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ON THE PROCESSES OF GROWTH OF THE LIVING BEING AND THE RELEVANCE OF RELATIONAL CATEGORIES TO UNDERSTAND IT[1]

1. *Introduction: towards a relational ontology in the philosophy of life sciences*

Considered from the perspective of the historical and epistemological inquiry, the entire history of biology has been crossed through by a specific tension, which is at the heart of many (sometimes ostensible) dichotomies – as that between continuity and discontinuity, persistence and change, regularity and contingency. In fact, while on the one hand biology's scope is primarily concerned with the identification of structural and functional states and patterns in living beings, on the other hand biological sciences has always dealt with an astounding interplay of maintenance, transformation and generation of diversity – which appears as one among the constitutive features of life.

In order to account for this constitutive and essential tension that characterizes the phenomena of life, in the last decades systemic approaches in biomedical sciences have undertaken the challenge to analyze biological systems *as a whole* – including their spatial-temporal development, their growth as a unity and their interaction with the environment (or, as we will argue, their biological history). By accounting for a multiplicity of levels, systems biology shifted biology's focus on what kind of causal relationships does matter in the scientific understanding of the living beings, tightly coupled with the issue concerning how different causes act at different levels of the hierarchical organization[2]. Under the lens of the historical-epistemological inquiry, systems biology picked up the baton of a long tradition of scientific insights, which recognized reductionist trends in biological and medical sciences and understood their intrinsic limitations – to name only two pivotal authors in the history of contemporary biomedical science, we can think of Claude Bernard's attention toward the control processes regulating organisms' *milieu intérieur*[3], as

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[2] M.A. O'Malley - J. Dupré, *Fundamental issues in systems biology*, «BioEssays», 27 (2005), pp. 1270-1276.

[3] D. Noble, *Claude Bernard, the first systems biologist, and the future of physiology*, «Experimental Physiology», 93 (2008), pp. 16-26.

well as Walter Cannon's emphasis on homeostasis as a key feature of living beings in maintaining stability and constancy[4].

The shift from gene to genome and the advent of -omics set the way for systems biology overcome the rigid tenets of mechanistic molecular biology, showing how organisms cannot be explained in terms of interconnected parts, but rather unitary systems defined by their organizational regulation.

Furthermore, during the last twenty years biological research saw the emergence of evolutionary developmental (informally «evo-devo») approaches, which shed light on organisms' developmental process, from a single cell through all its intermediate embryological stages, and all the way to birth, the early and adult maturation, and eventually senescence and death. Evo-devo and other major theoretical breakthrough in biological theory has also underlined the role played by niche construction, promoting the scientific understanding of those non random and selective modification of the environment by organisms, made in order to exert some influence over their own survival and reproduction[5]. At the same time, the overcoming of 'dogmatic' genetics has led the relatively new field of epigenetics to account for the effects of the environment on the organism, which can influence not only behavior or phenotype, but also the inner dynamics within cell nucleus – even affecting gene expression in ways that are either adaptive or pathological[6].

Living beings are constituted by a complex system of relationships, which persists and undergoes transformation over the passing of time. New trends in biological research reveal how biology is essentially committed to describing this dynamic entanglement of life processes, since biological understanding has to be achieved in systemic terms, rather than by isolating supposed causal factors. Such a scientific view of life, however, needs relative terms and entails relational issues, also on an ontological and epistemological level.

Indeed, while this shift in perspective is allowing a part of systems biologists[7] to account for the phenomena of life as a *hierarchy of processes* whose most striking characteristics are the intrinsic dynamism of every level (from molecules and cells to organisms and lineages) and a definite autonomy framed in a constitutive (more: essential) inter-relational order, for a long time traditional molecular biology has considered the components of a cell as something static and isolated, neglecting the pivotal role of dynamical interaction between them. Today, the development of systems

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[4] A.C Ahn - M. Tewari - C-S. Poon - R.S. Phillips, *The Limits of Reductionism in Medicine: Could Systems Biology Offer an Alternative?*, «PLoS Medicine», 3 (2006), p. e208, https://doi.org/10.1371/journal.pmed.0030208.

[5] F.J. Odling-Smee - K.N. Laland - M.W. Feldman, *Niche Construction: The Neglected Process in Evolution*, Princeton University Press, Princeton 2003; K. Laland - B. Matthews - M.W. Feldman, *An introduction to niche construction theory*, «Evolutionary Ecology», 30 (2016), 2, pp. 191-202.

[6] A.D. Goldberg - C.D. Allis - E. Bernstein, *Epigenetics: a landscape takes shape*, « Cell», 128 (2007), 4, pp. 635-638; C.D. Allis - T. Jenuwein, *The molecular hallmarks of epigenetic control*, «Nature Reviews Genetics», 17 (2016), pp. 487-500.

[7] Indeed, it has been highlighted that the overall field of systems biology encompasses two different approaches to the issue of integration in life phenomena, namely a 'globalist' and 'localist' one – the first aimed to the understanding of complex systems, the second interested in the integration of vast amount of data to find correlations. See S. Huang, *Back to the biology in systems biology: What can we learn from biomolecular networks?*, «Briefings In Functional Genomics And Proteomics», 2 (2004), pp. 279–297.

biology at the beginning of 21st century is slightly transforming biomedical sciences, for which the main challenge has now become to account for the *dynamic stability* of the organism: in other words, recent advances in biological knowledge have shown how parts maintain (and develop) a certain degree of autonomy, but they ontologically depend on the whole. From such perspective the scientific explanation of phenomena that express this kind of relationship on several levels – such as epigenetic memory, robustness, plasticity and vicariance[8] – became one of the main cogent goals of life sciences. Eventually, this is leading both scientists and philosophers of science to become increasingly aware that the methodological approaches required to account for the emerging complexity of living being are at odd with traditional decompositional principles, whose epistemological and ontological assumption lays on a mereological view of the natural world mediated by causal mechanistic categories.

The acknowledgement of the organizational dynamic of life phenomena became a practical acknowledgement of mereology's biggest limits within epistemology of biological sciences and opened a different path of inquiry in life sciences. Not surprisingly, the increasing prominence of these researches within the panorama of contemporary biological sciences has been coupled with the growth of a renewed critical thinking in philosophy of biology – whose major goal was to problematize (and account for) the results of new trends in biological inquiry[9]. Two major features of this research trends are, on the one hand, the overcoming of a simplistic and homogeneous concept of parthood in biological systems, coupled with the need to deal with the ontological foundations and the epistemic consequences of this shift in of scientific perspective.

For the scope of this article, we address a specific issue in the new philosophy of biology, i.e. the attempts to conceptualize the constitutive temporality of phenomena of life within a relational and processual framework. We start from the assumption that a systemic view of living beings needs to go beyond the application of mereological decompositional principles, and to advocate for a new epistemological and ontological framework, in order to account for the tension generated by the concomitance of contingent and stable features in living beings. Our aim is to highlight how the adoption of a relational and processual ontology can provide useful categories to account for the role of temporality in the process of growth of the living being – a topic which should be further problematized in the wider historical and philosophical debate on biological sciences Thus, in Section 2, we provide a review of proposed relational ontology, introducing the notion of Operational Integrating System, and in

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[8] A. Berthoz, *La Simplexité*, Odile Jacob, Paris 2008; Id., *La Vicariance. Le cerveau créateur de mondes*, Odile Jacob, Paris 2013.

[9] Many works have been written in recent years on the epistemological limits entailed in dogmatic reductionisms, as well as on the different and heterogeneous attempts to overcome them. Moving toward a systemic view of the phenomena of life did not question just reductionism and determinism. Also the «machine conception» of organism, that has been one of the most pervasive notions in modern biology, no longer seems endorsable both in epistemological reflection and in biology's theory and practice. Furthermore, this new trend in philosophy of biology reveals an interesting reprise of Aristotelian categories, and it suggests biological explanation as essentially a scientific inquiry in differences. In present days an extensive literature is available on such topics, making up a growing corpus of epistemological and philosophical reflections that would be impossible to summarize in this article, and we refer our readers to a recent selection of works and bibliographical article on these issues, published in *Emerging Trends in Philosophy of Biology*, «Acta Philosophica», 26 (2017), I, Special Issue, pp. 11-82.

Section 3, we stress the explanatory values that such relational ontology has in respect to the processes of growth in living beings. In Section 4, we provide a case study supporting our thesis drawing from cancer, seen as a disruption of the ongoing relational interactions that constitute an organism. Finally, in Section 5, we focus on and apply what we have discussed in Section 3 and 4, to the case studies provided by recent neuroscience of brain plasticity, suggesting how a relational ontology framework could be useful for a biological understanding of the central nervous system, especially in respect to the openness granted by its intrinsic open architecture.

2. *On a multi-unity view of organismic unity*

As we mentioned above, systemic approaches in biomedical sciences revealed how life phenomena should be characterized as a hierarchy of processes, whose dynamic nature appeals for an integrative view which encompasses all levels, from genes and proteins to tissues and organisms (and eventually, the environment). This multiplicity of levels – which gathers causal network interactions, retroactions and all the entailed systemic properties of the living system – characterizes every aspect of life, both physiological and pathological, and allows the organism to act as a substantial unity (at least of action) all through the organism's life. Indeed, since organisms are living systems in which the multiplicity of parts works in a unitary way, the stability of parts themselves depends both on the progressive amount of structural-functional features in the organism and on the several ways of integration of these levels (including pathological or abnormal disruptions of this same integration). On an epistemological level, it follows that understanding biological behaviors and dynamics implies thinking of an integrative model of the systemic organization, making explicit features of a non-univocal notion of it, able to account for different modes of causality in maintaining (or disrupting) the complex interaction that characterizes the living. Such models often emerge as relational dynamic processes with elements that acquire a specific explanatory relevance depending on the level of discussion and on the scientific question posed[10] – in this way revealing the need for a reconsideration of the ontological and epistemological limits of mereology. Indeed, notwithstanding the possibility to experimentally isolate a level for the need of a specific and limited abstraction, the hierarchy of process that constitutes complex systems – as biological entities are – acts always as *dynamic multi-unity,* not as a parts-whole organization. Recently, one of us has proposed a relational and processual ontology (whose entanglement with the epistemological dimension appears constitutive) that appears particularly useful if we want to account for the integrative features of life processes, in both normal and pathological conditions[11]. Such relational and processual ontology claims that the processes of biological determinations in an organisms – i.e the organism's growth – depend on a complex network of synchronic and reflexive interactions, which in turn intersects and overlaps in every moment with the diachronic dimension of life: thus, it can be useful to describe organisms by the notion of «Operational Integrating Sys-

[10] M. Bertolaso, *How Science Works: Choosing Levels of Explanation in Biological Sciences*, Aracne, Roma 2013.

[11] Ead., *Philosophy of Cancer. A dynamic and relational view*, Springer Science, Dordrecht 2016.

tems», in order to emphasize the functional multi-level stability of the parts and how the organismic dynamism is established and maintained.

Operational Integrating Systems do not lie on mereological assumptions, which characterize organisms as a part-whole organization regulated by bottom-up and top-down causal mechanisms; on the contrary, they stress how the emergence of systemic properties comes from causal emergent relationships, which become the crucial category by which any biological pattern and change has to be understood. The adoption of these concepts calls for a strong rethinking of causality, which should be thought to work «by holding», rather than «by doing». The concept of Operational Integrating System highlights the role of global structural and functional interaction between levels, framing the dynamic properties of biological organizations in a unitary concept. Furthermore, such proposed concept characterizes life as a multi-level dynamic regulation, resulting in a systemic organization whose disruption lead to the development of pathological states.

The conceptual and operative notion of Operational Integrating System clearly suggests how systems biology entails the need for an ontological and epistemological reflection on life phenomena. Since the identification of a given living system (an organism) is not obvious, the ontological clarification has to be subordinated to a reflection on what kinds of dynamics are relevant in order to characterize for the constitutive changes of a biological system and its ability to maintain a functional and behavioral unity. This can be made clear by underlining that the unity we are talking about is a *unity of action* – not to be confused with similar concepts, as system unity or organismal individuality in the traditional sense. Unlike these categories, indeed, unity of action admits degrees, that is, it allows the relationship between constitutive parts to be intended in a non-univocal manner, by focusing on the ways of regulation of dynamics' interrelation. This leads, in turn, to the issue of the temporal dimension of the organismic unity, in order to account for the subsequent transformation's of such interrelation – in other words, to account for the organism's biological history.

3. *The relevance of relational categories in explaining living beings's growth*

The multi-unity of action of the organism directly addresses the issue of persistence over time of functional properties through (and *not* despite) the change of the system's parts. Such unity, that allows the maintenance and persistence of the organism's constitution, requires two different modes of causation: first, a differentiation causal dynamics that expresses as the whole is organized through functionally heterogeneous elements and reflects the multiple levels of organismic organization, and second, a state-holder causality that can account for the unitary dynamic stability of the whole integrating those different levels of its organization. Indeed, it is unity that serves as the constitutive feature of any biological system, whose processual nature is reflected in the integration of its organization all through its growth.

From an epistemological point of view, biological understanding should avoid looking for isolated causal factors, and be directed primarily to the identification of those organization principles — in which, secondarily, single level discrete «mechanisms» can be framed and understood. What is at stake here is an explanatory account of the dynamic stability of an organism. Indeed, if we consider the living beings as an autonomous system able to maintain persistent integrity by continuous adjustments of its internal *milieu* and of the interactions with the environment, we have to adopt a perspective that is radically different from that traditionally proposed by deterministic causality, since the spatio-temporal continuous causal processes cannot be understood by a unique explanatory tool, which is neither necessary nor sufficient. This epistemological reflection addresses directly a relevant connected ontological issue: indeed, if we accept the dynamic nature of organism integrative organization, we should dismiss the wishful thinking of identifying univocal explanatory mechanisms (e.g. fixed genetic instructions, or deterministic models of part-whole relationship), shifting our attention to what seems to be the historical dimension of living beings. In a sense, as underlined by Bunge:

> The fact that in specific natural or formal systems the initial relations and properties of elements cannot teach us how they would be applied as the system evolves. Thus, the historical way by which a system of natural events operates is not a consequence of its description. It acts and it produces novelty (novel qualities and novel structures) in the real world, which leads to the conclusion that emergence has an ontological meaning[12].

Consistently with this view, we should rethink the notion of biological homeostasis in order to go beyond the concept of mere maintenance of given functional state, since it actually entails a unity of action that links up the discrete and continuum dimensions of biological processes into functional-structural patterns. Through the lens of a relational and processual ontology, living beings (as Operational Integrative Systems) survive not by maintaining a status quo, but exclusively by growing, adjusting the functional integration of the organism's level – eventually writing, by this growth, the organism's life history. The adoption of the term «history» seems particularly appropriate, since the on-going dynamism that continuously shapes the biological processes results both in their physiological irreversibility and in the intrinsic systemic mode of functioning of the organismic unity.

Processes involving memory (or less complex form of hysteresis) clearly shows the interconnection of these two features of life history. Cells keep track of their own functional career and trajectory within the organism. Stem cells' genomic configuration, for example, largely depends on their biological history in the organism and functioning within the organism: they actually possess a memory, physically made concrete in an epigenetic progressive stratification within the cell, characterizing the ongoing regulatory dynamics; so much the part belongs to the whole that its own history reflects the internal history of the organism. Also in neuroscience, evidences have been found highlighting the role for neural epigenetic modifications in experience-dependent neural structures, modifications that appear involved in the processes of synaptic plasticity, and selective gene expression in response to behavioral experience[13]. Epigenetics change as histone modification is known to be dynamically regulated during neural pathways formation[14], and such epigenetic mechanisms have been studied in relationship to higher cognitive functions as information encoding[15].

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[12] M. Bunge, *Emergence and convergence*, University of Toronto Press, Toronto 2003.

[13] F.A. Sultan - J.J. Day, *Epigenetics mechanisms in memory*, «Epigenomics», 3 (2011), 2, pp. 157-181.

[14] L. Peixoto - T. Abel, *The role of histone acetylation in memory formation and cognitive impairments*, «Neuropsychopharmacology», 38 (2013), pp. 62-76.

[15] K.M. Bieszczad et al., *Histone Deacetylase Inhibition via RGFP966 Releases the Brakes on*

But history is more than memory, since it entails – in a direct translation of the multilevel unity of organisms – a stratification of functional and structural changes for the sake of regulating the overall organization of living phenomena. Such stratification, whose every irreversible step contribute to the proper (or disrupted) ongoing of the general regulative dynamics, allows the system to undergo global structural changes without losing its unity – on the contrary, it maintain this unity right by adopting flexible and non-deterministic strategies to cope with the interaction of the organism's actions and constraints. In this respect, the crucial importance of history as such pivotal issue in the philosophical and scientific understanding of living systems has been well highlighted by Ignazio Licata:

> Now it is necessary to introduce a further distinction between dynamics and history. Dynamical systems are described by trajectories in a suitable phase space, but dynamics by itself does not include a distinction between the before, the after and the irreversible changing of the system. As in the case of a gas in a bottle, an observer who plays the reverse motion of each molecule would see nothing unusual, no «before» and no «after». The time arrow, the history and the improbability of events of the reverse-motion film come into play only taking into consideration the boundary conditions. The dynamic approach just associates a clock to the degrees of freedom of a system, but it is insufficient for measuring the global structural changes. To get these ones requires, instead, the observing of the constraints' stratification/modification, which is precisely the history of the system[16].

Thus growth, or life history, intrinsically depends on a constitutive and continuous orientation of the parts among themselves and depending on the contextual signals. Operational Integrative Systems selectively take over environmental signals, and by this allow the adequate growth of the organism, as the effects of changes in cell or tissue shape seem to show. In this framework, specific phenomena of organization maintenance, such as the robustness that appears as an ubiquitous property of complex living systems, can be understood as the persistence of an organismal trait under perturbations, that is, the property by which living systems maintain a function despite external and internal perturbations[17]. In a way, robustness is strongly correlated to the complexity of a system, as robustness drives internal complexity and is the most striking feature of the complexity systems, and it is currently one of the most powerful cross-disciplinary concepts relating both biological and artificial systems on the basis of their common organizational principles. Together with robustness, the broader concept of plasticity (meant as a general characteristic of living systems' organization) and other related specific phenomena such as v degeneracy and vicariance in the central nervous system appear as the characteristic features of biological history. Thus, in the following sections, we will draw from two subfields of biomedical sciences – i.e. oncology and neuroscience – some arguments to stress the value of relational and

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Sensory Cortical Plasticity and the Specificity of Memory Formation, «Journal of Neuroscience», 35 (2015), 38, pp. 13124-13132.

[16] I. Licata, *Incertezza: un approccio sistemico*, in. L. Urbani Ulivi (a cura di), *Strutture di Mondo. Volume secondo*, il Mulino, Bologna 2013, pp. 35-72, here p. 47.

[17] M. Bertolaso - S. Caianiello, *Robustness as Organized Heterogeneity*, «Rivista di Filosofia Neo-Scolastica», CVIII (2016), 2, pp. 293-303.

processual ontology in order to conceptualize the processes of growth in living beings and account for a consistent understanding of the dynamic nature of organisms.

4. *Cancer as a disease of biological history*

Cancer biology can really highlight the philosophical value of a relational ontology in understanding the processes of growth, not only because it provides several elements for a deeper understanding of living entities in both physiological and pathological conditions, but it also has a value for a historical reflection on the evolution of the explanatory models of cancer. Indeed, since the 1970s, cancer research holds to the epistemological constraints of Somatic Mutation Theory (SMT), focusing on genetic mutations and clonal expansion of somatic cells. SMT explained cancer as clonal expansion following genetic mutation. With the advancement of knowledge and experimental methods, the SMT weakened its strong assumptions, but survived through a wider category of models focused on the genetic and cellular levels, in which Cell-Centred Perspective can be recognized. The number of involved genes grew larger, as did the number of modes of genetic action; different molecular factors (e.g., epigenetic factors) entered the causal picture, and new concepts were coined (e.g., the Cancer Stem Cell, CSC). The importance of extra-genetic and extra-cellular factors became more and more apparent, and the causal role of interactions eventually prevailed, so that even the most important founders of the SMT ended up envisioning an incredible «wall of complication» with little clue of how this will be overcome.

Indeed, while reductionist and mereological approaches has for a long time understood cancer as a set of molecular parts or a mere process, a growing number of evidences coming from tissue microenvironment research, bioenergetics, epigenetics and physical chemistry tend to converge in the definition of cancer as essentially a genetically non-deterministic disease. These researches suggested that cancer should be understood as a disruption of the dynamic and continuous relational interactions that constitute an organism, whose main characteristic is indeed a progressive and multi-level disorganization from the genome and metabolic networks, to tissue integrity[18].

In this respect, the Tissue Organization Field Theory (TOFT) can be viewed as proposing an organism-centred perspective that is clearly different from the cell-centred perspective. TOFT emphasizes the importance of (micro) environmental factors and in many aspects plays down the autonomy of cells, moving towards an account of the neoplastic phenomenon at higher levels of biological complexity. Cancer can be thus primarily understood as a disease of tissue organization. In explanatory models of cancer this new dimension of analysis is characterized through the notion of fields. They are generally defined as groups of cells from which specific morphological structures (tissues and organs) develop through the mediation of biophysical and biochemical cues, mainly through epigenetic changes. In cancer, these epigenetic changes are aberrant. It has been thus used the term

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[18] C. Sonnenschein - A.M. Soto, *The society of cells: Cancer and control of cell proliferation*, Springer, New York 1999; S. Huang - D.E. Ingber, *Shape-dependent control of cell growth, differentiation, and apoptosis: Switching between attractors in cell regulatory networks*, «Experimental Cell Research», 261 (2000), pp. 91-103.

of cancerization fields[19]. The common idea is that in cancer the functional stability of a field is compromised, and that this notion of field concerns functional definition of parts and parts' stability as well.

Moreover, recently theoretical models are proposed that suggest that the uncoupling of processes (i.e. proliferation and differentiation) could lead to cancer[20]: similarly, coherence of molecular dynamics is, in fact, increasingly recognized as an organizing principle linked to the long-range coordination of biological processes[21]. Such evidences can explain the remarkable efficiency of biological systems: coherence is applied here as the coupling of cells within a 3D architecture. System's dynamics in a state space cannot be thus 'reduced' either to a molecular wiring diagram or, even, to the integrated functioning of parts: additional influences (i.e., those of the intracellular topology) must be taken into consideration in order to give a more reliable explanation of integrative functional dynamics.

Self-organization does not only pertain to topological order, but it also has its temporal manifestation, In this way, explanatory systems are not characterized in terms of molecules and cells, but cancer is rather explained in terms of a functional state of the system, identified by defining a functional state and describing it in organizational terms.

The biology of cancer thus shows that the stability of constitutive elements depends on the organization, and that there is a source of regulation in the biological context. Cells change their behaviour depending on their functional integration in the tissue. Alteration in cell communication alters gene expression, and the loss of integration of cells within a functional tissue leads to genetic instability and apoptosis. The collapse of levels, evident in cancer, results from the loss of the general functional integration of a biological entity. This means that the structure itself, once constituted, determines the relationships among parts and the stability of the parts themselves (although not their final survival). More generally, the multi-unity relationship is not properly described by linear causality (including back-and-forth feedback control): instead, we see a synchronic dependence of constitutive elements' stability on the maintenance of the organization.

The very definition of parts and interactions depends on the properties of the multi-unity dynamics. The heterogeneity of tumour cells can thus be related to the disruption of relational principles of integration that hold the normal developmental processes at different scales of the biological organization, and to the intrinsic capability of an organic system and parts to find new functional stable states. The multi-unity account of living entities and of organisms is an example of a current perspective that, emerging from vital fields of research, is also likely to drive biological research for the years to come, eventually impacting also our common – not only technical – thinking of organisms.

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[19] T. Ushijima, *Epigenetic field for cancerization*, «Journal of Biochemistry and Molecular Biology», 40 (2007), pp. 142-150.

[20] C.M. Nelson - M.J. Bissell, *Of extracellular matrix, scaffolds, and signaling: Tissue architecture regulates development, homeostasis, and cance*r, «Annual Review of Cell and Developmental Biology», 22 (2006), pp. 287-309.

[21] M. Plankar - E. Del Giudice - A. Tedeschi - I Jerman, *The role of coherence in a systems view of cancer development*, «Theoretical Biology Forum», 105 (2012), 2, pp. 15-46.

5. *Neuroscience and brain plasticity*

In respect to the processes of growth and the relevance of inter-relational categories to understanding them, also the central nervous system constitutes an important case study, since the brain is not only the central organ for adaptation of living beings to experiences, but also because the hierarchy of processes involved in its function can be considered, in several ways, a perfect example of Operational Integrating System — from cortical architecture to higher cognitive functions – whose continuous shaping reflect not only the organism's biological history, but also the cognitive one. All through the constant interaction with environment, organisms that are complex enough to have developed a nervous system are capable of changing the structural and functional architecture of their brain – while, at the same time, modifying themselves on a systemic level, by modulating the function of their neuroendocrine, autonomic, immune, and metabolic systems. Until the last decades of 20th century, the vast majority of brain sciences' epistemic panorama advocated for a peculiar form of mereological approach – i.e. «hardwired» forms of localizationism, as in traditional hard modularism – that imbued several of its theories and practices. However, in recent years, research on brain plasticity marked a shift in neuroscientist's investigations, moving scholars from older localization theories of the central nervous system to more systemic theories of the complex entanglement between cognition, brain, body and environment.

Contemporary neuroscience characterizes the nervous system by the integration of multiple functional levels in a unitary global mode of organization and action. The integrative function of the brain has always been a fundamental topic in neuroscience – at least since the seminal work of Sir Charles Sherrington, at the beginning of the 20th century[22] – and it is nowadays the key to understand not only brain's structural and functional development, but also the very ontology of higher cognitive functions. Since the work of Donald O. Hebb in the late 1940s, nervous system's ability to shape itself by the interaction between the organism and the environment represents the key-concept by which neuroscientific inquiry on the brain growth is led. According to the Hebbian theory, «neurons wire together, if they fire together»; by synchronically discharging their impulse, their cortical maps may overlap until functional unification, producing new neural pathways and expanding (or eventually reducing) the overall organization of neural networks[23].

In recent years, neurobiology is providing a more nuanced understandings of the brain complexity, especially in the light of the new plastic conception of the nervous system. The brain has the capacity to continuously reorganize itself by creating new neural pathways to let the individual to actively interact with his environment. Contemporary neurosciences look at the neuronal pathways in the brain in terms of «epigenetic landscapes», the brain being an organ continuously molded by individual's history and experience[24].

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[22] C.S. Sherrington, *The Integrative Action of the Nervous System*, Yale University Press, New Haven - London 1906.

[23] D.O. Hebb, *The Organization of Behavior*, Wiley, New York 1949.

[24] P. Bateson - P. Gluckman, *Plasticity, Robustness, Development and Evolution*, Cambridge University Press, Cambridge (Mass.) 2011.

Two features of brain growth are especially important for understanding how a complex entanglement of factors can change structural and functional organization of the cortex. On the one hand, the cells lining the subventricular zone are stem cells that remain active throughout life, producing new neural or glial progenitor cells that, under a subsequent migration that takes place even in adulthood, can form new neurons. While the role of these cells is still poorly understood they likely form the basis of at least one specific form of postnatal neurogenesis, especially after traumatic injury[25]. The second special feature of brain growth is that dendrites and spines show remarkable plasticity in response to experience and can form synapses in hours and possibly even minutes after some experiences[26]. At first sight, this would appear to be at odds with the process of overproduction of synapses followed by synaptic pruning – i.e., the process by which extra neurons and synaptic connections are eliminated in order to increase the efficiency of neuronal organization. While synaptic pruning is an important feature of brain development, the brain does continue to form synapses throughout the lifetime and in fact these synapses are necessary for learning and memory processes. Since the end of the 1980, neuroscientists have argued that there is a fundamental difference between the processes governing the formation of synapses in early brain development and those during later brain development and adulthood. Specifically, they argue that the early forming synapses are «expecting» experiences, which act to prune them back. They call these synapses «experience-expectant» and note that they are found diffusely throughout the cerebrum. In contrast, later synapse formation is more focal and localized to regions involved in processing specific experiences. They label these synapses as «experience-dependent». One curious aspect of experience-dependent effects on synapses is that not only do specific experiences lead to selective synapse formation but also to selective synaptic loss. Thus, experiences are changing neural networks by both adding and pruning synapses.

In a recent review, Kolb and Gibb defined seven features of brain plasticity:

1. Changes in the brain can be shown at many levels of analysis;
2. Different measures of neuronal morphology change independently of each other and sometimes in opposite directions;
3. Experience-dependent changes tend to be focal;
4. Plastic changes are time-dependent;
5. Experience-dependent changes interact;
6. Plastic changes are age-dependent;
7. Not all plasticity is good[27].

To the scope of our article, point 1, 4 and 5 seem the most important epistemological benchmark to validate the adoption of a relational and processual ontology in the study of the central nervous system. Indeed, alongside with general brain plasticity, specific

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[25] C.T. Gregg - T. Shingo - S. Weiss, *Neural stem cells of the mammalian forebrain*, «Symposium of the Society of Experimental Biology», 53 (2001), pp. 1-19.

[26] D. Bavelier - D.M. Levi - R.W. Li - Y. Dan - T.K. Hensch, *Removing brakes on adult brain plasticity: from molecular to behavioral interventions*, «Journal of Neuroscience», 30 (2010), 45, pp. 14964–14971.

[27] B. Kolb - R. Gibb, *Brain Plasticity and Behaviour in the Developing Brain*, «Journal of the Canadian Academy of Child and Adolescent Psychiatry», 20 (2011), 4, pp. 265–276.

form of it calls for a conceptual framing in an interrelational and integrative perspective: in particular, the concepts of «degeneracy» and «vicariance» in the central nervous system deserve philosophical attention. The concept of degeneracy refers to the behavior exhibited by a system in which multiple pathways are recruited to achieve functional plasticity. Degeneracy has to be distinct from redundancy and dilapidation, since the concept refers to the plasticity of those elements whose function overlaps in some cases, but diverges in others, and also because degenerate structures can produce new and different outputs under different constraints. A degenerate system will adopt different ways to generate the same output in a given context, showing extreme adaptability in response to unpredictable changes in context and output requirements. A recent study has shown the role of degeneracy in the degenerate structure of gene regulatory systems from the basic genetic code to flexible epigenomic modifications, and discuss how these structural features have contributed to organism complexity, robustness, plasticity and evolvability. According to Gerald Edelman, degeneracy is «the ability of structurally different elements of a system to perform the same function or the same output. It is a ubiquitous biological property, […] it is both necessary for, and an inevitable outcome of, natural selection»[28]. Edelman considers neuronal degeneracy (especially in the cerebral cortex), the neurobiological condition for the possibility of this dynamic complexity.

> In biological systems, degeneracy is almost invariably accompanied by complexity. A complex system may be considered as one in which smaller parts are functionally segregated or differentiated across a diversity of functions but also as one that shows increasing degrees of integration when more and more of its parts interact. Put otherwise, a complex system may be viewed as one that reveals an interplay between functional specialization and functional integration. Intuitively, it is easy to see that, below a certain level of complexity, there will be very few ways in which structurally different parts can interact to yield the same output or functional result. Accordingly, at low levels of complexity, degeneracy will be low or nonexistent. For a defined function, however, redundancy can still exist even in relatively simple systems[29].

Together with degeneracy, vicariance seems to be the main brain plasticity process observed in primates and other mammals. Vicariance can be defined as the substitution of one brain function by another, which readapts functional areas of the cortex to supply to functional loss from another area involved in a same process. Today, significant evidences have been gathered on the functional reorganization of motor cortex, as it can be observed after lesions or other injuries[30].

Contemporary neuroscientific research clearly indicates that experience can actually change both the brain's physical structure and functional organization, at any

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[28] G.M. EDELMAN - J.A. GALLY, *Degeneracy and Complexity in Biological Systems*, «Proceedings of the National Academy of Sciences of the USA», 98 (2001), 24 pp. 13763-13768, here p. 13763.

[29] *Ibidem*.

[30] A. JAILLARD - C.D. MARTIN - K. GARAMBOIS - J.F. LEBAS - M. HOMMEL, V*icarious function within the human primary motor cortex?: A longitudinal fMRI stroke stud*y, «Brain», 128 (2005), 5, pp. 1122-1138; P. CHEN - D.E. GOLDBERG - B. KOLB - M. LANSER - L.I. BENOWITZ, *Inosine induces axonal rewiring and improves behavioral outcome after stroke*, «Proceedings of the National Academy of Sciences of the USA», 99 (2002), pp. 9031-9036; M. RIJNTJES - C. WEILLER, *Recovery of motor and language abilities after stroke: the contribution of functional imaging*, «Progess in Neurobiology», 66 (2002), 2, pp. 109-122.

level, suggesting how the central nervous system possesses an «open architecture» that allows constant interaction between levels of organization inside the brain and – above all – with the world outside our skull. Interaction between organisms and the conditions proper of their environment – including, for our species, social interaction and individual experience, can play a crucial role in brain cell survival, regulating the formation and the decay of new synaptic connections, in an irreversible growth process that constitutes the brain's biological history.

All through the second half of the 20th century a very «hierarchy of plasticities» was revealed by scientific inquires into brain structures and functions, revealing how

> the central elements underlying many forms of plasticity are epigenetic processes, and plasticity operating at different levels of organization often represents different descriptions of the same process. Underlying behavioral plasticity is neural plasticity, and underlying that is the molecular plasticity involving epigenetic mechanisms[31].

The brain – with its anatomical and physiological peculiarity – is the fundamental condition for the «emergence» of cognitive functions on the basis of neurobiological mechanisms which allows an active and intelligent organism-environment interaction, while, in the same time, they mold themselves from within of this complex interaction. Each single brain appears necessarily as a unitary dynamic territory whose multiple connections and functional circuits are always modified by our perceptions, our actions, our daily experience and social relationships, in order to guarantee an adequate unity of action. The nervous system is hard to be understood by framing it in mechanistic and mereological categories (as an input-output mechanism, i.e., a reactive system): rather, the nervous system shows its active, systemic and dynamic organization, in which alterations in the activities of a single part may cause the radical reorganization of the whole nervous system, in order to maintain an efficient adaptation to environmental challenges.

In brain, therefore, multiple options are possible to produce new associative connections between the endogenous chemical activity, the motor behavior of the organism and his objectives and goals. This variability is not «noise» for the nervous system, rather it is a fundamental environmental fact that exerts selection pressure on the evolution of nervous system, which is strongly characterized by «functional non-univocality between impulses and effects: […] one and the same sequence of changes in forces may produce different movements on successive repetitions»[32].

6. *Conclusions*

Contemporary scientific understanding of physiological and pathological phenomena seems to support the adoption of relational and processual concepts/categories in order to account for the systemic modes of action and organization of organisms. Integration and the need for coupling in an organized way several hierarchies of processes, on many different levels, are the two main features of the proposed ontology and epistemology, which account for the unitary nature of biological processes right in virtue of the integration of multiple parts.

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[31] Bateson - Gluckman, *Plasticity, Robustness*, p. 43.

[32] N.A. Bernstein, *On the Co-ordination and Regulation of Movements*, Pergamon, New York 1967, p. 62.

As we argued, the concept of Operational Integrating System, as it is intended in the broader framework of the relational and processual ontology proposed, can account for what it seems a general feature of living beings, that is, the constitutive necessity to integrate multiple causal levels and their subsequent interactions in a systemic organization. Considering the proper differences – both on the level of scientific investigation and in the adoption of specific epistemologies proper to oncology and neuroscience – the ontological and epistemological value of such relational concept seems to apply to the scientific understanding of both neoplastic growth and nervous development.

In organisms, constitutive parts maintain their identity always in virtue of the overall interrelational organization, which grows in time as a unity of action that has its own history. By this achievement of systems biology and the philosophical attempts to conceptualize what appears as a striking paradigm shift in contemporary life sciences, we could dare a suggestive historical-epistemological analogy with Thomas of Aquinas' thought on the cosmos[33], since systems biology and the relational ontology based on it suggests that organism – after all, the microcosmos *par excellence* – is constituted in its part by a *multitudo*, in which «id quod est ex unis, quorum unus non est alterum»[34] (what it is constituted by unity, where one is not another), but this *multitude* is able to give birth to both an *unum* (that is, a substantial unity) and an *ordo* (the inter-relational system which defines the whole's persistence and history).

It is clear that further philosophical reflections are needed in order to clarify several issues entailed in the proposed approach – e.g. how the ontological and epistemological assumptions merge each other, or the mode of interaction between the operational integrating organization of living systems and their biological and physical constraints. Nevertheless, any attempt to move toward an ontological and epistemological reflection able to account for the complex entanglement of integration, organization and multicausality seems useful to overcome the conceptual and philosophical obstacles that constrained a scientific understanding of the living beings in the narrow roads of mereological perspective.

Abstract

Recent advances in biological sciences suggest that living beings have to be understood mostly in systemic terms, and characterized by the unitary integration of multiple level of causal dynamics over the time of their «life histories». Such focus on the interplay of synchronic and diachronic factors in the organism's processes of growth appeals to an overcoming of mereology, but it also entails the need for an ontological and epistemological reflection, which can find support in some recent experimental and theoretical advances from different subfields of biomedical sciences. In this paper, we advocate the value of a relational and processual ontology in order to account for the systemic and multi-level unity that characterizes the phenomena of life, firstly providing a review of relational ontology and of its value in relationship to temporality, secondly drawing suggestions from the analysis of developmental processes in oncology and neuroscience.

Keywords: Life History, Growth, Relational Ontology, Cancer, Brain Plasticity

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[33] J.J. Sanguineti, *Uomo e Cosmo nella Filosofia di San Tommaso*, in A. Stagliano (a cura di), *La creazione e l'uomo*, Messaggero, Padova 1992, pp. 67-93.

[34] Thomas Aquinas, *In I Sent*., d. 24, q. 1, a. 3.