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An Integrative Approach Toward Biology, Organisms, and Cancer

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Abstract

Over the last two decades, we have challenged the hegemony of the somatic mutation theory of carcino-genesis (SMT) based on the lack of theoretical coherence of the premises adopted by its followers. We offered instead a theoretical alternative, the tissue organization field theory (TOFT), that is based on the premises that cancer is a tissue-based disease and that proliferation and motility is the default state of all cells. We went on to use a theory-neutral experimental protocol that simultaneously tested the TOFT and the SMT. The results of this test favored adopting the TOFT and rejecting the SMT. Recently, an analysis of the differences between the Physics of the inanimate and that of the living matter has led us to propose principles for the construction of a much needed theory of organisms. The three biological principles are (a) a default state, (b) a principle of variation, and (c) one of organization. The TOFT, defined as “development gone awry,” fits well within the principles that we propose for a theory of organisms. This radical conceptual change opened up the possibility of anchoring mathematical modeling on genuine biological principles. By identifying constraints to the default state, multilevel biomechanical explanations become as legitimate as the molecular ones on which other modelers that adopt the SMT rely. Expanding research based on the premises of our theory of organisms will enrich a comprehensive understanding of normal development and of the one that goes awry.

Keywords

Developmental biology; Cancer; Somatic mutation theory; Tissue organization field theory; Constraints; Variation; Theory of organisms

1 Introduction

We scientists are part of the “world” we intend to observe, describe, and understand. This obvious fact poses a problem about the objectivity of our observations. Thus, objectivity is not a given, it has to be constructed. At this effect, scientific theories provide organizing principles and objectivity by framing observations and experiments. Among all the sciences, Physics has followed this general strategy and hence successfully managed to construct a rich set of general theories. Biology, instead, has only one general theory, that of evolution according to Charles Darwin. This is a theory about the relentless change that gave rise to a widely diverse variety of organisms. In this context, just two principles, namely, the generation of variation through reproduction and natural selection, provide the framework to deal with phylogeny.

Biologists, however, have yet to develop a theory of the organism that would deal with the timescale of the life cycle. They have been more adept to propose theoretical constructions during the nineteenth and in the first half of the twentieth century. In the last decades, their prevalent attitude has been to think, instead, that data are devoid of theoretical content, and that theory is unnecessary (as in “data speak by themselves”). Oftentimes, this view is accompanied by the belief that theoretical ideas borrowed from the mathematical theories of information are factual: for example, that development is a “program,” that molecules contain “information,” and that cells emit and receive signals. As a consequence of this distorted *Zeitgeist*, theories about particular biological phenomena, for example cancer, are kept as independent of the concept of organism. Staying with the particular subject of cancer, since the inception of the somatic mutation theory of carcinogenesis (SMT) at the beginning of the twentieth century, the growing number of lack of fit between this theory and experimental results has been met by a ceaseless list of only temporary, ineffective ad hoc fixes. We conclude that the lack of progress in areas of great biological complexity is a consequence of this theoretical paucity. To remedy this situation, we here address first some key points that illustrate the difference between the inert and the alive, then elaborate on our theory of organisms and later explain carcinogenesis from this theoretical framework.

In PART I of his chapter we offer a brief assessment of the differences between the inert and the alive and a short description of the principles for a theory of organisms, while in PART II, we address carcinogenesis within this context.

2 PART I. From the Inert to the Alive

Physical theories are grounded on stable mathematical structures that, in turn, are based on regularities such as theoretical symmetries. A physical object is both defined and understood by its mathematical transformations. These operations permit a stable description of space, a space that is objectivized as the space providing theoretical determination and which specifies the trajectory of the object (usually done by optimization principles). In sum, from this condensed analysis it can be concluded that physical objects are generic and their trajectories are specific [1, 2]. In Biology, instead, there is instability of theoretical symmetries, which are likely to change when the object is transformed with the passage of time, such as when a zygote develops into an adult animal. Thus, biological objects, i.e., organisms, are specific and hence they are not interchangeable. Their trajectories are generic and are not specified by the phase space [2].

Moreover, organisms are the result of a history (ontogeny and phylogeny). During such a history, a cascade of changes occur as a result of which organisms acquire variability and show contextuality depending on the environment in which they live. Unlike inert objects, organisms are agents, that is, they can and will initiate actions such as proliferation and movement. Additionally, organisms not only are able to create their own rules, they also have the capacity to change them [3].

We have recently proposed a theory of organisms that deals with ontogenesis and thus complement Darwin’s theory of evolution that addresses phylogenesis [4]. Our theory of organisms is based on three principles: namely, (a) the default state of all cells is

proliferation with variation and motility, (b) a principle of variation, and (c) the principle of organization. These principles provide a rather comprehensive understanding of the organism's ability to create novelty and stability and to coordinate these apparent counterparts. By profoundly changing both biological observables and their determination with respect to the theoretical framework of physical theories, these principles open up the possibility of anchoring mathematical modeling in Biology. We will next expand on the background under which those principles have been proposed.

2.1 The Root of a Theory of Organisms: The Cell Theory

The cell theory developed from contributions mainly made by Dumortier, Schleiden, Schwann, Virchow, and Remak [5]. In brief, this theory claims that all organisms are made up by cells (one or many), that each cell derives from another cell, and that cells are the fundamental unit of structure and function of organisms. Georges Canguilhem recognized two main components in the cell theory, each of them dealing with a fundamental question: (1) the composition of organisms, in which the cell is the element "bearing all the characteristics of life," and (2) the genesis of organisms [6]. The role of the cell in the genesis of organisms applies to both unicellular and multicellular organisms. In the latter instance, the egg from which sexed organisms are generated is a cell, and the development of such an organism can be explained by the division of the egg into daughter cells by their proliferation. In this regard, Claude Bernard considered the cell as "a vital atom." Bernard stated "In all in-depth analysis of a physiological phenomenon, one always arrives at the same point, the same elementary irreducible agent, the organized element, the cell" [Claude Bernard *Revue Scientifique*, Sept 26, 1874-cited in [6]].

When considering unicellular organisms, a cell and an organism are the same entity and remain as an individual. However, individuality cannot be attributed to both the cells of the multicellular organism and the organism that contains them. In this instance, the concept of level entanglement provides a useful perspective of the relationship between the organism and cells. This means that a zygote is both a cell and an organism, and with each cell division by the zygote and its progeny, these two levels of individuation become more obvious. In other words, following Gilbert Simon-don, individuation in multicellular organisms becomes a process rather than a thing [7]. All along, the cell theory plays a unifying role between evolutionary and organismal biology because it provides a link between the uni- or the multi-cellular individual and its progeny in which the cell itself is a vehicle of inheritance. Within this theoretical perspective, the cell remains as the irreducible locus of agency.

2.2 The Founding Principles

Which is the lineage of the principles of the theory of organisms? Again, those principles are (a) the default state, (b) the principle of variation, and (c) the principle of organization. Each of these principles has its own history. As a consequence of work that we began in the early 1970s while studying the role of estrogens on the proliferation of their target cells, we proposed the default state in order to explain the data we were then collecting [8]. The default state is firmly rooted in the cell theory and in the strict materiality of life.

Additionally, the default state is anchored on the notion that *the cell* (the original cell derived from LUCA) was an organism and is the origin of all organisms.

The joint work of Longo, Montévil, Sonnenschein, and Soto resulted in the integration of variation into the default state of proliferation and motility on the grounds that variation is generated at each cell division. In addition to this default state, a supracellular source of variation has been identified, namely, the “framing principle of non-identical iterations of morphogenetic processes in organogenesis” [9]. This type of variation accounts for the generation of mostly regular patterns of non-identical structures typically observed during organogenesis [9]. The work of Miquel, Soto, and Sonnenschein also addressed the generation of new observables, while examining the concepts of emergence, downward causation, and level entanglement [10]. In turn, the principle of variation can be traced back to Bailly and Longo’s analysis of the differences between the physical and biological objects, the concept of extended criticality [11], and of course, Darwin’s original idea of descent with modification. The relentless change inherent to the principle of variation points to the crucial difference between the theories of the inert and those of the living. The complementary principle of stability requires to be addressed as a main component of biological organization.

Historically, the *principle of organization* can be traced back to the concepts of autopoiesis [12], of closure [13] and of work-constraints cycles [14]. These concepts have been further elaborated by Montévil and Mossio [15]. This principle of organization is the fundamental source of biological stability. The notion of closure of constraints as the means to achieve and maintain stability was traditionally applied to intracellular processes. Mossio et al. also explored the concept that constraints are conserved at the time-scale of the process that is being constrained [15, 16]. Objectively, this concept of constraints opens a point of entry for the mathematization of biology. In fact, we modeled mammary gland morpho-genesis using the notion of default state and its constraints [17].

2.3 Articulating These Principles into a Set

Our three principles are firmly anchored in the biotic world. Following Darwin’ example, we consider unnecessary to delve into the transition from the prebiotic to the biotic world. By this we mean that we are agnostic about whether or not the principles that we propose to study organisms are relevant to the abiotic world; this is because even a hypothetical biochemical structure capable of instantiating closure is not an organism, and also because a self-replicating molecule is not equivalent to an organism undergoing multiplication. Our theoretical work narrowly addresses both uni-cellular and multicellular organisms.

In the current analysis about how the three principles we propose for our theory of organisms are related, we posit that they are irreducible to one another and none of them could be construed as the “condition of possibility” for the other two.

2.4 What Is the Role of the Default State?

Our proposal on the biological default state (proliferation with variation and motility) represents a fundamental biological postulate comparable to that of inertia in Physics. Hence, it does not require an explanation and it is implicit in the Darwinian view of

evolution. What does require an explanation is the identification and mode of action of the constraints that limit the instantiation of the default state both in unicellular and in multicellular organisms. In other words, what requires an explanation is the departure from the default state, namely, proliferative quiescence, lack of motility, and restrained variation [17].

2.5 What Is the Role of Constraints?

Biological constraints and their effects are crucial targets of research in the framework of a theory of organisms. Constraints force cells out of the default state, or modify them by reducing, hindering, or canalizing their ability to proliferate and/or to move. Such an inhibitory constraint eliminates the need to use the metaphoric and anthropocentric notion of “signal” because it acknowledges the agency of cells. In other words, cells cease to be passive, inanimate things on which one has to act upon (stimulate) in order for them to proliferate or to move.

The principle of organization aims at identifying specific constraints in an organism, and thus to verify whether a given constraint is functional, namely that, together with other constraints it establishes closure. In an organism, constraints are maintained by other constraints and in turn they maintain other constraints. Given the interdependence of the parts in an organism, it is insufficient to analyze a single constraint or a given set of constraints in isolation. Nonetheless, we obtained an insightful explanation of glandular morphogenesis by analyzing constraints on the default state in a 3D model of the breast [17]. Admittedly, additional constraints at the tissue level and organismal regulation acting via hormones should be studied for an increasingly comprehensive biological analysis.

Given that each cell division generates two similar but not identical cells, and by virtue of the default state together with the Darwinian notion of descent with modification, the principle of variation manifests itself in the default state. The principle of variation also applies at supra-cellular levels of biological organization as in the framing principle of non-identical iterations of morphogenetic processes [9]. According to the principle of variation, constraints should not be considered phylogenetic invariants. To the contrary, they are also subject to variation. For instance, a morpho-genetic process that is described as a set of constraints is not necessarily conserved in a lineage. Instead, this process will be altered both for some individuals and at the level of groups of individuals, for example in a particular species. Thus, constraints are subject to change.

2.6 How Does Mathematical Modeling Fits Within the Theory of Organisms?

Symmetries and conservation laws are strictly linked and are basic principles in both Mathematics and Physics. To the contrary, in Biology, variation is crucial to both the theory of evolution and the theory of organisms that we are proposing. Mathematicians have yet to be inspired to create structures that would open the possibility of formalizing biological concepts because of the hindrance posed by the principle of variation in Biology. Highlighting the differences between inert and live objects, however, opens the way to facilitate the understanding of what would take to arrive at the development of a “mathematical biology” that would play a comparable role to that it has played in Physics.

Of note, such an approach is very different from the applied mathematics transplanted directly from Physics that is routinely used to model biological phenomena [9, 18]. We favor, instead, to model biological phenomena using biological principles ([17] Montévil, this book).

3 PART II. A New Theory of Cancer, the Tissue Organization Field Theory

The tissue organization field theory (TOFT) adopts two main premises, namely, (a) cancer is a tissue-based disease akin to the process of morphogenesis during development (cancer is development gone awry) [8], and (b) proliferation with variation and motility is the default state of all cells [9, 19]. In PART I, we elaborated about (1) the premises adopted to propose a theory of organisms, (2) the epistemological basis of the exact sciences (Physics and Mathematics), and (3) the conceptual nuances in the biological sciences dealing with the interpretation of evidence related to unicellular and multicellular organisms. We insist in considering that although theoretical principles do not require experimental observation for their formulation, they frame experimental conditions under which empirical data can reproducibly show patterns consistent with the premises adopted to frame a theory, in this case the theory of organisms [20, 21].

3.1 The Theory of Organisms, the TOFT, Organogenesis, and Modeling from Biological Principles

How, when, and where does carcinogenesis fit within the theory of organisms? The TOFT proposes that carcinogenesis, like morpho-genesis, is a relational, contextual process. That is to say, teeth, hair follicles, feathers, mammary glands, lungs are formed due to reciprocal interactions between the mesenchyme and the epithelium. The relational interactions among different components of an organ cannot be reduced to discrete subcellular events [22]. In fact, morphogenesis, i.e., the generation of shape and form, is intimately dependent on physical forces generated by these cell-cell and cell-tissue interactions [23].

We proposed a model of mammary gland morphogenesis resulting from the principles outlined in PART I. Briefly, it consists of two basic components, a cellular one (epithelial cells), and a physical component (collagen-I matrix consisting of collagen fibers). As mentioned in PART I, cells are agents that move, proliferate, and generate mechanical forces that act on both the collagen fibers and their neighboring cells. As the collagen fibers get organized by the cells, they also constrain the ability of cells to move and to proliferate. We interpret this circularity in terms of a closure of constraints. Implementing this mathematical model revealed that constraints to the default state are sufficient to explain the formation of the two main components of the gland: namely, spherical structures called acini and elongated structures that branch (a ductal system). The results of this modeling effort suggest that cells also produce new constraints such as inhibitors of cell proliferation and motility. We posit that alterations of these constraints are at the root of carcinogenesis. This is consistent with reports that excess rigidity of the matrix gives rise to irregular structures unable to form a lumen, which are reminiscent of carcinoma in situ [24]. In the same vein, mammographic density, which is due to enhanced tissue rigidity, is an acknowledged risk factor for breast cancer. We next posit that the relaxation of any of these constraints in the

mammary gland morphogenesis model may lead to abnormal tissue organization, which if persistent may lead to carcinogenesis.

3.2 How Does the Above Narrative Relate to Empirical Evidence?

A widely used model in carcinogenesis consists of the treatment of normal, young female rats from susceptible strains with a chemical carcinogen or a physical one, like radiation. In the following few months, all or nearly all these animals develop mammary gland adenocarcinomas. Where does the chemical or the radiation ultimately act to induce cancer? Or, in other words, which is the target of the carcinogen? In order to test whether the target of the carcinogen was either (a) any of the cells in the epithelium, as proposed by the SMT, or (b) relational, namely, the interactions between stroma and epithelium and their cells as posited by the TOFT, we adopted a theory neutral approach. Namely, we separately exposed the stroma and the epithelium of rat mammary glands to N-methylnitrosourea (NMU), a carcinogen that has a short half-life (~20 min). Once the carcinogen was “cleared” from the “exposed” group (that is, 5 days after carcinogen exposure), a series of recombinants between epithelium and stroma were performed. The recombination of exposed stroma with normal non-exposed epithelial cells resulted in adenocarcinomas, which originated in epithelial ducts. The reverse combination did not generate tumors in their hosts [25]. Subsequently, we reported the normalization of epithelial tumor cells isolated from the NMU-induced mammary carcinomas which organized as normal mammary gland ducts when injected into normal mammary gland stroma [26]. Similar outcomes were obtained from recombining a quasi-normal, non-tumorigenic mammary epithelial cell line and irradiated stroma [27], and a non-tumorigenic prostate cell line and prostate cancer-derived fibroblasts [28]. Altogether this empirical evidence was consistent with explanations of carcinogenesis advanced by the TOFT and inconsistent with those of the SMT. Moreover, these experiments invalidate the SMT and contradict the idea that cancer is irreversible as implied by the dictum “once a cancer cell always a cancer cell” [29].

3.3 Using the TOFT to Explain “Cancer Puzzles”

Next, we examined published evidence collected in the field of cancer that has been perceived as representing quirks or “cancer puzzles.” This characterization was based on the difficulty in interpreting outcomes of experimental protocols that followed the genocentric approach of the SMT. Among those puzzles, it is worth recalling instances where, on the one hand, normal tissues transplanted into the “wrong” locations resulted in neoplasia while, on the other, genuine cancer tissues and their cells became normalized when placed in the midst of normal tissues (normal niches). One of the most spectacular of those puzzles is exemplified by experiments spanning 8 years, whereby Leroy Stevens, at the Jackson Laboratories in Bar Harbor, Maine, transplanted early mouse embryos into the testis of congenic mice. These embryos generated local teratocarcinomas that were subsequently transplanted for almost 200 generations from mouse to mouse. A group of researchers under the leadership of Beatrice Mintz verified the normalization of these teratocarcinoma cells when they were placed in early blastocysts of syngeneic mice; moreover, viable offspring showed a mosaic phenotype combining tissues derived from both the host’s normal cells and the grafted teratocarcinoma cells [30–32]. Also, some of these teratocarcinoma cells in mosaic male mice that ended up randomly in their testis contributed to their germ-line and

formed sperm that carried the genes of these formerly teratocarcinoma cells into their own progeny. The conclusions drawn from these and comparable experiments are that a cell from a neoplasm can behave as a normal cell does, both regarding its proliferative capability (both a normal and a cell belonging to a neoplasia generate two, and only, two daughter cells) and in its ability to carry a genome that responds to cues from distant or neighboring cells and extracellular matrix as a normal cell does [33]. Thus, genuine neoplastic tissues and cells are able to generate normal cells and tissues when grafted among normal cells.

A parsimonious argument can be offered when explaining the occurrence of cancers in offspring resulting from the fusion of mutated parental gametes (sperm and/or oocytes). These neoplasms are what we have described as *inherited inborn errors of development* (Inherited IED) [34, 35]. In such offspring, all the cells in their respective morphogenetic fields carry those genomic mutations. Those mutations may occur in genes whose protein products participate in the establishment of normal morphogenetic fields, and thus, morphogenesis will be impaired and this “development gone awry” may end up forming a neoplasm that would manifest postnatally as an organ malformation or a tumor or both. Examples of these rare Inherited IED are the Li-Fraumeni syndrome, retinoblastoma, BRCA 1 and 2-linked breast and ovarian tumors, the Lynch syndrome, and other syndromes that represent less than 2% of all clinical tumors. Obviously, carriers of these germ-line mutations have all their cells mutated and thus the morphogenetic field as a whole reflects the underlying defect in these syndromes. In these instances, mutations become “proximate” causes of the malformations and/or tumors.

Separately, the other subgroup of induced *inborn errors of development* can be generated when carcinogens (such as environmental endocrine disruptors, viral or radiation exposure, etc.) affect embryos during organogenesis [34]. The evidence already collected in this field is consistent with the notion that in addition to the above-referred documented instances of *inherited and induced inborn errors of development* (Induced IED), a percentage of *sporadic* cancers (about 98% of all clinical cancers) may have been initiated in the womb [36, 37]. Altogether, regardless of whether these neoplasms are due to germ-line mutations or the deleterious effects of carcinogens in utero can be attributed to the underlying process of “development gone awry” [19].

Phenotypes of epithelial cells are susceptible of being manipulated experimentally by changing the niche (epithelium/stroma) in which they originally land or are placed. In addition to the examples cited above from B. Mintz and her group, those of Barcellos-Hoff and Ravani [27] and ours [26], others have strengthened this concept. For instance, when mouse mammary tumor virus (MMTV)-“neu-induced” tumor cells mixed with normal mammary mouse epithelial cells were inoculated into cleared mammary fat pads (stroma), these cells became normalized and formed normal ducts together with normal epithelial cells [38]. In addition, these “tumor cells” became normal luminal, myoepithelial, and secretory mammary epithelial cells. Thus, a normal mammary gland microenvironment, comprised of stromal, epithelial, and host-mediated constraints, may combine to suppress the cancer phenotype during glandular tissue regeneration.

4 Conclusions

Twenty years ago we were puzzled by the lack of theoretical coherence in the fields of control of cell proliferation and cancer. After having proposed that proliferation and motility is the default state of all cells, including those in metazoans, we extended our theoretical exploration to carcinogenesis that led us to propose the TOFT. We used a theory-neutral experimental protocol that simultaneously tested the TOFT and the SMT. The results of this test favored adopting the TOFT and rejecting the SMT.

When using the three principles we proposed, namely, (a) a default state, (b) a principle of variation, and (c) one of organization, we have argued that carcinogenesis can be explained as a relational problem; that means that the release of the constraints created by cell interactions and the physical forces generated by cellular agency lead cells within a tissue to regain their default state of proliferation with variation and motility. Ultimately, carcinogenesis, defined as “development gone awry,” now fits well with the principles we propose for a theory of organisms.

This radical conceptual change opened up the possibility of anchoring mathematical modeling on genuinely biological principles. Turing identified an epistemological gap between modelization and imitation [39, 40]. While the former is based on a theory about the object being modeled, the latter is not. Thus, an analysis of the differences between the Physics of inanimate and that of the living matter has led us to propose principles for the construction of a much needed theory of organisms. In addition to this theoretical purpose, these founding principles have been useful for framing experiments and mathematical modeling. Finally, biological principles are needed to move beyond imitation. In this regard, the model of ductal morphogenesis referred to above is based on the basic principles of default state and the intrinsic constraints generated by the epithelial cells. By identifying constraints to the default state, multilevel biomechanical explanations become as legitimate as the molecular ones on which other modelers rely. Expanding research based on the premises of our theory of organisms will enrich a comprehensive understanding of normal development and of the one that goes awry.

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