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Research Article

Reconstructing emergent biological phenomena through comparative functional architectonics

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In biological knowledge, a central task over centuries has been determining how do organisms 'appear' from the structural elements they are composed of. Reformulated, this question is about the functional organization of organisms: what are they composed of, and what the roles of the different elements are in this organization. Traditionally, this question has been addressed through top-down reductionistic approaches addressing individual elements ('molecular pathways'). However, whereas such approaches provide a rich insight about lower-level elements and their interactions, they do not offer clues about how the higher level of organization ('the organism') emerges from such interactions: the possible number of work hypotheses is extremely large. To overcome this difficulty, we present an oppositely directed bottom-up approach based on inductive reasoning. In this methodology: 1) realizations of the 'molecular pathway' of interest in different contexts are compared, 2) following a strategy similar to that presented by Georg Pólya in his volumes of *Mathematics and plausible reasoning* (Pólya, 1954; 1968), the *archetype* (the "general case") of the 'molecular pathway' of interest is conceived. By analyzing the archetype, functional roles of the 'molecular pathway' of interest are further inferred back in the specific contexts. As a result of this back-and-forth approach, that we denominate *comparative functional architectonics*, a reduced set of plausible and experimentally testable hypotheses is obtained about relevant functional ties linking organism-level traits ('the phenotype') with corresponding lower-level elements. We present the rules to apply the proposed methodology, together with examples of returned results taken from our previous studies following the comparative functional architectonic approach (Pérez Koldenkova and Hatsugai, 2017; Pérez Koldenkova and Hatsugai, 2018; Panina et al., 2020). This work is primarily intended for the

doi.org/10.32388/URI5SF

community of ‘pathway biologists’: biologists whose research interests are related to the physiological relevance of particular ‘molecular pathways’, either *in vitro* or *in vivo*.

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About the organization of this work

> — And how did you make your fortune?
>
> — See, I bought an apple for two cents, washed it, and sold it for four cents. With these four cents, I bought two apples, washed them, and sold them for 8 cents. And then I got my inheritance.

This work analyzes how to bridge the different levels of organization of living beings. We show that in the case of living organisms, such bridging requires comparison between organisms belonging to phylogenetically-distant groups, in a methodology that we denominate *comparative functional architectonics*. To analyze what current factors hinder the reconstruction of the organism level of organization from the elements organisms are composed of, we undertook an analysis of the properties of the modern research object in biology. We compared the guise of the modern research object with another approach to describe living organisms, proposed around 2,500 years ago, but which received much less attention—despite allowing, in modern terms, to achieve the long-sought cross-level bridging.

The main difficulty encountered during the elaboration of the proposed comparative functional architectonic approach was the large thematic (and historical) distance between “the tools” used to justify it: 1) the methodology of comparison of dissimilar objects, and 2,3) two types of description of organisms (one that derived into the properties of the modern research object, and the other that historically has remained much less popular and ill understood). Hence, we applied the comparative functional architectonic approach to establish its own consistency. This required a not very short historical introduction in order to show how the guise of the modern research object was shaped. The subject of this part is slippery to the attention: at the beginning, individual personalities influenced the way we reason, whereas closer to our days it was more correct to talk about currents of thought. Yet we

doi.org/10.32388/URI5SF

tried to keep the focus on the same subject—the conception of the research object and the way it gradually acquired its modern guise.

In the next parts, the second approach to describe modern organisms is presented, together with evidence of its usefulness for cross-level reconstructions.

Then, the rules to conduct such reconstructions are provided.

Content

1. Introduction

> All that cannot be measured is evil.
>
> Science’s evil.

Current biological sciences conform relatively independent levels of knowledge that expand around discrete ‘measurables’. For the **‘organismic’** level such ‘measurables’ are organisms and their traits (in the scope of zoology, botany, embryology and other organism-level disciplines). For the suborganismic level —denominated here **‘biochemical’**— these ‘measurables’ are molecules, organelles and cells, in the scope of biochemistry, and molecular and cell biology. Advance of each biological discipline occurs mostly within the corresponding level, and results from each level rarely permeate into the other one. Thus, an ichthyologist or an ecologist specialized on *Danio* is rarely aware about the most recent results obtained using the multiple existing zebrafish mutants. Conversely, most researchers studying physiological processes of this organism as a model object are only rarely interested in nuances it can display in the different natural environments it can populate. Interdisciplinary approaches in most cases denote the joint application of different research methods, but again—mostly to analyze phenomena within the delimited level.

To fill this gap, a number of ‘see the big through the small’ technical approaches have been recently developed. Examples are high resolution microscopy with large fields of view (Ichimura et al., 2021; Chhetri et al., 2015; Chen et al., 2014; Kubota et al, 2017; Greenbaum et al., 2017; McDole et al, 2018; Gao et al., 2019), high-content analysis techniques, a steadily growing arsenal of activity indicators, bulk- and single-cell analysis techniques, and the composition of ‘lists’: databases and atlases of cells, organelles, or organisms’ responses to applied stimuli[1]. These advances have by purpose the distinction through segmentation, the characterization, and quantification of cell-level and subcellular elements to understand how the ‘organismic’ level emerges from their interactions.

This technological burst, however, is accompanied by an admitted concomitant lack of vision about *what exactly* is to be monitored and searched for. Hope is placed on machine learning-based big data analysis algorithms as tools that may help in devising and sorting this enormous diversity. Nevertheless, given the intrinsically complex organization of living objects, the number of possible work hypotheses about how the ‘organismic’ level emerges from ‘biochemical’-level elements is extremely large. This situation may indicate that the link between empirically-distinguishable levels of organization of living organisms is of a ‘non-measurable’ nature, and hence—is not directly observable.

In the present methodological work, we propose an approach to bridge the gap between levels of organization opposite to the top-down technical approaches mentioned above. We propose to follow up a bottom-up inductive inferencing strategy most explicitly expressed by George Pólya in his volumes of *Mathematics and plausible reasoning* (Pólya, 1954; 1968). Briefly, we understand that any taken organism is composed of molecules, cells and tissues. However, we typically have only a faint idea about how the particular organization of these elements (=the “biochemical core”) influences the “essence” (the form, organization, behavior) of a particular taxonomic species or a particular individuum. This is the type of knowledge an experienced physician can acquire after long-time observation of a significant number of patients.

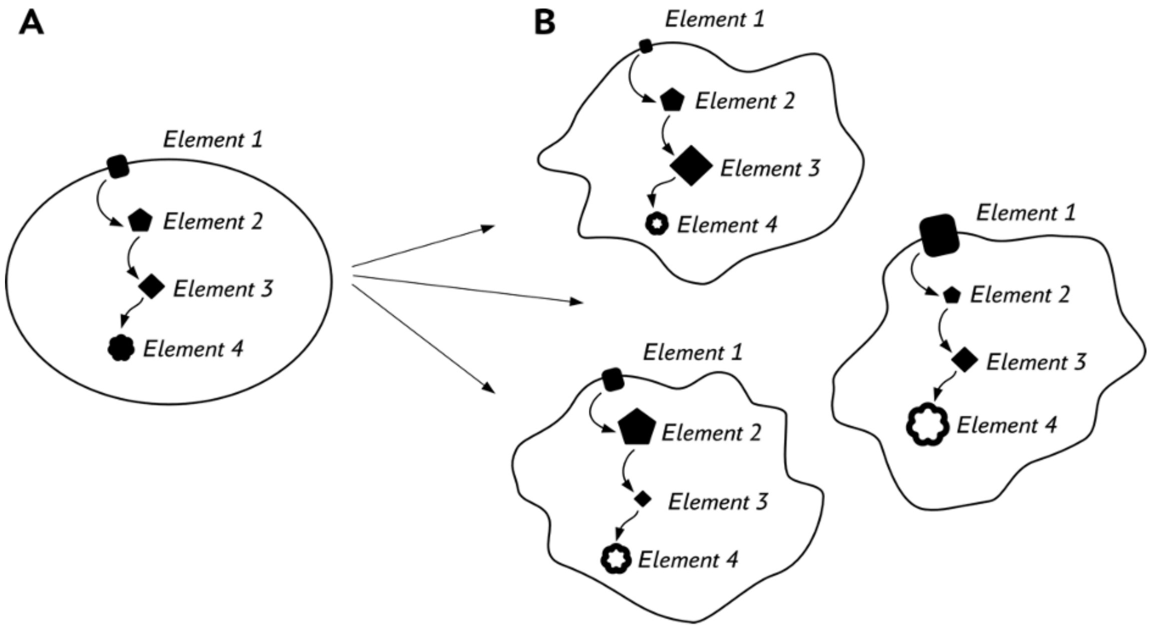

Fig.1. Typical representation of a 'molecular pathway' in a scheme, and a representation that considers naturally existing variability across cells.

A. Typical schematic representation of a cascade (a 'molecular pathway'). **B.** Actual realization of the cascade from **A** in different cells from a same organism, in cells from different organisms, or in conditions of health and disease. Differences in symbols sizes represent the natural variability existing in the activity of each elements of a pathway. Individualities/quirks refer both to activity variations of each element of the cascade, or to activity variations of the cascade as a whole (a 'molecular pathway').

For the 'biochemical' level we propose comparing instances of a 'molecular pathway' of interest (*individualities/quirks*—in reference to either individual elements of a pathway or the whole pathway, Fig.1) in different organisms or in different contexts within a same organism to conceive its 'general functional case'. Analysis of this general case allows determining the roles these *individualities/quirks* play in the different organisms/contexts, linking particular functional modifications at the 'biochemical' level to 'organismic'-level properties.

We propose a set of rules to conduct this back-and-forth analysis as part of a methodology we denominate *comparative functional architectonics*. By applying the proposed rules, plausible and experimentally-testable hypotheses can be formulated about the ways by which the 'organismic' level emerges from the 'biochemical' one. We specifically address the 'biochemical' level of organization, but show that *classic* systematics offers the appropriate methodological toolset required to approach the diversity observed at this level of organization of living systems.

2. Why is bottom-up inductive inference even possible in the case of living organisms?

> Any [physical] law is a constraint, not a precept. [Laws of physics] tell us about what cannot exist, yet you cannot deduce from them all what exists, and even less—all that can exist in principle. Unless you make friends with a Laplace's demon:-)
>
> No engine made by a human (of those that ever worked) contradicts the laws of physics. But engines cannot be deduced from laws of physics—they are invented, and that is a quite different intellectual operation. Laws are taken only as constraints within which it makes sense to search for a result. [...] The same applies to biological processes. If you were an alien that knows nothing about life on Earth, and you get, for example, some amount of acetylcholine, you can get to know absolutely all about its physical and chemical properties but even [with all this knowledge] you will not be able to conclude that this substance is a neuromuscular mediator in Earth's creatures. And that is because such a function cannot be inferred from the structure of the molecule. Such a function is not "inherent to it"; [this function] emerges only [in a situation] in which this molecule is part of living organisms [...] And even knowing about such a function, you will not be able to deduce from any physical or chemical law that it should be carried out by this particular compound. Because it could have perfectly [been carried] by any other substance, laws do not prohibit it. [...] It should not be assumed that if [a phenomenon] "follows a law", it is determined by such law in its entirety.
>
> bbzhukov, https://ivanov-petrov.livejournal.com/2135725.html (translation: VPK)

The quotation above summarizes the problem: generally speaking, knowing the elements of a lower level of organization is not enough to infer how the corresponding higher level of organization will look like. However, Pólya (Pólya, 1954; 1968) presented a methodology for proposing plausible conjectures, although for mathematical expressions. Can this methodology be applied in the case of living organisms? If the answer is *yes*, then why it is not used and preference is given to hypothetical-deductive approaches? To answer these questions, it is first necessary to analyze how the conception of the object of interest changed over time, influencing the inquiring questions it was subjected to, in the end turning —in the case of biological objects— into the discrete ‘measurables’ of the disconnected layers of organization, mentioned in the Introduction.

2.1. A “mosaic” or a “Venn diagram”: how the description type influences our conception of the analyzed object and determines possible subsequent operations with it

Let’s imagine a network-like structure. How it can be described?

For a physical structure like that shown in Fig.2A —a scale-free network (Barabási and Albert, 1999)— the relationship between the nodes composing it can be described considering the architecture (peer-to-peer, or tiered) and the topology of the network (with few identifiable configurations: ‘star’, ‘tree’, ‘ring’, ‘mesh’, and some others.). Such a network can be exhaustively described and reproduced by providing *a list* of the relationships of each of its constituting nodes-elements. From these properties of the elements the whole structure can be recreated.

Let’s imagine another situation: each of the elements-nodes of a structure can interact with each other by temporarily associating into blocks. Engagement into different short-living blocks allows elements to participate in the execution of different tasks within the same structure, with the resulting topological arrangements changing as a function of the performed task. This structure resembles a flexible Venn diagram, in which the elements remain the same, but the temporal sets they conform (and the resulting overlaps) can vary, and even perform mutually exclusive (although time separated) functions (Fig.2B, left). Such structure cannot be described by a simple list of its elements and all their possible relationships (Fig.2B, right): in such a case, the particular way in which each node partner with other nodes to perform specific tasks will be missed, and the information about the [temporal block arrangement/performed task] relationship will be lost. In this case, a *task-dependent* (rather than an element-dependent) representation turns desirable.

The former (elementaristic) and the latter (block) approaches are used to describe living organisms and their organization. In the first approach, at the ‘organismic’ level, nodes correspond to ‘measurables’— phenotypic traits. At the ‘biochemical’ level, nodes correspond to

individual compounds, structures, processes or ‘molecular pathways’, with variations in their observed activities derived from differences of quantities, proportions and/or intrinsic activity of individual compounds—*individualities/quirks* (Fig.1). Typically, these individual compounds, structures, processes or

doi.org/10.32388/URI5SF

‘molecular pathways’ are depicted in straightforward schemes without presenting sources of possible variation of their activity. In the second approach, an *intangible* component is added to the elementaristic traits—the block arrangements in which the elements can associate for determined lapses of time to perform particular tasks.

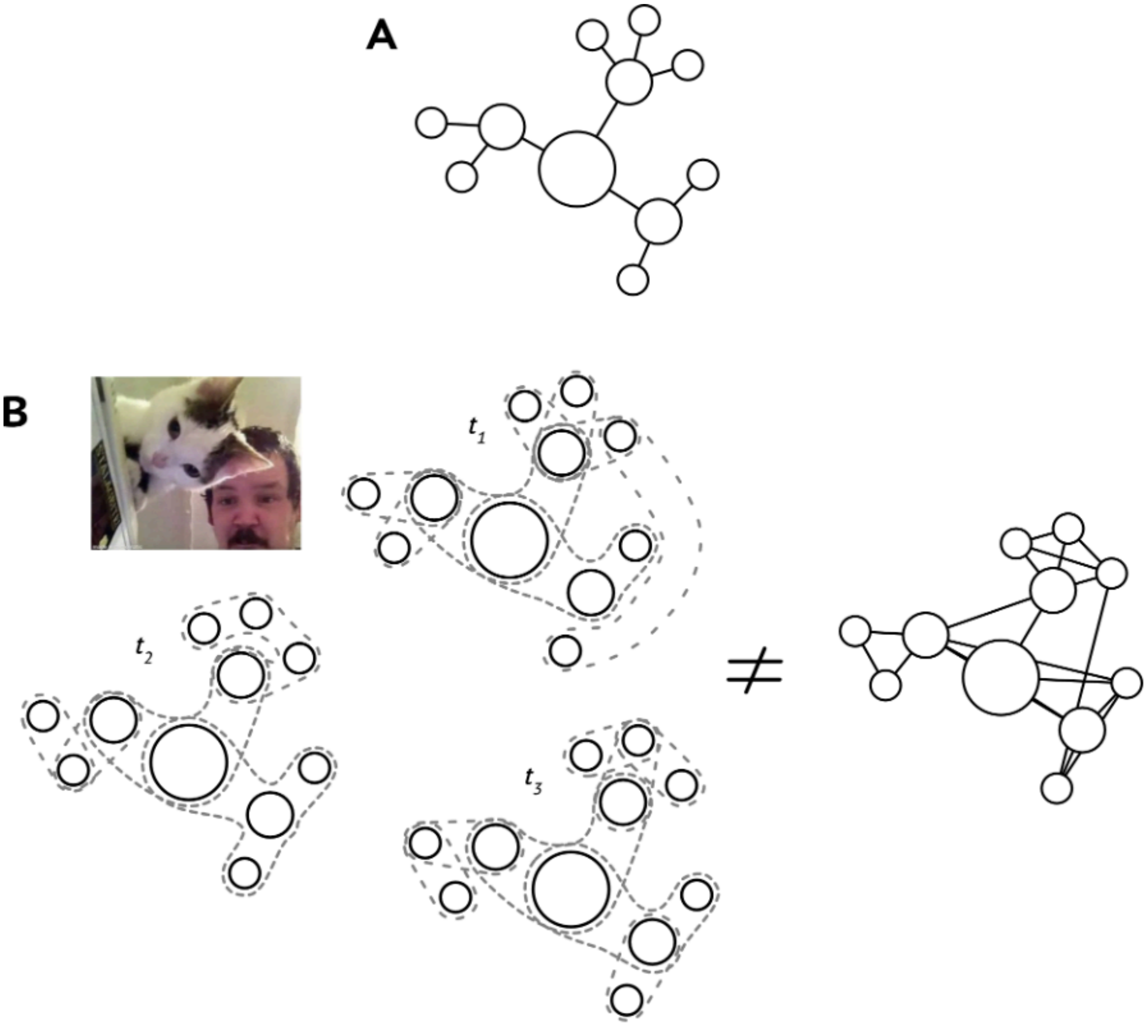

Fig.2. Possible organization types of different network-like structures.

A. A visual representation of a scale-free network. The size of each element depends on the number of links with other elements. **B.** Time-dependent block arrangements depicted as network-like structures. Even though the elements are those same that were used in **A**, their temporal arrangements (t_1, t_2, t_3) differ, and cannot be described by a single interactome (right), rather requiring a representation as dynamic Venn diagrams. Inset: a Venn diagram. Details in the text.

These two ways of description were introduced about 2,300 years ago by Plato and Aristotle as part of abstract reasoning, which general purpose (in modern terms) was to define the relationship between observable things and the concepts they represent. Coarsely, it can be said that in the platonic conception *ideas* (concepts) are considered more relevant than real things, and an order of priority is imposed to objects that range from observable things to the more and more abstract concepts corresponding to them. Aristotle's approach was different: he carried out his analysis from within Plato's order of priority, taking individual objects from the hierarchy as points of reference for his reasoning, and conferring each of them the ability to display a sort of 'activity' (a coarse analog of this term is 'agency', Barandiaran et al., 2009) that depends on the particular nature of the object. In other words, Plato considered observable things *instances* (~less important) of concepts. Unlike Plato, Aristotle typically gave more weight to those same *instances*, as actual realizations of the conceptual "landscape of potency". And in many cases Aristotle's reasoning was top-directed, deriving general principles —the *essence*, or the "landscape of potency"— that would encompass the embodied and observable naturally existing instances (Fig.3).

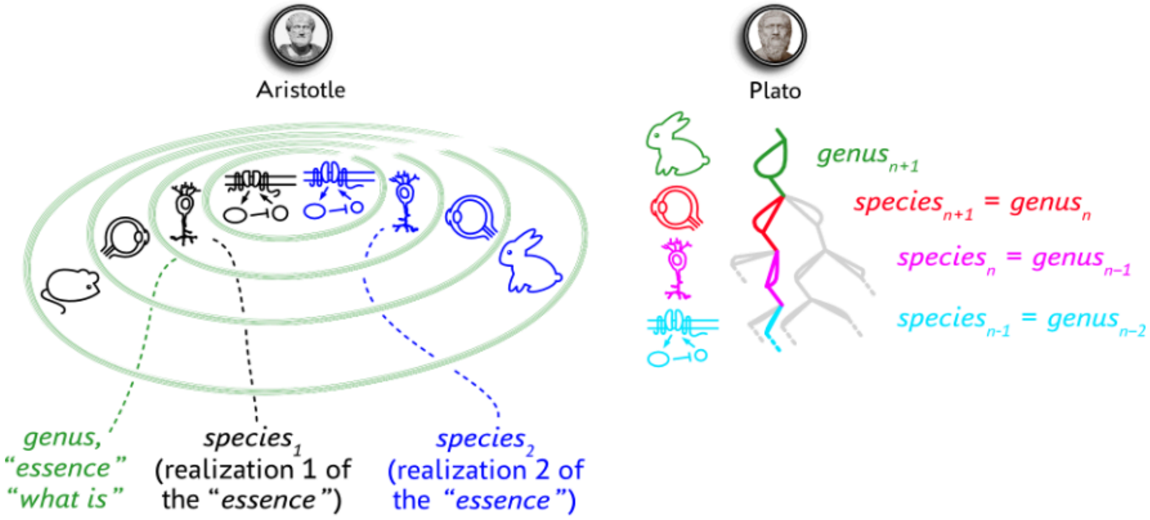

Fig.3. Graphical comparison of Aristotelian and Platonic genera and species. Platonic genera are the sum of Platonic species. Conversely, Aristotelian species are realizations of Aristotelian genera. Aristotelian categories are a-taxonomic: an Aristotelian genus is not equal to the sum of the corresponding Aristotelian species.

These very general and primordial frameworks differed also by the grounds on which objects were divided into parts. In Plato's approach, the whole could be divided without remainder into well-defined and easily identifiable parts. Aristotle's approach (more explicitly expressed in his work "On the parts of animals") was closer to comparative anatomy: he identified not parts of organisms themselves, but sorts of "functional units" to which the analyzed physical parts belong (Balme, 1987b; 2009). These functional units were then used to compare the organization of different organisms, and comparison itself was used as an indispensable step to understand the roles of those physical parts back in a particular organism (Fig.3). This is the same method Aristotle presented in his *Analytics* (Lennox, 2011), but specifically adapted to describe living forms, for which division into parts is not trivial (Balme, 1987b).

This difference between the two approaches determined the so called 'genus-species relationship': Plato's *genus* was no more than the sum of the *species*-instances composing it, whereas Aristotle's *species* constituted a materialization of the "landscape of potency" (the Aristotle's *genus*). Hence, Aristotle's idealistic *genus* was typically much larger than the sum of the corresponding Aristotle's instances-*species*. For a coarse analogy, it can be said that Aristotle's *genus* is related to his *species* in the same way as our mathematics relates to our physics. However, in Plato's sense the *genus* "mathematics" would include as *species* the different branches of this discipline.

Such differences in the conception of *genera* and *species* looks insignificant, but they had profound consequences. Over the time, as a result of a series of bottlenecks and misinterpretations, the Aristotelian *genus* gradually lost importance and concomitantly turned into the logical and formal *genus* of Plato. In its further evolution, the later lost its metaphysical content, which in the end resulted in conceptual weakness when addressing issues like complexity emergence.

2.1.1. The quest for reliable grounds of cognition: replacement of description meaningfulness by formalizability, and the construction of the research object in biological knowledge

> From the knowledge about how to grow shoulders of a giant,
> science has turned into the skill of laying bricks in a building

To the best of our knowledge, it remains yet to establish how through the ages these two primordial and very general reasoning frameworks influenced "the tasks to solve", "the formulation of intellectual questions", or "the reigning interests" of biology (i.e., the history of epistemology of biological knowledge). However, it is possible to present a coarse outline of the key aspects of this history, to understand how current science (including biology) turned elementaristic almost in its entirety. To make this gross reconstruction we primarily relied on the works of Georgy Lyubarsky (Lyubarsky, 2018), Igor Pavlinov (Pavlinov, 2018), John Henry (Henry, 2002) and Garland E. Allen (Allen, 1975).

Roughly, four periods can be identified during which were settled the way in which we currently conceive concepts and objects, the cognitive instruments to deal with them were elaborated, and the adaptation of these notions occurred to approach biological diversity. Changes affected not only notions about objects and their contexts, but also the type of questions that could have been formulated, driving a further change of concepts and cognitive instruments to approach them, and affixing conceptions which not unfrequently were not tested for their capacity to correctly reflect reality.

I. What a thing can and cannot be

After Aristotle's death, his works were lost for almost 200 years, and, upon their partial recovery, their interpretation was undertaken by neoplatonists, among them—Porphyry (III century) and Boethius (V century, in his commentaries to Porphyry). These initial (mis)-interpretations set the ground for the centuries-lasting neoplatonic understanding of Aristotle's thought. This neoplatonic interpretation was later inherited by the Byzantine Empire and the early Islamic philosophy, and was the base for the posterior re-entrance of the Greek thought into the West, influencing Medieval Scholasticism (12th-17th centuries), the European Renaissance (15th century) and the Age of Enlightenment (18th century), up to our days.

Porphyry (c.234-c.304) had to deal with two types of concepts: Plato's *ranked* concepts, and Aristotle's *non-ranked* concepts that resulted from generalization of individual instances (section 2.1). At a first glance, these two concept types were equal, but they differed in how their features were specified: properties of ranked concepts were set *by the hierarchy* they belonged to, whereas properties of non-ranked concepts could only be identified through comparison of the instances themselves. The Aristotelian conception resulted obscure to Porphyry, and he ended reducing the views of both philosophers to the hierarchical neoplatonist conception (Ebbesen, 1990). He followed the logic of the stoics: 'ideas' or 'essences' were replaced by 'laws' as links between phenomena that are themselves ruled by such laws; laws set the borders within which diversity had to be looked for. Porphyry also posed the question about the way to conceive genera and whether they were real ('are they subjective or objective?') —jointly known as the 'problem of the universals' which shaped further history of the object for more than thousand years, ultimately influencing the way we currently conceive objects and the way we reason about them.

Boethius (480-524) brought Aristotle's thought to the West and was one of the most influential figures in the application of Aristotle's philosophy for the elaboration of the Christian doctrine. He proposed an unstable solution to the problem of universals: universals could exist —or not— depending on subjective factors and on the organization of the thinker. Following Augustine of Hippo (354-430), he used the Aristotelian Categories to explain the trinitarian nature of God. Within the 10 Aristotelian Categories, he identified 2 types: the first 3 Categories referred to the *substance* of the object, making the *real thing*, whereas the other 7 referred to thing's *circumstances* or *qualities*, linking the thing with its environment. During further evolution of this scheme the *real thing* (the *essence*) gradually lost importance, and only *features/traits* were left (until our days) as working material. Ultimately, the object turned into a black box that, as it was argued, can be comprehended only through the features it displays.

John Scottus Eriugena (810-877) made an important statement: a definition is an operation that allows deciphering the content of a concept. However, this would lead to the understanding of what God is— something that was considered impossible. Nevertheless, it was possible to *divide* concepts and obtain their scopes (their volumes or mutual relationships). Similar shifts from the analysis of the content of a concept toward the analysis of its volume occurred several times afterwards as a result of the lack of appropriate cognitive instruments, in a hope that division of concepts will allow approaching an arisen question.

The problem of universals set an opposition between individual objects (instances), and the concepts they represent. In the course of the discussions three views were developed, the arguments of which were repeated numerous times. Realists shared a "platonic" view, arguing that individual things resulted from ideas/concepts. Mild realists (also regarded by us as conceptualists) considered that ideas/concepts are real, and are identified by the mind as distinctive features of the essence of objects. Nominalists argued that universals/ideas/concepts are just constructions of the mind, sort of labels aimed at facilitating manipulations with the visible and individual things which are the only real beings.

In the discussions and controversies between these views, Thomas Aquinas (1225-1274) proposed a solution that for a long time and by many people was seen as conclusive to the problem of universals. He reformulated the problem of universals to eliminate the opposition between instances and concepts. Roughly, Aquinas argued that in the perceptual world there are no ideas and hence we cannot achieve understanding from perception. We can, nevertheless, on the base of experience elaborate true ideas about objects, and such ideas/concepts are not some internal illusions. This doctrine was very successful and even today is highly influential, although currently it has been relegated to philosophy of religion because porting it to the world of perceptual things resulted nontrivial. Among contemporaries, however, the solution proposed by Thomas Aquinas encountered important rivals: the extreme nominalism of John Duns Scotus (1266-1308) and William of Ockham (1285-1347).

Duns Scotus professed an extreme separation of faith and mind. According to him, the mind, corrupted by the original sin, cannot judge about God. From this position, the rationalistic attempts of Thomas Aquinas appeared as false. A universal —argued Duns Scotus— is not something that exists in reality, but is a certain mode to think about some essence; it is a product of mind. Before Duns Scotus, a *species* was derived from the *genus* by the addition of a clear and identifiable *differentia specifica.* Duns Scotus postulated the existence of a *natura communis* as a universal essence shared by all members of a particular species or class of things. To this *natura communis*, properties (*formalitas*) were added that allowed specifying the quality of "being common for a group of things", or "being an individual thing". In Duns Scotus's understanding, *natura communis* produced species by adding *haecceitas* (a "thisness" that made a thing distinct from other things). *Haecceitas* was only known to God and by definition was inaccessible to the human mind (it was incommunicable and unintelligible to creatures). In the world postulated by Duns Scotus there was only room for God and a vast diversity of individual objects. Universals were eliminated and instead a *scheme of reasoning* was introduced that maintained the Aristotelian terminology, but replaced its meaning. Reasoning became *subdued to will* —to some law, rule, or model— that channeled reasoning. This approach became trending and leading as a philosophy of Modernity. What started as a dispute about individuation of the soul and angels gave rise to what later became the philosophy of science (Cross, 2022), becoming the *haecceitas* a predecessor of the Kant's 'thing-in-itself'.

Irruption of will into reasoning was also propitiated by the differences between the West and Arabic culture, from which an important part of Aristotle's legacy was recovered. Both cultures are based on different primary intuitions that have no common points at a higher conceptual level (Smirnov, 2001). Adoption of the Arabic thought implied the necessity to make a conscious effort to connect two concepts that became linked through the will and not following some intellectual operation. Through the work of Averroes (1126-1198), from the Arabic culture was also adopted the notion of a *replenishable list* (that would become a *complete list*, or *catalog*) of living organisms (Gaziel, 2012)—a methodological innovation derived from the development of neoplatonic reasoning, which later on gained importance as a cognitive instrument to study diversity. It was in the Averroean interpretation that Aristotle's thought rooted in the Université de Paris (13th century) and later in universities of Bologne, Padua, and Ferrara (14th century).

The worldview of Duns Scotus was further reduced by William of Ockham. Ockham argued that realists and conceptualists restrained God's will by the existence of eternal ideas/universals, that in his view, were "excessive" (later, this view turned into the "razor of nominalism"—"entities should not be multiplied beyond necessity"—attributed to Ockham; Thornburn, 1918). According to Ockham, ideas are created by God—and directly "rendered to the least detail". In addition, there was the human mind, which was able to create non-existing essences to deal with the diversity of these objects. Surrounding objects were not "moistened" by essences and therefore appeared as non-comprehensible and non-definable.

Concept-based reasoning was replaced by perception of individual things. As it was argued by nominalists, the common for several objects did not reflect the individuality of concrete things; concepts did not entirely represent the really existing individual things. Individuals belonging to such 'species' resembled each other, but the term itself was an arbitrary construct because there was no special natural reason to isolate that precise group. 'Species' turned into a constructive unit. Nominalists did not leave any substrate for commonality—neither common things ('*substances*'), nor common concepts ('*genii*'). Only the perceptual experience was left, that created in the mind some fuzzy feeling. When repeated, such feelings amplified each other, being perceived as *similarity*; the *genus* turned into the *similarity of provoked feelings*. Comprehension was to be achieved not trough concepts, but trough the empirical perception of individual things. This was the output of more than thousand years of scholasticism: things cannot be comprehended by the mind.

The principle of parsimony (the 'razor of nominalism') led to the experimental approach: the existence of an object was not guaranteed anymore by reasoning, but required immediate experimental evidence. Nominalism won the battle of views and served as ground for new non-rational formations—cognitive structures backed by the will (*schemes* of reasoning). From questions about what is truth and what are things, philosophers' attention was drawn to the question of the degree of certainty with which truth could be comprehended and to the methods through which such comprehension could be attained.

II. Mind's new instruments and habits

The next stage, encompassing the Renaissance, Modernity, and scientific revolution, was characterized by the rise of rationalism, the birth of science and the gradual separation of biological knowledge. In Renaissance the texts of the Antiquity were rediscovered and there was a surge of interest in ancient magical traditions, this time—on the new background of thousand-year legacy of scholastic philosophy.

In preceding centuries, the notion about essences worked as a bridge linking thoughts about reality and the organization of reality; the organization of reasoning was aimed at obtaining the ability to understand (the used subtleties-rich language was isomorphic to nature). This bridge was destroyed by the nominalistic-elementaristic concepts. In these conditions, it became possible to make judgments about nature only by appealing to indirect and ephemeral *properties* or *traits.* This time the subject of simplification was not reasoning, but reality itself. Nevertheless, at the same time this simplification led to a better comprehension of the remnant fragments of reality.

Previously, religion, magic, pure logic, empiricism constituted a single intellectual field where they mutually interacted, often leading to collisions. It was the delimitation of their fields of scope what allowed their further development, their specialization and the birth of science. From "natural magic" it was adopted the notion about the existence of occult properties or hidden causes (like, for example, magnetism, the influence of the Moon on tides, the ability of plants, minerals and animals to cure diseases, and others; Henry, 2002). In the work of Galileo Galilei (1564-1642) and John Locke (1632-1704) properties were divided into primary (*shape*, *size*, *quantity*, *motion*) and secondary (or "illusory"—like color, smell, sound, etc.). Directly observable properties started being considered "illusory", whereas the invisible and non-perceivable properties—as the "really existing" ones and more informative. This division led to the notion that nature hides its secrets which have to be discovered, setting the beginnings of science and promoting the interest in scientific equipment. From now on any question about any essence had to be formulated in terms of these real (*measurable*) properties (Henry, 2002). Hence, Renaissance is associated with the rise of interest in the perceivable world and the shift of the paradigm from the *interpretation of the "Book of Scripture"* toward the *interpretation of the "Book of Nature"*. This is how natural magic nurtured science (Henry, 2002; Grant, 2007). Nature started being considered a rationally-organized mechanism, that should be studied through a similarly rationally-organized simplifying method. An important characteristic of this time is the strengthening of the idea about the unity of Nature as a whole that is subject to the universal law of the universe.

The 16th century is also the time when taxonomy turned into a common intellectual practice. For instance, a taxonomy of laws was proposed in physics. General statements turned unimportant, and the place of certain statement was typically pointed in reference to some hierarchy. Bacon assigned to laws the meaning of universal forms on top of the tree of concepts (Steinle, 2009). This is the time when catalogs (*atlases*) became an important mean of initial comprehension. Cataloging, in turn, propitiated the development of means of description, classification and naming —taxonomization— of organisms.

This practice led to the increase of the complexity of the presented material (which organization became close to the hierarchical genus-species scheme of scholasticism), and started being considered more mechanistic (the organism was isolated from its natural context).

Like scholasticism, rationalism bet on the necessity for a True method (the Organon), but unlike the Organon of the scholastics which was focused on the rules of reasoning, the focus of the Organon of the European rationalism was centered on the understanding of the rules of Nature. This is also how the method was understood by René Descartes who proposed his Organon in the form of *Regulae ad directionem ingenii* (1626-1628).

Comprehension started by creating epistemic artifacts or cognitive universals: counting systems and numerals, written language, nomenclature, classification, hierarchization, ranking, measurement and others. The second period in the history of the object was characterized by the creation of the instruments ("ideations") that allowed the mind to operate with it.

The first scientific ideation was introduced by Galileo: he used "exemplar" phenomena that explicitly reflected some idea. Such exemplars were then used for the analysis of "complex" phenomena resulting from the mix of such "typical" individual phenomena. The object of the experiment was created with the construction of the experiment itself, and therefore the object depended on the organization of the world, on the task being solved, and on the ideas of the person conducting the trial. Only ideas that were contained in nature were relevant. Science became characterized by the introduction of ideal (non-natural) objects, which were nevertheless inherent to nature, not modifying it, but making it clear and accessible to comprehension. From this time on, the main problem became determining the proportion between the thing and the intellect; an important problem was the classification of objects' features-traits. The world stratified into a system composed of things to comprehend and the comprehending subject who elaborated hypotheses about those things. This was the "inductive way" of Galileo: he weighed his observations and considered that the content of our reasoning could correspond to reality; ideas organized nature. In his view, mathematical ideas were argued to directly exist in the world. To establish the credibility or falsity of mathematical formalizations obtained in this way Galileo used trials.

Another formalizing ideation —*tables*— was introduced by Francis Bacon. Tables contained what the experimenter considered to be a result, and, according to Bacon, from the analysis of contained values it was possible to detect some higher-level generalities. From this reduction of the observation took its beginnings the (unsolvable) problem of generalization in its modern form (in our reading: "what does the generalization of a certain class of 'measurables' correspond to?"). For the first time in history general concepts were *produced* from a trial—from a single table in an attempt to formalize empirical data.

Together, all these formalizations propitiated the rise of the weight of mathematics for scientific knowledge. This revolution was associated with the problem of "occult properties". The authority of years-old expertise and common sense was reduced (see below). The mathematical apparatus got complex in the periphery of attention, and then some changes occurred in the perception of the human beings regarding their expectations about the reliability of the obtained knowledge. In these conditions changed also the relationship to mathematics. With this time is associated the famous quote of Galileo "the Book of Nature is written in the language of mathematics".

However, mathematization did not mean experimentalism: critical empiricism was required previously and the requirement to "scrutinize" observations was a common motto of 15-16th centuries alchemy. The "experimental method" of these years rather relied on rhetorical techniques of persuasion. This was also the style of dissemination of knowledge introduced by Robert Boyle (1627-1691): through rhetorical techniques it was instilled to the reader that they were present during the trial. Close to rhetoric was also the philosophy of Rene Descartes. His rationalism contributed to a further increase of formalization with a concomitant reduction of content. To achieve this goal, Descartes chose to develop a clear general language devoid of ambiguities, that could serve to explain different natural phenomena. He developed several rules of reasoning that had to be observed both in natural philosophy and natural history: 1) only something that is explicit, unquestionable and clearly conceivable could be considered truthful, 2) any problem had to be divided into all the parts that could have been required to solve it, 3) reasoning had to move from simple and more general matters toward more complex and detailed ones (*deduction*), 4) when approaching any issue, a complete list of the corresponding details had to be made to be sure nothing was missed. This *voluntarism* was afterward developed in the philosophy of Immanuel Kant (Kojeve, 1964).

Scholasticism turned into science through the bottleneck of the works of René Descartes and Gottfried Wilhelm Leibniz. For Descartes, an important step in solving problems was the construction and manipulation of the objects in his mind. This visualization was related to the surge of the Observer's concept. Descartes also turned upside down the scheme of definitions: his definitions were based on rhetoric constructions that made use of external and visible properties, leaving aside the scholastic definitions based on essences, which later on disappeared. *Traits* took the place of things' *essences*.

Important for the scientific revolution that occurred during this period was the absence of intellectual traditions, as scholasticism lost its previous influence. New practices were acquired from already existing everyday activities and practices. The rise of jurisprudence contributed to the practice of application of "formulas" to objects that were considered similar, increasingly leading to the elimination of their content. The rise of mass education, supported by the wide adoption of printing and the introduction of teaching standards (Wilkins, 2011), was an important factor in the increase of the perception of listeners as homogeneous. Typography also served as a ground for the creation of the formal apparatus of taxonomic systems, and the widespread practice of confession set the tradition of correlating traits with ranks. Concomitantly with the adoption of these practices took place the crystallization of academies, leaded by Francis Bacon, and the rise of the entrance barrier for "real science".

An important step in the establishment of science as an independent activity was the appearance of the *Port Royal Logic* (1662), a book about the own language of science based on clear rules of thinking, about the ways in which results of reasoning had to be exposed, and more generally—about the organization of scientific knowledge. Some of the rules to be observed in the scientific activity were: 1) not leaving any unclear or ambiguous term without definition, 2) usage in definitions of only well-established or already clear terms, 3) as axioms could be considered only obvious statements, 4) the requirement to prove any unclear statement by using only previously provided definitions or accepted axioms, 6) the requirement of not getting confused by the ambiguity of terms, for which they had to be replaced in the mind by their definitions, 7) the requirement to analyze things following their natural order—from more general and simple (explaining first all what concerned the genus before approaching species), 8) when possible—the genus had to be divided into all pertaining species, any whole—into all pertaining parts, and any task—into its all pertaining cases. As it can be appreciated, these rules imply a top-down deductive scheme of reasoning.

Newly born science simultaneously set some properties of the object it had to work with, and of the context in which such work was to be carried on. This reduction was reflected in three key aspects — elementarism, mechanicalism and probabilism— analyzed below.

Elementarism: In the onset of science there were two trends, that jointly reflected the so-called decontextualization of facts (Slaughter, 1982): 1) the creation of certain system of groups for the observed facts (combinatoric tables, hierarchical trees, mathematical formulas), 2) the search of lowest-level elements. Facts were manipulated as symbols or constructive elements. Working at the "most elementary" level and in the most formal way possible was often considered the best route to achieve a deeper understanding of the laws of nature. Among influential personalities that made reference to primary elements were René Descartes, Blaise Pascal, Gottfried Wilhelm Leibniz, John Locke. In addition, atomism was the non-official philosophy of the Royal Academy of Science during this period of time (Slaughter, 1982).

In the 16th century also gained popularity the old creation of Raymond Lull (1232-1315)—a “machine” that made use of combinatorial operations with the original aim at proving the truth of the Christian doctrine. Llull’s machine contained a set of properties and attributes which in their different combinations could reflect —according to its creator— all possible statements that could be expressed in regard to our world. This approach implied that the world was made of discrete elements. However, in such a machine the number of elements was defined by its creator, resulting in a ranked hierarchy that was determined not by the properties of the object it had to represent, but by the creator’s will. Llull’s logic was not a tool for argumentation, but an instrument to find new combinations of properties. A similar transformation occurred in science in the second half of 20th century, when —now in big data analysis and individual disciplines— a combination of all traits started being taken for analysis without previous selection or weighing by their relevance.

Mechanicalism (term suggested by John S. Wilkins) implied the acceptance of explanations based only on mechanical interactions of hard bodies. After nominalism won the frameworks battle, the mind’s only choice was the possibility to play with discrete elements in a sort of combinatorics. Mechanistic explanation were tended to be used in explanations of the functioning of such non-appropriate objects like plants and animals.

Mechanicalism was professed by iatromechanists (Pierre Gassendi, René Descartes, Thomas Hobbs, Robert Boyle, Isaac Newton, John Locke) whose main opponents were iatrochemists (Tammy, 1996). The views of iatrochemists were more “ecological”: they did not isolate the object of interest from its environment, but took it as a whole with its surrounding. For iatrochemists almost any term implied not a noun, but a function, a process, a dynamic with a particular time course. One of the most famous iatrochemists, Paracelsus, did not work by elaborating some periodic system (a *list* that could describe a system like in Fig.2A). Instead, every time he made new series of local correspondence between plants, the soil they grew on, diseases and corresponding treatments (Fig.2B). However, mechanicalism took over because of its elementary character that allowed explaining a wide range of phenomena parting from few basic principles and because it was in line with the philosophic spirit of the time, expected from science. For Descartes, the founder of the school of iatromechanics, the important point of this conception were the mechanical interactions themselves: he aimed at representing the world as a passive matter that was moved by God’s will.

During the 17th century, mechanical philosophy turned as influential in explaining the functioning of living things as it was in more physical sciences. The reason of this success was not just related to the explanatory power of this philosophy (which in the case of organisms could not account for all the exhibited complexity). Mechanicalism was rather viewed as a highly comprehensive system capable to rival the reigning 'unscientific' and 'vitalistic' Aristotelianism, which was strongly linked to the social and cultural institutions of the time (Henry, 2002).

Probabilism: This aspect of science took its origins in the devastating religious wars of the time. Friar Bartolomé de Medina (1577) proposed that when several possible rational arguments coexisted concerning some particular issue of faith, a person was allowed to choose any, even the less probable of them. This was a conception of religious freedom (and ethical and intellectual freedom) which did not require authorities. However, this intellectual clarity and freedom was strictly subdued to rigorous discipline: it was possible to deviate even from the most probable and authoritative solutions, but it was necessary to follow certain rules. Reasoning was channeled—all bifurcations were open to the mind, but mind was not allowed to escape the channel; the mind was under the total control of the will which set the goals. These habits were strengthened by the imaginative practices of Jesuits, introduced by Ignatius of Loyola, in which the faithful had to imagine in details passages of the Bible.

"The major inspiration behind [...] eighteenth-century perceptions of revolutionary change in science was undoubtedly Isaac Newton", who gained his influence after his recognition by French intellectuals, despite disagreements between English and continental nominalisms regarding the origins of the activity of matter (Henry, 2002). In his *Principia mathematica* (1687), Newton introduced the hypothetical-deductive method, refusing to analyze the "what is" issue, linked to the essence of the things. Instead, his program brought the possibility *to predict the behavior* of things. Objects of physics and sciences alike were amenable to the operations proposed by Newton, and this determined the further formalization of these sciences. Newton's works were regarded "as the very model of the new mathematical way of doing physics" and "as a model of experimentalism" (Henry, 2002). Meanwhile, in biology no material was found to which the Newtonian approach could be applied, and biological knowledge continued to evolve in the form of descriptive natural history and rational classification.

At a first glance, it looked like biological objects did not constitute a homogeneous continuum of properties and did not allow the mathematization introduced by Descartes. Indeed, Francis Bacon divided the full corpus of knowledge into the analytical natural philosophy (which method was exact mathematics) and the descriptive natural history (the method of which was the qualitative genus-species hierarchical division). From this point on, classificationism and analytical mathematism parted in different directions. Nevertheless, classificationism served the same purpose as analytical mathematism, although for the drastically different biological material: in the case of inanimate objects the formalization rules were external to the objects of interest, whereas in the case of living organisms these formalization rules were internal to the objects, which were characterized by a huge diversity. The tendency to formalize something homogeneous (visible in natural philosophy) was also characteristic to natural history, although the nature of the working material determined the differences in the ways to solve arising problems and in the obtained results of manipulations. The universal character of the genus-species scheme, postulated by the scholastics, allowed integrating all available biological diversity into a single classification system, turning systematics into the "Queen of Biology" for several subsequent centuries.

III. Cognitive instruments applied to biological diversity: The rise and fall of systematics

The biological object inherited from the previous period was biological diversity with all of its myriads of traits. This was the material with which it was attempted to create a "natural system" of living forms, similar to the one that allowed the advance of mechanics and optics.

How such system had to be composed, considering that objects were increasingly represented as sets of different traits, and descriptions of organisms were based on quantity, place, form of anatomical structures—primary or 'measurable' properties?

A "real life" system had to provide criteria that could allow devising the available diversity of living forms. Sufficiently constant and sufficiently variable traits had to be identified, that could allow characterizing a group and describe diversity, respectively. It had to be determined how the vast amount of traits displayed by biological objects had to be arranged. Very probably, these were the reasons why the elaboration of the natural system of living things took off using as reference one of the most 'mosaistic' groups of organisms (and hence, one of the most amenable for isolation of individual traits): plants.

The first person who proposed weighing traits (according to their functional relevance for plants themselves) was Andreas Cesalpino (1524-1603). *Numerus*, *situs* and *figura* were proposed by him as trait's properties to elaborate the plant system even before Galileo talked about primary traits. Nevertheless, the work of Cesalpino was not understood by his contemporaries (that worked on the development of exact descriptive morphology) and only influenced his following Joachim Jungius (1587-1657). Jungius identified the basic elements of plants and formalized their representation so that any plant could be described as a combination of ‘measurable’ traits. In this way it became possible to obtain a ‘formula’ for any plant, to formulate analytical and quantitative arguments, and to attempt to comprehend the plant world through a reduction of description. Jungius’s work —through the influence of John Ray (1627-1705) — was the catalyst that later on made possible the appearance of the system of Carl Linnaeus (1707-1778).

Introduction of *absolute* and *individuated* ranks were other ideas that allowed the further advance of *taxonomic* representations. With the appearance of fixed ranks, taxa belonging to the same rank started being considered equal and to enclose a similar content—special traits that allowed identifying taxa of certain rank. Fixed ranks were introduced with the aim to compare the vast diversity of forms throughout a homogeneous continuum of traits.

Following Descartes, Carl Linnaeus (1707-1778) reduced not only the language but also the nature. Linnaeus replaced the nature by a formula, leading to the formulation of a true *analytical* or *constructive* (“Llull’s”) morphology. Traits for him were the alphabet of God’s language, and this analogy set the focus on the arbitrary character of combinations of traits rather than the correlations between them. This idea became trending and today the notion of wholes as combinations (mosaics) of traits is a common ground.

With the expansion of the system by its successors, the combinative ground of the Linnean morphology disintegrated under the weight of the increasing diversity of traits that no longer fitted the periodic character of the Linnean system. In addition, the Linnean constructive morphology could be developed for plants but not for animals, that are characterized by a higher degree of integrity than plants. In this way, the first morphological system in the end turned into a disordered set of traits.

Constructive morphology, ranks, nomenclature—all these conceptual instruments were established by Linnaeus, but a no less important factor was the metaphor through which they were interpreted: either from the point of view of a whole divided into parts (deductively), or as units-elements that are grouped into classes (inductively). Cesalpino’s methodology was deductive, because it derived the relative weights of traits from general principles, in this way determining the system’s contour. However, in practice the system was inductive, as it was developed for one plant family, and then it was expanded to other families. However, after Linnaeus —and the derogation of the rational morphology— the inductive interpretation became more influential and widespread, so the conceptual instruments developed by Linnaeus were interpreted mostly in an inductive way. In the end, this situation contributed to the establishment of empirical species as the discrete units of the natural system. Constructive morphology and other driving ideas of the time led to the leading role of species with their myriads of diagnostic traits, at the same time calling for the justification of this rank, and for an explanation of the causes of its existence in nature. Exemplars turned into sets of *diagnostic* traits, and systematics turned into systematics of such traits.

With the disintegration of the first analytical morphology surged the desire to elaborate a new constructive morphology that would —unlike the Linnean system— take into account *all* traits. Variants of the *rational* approach to morphology (after Cesalpino) were also proposed by Antoine de Jussieu (1686-1758), George Cuvier (1796-1832), and Augustin Pyrame de Candolle (1778-1841). Like Cesalpino, these systems relied on preliminary assumptions that allowed assigning particular ranks to traits. During this period of time there were also other approaches to elaborate the system. For example, George Bentham (1800-1884) and Joseph Dalton Hooker (1817-1911) proposed an approach that can be referred to as *pragmatism*, and which was aimed at arbitrarily fixing the number of ranks with the final goal to help botanists at memorizing the vast diversity of plants and traits. Finally, in a third, *inductivistic* approach, traits were not *a priori* ranked by relevance. Instead, the more frequent some trait was in different genera, the higher was considered its relevance for the system. This "internal weighing" was based on the analysis of the organisms (plants), and was an approach opposite to the external (researcher-led) weighing. The weight of a trait depended on the degree of stability it conferred to the system, without the necessity to invoke additional arguments. These were the characteristics of the system of Michel Adanson (1727-1806).

Adanson looked for gaps in the space of traits (=between taxa), and worked through *segmentation* and *combinatorics* of traits. Things were considered to be delimited by such gaps and data was interpreted through deduction. Taxa became externally definable. Previously, the system was organized from the top by a single unifying idea, but now the idea was completely different: from voids in the observed variability the empirical characteristics of species were deduced, and by combining the identified groups the higher taxa were then formulated.

These approaches to trait ranking were grounded on opposite views about how the natural system itself had to be conceived. In the model of *continuous* nature, it was considered that it is possible to find series of variation between traits and organisms —that nature does not make jumps— and therefore, taxa can be arbitrarily delimited by a researcher, and then grouped by convenience into higher taxa. Morphology in this view acted as a provider of traits that were used by the taxonomist to elaborate the taxa. Conversely, in the model of the *discontinuous* nature the focus was on the content of groups—the internal organization of organisms, which were identifiable through comparative anatomy (and which set the ranks of traits). This approach was characterized by a close interaction between morphology and taxonomy, and attention was paid to the identification of sharp breaks in the continuum of traits. The whole (the organism with its traits) was considered to be integrated through correlations of parts, and this was the source of discreteness. Both these approaches served as ground for the post-scholastic systematics up to the 20th century. However, in the 19th century the model of *continuous* nature became the most relevant as it was shared by the most influential systematists of the time (Adanson, Lamarck, de Candolle) (Stevens, 2002). Later on, this contributed to the establishment of species as the empirically-perceived objective rank (see above), and to the handling of objects and their traits as proposed by Adanson.

The creation of comparative anatomy by Félix Vicq-d'Azir (1748-1794) served as a start of zoology as an independent discipline. If botanists regularly expressed the idea that from knowledge about part of the plant diversity they could reconstruct the whole periodical and combinatorial system, it was clear that for animals most combinations will not be allowed in nature, due the lower degree of mosaicity in animals in comparison with plants. This idea was reflected in the concept of *correlations* introduced by G. Cuvier. Division of animals according to their symmetry planes (in Cuvier's *theory of embranchements*) led to the establishment of an *a priori* sharp division of traits by relevance, which established a strict hierarchy of traits. And, unlike in other rational approaches, this preconceived ranking was top-down directed. The introduction of criteria of homology by Étienne Geoffroy Saint-Hilaire (1772-1844), Johann Wolfgang von Goethe (1749-1832), Richard Owen (1804-1892) allowed establishing the correspondence between such ranks in different organisms. Comparative anatomy (morphology) brought traits, series of similarities, and defined the directions in which to develop the system. Taxonomists filled the system with taxonomical content, by determining the ranks of groups linked by homologies. Posterior attempts to compose a system for the animal world were made by Ernst Haeckel (1834-1919), Vladimir A. Beklemishev (1861-1919) (based on symmetry). Current attempts to compose such a system are based on genes.

An important alternative to these classification efforts was the work of Wolfgang von Goethe, which was continued by Lorenz Oken (1779-1851). Unlike the "structuralist" ('measurable'-based) classification approach of Cuvier, Goethe focused on the dynamic metamorphose which was much more difficult to formalize. This was one of the reasons why the Goethean work was not widely accepted among 19th century's systematists, although in the 20th century it recovered some of its momentum and is currently regarded to as one of the precursors of evo-devo (Pavlinov, 2018).

Systematics reigned as "the Queen of biology" until the middle of the 19th century. The natural system was considered the pinnacle of knowledge serving not only as a method but also as an explanation for the diversity of organisms. Conceptually, the achievements of systematics were rounded up by Immanuel Kant (1724-1804). Essences of things are hidden and unintelligible, hence, as we cannot comprehend things-in-themselves, we operate with arbitrarily chosen traits —with individual concepts— which are then arbitrarily linked into arguments. As a result, a system of arguments is obtained, the link of which with reality is indeterminable, or, in other words—is nonexistent. This is how the claim appeared about the impossibility of elaborating a comprehensive natural system of organisms, which is still maintained nowadays (Pavlinov, 2018).

In the second half of the 19th century the attention was drawn from systematics to the conception of evolution, which served as a new ground to explain the causes of biological diversity. Darwin was the first person who proclaimed that the natural system of organisms had to be *genealogical*. His conception stated that natural groups are almost entirely determined by a common origin, and contained a proposal about how to shift from similarity to kinship, and then to classification (Pavlinov, 2018). According to Darwin, traits were not grounds for classification, but rather constituted indicators of kinship. Instead of the essentialistic interpretation of traits, he proposed approaching them through quantitative criteria that would allow estimating kinship when a classification was elaborated. Hiatuses between natural groups, in Darwin's view, were only the result of extinction, and this could explain why groups are isolated.

From this time on, the role of systematics started to decline: the focus shifted from classification to the analysis of kinship, and the system of ranks turned into a sort of traditional means to formalize objects' descriptions. Nevertheless, the changes experienced by systematics in this period contributed to establish the guise of the biological object. First, the whole, as biological diversity, turned into the wholeness of an individual organism, and then—as the totality of an organism's traits. Second, from now on, an object was defined (isolated) through segmentation; it started being considered to be constituted as a mosaic of traits, and the idea to include all traits in the analysis of the object became trending. Third, traits themselves turned into measures of kinship, and consequently—as traits were chosen those properties which allowed their tracking along generations. These were the features of the object and of its context that were inherited to the 20th century's biology.

IV. The modern 'biochemical'-level research object.

In the beginning of the 20th century the relationship between the researcher and the research object became influenced by the drastic change in the scientific background, induced by shifts in the notion about the content, the tasks and principles of scientific research promoted by the positivist current of thought. On the one hand, advances attained by the physical sciences in the understanding of organization of our world propitiated the desire of biologists to achieve similar degrees of explanatory power. As scientific were started being considered those phenomena that were identified through physical methods and that were amenable to express in the language of physics. These new disciplines (physiology, biochemistry, genetics and ecology) were more akin to physicalist approaches and predominantly addressed individual objects, not being interested in diversity and in the organization of the obtained results in some general encompassing system. Trends were set toward the unification of science based on experimental proving, quantitative description and reduction to physical constants, and toward the concomitant elimination of the metaphysical component (associated with the study of diversity).

In 1888, Wilhelm Roux (1850-1924) raised an issue that broke with the interest in reconstructing phylogenetic trees and resulted (as it happened several times along history) in a thematic self-twist. This issue was related to the mechanisms by which few and seemingly homogeneous cells grow and differentiate into organized groups of highly specialized cells. The rise of this purely embryological question, further pushed by the results obtained by Hans Driesch (1867-1941) contradicting those of Roux, denoted the start of separation of research levels of organization—the 'organismic' and the 'biochemical' one. The possibility to identify and manipulate 'measurables' at each of these levels favored their further independent advance. At the same time, the work of Roux propitiated the transformation of the type of questions being asked in biological disciplines in such a way as to yield predictions that could be put to experimental test (Allen, 1975).

Since the first half of the 19th century also evidence started appearing that quantitative measures could be used to estimate phylogenetic relationships between organisms. This led to the development of biometry, methods of variative and discriminational statistics in an effort to understand hereditary patterns of traits within populations (Allen, 1975). The adoption of this "statistical mathematization" was further promoted by the elaboration of the so called "numerical taxonomy" by Peter H.A. Sneath and Robert R. Sokal (Sneath and Sokal, 1962). Later on, this statistical manner of thinking served as a means to approach hereditary problems in populational biology and other disciplines.

The second factor influencing the researcher-object relationship was the effect of the theory of evolution that set an entirely new framework for assumptions and for the formulation of research questions. The theory of evolution determined the domain (phylogeny), the focus, and the direction of experimental questions, and provided its own interpretation for biological diversity. The objects of the Darwinian theory of evolution, species, were the result of the process of interaction between individuals, and not real entities (Wilkins, 2009, p.230). Exemplars in Darwinian biology resulted from the replacement of the will by the progression of reproduction and the tendency of species toward self-preservation and reproduction, controlled by natural selection. Nothing, however, was explained about the causes behind the tendency toward self-preservation and reproduction: these features resulted from the worldview itself. This gap, and the technical impossibility of the time to uncover the mechanisms of heritable variations that arise and persist in a population, led to another change in the course of science into other direction. In his experiments, Thomas Hunt Morgan (1866-1945) separated big questions about the relationships between heredity, embryology, biochemistry, and evolution, that were not answerable by experiments, from simple questions that were experimentally testable on the *Drosophila* model. By elaborating such formal concept of genetics, that was devoid of chemical or physiological function, he and his group could "push ahead in an area where at least some answers were readily obtainable" (Allen, 1975).

A similar shift occurred in the 1950s-60s, when a return of biology occurred to the cellular level, because works on embryology in the search for the organizer (the general inducer of differentiation) and the "morphogenetic field" theory did not provide direct answers or even directions to approach the supracellular level and to advance the research on the mechanisms of development. This return was also propitiated by the concomitant development of techniques like radioactive tracers, electrophoresis, chromatography, and microsurgery that made it possible to carry out experiments on single cells. As it occurred on several previous occasions, science moved forward following the experimentalist and formalist pathway.

This trend was partially reversed since the second half of the 20th century with the advent of post-positivistic philosophy, that reintroduced the metaphysical component (accepting that scientific knowledge is not entirely free from researchers' beliefs, values, and experiences). For 'biochemical'-level disciplines this was reflected in the different hypotheses about how the 'organismic' level properties emerge (as examples can be mentioned discussions around the nature of conscience or intelligence). Yet the guise of the research object and the methodological approaches to handle it were already adopted. The different sets of traits at different levels of organization were not able to provide researchers with clues that could guide them in the understanding of the way in which the organism emerges from its constituting components.

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The properties of the objects of the ‘biochemical’ level typically do not rise some particular concern and can be considered part of the non-formalizable and non-explicit knowledge. We consider, however, that at least part of these properties can be reconstructed from characteristics of model organisms, from the analysis of those characters that are investigated and collected using current ‘biochemical’-level research methods, and, more generally —by analogy— from the analysis of science itself as a research object.

Model organisms serve as models for a wide range of systems and processes that occur in living organisms (Ankeny and Leonelli, 2020). Although they have their origin in the wild, they are constructed in such a way that they are considered controlled (and in many cases—homogeneous) environments for the study of ‘biochemical’ pathways. Ankeny and Leonelli (Ankeny and Leonelli, 2020) identified two aspects of model organisms: their representational scope (the range of organisms that is represented by a model organism, as model organisms can share genomic, developmental and mechanistic characteristics with other organisms), and representational target (the type of phenomena that model organisms are used to study).

Typically, the representational scope ascribed to model organisms is broader and more inclusive than that ascribed to other experimental organisms. This is due to the importance genetics has gained in the construction of representative models, introducing the “pure line” through abstraction from certain degree of populational-level variability characteristic for living organisms. Model organisms have also turned into anchors between levels of organization, being considered “placeless” artifacts and samples of nature, even though these organisms —being alive— defy such “role homogenization”.

In recent years, model organisms have also been explicitly used as reference for cross-species comparison in order to understand features of “non-model” organisms (Ankeny and Leonelli, 2020). These ‘reference’ role is nevertheless accompanied by efforts to develop the “natural history” of model organisms, as little is known about the “real life” of many of them (Ankeny and Leonelli, 2020; see also the Introduction). At the ‘biochemical’ level, certain similarity to this referencing role can be traced when referring to ‘canonical’ functions of ‘biochemical’ pathways.

Another issue related to model organisms can be called ‘determining to what extent does an individual represent a group’. For example, in experiments, when testing a response from an organism, it is *assumed* that a particular individual is largely similar to the other ones that belong to the same experimental group (the natural variability within such group is typically not considered an experimental variable itself). Conversely, when such individuals are themselves the object of study (for example—their development, or organs' maps), the result obtained from a single individual (for example, its developmental dynamics) cannot be extrapolated to the others' ones: establishing the similarity between developments and maps requires a multidimensional comparison of every element of the individuals conforming the experimental group. At the 'biochemical' level, the biochemical and signaling pathways' variations play the role of such *individualities/quirks* (Fig.1). However, in most cases, cascades are represented as straightforward schemes that do not transmit the existing variability in their activity across individual cells, that account for the heterogeneity observed at the cell populational level. The intrinsic variability (or pathways' plasticity) resulting from different activities of each of the elements composing such schematic cascades typically remains out of scope. A very recent study addressing this issue is, for example, the work by Cappelletti et al., 2021.

The most recent iteration of reduction in biology are single-cell technologies, of which the main focus has been placed on single-cell RNA sequencing (scRNA-seq; Zappia and Theis, 2021). In this approaches, it is unspokenly assumed that the functionality of the supracellular level results as a "sum" of the characteristics of individual cells (e.g., see Lähnemann et al., 2020). scRNA-seq reflects the maximally attainable level of mosaicity at the lowest possible common organizational level of biological diversity in living organisms, as cells are considered the minimal elements of life.

A recent review of software for the analysis of scRNA-seq data identified an increased focus on two main classes of tasks integration of datasets and cell classification (*taxonomy*) with a relative decrease in the number of tools to order cells into continuous trajectories (Zappia and Theis, 2021). Classification of cellular diversity (in the form of cell populational heterogeneity) is also the focus of scRNA-seq of cancer cells (Suvà and Tirosh, 2021). No spatial information is typically included in this type of analyses, being cell types inferred from the integration of spatial information with transcript or gene expression (Lähnemann et al., 2020; Suvà and Tirosh, 2021). In addition to these *inquiring* techniques there is also a toolkit of intrusive techniques like knock outs, knock downs, changes in gene expression, or gene replacements using gene editing tools (e.g., CRISPR-Cas). Genes in this case are implicitly assumed to play the role of key elements of the mosaic named 'organism'.

The modern research object's guise can also be inferred from the general approach toward modern science (Wang and Barabási, 2021). In the view of these authors, not only does the research object appear as a set of almost unstructured features/traits, but also the study of this setting (by researchers characterized by random qualities) is considered devoid of some intrinsic thematic hierarchy. Again, externally imposed “taxonomic traits” (“qualities”) of the research object and the researcher (“prolificity”?) are considered decisive in determining the probability with which a research theme can become successful within the ‘academic taxonomic system’. “[S] cientists and others see new theories or ideas emerging like some sort of hidden treasure, the correct trail to which certain geniuses have uncovered while myriads of incorrect trails were being followed by lesser minds” (Allen, 1975).

Altogether, the following features of the modern ‘biochemical’-level research object can be observed, that derived from historically established ways of its conception and from modern tools elaborated for its study: 1) it is defined *taxonomically* (=logically or ‘through segmentation’, “externally”), both in space and time, 2) it is taken in isolation (meaning that typically only a particular aspect of the research object is analyzed, even if studied in the context of a living organism), 3) it is typically compared through statistical methods in reference to a model organism, to a model conditions, or to a ‘canonical’ function, 4) the ascribed representational scope of the reference is typically broader than that of the non-reference, 5) it is typically analyzed from the mechanistic point of view, that involves descriptions in terms of ‘measurable’ properties, 6) genealogical linkage appears as one of the most important properties that allows introducing order into the set of properties of the ‘biochemical’ level object, 7) it is widely agreed that the ‘organismic’ level constitutes (and can be reconstructed from) a mosaic of ‘biochemical’ level elements, being genes considered a cornerstone piece among these elements, 8) the ‘biochemical’ level of organization is typically approached in a deductive, top-down, direction, in which the ‘top’ does not correspond to the ‘organismic’ level of organization, but rather to a researcher’s conception, 9) a typical way to assess the correctness of the researcher’s conception is by comparing predictions that derive from the researcher’s ‘model’ of the ‘biochemical’-level process with experimental results, 10) another important strategy to approach ‘biochemical’-level elements is the elaboration of atlases, full lists of “traits” (“-omics”), or maps that depict their mechanistic interconnections.

The previous versatile conceptual system was replaced by a drastically limited and fragmented system with a reduced comparative base. Is this new guise of the ‘biochemical’ level object sufficient to achieve the ability to reconstruct the ‘organismic’ level? Whatever the possible answer to this question could be, the study of the ‘biochemical’ level advances using this vision of the research object. Nevertheless, despite the strong prevalence of elementaristic genocentrism in studies of ‘biochemical’-level processes, there are also efforts to approach biological problems from the ‘organismic’ level perspective. An overview of such efforts, for example, are provided by the workgroup Return of the Organism in the Biosciences (ROTO, 2023) at Ruhr University, Germany.

2.2. Features of living systems that make possible inferring their organization

In previous sections we examined how the conception of the research object changed over time. The conceptual handling of living organisms largely followed that of inanimate objects, mostly to count with a way of thinking about their organization and functioning. Meanwhile, the nature of living organisms and how well they were described by those methods that were increasingly applied for their study were mostly left without attention. Several efforts were undertaken in this direction although, as it can be judged from today's biology, they were not widely recognized and adopted. In next section we retake this aspect as it is critical to achieve the possibility to reconstruct the 'organismic' level.

2.2.1. Differences in the organization of inanimate and living systems. Systematics as the appropriate conceptual toolset to approach biological diversity

Using the "mosaic/Venn diagram" contraposition from section 2.1, physical systems can be alikened to Venn diagrams with overlaps reduced to their extremes, or *mosaics* of constituting elements (Fig.2A). Such simple organization facilitates the derivation of laws of organization and interaction between elements from direct observation of causes and consequences (Beklemishev, 1994). Therefore, in physics, establishing that two objects of a same kind are commensurable (their equiparation) is trivial and does not require some special methodology of comparison. Such 'physicalism' prompted Karl Popper to argue that science is not interested in essences (in the '*what is*' of the research object—the Aristotelian *genus*, Fig.3) and should focus instead on answering the question *'how does the object respond?'* (Popper, 1959).

Unlike physical objects, living systems are characterized by a huge diversity of their composing elements (which abundance and activity can also vary; this is what we call *individualities/quirks*, see section 2.1) and by a hierarchical modular organization: composing elements have different 'weights' or 'importance' in the overall structure. Such organization type confers robustness and flexibility to living systems (Hartwell et al., 1999), but at the same time does not allow establishing straightforward 'causation': for example, the form of a leaf of a plant cannot be directly derived from its root's form (Lyubarsky, 1996). This is also the reason why similarities and differences in the case of living systems have to be established in a way different from how it is done in the case of inanimate systems: comparison of living systems has to consider their hierarchical organization, which is conditioned by the *history* of its establishment (Lyubarsky, 1996; Panina et al., 2020).

If the elements of some system are numerous, hierarchically organized and display many similarities and differences that do not change independently, it is possible to define categories of a higher level that encompass them, as concepts do (Beklemishev, 1994). This operation, in which the elements are first described, and then grouped minimizing the content loss of their description, is known as *systematization* or *classification*. Systematization is aimed at reducing the description of an object characterized by a large diversity of its elements by 1) establishing similarities between those elements, 2) establishing differences among them, and 3) establishing *the relevance* of those similarities and differences (Beklemishev, 1994). Hence, systematics is the most suitable methodology to approach biological diversity. Importantly, falsification or refutation by presenting opposite examples does not apply to systematization: systematization by itself serves as a ground to propose hypotheses that can be falsified. As a method, systematization includes all possible outputs: all classified elements can find their place in the resulting classification. Therefore, systematization is a method more general than falsification, as hypotheses can be falsified only within the framework of some classification (Lyubarsky, 2018). As Beklemishev noted, the world can be described only through methods of statistics and systematics, and in such description, the first have to be applied to categories created by the latter (Beklemishev, 1994).

A description is aimed at simplifying comparisons between objects, and at establishing and evaluating similarities and differences between them. Living organisms are typically described using taxonomy and morphology. In morphology, divisions are always carried by a single ground and therefore the resulting groups are not intersecting. In the taxonomic logic the situation is different: comparison is between whole objects each of which has many properties.

Taxonomy works with ‘measurable’ traits: either their quantities, spatial/temporal ratios, or their intensities. Taxonomy groups traits into a hierarchy based on their similarities and differences (Beklemishev, 1994). In taxonomy, groups can intersect by certain properties, and can even contain objects with and without certain property. Non-intersectability of groups is maintained by external rules: when classes are constructed, a same object is not included in two classes, even if the properties of those classes intersect. Hence, in taxonomy the main idea for the organization of diversity is the existence of taxonomic categories and fixed taxonomic ranks in the form of a researcher-formulated system and the corresponding method. Fixed ranks are used to achieve comparability across the system and between forms in a universal system (section 2.1.1).

The main idea to deal with empirical data in morphology is its organization in a hierarchy of parts of an organism. An advanced morphological description includes information about the relative importance of different organs, their functions, about the organization of functional systems and modules/blocks. At the 'organismic' level, stages of individual morphogeneses (their invariants and varieties) are in the scope of **morphology** (Beklemishev, 1994). Morphological analyses are typically based on multiple comparisons of the issue of interest in different organisms, and this is how levels of morphological description are obtained, with their corresponding taxonomic ranks (Lyubarsky, 2018). Morphology consists of **tectology** and **architectonics**. Tectology identifies 1) the types of structural elements the object is composed of, 2) any recurrent module (like vertebrates' somites or invertebrates' segments). Architectonics focuses on particular instances of such elements, focusing on them and their context within the whole. Both tectology and architectonics are used to determine the organization of the whole, both from the static (anatomy) and dynamic (embryology) point of views (Beklemishev, 1994).

Thus, 'biochemical' tectology describes the structural elements (individual molecular components as they are represented in schemes of cascades) and their possible repetitive arrangements ('poly-mers': dimers, tetramers, etc.)—i.e., the molecular 'measurables', mentioned in the Introduction. In turn, 'biochemical' architectonics describes specific interactions in which these elements can engage to carry out particular functions. This term, however, may also refer to the different (biological) species-specific environments in which a same molecular component has to carry out its function(s), and includes the variability intrinsically present in what we denominate *individualities/quirks*.

In section 2.1 we argued that the organization of living organisms resembles a flexible Venn diagram, with overlaps corresponding to functional ties that link 'measurable' elements. Numerous examples of the establishment of functional links during ontogenesis and evolution were presented in the work of Ivan I. Schmalhausen (1884-1963). Such linkages ("correlations" in his terminology), analyzed by functional morphology, contribute to the integration ('wholeness') of organisms (Schmalhausen, 1982). Examples of such linkages are the maintenance of proportions between organs' sizes during development (also examined by Spemann, 1936), and functional linkages—mutual influence between organs through mutual induction and functioning (see Silva et al., 2021; Revah et al., 2022 for recent examples). At the 'biochemical' level of organization, "correlations" are maintained by the pleiotropic effect of genes and protein moonlighting, to mention some examples. These types of interactions can supersede the duration of individual ontogeneses and be preserved or modified, as blocks, in phylogenetic series.

Addition of the functional aspect to a physical part or a trait (to a 'measurable') led to the concept of *meron* (Meyen, Schreider, 1976; Meyen, 1978). Unlike discrete, independent and elementaristic taxonomic *traits*, a *meron* carries information about functional correlations with other merons and its role in the whole organization (Lyubarsky, 1996, Pavlinov, 2018). At the same time, this same feature hinders the possibility to formalize the procedure of merons identification, making it dependent on the researcher's goals (Lyubarsky, 1993a; see a similar proposal in a recent work: Bongard and Levin, 2022). The share of the functional aspect in a meron can vary, but without it, a meron is reduced to a mosaic of non-interacting individual elements like those observed in physical systems (Lyubarsky, 1993b). Recalling the structures from the beginning of section 2.1., it can be said that *traits* correspond to units of structures like those presented in Fig.2A, whereas *merons* correspond to units of structures like those shown in Fig.2B.

It can be appreciated that merons are essentially similar to the functional units through which Aristotle pursued the description of living organisms (Fig.3 from section 2.1). In this representation, important are not the borders between objects or classes of objects (the segmented 'taxonomy'), but *objects themselves*, their *content*. In this way, reality is comprehended not through the imposition of preconceived schemes, but by capturing essential links between objects (Lyubarsky, 1996). And, unlike in the case of taxonomic units, non-intersectability between classes of objects in a meronomic description is determined in regard to one specific property (section 2.1.1), making such classes mutually-exclusive. Concepts, analogous to the concept of *meron*, are *anatomical constructions* (Boker, 1936), *functional components* (Klaauw, 1948), *dynamical patterning modules* (Benítez et al., 2018), *blocks* (Hartwell et al., 1999).

In a previous work we provided an example of organizational analysis that involved the concept of meron, when comparing plants and colonies of hydroid polyps (Pérez Koldenkova and Hatsugai, 2018): from the functional point of view, polyps' stolons are equivalent to plant internodes (both are "transporting" structures), whereas individual polyps were considered functional equivalents of plants' leaves ("feeding" structures). We proposed also that functional similarity expands to the 'biochemical' level: both plants and polyp colonies display propagating reactive oxygen species (ROS) signals, although in plants they are produced by proteins of the RBOH family, whereas in polyp colonies ROS are produced by mitochondria located at the polyp-stolon interface (Pérez Koldenkova and Hatsugai, 2018). Therefore, for the 'biochemical level' a protein with a specific function can be seen as a trait, a 'taxonomic feature', whereas a meron is rather a functional unit to which that protein belongs; a moonlighting protein can be seen as a protein involved in several functional units. For the 'organismic' level, Beklemishev distinguished the following major functional units: integrative, distributional, homeostatic, reproductive, covering, and musculoskeletal apparatuses (Beklemishev, 1994).

Merons are organized hierarchically, reflecting the hierarchy of functions, as is during their functioning that merons integrate into a wholistic organism (Lyubarsky, 2018). A meron carries an associated morphological trait (a 'measurable'), but this one does not necessarily evidence the role of the meron in the whole, and this is especially true at the 'biochemical' level of organization. For example, both plants and animals carry out orthologs of the Ca^{2+} permeable TPC channel, however their function in both lineages is still debated in spite numerous studies about the regulation of the activity of these channels (She et al., 2022).

Despite their multifunctionality, merons at the 'organismic' level of organization have a relatively constant shape (for example, a paw can be used to run, jump, swim, hold a prey—i.e., participate in feeding, etc.). Conversely, at the 'biochemical' level of organization merons are 'dissociatable' as their elements ('measurables' of the 'biochemical' level) associate into temporal functional blocks, and these 'measurables' can then recombine to perform different functions. Unlike merons of the 'organismic' level of organization, merons of the 'biochemical' level are dynamic in their composition. Multifunctionality of merons is, in this case, attained through the recombination of the elements composing them. Such organization allows reducing the number of required elements *per* performed functions (different functions can be performed with different combinations of a same set of 'measurables'; Hartwell et al., 1999). It also allows establishing links or correlations between functions: modification of the activity of a particular 'measurable' element is reflected on all the functions carried out by those merons of which such a 'measurable' forms part. In this way, merons —through the pleiotropic action of their components — integrate all elements into a wholistic organism (Hartwell et al., 1999).

The elaboration of these conceptual tools took place in 'organismic'-level disciplines (Meyen, Schreider, 1976; Meyen, 1977, 1978, 1984; Lyubarsky, 1996), hence, this is probably the reason why the objects chosen to study the whole-part relationship belonged to the 'organismic' level or organization. Organisms' wholistic organization (integrity) and their high degree of differentiation probably aided this election.

In a previous work, we proposed an organization of functional ranks for the 'biochemical' level (Panina et al., 2020; Fig.4). According to his hierarchy, **programs** are minimal functional units performed by a particular protein arrangement. However, part of these proteins can recombine and partner with other proteins to participate in the execution of a different function—a different program. It is possible that a hierarchy of programs can exist to perform hierarchically-organized functions, involving a common core of molecular actors. In such case a cell would functionally correspond to a set of such partially overlapping hierarchical functions, being the core conformed by highly conserved “hub” proteins. **Functional blocks**, in turn, are related to mutually-exclusive macroscopic functions (perceptible ‘anchors’ to describe to hierarchy of functions). The organization of functional blocks might not be very obvious, as we showed in our analysis of Ca^{2+} signaling (Panina et al., 2020). In our work we proposed the existence of two major cellular-level Ca^{2+}-related functional blocks: *migration-chemotaxis* and *proliferation-quiescence*-based, identification of which was key in the further analysis of Ca^{2+} signaling in multicellular organisms. For the case of Ca^{2+} signaling, we proposed that each of these two functional blocks includes more than one program, however, there might be cases when a functional block includes a single program. An overly similar classifications of functions were proposed previously (Karling, 1963; Mamkaev, 1987; Hartwell et al., 1999).

The above organization sets a division of living organisms different from traditional ‘measurable’-based ‘-omics’ approaches. Current biology aims at isolating and compiling individual traits, and examples of this tendency are multiple algorithms of segmentation developed for the analysis of microscopy images, the problem of individuality in the analysis of colonial, multicellular or social organisms, or the way in which the microbiome is approached in the case of holobionts.

Another feature of the organization of living systems can be appreciated in their comparison with scale-free networks (Barabási and Albert, 1999). The overall structure of living systems presented above resembles the hierarchical block organization of scale-free networks proposed in Ravasz et al., 2002, with an important addition related to the time-dependent dynamics: functional blocks must be mutually-exclusive, meaning that they cannot be executed simultaneously (e.g., a cell cannot migrate and divide at the same time, Panina et al., 2020).

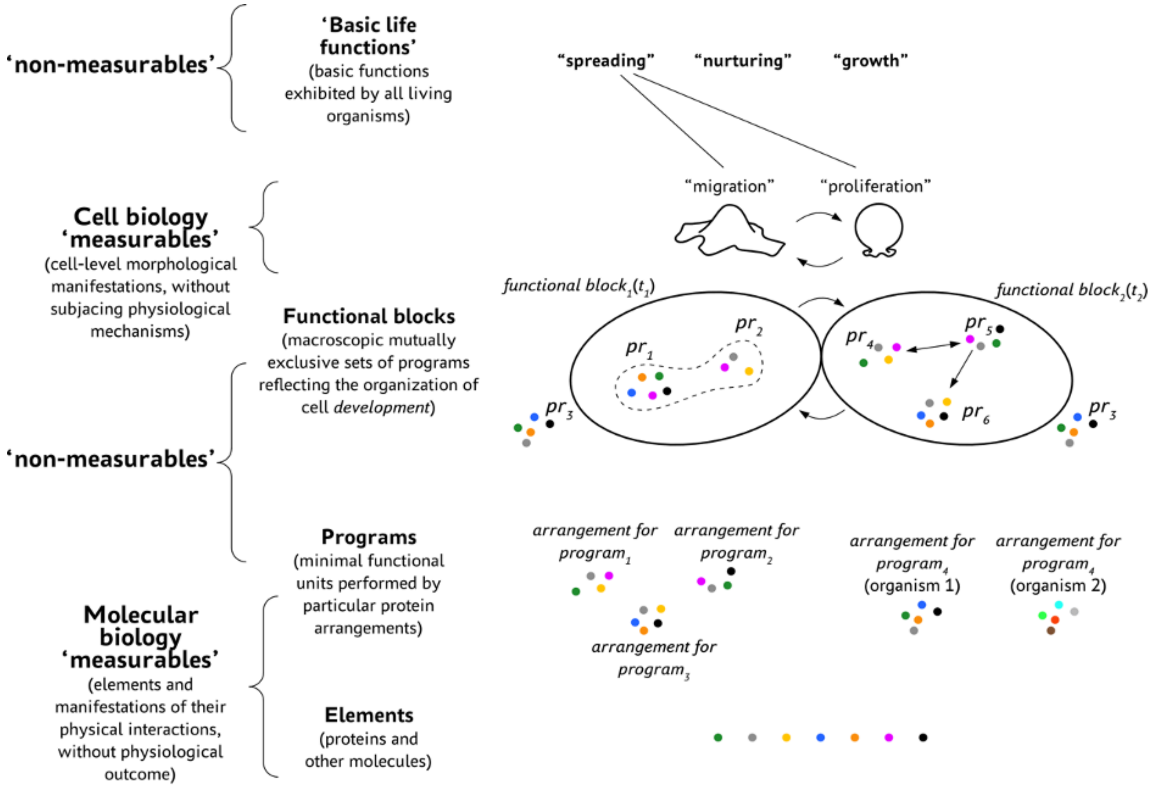


Fig.4. Schematic representation of the relationship between tangible (‘measurable’) elements and their intangible relationships in living organisms at different levels of organization.

Right: graphical representation of ‘measurables’ at different levels of organization of living organisms and of their possible intangible time-dependent relationships (as a hierarchy of functions). Examples of ‘measurables’ and their relationships are provided on the left. The scheme was elaborated for the particular case of functions of Ca^{2+} signaling (Panina et al., 2020), yet it may also apply for other functional hierarchies.

If a total or general interaction map (a scale-free network) is generated for such mutually-exclusive functional blocks we will obtain that their elements might be linked. However, inclusion of time as a variable will clearly separate task-dependent topologies, potentially resulting in some elements that never interact in a direct form because of temporal separation (a similar conclusion is presented in Hartwell et al., 1999). Therefore, there potentially exists a third functional rank, more general than programs and functional blocks, that comprises mutually-exclusive task-dependent functional blocks (as ‘basic functions of life’; for the case of Ca^{2+} signaling, such macro-function comprising both migration and proliferation could be denominated “spreading”). More generally, it is possible that living organisms’ organizations differ by their degree of “scale-freeness” or by an opposite characteristic—“self-interconnectedness" (integrity). For instance, it can be said that animals possess a higher degree of self-interconnectedness than plants do.

Above we described the structural (*static*) organization of living systems. However, these structures also display dynamics properties, the most interesting of which is perhaps the ability to display 'emergence', analyzed below.

2.2.2. Crossing the gap between levels of organization: when "more is better" meets "less is more"

> Philosophy is the most suitable math for the non-formalizable
> The end point of rationality is to demonstrate the limits of rationality.
> Blaise Pascal

> We are constantly deciding how much information is enough.... We need, of course, to do more with information than simply gather it. We need to arrange it into an overall picture, a model of the reality we are dealing with. Formless collections of data about random aspects of a situation merely add to the situation's impenetrability and are no aid to decision making. We need a cohesive picture that lets us determine what is important and what unimportant, what belongs together and what does not—in short, that tells us what our information ***means***. This kind of "structural knowledge" will allow us to find order in apparent chaos.
>
> Dörner D. (1997) The Logic of Failure: Recognizing and Avoiding Error in Complex Situations.

Epigraph to section 2 suggests that an exhaustive analysis of the elements of an organism is not enough to infer how the corresponding upper level of a system will look like. In other words, such analysis seems not sufficient to understand *how complexification occurs*. We could notice, however, that a similar bottom-up transition —in the form of generalization— was presented by Pólya, although for objects of a different nature—mathematical problems (Pólya, 1954; 1968). Here it is important to remember that scientific change (as *reasoning* or *learning*) has been frequently equated to evolution (and, as a particular case, learning has been equated to generalization—the attainment of a higher-level "taxon of cognition") (Wilson, 1990; Abraham, 2005; Sipser, 2006; Renzi et al., 2011; Chastain et al., 2014; Watson et al., 2014; Kouvaris et al., 2016; Watson et al., 2016; Pavlinov, 2018; Brun-Usan et al., 2020; Vanchurin et al., 2022).

In section 2.1. we presented an example of reasoning that goes in this, ‘top’, direction—the Aristotelian-like inductive reasoning. On this analogy we will examine how is crossed the gap between details and concepts (between *levels of organization*).

*

In 1960, in his famous lecture, Eugene Wigner noticed the unreasonable effectiveness of mathematics in natural sciences (Wigner, 1960): “mathematical concepts turn up in entirely unexpected connections. Moreover, they often permit an unexpectedly close and accurate description of the phenomena in these connections” that even allows predicting phenomena. The reason of such effectiveness has since then remained a major open question. However, instead of assigning hidden properties to mathematics, it is more correct to consider that complexity arisal in a system is possible if its higher complexity level complies with the mathematical regularities that may pertain to that level[2]. The attainment of a higher complexity level itself depends on the nature of the system (its Aristotelian ‘activity’ or ‘agency’, very roughly—the set of properties such system can display). The possible transition types depend on the nature of the system (e.g., a physical system composed of non-interacting particles, a physical system composed of interacting units, an intangible system like thought, etc.), that determines the type of ‘activity’ it can display.

Together, the ‘activity’/agency of the system experiencing complexification and the mathematical rules reigning at each of the levels of its organization play the role of “guiding constraints” or channels that were proposed to guide development (Waddington, 1942). As Wigner himself noticed: “the great mathematician fully, almost ruthlessly, exploits the domain *of permissible reasoning* [guiding] *and skirts the impermissible* [constraint]”—*in reasoning* (our emphasis and additions—*VPK*, *GYuL*). Hence, the more diverse is the nature of lower level of organization (=the more diverse are its elements), the larger (and therefore—more diverse and less predictable) can result the “landscape of potency”. Mathematics turns useful only for the formal description of those rules that may pertain to each level of organization of a system, although it is not able to describe the transition itself. Even if mathematics constitutes a “universal taxonomic system” that allows describing any biological process (implying that all fields of mathematics are mutually linked and can be derived from each other), is *the nature of the object* what determines which particular fields of mathematics it will obey and it will be described by. Hence, if the behavior of two objects is described by similar mathematical rules, then probably their *essences* are also similar. Within a world described only through mathematics —without an appeal to the nature of the objects mathematics acts on— Wigner’s mystery has no explanation. And in many cases biological objects are able to change their nature: from “particle”-like in flock motion to highly divergent natures in individual behavior.

How the transition between complexity levels is identified? In regard to mathematical problems, Pólya says: “[...] some experience in solving problems may teach us that many problems together may be easier to solve than just one of them—if the many problems are well coordinated, and the one problem by itself is isolated. Our original problem appears now as one in an array of unsolved problems. But the point is that all these unsolved problems form an array: they are well disposed, grouped together, in close analogy with each other and with few problems solved already. If we compare the present position of our question, well inserted in an array of analogous questions, with its original position, as it was completely isolated, we are naturally inclined to believe that some progress has been made” (Pólya, 1954). This is also the key point of the so-called *inventor’s paradox*, which states, somewhat against our intuition, that solving a general problem might be easier than solving a particular one.

We can notice that these operations are essentially similar to *classification* in classic systematics (presented in previous section). In all these cases lower-level elements are characterized by a sufficient degree of similarity, consistency in the combinations of their features and specificity of such combinations—characteristics that make possible their classification, leading to the formulation of a more general concept comprising them. Such elements, that pass unnoticeable if we take isolated objects exhibiting them, begin to stand out from the whole structure of the object’s organization if *an array* of objects carrying such elements is taken. In this case, a *pattern* of elements turns noticeable (Dörner [Dörner, 1997] called it supersignal—a result of the collapse of multiple features into one). The *pattern*—the upper, more general level of organization becomes determined by the action of guiding constraints on lower-level elements. The appearance of the *pattern* denotes the transition (Fig.5).

We use the word *pattern*, but leaving apart the tint of rigidity associated with this term, as a *pattern* emerges from the units of the functional architecture, merons, that can be compared with counterparts from another organism or from a different context of the same organism, and therefore can include the associated functional dynamics. Even if we are interested in a particular compound, the *pattern* will be defined by the corresponding ‘biochemical’ meron—the functional unit such compound is part of, i.e.—by the structural organization of the molecular pathway containing that compound, the relationship of the analyzed compound with others in the pathway(s) it is involved in, and the dynamics of such relationships. All these features allow defining the degree of functional similarity between instances of a similar compound in different organisms or in different contexts within the same organism. For example, we previously showcased that proteins of the Retinoblastoma family have remained conserved across plants and animals, but as part of functional complexes (the *pattern*) also characterized by a high degree of functional conservancy (Zluhan et al., 2020).

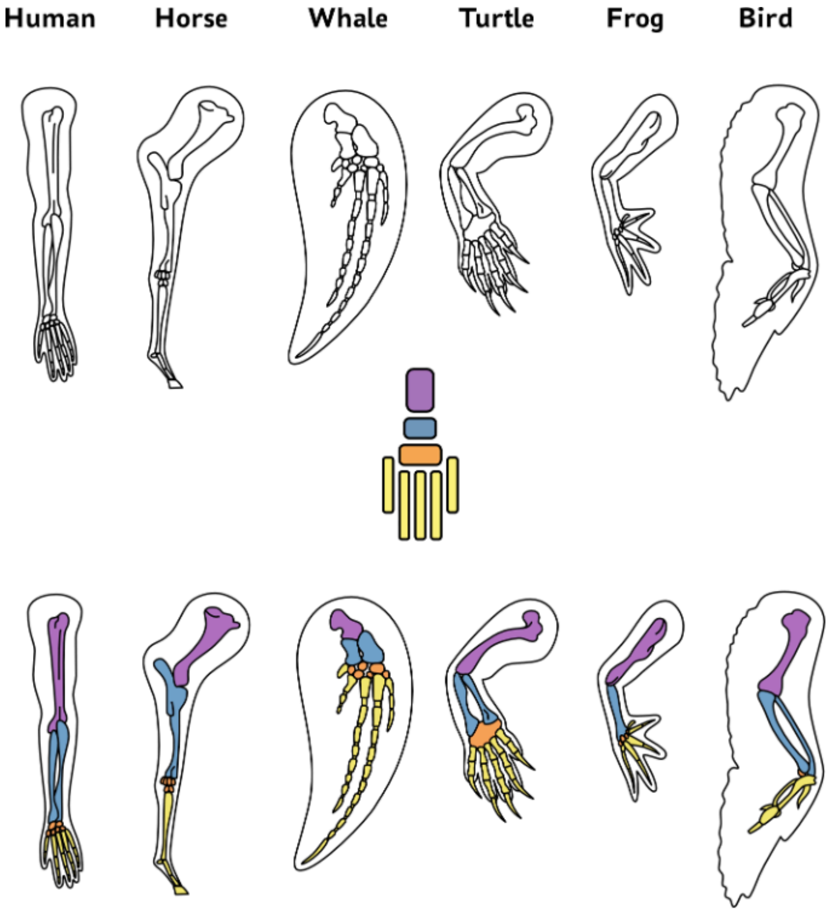


Fig.5. The emergence of a *pattern* as a classification procedure (on the example of the elements of the limbs of different organisms), and the meronomic hierarchy.

The composition of the “array of elements” (in this case—bones of limbs, top) allows identifying a general pattern (middle) using which the correspondence between individual elements can be established back into the analyzed organisms (bottom, in color). The correspondence between individual elements is established by using criteria of homology. A higher-level meron (in this case—the whole limb) serves as an archetype for a meron of a lower level (each of the bone elements depicted in color).

Briefly exploring the obtained system, we can observe that the higher the number and the diversity of elements at the lower level of organization, the higher is the possibility that a *pattern* of their interactions can emerge (being determinant for the possible evolutionary trajectories of an organism; Galliot and Miller, 2000; Hochberg et al., 2020). In this case, an expansion occurs of the "landscape of potency" within which a system can be realized. An example of similar reasoning is the proposal that the Last Eukaryotic Common Ancestor (LECA) was a population, and not some particular individual (O′Malley et al., 2019). The diversity of lower-level elements may result not from a direct increase of their number, but from the diversification of their functions. As a possible supporting example, multicellularity appears to be associated with the action of intrinsically disordered proteins (Kulkarni et al., 2022) that lack a specific conformation, favoring their engagement in different protein-protein interactions.

Nevertheless, it seems that a too broad diversity of elements can also *impede* complexity arisal, presumably as a result of excessive interactions between them (see a similar observation in Wang and Barabási, 2021). This situation, in systematics, can be alikened to the increase of the number of ranks: if the number of ranks becomes close to that of taxa, it is not possible to conduct a generalization and to attain a reduction of the description. This might explain at least some cases when gene loss (or anatomical structures loss—at the 'organismic' level, McShea, 2021) was found to accompany complexity increase during evolution (Albalat and Cañestro, 2016; Guijarro-Clarke et al., 2020; Fernández and Gabaldón, 2020; Fernández-Roldán et al., 2021). Therefore, organisms apparently favor a balance between integration of multiple functions ('reduction'; e.g., protein moonlighting, Jeffery, 2020; Singh and Bhalla, 2020) and redundancy ('excessiveness') that confers robustness to these processes with the benefit of energy spending minimization. The 'range' of this balance may determine the plasticity organisms can display in their evolutionary process.

There is a necessary clarification regarding our usage of the term **complexification** (or **complexity increase**). This term bears tints of absoluteness and unidirectionality, but there are situations that at first glance contradict such intuitively perceived meaning. An example of such case is *degeneration*. To avoid a possible dissonance between the term used (*complexification*) and the phenomenon described (*degeneration*), in the present work we use the term complexification in a *relative* sense. Thus, in our case complexification is the attainment —by a given structure— of the most complex state of those possible *in its own* environment, in other words—its attainment of the deepest possible degree of differentiation. In this way, we can talk about complexification as a "deploying" process even in cases like degeneration. In the present work we use the term "complexification" keeping this connotation in mind. We should note that following this interpretation the term "complexity" —when used to compare two or more systems—lacks some special meaning. This interpretation coincides with those views that consider that the hierarchy of logical possibilities of a system is determined in a top-down manner—from the whole down to its parts. This means that, at each stage of development, the biosphere determines the boundaries within which ecosystems can exist, and is within these boundaries that parts can have their potency realized. Hence, complexification appears *not* as a bottom-up self-organization of the whole from its elements, but as the opposite process of the realization of the whole through the delimitation (*differentiation*) of its parts. As it was shown in section 2.1, these whole-parts relationships differ in their conceptions of the limits of the elements composing the whole: self-organization is for parts that can be isolated through segmentation, whereas differentiation enhances their mutual dependence within the whole, making any delimitation dependent on the goal of such delimiting (section 2.2.1).

The relationship between the *pattern* and taxonomic traits used in systematics (section 2.2.1.) is not trivial: traits used to classify organisms do not necessarily correspond to those that drive their evolution (=those that make the *pattern*). For example, we can search for similarities in oxygen-gathering breathing systems (oxygen should *be captured, be distributed,* and *be used*), but the actual taxonomic traits that perform similar functions can strongly differ (e.g., lungs, gills, skin, etc.). Nevertheless, we can identify *functional* similarities between functional blocks: in all cases there are merons-gatherers, merons-distributors, and merons-users. Each of these structure types can be *functionally* compared (structural elements, architecture, turnover rates, etc.). We use systematics as a toolset to identify the traits that can conform a more general category. However, this methodological toolset is applied not to taxonomic traits ('Platonic' traits), but to *functional* ('Aristotelian') traits. The mismatch mentioned above is reversible: if a taxon is affixed, it will not be possible to say whether those merons that compose it can be found in other taxa as well. This merono-taxonomical inequivalence is called "the biological uncertainty principle" (Meyen, 1984).

We used bottom-up inductive inference as an example to analyze how complexification is attained. However, there is an important difference in the directions of bottom-up inductive inference and biological evolution. Whereas inductive inference is top-directed, from elements toward general concepts or Aristotelian *genii*, evolution advances from more general forms toward more specialized ones (in reasoning such change corresponds to a deductive top-down direction, parting from general concepts). Nevertheless, this general evolutionary process is typically accompanied by the complexification of particular living forms (a similar view was expressed in Zavarzin, 2006)—a top-directed process co-directed with generalization in reasoning. Therefore, inductive inference can be used as an analogy to analyze how biological complexity arises. Still, in evolution this process can occur only through material individuals, and not through their arrays or conceptual groups. How this can take place, has been proposed, for example, by Kouvaris et al., 2017. In the present work we will skip the analysis of the mechanisms of biological complexification.

2.3. Comparison as a strategy to infer the general role of an element in a whole

In sections 2.2.1 and 2.2.2 we analyzed the structural composition of living organisms, and how this composition changes over time. In this setup, lower-level elements (*species*) give rise through complexification to the upper organizational level (the emerging *pattern*) that corresponds to the gradually realizing Aristotelian *genus*.

According to Thomas Aquinas, a *species* originates from the *genus* through the addition of *differentia specifica*—the specifying difference or details distinguishing it from other species that belong to the same *genus*. Using this configuration, the *genus* —the upper level of organization— can be obtained following a reverse operation, by generalization of aspects common for lower-level elements and in abstraction from their particular differences. In this approach, comparison is carried out to identify possible variations of the *pattern* (realization of the *genus*) in different organisms. This requires recognizing the elements that conform the *pattern*, even if during evolution they arose on a different substrate or were subjected to modification. In other words, the aim of comparison is establishing the correspondence between the tectonic and the architectonic organization of the compared wholes (organisms).

Strategies to obtain such correspondence changed over time, as it was shown in section 2.1.1. The main concern, developed during the establishment of modern systematics and physicalistic disciplines, was the usage of *objective* criteria, free from the fuzziness and formalization hurdles associated with the subjectiveness of the concept of *similarity* (Lyubarsky, 1996). Current comparative approaches are strongly based on relatedness or kinship that are considered objective characteristics. However, similarity not always results from relatedness, and, conversely, structures with a same origin can play different functions in different organisms. In the present section the conceptual tools that allow overcoming these difficulties are analyzed.

2.3.1. The archetype—the 'meta' of the compared species-instances

In section 2.1.1. we analyzed how, over the course of centuries, the archetype —the Aristotelian *genus*—lost its strength. However, the logical concept that came in replacement, a genus *as the sum* of the elements composing it, was not able to display complexification. The archetype is neither a prototype, nor an ancestor, nor the sum of lower-level *species*. Then, what is it—the "landscape of potency" or the 'what is'?

The archetype is, as it was said, the Aristotelian *genus* for instances (observations, phenomena, experimental results, traits, particular 'molecular pathways', etc.). In Goethe's metaphor, the *Urpflanze* (the Plant Archetype) is a meta-plant, every part of which encompasses all possible variants of that part (a lower-level archetype of such plant part). Hence, an archetype can even encompass opposite characteristics (Lyubarsky, 1993a), and be formulated for essences as distant as plants and animals, making them comparable. The archetype can be compared to a set of axioms that includes all possible consequences (theorems and corollaries) that can be derived, even those yet to be discovered (Lyubarsky, 1996). By discovering the consequences, we, as a feedback, start better understanding the implications of the original set of axioms and their genuine depth. Analogs of the archetype concept in classical genetics emerges when accounting for allele penetrance and expresiveness, in populational genetics—when considering the norm of reaction, and an archetype's analog in morphogenesis is the concept of system of creods that make up the morphogenetic landscape.

The concept of archetype is closely related to systematics, however in *modern* systematics the archetype is typically not formalized: a good systematist learns to recognize model objects by observing a large number of them, and even such practice does not guarantee they success (Lyubarsky, 1996). This is the type of knowledge physicians can gain during their practice ('experience'), and the one we referred to in the Introduction. The reason why the archetype is not used in contemporary studies is the loss of the tradition of work with this concept and the shift to trait-based descriptions, as it was shown in sections 2.1 and 2.2.

The metaphysical archetype relates to material levels of complexity as follows: an archetype is the upper organizational level for species-instances, and *is organized* in the same way as those material objects and phenomena it comprises, including their dynamics (metamorphoses) and possible differences. Hence, in everyday life the higher organizational level typically has the same nature as the lower-level elements, e.g., material 'measurables' of the 'biochemical' level make a material 'organismic' level of organization.

Thus, the ‘organismic’ level of organization represents the gradually realizing potency of the archetype, that becomes embodied through complexification. Of note, the archetype differs from laws of physics: laws of physics denote cause-effect relationships between objects, not being interested in the nature of the objects to which such rules are applied or that result from their application.

Very much like living organisms (section 2.2.1), the archetype is composed of merons, which jointly conform the meronomic universe. In this universe, a meron of a higher level acts as an archetype for merons of a lower level (Fig.5; Meyen, 1973; 1978). Like in the case of organisms, the composition of an archetype is studied by tectology, and the integration of all merons into the outer archetype (the one elaborated *for a taxon*) is carried out by architectonics (section 2.2.1, Beklemishev, 1994). Also, like in the case of organisms, the division of the archetype into merons is goal-dependent.

It is important to note that the ‘organismic-level’ (‘outer’) archetype encompasses the elements of a taxon, but is at the same time constructed integer like an organism and can be divided into merons-parts. Of note, due to the high degree of integrity of organisms (the “self-interconnectedness” from section 2.2.1), the structure of a meron and its functional significance is primarily determined by the whole it belongs to, and not by some intrinsic features proper of the meron. Nevertheless, a meronomic representation in many cases reflects well the hierarchy of functions, unlike attempts to establish a taxonomic hierarchy of traits or anatomical features. Moreover, the discreteness of merons does not imply their disconnectedness: on the contrary, the higher the degree of differentiation of merons the stronger are the integrative forces tying them in the whole (Cuvier, 1800; Schmalhausen, 1982)—an aspect that, as we showed above, is not captured at all by scale-free representations.

If the ‘outer’ archetype includes the correlations between individual merons, ‘biochemical’-level archetypes (those formulated for merons) expand around the function(s) performed by merons. ‘Biochemical’ archetypes may include similar elements of ‘molecular pathways’ (which in this case correspond to *individualities/quirks*), but may also encompass a common function performed by different subjacing ‘molecular pathways’. For example, we showed previously that Ca^{2+} signaling is modified across kingdoms to preserve its general (“archetypic”) functions as orchestrator of cellular-level processes in multicellular organisms, despite the differences in the Ca^{2+} handling proteins responsible for Ca^{2+} signalization in plants and animals (Panina et al., 2020). As we showed from this analysis, the general role of Ca^{2+} signaling is not directly deducible from the analysis and comparison of individual elements composing the respective toolkits: certain degree of abstraction from their identities is required in order to make comparable the overall effect of Ca^{2+} signals in plants and animals. An example of a same ‘molecular pathway’ that plays contextually-opposite roles is the serotonergic system: in the dorsal and median raphe nuclei it is responsible for opposite responses to reward and aversive stimuli (Kawai et al., 2022). As the organization of an (‘outer’) archetype repeats that for a living organism, the organization of a biochemical archetype (for a ‘molecular pathway’) repeats that of programs-functional blocks (section 2.2.1; Fig.4). Such archetype includes as variants all the functions a pathway might be involved in, and the different contexts such pathway can be encountered in.

As a concept complementary to the archetype, we propose Bauplan to result from *averaging* of the two compared organisms. In this way, and unlike the *encompassing* archetype, the Bauplan reflects the invariant retained during evolutionary modifications. As in the case of the concepts of formal logic, which content decreases as their scope widens, the content of such a Bauplan is reduced as the taxonomic distance between the two compared organisms increases (Beklemishev, 1994). Thus for example, a common Bauplan for a plant and an animal will convey only a common core of highly conserved molecular pathways, with almost no coinciding morphological features. Such “phenotype averaging” is what better reflects the meaning of a Bauplan as the Woodger’s homologous structural plan subjected to evolutionary transformations (Woodger, 1945).

2.3.2. Homologies—the species-instances of the archetype

The most important conceptual change in the term *homology* since 1846 was the shift of its meaning from ‘similarities between compared archetypes’ (Owen, 1846; 1848; Boyden, 1943) to ‘methodologically-relevant traits to establish phylogenetic relationships’ (see Mamkaev, 2012). This shift has seemingly been propitiated by the conception of the passive determination of the phenotype by the genotype, and the alleged dissociability of the evolution of these two levels of organization (e.g., see Scotland, 2011; DiFrisco and Jaeger, 2021), propitiating their segregation to which we made reference in the Introduction.

Another source of discrepancy and fuzziness around the term homology is related to the term *analogy*. According to Owen, an *analog* is “a part or organ in one animal which has the same function as another part or organ in a different animal” whereas a *homolog* is “the same organ in different animals under every variety of form and function” (Owen, 1843). However, as noted by Boyden (Boyden, 1973), this definition does not provide criteria to distinguish homologies and further elaboration on these two terms led to their exchangeable usage.

Hence, most *current* notions of homology are a compromise between theory and past usage of the term (de Pinna, 1991), in which even the object of the definition is not strictly set (Ghiselin, 1976; Brigandt, 2002). Nevertheless, most current concepts of homology (proposed within phylogenetics, embryology, and phenetics) involve considerations of structure and inheritance (reproducibility responsible for a sort of phylogenetic or ontogenetic “memory”; Brigandt, 2002).

By contrast, our archetype-related concept of homology makes emphasis on the “scheme” of the object: on its parts, on parts of parts, on their correlations within and across levels, all this—in their spatial and temporal dynamics and variations. More specifically, in the archetype-based framework, lower-level elements —through guiding-constraints— conform the upper-level *pattern* (see section 2.2.2), and similarities found in the *patterns* of the two compared systems constitute homologies. Homology, thus, is reflected in that elements of a non-necessarily same nature can give rise to a similar (homologous) *pattern*. This homology (sameness) does not rely only on the kinship between the subjacent elements of the compared systems, and is *ahistorical*, (DiFrisco and Jaeger, 2021). A peculiarity of such archetypic homology is that it implicitly allows complexification. Thus, a first-time appearance of a *pattern* of a novel kind can be referred to as a *novelty*, and further reappearances of this *pattern* (even if based on different elements) would constitute its *homologs* (see further elaboration on the relationship between novelties and homologies in McKenna et al., 2021).

Hence, homology implies invariance. However, most current attempts to define homology look for some inner property of this feature to rely on (making such definitions circular; Brigandt, 2002), whereas the archetype-based homology concept is born implicitly considering the system’s organization (similar views, within a different homology framework, were exposed by Brigandt; Brigandt, 2009, p.84).

It can be observed that both these homology concepts (the conventional and the archetypic ones) converge when the inclusive archetype coincides with the averaging Bauplan (in the meaning presented in previous section). The higher the taxonomic distance between the compared organisms (and the lower the number of common morphological-structural traits) the higher is the possibility that only *functional* homologies can be established (Fig.6). It can be said, that in the case of Bauplan-homologies the two compared organisms share a common form-function factor (similar forms perform similar functions). However, in the case of archetype-homologies *function* appears as a wider criterion, that describes homologies better than structures. It can be added that Bauplan-homologies may or may not share common structural ancestry (see Brigandt, 2009 and Ereshefsky, 2012 and references therein). Thus, as indicated at the beginning of this section, homology does not always allow establishing ancestry, but rather propitiates the formulation of questions about the causes of the arisal of similarities.

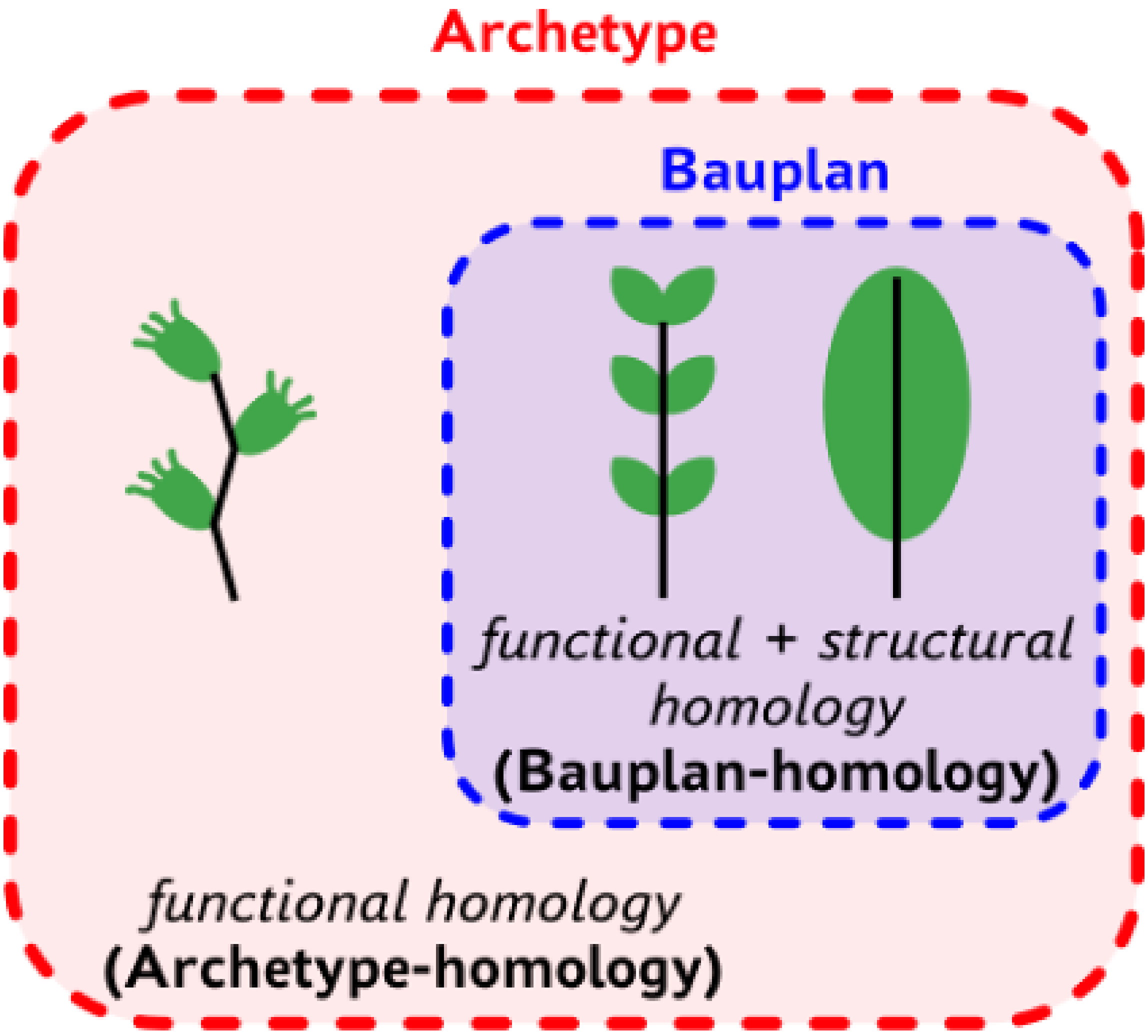


Fig.6. Relationship between the proposed concepts of archetype and Bauplan.

According to the proposed classification, a common Bauplan implies functional and structural homology (Bauplan-homologies), whereas an archetype implies functional homology (archetype-homology). Characters of the Bauplan (and the archetype of the corresponding level) may or may not share a common ancestry. Currently, as homologous are considered Bauplan-related traitsthat share a common ancestry. Example of a Bauplan-homology: homology between leaves of two plants. Example of an archetype-homology: homology between a plant leaf and a feeding structure of a polyp colony (nutrients are obtained in the periphery of the organism and distributed through a branched structure). Archetype-homologies have a limited, researcher-set scope (for example, no archetype-homology can be established between the particular nutrient compositions distributed by the feeding structures of polyps and plants).

In the previous paragraph is described only one case of the possible variations that can be observed within organisms. An orthogonal example is the case of the so-called dissimilar homologies, for example, the transformation of the reptiles' jaw joint into the mammals' inner ossicle (DiFrisco and Jaeger, 2021), in which the structural base of the homology is preserved, but instead the function of such structure drastically changes. This example constitutes an undoubted example of *current* (structural- and inheritance-based) homology, however, if the focus of a study is on the mechanisms of sound perception, the archetype-homolog of mammals' inner ossicle would be the structure formed by the columella and extracolumella in reptiles (if we turn to evolutionary relationships, the homolog of the reptile's columella is the mammallian's stapes, which is only a part of the ossicle-based sound transduction mechanism). It can be appreciated that the number and type of possible archetype-homologies can widely vary and hence we opt for presenting the general principle through which they can be understood, rather than providing disparate examples that can be explained through this concept of homology.

At the 'biochemical' level, archetype-homologs of a 'molecular pathway' are all the instances of this last that can be found either in different contexts within the same organism (including instances resulting from the expression of paralogous genes, but also those that result from variations in expression levels or activities of pathway's components, like the differences observed in the insulin pathway in the different casts of the *Harpegnathos saltator* ants, Yan et al., 2022), or in different organisms (for example, the co-option of a conserved regulatory module composed of the genes *vestigial*, *scalloped* and *wingless*, involved in the development of crustacean carapace and insect wings, Shiga et al., 2017; see also Clark-Hatchel and Tomoyasu, 2020). As in the case of the orthogonal example presented above, as archetype-homologs can also be considered instances of a molecular pathways which function changed during evolution, deviating from some typical function of most instances of such pathway.

Within the archetypic conception there is no strict difference between homology and analogy. Thus, for example, two similar processes-functions that have different underlying mechanisms can be considered analogous if the focus of interest is on the underlying mechanisms of functions, but in abstraction from subjacent mechanisms these functions can be considered homologous. We presented an example of such case in our analysis of Ca^{2+} signaling in plants and animals: in abstraction from their mechanisms of generation, Ca^{2+} signals themselves play a *homologous* function in the regulation of cellular-level processes in both plant and animals (we used such abstraction to infer a general role of Ca^{2+} signaling as an orchestrator of developmental processes in multicellular organisms). However, if we address *the* Ca^{2+} *signaling toolkits* responsible for evoking these signals in plants and animals, they will appear as drastically different (Panina et al., 2020), rather making *analogous* the Ca^{2+} signaling pathways of these two clades. Another example is deep homology, when the emergence of structures traditionally considered analogous —like insects' and birds' wings— depend on the activity of regulatory genes belonging to a same family (e.g., MADS gene regulators) potentially allowing the analogization of such structures (Pavlinov, 2011). In this way, in the archetypic conception, analogies are similarities, that rely on the researcher's perspective (see Bongard and Levin, 2022 advocating for the possibility of this type of analysis).

The concept of homology implies 1) the divisibility of a whole (of an organism or an archetype) into parts, 2) the existence of certain relationship between different parts of a same whole, and 3) between similar parts belonging to different wholes, being such wholes related to each other as parts of a whole of a higher level (Owen, 1848; Pavlinov, 2018). Thus, —as it happens in the case of archetypes— homologies are organized into hierarchical levels.

At different levels (molecules, parts of cells, cell types, tissues, developmental processes, large morphological structures, functional relationships, behaviors), homologies can appear as partially independent and even as contradicting homologies at other organizational levels (Brigandt, 2003; 2007, 2016; Assis, Brigandt, 2009). In some occasions it has been claimed that homologies at the DNA level are non-hierarchical, i.e., that homology can be established through direct comparison of the sequence of DNA fragments. Such statements imply a direct genotype-phenotype correspondence, which has been observed in some cases. For example, the sequence of activation of regulatory genes to some degree resembles the order in which groups of different taxonomic ranks appeared during evolution (Davidson and Erwin, 2006; Erwin and Davidson, 2009; Peter and Davidson, 2011; Lyubarsky, 2018; Pavlinov, 2018). Nevertheless, in many other cases such direct genotype-phenotype correspondence cannot be established, and moreover, examples exist directly contradicting such possibility. For example, the development of the chordate anterior-posterior axis in the urochordate *Oikopleura dioica* does not involve the retinoic acid signaling pathway, which was previously thought to be an indispensable innovation for the origination of the chordate body plan (Cañestro and Postlethwait, 2007). Similarly, this same organism lacks proteins of the Bcl-2 family, responsible for intrinsic apoptosis in most metazoans (Suraweera et al., 2022). de Beer stated: "[...] characters controlled by identical genes are not necessarily homologous. [Conversely,] homologous structures need not be controlled by identical genes, and homology of phenotypes does not imply similarity of genotypes" (de Beer, 1971, p.15). The same situation can be observed if we try to establish the correspondence of higher levels of organization with the phenotype: “we find not only that the same embryonic material can produce completely different things, but also that different material can produce the same organ” (von Bertalanffy, 1975, p.93). The same observations have recently been made for cell types (Rusin, 2022). These situations resulted in attempts to expand the concept of homology to reconcile possible variants of homology origination with the resulting structures (Pavlinov, 2018). Nevertheless, it should be noted that homologation through every of the above-mentioned levels might be possible for the case of Bauplan-homologies, i.e., when compared organisms share common form-function factors (see above).

In the archetypic conception, archetype-homologies are themselves archetypes for lower-level homologies. Thus, for the Goethean Urfplanze (the ‘outer’ archetype), the different leaf types (=leaves homologs) are instances of the leaf’s archetype, roots homologs are instances of the root’s archetype, etc. Similar reasoning can be applied to the organization of archetype-homologies at the ‘biochemical’ level of organization, where the instances are the *individualities/quirks*.

Within the archetype-based framework, homologies refer to possible relationship types between parts within the wider framework of whole-part relationship (being the archetype the whole) (Boyden, 1973). Thus, an archetype-homology can be established only between parts within architectures —between merons— but not between isolated parts (Beklemishev, 1994). The work of Aristotle, Theofrastus, Geoffroy Saint-Hilaire, Georges Cuvier, Johann Wolfgang von Goethe, Lorenz Oken, Richard Owen and others resulted in the formulation of the concept of homologous parts as a way 1) to compare body plans and establish whether they are variants of a same more general body plan, or are entirely different (general homology), 2) in regard to parts of two wholes—to be able to compare them and establish whether they are variants of a same part or not (particular homology), 3) in regard to parts of a same whole—to be able to compare different organs within such a whole to establish whether they correspond to repetitions of a same part, or are completely non-related (serial homology). These criteria were resumed in the work of Adolf Remane (Remane, 1954).

For the ‘organismic’ level, and more generally—for Bauplan-homologies, these criteria are primarily aimed at establishing the similarity between *physical* parts. For the ‘biochemical’ level, archetype-homologies by necessity make reference to *functions* and only in second place—to the elements underlying them. Hence, *homologous functions* are carried by a similar underlying set of elements (similar toolsets performing similar **programs**—see section 2.2.1), whereas in the case of *analogous functions* such toolsets differ, as we showed above for the case of Ca^{2+} signaling in plants and animals (Panina et al., 2020). In a functional description, the different functions constitute the different ranks.

Summing what was said above about analogies to the description of criteria of homology, it can be said that analogies are those similarities which are identified in addition to those that we identify directly. These additional similarities are perspective-dependent, making the concept of analogy relative (in regard to the researcher's reasoning).

Currently it is attempted to combine the phylogenetic and ontogenetic conceptions of homology as different aspects of process-homology. In this view, phylogeneses are viewed as evolution of ontogeneses (epigenetic programs), in which stably repeating trajectories of development correspond to process-homologies (Pavlinov, 2018) or dynamical archetypes (phylocreods; Waddington, 1962). Within this framework, the main attention is placed on the historical relationship existing between the evolution of genetic regulatory mechanisms of development and the definitive morphological structures (Pavlinov, 2018; Hall, 1992, 1994, 1995, 1996). It is considered that this relationship can be revealed by analyzing 1) the causes of structural similarity during ontogenesis, 2) the constrains that maintain the structural similarity in the course of phylogenesis, 3) the evolutionary factors that induce the appearance of developmentally individualized structures (Shubin, 1994; Pavlinov, 2018).

In the archetypic conception, the origin of homologies is relevant as well, but the central question in this case is "why do (archetype-) homologies appear in different organisms?" It has been proposed 1) that evolution follows certain morphological regularities, that can be understood only through the analysis of different groups and their phylogeneses, and 2) that the environment can impose similar forming restrictions on organisms (Mamkaev, 1983). Among those researchers that applied this reasoning in their work were Alexey A. Zawarzin (1886-1945; who applied this analysis to the evolution of tissues), Nikolay I. Vavilov (1887-1943; who applied this analysis to the evolution of higher plants, letting him the possibility to formulate the law of homologous series in variation), and Valentin A. Dogel' (1882-1955; who followed this approach in comparative anatomy of invertebrates). Yury Mamkaev (Mamkaev, 1983) proposed that in all these cases emerging analogies (=archetype-homologies) result from common principles of organization of the cells of eukaryotes, and the exposure of organisms or their parts to same forming conditions. It can also be proposed that during evolution individual elements in many cases don't change independently, but as part of the blocks they belong to. In this case the elements intrinsically carry information about their origin, and can be preserved when the organism is modified, constituting an uninterrupted flow of information (Wood, 1994). "The relationships between an organism and its environment, or the relationships of its constituting parts can be considered as a limited number of morphofunctional tasks. The number of such 'engineering' tasks is limited, and they appear again and again in different groups of organisms. The number of possible solutions is also limited and defined by the nature of the eukaryotic cell and its principles of organization, common for a large number of eukaryotic organisms. [...] Speaking generally, all the variants that can be possible on this constructive base are realized" (Mamkaev, 1983). A very recent example of such 'replicated radiation' driven by ecological adaptations in plants of the *Oreinotinus* lineage was presented in the work of Donoghue and coworkers (Donoghue et al., 2022). According to Valentin A. Dogel' (1920-1951), comparison of such series of independently acquired similarities should allow identifying the forming influence of the environment "in a pure form", without the influence of hereditary conditioning (Mamkaev, 2012). Two factors were postulated by Dogel' to underlie the independently acquired similarity: 1) a same mechanism of functioning, 2) a same morphological substrate. By separating morphofunctional systems into simple apparata, it can be observed that on the same morphofunctional base only few apparata can develop that perform similar functions. This leads to highly probable repetitions and coincidences at the level of traits, and hence—very likely also at the 'biochemical' level responsible for their appearance.

To conclude this section, it is necessary to mention that there is certain parallelism between our homology-related terminology and the one used in previous works by Ingo Brigandt, Marc Ereshefsky, Günter P. Wagner and other authors. For example, *merons* are conceptually close to *homeostatic property clusters* (Boyd, 1991). In addition, *natural kind* and *characters* (Ereshefsky, 2012) resemble our *archetype-homologies*. Nevertheless, as mentioned at the beginning of this section, most of these concepts are self-centered in attempts to formalize *a carrier* for homology.

2.4. Then, why are bottom-up inductive inferences possible in living organisms?—A resume

> I do not think that it is possible to explain the idea of analogy in completely definite terms of formal logic; at any rate, I have no ambition to explain it so. [...]
> [A] nalogy has to do with similarity ***and*** the intentions of the thinker. If you notice some similarity between two objects (or, preferably, between two systems of objects) and intend to reduce this similarity to definite concepts, you think analogically. [...] "*A* becomes more credible" or "*A* becomes less credible". Although everybody understands what this means, the consistent formal logician refuses to understand such statements, and he is even right. Pure formal logic has no place for such statements; it has no way to handle them. We could, however, widen the domain of formal logic in an appropriate way.
>
> Pólya G. (1968) Mathematics and plausible reasoning. V.II. Patterns of plausible inference.

> It is thus unlikely that we can deduce the circuitry or a higher-level description of a module solely from genome-wide information about gene expression and physical interactions between proteins. Solving this problem is likely to require additional types of information and finding general principles that govern the structure and functional modules.
>
> Hartwell, et al. (1999) From molecular to modular cell biology. Nature, 402(6761): 47-52. doi: 10.1038/35011540.

Counting with the information presented in previous sections and recalling the epigraph to section 2, we can now resume why is it possible to infer the 'organismic' level of organization from knowledge about its 'biochemical'-level elements.

Basically, traits are not taken in isolation from each other, but considering their mutual relevance in the overall organism's organization. In our 'biochemical'-level methodology it is assumed that the different 'measurable' traits are correlatively (functionally) linked, conforming a reduced set of *functional blocks* that are common for a certain number of living organisms belonging to different taxonomic groups. In different organisms the specific 'measurable' traits conforming similar functional blocks might be of different nature but still confer such blocks *functional equivalence*, which can be established through identification of functional similarities—*analogies* or archetype-homologies.

In our methodological approach, archetype-homologies are determined with a particular goal in mind: they have to serve as a base to infer the 'organismic' level of organization and thus—they have to propitiate complexification. This concept of homology differs from the carrier-centered concept of homology used in modern systematics to establish phylogenetic relationships: comparisons with model organisms (section 2.1.1.IV) does not offer clues about the relevance of the traits being compared, whereas in the case of archetype-homologies a hierarchy of archetypes of functions is elaborated, and are the particular realizations of these functional archetypes in particular living organisms what are compared. Hence, with the complexification goal in mind, the only homology concept that can cover all disparate cases of similarity presented in the literature (e.g., Minelli, 1997; Minelli and Fusco, 2013; Sattler, 2022) is our carrier-less and function-based concept which specifically allows comparing functional blocks-merons.

Following previous studies (works by Dogel', Mamkaev, Benítez et al., 2018), we argue that similar archetype-homologies lead to similar complexification processes (to the appearance of similar *patterns*), despite possible differences in the subjacing material elements. Conversely, taxonomic traits —which can be described objectively, strictly and formally— are nevertheless arbitrarily chosen with the aim to build a taxonomic system (*an atlas*), and this is the reason why, from the point of view of their content and meaningfulness, they do not allow complexification. Attempts were made to obtain upper-level properties through the usage of quantitative parameters like reaction time (Waddington, 1968) or adjacency relation, however these did not prove to be general solutions.

The meaningfulness of the concept of archetype-homology is contained in its architectonic relationships: a structure/process/'molecular pathway' (a meron) from the reference case(s) is taken in all its possible variations, in association with any other correlated changes that may take place within the organizations of the compared organisms. By elaborating such meronomic "cloud" or "universe" of variations-relationships for a structure/process/'molecular pathway' —and after establishing the correspondence with the architectonic elements and associations in the investigated organism— it becomes possible to reconstruct the role for such a structure/process/ 'molecular pathway' in the investigated organism. In this way, the huge unstructured elemental diversity is replaced by a structured diversity that restricts the possible interactions in which individual elements can engage. Application of such "universe" of variations-relationships to the corresponding elements (found through comparison) in the investigated organism, allows formulating plausible hypotheses about the roles of such elements in this last. This idea may seem trivial, but it is so only for close, carrier-based, Bauplan-homologies. Establishing the correspondence between elements of archetype-homologies —and even the identification of such homologies— can be a puzzling task, even though, once solved, it leads to an abrupt uncovering of the block organization of classes of structures/processes/'molecular pathways' that drastically simplifies the analysis of the corresponding instances. This is how analysis for the presence of (archetype-) homologies underpins comparison of particular realizations of 'molecular pathways' as a methodology. For the 'biochemical' (and more generally—for the suborganismic) level, we denominate this approach *comparative functional architectonics*.

At the 'organismic' level, the organization of 'measurables' (taxonomic traits) into ranked functional blocks results arguable to some researchers, as it can be appreciated from candid discussions between cladistists and *classic* systematists regarding the reality of ranks. Indeed, if Aristotle's understanding is followed, an animal's paw is part of different functional blocks when it is used for running, digging, fighting or scratching despite it still remaining *the same* body part—as might be argued by Aristotle's opponents. However, *temporal* 'task-driven' associations seem to be *the very mode of functioning* of traits at the 'biochemical' level of organization (i.e., of *individualities/quirks*, section 2.1). Molecular components combine into temporal arrangements to perform particular functions, but then partner in other combinations to perform other tasks (Fig.2C). Such fluid organization at the 'biochemical' level allows organisms to preserve their wholeness-integrity at the 'organismic' level during development and during the elicitation of responses to external cues (adaptation and escaping, healing and regeneration, diseases, etc.).

Thus, living organisms share common "functional blocks" —merons— that confer them particular phenotypic properties or abilities, like the "ability to fix nitrogen", the "ability to live in environments with high salinity", or the "ability to deal with a prolonged drought", but also "exhibit cancer as a disease", to mention some examples. This does not imply that functional similarity can always be established directly from criteria of common origin or kinship, as evolution is able to "rearrange" the elements of such blocks to perform other tasks. Therefore, the resulting upper level varies depending on the history (the followed creode, Waddington, 1957) through which it was established. The properties of 'measurable' elements —*tags*— alone do not allow inferring the upper level of organization. Inferring requires knowing the *'what is' —the function*, or correlative links that maintain the organism's wholeness/integrity— of measurable *individualities/quirks* in the architectonic organization of living organisms. This is the *essence* that has been persistently eradicated from objects in the centuries-long quest for objective representation devoid of metaphysics (sections 2.1.1, 2.2.2). Meaningful knowledge cannot be obtained solely from properties of *individualities/quirks*: it is also necessary to understand the general principles of systems' organization (and know the context of their evolution) to further deduce why a particular *individuality/quirk* was 'chosen' to fulfill a particular function in a particular organism, considering the roles of the other elements. The "*what is*" of an object is as well the "*what, in principle, it can be*".

3. Inferring the 'organismic' level of organization up from the 'biochemical' one

A discourse about the scientific method typically starts with a preexisting hypothesis and methods of its validation. However, nothing is said about how can hypotheses be proposed. A validation can be regarded to as a hypothesis destruction, however, constructing or proposing a hypothesis is much more challenging.

If the analyzed object is complex, we can attempt to describe it as a combination of its elements. In practice, however, this approach is not of much use and researchers typically try to reduce the number of possible descriptions. However, a fundamental limit to the (biological) research object is imposed by its structural organization and the limited number of correlations existing between its parts. The existence of such limit in turn implies that the number of merons that can be identified (and the number of views of a researcher) is also finite.

Researchers count with two methods to approach the object and its elements: 1) inductive logic (individual elements are generalized in order to formulate a concept—the Locke's empirical scheme), 2) the rationalistic scheme introduced by Descartes and Galileo (in which the foundations of cognition appear as obvious and are comprehended through intuition, and the details-elements are obtained through deduction from some general principles). This last ("hypothetical-deductive") method was proposed by Karl Popper (1902-1994) as the only adequate "scientific" method, that allows to falsify the proposed hypotheses, and to distinguish "scientific" knowledge from the "non-scientific" one. Popper, however, did not consider important the way in which hypotheses are created, as this process cannot be formalized. An opposite point of view was shared by the inductivists (Georg Henrik von Wright (1916-2003) among them). Nevertheless, currently inductive inferencing does not constitute a method, but a set of methods directing to insights. Within the inductivistic and descriptive methods it is possible to formalize the process of hypothesis formulation, which can then be tested using the hypothetical-deductive method. For this, the hypothesis has to explicitly suggests features or traits of the instances or group of instances that weren't part of the initial study, or has to suggest yet unknown features or traits of the instances included in the study. In other words, the hypothesis have *to contain predictions*.

Bridging the gap between a previously non-studied organism and its elements of the 'biochemical' level involves archetypic extrapolations: the reconstruction of an archetype from knowledge about a more general archetype, sister archetypes, merons. Any attempt to reconstruct the origination of an object requires comparison of the functional architectonics: from comparisons to extrapolations and their validation. Hence, comparison of the functional architectonics should be at the base of any attempt to describe the history of an object (Lyubarsky, 1996). First, the tectological composition is analyzed: categories and number of composing parts. Then, the architectonics (the meronomic composition) is compared in search for archetype-homologies. As it was mentioned (section 2.3), every meron constitutes an archetype, i.e., includes lower-order merons as variants. From this meronomic description it becomes possible to elaborate the 'outer' archetype. Such reconstruction of the archetype requires knowing the functions of the analyzed traits, although typically we do not know what are the functional relationships between most traits. It is important to note that “traits” here correspond both to structures as well as processes (although in the last case we refer rather to *invariants*, which can also be considered structures). Therefore, “processual” sciences (like physiology or biochemistry) can also be subjected to comparative functional architectonic analyses.

Thus, the goal is making reconstructions following weighed traits, and determining how they influence the organisms’ form (in a wide sense, i.e., including behavior up to its role in ecology). An important aspect to consider when undertaking such reconstructions is the type of variability that may be displayed by merons and ‘biochemical’-level elements (either among living organisms or in phylogenetic series).

It can be appreciated that an important requirement for the reconstruction is counting with a complete information about the analyzed object as the upper complexity level. This can be obtained either through long-term observation (or large-scale automatized monitoring) of details (see a similar strategy cited in Pólya, 1968, p.8), or by involving information from lower and upper levels of organization (a similar strategy is suggested in Dörner, 1997, p.187). In this second case, for the ‘biochemical’ level, the reconstruction appeals to behavioral, botanical or zoological (‘organismic’-level) knowledge, in addition to the physicochemical properties of the involved ‘biochemical’-level elements.

3.1. The general reconstruction pipeline

The general scheme of the proposed comparative method, that includes the inductive and deductive stages, looks as follows (Lyubarsky, 1993a, b):

1. The available previous experience is analyzed (this is *not* a model, that in this methodology comes as a result of a later stage of the research).

2. From the analysis of the previous experience, the object (the “phenomenon”) is identified. If the object is not correctly identified at this stage, a posterior correction will require significant efforts. Easy-to-identify objects are characterized by a high level of wholeness/integrity: all of their parts are highly correlated and behave together as a whole, as in the case of living organisms. Researcher’s experience brings the ability to quickly identify the research object or quickly correct its identification.

3. A preliminary description of the identified object is formulated by presenting its traits (its meronomic composition) through analogies with traits of similar objects, using criteria of homology. Without such comparison it is not possible to provide any description. The very process of identification of traits is based on a comparison of the analyzed object with others, and therefore is somehow intuitive. Within

this methodology it is not correct to part the research from a definition of the object or a phenomenon: a definition (for the 'biochemical' level—*the role*) comes as one of the results of the research.

This stage does not form part of a formal-logical scheme, but nevertheless influences the result of the study. Since J.S. Mill (Mill, 1843), the tradition of distinguishing description and definitions was lost (Mill considered that definitions do not have to uncover the nature of objects and can include all statements that can be issued with the object being defined as a subject). Description and definition are not the same, but in order to carry out an archetype-based study it is necessary to distinguish them. In the Aristotelian tradition, a *description* enumerates the traits of an object using a symbolic notation, whereas *definition* indicates the closest *genus* and the *species*-specific difference; such a definition indicates the unique place of a certain concept in a given worldview. There are several types of description (*genetic*, *structural*, *functional*, *ecological*) that cannot be reduced to each other, and therefore—must not be mixed. The description type itself depends on the chosen research subject, which is part of the non-explicit knowledge required for the study. By using the functional description, it is possible to reduce to number of iterations of the study, although functional relationships are typically known only for few of the available structures. In a real study it is first necessary to establish the functions of those parts that are critical to construct the archetype.

4. The object is presented as a pool of features or traits and functional links between them. Features or traits correspond to similarities and differences of the analyzed object with analogous objects. This pool of features conforms the archetypic universe. Functional links between features/traits have to be presented in an explicit form, allowing to explain how the object functions. When working with concrete features, the correspondence between two objects is established using criteria of homology (section 2.3.2). At this stage the description is formalized: the worldview is split into parts-merons through species-specific differences. The conception of the archetypic universe allows formulating analogisms (conjectures of analogy): inferring the existence of other individuals or phenomena that might be similar to the analyzed object (i.e., that belong to the same taxon). In other words, it is possible to carry out an archetypic extrapolation (a prediction). Analogisms allow formulating generalizations (as a pool of similarities) and abstractions (as a pool of differences).

5. In exceptional cases, the formulation of the archetypic universe denotes the end of the research. This occurs, for example, when the research object is unique or lacks changes/behavior, making its further observation meaningless. Nevertheless, a conclusion about such uniqueness is also a result of a comparison. No object can be considered unique without being compared with some other object.

However, in most cases, from the analysis of relationships between features/traits that compose the archetypic universe, and from the series of forms that belong to this universe, it is possible to infer how a feature of interest changes upon changes in the other features it is linked with, or upon changes in the “external conditions”. Such inferring is conducted through analogisms (using the method of extrapolation and working hypotheses): knowing the way in which features are mutually linked (knowing how they influence each other) it is possible to suppose how a change in one of them will be reflected on the others, or how they can mutually change under different external conditions.

6. The next stage is observational and experimental. Through observation of the object’s behavior in natural or artificial conditions, it is determined if by changing a particular feature the expected result is obtained. As a result of an experiment (or an observation) it can be explicitly said whether the hypothesis based on the archetypic universe passed the test or not. The hypothesis is about the linkage between features within the archetypic universe. Each element of this universe (=each feature) is a fragment of a long series of forms and cannot be formulated in some other way. This is the stage at which the model of the reconstructed system is formulated.

7. Typically, the result of an experiment is presented in terms of the hypothesis acceptance or rejection. In reality, however, this is an iterative process in which we appeal to the archetypic universe and scrutinize new hypotheses about linkages between the different features in this universe. However, “good” observations or experiments reveal facets of the archetypic universe that were previously hidden. At this stage the boundaries of the object change—together with its features, its description, and comparison series. The researcher’s experience is also modified, as at this point the world starts looking different. This is why a scientific research is iterative and cyclic. With each new iteration, the experience obtained from an experiment or an observation is analyzed, the archetypic universe is again compared and reconstructed (our conception about the object in the form of comparisons with other ones is remodeled). Then we conduct new experiments and observations to correct our experience.

Similar steps were proposed by Dietrich Dörner (Dörner, 1997) in order to avoid errors when dealing with complex systems: e.g., it is necessary to know “[...] how the causal relationships among the variables in a system work together in that system.”, “[...] how the individual components of a system fit into a hierarchy of broad and narrow concepts. This can help us fill in by analogy those parts of a structure unfamiliar to us.”, “[...] component parts into which the elements of a system can be broken and the larger complexes in which those elements are embedded. We need to know this so that we can propose hypotheses about previously unrecognized interactions between variables.” (Dörner, 1997, p.79).

As it can be appreciated, several stages of this method are hard to formalize.

3.1.1. De novo reconstructions

> It will seem not a little paradoxical to ascribe a great importance to observations even in that part of the mathematical sciences which is usually called Pure Mathematics, since the current opinion is that observations are restricted to physical objects that make impression on the senses. As we must refer the numbers to the pure intellect alone, we can hardly understand how observations and quasi-experiments can be of use in investigating the nature of the numbers. Yet, in fact, as I shall show here with very good reasons, the properties of the numbers known today have been mostly discovered by observation, and discovered long before their truth has been confirmed by rigid demonstrations. There are even many properties of the numbers with which we are well acquainted, but which we are not yet able to prove; only observations have led us to their knowledge. Hence we see that in the theory of numbers, which is still very imperfect, we can place our highest hopes in observations; they will lead us continually to new properties which we shall endeavor to prove afterwards. The kind of knowledge which is supported only by observations and is not yet proved must be carefully distinguished from the truth; it is gained by induction, as we usually say. Yet we have seen cases in which mere induction led to error. Therefore, we should take great care not to accept as true such properties of the numbers which we have discovered by observation and which are supported by induction alone. Indeed, we should use such a discovery as an opportunity to investigate more exactly the properties discovered and to prove or disprove them; in both cases we may learn something useful.
>
> Euler L., Opera Omnia, ser. 1, vol. 2, p. 459, Specimen de usu observationum in mathesi pura. (cited after Pólya, 1954)

The aim of *de novo* reconstructions is determining the organization of a previously unknown archetype and the identification of shared similarities (hierarchy of merons and common archetype-homologies) with already known archetypes. *De novo* reconstructions stand in relation to analogy-based reconstructions (next section) as biological evolution to inductive inferencing (section 2.2.2.): the former has a notable ‘searching’ (bottom-up) character, whereas the latter is ‘pulled’ by an already familiar upper layer of organization (its direction is top-down). Therefore, *de novo* reconstructions are aimed at identifying the hierarchy of functions of the analyzed organism and *searching* for (archetype-)

homologies shared with familiar objects belonging to a common genus/archetype. Once such homologies are identified, a *de novo* reconstruction turns into an analogy-based reconstruction, and further inferencing is conducted following the corresponding rules (sections 3.1, 3.1.2).

An important step of *de novo* reconstructions is the identification of functions for which we want to find analogs. The identification of such functions might be aided by knowledge about properties of the elements of the studied organism. Nevertheless, this kind of knowledge is not always sufficient to represent the 'behavior' of such elements in the whole organism. Moreover, a correct representation of the function of such element may potentially require the introduction of special terms additional to those used to describe the properties of such element when studied in isolation through reductionistic approaches.

De novo reconstructions are conducted through a gradual, and typically iterative, expansion of the area of search to reconstitute the full *pattern* to which an identified archetype-homology belongs (i.e., by identifying the functional block to which a found homology belongs). Such reconstitution is conducted through comparison by using criteria of homology, and the *pattern* itself can be delimited (=its corresponding elements be identified) by iteratively analyzing the functional significance of the obtained pattern in the archetype.

The archetype, in turn, sets the 'functional boundaries' of the pattern, and can serve as reference when the roles of the elements of the *pattern* are not entirely clear. For example, in our analysis of the orchestrating role of Ca^{2+} signaling in multicellular organisms, we first noted a correspondence between the effects of Ca^{2+} signaling on *proliferation progression* of plant and animal cells—a step that allowed us to look for similar effects on other cell-level processes, which ultimately led to the identification of Ca^{2+}-signaling related functional blocks, allowing us to propose the general orchestrating role of Ca^{2+} signaling in multicellular organisms. Upon the identification of Ca^{2+}-signaling related functional blocks, the *pattern* (the 'framework') was set within which it was worth searching for the particular roles of Ca^{2+}-permeable TPC and TRPML channels (Panina et al., 2020). Conversely, the study of these channels through reductionistic approaches rather led to the uncover of a still rising number of details about the intricate and complex mechanisms of their regulation by ligands and interaction partners.

Next, found elements of the *pattern* are docked, allowing to identify or predict the type of link existing between them. Given the degree of development of the different biological disciplines, currently this task can probably be carried out through literature analysis, although, as we have shown for plants (in comparison with animals) the type of such links between elements (or their mere existence) in many cases have not been identified. For example, in the analysis of the role of Ca^{2+} signaling in cell-level processes, we showed that it regulates proliferation progression of animal and plant cells, although the mechanisms differ; conversely, the role of this signaling pathway in quiescence of animals cells has been firmly established, but it has seemingly not been studied in plants. The same is true for the cases of cell apoptosis and differentiation: their regulation by Ca^{2+} signaling in plants has not been succinctly analyzed, despite evidence suggesting the participation of Ca^{2+} signaling in these processes (Panina et al., 2020). Considering the proposed general orchestrating role of Ca^{2+} signaling in these different processes (Panina et al., 2020), the "Ca^{2+} signaling *pattern*" would correspond to variations in the manifestation of this pathway in the elements of the *pattern* ('anchors' or 'references')—the cell-level processes (stemness, proliferation, quiescence, apoptosis, differentiation). Using these common 'anchors' as reference in the compared organisms (animals and plants), the reconstitution of the *pattern* was attempted.

The reconstitution of the *pattern*, therefore, can be conducted either simultaneously (typically, when compared organisms are closely related and/or the correspondence between the elements of the *pattern* is clear, like in the case of the highly conserved pRB-E2F machinery, Zluhan et al., 2020), or iteratively (typically, if the compared organisms are taxonomically distant and the correspondence between the elements of the organisms being compared is not obvious, also making unclear the limits of the *pattern*). In this last case, the number of possible correspondence alternatives between elements is gradually reduced, as has been observed in the case of complexification and in section 2.3. Both these methods to acquire knowledge about a system were also suggested by Dörner (Dörner, 1997, p.79; he referred to them as "analogy" and "observation", respectively). For instance, the observation of covariations was proposed by him as essential in order to acquire structural knowledge about a system.

In another example, from the analysis of the events associated with vacuolar convolution ('wrinkling') in plants (and the non-explicit reconstruction of the archetypic universe of this process), we *predicted* that one of the steps of this process is associated with the inhibition of the vacuolar NHXs transporters by a transient increase of the minor lipid PtdIns(3,5) P_2 (Pérez Koldenkova and Hatsugai, 2017). Subsequently, this effect was experimentally observed, first in yeast (Wilson et al., 2018), and then in a plant (Gradogna et al., 2020). On the other hand, another effect —the observed alcalinization observed after PtdIns(3,5) P_2 increase— could have several origins, and indeed, it appeared to result from inhibition of the anion transporter CLC-a (Carpaneto et al., 2017; see Note added in proof of Pérez Koldenkova and Hatsugai, 2017) and not from the possible V-ATPase activation. Together, these experimental results further strengthened the overall proposed scheme of vacuolar convolution, which steps can not be ‘reduced to a single experimental result’ (i.e., it cannot be assessed as an integral ‘organismic’-level process) forcing *to infer* the entire scheme, and providing the experiments only a *measure of credibility* with which such general scheme can be accepted. We refer the reader to our original publication (Pérez Koldenkova and Hatsugai, 2017) for a detailed description of the phenomenon of vacuolar convolution and to follow the reasoning behind the identification of the sequence of ‘biochemical’-level steps that, in our opinion, leads to the ‘organismic’-level convolution of the plant vacuole.

3.1.2. Analogy-based reconstructions

> Opera is when a tenor and soprano want to make love,
> but are prevented from doing so by a baritone
>
> George Bernard Shaw

> Having solved a problem with a real insight and interest, you acquire a precious possession: a pattern, a model, that you can imitate in solving similar problems. You develop this pattern if you try to follow it, if you score a success in following it, if you reflect upon the reasons of your success, upon the analogy of the problems solved, upon the relevant circumstances that make a problem accessible to this kind of solution, etc. Developing such a pattern, you may finally attain a real discovery. At any rate, you have a chance to acquire some well ordered and readily available knowledge.
>
> Pólya G. (1954) Mathematics and plausible reasoning. V.I. Induction and analogy in mathematics. pp.121-122

> In general, in trying to devise a proof by mathematical induction, you may fail for two opposite reasons. You may fail because you try to prove too much: your A_{n+1} is too heavy burden. Yet you may also fail because you try to prove too little: your A_n is too a weak support. You have to balance the statement of your theorem so that the support is just enough for the burden. And so, the machinery of the proof edges you toward a more balanced, better adapted view of the facts. This may be typical of the role of proofs in building up science.

> G. Pólya (1954) Mathematics and plausible inferences. V.I. Induction and analogy in mathematics. p.119

Analogy-based reconstructions have two aims: establishing the role of the investigated element (a ‘molecular pathway’) in the whole (the organism being reconstructed), and, using an appropriate reference organism or group of organisms,—to identify a common archetype that could aid evidencing such a role. This common archetype is used as a “fixed reference” at the upper level of organization which allows identifying the correspondence between archetype-homologies and comparing the functional and meronomic organization of the analyzed organism. For example, Georges Cuvier considered that correlations between parts of organisms are so strict, that counting with just a single part of an extinct organism it is possible to reconstruct the appearance of the other parts, as well as the appearance of the whole organism to which that part belonged. In practice, however, an extinct organism is reconstructed (inferred) by using its analogy to a close modern relative that shares the same archetype.

In the case of analogy-based reconstructions, it is assumed that the hierarchical functional organization of the studied whole is known, i.e., the possible organization alternatives and their consequences were analyzed. For the ‘organismic’ level the discipline that analyzes trait-function relationships is functional morphology, although this discipline does not typically address functional hierarchies, focusing on particular cases of form-function relationships.

New traits can originate at any stage of development and then irradiate either to earlier or later stages of development (Beklemishev, 1994). Under different evolutionary scenarios the processes of evolutionary radiation can differ: sometimes radiation takes place at the level of taxonomic families, but radiation may as well occur at the level of genera (Lyubarsky, 2018). The rank at which radiation occurred may reflect the hierarchy of functional blocks and the way in which they are linked (nested or chained), determining the plasticity of taxa in phylogenetic series. For example, it has been suggested that a hierarchical organization confers rigidity (less plasticity) to a system by imposing restrictions on self-nesting that could alter the order of regulation of parts belonging to different hierarchical levels (Lyubarsky, 1996).

The order in which particular traits originated can be suggested by phylogenetic reconstructions. However, the answer to the questions *how* and *why* has some trait appeared is provided by comparative functional architectonics, which, through the construction of the archetype, allows clarifying the links between individual traits. Thus, an important point in regard to these observations is that at the ‘organismic’ level the object (the organism) becomes subdued to considerations of systematics, turning such considerations into an additional reference level which should be taken into account when reconstructing the role of ‘biochemical’-level elements: taxonomic evidence (about ‘degrees of radiation’ or ‘variability of phenotypic traits’ in the form of visible ‘anchors’) may suggest the type of linkage exists between functional blocks. In the case of Ca^{2+} signaling, such ‘anchors’ correspond to the cellular-level processes regulated by Ca^{2+} signaling, namely: proliferation, quiescence, migration, chemotaxis, differentiation, apoptosis (Fig.4; Panina et al., 2020). In brain research, such major divisions should correspond to the different cognitive and behavioral traits that might be exhibited as variability in animal populations—curiosity, fear, aggressiveness, smartness, etc. Such preliminary classification allows establishing the organization of the ‘biochemical’ level in the form of mutually exclusive phenomena (involved functional blocks) and polar states within them (which might be regulated by a single or several individual programs; section 2.2.1).

Once the ‘biochemical’-level composition of the phenomenon of interest has been established, it is analyzed the relationship between its universe (‘the role of the element’—or *individualities/quirks*, which reflect the role either in different contexts of the same organism, or in different organisms) and the universe of structures and dynamics of the organisms in which the phenomenon of interest is observed (‘the context’). In other words, similarity is searched for between the organizations of functional blocks and programs (section 2.2.1) of the analyzed organism and in the reference archetype, using the criteria of homology.

In this analysis it is assumed that processes with similar composition (the ‘lower level’) and a similar outcome (the ‘upper level’) contain functional units with similar roles (‘archetype-homologies belonging to the biochemical level of interest’). This assumption is typically based on the similarity or complementarity of experimental results obtained in different organisms or contexts of a same organism, indicating a similar organization and similar functioning of such organization. The similarity of functions in this case appear as a ‘biological syllogism’ (see also section 2.3.2), suggesting the possibility to uncover other (not yet discovered or experimentally proven) features (e.g., a [not yet confirmed] patterned localization of $PI(3,5)\ P_2$ on the plant vacuolar membrane, contributing in this way to its wrinkling, or the predicted inhibitory effect of this same lipid on the NHX antiporters [experimentally confirmed later]; Pérez Koldenkova and Hatsugai, 2017). Hence, ‘biochemical’ level *individualities/quirks* can differ by: 1) synthesis/acquisition, 2) turnover, 3) elimination, 4) distribution, 5) activity, 6) interactions. As these aspects include considerations of timing, the introduction of an additional criterion of homology turns necessary, which allows evaluating the time-related architectonic relationship of the phenomenon of interest (e.g., simultaneity of the occurrence of the phenomenon of interest with other processes from its context, or a particular place of the phenomenon of interest in a sequence of processes).

Every of these aspects, their consequences, and organisms' specific variations are key in establishing the correspondence between elements of 'molecular pathways', so that comparisons are equiranked. The requirement of equality of ranks of the compared objects (structures or processes) was not approached in the work of Pólya due to the lack of the corresponding properties (complexity) by the objects he analyzed —mathematical expressions. *Parts* of biological objects of equal rank were denominated *homotypical* by Beklemishev (Beklemishev, 1994). According to him, two organizational units belong to *different* constructive levels if one forms part of the other, or is homotypic to a component of the other (i.e., when relationships of nesting are involved). Following the requirement of homotypi becomes especially evident in cases when the compared objects are composed of elements of different nature which still perform similar functions, like in the case of Dynamical Patterning Modules, Benítez et al., 2018). In such cases, establishment of homotypi can allow uncovering blank areas of knowledge ('not yet discovered correlations') in the understanding of organisms as wholes. Conversely, as it was shown above in section 2.3.2, genealogical approaches dispense with ranks—a feature that can be appreciated in comparative works conducted on transcriptomic, i.e., 'measurable' data (de Luis Balaguer et al., 2017).

Correlations between traits of an organism are not comprehensive: the organization of organisms is partially hierarchical, but also partially combinative (Beklemishev, 1994). The mixed organization of living organisms (functional blocks organized in different possible variants of hierarchy and combinatorics), and the possible effect of the environment on the rank at which evolutionary radiation occurred, does not allow to apply a single formalized approach to describe their organization types. Nevertheless, the existence of regularities in the development of individual subsystems underpins the reduced number of possible 'channels' of evolutionary change and the preservation of a biochemical Bauplan (section 2.3.1) over the course of evolution. In this way, the presence of regularities contributes to reducing the number of possible hypotheses about the organization of organisms. For example, a POU-IV transcription factor is responsible for the differentiation of mechanosensory cells both in *Bilateria* and *Cnidaria*, Ozment et al., 2021. Another example is the evolution following homologous series in variation —a law formulated by Nikolai I. Vavilov (Vavilov, 1922). Regularities are observed not only in the development of "normal" traits, but also of deviations (aberrations or abnormalities) which in plants may constitute other variants of the norm (Meyen, 1973) and in animals are typically associated with teratogenesis (Pavličev and Wagner, 2022). Regularities in the "transformation of homologies" have also been the subject of works on “transformation of developments” by Mae-Wan Ho (Ho, 1990; Ho, 1992; Ho and Saunders, 1993; Ho and Saunders, 1994) and Olivier Rieppel (Rieppel, 1990).

As a final step of analogy-based reconstructions a model is elaborated—the reconstructed whole, an instance of the ‘outer’ archetype with designated ‘correlations’ in the form of functional links between its ‘biochemical’-level elements. Important, this model type is qualitative; ‘mathematical models’ can be formulated only for their ‘measurable’ portions. Nevertheless, these qualitative models can be refuted if some of the steps of the reconstruction or some of the consequences are experimentally refuted (validation of reconstructions is analyzed in section 3.3). Otherwise, this type of models serves to analyze the “behavior” of the reconstructed organism and predict its possible responses.

The requirement of a common archetype in order to find archetype-homologies implies that between the case of interest and the reference(s) there must exist certain difference in the phenotypic trait of which the ‘biochemical’-level mechanism is being analyzed. This distance depends on the rank of the investigated function in the hierarchy of functions of the compared organisms, and can go from subgroups of organisms of a same species and up to phylogenetically very distant organisms for the case of very basic (‘core’) functions. For the analysis of every function its most differing (and in many cases—phylogenetically distant) examples have to be compared, as otherwise no sufficient information can be obtained in order to establish the architectonic linkages with other organizational levels. If closely related organisms are compared, critical information about such linkages might be missed, as in this case the important details of upper level (the *pattern*, section 2.2.2) will be indistinguishable. In other words, it will be impossible to construct the upper archetype (see the goals of analogy-based reconstructions at the beginning of this section). This corresponds to the Polya’s “weak support” situation mentioned in the third epigraph to this section.

A phenotypic trait can be represented by a more-or-less well defined nucleus with little variability, or by several states with little in common (e.g., Lyubarsky and Perkovsky, 2020). Variability of traits are described by the so-called Krenke’s rule (Meyen, 1973): “Every individual of given systematic unit, in its modificational and mutational variation may (but not necessarily must) reveal one or several characters which are not characteristic for the given unit, but are specified for related systematic units of the sane or higher rank. On the contrary, based on certain deviations, one can suggest the existence of corresponding related units, even though they are not known as yet”. As examples of individual variations —at the level of the nervous system— can be mentioned the distorted time perception (“split-day syndrome”, Pourriyahi et al., 2022), changes in memory accession (sudden memory loss and its posterior recovery;

Pozueta et al., 2022), hypercalculia (Ogun et al., 2022) the possibility of which emerges in vertebrates in view of the fact that even zebrafish posses the ability to estimate quantities (Messina et al., 2022); rhyming (Mendez, 2022), or, on the contrary—the astonishing preservation of functional capacity despite extensive brain damage (García et al., 2017), of which a particular case might be a case of *kinesia paradoxica*, when a patient's gait is severely impaired by Parkinson's disease, but the ability to ride a bicycle is nevertheless well preserved (Snijders et al., 2010). Examples of such deviations in plants that, unlike in vertebrates, can derive into new "norms" are carnivory (Preston et al., 2022). As it was mentioned above, deviations in plants can give rise to new "norms" due to a less integer organization of this group of organisms (Meyen, 1973). In general, reduction of the integrity of the system ("weak correlative links") turns the isolation of the study object (*an integer*) into a less trivial task (Lyubarsky, 1993a). Nevertheless, the analysis of all such deviations contribute to a better understanding of the archetype.

Establishing the most differing examples of the studied trait is aided by the identification (either in different organisms or in different contexts of the same organism) of the similar major divisions of such trait, mentioned above. The similarity of such divisions also allows identifying the suitable model organisms to analyze variations in the realization (*individualities/quirks*) of the studied 'biochemical'-level mechanism of the trait. As it was mentioned in section 2.3.2, archetype-homologies themselves may share a common carrier (see Conzelmann et al., 2013; Musser et al., 2021; Bowles et al., 2022; Cabin et al., 2022; LaPotin et al., 2022; Tong et al., 2022; for phylogenetically distant organisms this will be the so-called deep homology; Shubin et al., 1997), although this is not an absolute requirement: Ca^{2+} signaling can apparently fulfill close physiological functions in plants and animals despite drastic differences in the corresponding underlying toolkits (Panina et al., 2020).

Analogy-based reconstructions not only include cases when an archetype-homology is present both in the analyzed organism and the reference archetype. This reconstruction type may also include cases when one of the compared realizations lacks an element of the analyzed archetype-homology. Such cases, be them either carrier-dependent or carrier-less, allow studying what the role of a particular element is in the appearance of a particular trait, and in some cases exhibit mechanisms compensating a reduced or absent activity of such element. For example, the enzyme disulfide isomerase Ag1 is responsible for tail regeneration in *Xenopus laevis*, but was lost by ancestors of poorly regenerating vertebrates (Ivanova et al., 2021). In other example, it was shown that duplication of an enhancer of Sox9 is able to functionally replace the sex-determining Y chromosome, which is lost in males of the Amami spiny rat *Tokudaia osimensis* (Terao et al., 2022). Finally, compensatory mechanisms can be observed at the level of organs, even such complex ones as the human brain (García et al., 2017).

3.2. Considerations

3.2.1. Considerations about the method

> It is difficult to estimate the probability of the results of induction.
>
> Pierre-Simon Laplace (1814) Essai philosophique sur les probabilites; Œuvres completes de Laplace, vol. 7, p. CXXXIX.
>
> We know that the probability of a well-established induction is great, but, when we are asked to name its degree, we cannot. Common sense tells us that some inductive arguments are stronger than others, and that some are very strong. But how much stronger or how strong we cannot express.
>
> John Maynard Keynes

Attribution of an element to the field of interest, and its differentiation from other observable external elements depends on casualty and can be achieved only through time-averaged observation. This is why the method presented above is iterative and has as goal *mastering experience*. Other fields in which experience is obtained in a different way are, for example, construction, in which the experience is produced by the activity of the constructor, or mathematics, in which the experience is also not external: all mathematical phenomena are created by the mathematician, and objects can be created and described in a strict and correct form—unlike in the case of “natural experience”. We should note, however, that recently there were successful attempts to replace ‘natural experience’ by machine vision tools applied to large data sets (Yoshihara et al., 2022).

Application of the rules from section 3.1 returns as a result a limited set of experimentally-testable hypotheses. Very much like in the case of inductive logic in mathematics (Pólya, 1954; 1968) in no case are assured results obtained, but only plausible experimentally-testable predictions. Therefore, as Pólya himself noted (Pólya, 1954), several principles apply to these rules: 1) a researcher must be ready to reconsider any of they assumptions, 2) a view should be changed under reasons of weight, 3) views should not be changed stochastically, without special reason, 4) if the consequences of a conjecture hold true, an inference turns more plausible. Conversely, if the derivation is refuted, the inference should be rejected: a disproved consequence disproves the conjecture itself.

Unlike deduction, inductive logic is frequently regarded to as a fundamentally incomplete procedure, which allegedly cannot bring a researcher to a finally proven result. However, comparative functional architectonic *is a complete* inductive logic, because it includes the iterative analysis of the studied objects until exhaustion, and is not only able to offer some general cue about the result, but also contributes to the solution of the tasks of the research. Hence, the researcher acquires the ability not only to "reason plausibly", but also to solve problems, as a mathematician would.

Pólya (Pólya, 1968) noted: "in applying the calculus of probability to plausible reasoning, avoid numerical values on principle." (p.136), "[t] he weight of a plausible argument may be extremely important, but such importance is provisional, ephemeral, transient: would it be worthwhile to fasten a numerical value on something so transitory? (it possesses a value as far as the conjecture is at the forefront of the discussion; once it is integrated into the building of a theory [made with surrounding facts] its relative value decreases)" (p.138), "[y] et even more important than the number may be the variety [of consequences]. Consequences that are very different from each other, witnesses who are obviously independent, indications that come from different sides, count more heavily" (p.157).

3.2.2. Considerations about the researcher

> In opposition to demonstrative inference, plausible inference leaves indeterminate a highly relevant point: the "strength" or the "weight" of the conclusion. This weight may depend not only on clarified grounds such as those expressed in the premises, but also on unclarified unexpressed grounds somewhere in the background of the person who draws the conclusion. A person has a background, a machine has not.
>
> Pólya G. (1968) Mathematics and plausible reasoning. V.II. Patterns of plausible inference.

Typically, the researcher is considered an unalterable external observer. However, the whole study is organized by the researcher, and they has some characteristics that influences the study. These characteristics are not entirely subjective, and can rather be called intersubjective. Among such characteristics are the stage of development of the culture to which a researcher belongs, or the reigning worldview, or the language they uses. In accordance with their organization and experience, the researcher conducts the preliminary identification of the object, composes comparative series, identifies correspondences, structurizes the archetypic universe, conducts the experiments, etc. Such initial division of the studied object into aspects is part of the researcher's *experience*, that allows linking "objective data" to their interpretation. This division is part of the non-explicit knowledge about the object and is not entirely formalizable. The initial description derives from the researchers' own worldview, and from the worldview accepted by the scientific community at a certain stage of development ("the reigning paradigm").

At the end of the research cycle, when the researcher's experience is modified as a result of experiments or observations, the researcher themselves is changed. An iterative study changes not only the way in which the research object is conceived, but also the researcher themselves. The study becomes a mechanism of self-change: previously the observer was not able to distinguish, but now they can. This denotes a change in the researcher.

In the course of the study the researcher acquires two types of abilities: *knowledge* and *skills* (Lyubarsky, 1993b). *Skills* are related to the abilities of the researcher to perceive the organization of the diversity that is akin to the studied phenomenon (the relationship between the nucleus and the periphery of this diversity). Skills are reflected in the researcher's ability to identify the theme, to divide the universe into phenomena, to divide phenomena into merons, to select objects for comparison, to identify the relative importance of traits to formulate the diagnose of a taxon (the pool of its stable and unchanging properties; the species-specific difference which make it possible to distinguish a taxon), to identify the criteria of comparison, to identify the form of the organization of the archetype, to use terms correctly and prudently when using the descriptive method and when formulating the hypotheses to be tested. Skills are related to the so-called "systematist's gut feeling" when a specialist "feels" the object they works with, but lacks such "affinity" toward non-familiar objects.

Knowledge is fed back into the iterative scheme of the study. Unlike skills, knowledge is explicit and is allows making the archetypic description isomorphic to the structure of the analyzed phenomenon. New knowledge aids in clarifying tasks, simplifies the selection of a better object of comparison, and the introduction of changes in the diagnose of the archetype or of the volume of the taxon according to the acquired experience. In addition, introduction of new knowledge at each iteration of the study makes the final description of the analyzed part of the archetypic universe more robust toward the introduction of new information (observations, experimental results), as the archetypic universe becomes more and more complete.

3.3. Errors during reconstructions. Validation of reconstructions. Criteria of robustness of reconstructions

A taxonomy of typical cognitive errors made by humans was presented by Dörner and Güss (Dörner and Güss, 2022), and the way in which this kind of errors may affect the analysis of complex dynamic processes (in out case—iterative reconstructions), was presented in Dörner's work "The logic of failure" (Dörner, 1997). Some major cognitive errors that can be made when applying the comparative functional architectonic methodology are presented below.

A common human task is the search for a balance between our natural tendency to generalize and form abstract concepts and the need to adapt to particular ("embodied") circumstances (Dörner, 1997). For our methodology, this could imply attempts to conduct generalizations and abstractions (=formulate analogisms) before archetype-homologies are well identified.

The model of reality (in our case—of the object) may be explicit to the individual, but may also be implicit, in which case the object is not formalized (as it happens in the case of the archetype). Dealing with complex systems, according to Dörner, requires considering the non-obvious interrelations that might be present. One of the most common errors detected in tested subjects was that (complex) systems were dealt with not as integer systems, but as a bundle of independent minisystems (Dörner, 1997). Analyses turned even more complicated in cases when temporal configurations were added to spatial concepts (for example, successive steps were typically treated as individual events, Dörner, 1997).

Reaching some conclusion represents a sort of relieve. However, the conclusion can be put into question again if new information that muddies the picture is added (Dörner, 1997). An initial analysis based on comparative functional architectonics is slow and long. Inclusion of this new information may require changing the formulation of the archetype, a step which a researcher may want to skip.

In addition to these very general errors, there also errors associated with each step of the reconstruction pipeline.

3.3.1. Common errors during the reconstruction pipeline

Some common errors that can be made at each of the steps of the reconstruction pipeline are presented below:

At stage 2, errors are related to the wrong identification of the object. Correcting this type of errors at posterior stages of the analysis can be challenging.

At stage 3, the incorrect formulation of properties can occur or wrong properties/traits can be chosen. Another common error at this stage is mistaking correlated (linked) traits belonging to a same group as independent. In this case, different names and manifestations can be wrongly ascribed to a same phenomenon.

At stage 4, the most critical errors are related to incorrect conclusions about the composition of the system. In this case, the organization of the organism is inferred following some irrelevant links that, for some reason, the researcher considered meaningful. At this stage errors of formalization occur—excessive or wrong formalization, etc. This can traduce into wrongly reconstructed details. For example, plant vacuolar convolution includes as a step changes in the cytosolic pH induced by the minor lipid PI(3,5) P_2 (Pérez Koldenkova and Hatsugai, 2017). Nevertheless, as it was set in posterior studies, this step did not depend on the possible changes of the vacuolar H^+-ATPase activity, but involved instead the inhibition of a CLC-a anion transporter (Carpaneto et al., 2017). In this case the principle is maintained but the particular details differ.

At stage 5, trivial and useless hypotheses are frequently proposed, the revision of which does not significantly alter the archetypic universe.

Errors at stage 6 are related to language and interpretations: nature does not speak human languages and thus, experimental results can be incorrectly interpreted. The result of an experiment is a comparison with some hypothesis and therefore, if the object was not correctly identified from the beginning, the experiment will return a result that will be interpreted considering such incorrect conception. In addition, as Pólya noted, “you cannot be familiar with all domains, and you can still less be an expert in all domains” (Pólya, 1968, p.114). Hence, an experiment does not guarantee veracity and can lead to confusions.

3.3.2. Validation of reconstructions

> Aristotle noticed that reasoning conforms to certain ***patterns***. He observed, I imagine, such patterns in philosophical or political or legal or everyday arguments, recognized the patterns as they occurred, extracted and formulated them. These patterns are the syllogisms. The examples by which Aristotle finds necessary to support his syllogisms seem to bear witness to the idea that he discovered his syllogisms by a sort of induction—and how could he have discovered them otherwise? At any rate, the idea that the syllogisms may have been discovered inductively brings them a little nearer to our patterns of

> plausible reasoning. [...] [T] here is something unchangeable in the syllogism considered. Having once accepted the premises we cannot avoid accepting the conclusion. The inference of a demonstrative syllogism requires nothing from outside, is independent of anything not mentioned explicitly in the premises. In this sense, the syllogism is *self-sufficient*: nothing is needed beyond the premises to validate the conclusion and nothing can invalidate it if the premises remain solid. This "**self-sufficiency**" or "autarky" of the syllogism is, perhaps, its most noteworthy feature.
>
> Pólya G. (1968) Mathematics and plausible reasoning. V.II. Patterns of plausible inference.

In reconstructions, validations are conducted against the obtained structure (the hierarchical organization) of the archetypic universe and to the links between its elements. Ideally, the researcher should count with a worldview that can accommodate (=be isomorphic to) the hierarchical sequence of archetypes (a similar view was expressed in Pólya, 1968, part XV "The calculus of probability and the logic of plausible reasoning"). Such a worldview constitutes an Aristotelian syllogism, which is self-sufficient: "nothing is needed beyond the premises to validate the conclusion and nothing can invalidate it if the premises remain solid" (Pólya, 1968, p.112).

The reliability of analogisms as constructive units of such organization is established using the general criteria of reliability of comparisons (Remane, 1956): an analogism turns more robust 1) the closer are the archetypes of the compared objects (if there is no information about the meronomical organization of the archetypes, then taxonomic relationship has to be used as a criterion), 2) the higher is the number of shared merons in the compared archetypes (when the mutual taxonomical relationship of archetypes is unknown, but there is information about their meronomical organization), 3) when the closest merons in both archetypes display the higher variability (this is a proof of the similarity of the compared archetypes, and reduces the probability that the objects subjected to analogization are similar in regard to a particular merono-taxonomical inequivalence), 4) the closer to the nuclei of diversity are the reference and the analyzed merons (because the nuclear region shows lower diversity than the periphery; hence, comparison of peripheral objects even belonging to a same archetype results in a higher variability than comparison of objects belonging to nuclear regions of close archetypes); 5) the closer are the merons which similarity has already been established, and those that are being studied (as this increases the probability that the lower-level merons will also be similar); 6) the lower is the degree of novelty of the conclusion obtained as a result of the comparison (because the possible number of archetypes is limited, and they all share some common traits, being themselves mutually related as merons of the archetype of the Universe).

‘Outer’ archetypes are wholistic, meaning that their descriptions have a particular property: they can be referred to as “round” (or “syllogistic”) due to their integrity (“self-enclosedness”) and inner interconnectedness, implying that the issue from which the description was started can be reached from another viewpoint (unlike in “linear” descriptions of scale-free networks). The “linearity” of scale-free networks (“graphs”) implies they are “open-ended” (or “self-contained”), whereas the functional outcome of real genetic networks is constrained by organism- or environment-imposed boundaries that enclose such networks and set the ‘correlations’—the “boundary conditions” in which they have to operate.

The ‘outer’ archetype’s ‘roundness’ implies the interconnectedness between merons or lower-level archetypes. When validating the reconstruction, this means that predictions can be supported by results obtained from the analysis of other merons. This is how the study of the archetype speeds up the understanding of the organization of living organisms.

From a mathematical viewpoint, the ‘outer’ archetype as a system differs from those that can be described by Gödel’s incompleteness theorems (an example of which are “linear” and “open-ended” scale-free networks). This is an evidence for the necessity to the accurate usage of ‘open-ended’ scale-free networks representation of ‘molecular pathways’ when they are studied in their native context. This also implies that positive evidence supporting the formulated hypotheses to be tested belong to the same archetypic universe: a research is the exploration of the *genus* for the observations or experimental results the researcher parts from. At the same time, it might be difficult to propose possible negative evidence, as such evidence can be part of some knowledge outside the known meronomic universe, that can refuse (or, to be more exact—remodel) it. Together, this is the reason why as an output *plausible* hypotheses are obtained. By their experimental validation it is possible to revise whether the archetypic universe was conceived in a correct way or not. Moreover, as a consequence, the archetypic universe itself suggests the type of positive evidence that can be searched for. For example, from the contexts presented in each case, the following predictions were made: the existence of epithelial-to-mesenchymal-to-epithelial [EMET] waves during development (Panina et al., 2020); about the particular roles of Ca^{2+} and ROS long-distance signals in plant development (Pérez Koldenkova and Hatsugai, 2018); about the possibility that the hyperosmotic stress response relies on those mechanisms that induce lateral root formations (Pérez Koldenkova and Hatsugai, 2017); and the (later confirmed prediction) that NHX transporters are inhibited by PI(3,5) P2 increase (Pérez Koldenkova and Hatsugai, 2017).

3.3.3. Criteria of robustness of reconstructions

> ***Perhaps our confidence in a conjecture is never based on clarified grounds alone***; such confidence may need somehow our ***whole background*** as a basis. [...] Of course, you should not trust any guess too far, neither usual heuristic assumptions nor your own conjectures. To believe without proof that your guess is true would be foolish. Yet to undertake some work in the hope that your guess ***might*** be true, may be reasonable. Guarded optimism is the reasonable attitude.
>
> Pólya G. (1954) Mathematics and plausible reasoning. V.I. Induction and analogy in mathematics.

By robustness of an inference we can understand its capacity to withstand new iterations of the reconstruction pipeline and addition of new information to the reconstruction. The goal of a reconstruction is reducing the number or hypotheses to test, as their revision is typically the bottleneck in this type of studies. Assessing the robustness of conclusions in this case is a strategy to reduce the number of hypotheses to test.

Pólya presented the general criteria of credibility of conjectures, which allow evaluating the result of each iteration of the reconstruction procedure (Pólya, 1968):

> “The verification of a consequence renders a conjecture more credible” (p.5).
>
> “The verification of a new consequence counts more or less according as the new consequence differs more or less from the formerly verified consequences” (p.7).
>
> “The verification of a consequence counts more or less according as the consequence is more or less improbable in itself” (p.9).
>
> “A conjecture becomes more credible when an analogous conjecture turns out to be true” (p.10). In our methodology, a comparison is carried out between the organism of interest and an archetype (formulated for one or more reference organisms). Hence, with the increase of the number of species involved (as the detailing of the archetype increases) a reconstruction turns more robust.

> “A conjecture becomes somewhat more credible when an analogous conjecture becomes more credible.” (p.12).
>
> “The strength of the additional confidence resulting from an additional verification increases when the analogy of the newly verified consequence with the previously verified consequences decreases” (p.30).
>
> “The increase of our confidence in a conjecture due to the verification of one of its consequences varies inversely as the credibility of a consequence before such verification. The more unexpected [the verified] consequence is, the more weight its verification carries. —the more distant the fields from which supporting proves are obtained—the more reliable is the reconstruction” (p.121).

4. Conclusions: On embracing extreme ‘biochemical’ diversity

Here we presented a methodology for inferring the ‘organismic’ level of organization up from elements of the ‘molecular’ level: biomolecular compounds and pathways they conform. A key feature of the proposed methodology is its correspondence with the direction of the symmetry break of those phenomena it aims to describe. Unlike reductionistic approaches, that pursue at reconstructing an emergent level of organization by going in a direction *opposite* to that of the ‘emergence’, our methodology provides the appropriate conceptual framework and terminological toolset required for the adequate description of phenomena and features arising *along* the transition to the upper organizational level, in a manner *isomorphic* to the process of complexification, allowing to delve in the actual meaning of the observed features and phenomena.

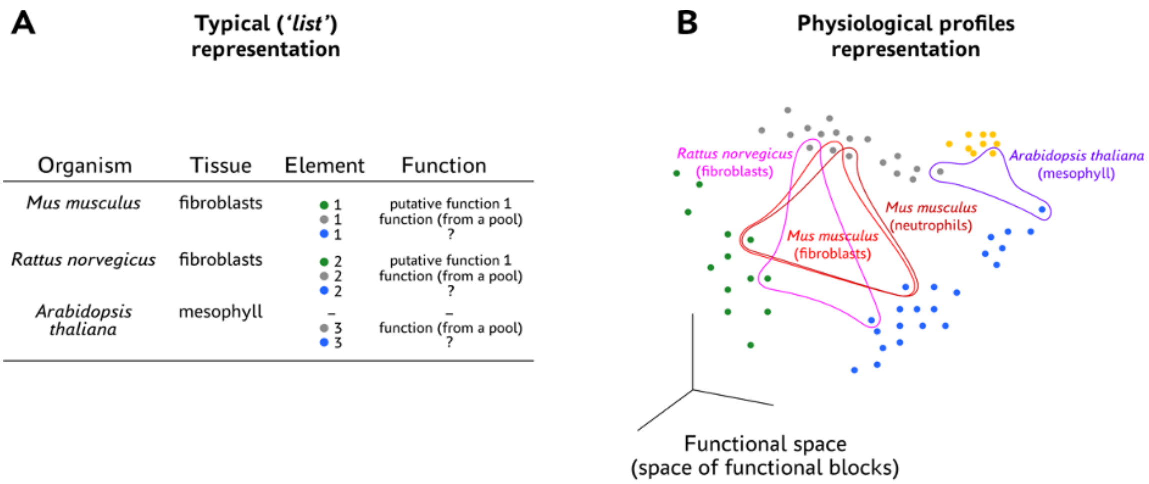
To sharpen the difference between the top-down and bottom-up approaches, we can propose a task that poses similar challenges to those described in the Introduction. This task is: *How to conceive modern science?* How to look at it? What criteria should be monitored to understand it? How to interpret the observations in order to formulate efficient and successful support programs? The technical approaches presented in the Introduction suggest that such understanding can be obtained by composing an *atlas* or *list* of scientists, containing their ‘variables’: fields of specialization, degrees obtained, academic trajectory, publication activity, funding amounted, and other (the more data—the better). Will be it possible, counting with all this information, to understand *what science is*—how is it evolving, how to direct it, how to address several of its nowadays problems, even considering the advantageous possibility *to get a report with any desirable depth of detail from any of the individually interviewed scientists—the utmost* *dream of any single-object scientist*? Conducting such an analysis could help evidencing the range of applicability of reductionistic approaches, and the extent to which they can help in understanding epiphenomena (science among them). Curiously, this type of analysis has been recently released (Wang and Barabási, 2021), allowing the reader to obtain an idea of the type of results that brings this methodology, applied to science as a whole.

Comparative functional architectonics relies on the comparison of *individualities/quirks—species*-instances of a same 'molecular pathway' in the different contexts in which it might be present, either in health or disease. It also considers cases when such pathway is absent in one of the compared objects in otherwise similar contexts. Such large-scale comparison allows determining the "metafunction" of a pathway not just in the particular conditions of an organ or disease, but more generally—at the 'organismic' level (an example is the difference existing in the insulin signaling pathway among different casts of the *Harpegnathos saltator* ants; Yan et al., 2022), or even 'inter-organismic' level (an example of such functional parallelism is the similarity of the proteomes in oil-rich seeds and tubers of plants, Niemeyer et al., 2022). As a result, information is obtained about the *differentiation-associated exaptation* of a pathway to perform context-specific functions. Differentiation-associated exaptation does not refer to complete changes in the function(s) of a pathway, but rather to its niche- (differentiation-)-dependent modification according to those specific conditions that are present in a particular context. The corresponding subtle changes in the activity of particular proteins may be attained through the involvement of compounds' isoforms, the activity of regulatory subunits, and the extent to which niche-associated exaptation can evolve (instead of being convergently replaced by a functionally-analogous, but independent pathway) is determined by the plasticity and dispensability of a particular pathway. This last, in turn, might be determined by particular physicochemical constraints (Kempes and Krakauer, 2020; Panina et al., 2020 for the particular case of Ca^{2+} signaling).

Therefore, in addition to the traditional top-down approach to the analysis of mechanistic causes of phenomena, we propose to pursue a bottom-up comparative *functional* analysis of *individualities/quirks* of an organism, either in health or disease (as has been done, but for transcriptome data, within The Tabula Sapiens Consortium, 2022, and more generally—in the Tabula Projects, czbiohub.org/tabula-projects; see also Liu and Zhang, 2022). The formulation of the archetype makes it possible using very distant species (even those belonging to different kingdoms, like plants or fungi) to better understand the nature of diseases specific of animals. Until now this approach has been based on gene-('carrier'-) centric 'deep homologies' (Shubin et al., 1997).

It is highly probable that the ability to display above exaptations strongly differs in different living organisms (this could be assessed by analyzing differences between the organisms analyzed within the Tabula Projects, czbiohub.org/tabula-projects). Different tissues and tissue layers may also display different degrees of activity of individual proteins and pathways. Analysis of such variations allows proposing an organization of archetype-based data in the form of *physiological profiles* (Klein et al., 2021) or *cell avatars* (as a concept additionally considering the associated cell deployment dynamics; Rusin, 2022)—an approach different from element-centered *atlases* and *databases* or the traditional *cluster of differentiation* markers (CD)-based taxonomic nomenclature (hcdm.org), which pays reduced attention to the functional aspect of the more than 400 identified markers at the level of the whole organism, and struggles with the everyday multiplying condition-response pairs. *Physiological profiles* also differ from the “conditional arrays” approach in which information about the ‘organismic’ level is obtained by subjecting living organisms to “arrays of conditions” (e.g., Genevestigator, Hruz et al., 2008, or Fauser et al., 2022). Instead, the archetype-focused *physiological profiles* representation would require elaborating a hierarchy of functions, playing particular organisms and context-specific ‘molecular pathways’ (functional blocks and programs) the role of realized instances (=Aristotelian *species*) of combinations and relationships of such functions (Fig.7). *Physiological profiles* may also allow a better description of organisms with a ‘non-cellular-level diversity’ —characterized by a poor marker-dependent cellular diversity but with a nevertheless high diversity (in the form of high redundancy) at the ‘biochemical’ level— like plants or placozoans (e.g., Romanova et al., 2020). The *physiological profiles* of such poorly differentiated (at the cellular level) organisms would probably occupy an intermediate place between strongly differentiated organisms, like mammals are, and unicellular eukaryotes. The existing hurdles in the definition of carrier-based homologies in plants and the fuzziness of their “norm” (Meyen, 1973) also suggest that diversity within their *physiological profiles* occurs at ranks of organization different from those characteristic for animals. A possible clue of such non-cellular level diversity is the apparent difference in the temperature-sensing mechanisms between *Arabidopsis* (as a dicot?) and members of the *Poaceae* family (Preston et al., 2022). It should be noted that transcriptome-based methods do not allow discerning the level at which molecular diversity in a living organism can occur.

In the case of unicellular eukaryotes, their organization implies that all processes are contained in a single cell, and therefore must be synchronized by some ‘circadian’-like factor (for example, the common-for-all-processes membrane potential) that feeds back to and from almost all physiological processes taking place in the same cell to prevent the simultaneous execution of mutually exclusive processes. Such organization, unlike that of cells in multicellular organisms that can uncouple and delegate part of these functions to other cells or the organism as a whole, make studying individual physiological processes in unicellular eukaryotes an especially difficult task (as the function of interest will imminently be influenced by other concomitantly occurring processes). Comparison with cells of multicellular organisms in this case can allow establishing how the functions of unicellular eukaryotic organisms are wired.



Organism	Tissue	Element	Function
Mus musculus	fibroblasts	● 1 ● 1 ● 1	putative function 1 function (from a pool) ?
Rattus norvegicus	fibroblasts	● 2 ● 2 ● 2	putative function 1 function (from a pool) ?
Arabidopsis thaliana	mesophyll	– ● 3 ● 3	– function (from a pool) ?

Fig.7. Comparison of the schematic representations of current element- or organism-centered atlases and the proposed archetype-based platform.

A. Typical representation of 'biochemical'-level elements as entries of an atlas, a list, or a map. **B.** Representation in the form of physiological profiles. In this representation, biological species (or particular contexts) appear as realizations of particular functions that involve different elements (colored dots) in different proportions and relationships (colored curves). Represented are only functions belonging to a same functional level, although a complete physiological profile should include a hierarchy of functions (a hierarchy of colored curves).

Determining the organization of functional blocks may allow shedding light on the reasons of the differences existing between evolutionary pathways of different taxonomic groups—an aspect that is not contemplated by contemporary genealogy-based systematics, and for which it has no tools to deal with. Moreover, organisms' architectonics may serve as a justification for the existence of different taxonomic ranks. Another interesting issue would be to determine the particular "minimal toolsets" —the minimal biochemical Bauplans— common for the major groups of multicellular organisms. We consider that such cores may include important and highly conserved 'hub' factors like proteins of the pRb and TOR families, to mention some examples. From the genetic and kinship-centered viewpoint such core would constitute an important part of the so-called last eukaryotic common ancestor (LECA), although the particular ways in which they are placed in the *physiological profiles* may underlie the differences existing between "ground-plans" of multicellular organisms. In addition, and unlike in the LECA concept, *physiological profiles* do not require LECA to be a single ancestor, but rather point to a biochemical point of convergence that could instead have been reached by a group of different organisms.

We presented the rules to *investigate* the organization of living organisms. Nevertheless, this kind of knowledge is as well indispensable to acquire the ability to *design* completely new, artificial, living forms, as Synthetic Living Machines (Ebrahimkhani and Levin, 2021) or Multi-cellular Engineered Living Systems (M-CELS, Aydin et al., 2022). Current conventional machines are elementaristic systems, and very probably future organism-like machine designs will look at keeping low the number of undesired interactions between their elements. We think, however, that the very nature of the components of living organisms—proteins, lipids, carbohydrates and other small molecules, make them prone to establish unpredictable merons resulting from non-contemplated interactions, as "design bugs", but at the same time—as source of biological variability. The usage of non-natural amino acids could partially solve this kind of problems, but as far as they are not encoded and inherited, which will make such interaction hereditary and subjected to evolution by not necessarily human-specified constraints.

An important issue to consider when designing artificial organisms is the dynamics of becoming of existing living forms. The organization of 'natural' multicellular organisms is established during development as a series of simultaneous complexification processes that converge on some point of ontogenesis that can be considered the peak of development (Waddington, 1941). In the course of development the different subsystems composing an organism behave as elements which then start behaving as a whole. At the next stage of complexification, this whole becomes itself an element that, along with others elements, becomes the next-level whole (Fig.8). This description coincides with the existence of critical stages of development (Carlson, 2008; Cochard, 2012; Moore et al., 2013), and with observations that deviations from the trajectory of development occur predominantly at embryonic and early stages of development, rather than at later stages of development and in adult forms (Levin, 2020). The particular arrangement and alternation of hierarchical and combinative stages during development is organism-specific and probably determines the stability or flexibility of particular body plans during evolution (Grene, 1974a; Sober, 1980, 2000; Dupré, 1993; LaPorte, 1997, 2004; Amundson, 1998; Wilson, 1999; Okasha, 2002; Rieppel, 2006; Walsh, 2006; Devitt, 2008; Love, 2009; Wilson et al., 2009; Müller-Wille, 2011; Wilkins, 2013; Pavlinov, 2018).

In this regard, a fundamental question that becomes critical for the validity of our claims regarding the organization of existing multicellular organisms and the way in which artificial multicellular organisms can be designed and constructed is related to the way in which organisms should be conceived. Are organisms simple mosaics of gene-encoded traits, or are they hierarchically-organized set of merons (Meyen, 1977; 1978) / Universal Functional Blocks (Ugolev, 1991) / modules (Wagner, 1996; Wagner, Altenberg, 1996) / blocks (Hartwell et al., 1999 / Dynamical Patterning Modules (Benítez et al., 2018) / functional blocks (Panina et al., 2020)? Works on mechanisms of development (Svetlov, 1978; Schmalhausen, 1982) firmly support the second option. However, there is also a large body of evidence in favor of the first possibility: relatively simple elementaristic approaches have been applied at the 'organismic' level to correct (Pai et al., 2018) or even control (Xu et al., 2021) development, and in medicine, a single or few simple compounds are used to regulate macro-level functions. Similarly, cancer can be seen as a highly mosaistic formation relatively independent from constraints imposed by an organism (Panina et al., 2020), and in some occasions modularity itself has been understood as mosaistic, for example, in certain approaches to "build" synthetic tissues from 3D-printed blocks (Alcinesio et al., 2022). Thus, where does the borderline lie between these two possible organization types—gene-dependent mosaistic and the one based on hierarchically organized functional blocks?

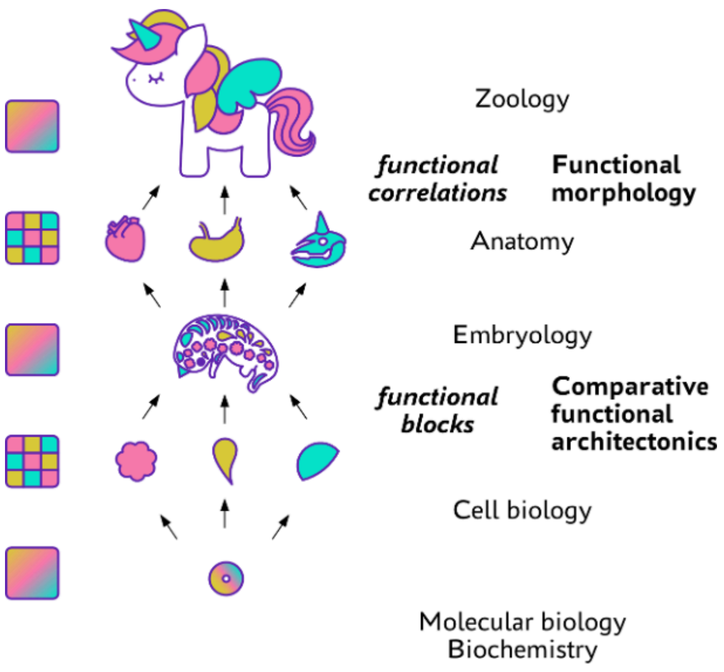


Fig.8. Development as a process of complexification.

Complexification is a sequence of stages in which a whole ("zygote", an 'integer') splits ("differentiate") into relatively independent elements ("mosaistic stage"), each of which, at a new stage of complexification, becomes a new whole. Each new whole is subjected to a new round of differentiation, and so on. Differentiation is accompanied by the establishment of "correlations". Complexification proceeds until the peak of development is reached (until no further differentiation is possible). Depicted is only one "timeline" of complexification that could take place in an abstract organism. Left: sequential change of 'mosaistic' and 'integral' stages for the presented timeline. Center: schematic representation of the changes occurring in an abstract organism, corresponding to the sequence of changes of 'mosaistic' and 'integral' stages. Right: rough division of biological disciplines that study each of the corresponding stage or a stage change.

Analysis of the ontogenesis in different organisms suggests that the interaction between levels of organization might be species-specific. Four types of such interlevel relationships were identified

(Schmalhausen, 1964; Belousov, 1987): in **Driesch's system** upper-level processes are robust against perturbations, unlike lower-level ones (fate change of individual cells does not influence the fate of the whole, that is significantly more robust; development in this case is notably equifinal). Example of such systems are vertebrates. In **emergent systems**, lower-level processes are robust, unlike those of the upper one (relocalization of individual cells do not change their fate, but such manipulation changes the fate of the whole; development in this case is mosaistic. Stages of development with these characteristics were called "epigenetic crises" (Waddington, 2011) and "critical periods of development" (Svetlov, 1978). Examples of such systems are annelids, mollusks, ascidians. **Holtfreter's systems** are characterized by the robustness of their developmental processes at both the lower and the upper levels of organization, making the fates of individual cells and the whole insensitive to such perturbations. An example of such systems are sponges. Finally, **epigenetic systems** are characterized by the sensitivity of both levels of organization to perturbations, hence they are typically regulated by a Driesch's system. Examples of such systems are plants. Despite this classification, however, a particular development does not proceed following just one of the above modalities, but includes features of several of them. Identification of the modules that underlie each type of development should suggest the way in which the study or rational modification of development should be undertaken. In this way, the reverse engineering task (Hartwell et al., 1999) might be solved depending on the desired features of the Synthetic Living Machine.

Altogether, what are the ranges of applicability that emerge for reductionistic and inductivistic approaches to analyze the 'biochemical' level of organization? As it has been historically shown, it depends on the goal. Comparative functional architectonics allows proposing hypotheses about the organization of living organisms, but detailing the mechanistic functioning of such blocks in organisms belonging to particular taxonomic groups, and the data to be used for such analyses (*species*-instances of different levels: elements, pathways or other 'measurables' and their particular interactions) are provided by reductionistic approaches. More specifically, reductionistic approaches are useful in cases when the intrinsic properties of the elements ('molecular pathways') are directly reflected on the organism's phenotype (we propose to denominate such effect *locality*; is for these *local* portions that mathematical models can be formulated, see section 3.1.2), whereas comparative functional architectonics is more advantageous in cases when the role of such elements, due to their multiplicity, cannot be directly deduced from their intrinsic properties (Fig.9).

The roles of pathways responsible for integrative functions ('hub pathways'), that define the 'biochemical core' of an organism, are better elucidated through comparative functional architectonics due to their roles in establishing organismic “correlations”. Nevertheless, ‘biochemical’ elements and pathways, in addition to their established major functions may have other (“non-canonical”) roles (see for example, Chen et al., 2022; Wasserman et al., 2022), which is in agreement with the intraorganismic “correlations” concept. The discovery of such “correlative” functions —if not conducted through comparative functional architectonics— is possible only by analyzing inconsistencies between results of experiments carried out following reductionistic approaches. There is, however, another recent alternative that allowed to uncover such non-canonical functions: the automated large-scale monitoring of phenotypic features, like the one used by Yoshihara and colleagues (Yoshihara et al., 2022). Using this technique, they uncovered the elements involved in the functional block responsible for gravitropism in plants: CCT2, a protein that functions in phosphatidylcholine biosynthesis; ATG5, a protein that functions in membrane remodeling during autophagy; UGP2, that produces the substrate for cellulose and callose polymer extension; and FAMA—a transcription factor. As it can be appreciated, knowing just the major (‘canonical’) functions played by these proteins would have been of limited help in proposing them as candidates for the gravity sensing mechanism in plants.

Above we mentioned that bottom-up inductive inferring (systematization) leads to reduction of descriptions. But how much reduction can be expected? Estimations that morphogenesis is regulated by around *50-60* differentiation pathways (Saetzler et al., 2011), can provide a notion about this balance by the numbers, and can provide a hint about the number of ‘biochemical’ level archetypes. Perhaps the composition of the minimal biochemical Bauplan mentioned above could serve as a starting point to start the search for ‘biochemical’-level archetypes.

In the case of the human brain, it has been estimated that the amount of data generated by a direct cataloging of its elements can reach up to 1 zettabyte (Ngai, 2022), turning just the analysis of such amount of information into an extraordinary challenge. From the comparative functional architectonics perspective, approaching the mammalian brain functional organization should involve the identification of functional ranks in the brain. In addition to conserved structures (e.g., Hain et al., 2022), several of the functional ranks will probably be hard to isolate, as the corresponding functions might be distributed among different —and not necessarily strictly delimited— physical structures of the brain (see Yost Hayden, 2022). Hence, the corresponding functional hierarchy can be established by the functional analysis of anatomically dissimilar brains of organisms belonging to different taxonomic species with nevertheless close cognitive abilities like mammals and corvids (Güntürkün and Bugnyar, 2016; Liao et al., 2022). Moreover, it seems that certain basic principles of nerve systems functioning can be as well expanded to invertebrates. This is indicated by the fact that both octopuses (de Souza Medeiros et al., 2021) and jumping spiders (Rößler et al., 2022) exhibit sleep patterns that are comparable to those seen in mammals. Addition of information about physiological changes related to the accentuation of particular traits (like curiosity, aggressiveness, but also impairment like deafness or blindness) would allow a better delimiting of the corresponding functional blocks, and the identification of the way in which functional blocks are linked.

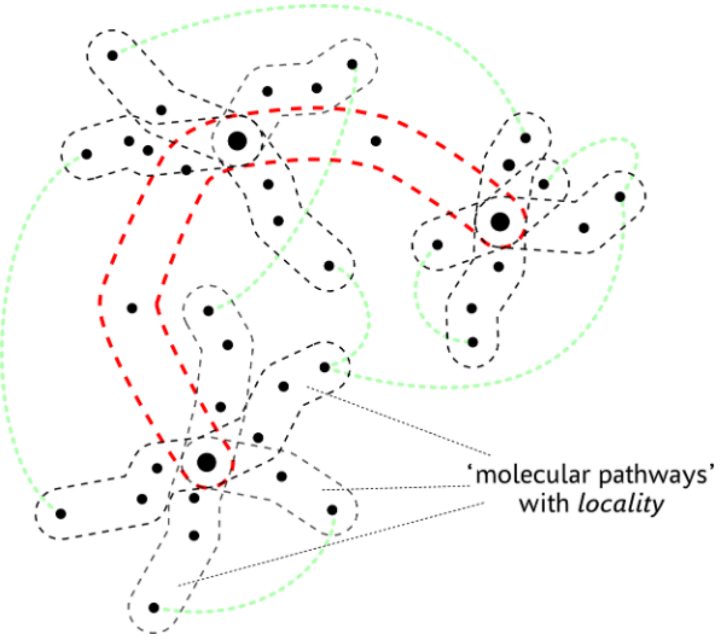


Fig.9. Areas of application of reductionistic approaches and comparative functional architectonics as a function of the organization of 'molecular pathways'.

According to the principle of 'correlations' 'molecular pathways' characterized by the property of *locality* have to feed their activity back to the organism. This can take place through other "open-ended" 'molecular pathways', for which the feedback may act as an input signal. In multicellular organisms the produced feedback signal, and the 'molecular pathway' processing it, may be physically separated, whereas in unicellular organisms they have to be interwoven. The linkage between elements indicates interaction, but does not imply the simultaneity of such interactions. The property of *locality* indicates that the cascade has a single phenotypic output. The 'downward' regulation of such cascades is exerted not through gene regulatory networks, but through external regulators (membrane potential, mechanical signals, chemical signals). The cascade outlined with a red dotted line corresponds to a higher functional level (it involves elements-hubs that form part of cascades with *locality*). Every of these arrangements is responsible for a program of a different level (see Fig.2). The "inner-interconnectedness" is achieved not only through interaction within 'molecular pathways', but also through feedback in the form of sensed external stimuli (dotted green lines). This configuration cannot be described as a scale-free network outside regions of *locality* of 'molecular pathways' and eliminates the "open-endedness" proper of scale-free networks.

Works on comparative functional architectonic like our previous ones (Pérez Koldenkova and Hatsugai, 2017; Pérez Koldenkova and Hatsugai, 2018) are considered to *precede* the research itself to establish its rationale and to design the appropriate experiments that will allow assessing the working hypotheses, for the formulation of which there is no established methodology. But what is the purpose of an experiment in our approach? Large sets of experimental results appear essential to compose comparison series. However, it can be noticed that in this case the weight of an experiment *as a proof* for a hypothesis is reduced. Instead, significantly increased are the requirements *to the theoretical background* on which the experiments are based upon. For example, establishing the (bauplan-) *homology* of neurons belonging to the primary motor cortex in three mammal species (BRAIN, 2021) required a several-years collaboration between 26 research teams, the analysis of 2.2 million+ of cells/nuclei, the additional assessment of more than a million cells for chromatin information, the analysis by Patch-seq for more than 500 neurons, amounting the obtained information 241.3 Tb (nature.com/immersive/d42859-021-00067-2/index.html; last access on December 1, 2022). From such "experiment-centered" view, how many experiments will be considered necessary to establish the functional *analogy* between Ca^{2+} signaling in plants and animals we postulated in a previous work with a wider scope (Panina et al., 2020)? *Is an experiment in principle suitable to prove an analogy?*

This may contrast with our claim of the experimental testability of hypotheses produced by the comparative functional architectonic approach. In this case, however, the criterion of trustworthiness of an assumption changes. This criterion, as we saw in section 3.3, widens and becomes related to the integrity and inner interconectedness of an upper-level framework. Roughly, experiments can be considered platonic elements (they will always "produce falsifiable science" in a bottom-up direction), whereas proving analogies requires a top-down approach and division of a wholistic higher-level archetype-like framework (see sections 2.1, 2.2.1). It is the correct formulation of the whole(s) (=the encompassing 'outer' archetype) what allows the correct identification of parts-analogs (section 3.1). These organizations basically repeat those in Fig.3.

Establishing analogies (as pattern recognition analyses) is where machine learning approaches could become game changers. However, the requirement of training sets in the form of *properly structured* raw data will still persist. The main difficulty in the application of these tools to biological tasks reside on the fact that current machine learning approaches use 'measurable' data type (describing the 'state' or 'value' of a variable, Zhang, 2018) but include functional relationships (in the form of the so-called knowledge-graphs) as semantic properties ('meaningful' data type, that describes the meaning of that 'state' or 'value') *based on human experience*. Semantic properties, however, still correspond to *tags* added to variables (section 2.1.1) and semantic capabilities in current AI approaches are achieved through 'score matching' between such tags of 'measurables' (Majumder et al., 2021; Steen and Hariharan, 2021). Thus, even a trained algorithm still creates a short-sighted deterministic and definition-driven archetype-like "*cloud*type" (Fig.10) that might obstruct exploratory research by leaving out of scope relationships not included in training sets (Foltz-Smith, 2020). To better understand this point, the following difference can be stressed: are large language models (LLMs) able to deduce features of modern science from the large corpus of scientific works they were trained on, or they just emit judgments about the state of science following "most linked" words in the texts of scientists whose research interests are related to the status of modern science, and that were used in LLMs' training? Another question that has to be tackled to determine the feasibility of the usage of current machine learning approaches to devise biological diversity is: how are related language and biological diversity powers? Is the power of biological diversity —at all its possible levels— larger, equal or lower than that of language? Answering this and other questions that may derive could give a cue on the possibility of the usage of natural language processors to approach the "language of Nature"—and the number of corresponding semantic parameters that might be required to describe living organisms using 'measurable' data type. However, even in this case "brute force" machine learning approaches will not provide a comprehensive understanding of the roles that individual elements play in the architecture of living organisms.

An important obstacle in the work with the archetype and archetype-homologies is related to their poor formalizability. Most modern tools (hardware included) are designed to work with segmented 'measurables'. Perhaps studies based on the *cloud*type will benefit from the usage of quantum computing, which logic of work is more akin to the archetype organization. It might be of interest that the lower-level elements (instances) of the archetype represent a sort of border conditions that might not require full coherence of the corresponding qubits involved in quantum computation, making it possible to set them by a conventional computing system paired to the quantum computer. Such pairing would presumably allow to effectively reduce the requirements of time in the superposition state (for this class of tasks) which has been one of the main obstacles to the wide adoption of quantum computing (Shor, 1995).

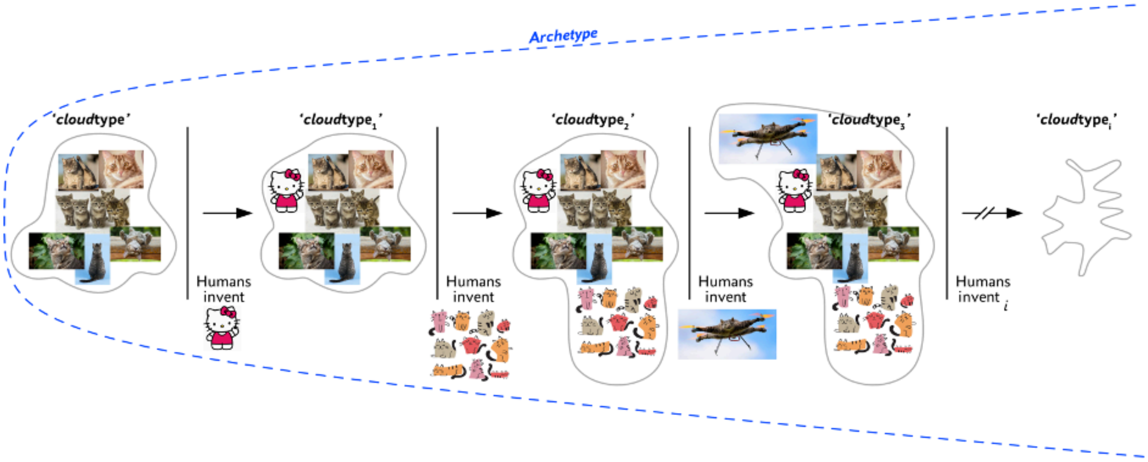


Fig.10. Difference between the archetype and a ML-constructed cloudtype—on the example of "what is a cat?".

Through training, the cloudtype becomes enriched with the different meanings humans associate with the concept of cat. In the end, the cloudtype may turn more knowledgeable than any individually taken human being, yet it still entirely depends on human creativity for further expansion, as humans operate with archetypes—the content of concepts, and not with some database of externally-defined properties (like the one a cloudtype is).

Formalization of archetypes is also hindered by differences in researchers' goals, which are reflected in different ways to conduct meronomic divisions (see Bongard and Levin, 2022). The total number of such possible divisions, although surpassing the number of objects any human can handle, is not infinite, as the number of mutual connections ("correlations" or function-oriented time-dependent arrangements, section 2.1) is limited. Therefore, it can be subjected to formalization, although a one more challenging than the "simple" formalization of elements. Important here is that elements do not combine freely in all possible combinations, but in more or less strict associations that can be determined through comparative functional architectonics, and which number is lower than that of the individual elements.

A very sensible drawback of the inductive approach we propose is that details-instances (isolated facts) of the general phenomenon being approached might be considered disparate, insufficient and disconnected. For example, to obtain a general idea about the cellular-level processes described in our previous work (Panina et al., 2020), we had to compare results obtained on organisms which are typically not considered experimentally comparable. Such peculiarity imposes the necessity to approach the studied phenomenon *in its totality* (as it requires approaching the archetype of this phenomenon), turning this requirement into an important initial barrier for the wide adoption of the results brought by this type of studies (mostly—because of the way in which specialization is currently achieved in science). It should be noted, however, that after this initial “slow” stage, the study of the different-level archetypes allows an *extremely fast* uncovering of the organization of organisms —in different taxonomic groups— by far surpassing the rate with which such uncovering can be attained (if at all) through reductionistic approaches. This is possible due to the postulated similarity and reduced number of functional blocks and body plans among living organism.

To conclude, it is necessary to mention that in philosophy of science the method presented in this work —comparative functional architectonics— has been historically regarded to as the *method of general typology*, or *the method of the (arche) type* (also known as the *method of morphological spectra*, Mamkaev, 2012). As it could be appreciated, a typological representation includes not only genus-species relationships, but also partitive relationships (typology orders objects’ diversity [taxonomy] and objects’ parts [meronomy]). We introduced our ‘biochemical’-level term (‘comparative functional architectonics’) for the sake of clarity, although we do not insist on its usage to avoid potential future conflicts in the analysis of the already existing vast literature on the application of this method at the ‘organismic’ level of organization. We should nevertheless point to the lack of a language for the appropriate representation of ‘biochemical’-level analogs of ‘organismic’-level typological concepts, like *styles*, *biomorphs*, α- and β-*archetypes*, *refrens*, *radicals*, *steresis*, *license* and others (Lyubarsky, 1996), that were left without analysis for the sake of shortness. For this same reason, several of the terms, concepts and views approached were presented anachronically. We intentionally did this for specific purposes of the present work and to avoid extensive related discussions and detailing. An accurate representation of the history of these concepts and discussions around them (when available) can be found elsewhere.

Throughout the text we referred to the analogy between top-directed inferring and development. Such assumption requires validation, and in sections 3, 3.3, and above, we presented a criterion to conduct it— the formulation of a wider innerly-interconnected framework that could serve as a ‘higher organizational level’ for the taken level of analysis. In the next, we will appeal to the analogy between inferring and development, and apply the rules from section 3, to formulate in an explicit form the top conceptual framework subjacing our studies on comparative functional architectonics (Fig.11)—the general theory of development.

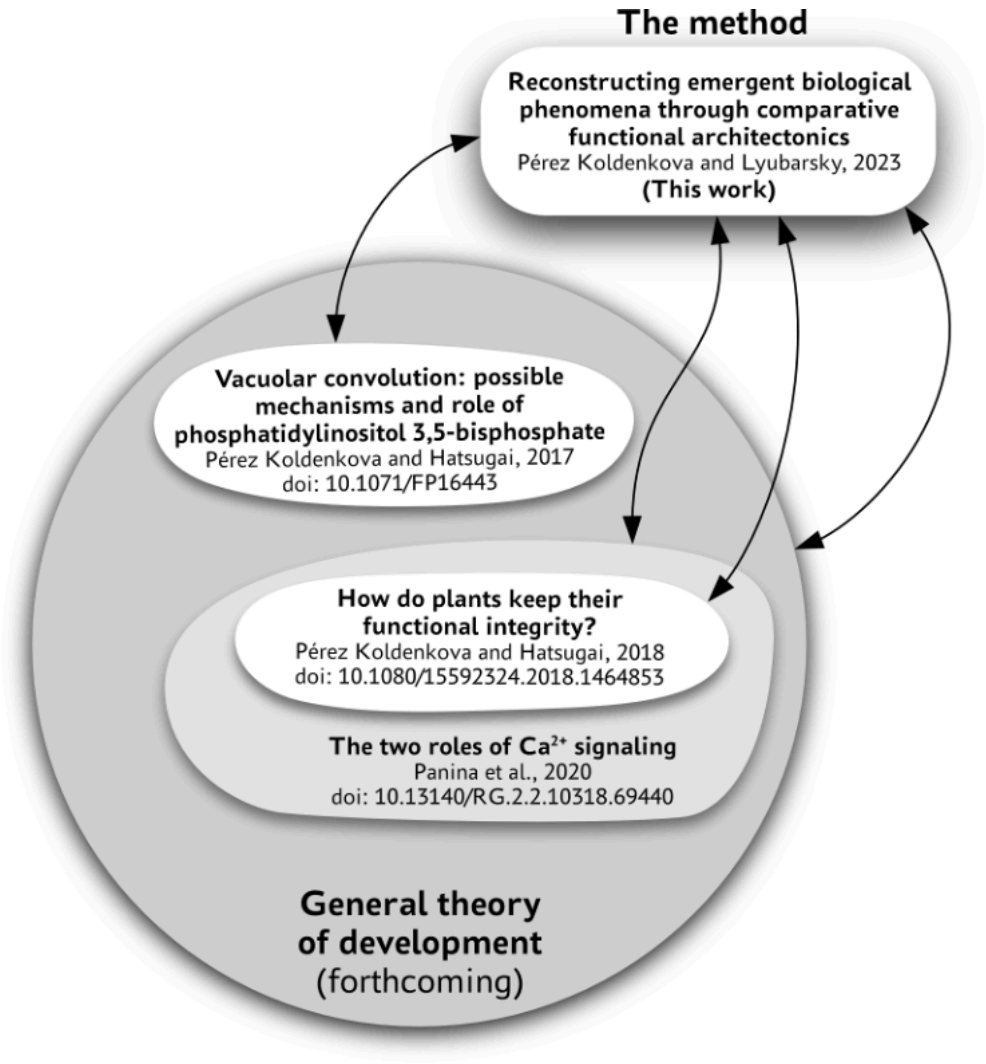


Fig.11 Relationship of our studies on the comparative functional architectonics approach outlined in the present work. Works: “Vacuolar convolution: possible mechanisms and role of phosphatidylinositol 3,5-bisphosphate.” (Pérez Koldenkova and Hatsugai, 2017). Predicted: the general scheme of processes leading to vacuolar convolution in plants. Status: a predicted step of the scheme was experimentally confirmed; proof of other steps of the scheme are pending. “How do plants keep their functional integrity?” (Pérez Koldenkova and Hatsugai, 2018). Predicted: the role of long distance signals in plant integrity maintenance. Status: proof of experimentally-testable steps is pending. “The two roles of Ca^{2+} signaling” (Panina et al., 2020). Predicted: the orchestrating role of Ca^{2+} signals in developmental processes of multicellular organisms. Status: proof of experimentally-testable steps is pending.

Contributions

Conceived the work—VPK. Added the magic—GYuL. Wrote the manuscript—VPK, aided by chatGPT (Dec 15, 2022–March 23, 2023 versions, https://chat.openai.com). Read, improved and agreed with the final manuscript version—GYuL, VPK.

Acknowledgments

The authors would like to thank *Boris Zhukov* (Moscow, Russia), *Evgenii Rudnyi* (Germany), *Igor Pavlinov* (Moscow State University, Russia), *Denis Tulinov* (Industrial Union "NeuroNet", Russia), *Anna Pavlova* (Russia) and *zlatopes* for providing useful information that helped to enrich the text. Discussions with *Leonid U.* (Russia) and *Elena Govorunova* (The University of Texas, USA) were used to elaborate parts of the text. The authors would also like to thank *John S. Wilkins* (University of Melbourne, Australia) and *Igor Adameyko* (Karolinska Institutet, Sweden) for their thorough revision, improvements and suggestions made to the manuscript. The help of Sasha, Tony and Lera was crucial for the elaboration of the text and is highly acknowledged. References to some of the studies cited in the present work were gathered from science popularization websites alev.biz, elementy.ru, quantamagazine.org, sciencedaily.com, phys.org, and newscientist.com. VPK would also like to thank Rusu, L.K., marinsita, P. Avendaño, J. Herrera and Denisse for their support and motivation during the work.

Image sources

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- **Fig.2** https://9gag.com/gag/aRXX6ry
- **Fig.3** https://en.wikipedia.org/wiki/Aristotle, https://en.wikipedia.org/wiki/Plato
- **Fig.5** https://ib.bioninja.com.au/_Media/pentadactyl-limb_med.jpeg (redrawn, modified)
- **Fig.8** https://www.clipartmax.com/max/m2i8H7A0G6H7K9G6/ (redrawn, modified)
- **Fig.10** https://club.foto.ru/forum/view_post.php?p_id=12796863 (modified), https://i.pinimg.com/originals/a8/07/e7/a807e70f2aade41bc18a0d1ba82bcbee.jpg (modified), https://media.baamboozle.com/uploads/images/570915/1653888455_255446.jpeg (modified), https://chudo-prirody.com/uploads/posts/2021-08/1628790810_98-p-morda-kota-foto-113.jpg (modified), https://www.shutterstock.com/image-photo/gray-kitten-resting-bizarre-posture-

149489132 (preview), https://www.pinterest.com.mx/pin/559501953686019665/ (modified), https://sprintally.com/top-10-fastest-cats-in-the-world/?feed_id=7112&_unique_id=60d32435483f4 (modified), https://in.pinterest.com/pin/637189047260010969/, http://clipart-library.com/clip-art/222-2225438_hello-kitty-vector-png.htm

Footnotes

[1] https://openorganelle.janelia.org/, http://www.theplantlist.org/, https://braininitiative.nih.gov/, https://www.proteinatlas.org/, https://www.plantcellatlas.org/, https://www.humancellatlas.org/, https://ngdc.cncb.ac.cn/aging/index, https://genevestigator.com/, https://esmatlas.com/, to mention some examples.

[2] See a similar opinion, but from the nominalistic viewpoint neglecting the existence of ideas in nature in https://www.newscientist.com/article/2349359-why-the-laws-of-physics-dont-actually-exist/

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.