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The basis of theory building in biology lies in the organism concept: a historical perspective on the shoulders of three giants

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Abstract
The rise of molecular biology went hand in hand with a marginalization of the integrative unit in biology – the organism. Although the new methodological approaches contributed to eminent progress in many fields, the often assumed sufficiency of restricting the focus to molecules is problematic. This was already clear to the founders of theoretical biology (Schaxel, Bertalanffy, and others). Although theories have long played a role in biology and can be traced back to antiquity, the field of theoretical biology was first established only in the early 20th century. Theoretical biology needs to take into account the specific features in living nature that are not tackled by other disciplines. Unsurprisingly, the organization of parts and processes together with the organism concept play a central role for such theoretical considerations. The phenomena shown by living beings cannot be traced back – in a mere "atomistic" way – to the behaviour of singled out parts alone. There are different kinds of interactions among all levels of organization in an organism, and they have to be grasped practically and theoretically. Microdeterminism, which refers to the idea that macroscopic phenomena are determined solely by events on the micro- or molecular level, must be complemented by macrodeterminacy (Weiss), which works in the diametrically opposite direction. The present paper underlines the key role of theoretical biology and its connection to the organism concept by examining their common historical development based on the contributions of Paul A. Weiss, Ludwig von Bertalanffy, and Rupert Riedl.

Keywords: organism, theoretical biology, Paul A. Weiss, Ludwig von Bertalanffy, Rupert Riedl

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1. Introduction

The organism concept is of central importance for theory building in biology.

Many theories in the sub-fields of biology, such as developmental biology, morphology or physiology, depend on how an organism is perceived. Whether the organism is thought of as an aggregate of independent parts or a system, with strong interconnections, determines theories e.g. about embryogenesis. The notion of how the organism is conceptualised – atomistic, modular or otherwise – plays also a crucial role for systematics and evolutionary biology (Kemp 2016, p. 16–36). In this regard, Kemp (2016, p. 18) holds that evolutionary conclusions from cladistic analyses depend on the assumption of an atomistic model of the organism.

Whether the organism is thought of as a passive stimulus response machine or an active agent determines theories about behaviour. For medicine the basic notions of the human organism play a vital role in prevention, diagnosis, treatment and research. Furthermore, the issue whether the organism constitutes an entirely optimised entity – with reference to engineered systems – influences the knowledge transfer towards technical applications in biomimetics (cf. Maier and Zoglauer 1994).

This makes it important to clarify the organism concept and make the assumptions about it ever more explicit. What is characteristic of basic concepts – such as the organism concept – is that they are essential and irreplaceable for theories, but that they are often presupposed and not defined in these theories. "This is particularly true of the two concepts which define the object of biology: life and organism" (Toepfer 2011, vol. 1, p. xxxv–xxxvi). Such terms also define the research field: What is investigated? Which methods must be used? What results can be expected? Depending on the explicitly or implicitly used organism concept, these questions must be tackled in different ways.

It has been noted that the absence of the organism concept in present-day biology has mainly been due to the dominance of molecular biology and new methods in that discipline (Laubichler 2005, p. 111). Symptomatic for such a negligence of the organism is the structure of a long-selling textbook on zoology. Alfred Kühn first published his textbook in 1922 with many editions ever since (Kühn 1961). It started with general considerations on organisms and the task of zoology. This chapter was deleted and, with the new authors, the book now starts on the cellular level (Wehner and Gehring 2013). Nevertheless, there has been a renaissance of interest in the organism from the sides of theoretical biology as well as philosophy (e.g. Callebaut et al. 2007; Henning and Scarfe 2013; Koutroufinis 2014; Longo et al. 2015; Toepfer and Michelini 2016). This is also reflected in other widely used modern textbooks such as Campbell et al. (2015), which starts with a broad overview and function-structure relationships on all levels of biological systems.

Renaissance implies earlier considerations about the organism. The list of masterminds who concerned themselves with the organism concept goes back to antiquity.

The focus of the present article is, however, on three eminent biologists who based their research on important considerations of the organism as linked to theoretical biology: Paul A. Weiss (1898–1989), Ludwig von Bertalanffy (1901–1972), Rupert Riedl (1925–2005). The historical perspective in this article yields insights into the importance of theories in biology and, connected with that, the importance of the organism concept. The organism concept as the basis of biological theory building is highlighted.

2. Theoretical biology

Theoretical biology was advocated since the early 20th century with different approaches. Reinke (1901) connected it to a vitalistic philosophy. The account of Uexküll (1920) is mostly pure philosophy. Ehrenberg (1923) attempted to deduce the phenomena of life from the necessity of death. Among the early writings, only the account of Schaxel (1919) seems to be directly relevant for biology as a natural science.

Until today many scholars have been involved in theoretical biology. Among them was Conrad H. Waddington, who framed theoretical biology as an "attempt to discover and formulate general concepts and logical relations characteristic of living as contrasted with inorganic systems" (Waddington 1968).

Several historical examples show how practically useful such theories can be in biology. Prominent examples are: Mendel's genetics and the Hodgkin–Huxley model on action potentials in neurons. The latter can be seen as a predecessor of today's systems biology (cf. Noble 2006, p. 58f).

Unsurprisingly, the request for more theoretical work in biology comes especially from systems research – to the extent that it notices biology as being more theoretical than physics (Gunawardena 2013).

Ludwig von Bertalanffy can doubtlessly be called a father of theoretical biology. His early work was an attempt to establish theoretical biology as a scientific field (Bertalanffy 1927; 1928a; b; 1932). Bertalanffy distinguishes between two areas in theoretical biology. The first deals with the epistemological and methodological basis of biology (Bertalanffy 1932, p. 38ff, 47; 1937a, p. 163f). This area focuses on the rational and logical analysis of the basis of knowledge in biology, where e.g. the problem of teleology has to be tackled. Furthermore, concepts – such as the mechanism concept – and methods have to be critically investigated. Today, theoretical biology in this sense is rather referred to as philosophy of biology or 'biophilosophy'. The second area is about developing theories in different fields of biology (Bertalanffy 1932, p. 6). The procedure here is similar to that in theoretical physics, where experiments are suggested that have to be performed in experimental physics. This is what is often understood by theoretical biology today. Note that theory is important for ordering the facts – not only after data collection. Rather, at the beginning of any biological research the theoretical framework already has to be considered (Bertalanffy 1928b, p. 55f; 1932, p. 33).

Bertalanffy made major contributions in both areas. With respect to the first area an often raised question is whether biology can be reduced to physics and chemistry. For Bertalanffy this question is of secondary importance which at that time could not be decided anyway (Bertalanffy 1930, p. 26). There are, however, issues in biology that had not been dealt with in physics and chemistry, e.g. order and organization, which are key features of organisms. Accordingly, those features could not be reduced to sciences of the inorganic realm because of the sheer lack of concepts and methods to deal with them. Similar arguments are valid for the concepts of wholeness, purpose, adaptation, and others (Schaxel 1922, p. 158; Bertalanffy 1927). Importantly, a false notion of physics seems to prevail among biologists. In physics not everything is necessarily reduced to the "atomistic" level. Thermodynamics is a case in point. In electro-magnetism a general mechanical and reductionistic account had to be thrown overboard. The law of the lever is useful without reduction to smaller parts, such as atoms. Similarly, also in biology, laws governing a "higher level" need not be reducible to the behaviour of small parts.

With respect to the difference between physics and biology, there is another important issue. Contrary to physical problems, the phase space (a multidimensional mathematical space in which the axes refer to variables that are required to describe the state and behaviour of a system) is not always pre-given at the onset of a process in biology. This is true for ontogeny as well as phylogeny. Longo and Montévil (2013) argue that a major aspect of biological evolution (but also ontogeny) is a continued change of the pertinent phase space. Bertalanffy anticipated this idea when criticising the pre-established arrangement in cybernetic systems (Drack and Pouvreau 2015, p. 549ff). Rather than merely examining the ready-made "circuits", he was also interested in the ontogenesis of regulatory systems, where the observables (that define the dimensions of the phase space) are not present at all times of an organism's life. For example, in an early-stage embryo there is no blood sugar level that needs to be maintained at a constant level.

An example that belongs to the second area of theoretical biology is contained in Bertalanffy's analysis of theories of development (Bertalanffy 1928b). At that time, many different theories had been – implicitly or explicitly – advanced, from vitalistic accounts to chemical theories, *Gestalt* theories, mechanistic theories and organismic theories. All of them were investigated with respect to logical consistency, validity of assumptions and their accordance with empirical facts. Even today, there is a tacit basis of theories and general assumptions at the core of most research programs (cf. Lakatos 1978) in various disciplines. Investigations and comparisons of theories are very useful in this regard and can serve as the basis for establishing new theories.

A major example of successful theory building in biology is the contribution of Gregor Mendel (1822–1884). His experiments on plant hybridization were only comprehensible in the light of his theoretical considerations, which eventually led to biological laws (Mendel 1866). His theoretical contributions were at least as important as his experiments and refer to an important aspect of organisms. He established a notion of how characters of an organism can be connected to some inherited entities and therefore anticipated the, at the time unknown, genes.

In a similar vein, Bertalanffy developed his growth equations. At the early 20th century, much work was done to investigate the change in mass or length of an organism over time. This resulted, on the basis of curve fitting, in certain empirical rules. This was not satisfactory for Bertalanffy, who strove for a deductive approach. The basis is the hypothesis of a cause. In his growth investigations, he assumed that the growth rate is a function of assimilation and dissimilation, which enabled him to build a mathematical model that combined physiological factors with morphological factors. By knowing the "metabolic type" of an organism, the "growth type" can eventually be predicted (Bertalanffy 1969, p. 175f, Pouvreau and Drack 2007). This was a major contribution to theoretical biology and mathematical biology.

Joseph H. Woodger (1894–1981), also an important figure in theoretical biology, followed a positivistic approach towards a more formal and axiomatic biology. For him, organism and hierarchy are, amongst others, important concepts that need to be considered in a deductive approach in biology. He demonstrated that there are theories in biology, such as Mendelian genetics, that can be axiomatised and formalized (Woodger 1937, Krohs 2005, p. 307).

Theoretical biology (*sensus* Bertalanffy) points to the bigger picture that has to be taken into account in biology. "The actual essence of life lies in the organisation of the substances and processes […] It is by no means enough for a knowledge of life when we know the single parts and processes in the finest details; we are allowed to speak of such a knowledge only if we know the laws which rule the order of all those parts and processes" (Bertalanffy 1932, p. 86). Such considerations spawned the demand for a holistic or organismic approach in biology.

Long before the emergence of molecular biology, already in the 19th century, the term "organismic" shows up in various contexts, e.g. 1886 in J. C. Burnett's "organismic standpoint" on diseases of the skin (Toepfer 2011, vol. 2, p. 821). Nonetheless, a theoretical framework has been developed only since the early 20th century.

Even before that, Immanuel Kant (1724–1804) provided important thoughts that are relevant for a conceptualisation of biology: "In such a product of nature [organism] every part not only exists *by means of* the other parts, but is thought as existing *for the sake of* the others and the whole, that is as an (organic) instrument. Thus, however, it might be an artificial instrument, and so might be represented only as a purpose that is possible in general; but also its parts are all organs reciprocally *producing* each other. This can never be the case with artificial instruments, but only with nature which supplies all the material for instruments (even for those of art). Only a product of such a kind can be called a *natural purpose,* and this because it is an *organised* and *self-organising being*" (Kant 1892, §65).

Julius Schaxel – who edited a series of books termed *Abhandlungen zur theoretischen Biologie* (Treaties in Theoretical Biology) – popularised the German term "organismisch", which was brought forward in 1906 by the entomologist Ludwig Rhumbler (Pouvreau and Drack 2007). William Emerson Ritter (1856–1944) is acknowledged as the founder of "organismic biology" in which the organism is conceived as a unit, its parts can only be explained with reference to this unit and the unit must be explained through the parts (Ritter 1919; Toepfer 2011, vol. 2, p. 821).

On this basis, Bertalanffy started his considerations on an organismic conception of biology and summarized its "leading principles": "*The conception of the system as a whole* as opposed to the *analytical* and *summative* points of view; the *dynamic conception* as opposed to the static and *machine-theoretical* conceptions; the consideration of the organism as a *primary activity* as opposed to the conception of its *primary reactivity*" (Bertalanffy 1952, p. 18f). Hence, the organism concept is in the centre of further theoretical considerations in biology. Investigating the mere physical and chemical events is insufficient.

3. The organism concept

The organism concept is a central reference point for all biological disciplines (Figure 1). No research in biology makes sense without reference to an abstract or concrete organism. That this is subsequently true for medicine as well is self-evident. Hence, every sub-discipline in biology and medicine has at least an implicit notion of the organism. Even though much research in biology is done on the small parts, i.e. on molecules, the interactions on this level occur within or in connection with an organism and thereby the parts' interactions depend on the larger system of the organism, while simultaneously the organism depends on the interactions of the parts. The parts and processes in an organism are functionally interdependent. Regulation is an important phenomenon to support this notion. In physiological as well as in developmental phenomena, regulation cannot be explained by (mentally) dissecting an organism into single parts and processes. The reactions in one part are not only dependent on its own state, but also on the states of superordinate parts or the whole organism, and therefore the organism has to be conceived as a united system (Bertalanffy 1932, p. 83). Physiologically, Bertalanffy notes that the whole organism determines the performance of the cells and not *vice versa* (Bertalanffy 1952).

The question then arises: What characterizes an organism, and how can it be defined? From Aristotle until today, what *living* means has been captured in lists of criteria (Toepfer 2005, p. 160).

As those criteria (e.g. metabolism, reproduction) are always found in specific natural entities, namely organisms, they can also be described as entities that fulfil such criteria. This is one way of starting to tackle the question what an organism is. Throughout history there have been many attempts of defining the organism in this manner. A short summary is provided by Toepfer's complex definition of the organism based on eight theoretical stations (Toepfer 2011, vol. 2, p. 795):

> An organism is a local, unstable harmony of heterogeneous materials (*Hippocrates*),
>
> it consists of a body which has specific activities and functions and is held together by a principle of unity (*Aristotle*),
>
> it resembles inorganic bodies insofar as its functions arise from the disposition and interaction of its parts and can be explained by laws of nature, without having to rely on metaphysical principles of form (*Descartes*),

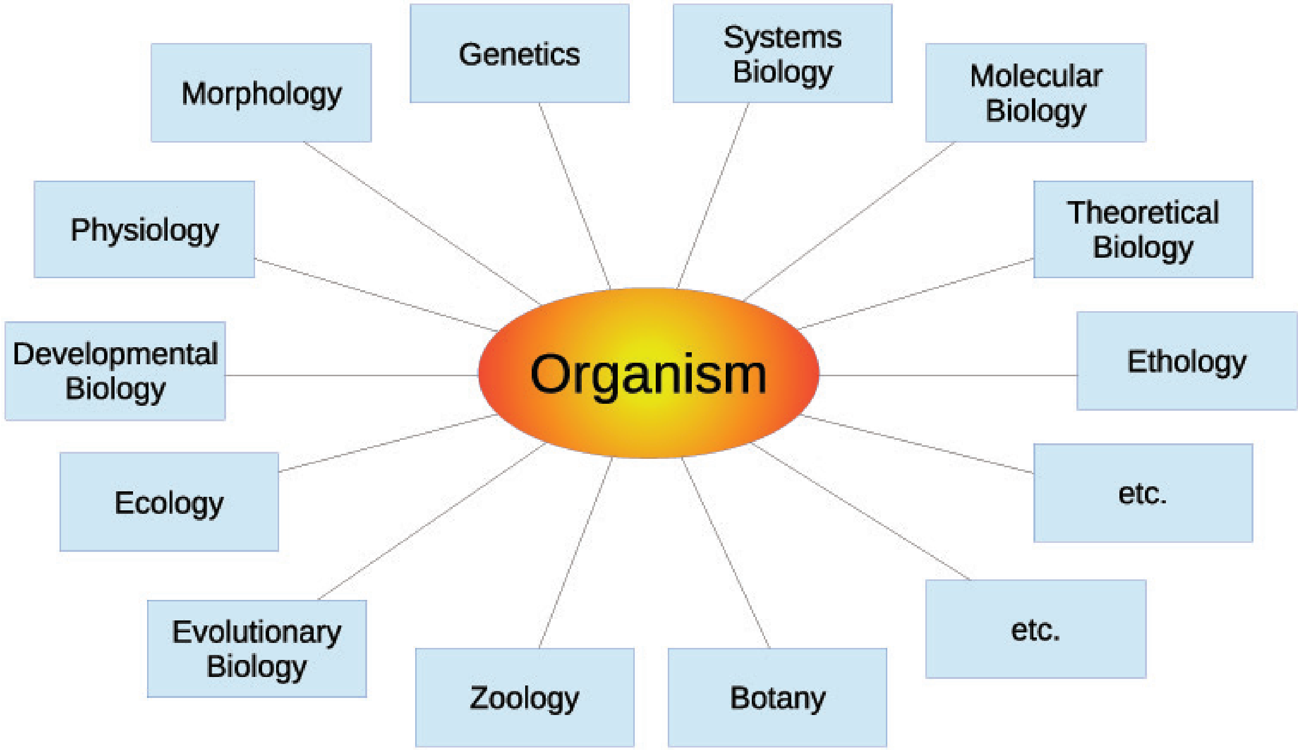

Figure 1. Every sub-discipline within biology (and also medicine) investigates features that are in one way or another linked to a living organism.

> despite their mechanistic explainability, organisms are substantial forms that have a specific organization and unity (*Borelli*),
>
> because their identity through the exchange of their materials is maintained, they are insufficiently determined as mere "bodies", the persistence of their identity does not depend on a certain amount of material, but on their organization as a structure of functions (*Locke*),
>
> this structure of functions can be analysed as a complex mechanism and has a hierarchical structure, consisting of an orderly subdivision down to the smallest parts (*Leibniz*),
>
> essential for the unity of the structure is not a central organizing principle or a central force, but the decentralized causal structure, for which the reciprocal relationship among the parts is essential (*Boerhaave*),
>
> organisms can therefore be fully analysed and explained as mechanical systems, their unity exists in so far as the relationship among the parts can be described as a functional (teleological) relationship, and on this basis they represent a methodically distinct class of objects (Kant). (Toepfer 2011, vol. 2, p. 795).

Rather than describing an organism by a list of properties, Bertalanffy pursues a particular aim when defining an organism. His definition aims to be the most general basic law of biological theories, i.e. starting from the definition it should be possible to derive theories and laws in a deductive manner (Bertalanffy 1932, p. 85).

Should a hypothetico-deductive system be possible in biology, then the organism concept has to be the topmost concept, because the essence of life lies in the organization of parts and processes (Bertalanffy 1932, p. 86). The characteristics of life (*Lebenscharakteristika*) – such as growth, motility, self regulation, self maintenance, or reproduction – are not claimed in the definition, but should rather be theoretically deduced from the definition (Bertalanffy 1932, p. 84). This definition of an organism, which he also terms a definition of life (*Lebensdefinition*), is:

> A living organism is a system consisting of a large number of different parts, organised in hierarchic order, in which a large number of processes are ordered in such a way that, through their continuous interactions within wide borders, with a continuous change of substances and energies, the system stays, even when disturbed from outside, in its own state, or it builds up that state, or these processes lead to the generation of similar systems(Bertalanffy 1932, p. 83).

Concise deductions of the characteristics of life from the organism-definition are the goal, but only hinted at by Bertalanffy. Note that he is not dogmatic about the definition and open to alterations. Nevertheless, the aim is to provide a concise conceptual framework for biology, for which "organism" is at the centre – similar to the energy-concept in physics (Bertalanffy 1932, p. 86).

As already noted, organisms have often been defined via a "checklist of properties" (such as: response to stimuli, growth, etc.). Díaz-Muñoz et al. (2016) attempt to overcome such definitions by investigating the cooperation, conflict and context of biological entities on various levels of size. Many biological entities can form another entity that is characterized by a "shared purpose", with a high degree of cooperation and a low degree of conflict among parts. In this conception the attention is shifted from the question "What is an organism?" to "When is an organism?" (Díaz-Muñoz et al. 2016). This is not exactly new when recalling the organism definition by Bertalanffy; it is also not a list of properties, but the basis for theory building. Díaz-Muñoz et al. (2016), however, put the context-dependent history in the formation of an organism in the foreground.

4. Features of the organism

4.1 The organism as a whole

The perspective of viewing the organism as a whole or a unit advocates a complementary approach to the one that focuses on parts. Within cell theory, multicellular organisms appear, to Bertalanffy, as an aggregate of building blocks termed cells. When criticising cell theory, he stated that in the multicellular organism the single cell plays another role than in the unicellular organism, i.e., it is a part of a unit of higher order. Furthermore, viewed from a physiological perspective, life is not the sum of single cell performances. Instead, those cell performances are also joined together to a unity on a higher level (Bertalanffy 1934, p. 350f). Medicine, however, had great successes with shifting to a localist view on diseases, based on Rudolf Virchow's cellular pathology (Eckert 2005, p. 201f). This, however, does not contradict a complementary holistic approach.

The founding father of theoretical biology was clearly not dogmatic about the holistic or organismic view. It is one of several important perspectives (besides a physico-chemical, a teleological, and a historical perspective) to take into account, and neglecting it would be false (cf. e.g. Bertalanffy 1928b, p. 88ff). With a conception that he later also used for his *General System Theory*, he even attempted to find a common ground for different views. Foremost, an organism is seen as a whole, and in this state of "wholeness" all parts interact with each other (Figure 2). Here the organism has to be grasped as a whole, a unity. Over time such an organism, or system, can develop into different other states in which certain interactions become weaker or disappear completely. In an early stage embryo, interconnections are seen as ubiquitous, but throughout development segregation can take place and one area of the body may only loosely interact with another. In a second state, one part can, in a centralized manner, steer many others. The third state, where the parts are completely independent from each other, is termed sum. It is probably not found in an organism, at least not as long as it lives. Another, more formal way of depicting this conceptualization is by means of differential equations (also shown in Figure 2). When each variable influences the time course of all variables, this refers to the state of wholeness. Considering that the parameters in the functions of the equations can change over time, it is possible that certain interactions among variables are weakened or disappear completely. This then can result in segregation, centralization or sum. The origin of new parts or processes that enter the system is, however, not covered by this formalism, but differential equations are not meant to be the ultimate and only tool for formalizing systems and their development.

This schema enables covering different phenomena in an organism; such that have the characteristic of wholeness and such that are based on mechanized or segregated structures. Merely investigating mechanized structures, or any structure with the assumption that it is "mechanized," however, can lead to the false conclusion that everything in the organism is mechanized.

For Bertalanffy, another very important issue on many levels in his organismic biology is the notion of organisms as active entities. They are not stimulus-response machines that only react to stimuli from the environment. This argument is particularly directed against behaviourism and the view of an organism as a machine which only performs stereotype behaviours when induced by cues from the environment. Cognition is interpreted as an active process, too (Bertalanffy 1972, p. 18). Reflexes are also not primary. A stimulus from the environment does not cause phenomena in an organism but it can rather modify them (Bertalanffy 1937b, p. 134). Furthermore, ontogenesis of an organism is driven by inner determining factors (Determinationsfaktoren) and is hence an active process (Bertalanffy 1928b, p. 171, 209). Where this activity comes from is another, and tricky, question.

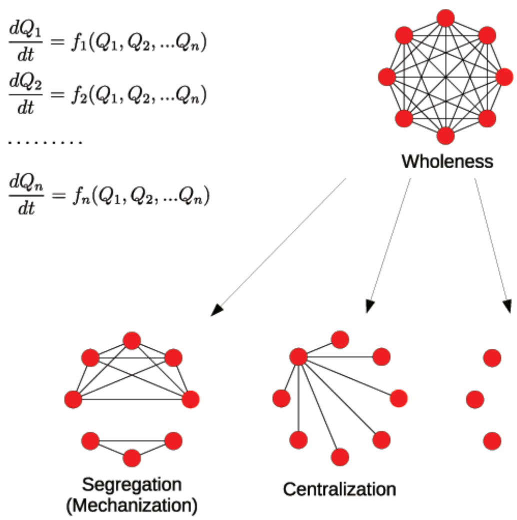

Figure 2. From wholeness to different possible other states (after Bertalanffy 1969, p. 56ff). The equations in the top left corner reflect the connections among the variables in a system

Only speculations were possible about the (causal) basis of spontaneous and active behaviour (Bertalanffy 1937b, p. 136).

The concept of activity is, however, tightly connected to the notion of an organism as an open system with regard to the exchange of matter and energy in a steady state (*Fließgleichgewicht*), because systems that are not open – which were the focus of interest in physics until the early 20th century – merely react to environmental stimuli and are passive with respect to the environment (Bertalanffy 1951, p. 79f). Hence, the open system concept of the organism, as elaborated on by Bertalanffy, is crucial. Far removed from thermal equilibrium, it allows organisms to build up complex structures and processes. The concept is widely acknowledged and has found its way into physical theories, but is not dealt with here (see Bertalanffy et al. 1977; Pouvreau and Drack 2017). With regard to the theory of evolution, again a mere passive process of adaptation to environmental factors has also been criticised (cf. Drack 2015). Taking the activity seriously, compared to a passive stimulus-response notion, leads to different research programs and questions. For instance, the question arises how the organism is constituted, whereby causes are not only sought in the environment.

With regard to organisms as active entities, a later developed concept should be mentioned, namely niche construction. It was brought forward by Lewontin (1982) and acknowledges that organisms can change their environment and do not passively adapt to ecological niches (Toepfer 2011, vol. 2, p. 678). "Thus organism and environment are both causes and effects in a coevolutionary process" (Lewontin 2000, p. 126). This notion is very much in line with Bertalanffy's concept of the active organism, and it clearly changes the theoretical considerations in ecology as well as in evolutionary biology. With such a notion, it is no longer possible to consider a specific environment as given and the only factor that drives evolution. Furthermore, organisms are not merely adapting their traits to a given niche but rather can change properties in the phase space that describes a niche; the term niche construction is therefore appropriate. This influences the conditions for natural selection. Accordingly, both concepts – natural selection and niche construction – must be equally incorporated in theories in ecology and evolution.

4.2 Levels of organisation

The hierarchical order in an organism was already mentioned in Bertalanffy's definition of an organism. This hierarchy aspect was also at the basis of another eminent thinker towards a system approach in biology – Paul A. Weiss. Working as an experimental embryologist, he developed crucial ideas for theory building in biology, among them the notion of a stratified determinism. Especially in embryology it is difficult to believe that everything is determined at the molecular level. In contrast, Weiss conceived the organism as a hierarchy of different structural levels where potentially each level can play a determining role for the others. This view is summarized in the "Chinese boxes" model that he repeatedly published (Figure 3). The arrows among the different levels from gene to environment indicate potential determining factors. Note that they go both ways from lower structural levels upwards and from higher levels downwards. Each "shell" must be seen as a potential originator and receiver. Of course, not all of these determining factors are known, and there is not necessarily a connection from each level to each other. The diagram illustrates a research program rather than showing definitely found interactions. "It is a matter for methodical research to replace the arrow symbols of our diagram by concrete information; but to ignore them, erase them mentally, or just give them names, will certainly not do" (Weiss 1973, p. 13). For some factors, it is possible to cross the levels without being altered, e.g. radiation, others may be transformed or filtered by the layers that they have to pass (Weiss 1950, p. 190).

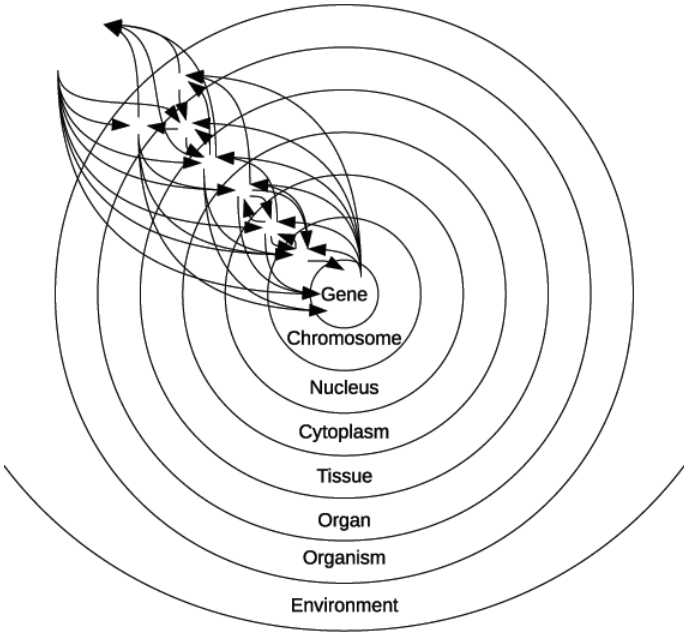

Figure 3. Chinese boxes diagram (modified from Weiss 1971, p. 40).

What this Chinese boxes diagram also refers to is Weiss' opposition against a mere "microdeterminacy", where everything in the organism is thought to be determined by the lowest levels. Instead, he holds that there is also "macrodeterminacy", which is indicated in the Chinese boxes diagram by the arrows from the higher to the lower levels. There is, however, not an absolute either/or between the two. Rather there are types of determinacy where one can be more dominant than the other. "What we came to discern on closer inspection was that determinacy is not an all-or-none proposition, but must be specified as to type, degree, and 'grain size.' Schematically, we can distinguish three types. (1) A consistently ordered pattern of a complex system may be determined as a whole, without the behaviour of its constituent units being determinate, that is, preprogrammed each for its individual task: 'macrodeterminacy without microprecision,' for short. (2) There are, however, as we noted, also group performances in which the courses of all components are rigidly predetermined in such a manner as to yield automatically a collective product of predesigned orderliness; this would connote 'macrodeterminacy through microprecision,' characterizing mechanisms in contrast to systems. (3) Intermediate between those two types are complex systems, the components of which are neither so uninstructed as in (1), nor so firmly structured and autonomous as in (2), and are still subject to cooperative interactions guided by the systemic pattern as a whole" (Weiss 1970, p. 123f). Unfortunately, Weiss does not clearly define the term determinacy, but puts it in relation to the degree of order: a high degree of order is equivalent to a high degree of determinacy (Weiss 1977, p. 37f).

Determinacy can perhaps be interpreted with respect to degrees of freedom, where determinacy lowers the degrees of freedom because it sets boundary conditions under which natural laws are "directed" in specific ways. Such an understanding also fits the interpretation by Polanyi (see below). Similar to Bertalanffy, Weiss also refers to physics, where striving to reduce every phenomenon to the microlevel was abandoned. It is possible to find laws of higher order about "macrorelations", as in thermodynamics, and there is no reason why this should be different in biology. The life sciences should "adopt macrodeterminacy regardless of whether or not the behaviour of a system as a whole is reducible to a stereotyped performance by a fixed array of pre-programmed microrobots" (Weiss 1970, p. 73).

For him, the flaw lies in "equating science with the doctrine of microprecise causality", or, as he wrote: "*microdeterminism*" (Weiss 1970, p. 71).

The overall architectural design of a cell (or higher biological system)

> cannot be explained in terms of any underlying orderliness of the constituents" and "the overall order of the cell as a whole does not impose itself upon the molecular population directly, but becomes effective through intermediate ordering steps, delegated to subsystems, each of which operates within its own, more limited authority" (Weiss 1970, p. 65ff). Hence, the order is also determined from "above.

Interesting with regard to the downward directed arrows in the Chinese boxes diagram is the approach of Michael Polanyi on boundary conditions. Boundary conditions are well known in mathematics and engineering. In a broader sense they can be seen as conditions that put limits or guides on the underlying constructions or processes, e.g. with respect to size, or limiting the degrees of freedom. In biology, the concept of boundary conditions can be applied on various hierarchical levels. On a higher level, the structure or shape of an organism "serves as a boundary condition harnessing the physical-chemical processes by which its organs perform their functions" (Polanyi 1968, p. 1308). The boundary conditions have a different status than laws. They mould the conditions for causal laws to act towards fulfilling a function. "[I]f the structure of living things is a set of boundary conditions, this structure is extraneous to the laws of physics and chemistry which the organism is harnessing. Thus the morphology of living things transcends the laws of physics and chemistry" (Polanyi 1968, p. 1309).

Polanyi's concept of boundary conditions is crucial for the position of Weiss (Weiss 1969, p. 21). Besides rejecting a mere physical approach in biology, boundary conditions are a shared feature of organisms and technical systems. Hence, they are also of central importance for the growing field of biomimetics.

The arrows in the Chinese boxes diagram (Figure 3) can be of different nature. Weiss refers to this fact by pointing out that living systems are "polytonic," including different "modalities," e.g., electric charge distribution, temperature gradients, chemical processes (Weiss 1971, p. 16f). The boundary conditions of Polanyi can in this regard also be interpreted as being polytonic because they can be present in different ways, e.g. as a specific shape of an organ, or the pH-value therein.

Importantly, the order of the parts and processes in an organism is not a mere result of microprecision on the molecular level. Whereas in a machine, as Weiss notes, the single small parts have to be precise and work together precisely to behave in the desired manner, in organisms there is more (imprecise) variation at the lower levels than on the higher levels. This can be shown with many examples from biology, where the arrangement of morphological structures appears much more ordered and regular at low microscopic magnification, compared to greater irregularities visible at higher magnifications. Examples that Weiss liked to use were the mitochondria in a sperm cell or the cilia on a protozoan (Weiss 1970, p. 66ff, figs. 59, 60).

This leads to his conception of order on higher structural levels: "Order in the gross with freedom in the small" appears as the "prime feature of any system" (Weiss 1974, p. 49). And this is connected to the notion of a higher degree of "determinacy" on higher levels. Determinacy can be found in the gross (i.e., all higher levels in living systems) despite indeterminacy in the small (Weiss 1970, p. 74). Such phenomena cannot be explained by a micro-precise molecular approach. Beyond a static view, the larger variation on the smaller size level is also reflected by developmental processes. While larger areas of an embryo can basically remain in place over time, the parts within them can change their positions considerably (Weiss 1973, p. 21, fig. 2).

To illustrate the higher variation or (in mathematical terms) the variance of the parts compared to the whole, Weiss repeatedly used the inequality $V_s \ll v_a + v_b + v_c \dots v_n$ to make his point. Here, the variance in the whole system (S) is much smaller when compared to the sum of variances in its parts ($a, b, c, \dots n$). Even though the variance is meant to include variables beyond mere position in space – he thought about summing up all the variances of the involved physical and chemical variables (e.g., Weiss 1973, p. 40f) – the notion is problematic at least from a practical point of view.

In a metaphorical way, however, Weiss' point can be illustrated by the following (made up) text: "The phaonmneal pweor of the hmuan mnid, aoccdrnig to a rscheearch at Cmabrigde Uinervtisy, it deosn't mttaer in waht oredr the ltteers in a wrod are, the olny iprmoatnt tihng is taht the frist and lsat ltteer be in the rghit pclae. The rset can be a taotl mses and you can sitll raed it wouthit a porbelm. Tihs is bcuseae the huamn mnid deos not raed ervey lteter by istlef, but the wrod as a wlohe. Amzanig huh? yaeh and I awlyas tghuhot slpeling was ipmorantt!" [sic!] (Available from: http://www.dyslexia.tv/definition/experince_dyslexia.htm [21 October 2013])

The analogy of phenomena (such as hierarchy) in living systems to texts or spoken literary compositions is often used (e.g. Polanyi 1968, p. 1310f; Riedl 2000, p. 105). In both cases there are higher and lower levels (in the case of a text: sentences, words, letters) effecting each other in both directions. This dyslexia text is another use of such an analogy, which illustrates that there can be more variation on the micro level (i.e. the letters) than on the higher level (i.e. the words), and the text still "works". Hence, there is no microprecise determinism. The whole is perceptible, although the parts are muddled. Importantly, such a text cannot be grasped in an analytico-summative manner. In analogy, also in biology an organism has to be studied on different structural levels, not just the molecular one.

Accordingly, different structural layers must also be considered in morphology (Riedl 2000, p. 123), a discipline that always takes the whole organism together with its parts into account. Considerations in morphology were what led Rupert Riedl to rethink the system conditions of the organism towards modifying the theory of evolution.

4.3 Organism and evolution

Darwin's theory was already challenged by Bertalanffy for being "analytico-summative" (selection and summation of single modifications of independent characters) and "reactive" (with respect to the environment). Darwin's theory is based on small changes of properties of an already existing organization (Bertalanffy 1934, p. 344f; Drack 2015). In this regard, the perspectives changed little even in more recent accounts on evolution, such as the synthetic theory of evolution.

With his approach on system conditions of evolution, Riedl (1975; 1977) – a student of Bertalanffy and a friend of Weiss – went beyond an analytico-summative perception of the organism. Evidence from morphology clearly shows that certain characters change considerably in the course of evolution, while others remain constant. Hence, different characters do change at different speeds, if at all. This is hard to explain with independent characters, each merely reacting separately to the environment.

The morphological evidence led Riedl to the notion that organisms are developmentally and functionally "burdened" due to the dependences among characters (Riedl 1977). For instance, in a joint such as the knee, the femur and the tibia have to fit together, because otherwise it would not work (Riedl 2000, p. 291). The surfaces that connect to each other have to have the same size. In the ancestors of tetrapods this was not an issue, because the bones in a fish did not have the function that a knee has. If such connections between different characters can be encoded in the genome, organisms that possess these couplings of genes are more successful than organisms in which each gene evolves individually.

The increasing connectedness of characters leads to system-dependent "burdens" (Wagner and Laubichler 2004). Hierarchies of dependences of characters and corresponding genes can thus arise. The knee is functionally dependent on the pelvis and the pelvis in turn on the vertebral column. Whereas characters that are little burdened can change widely (cf. toes in horses or humans), changes in heavily burdened characters (e.g. the vertebral column) are rather limited. In this view, systems of interdependences evolve over time, which should also be reflected in the genome. Burdens evolved historically, and the higher they are in the hierarchy the less they can be changed, even if this would lead to a better adaptation to the environment. While functional or developmental interdependencies become stronger, natural selection loses its dominance. This also means that new characters always evolve in an organism context, so that they depend on pre-existing characters. Moreover, with the coupling of genes, the role of chance in evolution is reduced, making certain evolutionary developments impossible (Riedl 1975). Hence, most mammalians possess seven vertebra; whether they are dolphins or giraffes does not matter. Similarly, the "wrong" orientation of the vertebrate retina, leading to the blind spot, cannot be changed (Riedl 2000, p. 294f). Today, such issues are investigated by referring to the concept of constraint rather than burden (cf. Wagner 2014). Furthermore, the character identity networks – introduced by Wagner (2007) – can be seen in direct connection to Riedl's accounts. Characteristic sets of regulatory genes can thereby determine e.g. individual cell types over long evolutionary distances. Riedl's approach, which was also at the root of Evolutionary Developmental Biology, was supported by the discovery of the universality of the Hox genes (Wagner and Laubichler 2004).

The account of interconnections in an organism was developed further by Riedl, whereby Weiss' Chinese boxes diagram (Figure 3) was an important basis (personal communication Riedl to MD). Riedl used Aristotle's four causes to conceptualize organisms. A case in point is the causes for a wing muscle in a chicken (Figure 4). The purpose or *causa finalis* (final cause) of this muscle is flying. Note that this final cause was not present at the beginning of evolution, but rather emerged due to the interaction of the organism with the environment; hence it is not problematic with respect to various notions of teleology or goal directedness in biology. In the layer model of Riedl the final cause operates on all the structural layers from top to bottom, i.e. all sub-structures of the wing must be arranged in such a way that the purpose can be fulfilled. Formal causes also operate from top to bottom, but only from one layer to the next lower layer. The higher levels provide the conditions for selection on the next lower level; i.e. in order to work properly the orientation of the wing muscle must conform to the wing's form. It is the form of the wing that provides a measure of selection and not the environment. The material causes of the wing muscle are, among others, the muscle fascicles, which are found on the next lower structural level, the components of which the muscle consists. The *causa efficiens* (efficient cause is an improper term because it suggests that all the other causes are inefficient) refers to the physico-chemical processes involved in metabolism that provide the power for the muscle (Riedl 2000, p. 163f, 211f, 259).

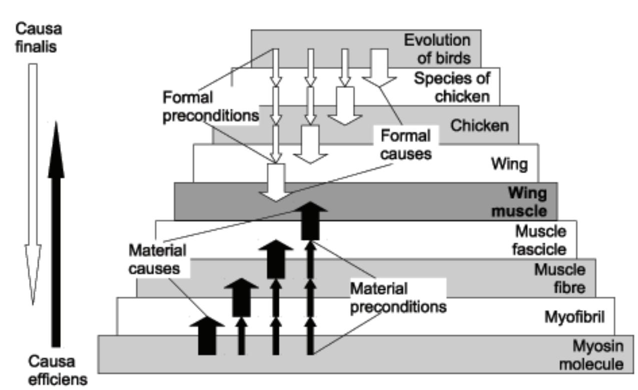

Figure 4. The layer model of Riedl, exemplified by the wing muscle of a chicken. (after Riedl 2000, p. 163f, 211f, 259).

A vast literature discusses the four causes of Aristotle, with different opinions on them (cf. Falcon 2015). The schema of Riedl, however, can serve as a heuristic tool when investigating organisms, whereby the various levels must always be taken into account. The arrows can, with this approach, be given more precise names, and how they "work" can be investigated in more detail.

The system approach of Riedl led him to the notion of burdens (*Bürden*) or constraints, which clearly play an important role in the theory of evolution. Without a proper notion of the organism, this opening up of a new perspective would not have been possible. The system approach in evolutionary biology is a prominent example for how the organism concept changed theory building, and how the connection between genotype and phenotype can be grasped from a different angle.

Finally, with respect to the organism concept, Bertalanffy's perspectivism should be mentioned (cf. Pouvreau and Drack 2007, p. 289ff): Biological systems, and therefore also organisms, need to be investigated from different angles and with different, independent methods in order to derive objective knowledge. Grasping the organism as a whole (*Ganzheit*) is one very important such perspective in biology and medicine. As Weiss noted, "there is no phenomenon in a living system that is not molecular, but there is none that is only molecular, either" (Weiss 1970, p. 53), and hence complementary investigations need to be performed. For the organism concept, all the here mentioned notions have to be considered.

5. Conclusion

The approaches of Weiss, Bertalanffy and Riedl show that it makes a difference for theory building whether the organism is conceived as a dynamic, hierarchic organization or an aggregate of parts or characters, whether it is conceptualised as active or passive, etc. The organism concept is intimately linked to every biological field. Accordingly, the discussed properties need to be considered in all of them, because they influence research explicitly or tacitly.

For Bertalanffy the organism-definition was even a concrete starting point to derive theories in a deductive way. For him, the organism concept was the topmost concept in biology, reflecting the essence of life: the organization of parts and processes. Whether his definition is exhaustive or not is a different matter; and Bertalanffy was open to extensions. With regard to recent developments, there are probably more features of organisms that need to be considered, such as symbiosis (cf. Gilbert et al. 2015), but the basic considerations from the first half of the 20th century remain valid.

The conceptualization of change in the organization in an organism over time (Figure 2) can comprise phenomena of wholeness as well as mechanized causal chains. Neither of those extremes is ever solely at work in the organism. Moreover, Riedl's notion of burdens/constraints points to different degrees of connectedness, albeit with an evolutionary perspective. There are many variations between completely independent and completely connected parts. The notions of Bertalanffy and Riedl are, however, compatible. For Bertalanffy, wholeness starts at the early embryo stage and, in the adult characters, can become segregated. In Riedl's approach on evolution the segregated parts can become functionally dependent on each other and give rise to interconnections and burdens. Hence, different degrees of interconnectedness within the organism are evident, either with a developmental or an evolutionary perspective. Furthermore, with the notion of burdens it is impossible to characterise organisms as fully optimised (if anything like that would be possible anyway) or completely adapted to the environment. This finding is interesting for biomimetics, where – from a multifunctional biological system – often only single functions are transferred to engineering.

Weiss' order in the gross with differences in details shows that it is important to investigate determining factors on higher structural levels of the organism. Moreover, incorporating this approach also means that biological laws can be found without reduction to the micro-level. As the three system thinkers have shown, hierarchical levels play an eminent role in developmental biology, physiology, and evolutionary biology.

The notion of the organism as an active entity is useful in evolutionary biology, for example when pointing to ecological niche construction. Moreover, it needs to be acknowledged in ethology, where the behaviour of an organism cannot be conceptualised as a mere stimulus-response-machine. Of course the reasons for these activities need to be investigated further, since the open system in a steady state allows for organisms to be active, but it does not explain such behaviour.

For medicine, the organism concept is important with regard to research into the causes of diseases, as well as for their (holistic) treatments. A complementary system approach, together with perspectivism, i.e. investigating a problem with different, independent methodological perspectives, is clearly useful for many diseases – even though it might turn out that for some diseases knowing the molecular level is enough for treatment.

The thoughts of the three biologists show how important the organism concept is and how it shapes theory building in biology. Different (implicit or explicit) accounts of the organism yield considerably different research programs. Hence it is eminently important to consider the organism concept in all future biological research.

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