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Perspectives on Organisms

Biological Time, Symmetries and Singularities

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Biological Time, Symmetries and Singularities

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To Francis Bailly,

for his humanism in science, his discreet enthusiasm, his openness to others' ideas while staying firm in his principles, his driven commitment to understand the thinking of others, his trusting generosity in the common endeavour to knowledge, his critical thinking tailored to better advance beyond the mainstream.

Foreword

by *Denis Noble*

During most of the twentieth century experimental and theoretical biologists lived separate lives. As the authors of this book express it, "there was a belief that experimental and theoretical thinking could be decoupled." This was a strange divorce. No other science has experienced such a separation. It is inconceivable that physical experiments could be done without extensive mathematical theory being used to give quantitative and conceptual expression to the ideas that motivate the questions that experimentalists try to answer. It would be impossible for the physicists at the large hadron collider, for example, to search for what we call the Higgs boson without the theoretical background that can make sense of what the Higgs boson could be. The gigantic masses of data that come out of such experimentation would be an un-interpretable mass without the theory. Similarly, modern cosmology and the interpretation of the huge amounts of data obtained through new forms of telescopes would be inconceivable without the theoretical structure provided by Einstein's general theory of relativity. The phenomenon of gravitational lensing, for example, would be impossible to understand or even to discover. The physics of the smallest scales of the universe would also be impossible to manage without the theoretical structure of quantum mechanics.

So, how did experimental biology apparently manage for so many years without such theoretical structures? Actually, it didn't. The divorce was only apparent.

First, there was a general theoretical structure provided by evolutionary biology. Very little in biology makes much sense without the theory of evolution. But this theory does not make specific predictions in the way in which the Higgs boson or gravitational lensing were predicted for physicists. The idea of evolution is more that of a general framework within which biology is interpreted.

Second, there was theory in biology. In fact there were many theories, and in many different forms. Moreover, these theories were used by experimental biologists. They were the ideas in the minds of experimental biologists. No science can be done without theoretical constructs. The so-called Central Dogma of Molecular Biology, for example, was an expression of the background of ideas that were

circulating during the early heydays of molecular biology: that causation was one way (genes to phenotypes), and that inheritance was entirely attributable to DNA, by which an organism could be completely defined. This was a theory, except that it was not formulated as such. It was presented as fact, a *fait accompli*. Meanwhile the pages of journals of theoretical and mathematical biology continued to be filled with fascinating and difficult papers to which experimentalists, by and large, paid little or no attention.

We can call the theories that experimentalists had in mind implicit theories. Often they were not even recognised as theory. When Richard Dawkins wrote his persuasive book *The Selfish Gene* in 1976 he was not only giving expression to many of these implicit theories, he also misinterpreted them through failing to understand the role of metaphor in biology. Indeed, he originally stated "that was no metaphor"! As Poincaré pointed out in his lovely book *Science and Hypothesis* (*La science et l'hypothèse*) the worst mistakes in science are made by those who proudly proclaim that they are not philosophers, as though philosophy had already completed its task and had been completely replaced by empirical science. The truth is very different. The advance of science itself creates new philosophical questions. Those who tackle such questions are philosophers, even if they do not acknowledge that name. That is particularly true of the kind of theory that could be described as meta-theory: the creation of the framework within which new theory can be developed. I see creating that framework as one of the challenges to which this book responds.

Just as physicists would not know what to do with the gigantic data pouring out of their colliders and telescopes without a structure of interpretative theory, biology has hit up against exactly the same problem. We also are now generating gigantic amounts of genomic, proteomic, metabolomic and physiomic data. We are swimming in data. The problem is that the theoretical structures within which to interpret it are underdeveloped or have been ignored and forgotten. The cracks are appearing everywhere. Even the central theory of biology, evolution, is undergoing reassessment in the light of discoveries showing that what the modern synthesis said was impossible, such as the inheritance of acquired characters, does in fact occur. There is an essential incompleteness in biological theory that calls out to be filled.

That brings me to the question how to characterise this book. It is ambitious. It aims at nothing less than filling that gap. It openly aims at bringing the rigour of theory in physics to bear on the role of theory in biology. It is a highly welcome challenge to theorists and experimentalists alike. My belief is that, as we progressively make sense of the masses of experimental data we will find ourselves developing the conceptual foundations of biology in rigorous mathematical forms. One day (who knows when?), biology will become more like physics in this respect: theory and experimental work will be inextricably intertwined.

However, it is important that readers should appreciate that such intertwining does not mean that biology becomes, or could be, reducible to physics. As the authors say, even if we wanted such a reduction, to what physics should the reduction occur? Physics is not a static structure from which biologists can, as it were, take things 'off the shelf'. Physics has undergone revolutionary change during the last century or so. There is no sign that we are at the end of this process. Nor would it be

safe to assume that, even if it did seem to be true. It seemed true to early and mid-nineteenth century biologists, such as Jean-Baptiste Lamarck, Claude Bernard, and many others. They could assume, with Laplace, that the fundamental laws of nature were strictly deterministic. Today, we know both that the fundamental laws do not work in that way, and that stochasticity is also important in biology. The lesson of the history of science is that surprises turn up just when we think we have achieved or are approaching completeness.

The claim made in this book is that there is no current theory of biological organisation. The authors also explain the reason for that. It lies in the multi-level nature of biological interactions, with lower level molecular processes just as dependent on higher-level organisation and processes, as they in their turn are dependent on the molecular processes. The error of twentieth century biology was to assume far too readily that causation is one-way. As the authors say, "the molecular level does not accommodate phenomena that occur typically at other *levels of organisation*." I encountered this insight in 1960 when I was interpreting experimental data on cardiac potassium channels using mathematical modelling to reconstruct heart rhythm. The rhythm simply does not exist at the molecular level. The process occurs only when the molecules are constrained by the whole cardiac cell to be controlled by causation running in the opposite direction: from the cell to the molecular components. This insight is general. Of course, cells form an extremely important level of organisation, without which organisms with tissues, organs and whole-body systems would be impossible. But the other levels are also important in their own ways. Ultimately, even the environment can influence gene expression levels. There is no *a priori* reason to privilege any one level in causation. This is the principle of biological relativity.

The principle does not mean that the various levels are in any sense equivalent. To quote the authors again: "In no way do we mean to negate that DNA and the molecular cascades that are related to it, play an important role, yet their investigations are far from *complete* regarding the description of life phenomena." Completeness is the key concept. That is true for biological inheritance as well as for phenotype-genotype relations. New experimental work is revealing that there is much more to inheritance than DNA.

The avoidance of engagement with theoretical work in biology was based largely on the assumption that analysis at the molecular level could be, and was in principle, complete. In contrast, the authros write, "these [molecular] cascades may causally depend on activities at different levels of analysis, which interact with them and also deserve proper insights." Those 'proper insights' must begin by identifying the entities and processes that can be said to exist at the higher levels: "finding ways to constitute theoretically biological objects and objectivise their behaviour." To achieve this we have to distance ourselves from the notion, prevalent in biology today, that the fundamental must be conceptually elementary. As the authors point out, this is not even true in physics. "Moreover, the proper elementary observable doesn't need to be "simple". "Elementary particles" are not conceptually/mathematically simple."

There is therefore a need for a general theory of biological objects and their dynamics. This book is a major step in achieving that aim. It points the way to some of the important principles, such as the principle of symmetry, that must form the basis of such a theory. It also treats biological time in an innovative way, it explores the concept of extended criticality and it introduces the idea of anti-entropy. If these terms are unfamiliar to you, this book will explain them and why they help us to conceptualize the results of experimental biology. They in turn will lead the way by which experimentalists can identify and characterize the new biological objects around which a fully theoretical biology could be constructed.

Oxford University,   Denis Noble

June 2013

Preface

In this book, we propose original perspectives in theoretical biology. We refer extensively to physical methods of understanding phenomena but in an untraditional manner. At times, we directly employ methods from physics, but more importantly, we radically contrast physical ways of constructing knowledge with what, we claim, is required for conceptual constructions in biology.

One of the difficult aspects of biology, especially with respect to physical insights, is the understanding of organisms and by extension the implications of what it means for an object of knowledge to be a part of an organism. The question of which conceptual and technical frameworks are needed to achieve this understanding is remarkably open. One such framework we propose is extended criticality. Extended criticality, one of our main themes, ties together the structure of coherence that forms an organism and the variability and historicity that characterize it. We also note that this framework is not meant to be pertinent in understanding the inert.

We are aware that our theoretical proposals are of a kind of abstraction that is unfamiliar to most biologists. An epistemological remark can hopefully make this kind of abstract thinking less unearthly. At the core of mathematical abstractions, not unlike in biological experiments, lies the "gesture" made by the scientist. By gesture we mean bodily movements, real or imagined, such as rearranging a sequence of numbers in the abstract or seeding the same number of cells over several wells. Gestures may remain mostly virtual in mathematics, yet any mathematical proof is basically a series of acceptable gestures made by the mathematician — both the ones described by a given formalism and the ones performed at the level of more fundamental intuitions (which motivate the formalisms themselves). For example, symmetries refer to applying transformations (e.g. rotating) and order refers to sorting (eg: the well-ordering of integer numbers and the ordering of oriented time), both of which are gestures. Since Greek geometry until contemporary physics, symmetries (defining invariance) and order (as for optimality) have jointly laid the foundation of mathematics and theoretical physics within the human spaces of action and knowledge. In summary, the theoretician singles out conceptual contours and organizes the World similarly as the experimenter prepares and executes scientific experiments.

From this perspective, biological theory directly relates to the acceptable moves, both abstract and concrete, that can be performedwhile experimenting and reflectiong on biological organisms. Symmetries and their changes, order and its breaking will guide our approach in an interplay with physics — often a marked differentiation. Again, the question of building a theory of organisms is a remarkably open one. With this book, we hope to contribute in explicitly raising this question and providing some elements of answer.

Interactions are as fundamental in knowledge construction as they are in biological evolution and ontogenesis. We would like to acknowledge that this book is the result and the continuation of an intense collaboration of three people: the listed authors and our friend Francis Bailly. The ideas presented here are extensions of work initiated by/with Francis, who passed away in 2009. We are extremely grateful to have had the priveledge to work with him. His insights sparked the beginning of the second author's PhD thesis which was completed in 2011.

We are also appreciative for the exchanges within the team "Complexité et Information Morphologique" (see Longo's web page), who included Matteo Mossio, Nicole Perret, Arnaud Pocheville and Paul Villoutreix. We also extend gratitude to our main "interlocuteurs" Carlos Sonnenschein and Ana Soto, Marcello Buiatti, Nadine Peyreiras, Jean Lassègue and Paul-Antoine Miquel. Additionally, we are grateful to Denis Noble and Stuart Kauffman who not only encouraged our perspective but also wrote a motivating preface and inspired a joint paper, respectively. We would also like to thank Michael Sweeney and Christopher Talbot who helped us with the english grammar.

Paris, June 2013   Giuseppe Longo[1]
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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 biophysical category: 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, 2011, Sonnenschein & Soto, 1999] and, in particular, [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.

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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.

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

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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].

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 coconstituted, 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 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

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

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 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:

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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.

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 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].

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[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].

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 complementary 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
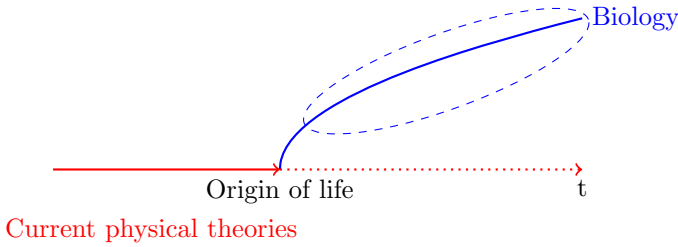
Fig. 1.1 *A scheme of the relation between physics and biology, from a diachronic point of view.* Theoretical approaches that focus on the origin of life usually follow the physical line (stay within existing physical theories) and try to approach the "bifurcation" point. The latter is not well defined 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.

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 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