Chapter 1
Introduction: Organization as a Scientific Blind Spot

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Abstract For most of the twentieth century, biology forgot or largely neglected organization. By this term, I mean a certain mode of interaction among the parts of a system, which is by hypothesis distinctively realized by biological systems. While a systemic trend is progressively pervading various biological fields – notably Evolutionary Biology, Systems Biology and Origins of Life – I suggest that organization still remains a blind spot of biological thinking. Therefore, I submit, biology should be enriched by an explicit and specific notion of organization, drawing in particular on the theory of autonomy, of which I recall some central tenets. I conclude with a brief overview of the scientific and philosophical tradition which has explicitly elaborated on biological organization, and of the more recent literature to which this book aims to contribute.

1.1 The Neglect of Organization

For most of the twentieth century, biology forgot or largely neglected organization. Since the establishment of the Modern Synthesis in evolutionary biology in the 1930s and 1940s, and the flourishing of molecular biology in the 1950s and 1960s, biological research has focused almost exclusively on entities described at the populational or molecular level, by adopting what is usually called "genocentrism," the perspective that places strong emphasis on genes as the fundamental determinants of biological phenomena (Rosenberg, 2007; Fox Keller, 2000).

As Gilbert and Sarkar have pointed out, "for most of this century, the major project of biology has been to reinterpret living properties as being epiphenomena of genes" (Gilbert & Sarkar, 2000: 5).

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The Modern Synthesis reconciled Darwin's theory of natural selection with Mendelian genetics through population genetics and put forward a reconceptualization of evolution as the change in allele frequencies in a population (Dobzhansky, 1937). Later, with the discovery of the structure of DNA in 1953, molecular biology underwent a comprehensive research program aimed at studying how the genetic program – a notion introduced simultaneously by Ernst Mayr on the one hand, and François Jacob and Jacques Monod on the other (Mayr, 1961; Monod & Jacob, 1961) – governs the synthesis of macromolecules and their interactions and, therefore, cell activity and functionality. The so-called "central dogma of molecular biology," i.e., the idea that biological information flows unidirectionally from DNA to proteins, was thereby interpreted as the idea that genes are the primary (if not sole) determinants of form, function, and behavior of organisms (Crick, 1966). In both evolutionary and molecular biology, genocentrism has therefore consisted in a reductionist stance, resulting in the neglect of biological organization as such.

By the term "organization" I mean a certain mode of interaction among the parts of a system, distinctively realized by biological systems, when compared to other kinds of natural systems, or to artifacts. Broadly speaking (I will return to this below), organization refers to a regime in which a set of entities happen to be related to each other so as to constitute a system that displays both functional differentiation and integration. Moreover, the activity of the whole system plays a role in maintaining its constituents over time: organized systems self-maintain. Let me point out right away that organization is typically, but not exclusively realized by organisms. For instance, it might be argued that colonies, symbioses, or, at a higher level of description, ecosystems can be described as organized systems, although they would not necessarily count as organisms. Accordingly, the notion of "organization" and that of "organism" should not be straightforwardly conflated, although they are closely related: organisms are organized systems, but organized systems are not necessarily organisms.

1.2 Organization as an Explanandum and an Explanans of Biology

Before reductionist and genocentric approaches became mainstream, many eminent biologists and philosophers put emphasis on the centrality of organization in biology. For instance, in his *Modern Theories of Development* (1933), Ludwig von Bertalanffy argued that "all vital processes are so organized that they are directed to the maintenance, production, or restoration of the wholeness of the organism." Therefore, he writes, "there is no 'living substance' because the characteristic of life is the organization of substances" (von Bertalanffy, 1933: 8).

At first sight, one might think that any biologist would easily agree with Bertalanffy. In a sense, it seems obvious that biological systems are organized and, hence, that biology should deal with their organization, its general principles and its various concrete manifestations. After all, biology emerged at the turn of the nineteenth century precisely as the science of "organized beings" (Gambarotto, 2018). Yet, several authors have noted that twentieth-century genocentric biology has lost sight of organisms (Laublicher, 2000; Huneman & Wolfe, 2010; Nicholson, 2014; Walsh, 2015) and thereby, I hold, of organization. What does this alleged neglect of organization consist in? Philosophically, I submit – following Huneman (2010) – that it has taken two different forms, related to the *explanandum* (what must be explained) and the *explanans* (what explains) of biology, respectively.

Firstly, organization is not the *explanandum* of genocentric biology; at best, the latter takes organization as a vague object of explanation. Indeed, the Modern Synthesis has been classically criticized because of its *atomization* of organisms, i.e., the fact of explaining biological traits separately as adaptations, without accounting for their integration as organized systems (Gould & Lewontin, 1979). As Huxley famously put it "every organism cannot be other than a bundle of adaptations" (Huxley, 1942: 20). Even though some advocates of the Modern Synthesis such as Mayr and Dobzhansky did disagree with such a radical view, it seems only fair to claim that the organized complexity of biological systems is not what this framework was designed to explain. Modern Synthesis' main explanandum is the evolution of adaptive traits as the result of differential selection acting on genes. In the case of molecular biology, it could certainly be argued that organization is the ultimate explanandum, insofar as the study of the parts taken separately is supposed to lead, in the long run, to an explanation of the whole system. Nevertheless, such a remote objective remained largely out of reach throughout the actual development of the discipline, which has seemed de facto unable to provide a molecular understanding of biological organization in all its characteristic complexity.

Secondly, organization does not play any explanatory role in genocentric biology. If it were the case, explanations would presuppose the fact that biological phenomena occur *because* biological systems are organized, and would not aim at explaining organization as such, by relying on more fundamental principles. Biology would explain phenomena in the light of their organizational nature. In evolutionary biology, the theoretical framework of the Modern Synthesis identifies natural selection as the main (and often sole) *explanans*, while the impact of organization in the evolutionary dynamics of biological systems is seldom taken into account. As for molecular biology, the rejection of organization as the explanans relies on more explicit theoretical reasons. Indeed, molecular genocentrism has advocated the idea that the specificity of biological phenomena is the fact that they are the result of the expression of a genetic program. Genes code for protein synthesis which, in turn, contributes to the realization of biological functions and, ultimately, of the whole organization. Accordingly, organization itself is explained by the expression of the genetic program (Mayr, 1961; Jacob, 1973).

It is worth noting that genocentrism has also influenced another research domain, that of the origins of life. Influenced by the flourishing of molecular biology, many researchers in this field have defended the idea that life on earth was initiated by the appearance of the first replicators, i.e., the first self-replicative molecules (the "first genes") (Pereto, 2005). On the one hand, organization should constitute – as it does for molecular biology – the ultimate explanandum, to the extent that self-replicative molecules are supposed to trigger an evolutionary process leading to the emergence of living systems endowed with organized complexity. Here again, however, the "replication first" approach has had a hard time in providing satisfactory explanations of the emergence of organized complexity. On the other hand, the "replication first" approach has explicitly excluded organization from the explanans, which seems at first sight an obvious move for a discipline that aims at explaining the *emergence* of life. Organized complexity cannot be adequately explained by appealing to an explanans that already implies organization. Rather, what could explain the emergence of organization would be the inherent capacity of (a population of) self-replicative molecules to generate more and more complex systems by evolving through natural selection – assuming that natural selection can operate before organized systems exist.

In recent times, genocentrism has been increasingly criticized. As it has been previously highlighted (Gilbert & Sarkar, 2000; Bateson, 2005), biology is paying more and more attention to the fact that biological phenomena should be studied by taking into account their distinctive complexity. Accordingly, a general trend toward a more organicist – or at least systemic – perspective can be easily perceived, not only in biology but also in related fields, like prebiotic chemistry. Importantly, recent organicist approaches challenge genocentrism not only on the side of the explanandum but also, and somehow more radically, on the side of the explanans: biology should be more inclusive and ambitious with the kind of phenomena to be explained and, at the same time, equip itself with more adequate explanatory tools.

1.3 The Anti-reductionist Trend in Evolutionary Biology

One of the fields in which an anti-reductionist reaction to genocentrism has been explicitly invoked is evolutionary biology, in the context of a lively debate about whether evolutionary theory needs a rethink (Laland et al., 2014). The debate puts into question the mainstream conceptual framework of the modern synthesis, leading to the call for an "extended evolutionary synthesis" (Pigliucci & Müller, 2010; Laland et al., 2015; Huneman & Walsh, 2017). The extended evolutionary synthesis puts emphasis on four key research themes whose implications, in the view of its advocates, converge on a different, "extended" understanding of the main factors that determine evolutionary change: constructive development, phenotypic plasticity, niche construction, and inclusive inheritance.

Constructive development refers to the idea that the development of organisms does not result from the execution of a genetic program but, rather, from multiple interactions between many factors within the developing system, as well as between the system and the environment (Oyama, 1985). Such a view has evolutionary implications, insofar as development is conceived as a process that facilitates the emergence of phenotypic variation (within and between individuals, populations, species, etc.) on which selection may operate (Minelli & Fusco, 2008). The classical conception of "developmental bias" that reduces the range of possible variations is replaced by a vision according to which development produces phenotypic novelty and affects evolutionary trajectories (Gerhart & Kirschner, 2007).

Phenotypic (or developmental) plasticity is the capacity of a given organism to generate different phenotypes to adapt to different environmental conditions. Plasticity can be seen as a generalization of constructive development: as such, it is meant to lead to phenotypic innovations and, thereby, to play a role in modulating adaptive evolution. In particular, a lively debate exists on whether – and if so, how – phenotypic plasticity can be consolidated by means of genetic accommodation, beyond phenotypic accommodation. As a consequence, adaptive phenotypic novelties would induce genetic changes in populations, and not vice versa (West-Eberhard, 2003).

Niche construction refers to all those processes through which the organism systematically modifies the environment and, thereby, the selective pressures acting on itself. Typical examples are the construction of dams, nests or webs, or the active intervention in the composition or distribution of nutrients in the environment (Odling-Smee et al., 2003).

Inclusive (or extended) inheritance challenges the idea according to which genes are the sole factors involved in biological inheritance. Rather, increasing experimental evidence shows that trans-generational similarities also rely on a variety of transmission processes that do not seem to require a genetic ground. Examples that are often mentioned include epigenetic, symbiotic, ecological, and cultural inheritance. The main implication for evolutionary biology consists in the fact that nongenetic inheritance would allow the transmission of acquired characteristics, thus being responsible for adaptive variations (Jablonka & Lamb, 1995, 2005).

Taken together, these recent research themes are promoting a shift from a genetic- to an organismic-centered view of evolution, insofar as each of them focus on phenomena with respect to which explanations relying on genetic determinism do not appear relevant or adequate. The general idea is that a better understanding of evolutionary trajectories requires taking into account a number of capacities and processes that cannot be described and explained by appealing only to genetic factors. Rather, biological systems as wholes become the relevant object with respect to which phenomena as development, plasticity, niche construction, and extended inheritance can be described and explained. When compared to the conceptual framework of the Modern Synthesis, it seems therefore clear that the organization of biological systems is being brought back to the foreground by the extended evolutionary synthesis, both as an explanandum and as an explanans (Nicholson, 2014). On the one hand, the EES pays more attention to phenomena that reflect the integrated activity of organized systems and their complexity; on the other hand, the explanatory strategy does not consist in deriving organization from more fundamental principles but, rather, in relying on organized systems (including, of course, organisms) and their characteristics in order to elaborate more adequate explanations of these phenomena.

There is therefore no doubt that the EES is more attentive to the organized complexity of the entities which are involved in evolutionary processes, like other authors remarked (Callebaut et al., 2007;[1] Wagner & Laublicher, 2000). Nevertheless, I submit, a conceptual characterization of biological organization as such has not yet been elaborated. In other words, the EES does not rely on a characterization of what is an organized system, which rather consists in a particular *level of description* at which phenomena are described and explanations are provided. The fact that the systemic shift is not accompanied by a characterization of organization has important implications for the explanatory scope and power of evolutionary biology. Some of the contributions to this book explore these implications. Here, I want to emphasize that, in spite of the increasing focus on it, organization remains a blind spot from the current EES views.

1.4 The Anti-reductionist Trend in Systems Biology

The systemic trend is also explicit in molecular biology with the emergence, in the early 2000s, of systems biology. Broadly speaking, systems biology was promoted in reaction to the genocentrism of classic molecular biology, as an approach that aims at shifting the view from genes to the larger systems in which genes are embedded. Rather than studying how gene expression generates biological complexity, systems biology focuses on how the biological system (typically, a cell) works and, in particular, how it regulates gene expression itself. It is now quite common to make a distinction, initially proposed by O'Malley and Dupré (2005), between two attitudes within systems biology: a "pragmatic" one and a "theoretic" one.

The first attitude includes the great majority of research in the field. Pragmatic systems biology can be described as an extension of molecular biology, which studies the interactions and dynamics of large molecular networks. Pragmatic (or "molecular") systems biology challenges genocentrism by considering large systems within which genes are a (crucial) component among many others. Different sets of molecular components (typically biopolymers) belonging to specific cellular organisms, under specific environmental conditions, are studied by different sub-fields: e.g., full cell genomes, as studied by genomics, the whole pool of RNA transcripts (awaiting translation, at a given time) by transcriptomics, the diverse proteins operating in the system by proteomics, metabolites by metabolomics, membrane lipids by lipidomics, and so on. Collectively, these sub-fields generate huge datasets that systems biologists are nowadays trying to interpret and integrate by using mathematical models and computer simulations (Nicholson, 2014: 352).

In spite of these innovations, systems biology can be said to place itself in continuity with the reductionist bottom-up strategies of classical molecular biology, insofar as the general objective consists in obtaining knowledge about the structure, function, organization, and dynamics of whole biological systems by elaborating

[1] Callebaut, Müller, and Newman, for instance, propose an "Organismic Systems Approach" to Evo-Devo, which explicitly elaborates on biological organization as a core notion.

models that integrate the parts and their relations (Saetzler et al., 2011: 3). Accordingly, the explanatory strategy operative in the field assumes organization as something that must be explained, but that does not play any explanatory role. More generally, as it has been pointed out by O'Malley and Dupré, molecular systems biology relies on a generic and theoretically ungrounded notion of "system," which designates the network of interacting molecules of different kinds. The central question is whether molecular systems biology can succeed in providing an adequate understanding of organized complexity through such a bottom-up explanatory strategy. Recently, several researchers have expressed skepticism in this respect (Mesarović & Sreenath, 2006; Bertolaso, 2011; Saetzler et al., 2011; Noble, 2017), arguing that the quantity and complexity of available data make more and more difficult their interpretation and integration. Data – the criticism points out – do not speak by themselves, and biologists are in trouble in asking them the relevant questions so as to get an adequate understanding of the whole organization.

This is where theoretical systems biology steps in. Instead of producing models that include more and more experimental data, theoretical systems biology looks for what Green and Wolkenhauer call "organizing principles" (Green & Wolkenhauer, 2013), which are used to select relevant data. One may say that while pragmatic systems biology aims at getting knowledge by adding more details, theoretical systems biology pursues the same objective by abstracting from details. The principles on which theoretical systems biology focuses are mathematical descriptions of recurrent constraints, relations, and patterns that are similar ("isomorphic") in different systems, not necessarily or exclusively biological. A classic example is homeostasis, the capacity to maintain an internal steady state in spite of external perturbation (Cannon, 1929). Other organizing principles have been applied to explain phenomena as flows and oscillations (see for instance the classical work of Goodwin, 1963, and recent developments). A milestone in this respect is the first mathematical model of the heart rhythm (Noble, 1962).

When compared to the pragmatic approach, theoretical systems biology makes a further step in challenging the reductionist perspective. Systemic principles are understood as general hypotheses, which means that they are supposed to explain the data (top-down) and not be explained by them (bottom-up). For instance, if one elaborates a model for accounting for a homeostatic behavior of a biological system, the question would not be "why is the system homeostatic?", but rather "how does the system manage to maintain that specific variable steady, given its (hypothetical) homeostatic capacities"? Accordingly, the notion of "system" is theoretically enriched, and its explanatory role enhanced by the expression of the principles.

Yet those principles are not meant to be distinctive to the biological realm. They are usually elaborated and formalized in other domains, as engineering and graph theory. For instance, negative feedbacks were formalized by cybernetics to account for homeostatic behavior in both animal and machines (Wiener, 1948). The transdisciplinary application of the principles is taken to be a fruitful explanatory strategy, which allows getting insights into the properties of biological systems by looking for analogies with physical systems or machines.

The strategy has proven successful and could certainly foster the acquisition of further knowledge. Nevertheless, it raises the question whether a full-fledged theoretical systems biology can rely on principles that are not designed to capture specific biological features, but more general systemic ones. While it is certainly true that biological systems are a class of physical systems, and therefore share with them (including artifacts and machines) common principles, a satisfactory theoretical framework of biological complexity should also look for *distinctive* biological principles.

One of the objectives of this book consists precisely in promoting the idea that theoretical biology should be endowed with a distinctive principle of organization, which would characterize biological complexity as such, above and beyond the different systemic principles that account for some of its features.

1.5 The Anti-reductionist Trend in the Origins of Life

In the origins of life field, the anti-reductionist alternative to the "replication first" view, which assumes that the individuals of an evolving population can be bare molecules, has taken the form of what is usually called the "metabolism first" view (Pereto, 2005). According to this perspective, the relevant starting point of the emergence of life is the spontaneous appearance of primitive self-catalytic metabolic networks, which would be a condition for the subsequent synthesis of replicators and genes.

The central objection of the "metabolism first" perspective to the "replication first" one is that a process of evolution by natural selection faces "bottlenecks" when it starts from a population of "naked" molecular species. In sharp contrast to the underlying assumptions of the competing view, the anti-reductionist approach argues that molecular replicators alone cannot generate the relevant kind of complexity leading to the appearance of life in the form of organized chemical systems.

Accordingly, the anti-reductionist view challenges the reductionist one with respect to the *explanans* that is adopted. Although it might seem obvious, the idea that we should not presuppose organization to explain the emergence of life (given that organization is taken as an inherent characteristic of life) leads to an impasse: if the explanans is too simple (in terms of its complexity), it cannot generate entities that are complex enough for our explanatory purposes. That is why the "metabolism first" approach does presuppose organization as an *explanans*, under the general hypothesis that some degree of organized complexity is actually required to bootstrap an evolutionary process leading to the appearance of living systems as we know them (Hordijk et al., 2011).

The general strategy consists in characterizing chemical systems (usually referred to as "protocells" or "proto-organisms," Rasmussen et al., 2008) that can appear spontaneously in plausible prebiotic environments and are endowed with the capacity of dynamically self-maintain and increase their functional complexity. Of course, organization cannot be the explanans of this very initial phase, in which organized systems emerge from the integration of different kinds of preexisting processes and components. Once these systems have appeared, however, the process toward primitive living cells implies a set of intermediate forms of organization, each playing a role in the emergence of the next, more complex one. During that long process, thus, each form of organization plays both the role of *explanans* of the next one and of *explanandum* of the previous one.

Although the systemic perspective on the origins of life is taking momentum, after the flourishing of "systems chemistry" as a research field important criticisms have also been addressed to it (Vasas et al., 2010), which explains that the debate is still lively in the field. One important issue is that – here again – the very notion of organization is not expressed in explicit conceptual and theoretical terms and, therefore, does not provide a sufficiently precise guidance in the elaboration of relevant protocells models (see Ruiz-Mirazo et al., 2017, for a discussion of this issue and a proposal).

1.6 What Is Organization?

The central objective of this book is to make a contribution to the current anti-reductionist trend in biology, by putting organization to the foreground. I submit that the systemic, or even organicist-thinking that is progressively pervading various biological fields should be enriched by an explicit and specific notion of organization, understood as both a fundamental explanandum and explanans in biology.

Adopting organization as an explanandum means that the object of biological explanation should be the phenomenon of organization itself in its various *realizations*, as well as its evolution. A satisfactory biological explanation should aim at making explicit how any specific phenomenon under scrutiny is to be understood as a manifestation or an aspect of organized complexity and, for this precise reason, biological. Beyond the fragmentation of reductionist approaches, anti-reductionist ones should hence aim at explaining biological phenomena by locating them into integrated organized wholes.

Adopting organization as an explanans, in turn, means conceiving it as a *theoretical principle* (Mossio et al., 2016). A theoretical principle is an overarching hypothesis that frames the intelligibility of the objects within a scientific domain. All biological systems, in all their diversity and richness of forms and kinds, comply with the principle, and are therefore organized. The crucial implication here is that theoretical principles enable explanations, but are not themselves the object of an explanation. Accordingly, the adoption of organization as an explanans means that biology presupposes the principle without trying to deduce it from something else, which would be precisely the reductionist stance.

A recent example of the adoption of organization as both an explanandum and an explanans is given by the model of a self-maintaining metabolic system, inspired by Robert Rosen's idea of (M,R)-systems (Piedrafita et al., 2010). The model is a computational simulation of a chemical network, made of three interlocking catalytic cycles, in which catalysts are produced by the very network that they contribute to maintain. Here, organization is the explicit explanandum in the sense that the model explores the conditions under which the system *as a whole* exhibits properties of organized – and therefore biologically relevant – systems, such as steady autocatalysis, robustness, and bi-stability. At the same time, organization is an explanans to the extent that the mutual dependence between the catalysts is presupposed as a background hypothesis and not obtained as a result. The model does not try to explain how and why catalysts get organized in the first place (i.e., mutually dependent); rather, it takes the very fact of being organized as an unexplained premise (an explanatory principle) and aims at explaining the properties of a system that realizes a specific instantiation of biological organization.

It is worth reflecting on this apparent contradiction, stemming from the double role of organization as both the explanandum and the explanans of biology. In the two cases, the term designates in fact different conceptual entities: as an explanandum, organization refers to its various concrete realizations in nature; as an explanans, it designates the general "regime" or "set of relations" that are common to all realizations. To make a (somehow very perilous) analogy, the dual role of organization as explanans and explanandum can be grasped by thinking to the role played by Newton's laws of motion in Classical Mechanics. On the one hand, the laws of motion are principles that are presupposed (i.e., not explained within the field), so as to provide explanation of physical phenomena; on the other hand, Classical Mechanics provide explanations of phenomena which realize (are in conformity with) the laws. Classical Mechanics presuppose the laws of motion so as to explain specific instantiations of these laws. In this very general sense, I submit that organization could play an analogous role in the biological domain.

Needless to say, for organization to play such a role, it should be characterized in a way that is more precise than the general and intuitive notions of "system" or even "organism" as they are currently employed in evolutionary and systems biology. So, the main question is: what does organization mean? To answer this question, let me spell out some guidelines that will be explored in the book. These guidelines are mostly inspired by the theory of biological autonomy, one of the contemporary heirs of the organicist tradition, to which I have myself contributed (Moreno and Mossio, 2015).

As already mentioned, organization designates a specific kind of complexity, a specific set of relations among elements. To a first approximation, organization refers to the differentiation of functional roles (i.e., division of labor) among the parts of a system and, at the same time, to their integration and coordination as a whole. Furthermore, and crucially, organization involves a generative dimension in the form of a mutual dependence, such that the very activity and existence of each organized part depends on its mutual relationship with the others. Organized parts have functions (Mossio et al., 2009; Saborido et al., 2011), which means that organization most basically designates *functional* complexity. Overall, biological organization is capable of self-determination, insofar as functional constraints collectively contribute to determine their conditions of existence. As I have argued elsewhere (Mossio & Bich, 2017), the capacity of self-determination provides a naturalized ground for purposiveness: biological organization can be legitimately said to be cause and effect of itself and thereby an intrinsically purposive regime.

Biological organization goes along with thermodynamic openness, which is the fact that organized systems continuously exchange energy and matter with the surroundings. The connection is theoretically deep, insofar as only thermodynamically open systems can possibly comply with the organization principle, although not any thermodynamically open system does. As all open systems, indeed, be they physical or chemical, biological systems are traversed by a flow of energy and matter, which takes the form of processes and reactions occurring in open thermodynamic conditions. In this respect, biological systems do not differ from other natural open systems. Yet, unlike "self-organizing" dissipative structures, they constrain and canalize the thermodynamic flow through the collective activity of their functional parts, which realize a specific form of mutual relationship, i.e., organization.

Because of their distinctive functional complexity, furthermore, organized systems (usually) do not appear spontaneously when some specific boundary conditions are met, as self-organizing structures do. Rather, organized systems are the result of a long historical evolutionary process of increase and preservation of complexity, which means in particular that any individual biological system is generated through the reproduction of other biological systems. In spite of their common thermodynamic grounding, hence, (biological) organization cannot be conflated with (physical) self-organization.

As the result of an historical process, biological complexity raises the central question of understanding how biological systems manage to maintain their stability while continuously undergoing variation (Montévil et al., 2016a; Longo et al., 2012, argue that biological variation is theoretically unprestatable). In this respect, I submit that the notion of organization plays a twofold explanatory role: on the one hand, organization allows explaining the stability of biological systems (both at the individual and evolutionary scale), and the maintenance of their constitutive dynamics over time; on the other hand, it provides a ground to understand how quantitative and qualitative innovations can be produced, and then preserved though its functional integration.

Lastly, let me emphasize again that biological organization should be conceived as a broader notion than that of "organism." Although organisms are – by hypothesis – organized systems, not all organized systems are necessarily organisms. For instance, some contributions to this book explore the idea that ecosystems might also be described as organized systems, without implying that they constitute a kind of organisms. Reciprocally, additional specifications should be added to characterize organisms among the broader set of organized systems. In this respect, a possible route is traced by the theory of autonomy, according to which organisms are autonomous systems, i.e., organized systems endowed with agential and adaptive capacities (see for instance Moreno and Mossio, 2015, section 4.4). As autonomous systems, in a word, organisms are organized adaptive agents.

1.7 Historical Overview

The historical roots of the notion of biological organization I refer to can be traced back to Immanuel Kant. In his *Critique of the Power of Judgment* (1790/1987, Kant argues that, unlike any other kind of system, the parts of biological systems do not and cannot exist by themselves, but only insofar as they constitute an organized whole which, in turn, is itself a condition of their own existence and functioning. In this sense, biological systems display self-organizing features that are absent in machines. In a watch, for example, every part is organically arranged in relation to the others, but the watch does not *produce* them. It "is certainly present for the sake of the other but not because of it." Hence the producing cause of the watch is the watchmaker, not the watch itself: "one wheel in the watch does not produce the other, and even less does one watch produce another, using for that purpose other matter (organizing it); hence it also cannot by itself replace parts that have been taken from it, or make good defects in its original construction by the addition of other parts, or somehow repair itself when it has fallen into disorder: all of which, by contrast, we can expect from organized nature." Based on these considerations, Kant claims that "an organized being is thus not a mere machine, for that has only a *motive* force, while the organized being possesses in itself a *formative* force (*Bildungskraft*), and indeed one that it communicates to the matter, which does not have it (it organizes the latter): thus it has a self-propagating formative power, which cannot be explained through the capacity for movement alone (that is, mechanism)" (Kant, 1790/1987: §65).

The Kantian focus on biological organization had continuity in the (mostly Continental) Biology of the nineteenth century, notably in the work of Goethe (1995) and Cuvier (1817). Cuvier's principle of the "condition of existence," for instance, claims that "the different parts of each being must be coordinated in such a way as to render possible the existence of the being as a whole" (1817 i., 6, quoted and translated by Reiss, 2009). By implying that the different parts are linked and coordinated, Cuvier's principle grounds and guides his empirical investigations in comparative anatomy and paleontology (Cuvier, 1805; see also Huneman, 2006, for an analysis).

Kant's and Cuvier's perspectives further influenced German organicist tradition leading to Johannes Müller's physiology (1837–1840) and Karl von Baer's embryology (1828). They both consider that, as Huneman writes "the proper object of life sciences should be a set of parts organizing itself as a whole, the development and the functioning of this specific kind of entity being the proper field of, respectively, embryology and physiology" (Huneman, 2010: 342).

Claude Bernard explicitly invokes Cuvier's view and claims that biological systems are to be conceived as organized entities, whose parts are interdependent and mutually generative. In his words, "The physiologist and the physician must never forget that the living being comprises an organism and an individuality… If we decompose the living organism into its various parts, it is only for the sake of experimental analysis, not for them to be understood separately. Indeed, when we wish to ascribe to a physiological quality its value and true significance, we must always refer to this whole and draw our final conclusions only in relation to its effects in the whole" (Bernard, 1865/1984, II, ii, x 1, 137, quoted and translated by Wolfe, 2010). Bernard's main focus is on the contribution of the organized parts – that must be investigated through the experimental method to the conservation of the internal milieu, in spite of the continuous variations taking place in the external milieu.

An important moment in the history of the scientific treatment of biological organization is represented by the so-called Theoretical Biology Club, that refers to a group of researchers including Woodger, Needham, and Waddington (Etxeberria & Umerez, 2006; Peterson, 2010). The Theoretical Biology Club promoted a scientific organicist perspective for biology and underwent a rigorous conceptual and theoretical treatment of various dimensions of the very idea of organization, including the analysis of internal relations (Woodger, 1929) and hierarchies (Needham, 1937). Another particularly relevant contribution is due to Ludwig von Bertalanffy (1952), who was one of the first authors that made explicit the fact that biological systems as thermodynamically open systems. Initially used by Bertalanffy as an argument against both vitalism and mechanism, the thermodynamic openness of biological systems remains central aspect role in the subsequent elaborations on organization.

Later on, the notion of organization played a central role in the organicist perspective that permeated embryology in the first half of the twentieth century. In particular, Paul Weiss refers to organization as the "coordinating principle" (Weiss, 1963: 190) that characterizes biological systems beyond local components and processes and that grounds their stability in the face of internal or external perturbations (Rosslenbroich, 2011; Bich & Arnellos, 2013; Nicholson & Gawne, 2015).

In the second half of the twentieth century, the conceptualization and scientific treatment of biological organization entered into a new phase, characterized by an increasing coherence and theoretical refinement. A milestone in this tradition is the account put forward by Jean Piaget (Piaget, 1967), whose core idea was to integrate into a single coherent picture thermodynamic openness and organizational closure. On the one hand, as emphasized by Bertalanffy, organisms are thermodynamically open systems, traversed by a continuous flow of matter and energy. On the other hand, they realize "closure," i.e., the mutual dependence between a set of constituents which maintain each other through their interactions and which could not exist in isolation.

In Piaget's view, closure captures a fundamental aspect of the very idea of "organization," through the association between division of labor and mutual dependence that it implies. In other words, biological organisms are organized precisely because they realize closure. The centrality of closure and its connection to organization, as well as its distinction from (and, yet, complementarity to) thermodynamic openness have become givens in most subsequent accounts of biological organization (Letelier et al., 2011).

One of the best-known accounts of biological organization is the one centered on the concept of autopoiesis (Varela et al., 1974; Varela, 1979) which, among other aspects, places heavy emphasis on the generative dimension of closure: biological systems determine themselves in the sense that they "make themselves" (autopoiein). Precisely because of their dissipative nature, the components of biological organisms undergo degradation over time; the whole system preserves its coherence and identity only insofar as it maintains and stabilizes not just some internal states or processes but the autopoietic system itself as an organized unity. In spite of its qualities, however, a central weakness of the concept of autopoiesis is that it does not provide a sufficiently explicit characterization of closure (Montévil & Mossio, 2015). Biological systems are at the same time thermodynamically open and organizationally closed, but no details are given regarding how the two dimensions are interrelated, what constituents are involved in closure, and at what level of description. In the absence of such specifications, it remains unclear in what precise sense closure would constitute a causal regime that distinctively characterizes biological organization.

A concerted attempt to answer this question was made by Robert Rosen. In *Life Itself* (Rosen, 1991), Rosen reinterprets the Aristotelian categories of causality and claims that the distinction between closure and openness should be grounded on a distinction between efficient cause and material cause. By relying on this distinction, Rosen's central thesis is that: "a material system is an organism [a living system] if, and only if, it is closed to efficient causation" (Rosen, 1991: 244). In turn, a natural system is closed to efficient causation if, and only if, all components having the status of efficient causes within the system are materially produced by the system itself. What matters here is that closure is located at the level of efficient causes: what constitutes the organization is the set of efficient causes subject to closure, and its maintenance (and stability) is the maintenance of the closed network of efficient causes.

Although Rosen's account represents a crucial step forward in the theoretical understanding of organization, I think that it still remains too abstract, and therefore hardly applicable as a guiding principle for biological theorizing, modeling, and experimentation. Rosen defines closure as involving efficient causes, but, without additional specifications, it might be difficult to identify efficient causes in the system: what entities actually play the role of efficient causes in a biological system? To deal with this issue, decisive insights have emerged from more recent literature that elaborates more explicitly on the "thermodynamic grounding" of biological systems (Bickhard, 2000; Christensen & Hooker, 2000; Moreno & Ruiz Mirazo, 1999) and the relations between closure and openness. In particular, Stuart Kauffman (2000) argues that biological organization implies a circular relationship between work and constraints, in the form of what he labels a "work-constraint (W-C) cycle." When a (W-C) cycle is realized, constraints that apply to the system are produced and maintained by the system itself. Hence, the system needs to use the work generated by the constraints in order to generate those very constraints, by establishing a mutual relationship – a cycle – between constraints and work.

More recently, a characterization of biological organization as "closure of constraints," which puts together many of the central ideas evoked above, has been proposed (Montévil & Mossio, 2015). Most of the contributions to this book actually rely on this characterization to further develop its implications.

1.8 The Current Context, and The Place of the Book

Nowadays, what is generically called "organicism" is undergoing resurgence, as an increasing number of philosophical, theoretical, and even formal accounts have advocated it as an integrative and fecund framework for biology (Gilbert & Sarkar, 2000). Among these accounts, the aforementioned theory of biological autonomy – originally elaborated by Varela (Varela, 1979) – is gaining momentum (Moreno & Mossio, 2015).

Recently, several studies have relied on the pioneering work mentioned above, and tried to further elaborate on the central notion of organization. Some have investigated its philosophical (Mossio & Moreno, 2010) and theoretical (Letelier et al., 2011; Wolkenhauer & Hofmeyr, 2007) implications, while others have developed applications to various domains, such as the already mentioned metabolic networks (see also Cornish-Bowden et al., 2013), physiological regulation (Bich et al., 2020), the transition from unicellular to multicellular organisms (Arnellos et al., 2014), organogenesis (Montévil et al., 2016b), ecology (Nunes et al., 2014), agency (Barandiaran et al., 2009), cognition (Barandiaran & Moreno, 2006), and the origins of life (Ruiz-Mirazo & Moreno, 2004). These are just a few examples showing the existence of a scientific perspective that aims at establishing an organizational framework for biology – whether or not they stem from the theory of autonomy – and elaborates on some recurrent theoretical themes such as openness, closure, constraints, agency, and circularities, as well as their connections with philosophical issues as teleology, functionality, normativity, historicity, and individuation.

The main objective of the book is to assess the prospects and the fecundity of the concept of organization in biological research, both as a philosophical foundation and as a theoretical principle able to generate models and experimental protocols. The various chapters deal with a variety of issues with respect to which an organizational perspective can be adopted and discussed. Collectively, they show that the notion of organization can nourish the current anti-reductionist trend, by guiding the elaboration of models and the connection with experimental biology.

In the second chapter (Chap. 2), Georg Toepfer recounts the history of the concept of organization, as used in relation to organic bodies. Toepfer underscores that organization becomes a defining feature of life from the seventeenth century and plays a central role in the establishment of biology as an autonomous scientific discipline. During the nineteenth and twentieth centuries, then, it has been supplemented by the concepts of evolution and regulation, which refer to the transformation and stabilization of organized systems, respectively. In its more recent formulations (notably in terms of constraints closure) – Toepfer argues – the specificity of organization is more explicitly tied to the specificity of *forms* that enable its realization. As he writes: "The only life-forces that exist are life-forms."

Charles Wolfe (Chap. 3) discusses the challenges that a naturalistic and non-foundationalist – and thereby scientifically workable – organicist project should take up. In his view, some versions of organicism suffer from at least three main hesitations or "instabilities," which relate to the interpretation of organismal properties (epistemological vs. ontological, irreducible vs. empirical), as well as the opposition with mechanism. Wolfe argues that "one more effort" should be made to overcome these instabilities, without giving in to the symmetrical temptations of objectification and subjectification of organisms. The very concept of organization is likely to play a crucial role in making this effort successful.

In Chap. 4, Gertrudis Van de Vijver and Levi Haeck focus on one of the instabilities noted by Wolfe, that between the epistemological and ontological interpretations of organisms as organized systems. They put forward an original transcendental stance, inspired by Kant's treatment of biological organization, according to which both the subject and the object involved in our understanding of organisms should be treated as organized living systems. Thereby, the enquiry about the properties of living organization is simultaneously an enquiry about the subject and the object of biological knowledge. Insofar as our rational capacities are a manifestation of life, studying the latter "folds back onto" the former and reveals that our cognition shares fundamental organizational properties with biological phenomena, starting with their purposiveness.

Cliff Hooker (Chap. 5) shares with Van de Vijver and Haeck the idea that cognition and life display common properties. As life, cognition is organized in a narrow, theoretically precise sense, which implies in particular the realization of agency, purposiveness, and anticipation. In a word, both life and cognition realize autonomy. Yet, instead of focusing on the epistemic loop between cognition and life, Hooker emphasizes that autonomy comes in degrees: in particular, cognition (and notably human cognition) relies on much more sophisticated anticipatory and adaptive capacities, when compared to noncognitive biological autonomy. The take home message is "unification without reduction": the concept of organization can be usefully put to work to provide a general understanding of cognition and life, while preserving their specific features.

Chapter 6 provides a counterpoint to the general message of the book. Olivier Sartenaer argues that organicism does not need organization to remain "chauvinist about organisms and autonomist about biology." Organicism can vindicate the irreducibility of organisms – and justify its epistemological autonomy – by showing that they comply with the requirements of transformational emergence. Sartenaer's argument is not that organization is an illegitimate concept, but that organicism could stand while discarding it. To the objection that, without organization, transformational emergence does not capture what distinguishes organisms from other emergents, Sartenaer replies that their specificity could be grounded in their being the outcome of specific transformational transitions during biological evolution. Yet, this solution begs the question whether biological evolution can be the evolution of anything else than organized systems.

Philippe Huneman (Chap. 7) offers a comparison between organizational and evolutionary approaches of organisms, that he labels "Kantian" and "liberal," respectively. While the former aim at characterizing organisms by appealing to a distinctive set of organizational properties, the latter situate organisms in a larger, continuous spectrum of biological individuals understood as units of selection. In liberal approaches, organisms are not the only biological individuals and, in addition, "being an organism comes by degrees." The comparison raises the question of the connections between the two conceptions of individuality, as well as between the two underlying theoretical frameworks. Huneman addresses this question and explores the prospects of a fruitful reconciliation between Kantian and liberal approaches.

In Chap. 8, Johannes Jaeger provides an answer to the question raised by Huneman. He advocates the radical idea according to which biological evolution cannot be but the evolution of organized systems. Evolutionary theory should move toward a fourth perspective, which would complement and succeed existing structural, functional, and processual perspectives. In particular, the fourth perspective is an agential perspective, centered on the hypothesis that evolving organisms are organized purposive agents. As such, not only organisms are what evolutionary processes operate on, but they also modulate such processes. As Jaeger, following Walsh, puts it: "Some things in evolution happen because organisms make them happen." The agential perspective relies on a naturalized understanding of purposiveness, provided by recent characterizations of organization as constraints closure. Importantly, Jaeger underscores that such an organizational purposiveness applies to individual organisms exclusively, and not to evolutionary processes as such. The existence of macroevolutionary trends is a different issue that should be explored separately.

Sharing Jaeger's perspective on the role of organization in shaping evolution – one might argue – still leaves room to the assumption that, while looking at the origins of life, organization initially emerged from evolutionary processes. In Chap. 9, however, Kepa Ruiz-Mirazo and Alvaro Moreno argue that things are more complicated. They put forward an account of biogenesis that also ascribes an explanatory role to the concept of organization. Again, the emphasis is placed on the interplay between individual organization and evolutionary processes, which take place at a different spatial and temporal scale. Their main thesis is that, to result in the emergence of complex biological organisms (as we observe them), biogenetic trends require complex enough, organized self-maintaining systems as a starting point. Complexity begets complexity, in the sense of generating functional variety and more sophisticated forms of control. In particular, Ruiz-Mirazo and Moreno emphasize the evolutionary significance of forms of regulation and heredity relying on dynamical decoupling, whose emergence has drastically enhanced individual adaptivity and cross-generation stability.

Gaëlle Pontarotti (Chap. 10) specifically deals with the connection between organization and heredity, a key ingredient of evolution. Pontarotti argues that the general trend beyond genocentrism implies a shift from a heuristic of replication, which sees evolution in terms of a competition among self-replicating objects, to a heuristic of collaboration, which emphasizes the mutual dependence of objects belonging to integrated wholes. The heuristic of collaboration can be applied to elaborate an organizational account of heredity, which characterizes the latter as the "trans-generational conservation of functional networks." Pontarotti submits that the organizational account allows expanding heredity beyond genes, while keeping the concept conceptually bounded. The extension avoids then the dilution of heredity into a too general concept of biological cross-generation stability. The chapter also discusses how the organizational account of heredity impacts some of the central tenets of evolutionary theory.

Chapter 11 shifts to the individual scale and explores the explanatory role that the concept of organization can have with regard to development. Leonardo Bich and Derek Skillings put forward an organizational view on development that, here again, makes determination reciprocal: not only development determines the establishment of biological organization but, reciprocally, organization enables developmental processes. As Bich and Skillings emphasize, the organizational view "favors a switch in perspective," whereby each stage of development is understood as an organized system aiming at its own maintenance, rather than being an intermediate step of a process tending to a final state (typically identified with the achievement of reproductive capabilities). Bich and Skillings argue that the organizational view accounts not only for maintenance but also for change, which is genuinely developmental only if it is controlled by regulatory functions exerted by the organized system. Regulation also draws the boundaries of development, which starts when regulatory functions appear and ends when the organized system ceases to undergo regulated change.

Maël Montévil and Ana Soto (Chap. 12) further explore developmental processes by discussing their recent efforts to model morphogenesis, and more specifically mammary ductal morphogenesis. In their model, Montévil and Soto have applied two principles: cells default state and organization. According to the default state, cells move and proliferate when unconstrained, in the presence of sufficient nutrients and space, while the organization of the multicellular system that they constitute exerts the constraints that canalize or inhibit the default state. In particular, Montévil and Soto show that the formation of mammal ducts is determined by the interplay between the constraints exerted by proliferating cells on the extracellular matrix (notably on collagen fibers), which in turn constrains cells proliferation and motility. The chapter also addresses important issues raised by the modeling practice relying on organization. These include the choice of those organized parts and constraints expected to play a role in determining the target phenomenon, and their insertion into a description of the whole organismal organization.

The last chapter (Chap. 13) shifts again to a different scale and discusses some theoretical and ethical implications stemming from the application of the organizational framework to the ecological domain. Charbel El-Hani, Felipe Lima, and Nei Nunes-Neto argue that the concept of organization provides a relevant tool to individuate ecosystems and to ascribe functions to their parts (both to items of biodiversity and abiotic items). In particular, they provide a detailed reply to some objections recently raised against the organizational account of ecosystemic functions. El-Hani, Lima and Nunes-Neto's contribution is particularly important because it shows that the concept of organization may be pertinently used to characterize biological systems in general, and not only organisms. Also, it opens the way to future research directions, which would explore the relations and interplay between nested levels of organization. Lastly, El-Hani, Lima, and Nunes-Neto argue that the concept of organization, by naturalizing intrinsic purposiveness, provides a ground to ascribe intrinsic value to ecosystems. In turn, this supports an original conception of sustainability, which is alternative to the usual anthropocentric interpretation.

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