On emergence and causality in the living world

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We discuss the concept of emergence, and try to show that it is one of the most significant issues in the study of complex living systems. We stress particularly that emergent properties possess a specific causal power, which is not reducible to the power of their constituents. The emergence of physiological functions is profoundly related to the self-organized dynamics of biological systems. The increasing complexity of cellular and organismal activity favors the emergence of novelties and the integration of the active parts into an autonomous whole.

EMERGENCE CAUSALITY SELF-ORGANIZATION
EPIGENETICS COMPLEXITY PARTS AND WHOLE

I. Introduction

This essay is aimed at highlighting the important fact that the specificity of complex biological activity does not arise from the specificity of the individual molecules that are involved, as these components frequently function in many different processes. For instance, genes that affect memory formation in the fruit fly encode proteins in the cyclic AMP (camp) signaling pathway that are specific to memory. It is the particular cellular compartment and environment in which a second messenger, such a camp, is released that allow a gene product to have a unique effect. Biological specificity results from the way in which these components assemble and function together. More precisely, we attempt at showing that complex biological levels of functionality result from self-organized processes.

For self-organization to act on macroscopic cellular structures, three requirements must be fulfilled: (i) a cellular structure must be dynamic; (ii) material must be continuously exchanged; and (iii) an overall stable configuration must be generated from dynamic components. Interactions between the parts, as well as influences from the environment, give rise to new features, such as network and collective behaviors which are absent in the isolated components. Consequently 'emergence' has appeared as a new concept that complements 'reduction' when reduction fails. Emergent properties resist any attempt at being predicted or deduced by explicitly calculation or any other means. In this regard, emergent properties differ from resultant properties, which can be defined from low-level configurations and information. For instance, the resultant mass of a multi-component protein assembly is simply equal to the sum of the mass of each individual component. However, the way in which we taste the saltiness of sodium chloride is not reducible to the properties of sodium and chloride gas. An important aspect of emergent properties is that they have their own causal power, which is not reducible to the power of their constituents.

The key concepts here are those of 'organization' and 'regulation', first of all because organization and regulation become cause in the living matter of morphological, functional and mental novelties. According to the principle of emergence, the natural and living worlds are organized into stages and levels that have evolved over different evolutionary times through continuous and discontinuous processes. Reductionists advocate the idea of 'upward causation' by which molecular states generally bring about higher-level phenomena, whereas proponents of emergence admit 'downward causation' by which higher-level systems may influence lower-level configurations. We would like to underline the philosophical importance of admitting 'downward causation' in the analysis of complex living systems (i.e. presenting and ever-increasing coupled activity of plasticity and complexity) by showing that chromatin forms and its structural modifications play a crucial role in the increasing complexity of gene regulatory networks, in the emergence of cellular functions and in development, as well as in the neurocognitive plasticity.

In order to make clear from the outset the content and meaning of what we mean by emergence, we want to stress the following features of that concept. It cannot be simply deduced or predicted from low-level elements. It implies that nature and living organisms exhibit different levels of organization and regulation (for living systems). Emergent phenomena may have causal power, especially downward causation. They depend on the *openness* and *nonlinearity* of the system in which they appear. Emergent properties are systemic and therefore they not concern the single elements or parts of the system. They generally appear at higher and complex

levels of organization; more precisely, they arise from self-organizing phenomena. Finally, we should highlight that these features of the notion of emergence play a very important role in biological processes, and they are not necessarily or completely satisfied in other disciplines, especially in physics.

II. The challenge of biological complexity: self-organization, emergence of novelties and the integration of the parts into a whole

The principal challenge facing systems biology is complexity. Systems biology defines and analyses the interrelationships of all the elements in a functioning system in order to understand how the systems works. At the core of the challenge is the need for a new approach, a shift from reductionism to an integrative perspective. More precisely, what is needed is to provide a conceptual framework for system biology research. The concept of a complex system, i.e. a system of subsystems each belonging to a certain category of living entities such as proteins, tissues, organs, etc., need first to be defined in general mathematical terms. It is rather clear, however, that for a deeper understanding in systems biology investigations should go beyond building numerical mathematical or computer models – important as they are. Biological phenomena cannot be predicted with the level of numerical precision as in classical physics. Explanations in terms of how the categories of systems are organized to function in ever changing conditions are more revealing. Non-numerical mathematical tools are appropriate for the task. Such a categorical perspective led us to propose that the core of understanding in systems biology depends rather on the search for organizing principles than solely on construction of predictive descriptions (i.e. models) that exactly outline the evolution of systems in space and time.

Biological systems are difficult to study because they are complex in several ways. One of the most important aspects of biological complexity is multi-levelness: the structural and functional organization of the human body into tissues and organs systems composed of cells. From molecules to organs, levels are inter-related and interdependent, so that the organism is able to conserve and adopt the integrity of its structural and functional organization against a setting of continuous changes within the organism and its environment. This capacity, usually described as 'robustness', is a consequence of non-linear spatial-temporal intra- and inter-cellular interactions.

To understand disease-relevant processes, we therefore require methodologies that allow us to study non-linear spatial-temporal systems with multiple levels of structural and functional organization. Non-linear dynamics plays an important role for the explanation of highly non-linear biological behaviors such as biochemical and cellular rhythms or oscillations. According to biodynamics, biological systems are seen as open systems of non-linearly interacting elements. Consequently, the field of biodynamics might be defined as the study of the complex web of non-linear dynamical interactions between and among molecules, cells and tissues, which give rise to the emergent functions of a biological system as a whole. The work of non-linear dynamical interactions favors the self-organization of emergent macroscopic patterns, including temporal oscillations and spatial-temporal wave patterns, especially in chemical and biological systems. Numerous examples are now known at all levels of biological organization. The formation of biological rhythms and oscillatory dynamical states of different periodicities plays a fundamental role in living organisms.

The processes that underlie cellular oscillators are organized in complexly coupled biochemical networks, wherein feed-forward and feedback information flows provide the links between the different levels in the hierarchy of cell biochemical

network organization. Such networks are also central components of the cellular machinery that controls biological signaling. Recently scientists were enabled to investigate the properties of biological signaling networks such as their capacity to detect, transduce, process and store information. It was found that cellular signaling pathways may also exhibit properties of emergent complexity. Such findings serve to demonstrate the impossibility to predict the dynamics of cellular signal transduction processes only on the basis of isolated signaling molecules and their individual microscopic actions. In order to develop an integrative, dynamical picture of biological signaling processes, therefore, it will be necessary to characterize the nonlinear relationships among the different molecular species making up the biochemical reaction networks, which control all aspects of cellular regulation as, for example, from RNA transcriptional control to cellular division.

Self-organization, that is the capacity of any complex living organism to intrinsically produce new properties and behaviors of organization and regulation, cannot be addressed by purely reductionist approaches. Living organisms present the following two fundamental features. (1) They are thermodynamically open systems; that is, they are in a state of permanent flux, continuously exchanging energy and matter with their environment. (2) They are characterized by a complex organization, which results from a vast network of molecular and cellular interactions involving a high degree of nonlinearity. Under appropriate conditions, the combination of these two features, *openness* and *nonlinearity*, enables complex systems to exhibit properties that are *emergent* or *self-organizing*. In biological systems, such properties may express themselves through the spontaneous formation, from (almost) random molecular interactions, of long-range correlated, macroscopic dynamical patterns in space and time – the process of *self-organization*. The dynamical states that result from self-organizing processes may have features such as excitability, bi-stability, periodicity, chaos or spatial-temporal patterns formation, and all of these can be observed in biological systems.

Self-organizing processes may give rise to new, unexpected properties and behaviors in living systems, also called *emergent properties*. Emergent properties can be defined as properties that are possessed by a dynamical system as a whole but not by its constituent parts. Otherwise stated, emergent phenomena are phenomena that are expressed at higher levels of organization in the system but not at the lower levels. The concept of self-organization implies the existence of a dynamical interdependence between the molecular interactions at the microscopic level and the emerging global structure at the macroscopic level (see Karsenti 2008; and Misteli 2001). In other words, there is an active combination of upward and downward processes. The upward process indicates that, under non-equilibrium constraints, molecular interactions tend to spontaneously synchronize their behavior, which initiates the beginning of a collective, macroscopically ordered state. At the same time, the downward process indicates that the newly forming macroscopic state acts upon the microscopic interactions to force further synchronizations. Through the continuing, *energy-driven* interplay between microscopic and macroscopic processes, the emergent, self-organizing structure is then stabilized and actively maintained.

The above argument reveals that the origins and dynamics of emergent, macroscopic patterns, particularly in biological systems, cannot be simply deduced from the sum of the individual actions of the system's microscopic elements. What is needed is an analysis of the system's collective, macroscopic dynamics, which result from the complex web of molecular interactions between elements.

In spite of these theoretical and epistemological advances in the attempts

to obtain a better understanding of biological systems, the reductionist approach remains dominant, and systems biology is often seen as no more than integration of diverse data into models of systems. Reductionism in biology, and especially in biochemistry, has consisted in separating cell into their components, which were then separated into smaller components, and then studied in isolation. The reductionist stage was certainly necessary, but the time has come to move beyond this, beyond even studying the interactions of the components with one another, because all of them form parts of a whole, and their presence in the whole can only be understood by considering the need of the whole. As was recently emphasized by many scientists (see Cornish-Bowden & Cárdenas 2005; Bains 2001), this way of thinking needs to be changed if systems biology is to lead to an understanding of life and to provide the benefits that are expected from it. The emphasis ought to be on the need of the system as a whole for understanding the components, not the converse. For example, general properties of metabolic systems, such as feedback inhibition, can be properly understood by taking account of supply and demand; i.e. the requirements of the system as a whole (Cornish-Bowden & Cárdenas, 2005).

For long time, and especially in the last sixty years, biological science has privileged analytical method, i.e. the splitting up of the living systems into ever-smaller units. Even systems biology has been recently characterized by most of molecular biologists as the integration of knowledge from diverse biological components and data into models of the system as a whole. In fact, this sort of definition is entirely reductionist, and makes systems biology into little more than a euphemism for the type of approach that systems biology theorists criticized: instead of using a view of the whole system as a way to understand its components, it seeks to explain the whole in terms of a vast list of components.

To show the effective causal role played by wholeness and systemic properties in biology, let us consider the three following examples (here we follow closely Cornish-Bowden and Cárdenas 2005). (1) The first concerns the many cases of cooperative feedback inhibition of metabolic pathways, which are now well-known, such as the inhibition of aspartokinase in bacteria by lysine. This type of observation is often explained by supposing that the biosynthetic flux is regulated by this feedback inhibition, and would be subject to uncontrolled variations if there were no feedback loop. However, as the previous mentioned authors pointed out, this explanation is wrong, because fluxes can be controlled perfectly well without feedback inhibition, whether cooperative or not. The need comes not from flux control but concentration control: without feedback inhibition in this pathway the rate at which lysine would be synthetized would still match the rate at which it is used in protein synthesis, but there would be huge and potentially damaging variations in the concentration of lysine and the intermediates in the pathway from aspartate. This sensitivity of metabolite concentrations to perturbations has major implications for the regulatory design of metabolism in living organisms. To understand this, it is necessary to represent biosynthesis pathways in a way that allows analysis in terms of supply and demand; that is to say, in a more complete way than is usually in textbooks of biochemistry. These typically show, for example, the biosynthesis of lysine as a series of reactions that begin with aspartate and end with lysine. However, lysine is not in any meaningful sense the end-product: it is made not as an end in itself but as a starting material for other processes, principally, in this case, protein synthesis. As protein synthesis accounts for most of the metabolic demand for lysine, it determines the rate at which it needs to be synthetized from aspartate. Omitting the conversion of lysine into protein from the pathway means omitting the one step that explains the feedback inhibition of

aspartokinase by lysine. This inhibition cannot be explained solely in terms of the components concerned, aspartokinase and lysine, but requires consideration of the whole system, including protein synthesis.

(2) The second example concerns the failure of genome sequencing to provide an effective explanation of how living organisms develop and evolve. There are at least two fundamental reasons for this failure. (i) The first is related to the essential fact that the expression of genome, i.e. its state of activity, stand beyond the gene sequences, and depend much more upon the peculiar spatial organization of the genome into the chromatin and the chromosome. Moreover, the functional properties of genomes are strongly determined by their cellular organization. It must be stressed the functional relevance of spatial and temporal genome organization at three interdependent levels: the organization of nuclear processes; the organization of chromatin into higher-order domains; and the spatial arrangement of chromosomes and genes within the nuclear space. Each of these levels has regulatory potential, and all are interdependent. There is increasingly evidence that the higher-order, topological organization of the genomes exert fundamental influence on their functional properties, and on many cellular processes, including expression and genome stability (for more details, see Misteli, 2007; Cremer et al. 2006).

(3) The third example regards the relationship between genotype and phenotype. We know that for more than half a century the prevalent 'dogma' was to think that the genotype completely and unidirectionally determine the phenotype and hence the fate of any complex living organism. Now, to be more precise, the problem is not much that genome sequences contain no phenotypic information, but that we do not have reliable methods for undertaking all of the steps involved in deducing a phenotype from them.

> A list of putative gene products, or even a list of putative enzymes, is not a phenotype, and converting it into a phenotype requires construction of plausible metabolic map, which then need further work to convert it into a possible phenotype. Finally, the possible phenotype can only become a real phenotype when all relevant kinetic and regulatory properties are considered, together with information about how all the components are organized into a three-dimensional whole – even a four-dimensional whole, given that the times when different components are made may be just as important as where they are placed (Cornish-Bowden, 2006).

III. Some remarks on the problem of causation in biological sciences

Complex living systems consist of several organizational levels, which often are interdependent in different ways. This multi-layered organization poses the problem of causation, which is scientifically and philosophically profound. This is especially true for the metabolic, cellular and physiological systems, as well as for the nervous and cognitive systems. In all these systems upward and downward causation are causally interrelated. This important fact has led the heart physiologist Denis Noble to argue that there is no privileged level of causality in biological systems. Moreover, higher levels in biological systems exert their influence over the lower levels. Each level provides the boundary conditions under which the processes at lower levels operate. Without boundary conditions, biological functions would not exist (Noble 2012).

Studying the causal pathways in brain dynamics, the Sweden biologist Hans Liljenström remarks that downward causation from larger to smaller scales could be regarded as evidence that multi-level 'both-way' causation occurs (Liljenström

2016). He investigated, on the one hand, how cortical neurodynamics may depend on structural properties, such as connectivity and neuronal types, and on intrinsic and external signals and fluctuations; on the other, to what extent the complex neurodynamics of cortical networks can influence the neural activity of single neurons. More precisely, Liljenström attempted to show that the neural activity at the microscopic level of single neurons is the basis for the neurodynamics at the mesoscopic network level, and fluctuations may sometimes trigger coherent spatial-temporal patterns of activity at this higher level. Irregular chaotic-like behavior can be generated by the interplay of neural excitatory and inhibitory activity at the network level. This complex network dynamics, in turn, may influence the activity of single neurons, causing them to fire coherently or synchronously. Thus, Liljenström conclude: «this downward causation is complementary to the upward causation» (2016, 189).

From simulation results, applying both to bottom-up mechanisms like noise-induced state transitions, and to top-down processes like network modulation of neural activity, Liljenström is led to stress that events and processes at microscopic level of single neurons can influence the mesoscopic Neurodynamics of cortical networks, which in turn are associated with cognitive functions ate the macroscopic level.

> It is apparent that internal noise can cause various phase transitions in the network dynamics, that may have effects on higher level functions. For example, an increased noise level in just a few network nodes can induce global synchronous oscillations in cortical networks and shift the system dynamics from one dynamical state to another. This in turn can change the efficiency in the information processing of the system (185).

This kind of situation, however, needs to be related (or can be correctly understood only in relation) to another important aspect of the neurodynamics of cortical networks. In fact,

> [...] neuromodulation, whether related to the level of arousal or as a consequence of attention, can regulate the cortical neurodynamics, and hence the activity of its constituent neurons. The firing patterns of single neurons are thus, to a certain degree, determined by the activity to the network level (and above). For example, neurons in visual cortex may fire synchronously and in phase, as a result of cholinergic modulation during attention (186).

These arguments show clearly that the intricate web of interrelationships between different levels of neural organization, with inhibitory and excitatory feed-forward and feedback loops, with nonlinearities and thresholds, noise and chaos, makes any attempt to trace the causality of events and processes futile. In line with the ideas of Noble, it seems obvious that there is, in general, both upward and downward causation in biological systems, including the nervous system. This also makes it impossible to say that mental processes are simply caused by neural processes, without any influence from the mental on the neural. R. W. Sperry already stressed this crucial point when he wrote:

> A traditional working hypothesis in neuroscience holds that a complete account of brain function is possible, in principle, in strictly neurophysiological terms without invoking conscious or mental agents; the neural correlates of subjective experience are conceived to exert causal influence but no mental qualities per se. This long-established materialist-behaviorist principle has been challenged in recent years by the introduction of a modified concept

> of the mind-brain relation in which consciousness is conceived to be emergent and causal. Psychophysical interaction is explained in terms of the emergence in nesting brain hierarchies of high order, functionally derived, mental properties that interact by laws and principles different from, and not reducible to those of neurophysiology. Reciprocal upward and downward, interlevel determination of the mental and neural action is accounted for on these terms without violating the principles of scientific explanation and without reducing the qualities of inner experience to those of physiology. Interaction of mind and brain becomes not only conceivable and scientifically tenable, but more plausible in some respects that were the older parallelist and identity views of the materialist position (Sperry 1980, 195). **1**

1 See also Eccles (1986).

In the light of the last remark, it might appear quite meaningless the debate on the philosophical distinction between the 'functionalist' version and the 'monist' version of ('non-reductive' 'physicalism'). While in the first version, one maintains that mental phenomena are realized in physical properties and processes, in the monist version one holds that every event that can be given a mental description can also be given a physical description (see Sperry 1980; Eccles 1970 and 1986). In either version, even though there are no scientific laws by which mental phenomena could be 'reduced' to physical phenomena, the underlying causality of the world remains entirely physical.

In life sciences, we need to rethink the concept of biological causality in newly, more profound terms. One key point is that higher-level phenomena cannot be understood simply by analyzing the lower levels. The importance of systems biology is connected to the limitations of molecule-centered approaches. Systems biology has shifted the focus from identification and characterization of molecular components towards and understanding of networks and functional activity. However, a further significant shift remains to be done: re-focusing our attention away from pathway-centered approaches to an understanding of complex multilevel systems. In other words, our understanding of cellular functions must be integrated across multiple levels of structural and functional organization: from cell tissues and organs to the whole organism, and from cell functions (growth, proliferation, differentiation and apoptosis) to the physiology of organs or the human body. To quote H. Kacser (1986), "to understand the whole, one must study the whole". The idea is that, if you want to understand a tissue, you need to study it as a whole. Now, organs and tissues are multi-level systems manifesting both 'bottom-up' determination and 'top-down' determination: the whole (organ or tissue) is the product of the parts (tissues or cells, respectively), but the parts in turn depend upon the whole for their own functioning and maintenance. In more philosophical terms, this means that higher-level systems in biological phenomena may change in very significant ways properties of lower-level systems or entities. In other words, these entities behave at lower levels in novel and irreducible ways.

Following O. Wolkenhauer and A. Muir (2011), we stress that living systems, from organisms to organs, tissues and cells are phenomena of organized complexity whose relationships and properties are largely determined by their function as a whole. The tissues of our human body are self-organizing systems: every cell owes its role to the action of all its surrounding cells, and also exists for the sake of the others. The whole (tissue) and its parts (cells) reciprocally determine functioning of each other. For instance, the pacemaker rhythm of the heart is not only caused by the activity of the ions channels at the molecular level, but is also dependent on the functioning of the organ, and even the body, as a whole. The systems biologist Denis Noble demonstrated the importance of such downward causation in simulations of

the heart rhythm, where feedback from cell voltage was removed and fluctuations in ion current ceased. To understand such phenomena in multi-level systems, it is not only important to understand molecular mechanisms but also to understand the organizational maintenance of the system at higher levels.

IV. On the role of loops of interactions and emergent properties in biological systems

The aim of this section is to at highlight the importance of a systems biology approach. System biology is about *interactions* rather than about constituents, although knowing the constituents of the system under study may be a prerequisite for starting description and modeling. Interactions often bring about new properties or *emergent properties*. For instance, a system may start oscillating although the constituent alone would not. Another important example is that evolutionary biologists have wondered for long jump-like transitions can occur in evolution. From the viewpoint of systems theory, the answer arises from bifurcations. In a non-linear system, at certain points in parameter space, called *critical points*, bifurcations occur, that is, a small change in a parameter leads to a *qualitative* change in system behavior, e.g. a switch from steady state to oscillation. It is clear that the number of potential interactions within a system is far greater than the number of constituents. If only pairwise interactions were allowed, the former number would be $n2$ if the latter number were denoted by n. The number of interactions is even larger if interactions within triples and larger sets are allowed, as is the case in multi-protein complexes.

In the sense of systems biology, a biological phenomenon or being is a *system* if emergent properties result from it. Genomics has certainly been a very important and fruitful undertaking and gave us much new insights into molecular biology. However, much of molecular biology is based on reductionism and simple determinism. It is an extreme exaggeration to say that the human genome has been deciphered. Besides the fact that not all ORFs functions have been assigned yet, it should be acknowledged that even if all functions were known, we would be far from understanding the phenomenon of life because knowledge of all the individual gene products does not say much about the interactions between them, and even less does about the content and meaning of such interactions. According to a system's view of life, the study of the dynamics and interaction networks is essential for understanding the ways in which living organisms regulate their cellular activity and organize their physiological growth. One of the major goals of systems biology is to find appropriate ways of diagramming and mathematically describing the specific, complex interactions within and between living cells. Because complex systems have emergent properties, their behavior cannot be understood or predicted simply by analyzing the structure of their components. The constituents of a complex system interact in many ways, including negative feedback and feed-forward control, which lead to dynamic features that cannot be captured satisfactorily by linear mathematical models that disregard cooperativity and non-additive effects. In view of the complexity of informational pathways and networks, new types of mathematics are required for modeling these systems (for more details, see Boi 2005 and 2011).

It is worth of noticing that the specificity of a complex biological activity does not arise from the specificity of the individual molecules that are involved, as these components frequently function in many different processes. For instance, genes that affect memory formation in the fruit fly encode proteins in the cyclic AMP (cAMP) signaling pathway that are not specific to memory. It is the particular

cellular compartment and environment in which a second messenger, such as a cAMP, is released that allow a gene product to have a unique effect. Biological specificity results from the way in which these components assemble and function together. Interactions between the parts, as well as influences from the environment, give rise to new features, such as network behavior which are absent in the isolated components. Consequently, emergence has appeared as a new concept that complements "reduction" when reduction fails. Emergent properties resist any attempt at being predicted or deduced by explicit calculation or any other means.

V. Reductionism and emergence

The reductionist method consists in analyzing biological systems by dissecting it into their constituent parts and determining the mechanistic (physicochemical) connections between the parts. The reductionists assume that the isolated molecules and their structure have sufficient explanatory power to provide an understanding of the whole system. This radical deterministic standpoint was advocated by Francis Crick by claiming that «The ultimate aim of the modern movement in biology (he refers of course to molecular biology) is to explain all biology in terms of physics and chemistry» (1970, 561). Such reductionist mindset arises from the belief that because biological systems are composed solely of atoms and molecules, without the influence of other kinds of forces or laws, it should be possible to explain them using the physicochemical properties of their individual components, down to the atomic level. The most extreme manifestation of the reductionist view is the belief that is held by neuroscientists (see Changeux 1983) that consciousness and mental states can be reduced to chemical reactions that occurs in the brain. In the recent decades many biologists have become increasingly critical of the idea that biological systems can be fully explained using only physics and chemistry. And, in fact, there is now important evidence that the biology, development, physiology, behavior or fate of a human being cannot be adequately explained by the reductionist standpoint that considers only (classical or not) physical and chemical laws. A more open and integrative approach considers biology as an autonomous discipline that requires its own entities and concepts that are not (necessarily and completely) found in physics and chemistry.

Biological complexity and specificity results from the way in which single components like molecules, genes and cells self-organize and function together when constituting a whole (a tissue, an organ, an organism), say a whole system including different subsystems. Not only the interactions between the parts and the influence from the environment (think of epigenetic factors, both chemical and spatial, that mediate the complex relationship between the genomes and the micro- and macro biophysical environments), but also the systemic properties of the whole that exert an action on the components, give rise to new features, such as network behavior and functional properties, which are absent in the isolated components.

This means that we need to consider 'emergence' as an effective new concept that complements 'reduction' when reduction fails, and allow to consider those specific systemic properties of the whole responsible for biological organization and regulation at higher levels. Emergent properties o not result from properties pertaining to simple components of biological systems. They resist any attempt at being predicated or deduced by explicitly calculation or any other analytical means. In this regard, emergent properties differ from 'resultant' properties, which can be predicted from lower-level components.

> For instance, the resultant mass of a multi-component protein assembly is simply equal to the sum of the masses of each individual component. However, the way in which we taste the saltiness of sodium chloride is not reducible to the properties of sodium and chlorine gas. An important aspect of emergent properties is that they have their own causal power, which is not reducible to the powers of their constituents. For instance, the experience of pain can alter human behavior, but the lower-level chemical reactions in the neurons that are involved in the perception of pain are not the cause of the altered behavior, as the pain itself has a causal efficacy (Van Regenmortel 2004, 146).

Advocating the reductionist idea of 'upward causation' means to maintain that molecular components and states suffice to determine higher-level processes occurring in biological systems. However, without denying a certain role of methodological reductionism in science, today we are led to recognize the important role played by the concept of emergence in many fields of the natural and life sciences, as well as to accept 'downward causation' by which higher-level systems and processes influence lower-level configurations and entities. Emergence is essentially linked to the intrinsic and peculiar complexity of living systems. The existence of emergent properties is an outcome of the complexity of living systems. In other words, in order to solve the increasingly complexity, linked to the stages of the developments of tissues and organs and the construction of global physiological systems, living multicellular organisms self-organize giving thus rise to newly, needed regulatory and functional properties.

VI. Many levels of causation are needed for thinking the biological complexity and functionality.

Many theoretical ideas and experimental findings in life science over the last three decades lead to review profoundly the ideas about properties and behaviors of biological systems. Among them, maybe the most important is the principle of causality in biological sciences, as it has been conceived by molecular biology. This fundamental issue is raised by Denis Noble when he asks: «Must higher level biological processes always be derivable from lower level data and mechanisms, as assumed by the idea that an organism is completely defined by its genome? Or are higher level properties necessarily also causes of lower level behavior, involving, actions and interactions both ways?» (2011, 1). According to Noble,

> [...] downward causation is necessary and this form of causation can be represented as the influences of initial and boundary conditions on the solutions of the differential equations used to represent the lower level processes. (...) *A priori*, there is no privileged level of causation. (...) Biological relativity can be seen as an extension of the relativity principle in physics by avoiding the assumption that there is a privileged scale at which biological functions are determined (1).

There is increasingly evidence, experimental and theoretical, of the existence of downward causation from larger to smaller scales. Today, one is enabled to visualize exactly how multilevel 'both-way' causation occurs. There is none *a priori* reason why one level in a biological system should be privileged over other levels when it comes to causation. There are various forms of downward causation that regulates lower level components in biological systems.

Looking more closely to molecular biology, the essence of the central dogma is that 'coding' between genes and proteins in one-way. It would be better the word 'template' to 'coding' since 'coding' already implies a program. The concept of

a genetic program is indeed one of the most relevant problem of molecular biology because there is no a genetic program at all. The argument runs as follow (for more details, see Noble 2011). The sequence of DNA triplets form templates for the production of different amino acid sequences in proteins. Amino acid sequences do not form templates for the production of DNA sequences. What was shown by Crick, Watson and their followers is that template works in only one direction, which makes the gene appear primary. So, what the genome really causes? The coding sequences form a list of proteins and RNAs that might be made in a given organism. According to Noble

> These parts of the genome form a database of templates. To be sure, as a database, the genome is also extensively formatted, with many regulatory elements, operons, embedded within it. These regulatory elements enable groups of genes to be coordinated in their expression levels. And we know that the non-coding parts of the genome also play important regulatory functions. But the genome is not a fixed program in the sense in which such a computer program was defined when Monod and Jacob introduced the idea of the "genetic program" (*programme génétique*) in the sixties. It is rather a 'read-write' memory that can be organized in response to cellular and environmental signals. Which proteins and RNAs are made when and where is not fully specified. This is why it is possible for the 200 or so different cell types using exactly the same genome. A heart cell is made using precisely the same genome in its nucleus as a bone cell, a liver cell, pancreatic cell, etc. Impressive regulatory circuits have been constructed by those who favor a genetic program view of development, but these are not independent of the 'programming' that the cells, tissues and organs themselves uses to epigenetically control the genome and the patterns of gene expression appropriate to each cell and tissue type in multicellular organism (2011, 3). **2**

2 See also Noble (2008; 2006).

The important point to stress is that the circuits of major biological functions necessarily include non-genome elements. This tells us that the genome alone is far from being sufficient. Barbara McClintock (1984) first described the genome as 'an organ of the cell'. Indeed, DNA sequences do absolutely nothing until they are triggered to do so by a variety of transcriptions factors, which turn genes 'on and off' by binding to their regulatory sites, and various other forms of epigenetic control, including methylation of certain cytosines and interactions with the tails of the histones that form the protein backbone of the chromosomes. All of these, and the cellular, tissue and organ processes that determine when they are produced and used, 'control' the genome. In the neurosciences, a good example of downward causation is what neuroscientists call electro-transcription coupling, since it involves the transmission of information from the neural synapses to the nuclear DNA.

So, there is strong evidence that the genome does not completely determine the organisms. Multi-cellular organisms use the same genome to generate all the 200 or so different types of cell in their bodies by activating different expression patterns. The regulatory parts of the genome are essential in order the genome be activated. The mechanisms and patterns of activation are just as much part of the organism's construction and the genome itself. It is time to recognize that there exist various forms of downward causation that regulates lower level components in biological systems. In addition to the controls internal to the organism, we also have to consider the influence of the environment on all the levels. Causation is, therefore, two-way. A downward form of causation is not a simple reverse form of upward causation. It is better seen as completing a feedback loop that expresses a functional integration of the various levels of causation, including in particular the concentrations and

locations of transcription and post-transcription factors, and the relevant epigenetic influences. All those forms of downward causation naturally consider the role of cell and tissue signaling in the generation of organizing principles involved in embryonic induction, originally identified in the pioneering work of Hans Spemann and Ilde Mangold (1924). The existence of such induction is itself an example of dependence on boundary conditions, that is those conditions which define what constraints are imposed on a biological system by its environment. That because boundary conditions are somehow involved in determining initial conditions (the state of the components of the system at the time at which we start analyzing and modelling it), they can therefore be considered as a form of downward causation. The induction mechanisms emerge as the embryo interacts with its environment. Morphogenesis cannot be explained only by the genome. Put in different terms, the emergence of new morphological and physiological forms in the embryo of a human being cannot be derived and understood from the level of the genome.

There is real ('strong') emergence because contingency beyond what is in the genome, i.e. in its environment, also determine what happens at the higher level of morphogenesis. Multi-cellular organisms are multi-level systems, and each level, from molecules and cells to tissues and organs, possesses a specific organization with increasing complexity when one passes to higher order systems. This organization has causal power. The idea of multicellular causation considers seriously the fact that complex organization of highest levels, such as the global properties and activity of cells and the systemic properties and state of organisms, may act on the functions of the components, particularly genes and proteins. Downward causation leads us to shift our focus away from the gene as the unit of development and evolution to that of the whole organism. It might be that the concept of downward causation will play an important role in the reappraising of the mind-body problem (how and why mental states may act on neural states), and in the philosophy of perception and action (perceptual global effects, intentionality, free will, etc.). Finally, we need to stress that one of the major theoretical and experimental outcomes of multilevel modelling is that causation in biological systems runs in both directions: upward from the genome and downward from all other levels. There are feed-forward and feedback loops between the different levels of causation.

To conclude, we would like to stress the fundamental fact that organisms are more than, and a reality profoundly different from the genes that look after their assembly. Mechanical, chemical and cultural inputs from the environment, epigenetic cues, also have an effect on the final phenotype. In fact, continued environmental influences on the adult phenotype continue to affect its characteristics. The open question is whether the epigenetic cues can become causative agents of phenotypic modifications. Within a biological multi-level, astonishing complex reality, higher levels result from lower-level processes (genes up to phenotype), and lower levels result from higher-levels processes (organism's properties to epigenetics mechanisms of genes expression and regulation), so that upward and downward causation are in different ways and in both directions deeply interlaced. Some epigenomic cues seem to be assimilated into the genome, as already C. H. Waddington showed (1953; see also Boi, 2009). The evolved genome therefore incorporates epigenomic cues or the expectation of their arrival. Genomes are more than linear sequences, in fact, they exist as elaborate spatial and physical structures, and their functional properties are strongly determined by their cellular organization and by the interactions that organisms develop with the environment.

References

Bains, W. (2001). The parts list of life. *Nat. Biotechnology*, 19, 401-402.

Boi, L. (2005). Topological Knot Models in Physics and Biology. In Id. *Geometries of Nature, Living Systems and Human Cognition. New Interactions of Mathematics with Natural Sciences and Humanities* (203-278). Singapore: World Scientific.

Id. (2009). Epigenetic phenomena, chromatin dynamics, and gene expression. New theoretical approaches in the study of living systems. *Rivista di Biologia/ Biology Forum*, 103 (4), 27-58.

Id. (2011). Plasticity and complexity in biology: topological organization, regulatory protein networks, and mechanisms of genetic expression. In Terzis, G. & Arp, R. (eds). *Information and Living Systems: Philosophical and Scientific Perspectives* (287-338). Cambridge, MA: MIT Press.

Changeux, J.P. (1983). *L'homme neuronal*. Paris: Fayard.

Cornish-Bowden, A. & Cárdenas, M.L. (2005). Systems biology may work when we learn to understand the parts in terms of the whole. *Biochemical Society Transactions*, 33 (3), 516-519.

Cornish-Bowden, A. (2006). Putting the systems back into systems biology. *Perspectives in Biology and Medicine*, 49 (4), 1-9.

Cremer, T. et al. (2006). Chromosome territories – a functional nuclear landscape. *Curr. Opin. Cell Biol.*, 18, 307-316.

Crick, F.H.C. (1970). The central dogma of molecular biology. *Nature*, 227, 561-563.

Eccles, J. C. (1986). Do mental events cause neural events analogously to the probability fields of quantum mechanics?. *Proceedings of the Royal Society of London. Series B, Biological Sciences*, 227, 411-428.

Kacser, H. (1986). On parts and wholes in metabolism. In Welch, G.R. & Clegg, J.S. (eds). *The Organization of Cell Metabolism* (327-337). New York: Plenum Press.

Karsenti, E. (2008). Self-organization in cell biology: a brief history. *Nature Reviews Molecular Cell Biology*, 9, 255-262.

Kauffman, S. (1993). *The Origins of Order. Self-organization and selection in evolution*. Oxford: Oxford University Press.

Liljenström, H. (2016). Multi-scale Causation in Brain Dynamics. In Kozma, R. & Freeman W.J. (eds.). *Cognitive Phase Transitions in the Cerebral Cortex– Enhancing the Neuron Doctrine by Modeling Neural Fields* (177-186). Basel: Springer International Publishing Switzerland.

McClintock, M. (1984). The significance of responses of the genome to challenge. *Science*, 226, 792-801.

Misteli, T. (2001). The concept of self-organization in cellular architecture. *The Journal of Cell Biology*, 155 (2), 181-185.

Id. (2007). Beyond the sequence: Cellular organization of genome function. *Cell*, 128, 787-800.

Noble, D. (2006). *The music of life* Oxford: Oxford University Press.

Id. (2008). Genes and causation. *Philosophical Transactions of the Royal Society A*, 366, 1125-1139.

Id. (2011). A theory of biological relativity: no privileged level of causation. *Interface Focus*, 1-10.

Sperry, R.W. (1980). Mind-Brain Interaction: Mentalism, Yes; Dualism, No. *Neuroscience*, 5, 195-206.

Van Regenmortel, M.H.V. (2004). Biological complexity emerges from the ashes of genetic reductionism. *Journal of Molecular Recognition*, 17, 145-148.

Waddington, C.H. (1953). Genetic assimilation of an acquired character. *Evolution*, 7, 118-126.

Wolkenhauer, O. & Green, S. (2013). The search for organizing principles as a cure against reductionism in systems medicine. *The FEBS Journal*, 280, 5938-5948.