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Elements of Relational Biology

Variation, Plasticity and Interfaces with the Ecosystem

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Abstract

Drawing primarily on our own writings, this chapter proposes a general framework for thinking about relational biology. New concepts, such as “enablement” and “thickness,” are discussed from a hermeneutic philosophical perspective. In contrast to determinism and a biology based on invariants and a space of possibilities given a priori, we argue that biology must be understood in terms of variation, historicity, and relations. Organisms are not pre-established units that subsequently enter into relationships; rather, they are historical configurations of relationships and constraints. The hermeneutic perspective allows us to consider not only organisms, but also—and above all—the constitution of their possibilities. To illustrate and support the theoretical argument, we offer the examples of the immune system and brain plasticity. Enabled biological possibilities are constituted and channeled relationally as certain possibilities become “thicker” than others. Thus, this framework helps rationalize the extreme diversity, or, in other words, the singularity, of the immune and nervous system across organisms.

Keywords Variation; Historicity; Enablement; Thickness; Plasticity; Immunity; Brain

1 Introduction

In this paper, we aim to propose theoretical elements for rethinking the role and centrality of “relationality” in biology. Therefore, it is necessary to challenge certain “dominant” ways in which biology and life are conceived. Furthermore, it is necessary to explore some epistemological and philosophical tools that could help redirect customary methods in the philosophy of science. The new concepts proposed here introduce a new conception of relationality, which will be applied to the immune system and the brain.

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What is life? What is an organism? This way of asking questions determines the form of the answer. The question “What is it?” requires that the answer be a definition. To define means to draw boundaries (“finis” in Latin), within which lie the essential elements that characterize the object of knowledge. Even when essential elements are not explicitly mentioned, the definition remains the fundamental element of knowledge. Is it always possible to answer questions with complete and well-formed definitions capable of encompassing all aspects of life? In biology, this question has often been addressed through the search for a fundamental invariant.

Is it really possible to identify invariants of life? If one believes that an invariant of life exists and adopts a reductionist philosophical approach, the answer to this question is affirmative. Indeed, molecular biology originated in precisely this way. Monod and Jacob, the great founders of the theoretical framework that dominates genocentric molecular biology, asserted that the fundamental invariant of life is DNA. This line of reasoning represents a way of organizing knowledge that is undoubtedly useful in many respects. However, when a way of organizing thought becomes the only means of constructing an ontology, it amounts to imposing a rationality on nature that, in reality, merely mimics our own method of rational—if not ethical—reasoning².

However, it should be noted that physics does not ask “what is matter” or “what is energy,” but rather analyzes and organizes them, correlating and distinguishing them through mathematics, using their fundamental properties to define “what an electron is,” “what a Higgs boson is,” and so on... At the heart of the organization of inert matter and its dynamics lies its analysis in terms of “invariants” and “optimality” (the conservation principles and geodesics in phase spaces provided by the theory)—both of which are to be understood in terms of “mathematical symmetries”; we will return to this later. In biology, the limitations of this approach became apparent immediately, but the need for a different epistemological approach—which remains a minority view in biology—makes it difficult to consider other methodologies.

Consequently, thinking in a radically relational way poses a scientific challenge because, normally, building a science means grounding it in fundamental invariants—or at least that is the key insight from mathematics and physics. This is also an epistemological and philosophical challenge because it requires “moving beyond” the approaches that have characterized the philosophy of science thus far.

When the scientific observable changes, we must change our way of thinking—our scientific perspective. Within physics itself, this has been achieved without altering the laws of conservation—the foundation of all dynamics of inertial systems: the transition from Galileo to Newton, to hydrodynamics, thermodynamics, microphysics, relativity, and so on, has required significant shifts in perspective, sometimes unifying in nature (for example, Newton, Maxwell, Einstein: falling apples and planets, electricity and magnetism, gravitation and inertia...), never “reduced” to a “lower level.” Despite the “unifications” that are still lacking—such as that of relativistic and quantum fields—the great theoretical unity lies in the principles of conservation or symmetry: “every fundamental principle in physics is a principle of symmetry,” observes H. Weyl³.

² From this perspective, it is worth noting that molecular biologists had come to assert that the “non-coding” parts of DNA were “junk” DNA. We will return to the topic of “ethics” in relation to the notion of “imperative Pythagoreanism”: cognition and living beings follow orders and instructions (coded ones), as those that are omnipresent in the technosciences, from computers’ operating systems to “instructions/orders” in DNA.

³ The conservation principles are expressed by continuous symmetries in the equations (Noether’s Theorems, Kosmann-Schwarzbach (2011)).

On the contrary, Darwin bases his theory on a “principle of non-conservation,” his first principle (in four of the first six chapters of *On the Origin of Species*): “descent with modification” and “motility” (allopatric speciation is a starting point in (Darwin 1859)). In other words, organisms—phenotypes, that is, the relevant observable traits—change, as a matter of principle, over time and at each reproduction.

Thus, since Galileo, physics has analyzed what alters the “conservation” (gravitation and friction, which alter Galilean inertia) of generic objects along specific trajectories: one falling body is equivalent to another; one electron is identical to all others—they are *generic*, a property of symmetry by permutation; they follow optimal (*specific*) paths defined on appropriate phase spaces and derived from conservation principles, such as symmetries. The “objects” of biology are, first and foremost, ever-changing; they continually break symmetries, they are specific, while their trajectories are generic, possible ones (Bailly and Longo 2006). Furthermore, the relational and historical “constraints” that “enable” them—making their dynamics viable and locally “stable”—must be analyzed (Longo et al. 2012; Montévil and Mossio 2015). Biological evolution, unfolding over historical time at rhythms specific to the organism, is intertwined with the synchronic relationality at the heart of our reflection.

What, then, is an organism? It is not possible to answer this question through a completely general definition, nor even in a “specific” case. As we shall see, the organism is intelligible only at the intersection of a historical (evolutionary) trajectory and a relational (ecosystemic) structure. In other words, at most, it is possible to attempt to provide a history (in the sense of the humanities (Longo 2018)) of an organism (Montévil 2019) and analyze it within an ecosystemic context—the focus of our analysis—an epistemology that Montévil and Mossio (2020) define as “hybrid.” Through this approach, it is possible to define a specific organism on a case-by-case basis, which is and remains an object characterized by change.

From a philosophical standpoint, the analytical linguistic turn and 20th-century hermeneutics have destabilized the problem of the search for essence, which is still present in molecular biology. A linguistic structure has been proposed within biology: the sequences of four letters in the DNA alphabet are said to be the fundamental invariant of living beings. This is not enough. In this regard, philosophical hermeneutics has sought to engage with reality by attempting to grasp its dynamism and relational nature. *Mutatis mutandis*, it offers interesting conceptual tools for making definitions dynamic and for adequately addressing the problems posed by biology.

In summary, biology raises two fundamental questions: (i) rethinking the concept of relation, in opposition to reductionist perspectives and beyond physics; (ii) placing the concept of time at the heart of biological thought.⁴ These aspects require us to rethink the very domain of biology and its object of inquiry in order to distinguish it from physics, and the present chapter proposes new conceptual tools to tackle this challenge. First, Sect. 2 outlines the relational biology framework that we envision can respond to the needs posed by question (i), while Sect. 3 explains how the temporal dimension (and thus historicity) are subsumed as central in this framework, thus addressing question (ii). Sect. 4 further elaborates upon two key notions of our relational account, that is, the one of relational space and that of thickness. Sect. 5 discusses two paradigmatic examples of

⁴ Obviously, the concept of historicity is already present within evolutionism—yet not really in neo-Darwinism (the “optimum methods” of neo-Darwinism are independent of time), but here we want to consider time more generally—or in its multidimensionality—and assign it a crucial epistemological role; for example, by treating it as an operator rather than a parameter, as physics has done from Galileo to Schrödinger.

‘relational’ systems: the immune system (Sects. 5.1-5.3) and the brain (Sect. 5.4), whose constitutive relationships with the surrounding ecosystem underlie their plasticity and heterogeneity. Sect. 6 offers a summary and some concluding remarks.

2 Space and Relationality in Biology

A scientific turning point is often a matter of a shift in perspective—that is, a new way of looking at the same phenomena or the same area of knowledge from a different point of view. This shift in perspective may also be based on the choice of a different priority: the same objects or the same conceptual structure, but a different epistemic assessment of “what comes first.” In a certain sense, the shift from Pythagoras’s ontological prioritization of numbers to Euclid’s geometry—based on axioms for “producing/drawing,” as Euclid puts it, segments, lines, circles, parallel lines...—establishes different priorities: spatial symmetries take precedence over numbers.⁵ We know what happened two thousand years later, when some scientists decided to look at planetary systems from a different perspective—namely, from the Sun’s point of view. Turning to an important biological example of a shift in perspective—cancer—Soto and Sonnenschein proposed considering tissue as a relational structure among cells, rather than the cell as a scientific observable (Sonnenschein and Soto 1999), and not reducing the problem of cancer to DNA, conceived as the essence of the cell and thus of its pathologies. In our view, the problems and limitations of mainstream molecular biology and its epistemology highlight the need for a methodological and philosophical shift: cancer, for example, would be the failure of a triangular relationship between “tissue, organism, and ecosystem.”⁶

To move from the reductionist and deterministic perspective typical of molecular biology (Monod 1970 and Jacob 1970) to a relational perspective, we need to view biology as something distinct from physics, though not in contradiction with it. For this reason, new epistemological tools are needed—ones that move away from the idea that it is necessary to create “a physical theory of evolution” (Monod 1970), based on a fundamental invariant, DNA. The consequence of this is that, in biology, philosophical, epistemological, and mathematical tools are often applied uncritically (Bailly and Longo 2006; Sarti et al. 2022; Marinucci 2023). During the 18th and 19th centuries, the scientific and epistemological categories that accompanied the development of physics were established and subsequently applied to biology: from the role of invariants (beginning with Galilean inertia, a principle of invariance and conservation) to differential calculus. In short, over the course of four exceptionally fruitful centuries, a very powerful physical “structure of determination” was proposed: within predefined spaces of possibilities (of “phases”—observables and relevant parameters), defined in different ways by different theories, “optimal trajectories” were studied, even in highly abstract spaces, such as in quantum physics, where, moreover, “determination” may not imply predictability.

As far as biology is concerned, we need to move beyond deterministic approaches—in which the space of possibilities and the “laws” of dynamics⁷ are “determined a priori”—and study biological phenomena from a different perspective: a historical and relational one. Of course, the concept of

⁵ Euclid’s axioms maximize symmetries, and the proofs are based on rotations and translations—that is, on symmetries of the plane (Longo 2011).

⁶ Endocrine disruptors, which have been extensively studied by C. Sonnenschein and A. Soto (Soto and Sonnenschein 2010), interfere with the relationships between cells, tissues, and organisms within an ecosystem, as they regulate cell reproduction.

⁷ See, in this regard, Sects. 6.1–6.4.

relation has long been discussed in scientific circles, so it is necessary to understand what constitutes this new relational approach that is outlined here.

The concept of relation is also present in reductionist and deterministic approaches. Jacob asserts that epigenetic elements play a role in the selection of possibilities (Jacob 1970, p. 18) rather than in their constitution. Possibilities are determined by DNA, which, as we noted, is considered the fundamental invariant of life. However, DNA, viewed as a biological invariant, bears a strong resemblance to the question of the necessity of an essence—and thus goes far beyond modern physics.⁸ From this perspective, a radically relational theoretical framework cannot admit of a fundamental invariant. On the contrary, if theoretical invariants are posited—or even more so if one conceives of the forms of living beings as expressing an essence—biological relationships are not constitutive, since they are predetermined by the elements that compose them.

On the contrary, as evolution demonstrates—or as will be seen in relation to the immune system and the brain—biological plasticity and its configurations cannot be fully determined a priori, but change under historical-relational constraints. In other words, there is no principle of invariance or conservation capable of subsuming all possible variations a priori. For this reason, from a relational perspective, it is possible to adopt, on the grounds of empirical evidence, variation as a theoretical principle, since it cannot be explained as a theoretical object. After all, variation is not an accidental element in the development and evolution of living beings: as Darwin's first principle states, "reproduction with variation" ("descent with modification")—this is the primary driving force of evolution, and thus of life itself.

From an epistemological perspective, thinking about relationships means setting aside the question "What is it?" and the search for definitions as stable points from which to begin and at which to conclude scientific inquiry (as mentioned at the beginning of this text). It must be emphasized that approaches based on fixed definitions remain fundamental for studying individual elements of biological systems, precisely because they define their specific object of study. However, they are misleading when applied to a relational biology that takes variation as its theoretical principle. In the first case, following Platonic logic, the definition of "what" makes it possible to determine "how" the scientific object "is." In the relational case, following Nietzsche and the later Wittgenstein, it is the "how" that defines the "what" in each instance. The description of a biological phenomenon allows us to define what it is, not because it defines an essence, but because it tells an (evolutionary) story and characterizes a certain type of recurring (ecosystemic) interaction (relationality). Furthermore, these interactions are as dynamic as the definitions they produce. They do not seek merely to describe a sequence of individual configurations. From this perspective, biological interactions can reproduce the same effects because they are historically canalized, and not because of their essence or molecular stereospecificity (exact interactions between molecules that would determine their dynamics). The identity of biological structures is not fixed but consists of shifting dynamics. For this reason, the intelligibility of a biological object—an organism, a phenotype—lies at the intersection of a historical trajectory and a relational context (Montévil and Mossio 2020; Marinucci 2023). In particular, it becomes intelligible only through its "history": belonging to a species, clade, or more precisely to a "taxon," identifies a common ancestor shared by an entire "set" of organisms.

⁸ In this regard, it is very interesting that Monod also uses terminology that we might consider "theological." He asserts that, given the biological invariant (DNA), life is a "revelation" of what is contained within it, not a "creation" (Monod 1970).

When the “closures of constraints” (Montévil and Mossio 2015) that canalize biological interactions loosen, break, or change, they produce different effects: in this approach, DNA, for example, is viewed as a (highly significant) constraint on molecular dynamics—highly significant because it is a physicochemical trace of the entire evolution. From a relational perspective, canalization in and of itself does not define a biological interaction, but rather limits the expression of biological variation (Marinucci 2023); however, biological changes—such as how DNA can change or be modified—can alter biological dynamics and constraints. In other words, adopting variation as a theoretical biological principle (Montévil et al. 2016; Marinucci 2023) allows us to conceive of relationality as constitutive of biological objects, subject to historical constraints. Evolutionary historicity, therefore—composed of ecosystemic and organic relationships—creates “closures of constraints”⁹ that, by limiting and shaping variation, produce the “relative” (contingent, historical) dynamic stability of organisms. These simple statements summarize the importance of thinking using different hermeneutic approaches, in science and beyond.

Two characteristics are fundamental to a radically relational approach: 1. the absence of a fundamental invariant (such as DNA or organizational structures—for example, autopoietic ones, etc.) whose changes can be observed, and instead assuming variation as a principle; 2. proposing relational interaction (the “how”) as constitutive of the biological object (the “what”), according to history and contexts.

At this point, some clarification is needed regarding the concept of “relationship” in reductionism and relational biology (Marinucci 2023). “Reductionism” is not a scientific practice, but it is a philosophical concept. According to the latter, in order to know nature, it is necessary to decompose it into the constituent elements that allow to describe it completely. Reductionism has a strong ontological commitment. From a methodological perspective, one of the characteristics of reductionism is that it conceives the elements of a system as distinct and separable. In this sense, it is possible to define them and make them interact.

Within the relational frame, the elements of a system are firstly considered as *distinct* and *inseparable*.¹⁰ The inseparability opens the door to complexity and to the singularity of life with respect to physics, of something that is intrinsically beyond determination and whose analysis requires a different epistémé. The shift from “distinct and separable” to “distinct and inseparable” shows that a truly relational approach arises from overcoming the limitations of reductionist and deterministic approaches and, above all, from moving beyond the logical-analytic philosophical perspective. In biology, relationships are intrinsically dynamic; consequently, they do not produce a relational space (an organ, an organism, an ecosystem), but *are* that relational space¹¹ (Marinucci 2023). For this reason, the dynamism of biological relationships is always productive. The fact that

⁹ The autopoietic approach has been thoroughly revised by the work of Montévil and Mossio (Montévil and Mossio 2015): “closure of constraints” is an in-depth analysis of how processes generate constraints that channel or enable those processes, with many possible levels of entanglement; this was further extended to a “historical and relational approach” in (Montévil and Mossio 2020).

¹⁰ This concept is found in (Deleuze and Guattari 1994). In the context of this paper, it is used differently. The first difference lies in the biological context, which Deleuze does not explicitly address. The second lies in the fact that, in our relational approach, the structures created are dynamic and both provide and modify the identity of the elements.

¹¹ Relational space cannot be separated from relationships; therefore, it is not a product of the latter. Organic tissues cannot be separated from the relationships that constrain them. In fact, the disruption of relationships may lead to cancer. Furthermore, it is important to state that relationships are the relational space, because in biology, no object exists separately from its context. Instead of “object” and “context,” we propose that relationships are the relational space.

the elements of a relational space are distinct and inseparable means that they define themselves and their functions through interaction (they are inseparable). This means that the mode of interaction produces different qualities that cannot be reduced to the sum of its constituent elements. In fact, when the closures of constraints loosen or break, the interactions themselves produce different qualities (for example, pathologies or evolutionary change).

It is therefore necessary to give epistemological priority to the “spaces of biological relationships.” An ecosystem is not viewed as the result of interacting organisms; rather, organisms are analyzed as the result of their ecosystemic and historical relationships. A tissue is not viewed as a network of interacting cells; rather, cells are understood as components and as the result of a tissue structure: even though they share the same origin (the zygote) in a multicellular organism, they vary greatly from one tissue to another. First and foremost, what matters is not what the cells are, individually, but what they do, collectively, as a tissue structure. It is important to reiterate that “relational space” means that cells—or biological entities—define themselves and their functions within a relationship (they are distinct yet inseparable). As we will see later in the case of the immune system, the intelligibility of the proteins themselves—which mediate interactions between cells—is based on the fact that they have evolved and act within a relational context. Of course, this does not prevent us from reasoning about proteins, cells, and organisms, but always and first and foremost within a context—indeed, within a historical context: an organism or an ecosystem is the relational outcome of a history, and nothing about them can be understood without an ontophylogenetic historical and relational perspective¹².

3 Biological Time

What do terms like “time” and “history” mean in biology? If the elements of a relationship are defined through their interaction, temporality becomes fundamental, as evolution demonstrates. It is necessary to recognize that time and history are fundamental because they are constitutive in biology.¹³ On the contrary, in physics, history and temporality play no epistemological role in the understanding and/or constitution of generic physical objects. In physics, time is the framework within which a phenomenon is described (dx/dt), or the context in which events occur—Galileo’s great invention, based on his analysis of falling bodies, a process that he parametrized on time. The processual time of emergent physical phenomena is linked to their dynamics, but it does not serve to define physical objects, which remain generic and interchangeable, even in physical “emergence” phenomena (Longo 2025). For example, a hurricane from 300 millions years ago can be studied just like a hurricane today, and the molecules that make it up—whose network of interactions determines the emergent phenomenon—do not change over time. This is not the case for living beings: in an ecosystemic dynamic, not only does the network of interactions change, but so do the components of the network—the organisms—which evolve. In other words, the objects (organisms)

¹² An organism can be defined only as a process and analyzed as the result of a phylogenetic history (Lecointre et al. 2001); but also the first questions a doctor asks concern your age and medical history, your current ways of life.

¹³ Of course, this shift in perspective has a long history. First and foremost, Darwin, who proposed the two principles of heredity that enable us to understand biological historicity: reproduction with variation and selection. Then there is the organicist perspective. The challenge lies in connecting and enriching these two theoretical frameworks, particularly by overcoming certain limitations of the organicist approach. By the latter, we mean a long tradition stretching from the epigenetics of Waddington and McClintock to the autopoiesis of Maturana and Varela (Moreno and Mossio 2015).

in the ecosystem network change through their interactions. Furthermore, the transformations of the network as well as the interactions among biological rhythms constitute the time of evolution, which in turn also modifies the rhythms and their interactions (Longo 2021; see also, on the current “disruption” of the temporal fine-tuning between angiosperms and pollinators: Montévil 2025). The historical dimension thus becomes intrinsic to the characterization and understanding of organisms.

In biology, to summarize, it is not possible to provide a definition of life, because history plays a fundamental role. Furthermore, it is possible to propose multiple histories of life precisely because there are no fundamental invariants. Even DNA is a historical product, subject to change: indeed, it “follows” the historical and ecosystemic dynamics that shape or select it (West-Eberhard 2003). Historicity, in the sense of the philosophy of history, is a useful tool for conceiving of biology¹⁴, and evolutionism is the theory that recognizes historicity as playing a fundamental role, constitutive of the object of knowledge.

Time is undoubtedly central not only from an evolutionary perspective but also within organisms. On the one hand, organisms are “historical” in the evolutionary sense; on the other hand, their evolution has given rise to internal rhythms that enable their survival—another temporal dimension. A clear example is the heart rhythm. Here, too, this is a relational element because, even when considering only human beings, each person has their own heart rhythm, and this diversity does not indicate the presence of a pathology. Noble states that the heart rate is an oscillation without an oscillator (physically nonsensical). He argues that the rhythm is set up by the entire organism at a critical transition during embryogenesis (Noble 2006). It is relational and therefore inevitably specific to the individual organism. In other words, it expresses the uniqueness of the living being.

From a relational perspective, it has been argued that biological interactions and “closures of constraints” specify and enable the application of the concept of relational space to reality. “Relational space” is the theoretical object that represents organs, organisms, ecosystems, etc. Since they are constituted relationally and historically, organs possess both the similarities typical of their species (phylogeny) and the singularity typical of the ontogenetic relationality of each living being. Relational spaces, as demonstrated by the heart rate, cell reproduction, etc., constitute rhythms.

Biological time can be considered the result of biological interactions (Marinucci 2023). At the same time, it is an operator (Bailly and Longo 2009; Longo and Montévil 2014) that acts actively, contributing to the production of biological structures. These structures are dynamic, and their complexity can be studied and monitored through the times and rhythms that characterize them. Once again, then, time appears as the result of dynamics inherent to the organisms themselves. This gives rise to a circular (hermeneutic) logic, in which time as an operator and time as a result intersect productively. These structures are in themselves ever-changing, devoid of “essence”—that is, repeatedly and continuously subject to biological time: the invariants are “historicized,” contingent, and possess their own “characteristic” times, just like the constraints that stabilize them (Montévil and Mossio 2015). It is clear that these two notions of time are complementary.

¹⁴ It is also possible to conceive of history as that in which an essence manifests itself (“reveals itself”); however, in this way, as mentioned, the relational perspective is abandoned. In reality, the very premise of all physical theories—from Aristotle to Einstein and Schrödinger—that the *hic et nunc* is the realization of a possible (the space of dynamics must be pre-given) does not assign to the relationship the co-constitutive role of the object, its history, and its world.

Furthermore, on the one hand, there is the (irreversible) time of physics (thermodynamics), and on the other, the rhythms of living beings. Their relational coordination—and the distortions of this coordination—also contribute to historical and evolutionary time (Longo 2021). Obviously, the temporal dimensions of physics also operate in biology—the time of the thermodynamic processes at play, as well as specific physical frequencies, such as the circadian *frequency* (linked to the Earth’s rotation). Physical time interacts with biological time, but does not determine it (Bertolaso et al. 2026, forthcoming). It can be at the origin of biological time, just as the light-dark cycle is at the origin of organisms’ circadian *rhythms*. But these frequencies and rhythms then become relatively autonomous: “jet lag” demonstrates how the misalignment between the two causes distress and gradual adjustment—in this case, physics prevails and the organism adapts by changing, an aspect of its resilience.

4 The Domain of Relational Biology

As mentioned, discussing relationality in biology entails making profound changes. So far, we have considered the concepts of relation, space of possibilities, and time. In our view, a relational approach must define the biological object in relation to the physical object as well. This can be done through a brief comparison with physics (for further reading, see Marinucci 2023; Bailly and Longo 2006).

In both classical and quantum physics, the possibilities are always given a priori, albeit in different ways. In contrast, in biology, the possibilities are not entirely predictable a priori (Kauffman 2000; Bailly and Longo 2006). We recall that in physics objects are generic (symmetric, interchangeable, “indifferent”) and trajectories are specific (necessary singularities), while in biology objects are specific (historical singularities) and trajectories are generic (the indifference of future possible trajectories). It is thus necessary to consider the biological object in its singularity, in its contingency, albeit canalized by its evolutionary history. Precisely the irrepressible biological contingency enables the permanent possibility for “radical variation” (a ‘hopeful monster’). It represents an ever-present, yet indeterminable possibility. From this point of view, biology deals not only with possibilities but also with the constitution of new possibilities. It is not possible to infer the presence of inner ear bones from the jaw of a Devonian vertebrate (Longo et al. 2012).

While the biological object is specific, what constitutes it (its DNA, its organization) is historical-empirical; these are “historicized invariants” (Longo 2018). In other words, for biological research, they represent “historical-empirical a priori.”¹⁵ In other words, it is a matter of “a priori not of truth [. . .] but of a history that is given” (Foucault 2000, p. 170 ff.), i.e., no atemporal invariant (no truth) of a physical type is reached through them. In other words, explaining the organization of a historical-empirical a priori does not mean discovering its essence, but rather reconstructing its ontological-phylogenetic history.

To summarize, in general, we can say that: 1. relational space is the theoretical object of relational biology; 2. every relational space has its own historical-empirical organization (closures of constraints) (e.g., tissues, organisms, etc.); 3. this organization reveals the contingent trajectory of the theoretical object of biology, not its essence; 4. organisms, as historical-empirical a priori, are

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This quote from Foucault (Foucault 2000) is used here outside its original context (see Marinucci 2023).

theoretical objects that are (a) real, in that they historically exist, and (b) possible, in that they form the basis for their evolution.

As mentioned, in biology the complete list of possibilities is not given a priori; this means that the historically existing phenotypes (historical-empirical a priori) are known¹⁶. They change, insofar as they are relational objects; it is therefore interesting to describe this change. In other words, it is interesting to understand how new possibilities arise in biology, without claiming to determine them. The main feature that distinguishes biology from physics is that biology also deals with the constitution of the possible.

From this perspective, organic equilibrium is given by the relational space that changes over time and by the temporary stability (historicized invariant) of the “closures of constraints,” which lie at the center of biological organization. The contingency of organisms allows us to speak of the constitution of possibility without proposing a “structure of determination” for it, because organisms (historically and empirically a priori) have specific/historical structures and interact with a specific environment (they are inconceivable without that environment, and vice versa). The biological space of possibilities contains: 1. historically known possibilities (in every type of reproduction, phenotypes similar to those established by evolution are possible); 2. the “hopeful monster” (an unthinkable radical variation¹⁷); 3. “enabled” phenotypes (possibilities that can be interpreted through the interaction between historical and relational contingency and organisms).

4.1 The Constitution of the Possibilities: Enablement and Thickness

Given that the elements of a biological relationship are distinct yet inseparable, the application of physical causality (whether linear or complex) is problematic. In fact, the way in which biological interactions occur can not only produce different objects, but the elements of the relationship themselves are defined within the relationship and are conceptually (and biologically) inseparable from it. For this reason, it is interesting to further discuss the concepts of “enablement” (Longo et al. 2012) and “thickness” (Marinucci 2023).

As mentioned in the introduction, it is necessary to reconsider certain epistemological and philosophical concepts that are used in biology but that derive from physics and are often applied uncritically. In the theory of general relativity, there is already a departure from the concepts of earlier physics: “In general relativity, causes become interactions, and these interactions themselves constitute the tissue of the universe of their manifestations—its geometry: if we distort this tissue, the interactions change; if we intervene in the interactions, it is the tissue that becomes distorted” (Bailly and Longo 2006, p 60). In biology, the characteristics and deformations that express relational space refer both to the actual elements of an organism or an ecosystem and to what they make possible.

Relativity is always bound up with and is based first and foremost on invariant properties, through which objects and their trajectories are defined in physical spaces, such as geodesics in appropriate “phase spaces” (recall: spaces of observables and relevant parameters).¹⁸ In contrast, in biology, variation is always active (it is a theoretical principle), and this occurs within a space of changing

¹⁶ Relationality allows us to understand organisms insofar as they are dynamic. It applies both to the intelligibility of organisms and to the relational space that they are, for example, within an ecological niche. In other words, it is an evolutionary relational ontology. A preliminary discussion can be found in (Marinucci 2023).

¹⁷ For example, placental development resulting from a retroviral infection (Imakawa et al. 2022).

relationships, where it is impossible to fix the observables and relevant parameters a priori. This can, however, allow for the analysis of individual organisms within an ecosystem or individual cells within a tissue, but only after—or as part of—the relational structure that constitutes their horizon of meaning.

While in physics the possibilities are always given a priori, in biology the question is rather: how is a new possibility enabled? An evolutionary niche makes a biological dynamic possible, while it is also modified by that dynamic. In general, enablement allows us to conceive of certain possibilities for a new organism. Thickness is a tool for analyzing the transition from the possible to the real based on existing organisms and phenotypes. As mentioned, relational space is not constituted by the relationship between its elements, but is this relationship itself. Furthermore, the very elements of a relationship are defined during interaction. Consequently, organisms, ecosystems, etc., are relational spaces that exist within relational spaces. Their contingency and relationality enable something that can enter the realm of the real (a new phenotype). The enabled phenotypes or morphological changes have varying thickness, depending on the context. Here is an example. The kiwi is a well-known bird that, over the course of evolution, has lost the functionality of its wings, to the point of nearly losing them altogether. Some factors that were certainly important to this change include the fact that it is insectivorous (historical contingency), that its environment offers an abundance of food on the ground, and that there are no terrestrial predators (environmental contingency). Now, other factors certainly come into play, but the point is that, among countless environmental and phylogenetic variables, some are relevant. From an epistemological and theoretical point of view, these variables do not “explain” the real kiwi, but interpret it as a possibility. The point is that, by focusing on variations, it is possible to construct, a posteriori, the set of all relevant variables that influenced the kiwi’s enablement. In other words, and to summarize a crucial point: the new kiwi is not causally determined, but its enablement (i.e., what “makes it possible”) should be conceived and conceptualized. Given that phenotypes do not appear deterministically or causally in evolution, other changes were enabled (for example, the shape of the beak, the legs... see Darwin’s analysis of the Galápagos finches). Consequently, it is necessary to interpret the development of the relationships among the possibilities that were realized in a specific phenotype.

An analysis of the contingency of the kiwi allows us to assign weight to what is enabled. If enablement is a qualitative tool, thickness is the quantitative characterization of what is enabled. If multiple possibilities are enabled, analyzing the relationship between the stability of organisms and change allows us to track the evolution of the phenotype. If the environment changes, the organism does not have to change, but it can change or improve its adaptation. Thickness (Marinucci 2023) allows us to measure the extent to which an organism’s relational stability is capable of responding to environmental changes. Enablement and thickness allow us to reason about possible phenotypes. Nevertheless, the “hopeful monster” remains possible yet at the same time unthinkable, as it may represent a radical novelty.

¹⁸ Einstein initially referred to his approach as “Invariantentheorie.” As H. Weyl pointed out: “All the fundamental principles of physics are based on properties of symmetry”—symmetries, understood as groups of continuous transformations, constitute the mathematical framework of the properties that remain invariant under such transformations..

In conclusion, what is fundamental in biology is to think in terms of relationships, to consider variation as a principle, and to view the elements of a biological system as distinct and inseparable within the time and space of the ecosystem. If relationships do not constitute, but rather are, the relational space, then the theoretical objects are the relationships themselves, while the real objects are the tissues, organisms, ecosystems, and so on. Studying an organism means studying the constraints (relational equilibrium) that maintain its relational stability. The organism is therefore a product of evolutionary time and is characterized by its relationships. From this perspective, the organism can be considered a historical-empirical *a priori* (Marinucci 2023). Historicity implies radical contingency, and this is one of the key elements distinguishing biology from physics, in that biology deals with the constitution of a possibility that cannot be predetermined. This latter aspect leads to the need to conceive of new theoretical and specifically biological tools, such as “enablement” and “thickness” recalled above.

The next two sections of this paper are devoted to the immune system and the brain as examples of relational biology. These examples seek precisely to describe the plasticity of living organisms.

5 The Organism and the Ecosystem: Two Major Interfaces

The organism relates to the context in a particularly relevant way by two major “interfaces”: the immune system and the brain. Both these systems are the locus of a maximal “production of diversity” or “heterogenesis”: this allows continual adaptation to and the active modification of the environment. The concept of relational space is used precisely to capture this dynamism. Heterogenesis is produced in them in very different ways: in the brain, plasticity of neurons and of their connections and networks is at the core of it; in the immune system, it relies on the diversity of its protein repertoires and cellular components, which in turn enables immune response plasticity. Let us then briefly summarize some key aspects of these components of relational life.

5.1 Immune Heterogeneity: The Canalized Diversity of Immune Protein Repertoires

The immune system occupies centre stage in establishing and mediating the relation between the organism and its environment, contributing in this way to defining the boundaries of the organism itself ([Pradeu et al. 2019](#)). This relation entails a continual encounter with biological novelty, e.g. in the form of newly emerging pathological threats, and thus relies on evolved means to adapt and react to them, and subsequently to retain a memory of them. Crucially, the immune system’s ability to respond to and remember a previously encountered pathogen hinges upon its intrinsic heterogeneity and, relatedly, plasticity. Plasticity is not a given *a priori*, but rather an evolutionary outcome: it depends on—and manifests itself in various forms—based on the contingent relationships between organisms and their environment. In general, the immune system defines itself (what it is or becomes) based on how it interacts.

To zoom into concrete examples of heterogeneity and plasticity, it is useful to introduce in more detail some of the protein-protein interactions that enable immune response initiation and coordination. In particular, we focus on the so-called adaptive arm of the immune system, which is found only in vertebrates and is capable of molecularly specific and memory-inducing responses.

Key cells of the adaptive immune system are T and B lymphocytes. T lymphocytes possess receptors, i.e. surface proteins, that bind protein fragments (typically referred to as ‘antigens’) presented to them by specialized molecular complexes known as MHCs (major histocompatibility

complexes, which belong to two major subfamilies, class I and class II). MHCs are attached to the surface of almost all host cells and constantly present antigens of endogenous or exogenous origin to the immune system. The currently accepted view – deriving from Burnet’s clonal selection theory (Burnet 1959) – is that lymphocytes with a specific receptor (i.e., a lymphocyte clone) that can bind pathogen or tumour-associated antigens with sufficient strength become ‘activated’. (Note that activation happens in concomitance with co-stimulating molecular interactions involving other surface receptors and molecular mediators released by neighbouring immune cells in the inflammation site). This phenotypic state, consisting of activated intra-cellular biochemical reactions, enables effector functions; for instance, it enables so-called cytotoxic lymphocytes to clear the infected or malignant cells that initiated their activation. The three-protein interaction at the core of this process – between the T lymphocyte receptor, the antigen, and the MHC molecule – harbours an astounding degree of heterogeneity, or diversity, generated and canalized across ontogenetic and phylogenetic trajectories.

First, the diversity at the level of the receptor’s amino acid composition is actively produced during T-lymphocyte development in the thymus through a stochastic process known as V(D)J recombination. Statistical modelling has allowed researchers to extrapolate, from the available receptor data, the level of potential diversity embedded by this process, quantifying it to be equivalent to the effective repertoire size of $\sim 10^{61}$ different sequences ([Mora and Walczak 2018](#)). Diversity production through the V(D)J recombination leverages the stochasticity of molecular events of gene-segment extraction and re-arrangement and mutations, yet such a stochasticity is canalized by functional constraints. Indeed, a subsequent step of so-called thymic selection leads to the elimination of poorly reactive, or potentially autoreactive receptor-bearing lymphocytes, ahead of their release in the blood circulation. It has been estimated that selection reduces the potential diversity of T lymphocyte receptors to an effective size of $\sim 10^{19}$ sequences ([Mora and Walczak 2018](#)). The typical human repertoire of $\sim 10^{11}$ distinct T lymphocyte receptors can be thus conceptualized, in biostatistical terms, as a randomly drawn sample from this vast pool of potential diversity. In other words, the potential diversity of immune receptors is so huge that the majority of them in one individual are practically unique to that individual, thereby instantiating and exemplifying organismal specificity already at the molecular level. In other words, the contingency of biological relationships expresses the uniqueness of each individual’s immune system. This, in turn, is expressed through what is “enabled” and through the “thickness” that certain possibilities have relative to others. In this way, relationality through “thickness” directs the formation of a specific immune configuration.

Second, MHC genes are the most polymorphic genes in vertebrates, that is, they exhibit an unprecedented allelic richness which contributes another layer of diversity, this time at the population level. For instance, in humans, there are over 30,800 MHC class I alleles currently annotated¹⁹. Each allele’s antigen-binding groove has a specific biochemical composition that tends to present as antigens only protein fragments endowed with chemically complementary groups of amino acids. Since every individual inherits only 6 MHC alleles (3 from each parent), the landscape of antigens presented at the intra-individual level will be extremely diverse across different people, contributing to the observed inter-individual variability in disease susceptibility and outcome ([Howell 2014](#)).

¹⁹ See: <https://hla.alleles.org/pages/genes/statistics/>.

Diversity of immune receptors at the individual level, and the diversity of MHC alleles at the population level, are hypothesized to be functionally instrumental to immune protection: a diverse pool of molecules that can, on the one hand, present antigens with different molecular compositions and, on the other hand, recognize these antigens through binding, broadens the range of novel pathogens to which the organism can respond. Diversity in the amino acid composition of immune proteins can thus be seen as a form of anticipation of the potential diversity of antigenic challenges. Such diversity is not limited to the amino acid composition of immune receptors, but involves their structure as well: structural flexibility endows their antigen-binding interfaces with adaptability ([Rini et al. 1992](#)), a characteristic which ensures openness towards structurally diverse antigens. This is relevant especially for the other main class of immune receptors, namely B-lymphocyte receptors (also known as antibodies when in soluble form), which can bind to entire proteins with their tridimensional configuration instead of MHC-presented protein fragments.

5.2 Immune Plasticity and Memory as Propulsive Constraints

A more specific mode of anticipation is the one built up through the immune system's maintenance of long-term memory of past infections. As recalled by [Miquel and Hwang \(2016\)](#), immune memory is a powerful manifestation of organismal plasticity acting in the form of 'constants with propulsive value' à la Canguilhem ([Canguilhem 1943](#)). They are 'those which are stabilized in new constants but whose stability will not keep them from being eventually transcended again' (English translation from [Canguilhem 1991](#), p. 206): in other words, constants with propulsive value correspond to a form of stabilization that can produce new stable values, by virtue of the organism's normative capacity, thus another example of historicized rather than absolute invariance. As such, propulsivity is proper to biological constraints that are dynamically co-constituted with the environment by means of their own dynamics, enabling novelty to emerge ([Miquel and Hwang 2016](#)). By being constituted relationally, immune memory is inherently dynamic. The relational space creates constraints that enable new possibilities, the contingency of which allows for the expression of configurations with increased thickness. In other words, the constraints (thickness) direct the propulsive force, in that the possible (enabled) configurations are always contingent.

In practice, after an immune response, a subset of the T lymphocytes that were activated in an antigen-specific fashion enters a pool of cells called 'memory'. These cells carry forward and propagate to daughter cells molecular traces of their previous activation that essentially redefine the lymphocyte-antigen binding regime required for reactivation upon re-exposure to the antigen (particularly by decreasing the antigen doses required). In this sense, we can say that immune memory, via its own dynamics and in synergy with the organism's history of antigen encounters, reshapes the conditions enabling an immune reaction, giving rise to novel constraints. They reconfigure memory, without limiting its further plasticity or that of the immune system in general. In this sense, also the characteristic times of response become proper to the individual organism, and generated by the underlying history.

The immune system is equipped with other processes that result in a dynamical, memory-maintaining, antigenic context-dependent update of its own functioning constraints. One such process is somatic hypermutation, which occurs in germinal centres and involves B lymphocytes entering these structures after antigen exposure. In this process, an enzyme (the activation-induced cytidine deaminase enzyme) introduces random mutations in the B-lymphocyte receptor sequence that alter its binding affinity towards the antigen; lymphocyte variants with high binding affinity are

selected and continue their life as antibody-secreting cells or as part of the memory pool. It has been suggested that this selection step may also induce structural rigidification resolving the potential polyreactivity of flexible lymphocyte regions into an antigen-specific binding configuration, yet evidence of this is still elusive (see [Cagiada et al. 2025](#), and references therein). Somatic hypermutation is another example of a process generating diversity, which is in this case channelled towards potent and specific immune reactions against threats encountered during the organism's lifetime.

Lymphocytes display a high level of plasticity also in their phenotype, whose acquisition is tightly regulated by their ever-changing context of interactions with other immune cells and by nutrient availability, further attesting to the propulsivity of the space of constraints enabling and canalizing immune response. Helper T lymphocytes promote the effector functions of cytotoxic T lymphocytes via release of soluble mediators that co-determine activation of the latter, together with antigen binding. Furthermore, the specific effector functions exerted upon activation depend on intracellular protein expression levels and reactions and can adapt to immunological stimuli in a specific micro-environment and thus end up varying, for the same cell type, from an inflammation-inducing role to an immunosuppressive one to simple tissue homeostasis ([Chi et al. 2024](#)). Finally, it is increasingly becoming acknowledged that the quiescent state of naive (i.e., not-yet-activated) lymphocytes, once thought to be their default state, is actively controlled and enforced by inhibitory interactions with other immune cells ([Chapman et al. 2020](#)).

5.3 The Relational Nature of the Immune System

The canalized diversity, plasticity, and capacity for memory formation of the immune system reveal the deeply relational nature of its constitution, both along ontogenetic and phylogenetic trajectories. As we have just seen, the study of plasticity and memory shows that lymphocytes' activated and proliferative state, as well as effector functions, cannot be characterized separately from their set of synchronic and diachronic relations.

At the ontogenetic level, T lymphocyte development sculpts a repertoire of immune receptors that is intrinsically individual, since the retention of stochastically generated receptors is contingent on the landscape of endogenous antigens, which in turn is constrained by the individual's MHC genetic makeup. The repertoire is then further shaped by interactions with exogenous or tumour-associated antigens, thus making it not only dependent on the circumstantial factors of its development, but also on the subsequent individual immunological history. Even the repertoire's 'initial conditions' (in other words, contingency) matter to its specificity: the transfer of maternal immune cells to the infant during pregnancy and via breastfeeding plays various roles in early immune protection and development ([Laouar 2020](#)).

At the phylogenetic level, the evolutionary origin and explanation of MHC polymorphism have been subjects of intense debate, and it is now generally accepted that it has been driven and maintained by host-pathogen interactions ([Spurgin and Richardson 2010](#)). Among the posited modes of action by which host-pathogen interactions might have favoured MHC diversity there is the antagonistic coevolution hypothesis: pathogens evolve to evade immune responses to antigens presented by common MHC alleles, which in turn confers a selective advantage to hosts bearing new (or rarer) alleles ([Kubinak et al. 2012](#)). Such a scenario highlights also how host adaptive immunity (including but not limited to the MHC-restricted T-lymphocyte responses) steers pathogen evolution towards immune escape: in other words, the host immune system channels viral

evolutionary possibilities, thereby exemplifying a striking case of thickness. Indeed, quantifying this type of immune-mediated selective pressures on different viral regions has allowed the forecasting of the dominant strain in the following year for infectious diseases such as Influenza ([Lässig et al. 2017](#)).

5.4 Another Interface with the Environment: Brain Plasticity and Differential Heterogenesis

Neuroplasticity, or the brain's capacity to adapt its structure and function in response to experience, injury, or environmental demands, stands as one of the most transformative concepts in modern neuroscience. Traditionally, plasticity has been understood as the nervous system's ability to reorganize itself at multiple scales—from synaptic and neurons' shape adjustments to large-scale network rearrangements—enabling learning, memory, and recovery from damage (Bear et al. 2020; Margetis and Vadakekut 2026). The nervous system operates through assemblies of chemically interacting neurons. The branching extensions of neurons (dendrites) allow them to sense molecular regulators released by other neurons through cell-to-cell junctions, the synapses.

At the cellular level, plasticity includes mechanisms such as synaptogenesis, dendritic remodeling, and, rather exceptionally, neurogenesis, which may take place in regions like the hippocampus and olfactory bulb (Eriksson et al. 1998; Holtmaat and Svoboda 2009). Functional plasticity is also underpinned by molecular regulators, exchanged across neurons, including neurotrophins like BDNF, neuromodulators such as dopamine and serotonin, and epigenetic modifications that influence gene expression (Kandel et al. 2014; Sweatt 2016).

Beyond the cellular and molecular scales, plasticity manifests also in broader network-level phenomena. Cortical remapping, for instance, allows sensory or motor cortices to reorganize following injury, as seen in cases of limb amputation or stroke, where adjacent brain areas assume the functions of damaged regions (Berthoz 2013). Cross-modal plasticity further demonstrates the brain's adaptability, as sensory cortices originally dedicated to one modality—such as the visual cortex—can be repurposed to process other sensory inputs, as observed in blind individuals who exhibit enhanced auditory or tactile processing (Bavelier and Neville 2002). A particularly compelling example of this adaptability is vicariance, where undamaged brain regions compensate for lost functions, enabling partial recovery after injuries like stroke or traumatic brain injury (Chollet et al. 1991; Taub et al. 2002; Berthoz 2013). Clinical studies have shown that such compensatory mechanisms are not merely reactive but can be actively shaped through rehabilitation, which leverages the brain's inherent plasticity to restore or reorganize function (Galletto and Sacco 2017; Yang et al. 2026).

However, plasticity is not universally beneficial. Maladaptive forms of plasticity can contribute to pathological conditions, such as epilepsy, chronic pain, or addiction, where aberrant synaptic reorganization leads to hyperexcitability, sensitization, or compulsive behaviors (Kauer and Malenka 2007).

Within this context, the work of Alessandro Sarti and his colleagues introduces a novel theoretical framework: differential heterogenesis. This concept, rooted in the philosophical traditions of Gilles Deleuze and Félix Guattari, offers a radical reimagining of plasticity not as a series of adaptive changes within fixed constraints, but as a dynamic, open-ended process of form emergence from heterogeneous assemblages. In (Deleuze and Guattari 1987) “heterogenesis” is defined as the

genesis of forms emerging from a multiplicity of heterogeneous differences. Unlike structuralist models, which assume homogeneity in the equations governing change, heterogenesis emphasizes the morphodynamic nature of form creation, where new structures arise from the interactions of disparate, non-uniform elements, including the change of the very “laws” of the dynamics. Differential heterogenesis is then a way to understand the brain’s plasticity as a continuous process of becoming (Sarti et al. 2022): plasticity is not merely a reactive adjustment to external stimuli but an emergent phenomenon where forms and functions arise from the interplay of heterogeneous, time-varying constraints. These interactions of biological heterogenesis are always constrained by the context—or, more precisely, by the relational space. Therefore, “biologically enabled” possibilities are not abstract possibilities, but possess a thickness that directs them toward certain configurations rather than others. This perspective challenges the traditional mechanistic models of plasticity, which often assume predetermined rules or fixed spaces of possibilities. Instead, differential heterogenesis treats plasticity as a dynamic process where the very constraints governing change—such as synaptic rules or network dynamics—can themselves evolve over time and space. This framework allows for a more nuanced understanding of phenomena like vicariance, where functional takeover by undamaged regions is not simply a shift in activity but the emergence of new functional forms from complex, heterogeneous interactions (Sarti et al. 2022). For example, in the context of stroke recovery, differential heterogenesis frames the process not just as a compensatory activation of peri-infarct regions but as the emergence of new functional configurations from the heterogeneous interactions between neurons, glia, and vascular systems (Cramer 2008).

Brain plasticity is thus understood in a relational context, not as a static or merely adaptive system, but as a dynamic, self-organizing entity capable of continuous becoming. In this way, which is in a sense “complementary” to the immune system’s processes of production of diversity by intensive “reproduction with variation”, the organism constitutes itself in relation to the environment while continually using and modifying its ontogenetic and evolutionary constraints on a network of basically non-reproducing cells, the neurons.

Of course, this approach to the brain radically departs from “Descartes’s error” (the mechanical conception of life and brain), as per the title of a famous book (Damasio 1994), but also from “Broca’s error” or the rigid localization of brain functions (Duffau 2016). Even more generally, “the wet brain is a differential neuromagma that goes far beyond the connective scheme of the network and contains all the uncertainties and indeterminacies of material concatenations” (Sarti et al. 2022, p. 130). This is at the material core of the brain’s relational function at the interface with the environment. The fact that the context is relational—and therefore contingent—shows that the application of heterogenesis theory is linked to the production of “possibilities” enabled by specific relationships. Within such a changing phase space, interaction directs (thickness) the brain’s plasticity in one or more directions rather than in others.

Let us conclude by referring also to some similarities between the nervous and immune systems presented above. Indeed, as mentioned in (Pradeu 2019, p. 54): “The nervous and the immune systems are often said to be similar, that is, to share several important features. Similarity can be at a structural level. Both systems communicate via soluble ligands and receptors. Molecules that mediate such communication include cytokines, chemokines, neuropeptides, neurotransmitters, neurotrophins (Camacho-Arroyo et al. 2009), and their receptors. [...] The detailed resemblances

and differences between the neural and immunological “synapses” are an important object of study (Dustin and Colman 2002).”

As a further theoretical link, in (Edelman 1974, 1987) a Darwinian framework to understand both the immune system and the brain is developed, emphasizing Darwin’s principles of (re-)production with variation and selection as the driving force behind their organization and function. In the case of the brain, Edelman stresses the explosive production of synaptic connections, in particular in early stages of life. These are later selected by their use, i.e., the unused connections are excluded. Thus, these theories—clonal selection theory for immunology and neuronal group selection theory (or neural Darwinism) for neuroscience — propose that both systems operate through individual or population and group-based variation and selective retention. In either case, though through different processes, degeneracy (i.e., structurally distinct but functionally overlapping activities (Edelman 1987)) and redundancy are at the core of these processes.

6 Conclusions

In this contribution we have established the need to go beyond physicalist and reductionist assumptions in biology, to acknowledge variation and historicity as intrinsic dimensions of living beings, and to subsume them in our theories as fundamentally relational. We have described aspects of the immune and the nervous system – paradigmatic ‘interface’ systems between an organism and its context – that can help the reader appreciate how relationality shapes onto-phylogenetic trajectories in life.

Furthermore, we discussed a relational theoretical framework specific to biology, proposing new concepts. If the relational space allows us to conceive of dynamic configurations—linked to contingent constraints—and enables the constitution of new possibilities, the intrinsic contingency of biological relationships provides a depth (direction) to these possible configurations, in that they are not possible in the same way in every living being. The expression of heterogeneity and plasticity is therefore linked to ontophylogenetic constraints. These constraints simultaneously “limit” and create new possibilities with their own thickness – they are propulsive.

The notions of variation, relational space, and historical a priori set the stage for novel epistemologies that in our opinion should frame theoretical efforts in life sciences. The mathematics that possibly will be able to embrace these dimensions is extremely challenging – due to the tension between the radical variability of biology and the invariants needed for mathematical conceptualization – and is largely still to be written. As a preliminary consideration in this direction based on our discussion, we can say that mathematization should account for, as core features: the heterogeneity and contextual relations of relevant observables (be they molecules, cells, or organisms); the stochasticity of their evolution; and plastic changes in their enabling constraints, as attempted by differential heterogenesis approaches.

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