of both. In short, the asymptotic hypothesis and treatment allowed Boltzmann to ignore the entailed Newtonian trajectory of individual particles and to give statistical account of thermodynamics.

The unity of science is a beautiful project, such as today's search for a theory unifying relativistic and quantum fields, yet unity cannot be imposed by a philosophical prejudice. It is instead the result of hard work and autonomous theorizing, followed, perhaps and if possible, by unification. And, if we do not have different theories, as for different phenomenal frames, there is nothing to unify.

REDUCTIONISM (SCALE)   The methodological assumption that we should understand phenomena beginning at the small scales is, again, at odds with the history of physics. Thermodynamics started at macroscopic scales, as we said. As for gravitation and quantum fields, once more, in spite of almost one century of research, macroscopic and microscopic are not (yet) understood in a unified framework. And Galileo's and Einstein's theories remain fundamental even though they do not deal with the elementary.

The hope for "theory of everything" aims to overcome, first, this major difficulty, while there is no *a priori* reason why it would help, for example, in the understanding of non-equilibrium thermodynamics (except possibly in the case of black holes thermodynamics, [Rovelli, 1996], a remote issue from ours). Non-equilibrium thermodynamics remains mainly under theoretical construction and seems instead particularly relevant for life sciences. Moreover, and this point is crucial for this critique of reductionism, the current understanding of microscopic interactions, in the standard model, does not involve a fundamental, small scale; on the contrary it "hangs" between scales (by renormalization methods):

> QFT [Quantum Field Theory] is not required to be physically consistent at very short distance where it is no longer a valid approximation and where it can be rendered finite by a modification that is, to a large extent, arbitrary.   *[Zinn-Justin, 2007]*

Another example is the question of (scale) reductionism, which is approached by [Soto et al., 2008]. In the latter, the key role of time, with respect to biological levels of organization, is evidenced. We will approach this question in a comple-

mentary way, on smaller time scales — yet with a proper biological time — an "operator", we shall say in biology, both in a mathematical sense and by the role of the historical formation of biological entities.

Finally, scale reductionism is in contrast with the modern analysis of renormalization in critical transitions, see [Longo et al., 2012c], where scales are treated by cascades of mathematical models with no privileged level of observation. Critical transitions will be extensively discussed in this book.

The conclusion of this section is that we understand biological theorizing as a process of constitution of objectivity and, in particular, of organisms as *theoretical objects*. Science is not the progressive occupation of reality by more or less familiar conceptual and technical tools, but the permanent construction of new objects of knowledge, new perspectives and tools for their organization and understanding, yet grounded also on historically constructed knowledge and empirical friction.

1.2.2 The elementary and the simple

We mentioned that the points we made above are not philosophical prerequisites for a genuine intelligibility of biological phenomena, however, the technical aspects we hinted to in our critique will help us to provide both, we hope, philosophical and scientific insights. This is our aim as for the notion of "the physical singularity of life phenomena" developed in [Bailly & Longo, 2011], which we recall and further develop here. The "singularity" stems both from the technical notion of extended criticality below and from the historical specificity of living objects. Critical transitions are mathematical singularities in physics, yet they are non-extended as they are described by point-wise transitions, see chapter 6.

Biological objects are "singular" also in the sense of "being individual", that is, the result of a unique history. One may better say that they are specific (see the duality in chapter 7 with respect to physics).

In other words, we will widely use insights from physical theories, but these insights will mainly be a methodological and conceptual reference, and will not be rooted in an epistemic physicalism. Indeed, our approach may lead almost to the opposite: we will use the examples from physical theorizing as tools on the way to construct objectivity, and this will lead us, in some cases, to oppose biological theorizing to the very foundations of physical theories — typically, by the different role played by theoretical symmetries (in chapter 7 in particular). Moreover, we will recall the genericity of the inert objects, as invariant with respect the theory and the experiments, and the specificity of their trajectories (uniquely determined by the geodetic principle). And we will oppose them to the specificity (historical nature) of the living entities and the genericity of their phylogenetic trajectories, as possible or compatible ones in a co-determined ecosystem, see chapter 7. Yet, the very idea

of this (mathematical) distinction, generic vs. specific, is borrowed from physical theorizing.

Further relations with physical theories will be developed progressively in our text, when needed for our theoretical developments in biology.

Before specifying further our approach to biological objects, we have to further challenge the Cartesian and Laplacian view that the fundamental is always elementary and that the elementary is always simple. According to this view, in biology only the molecular analysis would be fundamental.

As we mentioned, Galileo and Einstein proposed fundamental theories of gravitation and inertia, with no references to Democritus' atoms nor quanta composing their falling bodies or planets. Then, Einstein, and still now physicists, struggle for *unification*, not reduction of the relativistic field to the quantum one. Boltzmann did not reduce thermodynamics to the Newtonian trajectories of particles, but assumed the original principles recalled above and *unified* at the asymptotic limit the two intended theories, thermodynamics and particles' trajectories.

Thus, there is no reason in biology to claim that the fundamental must be conceptually elementary (molecular), as this is false also in physics. Moreover, the proper elementary observable doesn't need to be "simple". "Elementary particles" are not conceptually / mathematically simple, in quantum field theories nor in string theory. In biology, the elementary living component, the cell, is (very) complex, a further anti-Cartesian stand at the core of our proposal: a cell should already be seen as a Kantian whole.

In an organism, no reduction to the parts allows the understanding of the whole, because the relevant degrees of freedom of the parts, as associated to the whole, are *functional* and this defines their compatibility within the whole and of the whole in the ecosystem. In other terms, they are definable as components of the causal consequences of properties of the parts. Thus, only the microscopic degrees of freedom of the parts can be understood as physical. Further, because of the non-ergodicity of the universe above the level of atoms, inasmuch at ergodicity is well defined in this context (see chapter 8), most macromolecules and organs will never exist. Note also that ergodicity would prevent selection since it would mean that a negatively selected phenotype would "come back" in the long run, anyway.

As mentioned above and further discussed below, the theoretical frame establishes the pertinent observables and parameters, i.e. the ever changing and unprestatable phase space of evolution. Note that, in biology, we consider the observable and parameters that are derived from or relative to Darwinian evolution and this is fundamental for our approach. Their very definition depends on the intended organism and its integration in and regulation by an ecosystem. Selection, acting at the level of the evolving organism in its environment, selects organisms on functions (thus on and by organs in an organism) as interacting with an ecosystem. The phenotype, in this sense constitutes the observables we focus on.

1.3 A short synthesis of our approach to biological phenomena

A methodological point that we first want to emphasize is that we will focus on "current" organisms, as a result an in the process of biological evolution. Indeed, numerous theoretical researches are performed on the question of the origin of life. Most of these analyses use physical or almost physical theories as such, that is they try to analyze how, from a mix of (existing) physical theories, one can obtain "organic" or evolutive systems. We will not work at the (interesting, per se) problem of the origin of life, as the transition from the inert to the living state of matter, but we will work at the transition from *theories* of the inert to *theories* of living objects. In a sense this may contribute also to the "origin" problem, as a sound theory of organisms, if any, may help to specify what the transition from the inert leads to, and therefore what it requires.

More precisely, the method of mathematical biology and biophysical modeling quoted above is usually the transformation of *a part* of an organism (more generally, of a living system) into a physical system, in general separated from the organism and from the biological context it belongs to. This methodology often allows an understanding of some biological phenomena, from morphogenesis (phyllotaxis, formation of some organs . . .) to cellular networks and more, see above. For example, the modeling of microtubules allows to approach their self-organization properties [Karsenti, 2008], but it corresponds to a theoretical (and experimental) *in vitro* situation, and their relation with the cell is not understood by the physical approach alone. The understanding of the system in the cell requires an approach external to the structure of determination at play in the purely physical modeling. Thus, to this technically difficult work ranging from morphogenesis and phyllotaxis to cellular networks, one should add an insufficiently analyzed issue: these organs or nets, whose shape and dynamics are investigated by physical tools, are generally part of an organism. That is, they are regulated and integrated in and by the organism and never develop like isolated or generic (completely defined by invariant rules) crystals or physical forms. It is instead this integration and regulation in the coherent structure of an organism that contributes in making the biologically relevant situations, which is mostly non-generic, [Lesne & Victor, 2006].

The general strategy we use, is to approach the biological phenomena from different perspectives, each of them focusing on different *aspects* of biological organization, not on different *parts* such as organs or cellular nets in tissues . . . . The aim is to propose a basis for a partially mathematized theoretical understanding. This strategy allows us to obtain relatively autonomous progresses on the corresponding aspects of living systems. An essential difficulty is that, *in fine*, these concepts are fully meaningful only in the interaction with each other, that is to say in a unified framework that we are contributing to establish. In this sense, then, we are making progresses by revolving around this not yet existing framework, proposing and browsing these different perspectives in the process. However, this allows a stronger
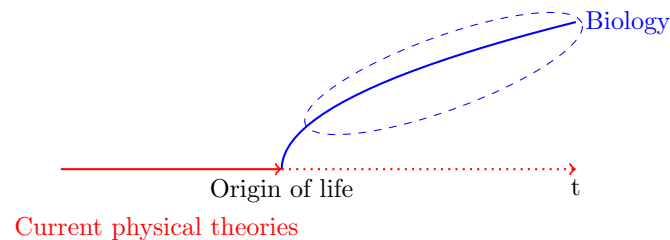
Fig. 1.1: *A scheme of the relation between physics and biology, from a diachronic point of view.* Theoretical approaches that focus on the origin of life usually follow the physical line (stay within existing physical theories) and try to approach the "bifurcation" point. The latter is not well defined since we don't have a proper theory for the biological entities that are supposed to emerge. Usually, the necessary ingredients for Darwinian evolution are used as goals. From our perspective, a proper understanding of biological phenomena need to focus directly, at least as a first (huge) step, on the properly biological domain, where the Darwinian tools soundly apply, but also where organisms are constituted. It may then be easier to fill the gap.

relation to empirical work, in contrast to theories of biological autonomy, without losing the sense of the biological unity of an organism.

The method we follow in order to progress in each of these specific aspects of life can mostly be understood as taking different points of view on organisms: we look at them from the point of view of time and rhythms, of the interplay of global stability vs. instability, of the formation and maintenance of organization through changes . . . . As a result, we will combine in this book a few of these theoretical perspectives, the principal common organizing concepts will be biological time, on one side, and extended criticality on the other. More specifically, the main conceptual frames that we will either follow directly or that will make recurrent appearance in this text are the following:

BIOLOGICAL TEMPORAL ORGANIZATION   The idea is that, more than space or energy, biological time is a crucial leverage to understand biological organization. This does not mean that space or energy are irrelevant, but they have a different role from the one they play in physics. The reason for this will be explained progressively throughout the book. The approach in terms of symmetry changes that we develop in chapter 7 provides a radical argument for this point of view. Intuitively, the idea is that what matters in biological theorizing is the notion of "organization" and the way it is constructed along and, we dare to say, *by* time, since biological time will be an operator for us, in a precise mathematical sense. In contrast to this, the energetic level (say, between mammals of different sizes) is relatively contingent, as we will argue on the grounds of the allometric relations, in chapter 2, where energy or mass appear as a parameter. Some preliminary arguments from physics are provided by the role of time (entropy production) in dissipative structures [Nicolis & Prigogine, 1977] and by the non-

ergodicity of the molecular phase space, discussed in [Kauffman, 2002, Longo et al., 2012b].

EXTENDED CRITICAL TRANSITIONS   A large part of our work will use the notion of extended critical transition [Bailly, 1991, Bailly & Longo, 2008, Bailly & Longo, 2011] to understand biological systems. This notion is relatively complex, in particular because of its physical prerequisites, and we will introduce it progressively in this book. Notice that it provides a precise meaning to the idea of the physical singularity of life phenomena.

ENABLEMENT   Biologists working on evolution often refer to a contingent state of the ecosystem as "enabling" a given form of life. A niche, typically, enables a, possibly new, organism; yet, a niche may be also constructed by an organism. In [Longo et al., 2012b] et [Longo & Montévil, 2013] an attempt is made to frame this informal notion in a rigorous context. We borrow here from that work to correlate enablement to the role of symmetry changes and we provide by this a further conceptual transition from physics to biology.

ANTI-ENTROPY   This aims to quantify the "amount of biological organization" of an organism [Bailly & Longo, 2003, Bailly & Longo, 2009] as a non-reducible opposite of entropy. It also determines some temporal aspects of biological organization. This aspect of our investigation gives a major role to randomness. The notion of randomness is related to entropy and to the irreversibility of time in thermodynamics and statistical mechanics. As a result, we consider a proper notion of biological randomness as related to anti-entropy, to be added on top of the many (at least three) forms of randomness present in physical theories (classical, thermodynamical, quantum).

1.4 A more detailed account of our main themes: Time Geometry, Extended Criticality, Symmetry changes and enablement, Anti-Entropy

The purpose of this book is to focus on some biological phenomenalities, which seem particularly preeminent, and try to approach them in a conceptually robust manner. The four points below briefly outline the basic ideas developed and are meant to provide the reader with the core ideas of our approach, whose precise meaning, however, can only be clarified by the technical details to which this book is dedicated.

1.4.1 Biological time.

The analysis of biological rhythms does not seem to have an adequate counterpart in mathematical formalization of physical clocks, which are based on *frequencies* along the usual, possibly oriented, time. Following [Bailly et al., 2011], we present a two-dimensional manifold as a mathematical frame for accommodating autonomous biological rhythms: the second dimension is compactified, that is, it is a circular fiber orthogonal to the oriented representation of physical time. Life is temporally paced by both external (physical) rhythms (circadian, typically), which are frequencies, and internal ones (metabolism, respiration, cardiac rhythms). The addition of a new (compactified) dimension for biological time is justified by the peculiar dimensional status of *internal* biological rhythms. These are pure numbers, not frequencies: they become average frequencies and produce the time of life span, when used as coefficient in scaling laws, see chapter 2. These rhythms have also singular behaviors (multi-scale variations) with respect to the physical time, which can be visualized in our framework. In contradiction with physical situations, the scaling, however, does not seem to be associated to a stable exponent. These two peculiar features (pure numbers and fractal-like time series) are the main evidences of the mathematical autonomy of our compactified time with respect to the physical time. Thus, the usual physical (linear) representation of time may be conveniently enriched, in our view, for the understanding of some phenomena of life: we will do it by adding one dimension to the ordinary physical representation of time.

Besides rhythms, an extended form of present is more adequate for the understanding of memory or elementary retention, since this is an essential component of learning, for the purposes of future action, even in some unicellular organisms. Learning is based on both memory and "protention", as pre-conscious expectation. Now, while memory, as retention, is treated by some physical theories (relaxation phenomena), protention seems outside the scope of physics. We then suggest some simple functional representation of biological retention and protention.

The two new aspects of biological time allow to introduce the abstract notion of "biological inertia", as a component of the conceptual time analysis of organisms. Our approach to protention and retention focuses on local aspects of biological time, yet it may provide a basis to accommodate the long range correlations observed experimentally, see [Grigolini et al., 2009]. Indeed, this kind of correlations is relevant for both aspects of our approach to biological time, and fits in the conceptual framework of extended criticality below.

Another aspect of biological time, discussed in chapter 7, is the time constituted by the cascade of symmetry changes which takes place in extended critical transitions. In other terms, this time is defined by the ubiquitous organizational transformations occurring in biological matter. Here, time corresponds to the *historicity* of biological objects and to the process of biological individuation, both ontogenetic and phylogenetic. Indeed, time is no longer the parameter of trajectories in

the phase, space since the latter is unstable (chapter 8); therefore we will stress that temporality, defined by the changes of phase space, requires an original insight, in biology.

1.4.2 Extended Criticality.

The biological relevance of physical theories of criticality is due first to the fact that, in physics, *critical phase transitions* are processes of changes of state where, by a sudden change (a singularity w. r. to a control parameter), the global structure of the system is involved in the behavior 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 (e. g. in second order transitions, such as the para-/ferromagnetic transition). Physically, this means that the determination is global and not local. In other words, a critical transition is related to a change of phase and to the appearing of critical behaviors of some observable — magnetization, density, for example — or of some of its particular characteristics — such as correlation lengths. It is likely to appear at equilibrium (null fluxes) or far from equilibrium (non-null fluxes). In the first case, the physico-mathematical aspects are rather well-understood (renormalization as for the mathematics [Binney et al., 1992], thermodynamics for the bridge between microscopic and macroscopic description), while, in the second case, we are far from having theories as satisfactory. We present physical critical transitions in chapter 6.

Some specific cases, without particular emphasis on the far from equilibrium situation, have been extensively developed and publicized by Bak, Kauffman and others (see [Bak et al., 1988, Kauffman, 1993, Nykter et al., 2008a]). The sand pile, whose criticality reduces to the angle of formation of avalanches in all scales, percolation (see [Bak et al., 1988, Laguës & Lesne, 2003]) or even the formation of a snowflake are interesting examples. The perspective assumed is, in part, complementary to Prigogine's: it is not fluctuations within a weakly ordered situation that matter in the formation of coherence structures, but the "order that stems from chaos" [Kauffman, 1993]. Yet, in both cases potential correlations are suddenly made possible by a change in one or more control parameter for a specific (point-wise) value of this parameter. For example, the forces attracting water molecules towards each other, as ice, are there: the passage below a precise temperature, as decreasing Brownian motion, at a certain value of pressure and humidity, allows these forces to dominate the situation and, thus, the formation of a snow flake, typically.

Critical transitions should also be understood as sudden symmetry changes (symmetry breaking and formation of new symmetries), and a transition between two different macroscopic physical objects (two different states of matter, in the language of condensed matter physics), with a conservation of the symmetries of the components. The specific, local and global, symmetry breakings give the variety

and unpredictability of organized forms and their regularities (the new symmetries) as these transitions are constituted by the fluctuations in the vicinity of criticality. In physics, the point-wise nature of the "critical point" of the control parameter is an essential mathematical issue, as for the treatment by the relevant mathematics of "renormalization" in theories of criticality, see chapter 6 and [Binney et al., 1992].

Along the lines of the physical approaches to criticality, but within the frame of far from equilibrium thermodynamics, we consider living systems as "coherent structures" in a continual (extended) critical transition. The permanent state of transition is maintained, at each level of organization, by the integration/regulation activities of the organism, that is by its global coherent structure.

In short, following recent work [Bailly & Longo, 2008, Longo & Montévil, 2011a], but also on the grounds of early ideas in [Bailly, 1991], we propose to analyze the organization of living matter as "extended critical transitions". These transitions are extended in space-time and with respect to all pertinent control parameters (pressure, temperature etc.), their unity being ensured through global causal relations between levels of organization (through integration and regulation). More precisely, our main theoretical paradigm is provided by the analysis of critical phase transitions, as this peculiar form of critical states presents some particularly interesting aspects for the biological frame: the formation of extended (mathematically diverging) correlation lengths and coherence structures, the divergence of some observables with respect to the control parameter(s) and the change of symmetries associated to potentially swift organizational changes. However, the "coherent critical structures" which are the main focus of our work cannot be reduced to existing physical approaches, since phase transitions, in physics, are treated as "singular events", corresponding to a specific well-defined value of the control parameter, just one (critical!) point as we said. Whereas our claim is that in the case of living systems, these coherent critical transitions are "extended" and maintained in such a way that they persist in the many dimensional space of analysis, while preserving all the physical properties mentioned above (diverging correlation lengths, new coherence structures, symmetry changes . . .). In other words, the critical transitions we look at are to be analyzed as taking place through an interval, not just a point, with respect to each control parameter. Thus, a living object is understood not only as a dynamic or a process, in the various possible senses analyzed by physical theories, but it is a *permanent critical transition*: it is always going through changes, of symmetries changes in particular, as analyzed below. We then have an extended, permanently reconstructed and changing *global* organization constituted by an interaction between local and global structures, since the global/local interplay is proper to critical transitions. We consider this perspective as a conceptual tools for understanding diversity and adaptivity.

Our analysis of extended criticality is largely conceptual, because of the loss of the mathematics of renormalization, which applies to point-wise phase transitions. Moreover, there seems to be little known Mathematical Physics that applies to physically singular, far from equilibrium critical transitions, *a fortiori* when the transition

is extended. The other major conceptual and technical difficulty is also due to the instability of the symmetries involved. The issue we will focus on then, is how to objectivize biological phenomena, since, in contradiction with the physical cases, they do not not seem to be theoretically determinable within a specific, pre-given phase space and this because of the key biological role of symmetry changes.

1.4.3 Symmetry changes and enablement

As a fundamental conceptual transition between theories of the inert and of the living, we extensively focus on the different role of symmetry changes. Symmetry changes correspond, in physics, to the transition to a new state of the matter, or, even, in some cases, to a radical change of theory (recall the transition from theories of particles to hydrodynamics). In biology, instead, we will focus in chapter 7 on their constitutive role: the analysis of symmetry changes provide a key tool for constructing a coherent biological knowledge. As mentioned above, extended criticality is based on symmetry breakings and (re)constructions; our understanding of randomness, variability, adaptivity and diversity of life will largely rely on them. Moreover, in the passage from physics to biology, we will use these permanent dynamics to justify the introduction of "enablement" in [Longo et al., 2012b] and [Longo & Montévil, 2013], see chapter 8. Life and ecosystemic changes allow (enable) new life. (Changing) niches enable novelty produced by "descent with modification", a fundamental principle of Darwin's, while new phenotypes produce or co-constitute new niches. In our view, enablement is a fundamental notion, often used in the language of evolution, that we try to frame here in a coherent theoretical perspective. In contrast to the inert, whose default state is, of course, inertia, organisms interact with the surrounding world by acting (reproduction with modification and motility), use enabling conditions (are enabled by the environment), while producing new enabling conditions for further forms of life.

The analysis of enablement will lead us to the final main theme of this book: an understanding of the increasing complexity of phenotypes, through evolution. Often by sudden transitions, or by "explosions" as for richness of news phenotypes (Eldredge's and Gould's punctuated equilibria, see [Eldredge & Gould, 1972]), organisms complexify as for the anatomical structure through evolution. Our aim is to objectivize this intuition and the paleontological facts supporting it, by a sound mathematical understanding: anti-entropy will provide a possible quantification of phenotypic complexity and of its unbiased diffusion towards increasing values. It only makes sense in presence of continual symmetry changes and enablement.

1.4.4 Anti-entropy

In chapter 9, we develop our systemic perspective for biological complexity, both in phylogenesis and ontogenesis, by an analysis of organization in terms of "anti-entropy", a notion which conceptually differs from the common use of "negative entropy". Note that both the formation and maintenance of organization, as a permanent reconstruction of the organism's coherent structure, go in the opposite direction of entropy increase. This is also Schrödinger's concern in the second part of his 1944 book. He considers the possible decrease of entropy by the construction of "order from order", that he informally calls negative entropy. In our approach, anti-entropy is mathematically presented as a new observable, as it is not just entropy with a negative sign (negative entropy, as more rigorously presented in Shannon and in [Brillouin, 1956]). Typically, when summed up, equal entropy and negative entropy give 0. In our approach, entropy and anti-entropy are found simultaneously only in the non-null critical interval of the living state of matter. 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. Along our wild analogy, matter and anti-matter never give 0, but a new energy state: the double energy production as gamma rays, when they encounter in a (mathematically point-wise!) singularity. Analogously, entropy and anti-entropy coexist in an organism, as a peculiar "singularity": an extended zone (interval) of criticality.

To this purpose, we introduced two principles (existence and maintenance of anti-entropy), in addition to the thermodynamic ones. These principles are (mathematically) compatible with the classical thermodynamic ones, but do not need to have meaning with regard to inert matter. The idea is that anti-entropy represents the key property of an organism, even a unicellular one, to be describable by several levels of organization (also a eukaryotic cell possesses organelles, say), regulating, integrating each other — they are parts that functionally integrate into a whole, and the whole regulates them. This corresponds to the formation and maintenance of a global coherence structure, in correspondence to its extended criticality: organization increases, along embryogenesis say, and is maintained, by contrasting the ongoing entropy production due to all irreversible processes. No extended criticality nor its key property of coherence would be possible without anti-entropy production, since always renewed organization expresses and allows the maintenance of the extended critical transition.

Following [Bailly & Longo, 2009], we apply the notion of anti-entropy to an analysis of Gould's work on the complexification of life along evolution in [Gould, 1997]. We thus extend a traditional balance equation for the metabolism to the new notion as specified by the principles above. This equation is inspired by Gibbs' analysis of free energy, which is hinted as a possible tool for the analysis of biological organization in a footnote in [Schrödinger, 2000]. We will examine far from

equilibrium systems and focus in particular on the production of global entropy associated to the irreversible character of the processes. In [Bailly & Longo, 2009], a close analysis of anti-entropy has been performed from the perspective of a diffusion equation of biomass over phenotypic complexity along evolution. That is, we could reconstruct, on the grounds of general principles, Gould's complexity curve of biomass over complexity in evolution [Gould, 1997]. We will summarize and update some of the key ideas of that work. Once more, Quantum Mechanics indirectly inspired our mathematical approach: we borrow Schrödinger's operatorial approach in his famous equation but in a classical framework. Classically, that equation may be understood as a diffusion equation. As a key difference, which stresses the "analogical" frame, we use real coefficients instead of complex ones. Thus we are outside of the mathematical framework of quantum mechanics and just use the operatorial approach in a dual way, for a peculiar diffusion equation: the diffusion of bio-mass over phenotypic complexity.

1.5 Map of this book

It should be clear by now that this book is at the crossroads of (theoretical) physics and biology. As a consequence, certain passages will use mathematical techniques that can seem of some difficulty for the non-mathematically trained reader. However, the main mathematical tools used in this book are very simple and we will try to explain them both conceptually and intuitively in the text. Similarly, we will refer to numerous physical ideas that we will explain qualitatively (and for a few of them, quantitatively). The prevalence of physical concepts will be especially marked in the chapter 5 and 6, however these concepts will be gradually introduced. In any cases, the the more technical parts of the book may be skipped at first reading, as suggested on place, and the qualitative explanations should be sufficient to proceed to our biological proposals. In general, we do not think at all that, in scientific disciplines, there is "as much scientific knowledge as there is mathematics". For example, the notions of extended criticality and enablement are represented only at a conceptual level. Mathematics is used here just when it helps to better specify concepts, if possible and needed, typically and more broadly to focus on invariance and symmetries. it is also used when it has some "generative" role, i. e. when it suggests how to go further by entailed consequences within or beyond proposed frameworks: the case of "biological inertia" in chapter 4 is a simple example of the latter form of entailment.

It is worth mentioning that despite conceptual and formal links between the chapters, most chapters retain a certain level of autonomy and can be read independently.

As for the references we will make to empirical evidences, we will start from some broadly accepted forms of "scaling". In chapter 2, we will review them in various contexts, where our choice of results is motivated by their relative robustness

and by the theoretical role that they will play later. We will in particular try to assess their experimental reliability and the variability that is observed. This step is important since we will use these observations (including variability) both technically and conceptually, as examples, in the rest of this book.

Since biological rhythms are associated to relatively robust symmetries, we will consider the question of biological temporal organization directly, first by analyzing rhythms, in chapter 3, then by an analysis of the "non-linear" organization of biological time. More precisely, we first propose a bidimensional reference system for accommodating biological rhythms, by which we may take scaling behaviors of different nature into account. Then, in chapter 4, we will approach the local structure of biological time, through the notions of protention and retention, thus providing an elementary mathematical approach of the notion of "extended present".

Chapter 5 provides a conceptual (and light technical) introduction on the role of symmetries in physical theories. This chapter provides some background and examples to set the subsequent developments. The next chapter, chapter 6, will provide an elementary introduction to physical critical transitions. Both chapters are intended to introduce the notions required for the following.

In chapter 7, we will approach the structures of determination of biological phenomena by the notion of theoretical symmetries. This will allow us to contrast the status of biological objects with the status of the physical objects. As a matter of fact, for the latter, the theoretical symmetries are stable, while we will characterize biological processes as undergoing ubiquitous symmetry changes. This will allow us to provide a proper notion of variability and of biological historicity (as a cascade of symmetry changes).

Since this perspective yields a fundamental instability of biological objects, our theoretical proposal "destabilizes" the physical approach to objectivization, for biological objects. Chapter 8 explores the consequence of this approach on the notion of phase space in biology (that is on the space of the theoretical determination). Namely, in this context, the relevant space of description is changing and unpredictable. The notion of "enablement" provides an understanding of biological dynamics by adding on top of causality a novel theoretical insight on how the active default state of living entities continually constructs and occupies new niches and ecosystems.

In chapter 9, we revisit the quantified approach to biological complexity, as "anti-entropy", introduced in [Bailly & Longo, 2009]. By this, we will develop an analysis of that notion in terms of symmetry and symmetry changes, on one side, and analyze some regenerative aspects of biological organization on the other side. We will also discuss the issue of the associated notion of randomness.

We conclude by philosophical reflection on how we moved from physics to biology, chapter 10.